# Erythropoietin or darbepoetin for patients with cancer (Review)

**Tonia T, Mettler A, Robert N, Schwarzer G, Seidenfeld J, Weingart O, Hyde C, Engert A, Bohlius J**

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# Erythropoietin or darbepoetin for patients with cancer

Thomy Tonia[1], Annette Mettler[1], Nadège Robert[2], Guido Schwarzer[3], Jerome Seidenfeld[4], Olaf Weingart[5], Chris Hyde[6], Andreas Engert[7], Julia Bohlius[1]

[1]Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland. [2]Pharmacy, Kantonsspitalapotheke Winterthur, Winterthur, Switzerland. [3]German Cochrane Centre, Institute of Medical Biometry and Medical Informatics, University Medical Center Freiburg, Freiburg, Germany. [4]Department of Quality and Guidelines, American Society of Clinical Oncology, Alexandria, VA, USA. [5]Cologne, Germany. [6]Peninsula Technology Assessment Group (PenTAG), University of Exeter Medical School, University of Exeter, Exeter, UK. [7]Cochrane Haematological Malignancies Group, Department I of Internal Medicine, University Hospital of Cologne, Cologne, Germany

Contact address: Julia Bohlius, Institute of Social and Preventive Medicine, University of Bern, Bern, 3012, Switzerland. jbohlius@ispm.unibe.ch.

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## ABSTRACT

### Background

Anaemia associated with cancer and cancer therapy is an important clinical factor in the treatment of malignant diseases. Therapeutic alternatives are recombinant human erythropoiesis stimulating agents (ESAs) and red blood cell transfusions.

### Objectives

To assess the effects of ESAs to either prevent or treat anaemia in cancer patients.

### Search methods

This is an update of a Cochrane review first published in 2004. We searched the Central Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE and other databases. Searches were done for the periods 01/1985 to 12/2001 for the first review, 1/2002 to 04/2005 for the first update and to November 2011 for the current update. We also contacted experts in the field and pharmaceutical companies.

### Selection criteria

Randomised controlled trials on managing anaemia in cancer patients receiving or not receiving anti-cancer therapy that compared the use of ESAs (plus transfusion if needed).

### Data collection and analysis

Several review authors assessed trial quality and extracted data. One review author assessed quality assessment and extracted data, a second review author checked for correctness.

**Main results**

This update of the systematic review includes a total of 91 trials with 20,102 participants. Use of ESAs significantly reduced the relative risk of red blood cell transfusions (risk ratio (RR) 0.65; 95% confidence interval (CI) 0.62 to 0.68, 70 trials, N = 16,093). On average, participants in the ESAs group received one unit of blood less than the control group (mean difference (MD) -0.98; 95% CI -1.17 to -0.78, 19 trials, N = 4,715). Haematological response was observed more often in participants receiving ESAs (RR 3.93; 95% CI 3.10 to 3.71, 31 trials, N = 6,413). There was suggestive evidence that ESAs may improve Quality of Life (QoL). There was strong evidence that ESAs increase mortality during active study period (hazard ratio (HR) 1.17; 95% CI 1.06 to 1.29, 70 trials, N = 15,935) and some evidence that ESAs decrease overall survival (HR 1.05; 95% CI 1.00 to 1.11, 78 trials, N = 19,003). The risk ratio for thromboembolic complications was increased in patients receiving ESAs compared to controls (RR 1.52, 95% CI 1.34 to 1.74; 57 trials, N = 15,498). ESAs may also increase the risk for hypertension (fixed-effect model: RR 1.30; 95% CI 1.08 to 1.56; random-effects model: RR 1.12; 95% CI 0.94 to 1.33, 31 trials, N = 7,228) and thrombocytopenia/haemorrhage (RR 1.21; 95% CI 1.04 to 1.42; 21 trials, N = 4,507). There was insufficient evidence to support an effect of ESA on tumour response (fixed-effect RR 1.02; 95% CI 0.98 to 1.06, 15 trials, N = 5,012).

**Authors' conclusions**

ESAs reduce the need for red blood cell transfusions but increase the risk for thromboembolic events and deaths. There is suggestive evidence that ESAs may improve QoL. Whether and how ESAs affects tumour control remains uncertain. The increased risk of death and thromboembolic events should be balanced against the potential benefits of ESA treatment taking into account each patient's clinical circumstances and preferences. More data are needed for the effect of these drugs on quality of life and tumour progression. Further research is needed to clarify cellular and molecular mechanisms and pathways of the effects of ESAs on thrombogenesis and their potential effects on tumour growth.

## PLAIN LANGUAGE SUMMARY

**Erythropoietin or darbepoetin for patients with cancer**

Introduction

Researchers in The Cochrane Collaboration conducted a review of the effect of epoetin and darbepoetin for people with cancer. After searching for all relevant studies, they found 91 studies with up to 20,102 people. Their findings are summarized below:

What the research says:

In people with cancer-related anaemia:

- Epoetin and darbepoetin decrease the need for red blood cell transfusions; however, they also increase the risk for hypertension, thromboembolic events and deaths

- It is not clear whether epoetin and darbepoetin improve quality of life, by making you feel less tired

When you have cancer, you often also have anaemia. Anemia means having lower than normal red blood cells in your blood. This might become even worse with cancer treatment such as chemotherapy and it is measured by the amount of haemoglobin in your red blood cells. As haemoglobin is responsible for carrying oxygen throughout your body, when you have anaemia you might experience symptoms such as extreme tiredness, shortness of breath, dizziness and chest pain. In order to treat anaemia, doctors often use red blood cell transfusions. Transfusions improve the symptoms of anaemia very quickly; however, they can have some infrequent complications like allergic reactions or transmission of infectious diseases.

Epoetin and darbepoetin belong to a group of medications called 'Erythropoiesis Stimulating Agents'. Erythropoietin is the name of a hormone produced mainly in the kidney, which takes part in the production of red blood cells. Epoetin and darbepoetin work in a similar way to this hormone to increase the number of red blood cells and treat anaemia. Epoetin and darbepoetin are not used as anti-cancer therapy but as supportive treatment to treat anaemia caused by cancer or anticancer therapy. These drugs are marketed as Epogen®, Procrit®, (Eprex®), Recormon®, and Aranesp® and are given subcutaneously.

What happens to people with cancer related anaemia who take epoetin or darbepoetin:

- Twenty-five out of 100 persons receiving epoetin or darbepoetin had to undergo red blood cell transfusions, compared to 39 out of 100 persons not receiving epoetin or darbepoetin.

- More people who received epoetin or darbepoetin died during and up to 30 days after the end of study compared with people who took placebo or underwent standard treatment. The increased risk for people taking epoetin or darbepoetin was 17%. One hundred and fourteen out of 1,000 persons receiving epoetin or darbepoetin died, compared with 98 out of 1,000 persons not receiving epoetin or darbepoetin. We could not identify particular characteristics of people or treatment strategies that increased or decreased the risk for dying.

- Concerning long-term survival people taking epoetin or darbepoetin were 5% more at risk for dying than people taking placebo or receiving standard treatment.

- People receiving epoetin or darbepoetin rated their fatigue symptoms to be an average of 2.08 points improved on a scale of 0-52 points after 3-4 months, compared with people taking placebo or having standard treatment. This improvement, however, is less than the 3.0 point increase which is considered to be the minimum required for the patient to feel a difference in his experience of fatigue-related symptoms using this scale.

- People taking epoetin or darbepoetin rated their fatigue and anaemia symptoms had to be an average of 6.14 points improved after three to four months, on a scale of 0-80 points. This improvement is considered to reflect a positive change in the way patients experience their fatigue and anaemia related symptoms, as it is more than four to five points of increase which is the minimum required for this scale.

- Seven people out of 100 who took epoetin or darbepoetin suffered a thromboembolic event such as stroke and myocardial infarction compared with five people out of 100 who did not receive epoetin or darbepoetin.

- Six out of 100 people receiving epoetin or darbepoetin developed high blood pressure compared with four out of 100 people who took placebo or had standard care.

## SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

**Erythropoietin or Darbepoetin for patients with cancer**

**Patient or population:** patients with cancer
**Settings:**
**Intervention:** Erythropoietin or Darbepoetin

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of Participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Control | Erythropoietin or Darbepoetin | | | | |
| **Overall survival** | **Low** | | **HR 1.05** (1 to 1.11) | 19003 (78 studies) | ⊕⊕⊕⊕ **high** | |
| | **50 per 1000** | **52 per 1000** (50 to 55) | | | | |
| | **Moderate** | | | | | |
| | **142 per 1000** | **149 per 1000** (142 to 156) | | | | |
| | **High** | | | | | |
| | **250 per 1000** | **261 per 1000** (250 to 273) | | | | |
| **On-study mortality** Death occurring up to 30 days after active study protocol | **Low** | | **HR 1.17** (1.06 to 1.29) | 15935 (70 studies) | ⊕⊕⊕⊕ **high** | |
| | **10 per 1000** | **12 per 1000** (11 to 13) | | | | |
| | **Moderate** | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| | **59 per 1000** | **69 per 1000** (62 to 75) | | | |
| | **High** | | | | |
| | **98 per 1000** | **114 per 1000** (104 to 125) | | | |
| **Thrombotic events** | **Low** | | **RR 1.52** (1.33 to 1.73) | 15278 (57 studies) | ⊕⊕⊕◯ **moderate**[1] |
| | **20 per 1000** | **30 per 1000** (27 to 35) | | | |
| | **Moderate** | | | | |
| | **46 per 1000** | **70 per 1000** (61 to 80) | | | |
| | **High** | | | | |
| | **100 per 1000** | **152 per 1000** (133 to 173) | | | |
| **Quality of Life - Change in FACT-Fatigue (13 items)** FACT-F 13 sub-scale | | The mean quality of life - change in fact-fatigue (13 items) in the intervention groups was **2.08 higher** (1.43 to 2.72 higher) | | 4965 (18 studies) | ⊕⊕◯◯ **low**[2,3] |
| **Quality of Life - Change in FACT-Anaemia (20 items)** FACT-An 20 | | The mean quality of life - change in fact-an (20 items) in the intervention groups was **6.14 higher** (4.55 to 7.73 higher) | | 1085 (6 studies) | ⊕⊕◯◯ **low**[4,5] |

| | | | | | |
|---|---|---|---|---|---|
| **Participants receiving red blood cell transfusions** | **Low** | | **RR 0.65** (0.62 to 0.68) | 15877 (70 studies) | ⊕⊕⊕○ **moderate**[6] |
| | **300 per 1000** | **195 per 1000** (186 to 204) | | | |
| | **Moderate** | | | | |
| | **389 per 1000** | **253 per 1000** (241 to 265) | | | |
| | **High** | | | | |
| | **700 per 1000** | **455 per 1000** (434 to 476) | | | |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**CI:** Confidence interval; **RR:** Risk ratio; **HR:** Hazard ratio;

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1] A funnel plot analysis revealed a significant asymmetry, suggesting that negative results (in this case no thrombotic event) have been underreported

[2] Only 18 out of a total of 91 studies assessing FACT-13 reported this endpoint, which suggests some reporting bias, even if the funnel plot did not show an asymmetry. 13 more studies (i.e. studies that stated they either used FACT-F or that they used FACT-An 47 but do not report separately for FACT-F or report it in a way that we cannot use.

[3] Overall, it seems that there is an effect to fatigue-related symptoms for patients treated with ESAs compared to controls; this effect, however, did not reach the threshold for a clinically important difference defined as 3.0.

[4] Only 6 out of a total of 91 studies assessing FACT-20 reported this endpoint, which suggests some reporting bias, even if the funnel plot did not show an asymmetry. Data from 19 studies addressing QoL can not used for review in cause of missing data (i.e.16 studies that stated they either used fact-an or that they used fact-an 47 but do not report separately for fact-an). Out of these 4 studies which refer to "FACT-An"/ to "fatigue sub-scale", were not useable because we cannot safely say to which instrument they are refer to.

[5] Overall, the effects of ESAs to fatigue and anaemia related symptoms seem to be beneficial and the difference between groups reaches both statistical and clinical significance (clinically important difference defined as 4-5).

6 A funnel plot analysis showed significant asymmetry between the studies, suggesting that negative results were under reported.

# BACKGROUND

## Description of the condition

Anaemia, defined as a deficiency in the concentration of haemoglobin-containing red blood cells, is a widely prevalent complication among cancer patients (Knight 2004). The prevalence of anaemia varies according to the type of neoplasia (Monnerat 1999). Patients with haematological malignancies frequently experience anaemia. At the time of diagnosis, 30% to 40% of patients with non-Hodgkin's lymphoma (NHL) or Hodgkin's lymphoma (HD) and up to 70% of patients with multiple myeloma are anaemic; the figures are even higher in myelodysplastic syndromes (Garton 1995; Greenberg 1994). The extent of anaemia is also influenced by the type of cytostatic treatment. It is known that the proportion of anaemic patients with solid cancers rises up to 50% after chemotherapy or combined radiochemotherapy (Dalton 1998; Harrison 2001; Ludwig 1998; Reed 1994).

The National Cancer Institute and others have agreed to use the following classification for anaemia based on haemoglobin (Hb) values (Groopman 1999):

- Grade 0, within normal limits, Hb values are 12.0 to 16.0 g/dL for women and 14.0 to 18.0 g/dL for men
- Grade 1, mild (Hb 10 g/dL to normal limits)
- Grade 2, moderate (Hb 8.0 to 10.0 g/dL)
- Grade 3, serious/severe (Hb 6.5 to 7.9 g/dL)
- Grade 4, life threatening (Hb less than 6.5 g/dL).

The pathophysiology of tumour anaemia is multi-factorial ( Mercadante 2000). In advanced stages of haematological malignancies, bone marrow involvement with malignant cells often leads to progressive anaemia. After exclusion of other causes, e.g. iron or vitamin deficiencies, occult bleeding, autoimmune haemolysis or pure red blood cell aplasia, anaemia can be related to "anaemia of chronic disorders". It is characterised by a close interaction between the tumour cell population and the immune system, leading to the activation of macrophages and increased expression of various cytokines, especially Interferon-g, Interleukin-1, Interleukin-6 and tumour necrosis factor. This is followed by insufficient endogenous erythropoietin synthesis, suppressed differentiation of erythroid precursor cells in the bone marrow and alterations of iron metabolism (Johnson 1990; Ludwig 1998; Nowrousian 2002a; Spivak 1994a). For example, the elevation of interleukin 6 (Il-6) leads to an up-regulation of Hepcidin and a diminished erythropoietin-synthesis. Hepcidin is one of the mediators that are released in inflammatory processes. It causes the destruction of another protein called ferroportin, which is important for the transport of Fe2+ from the enterocyte and the macrophage into the blood (Ganz 2011). The anaemia of chronic disorders, or chronic tumour anaemia is the most common type in patients with malignant disease, although it is often aggravated by chemo- or radiotherapy. In particular, platinum-based chemotherapy regimens may diminish endogenous erythropoietin production by damaging renal tubular cells (Wood 1995).

Manifestation and severity of anaemia vary considerably among individual patients. Mild-to-moderate anaemia can cause typical symptoms including headache, palpitations, tachycardia and shortness of breath. Chronic anaemia may result in severe organ damage affecting the cardiovascular system, immune system, lungs, kidneys, muscles and the central nervous system (Ludwig 2001; Nissenson 1992). In addition to physical symptoms, the subjective impact of cancer-related anaemia on quality of life (QoL), mental health and social activities may be substantial. Clinical studies have reported correlations between Hb levels and quality of life domains, for example mood, appetite (Leitgeb 1994), and the ability to work (Cella 1998; Thomas 1998).

Another aspect of anaemia in patients with malignant disease is the effect on the tumour itself. For malignant diseases such as Hodgkin's Disease (HD), chronic lymphocytic leukaemia (CLL), cervical carcinoma and cancer of the head and neck, anaemia has been reported to be an independent prognostic factor (Caro 2001; Hasenclever 1998; Nowrousian 2002b; Van Belle 2003). There is evidence that anaemia, with the consequence of increased tumour hypoxia, might result in a poorer response to radio- or chemotherapy (Hockel 1993; Nordsmark 1996; Van Belle 2003; Vaupel 1989; Vaupel 2000). Severe symptoms of anaemia may also necessitate dose reduction or delay of chemotherapy. All these factors may lead to a higher tumour burden and a decreased overall survival (Glaser 2001; Grau 2000; Knocke 1999). These observations have generated the hypothesis that strategies to diminish cancer-related anaemia might alleviate not only anaemia-related symptoms and improve quality of life, but also might improve tumour response and extend overall survival time. However, randomised controlled trials testing this hypothesis have generated conflicting evidence (Antonadou 2001; Henke 2003; Leyland-Jones 2005).

Historically, blood transfusion was the conventional treatment of choice for severe cancer-related anaemia. The literature reports a critical degree of anaemia as a Hb level below 8 g/dL, while mild-to-moderate anaemia (Hb level 8-10 g/dL) usually has been left untreated (Carson 2012; Cella 1999; Glaspy 1997a; Henry 1992; Koeller 1998). Although homologous blood transfusion is the fastest method to alleviate symptoms, short- and long-term risks exist (Engert 2000). Potential complications associated with blood transfusion are transmission of infectious diseases, transfusion reactions, allo-immunisation, over-transfusion and immune modulation with possible adverse effects on tumour growth (Landers 1996). The risk of severe infectious complications of blood transfusions are 1: 30.000 to 1:250.000 units of blood transfused for Hepatitis B, 1:30.000 to 1:150.000 for Hepatitis C and 1:250.000 to 1:1.000.000 for HIV (Goodnough 1999). Other complications such as allergic reactions and death due to major incompatibilities are infrequent but may be of concern (Williamson 1999). The development of intensified anti-neoplastic therapies has increased the risk for blood transfusion, prompting oncologists to weigh the

advantages and disadvantages of this treatment.

### Description of the intervention

Recombinant human erythropoietin is a treatment option for cancer-related anaemia. Human erythropoietin is an acidic glycoprotein hormone. Approximately 90% of the hormone is synthesised in the kidney and 10% in the liver (Koury 1988; Koury 1991). Basal production maintains a relatively constant plasma concentration of erythropoietin in individuals, within a range from 9 to 26 mU/mL. Tissue hypoxia is the most important trigger for increased synthesis. The effects of erythropoietin in the bone marrow are mediated by a specific surface receptor located mainly on erythroid progenitor and precursor cells (D´ Andrea 1989; Spivak 1994b). Two major functions of erythropoietin are described: stimulating progenitor cell proliferation and maintaining their viability (Koury 1990).

Several short- and long-lasting forms of recombinant human erythropoiesis-stimulating agents (ESAs) are available, including Epoetin-a and Epoetin-ß and darbepoetin-a (Darbepo) (Glaspy 2003; Halstenson 1991; Hedenus 2002; Joy 2002; Storring 1998; Vansteenkiste 2002). Recently, novel ESA molecules, such as continuous erythropoietin receptor activator (CERA) (Gascon 2010b), and biosimilars (epoetin theta, epoetin delta) have been developed (Jelkmann 2010). Clinical trials directly comparing Epo and Darbepo have been published and suggest that Epo and Darbepo are similarly effective with regard to Hb response and proportion of patients transfused (Alexopoulos 2004; Glaspy 2003; Schwartzberg 2004; Waltzman 2004). Based on these data, it seemed justified to combine both short- and long-lasting erythropoietin formulations in one meta-analysis.

### How the intervention might work

Erythropoietin was first approved for the treatment of anaemia in chronic kidney failure. In 1990, erythropoietin was introduced in cancer therapy regimens for patients with multiple myeloma. A pilot study showed haematological response rates of 85% and an improved performance status (Ludwig 1990). Adverse effects such as hypertension, headaches and thrombotic events conclusively attributable to erythropoietin treatment were reported in very few patients (Beguin 1998). However, several randomised controlled trials reported increased incidences of thrombotic events, tumour progression and deaths (Hedenus 2003; Henke 2003; Leyland-Jones 2005; Overgaard 2009; Smith 2008; Thomas 2008; Untch 2011_1; Wright 2007).

### Why it is important to do this review

Since ESAs were licensed for the treatment of anaemia in cancer patients, more than 20 systematic reviews and meta-analyses have been published. While there is clear evidence that ESAs reduce the need for red blood cell transfusions, increase Hb levels and also increase the risk for thromboembolic complications, there is ongoing debate on the effects of ESAs on QoL, tumour progression and mortality (Aapro 2006; Aapro 2008; Aapro 2009; Bennett 2008; Bottomley 2002; Cella 2004; Clark 2002; Devon 2009; Glaspy 2010; Hedenus 2005; Hellström-L 1995; Jones 2004; Kimel 2008; Lambin 2009; Ludwig 2009; Minton 2008; Minton 2010; Quirt 2003; Quirt 2005; Ross 2003; Ross 2006; Ross 2007; Seidenfeld 2001b; Seidenfeld 2001a; Seidenfeld 2006; Tonelli 2009; Wilson 2007).

The first Cochrane review (published in 2004 in *The Cochrane Library* and 2005 as print publication) on this subject included 27 randomised controlled studies on erythropoietin with 3,287 adults, published between 1985 and April 2002 (Bohlius 2005) in collaboration with authors from a previous review conducted for AHRQ (Seidenfeld 2001a; Seidenfeld 2001b). For the first update, we included trials published between 2002 and 2005 in collaboration with an independent review team from the Department of Public Health and Epidemiology at the University of Birmingham and the support of the UK Department of Health (Bohlius 2006a). In 2009, we conducted a separate meta-analysis based on individual patient data (IPD), which focused on on-study mortality and overall survival in all cancer patients and in patients receiving chemotherapy (Bohlius 2009a; Bohlius 2009b).Given that this analysis was restricted to survival outcomes, we present here the second update of the Cochane Review, including all relevant outcomes and integrating results generated for the IPD analysis as well as recently published trials.

## OBJECTIVES

To systematically review evidence on the outcomes of using recombinant human erythropoietin or darbepoetin to prevent or alleviate anaemia in patients with malignant disease, with respect to haematological response, red blood cell transfusion need, changes in quality of life, tumour response, on-study mortality, overall survival and adverse events.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

We included randomised controlled trials using recombinant human erythropoietin or darbepoetin to treat or prevent anaemia in patients with malignant disease. Placebo control, as opposed to

"no treatment", was not required for inclusion, but was considered in evaluating study quality. We excluded trials in which patients were allocated by a quasi-random method, for example date of birth or day of month, as we considered this study design to be of poor quality leading to unreliable results. We included only trials with more than 10 documented participants in each study arm or relevant stratum. We excluded interim analyses of ongoing studies. We included studies that were stopped or suspended prematurely. The searches did not include language restrictions.

### Types of participants

We included only participants diagnosed with malignant disease, using clinical and histological/cytological criteria, regardless of type or stage of the disease or previous therapy. All study participants had to be anaemic or at risk for anaemia from chemotherapy, radiotherapy or combination therapy, or the underlying malignant disease. Other causes of anaemia, such as haemolysis, iron deficiency and occult bleeding, had to have been excluded. We included studies with patients of every age. We excluded trials if more than 80% of participants were diagnosed with an acute leukaemia.

### Types of interventions

We included studies evaluating the use of recombinant human erythropoiesis-stimulating agents (ESAs) to prevent or reduce anaemia in cancer patients, given singly or concomitantly with chemotherapy, radiotherapy or combination therapy. ESAs could be administered subcutaneously or intravenously. In previous versions of this review, we required dosages of at least 300 U/kg body weight per week (epoetin-a and beta) given for at least four weeks. For the current update we removed this criterion and we included studies or study arms with low dosages as well. We allowed dose adaptation of ESAs depending on haematological response. Concomitant supportive treatments, e.g. granulocyte colony-stimulating factors (G-CSF), had to be given equally in all study arms. In previous versions of this review, this criterion applied to iron supplementation as well. However, for the current update, we have changed this criterion and included trials using iron supplementation in the experimental but not in the control arm as well. We excluded trials on high-dose myeloablative chemotherapy regimens followed by bone marrow or peripheral blood stem cell transplantation, as well as trials using erythropoietin for short-term preoperative treatment to correct anaemia or to support collection of autologous blood prior to cancer surgery.

Included trials addressed one or more of the following comparisons of interest:

1. ESAs versus placebo or no treatment.
2. ESAs and red blood cell (RBC) transfusion as necessary versus observation and RBC transfusion as necessary, alone or with placebo.
3. ESAs plus conventional-dose cancer therapy (non-myeloablative chemotherapy and/or radiotherapy) versus identical therapy alone or with placebo.
4. ESAs and RBC transfusion as necessary plus conventional-dose cancer therapy versus observation and RBC transfusion as necessary plus identical therapy, alone or with placebo.

### Types of outcome measures

#### Primary outcomes

- Haematological response

Measured as a binary outcome (proportion of patients with an increase in Hb level of 2 g/dL or more, or an increase in haematocrit of 6% points or more; measured as continuous data (change in Hb level from baseline until end of study). Of note, in the previous review we had restricted this outcome to studies with baseline Hb levels < 12 g/dL; in the current update we have removed this restriction.

- Patients receiving RBC transfusions
- Number of RBC units transfused per patient
- Overall survival
- On-study mortality. Of note, we added on-study mortality as a new outcome to the current update of the review.

#### Secondary outcomes

- Tumour response (complete response)
- Changes in quality of life including cancer-related fatigue and anaemia symptoms, measured with the Functional Assessment of Cancer Therapy Anaemia (FACT-An) Total scale (47 items), Anaemia sub-scale (20 items), or Fatigue sub-scale (13 items). We have chosen this instrument and its sub-scales because they have been widely used in ESA trials and have good responsiveness to change and good convergent and discriminant validity (Cella 1997; Cella 2002; Cella 2007; Yellen 1997).
- Adverse events (thromboembolic events, hypertension, haemorrhage/thrombocytopenia, rash/irritation/pruritus, seizures)

## Search methods for identification of studies

We used the following sources to identify the studies for this updated review:

1. Previous Cochrane reviews on the effects of ESAs on cancer patients, mainly Bohlius 2006a and Bohlius 2009a; Bohlius 2009b.
2. Electronic search in bibliographic databases.
3. Conference Proceedings.

4. ODAC Documents 2004, 2007 and 2008 (see next section).

5. Reference lists of other systematic reviews and meta-analyses.

Electronic searches Search strategies have been adapted from those suggested in the Cochrane Handbook for Systemtatic Reviews of Interventions (Lefebvre 2011). For detailed search strategies for each database, please refer to Appendix 1; Appendix 2; Appendix 3.For previous searches for this review see previous version of the review (Bohlius 2006a). For the current version, we identified relevant trials in any language through electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and EMBASE. We conducted the initial search for the period 2004 to September 2009. We updated the search using the same search strategy in January 2011 and in November 2011. We did not use language restrictions. The full search strategy is on file.

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### Searching other resources

***Conference Proceedings***

We searched conference proceedings of the American Society of Clinical Oncology, American Society of Hematology and European Society of Medical Oncology from January 1989 to December 2001 for the original Cochrane review; from January 2000 to December 2004 for the first update; and from January 2005 to November 2011 for the present update. We conducted searches of conference proceedings online, with CD-ROMs or by handsearching.

***Ongoing trials***

For the previous versions of this review, we searched various sources for ongoing studies. For the current update we did not search specifically for ongoing trials in online registries.

***Contact with authors***

For previous versions of this review, we contacted groups or individuals as well as pharmaceutical companies who conducted randomised trials on recombinant human erythropoietin in cancer patients. For the current review, we contacted authors only to clarify eligibility of studies, if necessary.

***Reference lists***

We checked reference lists of identified guidelines, systematic reviews and clinical trials for additional information.

***Oncology Drug Advisory Committee Documents***

For the current update, we evaluated documents presented at the Oncology Drug Advisory Committee (ODAC) hearing at the USA Food and Drug Administration (FDA), held in May 2004, May 2007 and March 2008. These documents include briefing documents plus additional power point presentations prepared by medical review authors of the FDA (FDA ODAC 2007; FDA ODAC 2008; Luksenburg 2004), as well as documents and additional power point presentations prepared by the companies Roche, Johnson & Johnson and Amgen (Amgen ODAC 2004; Amgen ODAC 2007; Amgen ODAC 2008; Johnson & Johnson ODAC 2004; Roche ODAC 2004). All of these documents are publicly available at FDA web pages.

## Data collection and analysis

### Selection of studies

Several review authors screened titles and abstracts of studies identified from the above sources according to the eligibility criteria stated previously. We did this step in duplicate. For the first Cochrane review this was undertaken by Simon Langensiepen and Julia Bohlius, for the first update this was undertaken by Jayne Wilson, Sunsan Brunskill, Julia Bohlius, Olaf Weingart and Sven Trelle. For the current update this was done by Annette Mettler, Julia Bohlius, Nadège Robert and Thomy Tonia. If eligibility could not be adequately assessed by screening the title and abstract, we obtained a full text version of the study for assessment. Studies that appeared to meet the inclusion criteria in the initial screening were further assessed for eligibility using a form containing the following questions.

1. Is the study described as randomised?
2. Did the participants in the study have a previously treated or untreated malignant disease?
3. Were the participants anaemic or at risk for anaemia from chemotherapy and/or radiotherapy or their malignant disease?
4. Was one group given Epoetin-a or Epoetin-ß or Darbepoetin-alfa or any other ESA subcutaneously or intravenously?
5. Did the control group receive the same care (e.g. chemotherapy and supportive therapies) with or without placebo?
6. Did the study document relevant outcome measures?

To be eligible, studies had to meet all of the criteria stated above. If there was insufficient information to judge eligibility, we contacted the first author of the report for clarification. We resolved

any disagreements between the review authors by discussion. We identified duplicate reports.

### Data extraction and management

Data extraction was performed by one review author and facts were checked by a second review author. For the original Cochrane review this was done by Simon Langensiepen and Julia Bohlius. For the first update all publications until September 2004 were extracted by Julia Bohlius, Jayne Wilson and Susan Brunskill. For the current update, data were extracted by Julia Bohlius, Olaf Weingart, Annette Mettler, Nadège Robert and Thomy Tonia. For the previous version QoL data were extracted by Jayne Wilson, Susan Brunskill and Chris Hyde. For the current version, QoL data were extracted by Thomy Tonia, Annette Mettler, Nadège Robert and Julia Bohlius. For data extractions we used a standardised data extraction form. This form included the following items.

- General information: title, authors, source, contact address of corresponding author, year of publication, any duplicate publications, trial setting, recruitment dates, funding.
- Trial characteristics: design, method of randomisation, concealment of allocation, blinding of patients and clinicians.
- Patients: sampling, inclusion and exclusion criteria, sample size, baseline characteristics, similarity of groups at baseline, diagnostic criteria, withdrawals, losses to follow-up.
- Interventions: placebo use, dose, dosing regimen, duration, route of administration, RBC transfusion trigger, co-medications with dose, route and timing
- Outcomes: outcomes as specified above.

We resolved disagreements arising at any stage by discussion and consensus.

**Referencing of studies**

If we identified several publications for one study, we extracted the data from the most recent publication and amended this with information from other publications. We used the following suffixes to indicate the source of data.

- We indicated data that were taken from either full text or abstract publication or based on personal communication with author name and year of publication
- We cited data that were taken from the individual patient data meta-analysis by Bohlius 2009a;Bohlius 2009b using the reference for the original study and adding the suffix "IPD". For example, we cited survival data for the Hedenus 2003 which we had taken from the individual patient data meta-analysis by Bohlius 2009a; Bohlius 2009b as "Hedenus 2003 IPD"
- We assigned the following suffixes to data taken from an ODAC presentation:
    - J&J 2004 if we took the data from a J&J presentation for the ODAC 2004 hearing
    - J&J 2007 if we took the data from a J&J presentation for the ODAC 2007 hearing
    - Roche 2004 if we took the data from a Roche presentation for the ODAC 2004 hearing
    - FDA 2004 if we took the data from a FDA presentation for the ODAC 2004 hearing
    - FDA 2007 if we took the data from a FDA presentation for the ODAC 2007 hearing
    - Amgen 2007 if we took the data from an Amgen presentation for the ODAC 2007 hearing
- For each unique study we assigned a five digit random number, entered for each reference in the "other" field. These numbers are identical to the numbers assigned to the studies in the IPD review by Bohlius 2009a; Bohlius 2009b. We assigned new five digit numbers for studies which we had not included in the IPD review.
- For studies comparing more than one experimental arm to one control arm, we assigned a separate reference for each study arm. We labelled these study arms with the author and publication year of the main publication and added the suffixes a; b; c etc. For example, the study by Cazzola 1995 compared four different experimental study arms with one control group. The four different study arms are listed in the included studies and the data analyses as Cazzola 1995a; Cazzola 1995b; Cazzola 1995c and Cazzola 1995d.

Due to this referencing system a given study may appear more than once in the list of included studies. The total number of unique studies included is 91. For these 91 studies, a total of 198 study identifiers are listed in the sections Included studies and Characteristics of included studies.

**Methods for QoL**

In the previous review, we included any validated QoL instrument. For the current update, we restricted the analysis to studies meeting the inclusion criteria and also reporting QoL data using one of the following instruments.

a) FACT-F 13: Functional Assessment of Cancer Therapy Fatigue sub-scale, consisting of 13 fatigue-specific questions

b) FACT-An 20: Functional Assessment of Cancer Therapy Anaemia sub-scale, consisting of 20 questions (13 from FACT-F, plus 7 anaemia specific questions)

c) FACT-An 47: Functional Assessment of Cancer Therapy Anaemia total score, consisting of 47 questions (20 from the FACT-An sub-scale plus 27 from the FACT-General scale)

In the previous update, we excluded studies that did not clearly state the number of participants contributing to QoL data. For the current update, we decided to also include studies that did not report the exact number of participants contributing QoL data, in order to get as much information as possible. We included all studies reporting change between baseline and end of treatment per group. We limited the included QoL data to scores of the full

instruments or sub-scales that have been validated as stand-alone instruments.

Rather than focusing on statistical significance, meaningful interpretation of QoL results emphasizes the degree to which differences between treatment and control arms exceed a Clinically Important Difference (CID) previously established for the QoL instruments utilized. For FACT-Fatigue, this has been estimated to be three (Cella 2002) and for FACT-An 20 four to five (Cella, personal communication, March 2010). For FACT-An 47 a CID has not yet been established.

## Assessment of risk of bias in included studies

### Quality Assessment

Two review authors independently assessed the full text articles of the eligible studies for quality. For the original Cochrane review this was undertaken by Simon Langensiepen and Julia Bohlius. For the first update this was done by Julia Bohlius and either Jayne Wilson or Susan Brunskill for the trials published until September 2004, and Julia Bohlius and Sven Trelle for trials published between September 2004 and April 2005. For the current update, this assessment was conducted by Annette Mettler, Nadège Robert and Thomy Tonia. For the original Cochrane review, we contacted all first authors or sponsoring pharmaceutical companies of the included trials in order to obtain detailed information on the study design. For the previous and current update (years 2002 to November 2011) this was not undertaken due to time limitations. However, for the IPD review (Bohlius 2009a; Bohlius 2009b) we had access to the clinical study reports of the included studies and used these to assess the quality of studies. We integrated these assessments in the current review update. For all other studies, we took this information from publications.

To assess the methodological quality and the risk of bias, we designed a quality assessment form specifically for the topic of this review, according to the recommendations in Chapter Eight of the *Cochrane Handbook for Systematic Reviews* ( Higgins 2011a). The sources we used for designing this form are: Alderson 2005; Jüni 2001; Moher 2001; Verhagen 1998) and the form contains the following questions.

1. Was allocation truly random?
2. Was the treatment allocation concealed?
3. Were study participants blinded (masked) to the treatment they received?
4. Were study clinicians blinded (masked) to the treatment received by individual study participants?
5. Did the analysis include an intention-to-treat (ITT) analysis?

We excluded studies from the analysis if they were not truly randomised or had inadequately concealed treatment allocation, e.g. if participants were assigned to treatments in alternate order, or according to their birth dates, or the day of the week they arrived at the treatment centre. We tested the effect of individual quality variables (allocation, blinding, ITT) in subgroup analyses. Because of the problematic use of quality summary scores, we did not use summary scores (Jüni 1999; Schulz 1995). We assessed baseline participant characteristics to see if the groups were balanced at baseline. We also assessed whether the number of patient withdrawals, dropouts and lost to follow-up was reported for each study group; however, we did not use this information for the analyses.

For the present update we applied additional quality criteria to assess the quality of studies reporting data on tumour control. These criteria were as follows.

1. The study population had to be homogenous, i.e. all participants had to have the same tumour type and - if relevant - the same tumour stage. Alternatively, the study had to be stratified by tumour type or tumour stage.
2. The participants of the study had to receive a predefined, identical anticancer therapy. As above, we considered a study to meet this criterion if the study was stratified by treatment.
3. The study had to be designed to assess tumour response or tumour control prospectively or tumour control/response had to be the primary or secondary study outcome.

## Dealing with missing data

### Incomplete reporting of data

As suggested in Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b), we took the following steps in addressing missing data.

For studies that did not report the number of patients evaluated for a given outcome, we used the number of patients randomised per study arm as denominator. In studies where only the total number of population was reported (and not the number of patients per arm) and where the randomisation was 1:1, we assumed that randomisation was 1:1 for a given outcome as well, thus assuming that the outcome was calculated using ITT analysis.

Binary data: if only percentages but not absolute number of events were reported, we used percentages to calculate numerators.

Continous data: If estimates for mean and standard deviations (SD) were not reported, we used the methods published by Hozo et al to convert median and range estimates of outcomes such as Hb change into mean and SD (Hozo 2005). If mean change was not reported, we calculated this as the difference between end of treatment and baseline value. If SDs were not reported, we estimated them from standard errors, confidence intervals or ranges, whenever reported. If numerical data were not reported, we estimated means and/ or SDs from graphs or figures. If SDs and means were reported for subgroups only, we calculated a pooled SD by pooling the SDs of the two different subgroups. For some studies it was not clear whether the reported numbers were referring to SDs or SEs. To maximise the likelihood that our assumptions were valid, we assumed that the numbers were SDs and converted them to SEs and vice versa. We then assumed that the numbers were referring to SDs or SEs depending on which one seemed more likely for this outcome, as suggested in Deeks 1997. If mean change between

baseline and end of treatment and corresponding SD was not reported, they were calculated by using a correlation coefficient. In addition, we used secondary sources to identify data that were not reported in the original publication. These secondary sources included ODAC briefing documents and other meta-analyses. For example for QoL we retrieved data from secondary publications, that had attempted to retrieve missing information from authors (Minton 2008; Minton 2010) or imputed data (Tonelli 2009). To account for all these calculations, we conducted a subgroup analysis taking into account the source of data, as well as a sensitivity analysis differentiating between the studies for which we had to impute data in some way and those for which we did not impute any data.

Handling of discrepant data: If a study was published in several different publications, reports and presentations, we extracted the most recent or most comprehensive data. We compared the data of one study taken from different sources. If the data from different sources were discrepant, we applied the following rules to decide which data to use for analysis.

- Most complete data set, e.g. where the sample size is largest OR data with consistent outcome definitions across trials were chosen for analysis.
- If for one study outcome two different analyses were available (e.g. adjusted versus unadjusted analysis), we chose the unadjusted data for analysis.

Age: if age was not reported but the cancer was typical for adults, e.g. breast cancer or non-small cell lung cancer (NSCLC), we classified the study as conducted in an "adult" population.

### Assessment of heterogeneity

As suggested in Chapter 9 of the *Cochrane Handbook of Systematic Reviews on Interventions* (Deeks 2011), we explored potential causes of heterogeneity by performing sensitivity and subgroup analyses for primary and selected secondary outcome measures (see below). We used the P value of the homogeneity test and the $I^2$ statistic only to describe the extent of heterogeneity inherent in a meta-analysis.

### Assessment of reporting biases

In meta-analyses with at least 10 trials, we generated a funnel plot and performed a linear regression test (Egger 1997) to examine the potential presence of bias. We considered a P value of less than 0.1 as significant for the linear regression test (Sterne 2011).

### Data synthesis

We performed analyses according to the recommendations of Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011).

We assumed a fixed-effect model for all meta-analyses. For binary data, we used the risk ratio as a measure of treatment effect and we used the Mantel-Haenszel method for pooling. We used the estimated overall RR and a range of plausible values for the baseline-risk to estimate numbers needed to benefit (NNTB) and numbers needed to harm (NNTH). For continuous data, we calculated the mean differences (MD) if the outcome was measured on the same scale in all trials. For QoL we combined only identical scales and sub-scales in a given meta-analysis. For time to event data, i.e. overall survival, we calculated hazard ratios (HR) based on individual patient data (IPD). If IPD were not available, we calculated the HR from published reports including secondary analyses (Bohlius 2009a; Bohlius 2009b), using methods described in Parmar et al (Parmar 1998) or binary mortality data. We performed all analyses using Review Manager (RevMan) 5.1; we used the statistical software package R (Ihaka 1996) for additional analyses that could not be done with RevMan 5.1.

In addition to subgroup analyses, we conducted random-effects meta-regression (see Section 9.6.4, Cochrane Handbook) for the following outcomes: Hb response, Hb change, participants receiving red blood cell transfusions, FACT-Fatigue, FACT-An 47 using R function rma.uni in R package metafor (Viechtbauer 2010). We used the DerSimonian-Laird method to estimate the between-study variance in meta-regression. In model selection, we considered all covariates showing a significant effect ($P < 0.05$) in a univariate analysis. We restricted the analysis to studies providing information on all variables that were statistically significant in univariate analyses. For model selection, we used a back-wise selection method; we removed consecutively the covariate with the largest P value as long as the P value was larger than 0.05.

In several studies different ESAs, dosages, and routes or schedules of administration were compared with one control group (Cazzola 1995; Henke 1999; Kotasek 2003; Kunikane 2001; Osterborg 1996; Smith 2003; Suzuki 2008; Ten Bokkel 1998; Thatcher 1999). For each multi-arm study, we divided and randomly assigned control patients to the corresponding number of separate treatment groups for entry into RevMan (base model). As this might influence the weighting of the studies and thus the pooled results, we alternatively merged the two (or more) active arms of one study into one single experimental arm and compared it to the entire control group. We compared and described results for each outcome.

### Subgroup analysis and investigation of heterogeneity

We conducted subgroup analyses using the following factors, if appropriate.·

- Hb at study entry (Hb level < 10 g/dL versus 10 to 12 g/dL versus >12 g/dL versus unclear/not reported)
- Solid tumours versus haematological malignancies (excluding myelodysplastic syndrome (MDS)) versus MDS versus mixed versus unclear versus not reported)
- Age (children versus adults)
- Age (only children versus adults > 18 years versus > 70% non-elderly adults aged 18-65 versus only non-elderly adults

versus > 70% elderly adults aged > 65 years versus only elderly adults aged > 65 years)

- Type of treatment given (chemotherapy versus radiotherapy/radiochemotherapy versus no therapy versus other)
- Type of treatment given (> 70% of patients receiving platinum-based chemotherapy versus < 70% of patients receiving platinum-based chemotherapy versus chemotherapy without platinum versus chemotherapy some (not quantified) patients receiving platinum versus chemotherapy no details given versus radiochemotherapy versus radiotherapy versus no therapy versus other). We categorised studies with less than 70% of patients receiving chemotherapy as "other" (P-174 IPD; Rose 1994 IPD)
- Short-lasting ESA versus long-lasting ESA
- Duration of ESA medication (six to nine weeks versus 12 to 16 weeks versus more than 20 weeks)
- Iron supplementation (fixed iron supplementation versus iron as necessary versus no explicit statement/no iron versus explicit NO iron versus iron handled differently in study arm)
- Study quality parameters (concealment of allocation, masking, intention-to-treat analysis)
- Source of data (full text publications versus abstract publications versus unreported data versus data reported at FDA/ODAC hearing versus other)

Compared to the previous version of this review, we added new subgroups to differentiate with more detail different age groups and different anti-cancer therapy groups. For the subgroup "iron supplementation", we added the categories "iron given differently in both study arms", because of the change in the inclusion criteria described above and "explicitly stated NO iron". However, no study was included in the latter subgroup. For the subgroup "publication", we added the category "other", containing clinical trial results from sources that did not fit any other category. We dropped the following subgroup analyses as they did not seem to be relevant any longer or insufficient information was available: Number of drop outs documented; use of G-CSF.

### Sensitivity analysis

To test the robustness of the results, we conducted random-effects meta-analyses. We reported the estimates of the random-effects only a) if they showed a difference to the fixed-effect model or b) if they were necessary to allow for comparison with other meta-analyses in the discussion section. We explored the influence of single large studies and the influence of different data sets, e.g. adjusted versus unadjusted data.

## RESULTS

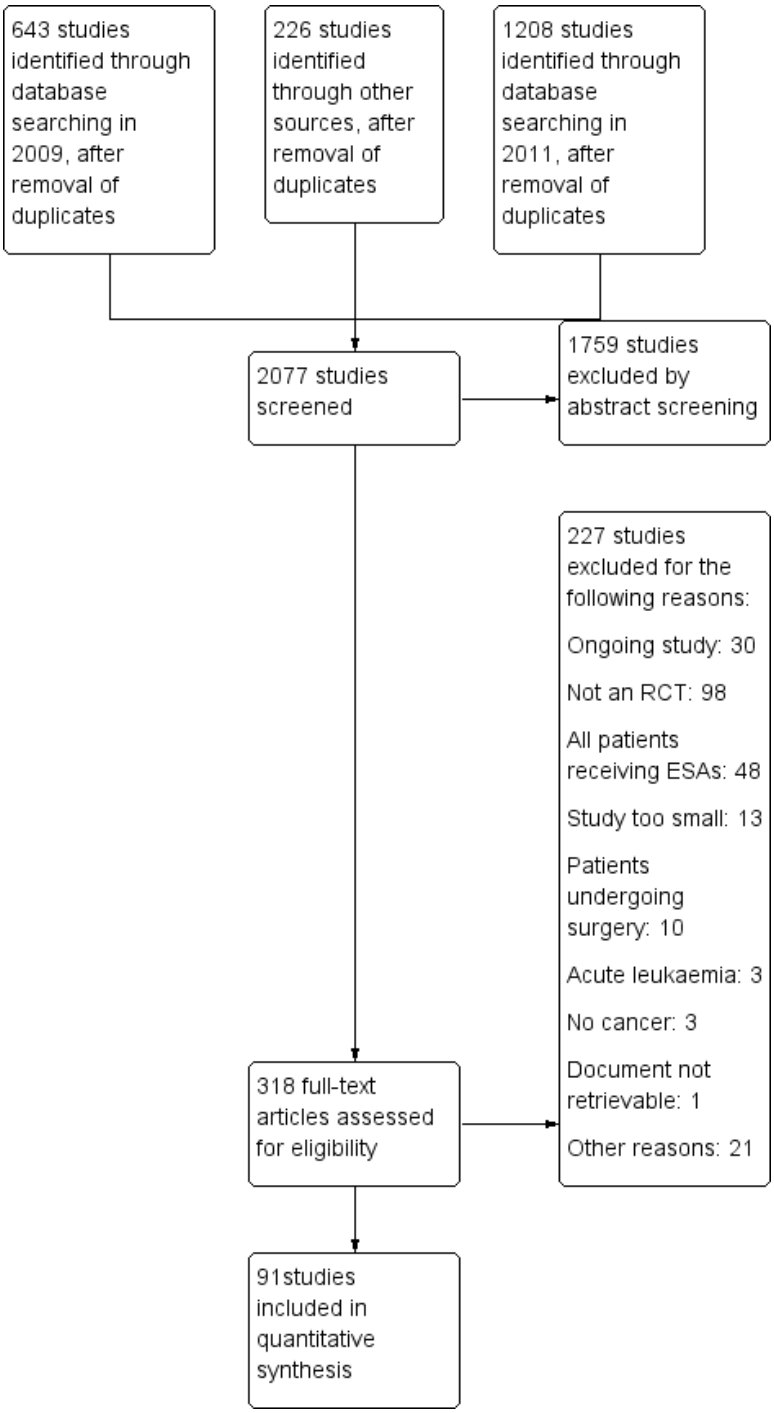
### Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

### Results of the search

Our initial literature search in March 2001 retrieved 1,592 references. For the first update of this review the Birmingham team identified and screened another 1,859 references. For the current update, we identified and screened a total of 2,207 references (999 at the first search on September 2009 and 1208 at the two searches conducted in 2011 (January and November)). For details, see the PRISMA flow diagram in Figure 1.

**Figure 1. Study flow diagram.**



## Included studies

The previous update of the Cochrane review (Bohlius 2006a) evaluated 57 studies with 9,353 participants. In the current update we include a total of 91 studies with 20,102 participants. All included trials were reported in English. Details are displayed in the Characteristics of included studies table. For those 91 studies, 198 references were included, see details as described in "Referencing of studies" in the Methods section.

*Studies that were previously excluded and are now included*

Four of the previously excluded studies are included in the current update, due to the change in the iron supplementation rule: for this update, studies are also included if they had different iron supplementation policies between the different study arms (Blohmer 2011; Moebus 2007; Rosen 2003; Sweeney 1998). We had previously excluded another study by mistake, we have now included this study (Gebbia 2003).

*Studies that were previously included and are now excluded*

We excluded two of the previously included studies (Henze 2002; Vadhan-Raj 2004 ) because a substantial number of participants underwent major surgical procedures during ESA treatment.

*Studies that were previously ongoing and are now included*

We included four studies that were previously ongoing (Aapro 2008; Antonadou 2001; Charu 2007; Pronzato 2010).

*Updated data for already included studies*

If new publications supplemented or updated information from earlier sources, we added the new data and cited the new source as the study name. This led to the following changes: we replaced Coiffier 2001 with Boogaerts 2003, Janinis 2003 with Christodoulou 2009, EPO-CAN-15 with Goss 2005, N93 004 with Grote 2005, EPO-GBR-7 with Hoskin 2009, Machtay 2004 with Machtay 2007, Milroy 2003 with Milroy 2011, Savonije 2004 with Savonije 2005, GOG0109 with Thomas 2008, EPO-CAN-20 with Wright 2007, we amended Razzouk 2004 with Razzouk 2006, and Pronzato 2002 with Pronzato 2010.

*Newly identified studies*

Screening the references of other reviews on this subject, led to the identification and inclusion of three new studies (Gebbia 2003; ML17616 2006; ML17620 2006 ). We included three studies (EPO-GER-20 IPD; Kotasek 2002 IPD; OBE/EPO-INT-03 IPD) that were previously unpublished and retrieved for the IPD review (Bohlius 2009a; Bohlius 2009b). We identified 23 additional new studies that were published after the search for the previous review was conducted. We included these studies in the present update. From those, we had also included 11 in the IPD review (Aapro 2008; Debus 2006 J&J 2007; Gordon 2008; Hernandez 2009; Milroy 2011; Pirker 2008; Ray-Coquard 2009; Smith 2008; Strauss 2008; Untch 2011˙1; Wilkinson 2006) and we identified twelve from the literature search update (Engert 2010; Fujisaka 2011; Gupta 2009; Katakami 2008; Krzakowski 2008; Mystakidou 2005; Overgaard 2009; Suzuki 2008b; Tsuboi 2009; Tjulandin 2010; Tjulandin 2011; Winquist 2009).

*Other changes*

In the previous review (Bohlius 2006a), we had excluded studies and study arms with very low ESA dosages, in the current update we included all studies and study arms regardless of ESA dosage, for example see Cazzola 1995.

***Study population***

*Hb level:* We grouped studies by mean or median baseline Hb level at study entry. Thirty studies examined a study population with mean or median Hb below 10 g/dL at study entry, 38 had a baseline Hb between 10 and 12 g/dL and 18 studies sought to prevent anaemia, thus Hb at baseline was > 12 g/dL. Because of missing information, five studies could not be categorized Debus 2006 J&J 2004; EPO-GER-20 IPD; ML17620 2006; OBE/EPO-INT-03 IPD; P-174 J&J 2004). Trials that directly compared the outcomes of initiating erythropoietin treatment at alternative Hb thresholds were not included in the present review.

*Disease:* Fifty-nine studies analysed participants with solid tumours only, 12 studies included patients with haematological malignancies only, two trials included exclusively patients with MDS (Italian 1998; Thompson 2000) while 18 trials included patients with both solid tumours and haematological malignancies.

*Treatment:* The majority of participants received concomitant chemotherapy, which was given in 63 studies. In seven studies participants were treated with radiotherapy and in eight with radiochemotherapy. In nine trials no concomitant anticancer therapy was given. Finally, we categorized the type of anti-cancer therapy administered as "unclear" in one study (Winquist 2009) and three studies with less than 70% of patients given chemotherapy as "other" (P-174 J&J 2004; Rose 1994; Rosenzweig 2004).

*Age:* All studies but one (Razzouk 2006) evaluated adult participants.

*Intervention:* All trials compared erythropoiesis-stimulating treatment initiated at study entry (plus RBC transfusion if necessary) with observation and transfusion of RBCs when the patient's Hb level fell below a defined threshold or at the discretion of the treating physician.

*Study drug:* Short-lasting erythropoietin*s* (including epoetin alpha, epoetin beta, epoetin theta) were administered in 76 studies and darbepoetin in 15 studies.

*Duration:* Duration of study medication was up to nine weeks in 17 studies, between 12 and 16 weeks in 50 studies and more than 17 weeks in 21 studies. In three studies the duration of study drug administration was unclear or not reported (EPO-GER-20 IPD; EPO-INT-1 J&J 2004; OBE/EPO-INT-03 IPD).

*Route of administration*: In all but three studies erythropoietin was administered subcutaneously. In two studies erythropoietin was

given intravenously (Razzouk 2006; Wurnig 1996). Another study compared intravenous with subcutaneous administration (Henke 1999).

More details are provided in the table Characteristics of included studies.

### Excluded studies

Overall, we excluded 227 trials, for reasons documented in the Characteristics of excluded studies. Thirty studies were excluded as ongoing trials (see next section) while one study was not retrievable.The largest group was excluded for not being randomised controlled trials (98 studies). We excluded 48 studies because participants of both study arms received ESAs, while we excluded 13 studies since they randomised less than 10 participants per study arm, our current threshold for inclusion. We excluded two previously included studies (Henze 2002; Vadhan-Raj 2004) from this update, since most of their participants underwent surgery during the study; the same reason for exclusion was applied to another eight studies. Three studies were excluded due to the participants not having cancer, while three more due to the participants having acute leukaemia. Finally, 21 studies were excluded for other reasons, documented in the Characteristics of excluded studies.

**Ongoing trials**

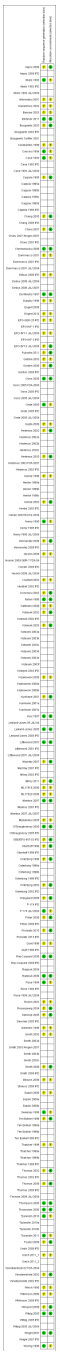
Overall, we identified 30 studies that are currently ongoing. For the previous Cochrane update, 29 trials were identified as ongoing. Since then, five were completed and are included in the present meta-analysis (Aapro 2008; Antonadou 2001; Charu 2007; Pronzato 2010; Thomas 2008). We identified a mistake in the ongoing trials of the previous version: namely CDR0000068669 and EORTC 22996-24002 were in fact the same study, now identified as Lambin 2006.Three of the previously ongoing trials are now excluded (Elsaid 2001; Miller 2004; Steensma 2011). Additionally, note that we were uncertain whether H Thomas 1997 and R Thomas 2002 are the same studies as the included Thomas 2002. We did not contact the authors and we, therefore, refer to these three documents as separate studies, with the first two still considered as ongoing trials. The remaining 20 trials are still ongoing.

We newly identified another 10 trials ongoing. We had excluded one (Gamucci 1993) in the previous Cochrane update and we identified another six (Boehrer 2010; Delarue 2009; Gascon 2010; Ghavamzadeh 2010; Liang 2009; Yousseff 2011) by the 2011 literature search. We identified the remaining three (Nitz 2008; Park 1996 and Rexer 2006) by other sources.

## Risk of bias in included studies

For risk of bias table see Figure 2.

**Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study. If for a given study more than one reference was included we reported our judgement only for the main reference and left the other references of the same study empty.**



### Allocation

**Randomisation and concealment of allocation.**

All included studies were described by the authors as randomised. For 27 studies we had some information on the methods used for randomisation, for 64 studies details were unavailable or the reporting was unclear. For 50 studies we judged the method for concealing allocation of treatment to be adequate. In 41 studies the method for allocation concealment could not be determined.

### Blinding

**Masking**

Forty-six trials used a placebo control, 45 trials did not.

### Incomplete outcome data

Most studies included intention-to-treat analyses in their reports, or excluded less than 10% of the patients randomised in the study from the analysis. However, the number of participants evaluated in a study varied between the outcomes assessed. Therefore, for each of the outcomes, we made an assessment as to whether or not the analysis was based on intention-to-treat or excluded less than 10% of the participants initially included. This information is displayed in the specific outcomes section in RevMan.

### Selective reporting

For the first version of the Cochrane review, we contacted first authors to obtain unreported data on study design, participant characteristics and selected outcome data. For 19 of the 27 trials included in the first Cochrane review additional unpublished data were provided by the authors or pharmaceutical companies (Abels 1993; Cascinu 1994; Case 1993; Cazzola 1995; Boogaerts Coiffier 2001; Dammacco 2001; Del Mastro 1997; Henry 1995; Italian 1998; Kurz 1997; Littlewood 2001; Oberhoff 1998; Osterborg 1996; Osterborg 2002; Rose 1994; Ten Bokkel 1998; Thatcher 1999; Thompson 2000; Throuvalas 2000). For the update of the present review, authors of published reports were not contacted to obtain missing information.

***Publication bias***

Funnel plot analyses were performed to investigate publication bias or other biases and are reported in the specific outcome sections.

***Reporting bias***

No single outcome was reported consistently by all studies (N = 91) included in this systematic review. Some outcomes were estimated based on large proportions of the 91 studies and 20,102 participants included:

95% for overall survival (19,003/20,102), 79% for on-study mortality (15,935/20,102), 80% for risk of transfusions (16,093/20,102), 77% for risk of thromboembolic events (15,498/20,102) and 58% for change in Hb (11,609/20,102). For other outcomes, fewer participants were included in the meta-analyses: 36% (7,228/20,102) for hypertension, 32% (6,413/20,102) for haematologic response, 25% (5,012/20,102) for complete tumour response, 25% (5,012/20,102) for number of units transfused and 22% (4,507/20,102) for thrombocytopenia/haemorrhage.

For some outcomes only small proportions of participants could be evaluated, which questions the validity of the results achieved: 14% (2,890/20.102) for seizure, 12% (2,485/20,102) for rash.

Statistically significant differences between data taken from full text publications, abstract publications and unpublished data were found in the subgroups analyses for Hb response, Hb change, risk for transfusions and number of units transfused.

### Other potential sources of bias

For some studies more than one source of data was available (e.g. unpublished data from the authors, FDA reports, IPD review). As for intention-to-treat mentioned above, we recorded the source of data separately for each outcome.

## Effects of interventions

See: **Summary of findings for the main comparison** Erythropoietin or Darbepoetin for patients with cancer

### Primary outcomes

#### (1) Haematological response

We defined this binary outcome as the proportion of participants with an increase in haemoglobin (Hb) level of 2 g/dL or more, or increase in haematocrit of six percentage points or more, unrelated to transfusion.

Overall, 31 trials including 6,413 participants were analysed. Of those studies, 22 trials including 4,307 participants were included in the previous Cochrane reviews (1985 to 2006). Nine trials (N= 2,106) were newly identified and added to the analysis (Aapro 2008; Charu 2007; Milroy 2011; ML17616 2006; ML17620 2006; Razzouk 2006; Suzuki 2008; Tjulandin 2010; Tjulandin 2011). As some of the trials (Cazzola 1995; Hedenus 2002; Kotasek 2003; Osterborg 1996; Smith 2003; Suzuki 2008; Tjulandin 2010) were split into subsets for analysis purposes, the number of trials displayed is 46.

We observed haematological response in 2,050 out of 3,710 participants in the erythropoietin and darbepoetin groups compared with 434 of 2,703 in the control groups, corresponding to a risk ratio (RR) for haematological response under the treatment with

erythropoietin or darbepoetin of (RR 3.39; 95% confidence interval (CI) 3.10 to 3.71). There was significant statistical heterogeneity between the trials ($I^2$= 53%), indicating that variation between trials in the magnitude of ESA effects on haematological response was larger than what would be expected from chance alone. However, all studies indicated a beneficial effect of ESAs with regard to haematological response. The funnel plot analysis was asymmetric (P = 0.0015), suggesting that beneficial effects were over reported. In seven studies (Cazzola 1995; Hedenus 2002; Kotasek 2003; Osterborg 1996; Smith 2003; Suzuki 2008; Tjulandin 2010), two or more epoetin dosages or preparations were compared with one control group. Merging the active arms into one experimental arm for each of those four studies did not influence the overall result markedly (RR 3.42; 95% CI 3.12 to 3.74). Compared with the previous review (RR= 3.43 (95% CI 3.07 to 3.84, 22 trials, N = 4,307, Bohlius 2006a) neither the point estimate, nor the confidence interval have changed substantially.

To identify the source(s) of heterogeneity, subgroup analyses were performed. Univariate analyses identified significant differences (P < 0.05) between subgroups for baseline Hb level, age, type of anti-cancer therapy, iron supplementation, duration of treatment, placebo control and type of publication. The backward selection resulted in a multivariate model containing the covariates Hb at baseline, age and iron supplementation. The final model is presented in Additional Table 1. For each combination of Hb at baseline, age and type of iron supplementation the risk ratio can be calculated from Table 1. For example, the logarithm of the risk ratio for a trial including adults with Hb between 10 and 12 g/dL at baseline and receiving iron as necessary is Intercept + adults + Hb 10-12 g/dL + iron given as necessary = 0.81 + 0.62 + 0.35 = 1.78. Accordingly, the risk ratio is 5.93.

We calculated numbers needed to benefit (NNTB) for several hypothetical baseline risks. In a population with an underlying risk [likelihood] of 6% to achieve haematological response, the NNTB would be 6.97 (95% CI 6.15 to 7.94); thus, about seven patients would need to be treated to achieve one additional Hb responder. In a population with an underlying risk of 16% the NNTB would be 2.62 (95% CI 2.31 to 2.98); thus, about three patients would need to be treated to achieve one additional Hb responder. In a population with a hypothetical baseline risk of 30% the NNTB would be 1.39 (95% CI 1.23 to 1.59); thus, one to two patients would need to be treated to achieve one additional Hb responder. Overall, the analysis confirms prior evidence that ESAs yield haematological response in most but not all patients with malignant disease.

#### (2) Change in haemoglobin level from baseline until end of study

Fifty-six studies including 11,609 participants reported the hb change from the start until the end of the study. Fifteen of those were included in the 2006 update (Bohlius 2006a). As some of the trials had multiple experimental arms (Cazzola 1995; Hedenus 2002; Henke 1999; Kotasek 2003; Krzakowski 2008; Kunikane 2001; Osterborg 1996; Smith 2003; Ten Bokkel 1998; Tjulandin 2010), the number of trials displayed in MetaView is 75. For this update, we included not only studies that reported the mean Hb change from baseline, but also studies that reported baseline and end of treatment (EOT) Hb values only, see Methods section.

The meta-analysis showed that the mean difference was 1.57 (95% CI 1.51 to 1.62), showing a statistically significant difference in favour of treatment. There was, however, substantial heterogeneity between the trials (test for heterogeneity $I^2$ = 87%), although all but one study indicated a beneficial effect of ESAs with regard to Hb change. Funnel plot analysis did show some evidence for significant asymmetry (P = 0.037), suggesting that beneficial findings were over reported. Merging each multi-arm trial into a single data set (i.e. a two-arm trial) did not change the results (mean difference (MD) 1.56, 95% CI 1.51 to 1.62).

Examining the single studies, most of them reported a statistically significant change in Hb level for participants treated with erythropoietin or darbepoetin. A few studies, however, did not report a significant effect on Hb change (Cazzola 1995; Leyland-Jones 2005; Razzouk 2006). Overall, the MD ranged from (MD -0.06; 95% CI -1.77 to 1.65, Cazzola 1995a) to (MD 3.30; 95% CI 1.13 to 5.47, Henke 1999c).

To identify the source(s) of heterogeneity, we performed subgroup analyses. Univariate analyses identified significant differences between subgroups for baseline Hb level, different malignancies, age, type of anti-cancer therapy, short-lasting versus long-lasting ESA, duration of ESA treatment, iron supplementation, masking, intention-to-treat and type of publication. The backward selection resulted in a multivariate model containing the covariates type of ESA and age. The final model is presented in Additional Table 2 For each combination of type of ESA and age (adults or children) the mean difference can be calculated from Table 2. For example, the mean differences for a trial in adult patients receiving short-lasting ESA is = Intercept + short lasting ESA = 1.15 + 0.56 = 1.71. Overall, there is a statistically significant effect of ESAs on Hb change; compared with controls patients receiving ESAs achieve on average an increase of Hb levels of 1.57 g/dL from baseline to end of treatment (between 1.51 and 1.62 g/dL in 95% of patients).

#### (3) Patients receiving RBC transfusions

Overall, the updated analysis included 70 trials with 16,093 participants. Of those, 42 trials with 6,510 participants were included in the previous Cochrane review (Bohlius 2006a). Thirty trials were newly identified and added to the analysis. (Aapro 2008; Blohmer 2011; Charu 2007; Engert 2010; EPO-INT-3 J&J 2004; Fujisaka 2011; Gebbia 2003; Gordon 2008; Goss 2005; Grote 2005; Gupta 2009; Hernandez 2009; Katakami 2008; Krzakowski 2008; Leyland-Jones 2005; Milroy 2011; Moebus 2007; O'Shaughnessy 2005; Pronzato 2010; Pirker 2008; Ray-Coquard 2009; Rosen

2003; Smith 2008; Strauss 2008; Tjulandin 2010; Tjulandin 2011; Tsuboi 2009; Untch 2011˙1; Wilkinson 2006; Wright 2007). Two studies that were included in the previous review (Henze 2002; Vadhan-Raj 2004 ) were excluded from the current version because study participants received major surgery during ESA treatment. As some trials with multiple experimental arms were split into subsets (Cazzola 1995; Hedenus 2002; Kotasek 2003; Krzakowski 2008; Kunikane 2001; Osterborg 1996; Smith 2003;Ten Bokkel 1998; Thatcher 1999; Tjulandin 2010) the number of trials displayed is 88.

The risk ratio to receive red blood cell transfusions was statistically significantly reduced in the study groups receiving ESAs by 35% (RR 0.65, 95% CI 0.62 to 0.68). There was statistically significant heterogeneity between the trials ($I^2$ = 60%) indicating that variation in the effect of ESAs between trials was larger than would have resulted from chance alone. However, the majority of studies indicated a beneficial effect of ESAs with regard to the need of red blood cell transfusions. A funnel plot analysis showed significant asymmetry between the studies (P < 0.00001), suggesting that beneficial findings were over reported. Ten studies compared two or more ESA dosages/formulations with one control group. Merging the active arms of each study into a single experimental arm and comparing it to the study's entire control group did not substantially change the overall result (RR 0.65; 95% CI 0.62 to 0.68). Compared with the previous version of this review, the results did not change markedly (Bohlius 2006a: RR 0.64, 95% CI 0.60 to 0.68, 42 trials, N = 6,510).

To identify the source(s) of heterogeneity, we performed subgroup analyses. Univariate analyses identified significant differences (P < 0.05) between subgroups for baseline Hb level, different malignancies, age, type of anti-cancer therapy, iron supplementation, concealment of allocation, placebo control, intention-to-treat analysis and type of publication. The backward selection resulted in a multivariate model containing the covariates Hb at baseline and underlying malignancy. The final model is presented in Additional Table 3. For each combination of Hb level and type of malignancy, the risk ratio can be calculated from Table 3. For example, the logarithm of the risk ratio for a trial in patients with solid tumours and baseline Hb level 10-12 g/dL is = Intercept + solid + Hb 10 to 12 g/dL = -0.22 + -0.39 + -0.15 = -0.76. Accordingly, the risk ratio is 0.47.

To estimate the absolute effectiveness of erythropoietin, we applied the overall risk ratio of (RR 0.65; 95% CI 0.62 to 0.68) to a range of plausible values for the baseline-risk. In a hypothesised population with an estimated risk of 30% to require RBC transfusions the NNTB is 9.52 (95% CI 8.77 to 10.42): about nine to 10 patients would need to receive ESAs to spare one patient from RBC transfusion. In a hypothesised population with an estimated risk of 50% to require RBC transfusions, the NNTB is 5.71 (95% CI 5.26 to 6.25): about five to six patients would need to receive erythropoietin to spare one patient from RBC transfusion. In a hypothesised population with an estimated risk of 70% to require RBC transfusions the NNTB is 4.08 (95% CI 3.76 to 4.46). In this setting about four patients would need to receive erythropoietin to spare one patient from RBC transfusion.

Overall, the data confirm results from prior analyses that ESAs reduce the risk ratio to receive RBC transfusions in patients with malignant disease. The effect size might be influenced by the underlying disease.

#### (4) Number of red blood cell units transfused

Overall, 19 studies evaluating a total of 4,715 patients are included in this update. Of those, 14 studies with 2,353 patients were included in the previous review (Bohlius 2006a). Five trials with 2,362 participants were newly identified and added to the analysis (Engert 2009; Grote 2005; Hernandez 2009; Savonije 2005; Thatcher 1999). As four multi-arm studies were split into subsets (Ten Bokkel 1998; Thatcher 1999; Osterborg 1996; Cazzola 1995), the number of studies displayed in Meta-View is 25.

The overall mean difference showed a statistically significant benefit for participants receiving ESAs (MD -0.98; 95% CI -1.17 to -0.78): the ESA group received on average 0.98 units of blood less per participant than the control group, who received an average of 3.65 units. Overall, there was moderate statistical heterogeneity between the trials ($I^2$ = 30%). All but one study indicated a reduced need of red blood cell units in patients receiving ESAs compared to controls. A funnel plot analysis did not show statistically significant asymmetry (P = 0.558). In four studies, two or more different ESA dosages were compared with one control group (Cazzola 1995; Osterborg 1996; Ten Bokkel 1998; Thatcher 1999). Merging the active arms of each study into a single experimental arm and comparing each to that study's entire control group did not substantially change the overall result (MD -0.98; 95% CI -1.17 to -0.78). Compared with the previous review (Bohlius 2006a: MD -1.05; 95% CI -1.32 to -0.78, 14 trials, N = 2,353), the overall result did not change markedly.

Subgroup analyses were conducted for all the comparisons and were found to be statistically significant for different age groups (test between subgroups P = 0.02), duration of ESA therapy (test between subgroups P = 0.03) and type of publication (test between subgroups P = 0.04). However, the absolute differences between subgroups were small.

Overall, the analysis suggests that ESAs modestly but statistically significantly reduces the number of RBC units transfused per patient.

#### (5) Overall survival

We defined overall survival as longest follow-up available. Overall survival data were available from a total of 78 trials including 19,003 participants. Of those, 42 trials including 8,167 participants were included in the 2006 Cochrane review (Bohlius 2006a). Of these, we excluded one study which we had in-

cluded in the previous review Vadhan-Raj 2004 from the current version because study participants received major surgery during ESA treatment. For 30 previously included studies data were updated with newly available information from the individual patient meta-analysis (Bohlius 2009a; Bohlius 2009b). Thirty-seven trials were newly identified and added to the analysis Aapro 2008; Antonadou 2001; Blohmer 2011; Charu 2007 IPD; Christodoulou 2009; Debus 2006 IPD; Engert 2010; EPO-GER-20 IPD; Fujisaka 2011; Gordon 2008 IPD; Gupta 2009; Hernandez 2009; Huddart 2002 IPD; Kotasek 2002 IPD; Krzakowski 2008; Milroy 2003 IPD; ML17616 2006; ML17620 2006; Moebus 2007 IPD; Mystakidou 2005; OBE/EPO-INT-03 IPD; Overgaard 2009; Pirker 2008 IPD; Pronzato 2010 IPD; Quirt 1996 IPD; Ray-Coquard 2009 IPD; Rosen 2003; Strauss 2008 IPD; Strauss 2008 IPD; Sweeney 1998; Thomas 2002 IPD; Tjulandin 2010; Tjulandin 2011; Tsuboi 2009; Untch 2011˙2; Wilkinson 2006 IPD; Winquist 2009. Two studies (Krzakowski 2008; Tjulandin 2010) were split into subsets and four studies (Cascinu 1994; Hedenus 2002; Kurz 1997; Sweeney 1998) reported zero events; as a result the overall number of studies displayed in Meta-View is 80.

The overall estimate is a hazard ratio (HR) of 1.05 (95% CI 1.00 to 1.11) in favour of placebo/no treatment. The heterogeneity between the trials was low, with an $I^2$ of 21%. Funnel plot analysis did not suggest asymmetry (P = 0.92).

In two studies (Krzakowski 2008; Tjulandin 2010), two different ESA dosages or formulations were compared with one control group. Merging the active arms into one single experimental arm compared with the entire control group did not influence the overall result (HR 1.05; 95% CI 1.00 to 1.11).

Although no statistically significant heterogeneity was apparent, we conducted subgroup analysis to explore the underlying clinical heterogeneity to assess the influence of clinical differences between the studies. Tests for heterogeneity between subgroups showed statistically significant differences for the analyses of baseline Hb levels (P = 0.02), iron supplementation (P = 0.005) and intention-to-treat analysis (P = 0.02). However, when excluding studies with unclear values for the subgroup analyses conducted, none of the analyses remained statistically significant. Statistically significant differences were not detected for any of the other subgroup analyses conducted.

We further investigated how single large studies influenced the overall results. There was no single study that contributed more than 10% weight to the overall analysis. There were four studies which each contributed more than 5% weight to the analysis ( Aapro 2008 IPD; Debus 2006 IPD; Pirker 2008 IPD; Smith 2008 IPD). Taken together these four studies contributed 27% weight to the overall analysis. Of those, two suggested a negative impact on survival (Aapro 2008 IPD; Smith 2008 IPD) and two suggested a beneficial impact on overall survival (Debus 2006 IPD; Pirker 2008 IPD). Exclusion of the two unfavourable studies resulted in an HR of 1.04 (95% CI 0.98 to 1.10). Exclusion of the two favourable studies resulted in an HR of 1.08 (95% CI 1.02 to 1.14). We also investigated the effects of adjusted and unadjusted data where different results were reported (Henke 2003; Littlewood 2001). Using adjusted instead of unadjusted data for the Henke 2003 and Littlewood 2001 studies did not change the overall result (HR 1.05, 95% CI 1.00 to 1.11; adjusted data).

In summary, there is no evidence that erythropoietin or darbepoetin improves overall survival. Based on the data available it was not possible to clearly identify a subgroup of participants that was at higher or lower risk to experience detrimental effects from ESAs.

#### (6) On-study mortality

We defined on-study mortality as deaths occurring up to 30 days after the active study period. Such data were available for 78 studies including 15,935 patients. Two studies (Krzakowski 2008; Tjulandin 2010) were split into subsets and eight studies (Cascinu 1994; Del Mastro 1997; Hedenus 2002; Kurz 1997; Moebus 2007 IPD; Strauss 2008 IPD; Sweeney 1998; Untch 2008 IPD) reported zero events; as a result, the overall number of studies displayed in Meta-View is 72.

The overall estimate showed an HR of 1.17 (HR 1.17; 95% CI 1.06 to 1.29) in favour of control. There was no heterogeneity between the studies ($I^2$ = 0%). A funnel plot analysis did not show evidence for significant asymmetry (P = 0.693).

Although there was no evidence for any statistical heterogeneity between the studies ($I^2$ = 0%), we conducted predefined subgroup analyses. Univariate analysis identified statistically significant differences only for intention-to-treat analyses (P = 0.04). No robust statistically significant differences were identified for any of the other subgroups of interest (i.e. baseline Hb level, type of malignancy, duration of treatment, type of anti-cancer therapy, age, iron supplementation, type of publication, epoetin versus darbepoetin, type of data, concealment of allocation and masking).

We conducted a sensitivity analysis including eight additional studies. For seven of those (Antonadou 2001; Blohmer 2011; Christodoulou 2009; Engert 2009; Gupta 2009; Overgaard 2009; Winquist 2009), we calculated on-study mortality from Kaplan Meier curves for overall survival and for the remaining study (Tsuboi 2009), we used long-term mortality data. This sensitivity analysis yielded similar results; with an HR of 1.16 (95% CI 1.05 to 1.27, 78 trials, N=19,018).

We further investigated how single large studies influenced the overall results. There were two studies (Leyland-Jones 2005 IPD; Smith 2008 IPD) which each contributed more than 10% weight to the analysis. Taken together these four studies contributed 28% weight to the overall analysis. Both studies suggested a negative impact on mortality. Exclusion of these two unfavourable studies resulted in an HR of 1.09 (95% CI 0.97 to 1.23).

Overall, there is evidence that ESA treatment increases mortality in cancer patients during active study period compared with controls.

**Secondary outcomes**

**(7) Tumour response (complete response)**

Tumour response (complete response) data were available from a total of 15 trials including 5,012 participants. Of these, 11 trials were included in the previous Cochrane review (Bohlius 2006a). Two previously included studies (Bamias 2003; Vadhan-Raj 2004) were excluded from the current update since they did not explicitly state that they evaluated *complete* tumour response. We replaced previous data with updated study results where available (Grote 2005; Hoskin 2009; Machtay 2007). We included four additional studies published since 2006 (Engert 2009; Strauss 2008; Untch 2011˙1; Wilkinson 2006). Since two multi-arm trials were split into subsets (Cazzola 1995; Ten Bokkel 1998) the number of trials displayed in MetaView is 19.

The overall estimate shows a risk ratio of 1.02 (RR 1.02; 95% CI 0.98 to 1.06) that was not statistically significant. There was no significant heterogeneity between the trials ($I^2$ = 0%). Funnel plot analysis did not show strong evidence for asymmetry (P = 0.149). Merging the multi-arm trial into one data set did not change the overall result (RR 1.02; 95% CI 0.98 to 1.06, 15 trials). Compared to the previous report (RR fixed-effect: 1.12; 95% CI 1.01 to 1.23, random-effect: 1.09, 95% CI 0.94 to 1.26, 13 trials , N = 2833), the updated review shows more conservative results. Only five of the included studies (Engert 2009; Hoskin 2009 GBR-7 FDA 04; Machtay 2007; Strauss 2008; Untch 2011˙1) met our specific quality criteria for assessment of tumour response (see Methods section). For the five studies meeting these criteria, the risk ratio was 0.99 (95% CI 0.95 to 1.02, five studies, N=2,476). For the remaining 10 studies with low quality the point estimate for RR suggested there might be a benefit for patients receiving ESAs, but the confidence interval did not reach statistical significance (RR 1.15, 95% CI 0.98 to 1.36, 10 trials, N = 2,536), with some evidence for a difference between subgroups tested (P = 0.07).

In conclusion, the data available suggest that ESAs do not have a beneficial effect on tumour control. The data are insufficient to exclude detrimental effects.

**(8) Changes of health-related quality of life**

Twenty-three studies including 5,584 patients reported results on QoL, as measured with FACT-F, FACT-An 20 or FACT-An 47. In order to perform a meta-analysis for the FACT measures, we had to extract means and SDs. In cases where no numerical data were given, we calculated means and/ or SDs from graphs or figures (Boogaerts 2003; Charu 2007; Gordon 2008; Hedenus 2003). In one trial (Christodoulou 2009) where SDs were reported separately for platinum and non platinum chemotherapy, we calculated a pooled SD by pooling the SDs of the two different subgroups. For the same study we also imputed the mean and the SD for changes between baseline and end of treatment, by using a correlation coefficient. For one study with missing SDs (Littlewood 2001) and no other way of imputing them, we used the SDs that have been already published by another meta-analysis (Tonelli 2009). According to the authors of this meta-analysis, the SDs were calculated as follows: for FACT-fatigue they imputed the SD using the baseline SD reported in another publication for the same study (Fairclough 2003) and for the FACT-An the SD was imputed using the average of the SDs from other studies who reported a SD for FACT-An (personal communication with Dr. Lloyd, February 2010). For two further studies (Kotasek 2003; Vansteenkiste 2002), we used the mean and SDs reported in a meta-analysis by Minton and colleagues (Minton 2008). These data were not available in the publications and were obtained by the authors of the meta-analysis from the authors of the original studies or the pharmaceutical companies (personal communication with Dr. Minton, February 2010). To account for all these calculations, we conducted a sensitivity analysis, differentiating between the studies for which we had to impute data in some way and those for which we did not impute any data. One study (Christodoulou 2009) reported results separately for participants treated with platinum-based chemotherapy and those treated with non-platinum-based chemotherapy. It is therefore included in both the platinum and non-platinum chemotherapy subgroups for all the QoL outcomes below.

*a) FACT-F 13 sub-scale*

A total of 18 studies (4,965 patients) reported data for this outcome. The MD was 2.08 (95% CI 1.43 to 2.72). Heterogeneity between the included studies was moderate ($I^2$ = 53%). A funnel plot analysis showed significant asymmetry (P = 0.02772) with over reporting of studies that showed beneficial effects of ESAs.

The beneficial effect of ESAs on QoL measured with FACT-F 13 was significantly larger in patients receiving chemotherapy than in those receiving radiotherapy or no anticancer therapy (P < 0.0001). Patients with Hb levels below 12 g/dL also had significantly (P = 0.0025) larger effects compared to patients with baseline Hb level > 12 g/dL, however, only one trial using radiotherapy had Hb levels > 12 g/dL at baseline (Hoskin 2009). The effect of epoetin was significantly (P < 0.0004) different from darbepoetin, however, the association is potentially confounded by three darbepoetin trials without anticancer therapy (Charu 2007; Gordon 2008; Smith 2008). The observed effect was larger in unblinded trials (MD 3.76, 955 CI 2.60 to 4.92) compared with double-blind trials (MD 1.33, 95% CI 0.56 to 2.10, P = 0.0006). Significant differences were also observed for age group (adults versus >70% non-elderly adults, P = 0.008). The backward selection resulted in a model containing the covariate type of ESA formulation, see Table 4. The MD for a trial in patients receiving short-lasting ESAs is = Intercept + short lasting ESA = 1.09 + 2.20 = 3.29. However, in these analyses single studies were compared to groups of studies and thus results are not readily interpretable.

One trial (Tsuboi 2009) reported two different sets of scores for the control group: in one set they substituted the missing data of two patients by the maximum decrease in score for all patients.

The other set of results did not include data for these two patients. We used the scores without the substitution for the main analysis and we conducted a sensitivity analysis using the scores with the substituted data. The results did not change much, with the MD being 2.10 (95% CI 1.46 to 2.75, 18 studies, N = 4,967) and remained statistically significant (P < 0.00001).

Overall, it appears that there is an effect on fatigue-related symptoms for patients treated with erythropoietin or darbepoetin compared with controls; this effect, however, did not reach the threshold for a clinically important difference defined as 3.0 (Cella 2002).

*b) FACT-An 20*

Six studies were included for this outcome (Chang 2005; Christodoulou 2009; Littlewood 2001; O'Shaughnessy 2005; Savonije 2005; Wright 2007). The estimated MD is 6.14 (95% CI 4.55 to 7.73, N = 1,085). There was no evidence for statistical heterogeneity between the studies ($I^2$ = 0%). A funnel plot analysis was not done, because less than 10 studies were included in this analysis.

Subgroup analyses did not identify any significant differences in the magnitude of effect between the different subgroups. Of note, FACT-An 20 improvements were seen across all Hb baseline subgroups (Hb < 10, 10 to 12 and > 12 g/dL).

Overall, the effects of ESAs on fatigue- and anaemia-related symptoms appear to be beneficial and the difference between groups reaches both statistical and clinical significance (clinically important difference defined as four to five), however only six studies were included in this analysis.

*c) FACT-An Total 47*

Nine studies, including 1,815 participants, reported data for this outcome. The estimated MD is 6.92 (95% CI 4.59 to 9.25). As one multi-arm study (Krzakowski 2008) reported results separately for each arm, the number of studies appearing in Metaview is 10.Heterogeneity between the studies was quite high ($I^2$ = 85%). A funnel plot analysis was not done, because less than 10 trials were included in this analysis. Merging the two arms of the multi-arm study mentioned above in one data set did not change the results (MD 6.92; 95% CI 4.59 to 9.25, nine studies, N = 1,815) or heterogeneity markedly ($I^2$ = 87%).

One study (Mystakidou 2005) reported an unusually high change for the treatment group (a mean change of 43.3 when the average mean change from all the other studies is 5.14). We, therefore, conducted a sensitivity analysis in which we excluded this study. The results are indeed different than the original analysis with a MD of 3.46 (95% CI 0.96 to 5.96, eight studies, N = 1,715). The statistical heterogeneity between the studies almost disappeared ($I^2$ = 0%). The results, however, remained statistically significant (P = 0.007).

We conducted sub-group analysis that revealed the following subgroups as having significantly different magnitudes of ESA effect between each other: imputed versus non-imputed data (P = 0.005), baseline Hb level (P < 0.0001), type of anti-cancer therapy (P < 0.0001), duration of ESA treatment (P < 0.0001) and ITT analysis (P = 0.01). The backward selection resulted in a model containing the covariate type of anticancer therapy, see Additional Table 5. However, differences can also be explained by the study conducted by Mystakidou 2005 (see paragraph above), when removing this study no significant differences between subgroups were evident (data not shown).

Overall, there is a statistically significant difference between patients treated with ESAs and controls when combining QoL parameters and fatigue- and anaemia-related symptoms, which is however, most likely not clinically important.

### (9) Adverse events

#### (9.1) Thromboembolic events

Data from thromboembolic complications were available from a total of 57 trials, including 15,498 participants. As three multi-arm trials (Osterborg 1996; Ten Bokkel 1998; Thatcher 1999) were split into subsets and four studies reported zero events (Cascinu 1994; Gupta 2009; P-174 J&J 2004; Thatcher 1999a), the number of studies displayed is 60. Thirty-five studies including 6,769 participants were included in the 2006 update of the Cochrane review (Bohlius 2006a), results for 23 studies were newly identified (Aapro 2008; Blohmer 2011; Charu 2007 Amgen 2007; Debus 2006 J&J 2007; Engert 2009; Fujisaka 2011; Gordon 2008; Gupta 2009; Hedenus 2003 FDA 2007; Hernandez 2009; Milroy 2011; Moebus 2007 J&J 2007; Overgaard 2009; Pirker 2008; Pronzato 2010; Ray-Coquard 2009; Smith 2008; Strauss 2008; Tjulandin 2011; Tsuboi 2009; Untch 2011˙1; Wilkinson 2006; Winquist 2009). We removed one study from the analysis because a substantial number of participants underwent major surgical procedures during ESA treatment (Vadhan-Raj 2004).

The overall risk ratio to suffer thromboembolic complications was increased by 52% for patients receiving ESAs (RR 1.52; 95% CI 1.34 to 1.74). There was no significant statistical heterogeneity between the trials ($I^2$ = 0%). A funnel plot analysis revealed a significant asymmetry (P = 0.02137), suggesting that harmful events (in this case thrombotic event) have been over reported. Merging the multi-arm trials into one data set, did not change the results (RR 1.53; 95% CI 1.34 to 1.74). Compared with the results from the previous Cochrane review (RR 1.67; 95% CI 1.35 to 2.06, 35 trials, N = 6,769, Bohlius 2006a), results are similar. Subgroup analyses for predefined variables did not show robust evidence for statistically significant differences in magnitude or direction of the ESA effect between any of the subgroups tested (e.g. baseline Hb level, type of malignancy, duration of treatment, type of anti-cancer therapy, age, iron supplementation, type of publication, epoetin versus darbepoetin, type of data, concealment of allocation and masking).

We calculated numbers needed to harm (NNTH) for several hypothetical baseline risks. In a population with an underlying risk

of 2% the NNTH would be 96 (95% CI 68 to 147), thus one thromboembolic complication would occur for about every 96 patients treated. In a population with an underlying risk of 5% the NNTH would be 38 (95% CI 27 to 59), thus for every 38 patients treated with ESAs one additional thromboembolic complication might happen. In a population with a hypothetical baseline risk of 10% the NNTH would be 19 (95% CI 14 to 29), thus for every 19 patients treated one additional thromboembolic complication may happen.

In conclusion, the data available for the present analysis confirm and strengthen conclusions from the prior versions of this review that treatment with ESAs increases the risk of thrombosis or related complications.

### (9.2) Hypertension

Hypertension data were available from a total of 31 trials including 7,228 participants. Of these trials, 16 including 2,263 randomised participants were included in the updated Cochrane review of 2006 (Bohlius 2006a), for 15 studies Fujisaka 2011; Gordon 2008; Hernandez 2009; Hoskin 2009; Krzakowski 2008; Milroy 2011; Osterborg 2002; Pirker 2008; Razzouk 2006; Savonije 2005; Smith 2008; Tjulandin 2010; Tjulandin 2011; Tsuboi 2009; Wilkinson 2006 data were newly identified. As six of the trials were split into subsets (Krzakowski 2008; Kunikane 2001; Osterborg 1996; Ten Bokkel 1998; Thatcher 1999; Tjulandin 2010) and two trials reported zero events (Cascinu 1994; Iconomou 2003) the number of trials displayed in MetaView is 37.

The risk ratio to develop hypertension for erythropoietin-treated participants was increased by 30% (fixed-effect model RR 1.30; 95% CI 1.08 to 1.56), reaching statistical significance (P = 0.006). Using the random-effects model, however, the result was not statistically significant (RR 1.12, 95% CI 0.94 to 1.33). There was no statistical heterogeneity between the trials ($I^2$ = 0%). A funnel plot analysis revealed significant asymmetry (P value < 0.001), suggesting that harmful events (in this case hypertension) have been over reported. Merging the different arms of the multi-arm trials did not change the overall result (RR 1.31, 95% CI 1.09 to 1.58). The updated results are similar to the previous Cochrane review (RR 1.24; 95% CI 1.00 to 1.54, 16 trials, N = 2,263 Bohlius 2006a). One single study (Rose 1994) contributed 40% weight to this analysis. Excluding this study, the effect of ESAs on hypertension increased: fixed-effect: RR 1.52; 95% CI 1.18 to 1.97, random-effects: RR 1.40; 95% CI 1.07 to 1.83. For another trial, both published and unpublished data were available (Dammacco 2001). In the published sources 3/69 participants in the erythropoietin group and 1/76 participants in the control group were reported to suffer from hypertension. In the unpublished study report 43/69 participants in the erythropoietin group and 36/76 in the control group had hypertension. Including these data instead of the published numbers did not change the overall results significantly, (fixed-effect model: RR 1.29; 95% CI 1.10 to 1.52), random-effects model: RR 1.16; 95% CI 1.00 to 1.35).

We calculated numbers needed to harm for several hypothetical baseline risks. In a population with an underlying risk of 2% the NNTH would be 167 (95% CI 89 to 625), thus one patient would be affected with hypertension for about every 167 patients treated. In a population with an underlying risk of 5% the NNTH would be 67 (95% CI 36 to 250), thus for every about 67 patients treated with ESAs one additional episode of hypertension might happen. In a population with a hypothetical baseline risk of 10% the NNTH would be 33 (95% CI 18 to 125), thus for every about 33 patients treated, one additional hypertension episode may happen.

Overall, the data available in this analysis provide suggestive but not robust evidence, that ESAs in the treatment of cancer patients may increase the risk ratio to suffer from hypertension.

### (9.3) Haemorrhage/Thrombocytopenia

Haemorrhage/thrombocytopenia data were available from a total of 21 trials including 4,507 participants. Of these trials, 10 including 1,488 randomised participants were included in the update of the Cochrane review in 2006 (Bohlius 2006a). Eleven additional trials Fujisaka 2011; Gebbia 2003; Goss 2005; Gupta 2009; Milroy 2011; Pirker 2008; Savonije 2005; Strauss 2008; Tsuboi 2009; Untch 2011˙1; Witzig 2005) including 3,019 participants were added for this update. As three of the trials were split into subsets (Kunikane 2001; Osterborg 1996; Thatcher 1999) and three trials report zero events (Cascinu 1994; Gupta 2009; Osterborg 1996b), the number of trials displayed in MetaView is 24.

The risk ratio to develop thrombocytopenia was increased for erythropoietin-treated participants (RR 1.21; 95% CI 1.04 to 1.42), reaching statistical significance (P = 0.01). When using the random-effects model, the results were also statistically significant (RR 1.18, 95% CI 1.02 to 1.36). There was no statistical heterogeneity between the trials ($I^2$ = 0%). The funnel plot analysis did not show a significant asymmetry (P = 0.698). Results are similar to the previous review (RR = 1.13, 95 % CI 0.08 to 1.60, 10 trials, N = 1,488 Bohlius 2006a), however, the larger number of included studies and patients increased statistical power and the updated result reached statistical significance. Merging the arms of the multi-arm trials mentioned above in one data set did not substantially change the results (RR 1.21, 95% CI: 1.04 to 1.41). Subgroup analyses were not performed.

We calculated numbers needed to harm for several hypothetical baseline risks. In a population with an underlying risk of 2% the NNTH would be 238 (95% CI 122 to 1,250), thus one patient would develop thrombocytopenia or haemorrhage for about every 238 patients treated. In a population with an underlying risk of 5% the NNTH would be 95 (95% CI 49 to 500), thus for about every 95 patients treated with ESAs one additional case of thrombocytopenia or haemorrhage might happen. In a population with a hypothetical baseline risk of 10% the NNTH would be 48 (95%

CI 24 to 250), thus for every 48 patients treated one additional case of thrombocytopenia or haemorrhage might occur.
Overall, there is some evidence, that ESAs may increase the risk for thrombocytopenia/haemorrhage.

#### (9.4) Rash, Irritation, Pruritus

Data were available from a total of 16 trials including 2,485 participants. Of those, eight trials with 675 participants were included in the 2006 update (Bohlius 2006a). Data from eight more trials including 1,810 participants were added for this update. As two of the trials were split into subsets (Osterborg 1996; Thatcher 1999) and two trials reported zero events (Gupta 2009; Kurz 1997) the number of trials in MetaView is 18.
Overall, 53 events of skin rash, irritation or pruritus were reported in the erythropoietin group (N = 1,359) and 27 cases in the control group (N = 1,126) , resulting in a risk ratio of 1.49 (95% CI 0.99 to 2.24). There was no significant heterogeneity between the studies ($I^2$ = 0%). Merging the different subsets of the multi-arm trials into one did not change the results (RR1.50, 95% CI 1.00 to 2.27). The funnel plot analysis did not show a significant asymmetry (P = 0.745). Further sensitivity analyses were not done. Compared with the previous Cochrane review (Bohlius 2006a), results are similar (RR 1.17; 95% CI 0.63 to 2.18, eight trials, N = 675 Bohlius 2006a). Based on the data available there is insufficient evidence to conclude that erythropoietin increases the risk of skin reactions.

#### (9.5) Seizures

Data on seizures were available from eight trials including 2,890 participants (Cascinu 1994; Case 1993; Gordon 2008; Henry 1995; Hernandez 2009; Pirker 2008; Savonije 2005; Smith 2008). Three of those trials (Cascinu 1994; Case 1993; Henry 1995) including 389 participants were included in the 2006 version of the Cochrane review (Bohlius 2006a), data from five further trials including 2,501 participants have been added to this update (Gordon 2008; Hernandez 2009; Pirker 2008; Savonije 2005; Smith 2008. Overall, 19 events of seizure were reported in the erythropoietin group (N=1,583) and 21 events in the control group (N = 1,307), resulting in a risk ratio of 0.77 (95% CI 0.42 to 1.41). There was no significant statistical heterogeneity between the trials ($I^2$ = 3%). Overall, there was no evidence for significant differences between the treatment groups compared.

## DISCUSSION

### Summary of main results

This systematic review analysed the effectiveness and safety of erythropoiesis-stimulating agents (ESAs) for managing anaemia in cancer patients. The primary findings of this updated review are as follows: ESAs significantly reduce the need for red blood cell transfusions and increase haematological response in cancer patients. However, there is also strong evidence that ESAs increase mortality during study period and some evidence that ESAs reduce overall survival. In addition, there is strong evidence that ESAs increase the risk for thromboembolic complications and some evidence that ESAs increase the risk of hypertension and thrombocytopenia/haemorrhage. The available data are insufficient to evaluate the effect of ESAs on tumour response. Their effect on patients' quality of life (QoL) and specific anaemia- and fatigue-related symptoms (FACT-An) reaches statistical and clinical significance; however, while it reaches statistical significance, it fails to reach clinical significance for fatigue-related symptoms only (FACT-F).

### Overall completeness and applicability of evidence

The main strength of the newly updated review is the large number of studies and patients included. All studies were systematically evaluated and outcomes from previous versions of this review updated.

### Quality of the evidence

The main weakness of this review are reporting and publication biases. For the outcomes mortality during study period and overall survival this was less of a problem, since we used results that were generated in an individual patient data meta-analysis (Bohlius 2009a; Bohlius 2009b), which had included the majority of studies in the field. However, besides survival and mortality, no other outcomes were assessed in that review and thus for the remaining outcomes we had to rely on the published evidence. For several of these outcomes only a few studies could be evaluated. For example, hypertension was reported in only 31 of 91 studies, thrombocytopenia in 21 and thromboembolic complications in 57 of 91 studies, haemoglobin (Hb) response in 31 and the number of red blood cell units transfused in 20 of 91 studies. Similarly, numerical QoL data for FACT-An or FACT-F were only reported in 23 out of 91 trials. For some but not all of these outcomes, the suspected publication bias was further supported by asymmetric funnel plots. The numbers indicated here underline the lack of complete outcome reporting for a major part of studies and outcomes. In the light of these apparent reporting biases, we estimate that both the beneficial (number of patients transfused, QoL (FACT-F), Hb response, change in Hb) as well as the harmful effects of ESAs other than mortality (thromboembolic events, hypertension) have been overestimated in our present analysis.

## Agreements and disagreements with other studies or reviews

This and previous analyses provide consistent evidence that ESAs reduce the risk for RBC transfusions by approximately 30% to 40%. The point estimated generated in the current update is in line with previous (Bohlius 2006a) and other systematic reviews and meta-analyses (Tonelli 2009). fOur analysis also provides consistent evidence that ESAs reduce the average number of RBC units transfused. Participants on ESAs received on average one unit of RBCs less (mean difference (MD) -0.98, 95% confidence interval (CI) -1.17 to -0.78) compared with controls which is in line with a previous, independent meta-analysis, reporting a weighted mean difference (WMD) of −0.80 units (95% CI −0.99 to −0.61) (Tonelli 2009 HTA).

Apart from improving physiologic parameters such as Hb and haematocrit, erythropoietin was also hypothesised to improve QoL and to alleviate fatigue. Improved QoL after ESA treatment was previously reported in community based, single-arm studies (Demetri 1998; Gabrilove 2001; Glaspy 1997). However, these data were inconclusive because they lacked controls. Later, several randomised controlled studies were conducted to investigate this question. QoL trials require specific methodological standards, such as the use of validated instruments, double blinding, a prospective plan to minimise missing data, investigating the pattern of missing data, and addressing missing data in the analysis (Aaronson 1991; Brandberg 2000). Our updated analysis does not provide evidence for a clinically important improvement of fatigue in patients receiving ESAs compared to controls. This result is more conservative compared to previous meta-analyses on the same topic (Minton 2010; Tonelli 2009). While previous analyses identified differences for FACT-F just at (MD 3.00; 95% CI 1.36-4.64; 10 RCTs, N = 3,169) (Tonelli 2009) or above (MD 3.72; 95% CI 2.38-5.06; 12 RCTs, N = 2,671) (Minton 2010, personal communication) the threshold for a clinically important difference, our analysis showed a MD of 2.08 (95% CI 1.43-2.72, 18 RCTs, N = 4,965) which is below the estimated threshold of 3.0 (Cella 2002) . For FACT-An 20 there seems to be a clinically important improvement in patients receiving ESAs with a MD of 6.14 (95% CI 4.55 to 7.73, six studies, N = 1,085), which is above the CID for FACT-An, defined as four to five (Cella, personal communication March 2010). However, only a small number of published RCTs on ESAs reported QoL outcomes and therefore more evidence is needed for definitive conclusions. For FACT-An 47 there is no established CID; however, we expect it to be at least above five, as this is the threshold for FACT-An 20, which includes less than half the questions of FACT-An 47. In our analysis there was no robust evidence for a clinically important improvement of QoL measured with FACT-An 47.

Besides the beneficial effects of ESAs indicated above, our review also identified harmful effects, including an increased risk for thromboembolic events, hypertension, thrombocytopenia, death during study period and potentially decreased overall survival. The increased risk for thromboembolic events in patients receiving ESAs has been observed and reported by single RCTs (Aapro 2008; Goss 2005 J&J 2004; Pirker 2008) and previous meta-analyses on the same topic (Aapro 2008; Aapro 2009b; Bennett 2008; Bohlius 2006a; Glaspy 2010; Ludwig 2009; Ross 2006; Seidenfeld 2006; Tonelli 2009). The effect estimates generated are comparable across the different meta-analyses reported. The impact of baseline Haemoglobin levels has not been clarified to date. While one individual patient data meta-analysis restricted to studies using Darbepoetin for patients receiving chemotherapy suggested an increased risk for thromboembolic events with higher baseline haemoglobin levels (Ludwig 2009), this was not confirmed in a second IPD analysis restricted to RCTs comparing epoetin beta verus control (Aapro 2009b). In this analysis, the risk for thromboembolic events decreased with increasing baseline haemoglobin levels (Aapro 2009b). Besides, there are reports that ESAs are inherently thrombogenic irrespective of baseline or current Hb levels (Barbera 2010; Fuste 2002; Malyszko 1995; Stasko 2002; Stohlawetz 2000). Strategies to reduce the risk for thromboembolic events by using e.g. anti-coagulating drugs have not yet been evaluated in randomised controlled trials (Aapro 2009a).

Patients receiving ESAs may also have an increased risk for hypertension. In patients with chronic renal failure, hypertension is a common adverse effect of ESAs (Palmer 2010). This increase in blood pressure can be partly explained by the elevated blood viscosity and the loss of hypoxia-induced vasodilatation in association with the increased Hb level (Cirillo 1993). The present analysis shows some evidence that ESAs also increase the risk for hypertension in cancer patients by approximately 30%. However, the result was statistically significant only in the fixed-effect model and not in the random-effects model. In addition, only 31 of 91 studies reported for this outcome. A funnel plot analysis revealed a significant asymmetry (P value < 0.001), suggesting that negative results (in this case no hypertension) have been underreported. Thus, the effect of ESAs on hypertension might be overestimated in the present analysis. A previous meta-analysis in cancer patients has also identified an increased risk (RR 1.41, 95% CI 0.94 to 2.12, 17 studies, 3,792 patients) which failed to reach conventional level of statistical significance (Tonelli 2009). We also found some evidence that ESAs increase the risk for thrombocytopenia and haemorrhage (RR 1.21, 95% CI, 1.04 to 1.42, 21 trials, 4,507 patients, no evidence for publication bias), which has not been reported before. While the increased risk for thromboembolic events has been established, hypertension and thrombocytopenia/haemorrhage require closer monitoring in future studies.

In the current update of the systematic review, we found no evidence for a beneficial effect of ESAs on tumour control. At the same time, uncertainties remain as important information on tumour grade, tumour stage, intensity of anti-neoplastic treatment received, timing and method of tumour response assessment were not reported. Relevant studies such as the Henke 2003 or the Antonadou 2001 study could not be included in the meta-anal-

ysis, as they did not report data for complete tumour response. Overall, the data were not sufficient either to exclude or to prove a tumour promoting effect of erythropoiesis-stimulating factors.

Single randomised controlled trials and previous meta-analyses based on individual patient data (Bohlius 2009a; Bohlius 2009b) have reported an increased risk for death during the active study period. In the current review we have differentiated the active study period, defined as mortality during ESA treatment plus a short follow-up time of 30 days, versus overall survival defined as the longest follow-up available. We integrated the data that were generated previously for the individual patient data meta-analysis (Bohlius 2009a; Bohlius 2009b) as well as studies which were not included in the IPD review. The updated review confirms the previous IPD review (Bohlius 2009a; Bohlius 2009b) showing an increased risk for on-study mortality including all cancer patients (HR present meta-analysis: 1.17, 95% CI 1.06 to 1.29, 70 studies, 15,935 patients; HR IPD review: 1.17, 95% CI 1.06-1.30, 53 studies, N = 13,933). These results are in line with other meta-analyses of on-study mortality regardless of underlying cancer therapy. Aapro 2009b reported an HR of 1.13 (95% CI 0.87 to 1.46, 12 studies, N = 2,297) in studies on epoetin beta and Ross 2006 reported an HR of 1.14 (95% CI 0.90 to 1.45, 17 studies). Both meta-analyses failed to reach conventional levels of statistical significance which may be explained by the fact that fewer studies and patients were included in each of these analyses. There was some evidence that ESAs decreased overall survival defined as longest follow-up available (HR 1.05, 95% CI 1.00 to 1.11). As in the previous review (Bohlius 2009a; Bohlius 2009b), the effect was small and of borderline statistical significance. It remains uncertain whether or not the risk is also increased in the subset of patients receiving chemotherapy while also receiving an ESA. In the current updated review the HR for on -study mortality in patients receiving chemotherapy is 1.10 (95% CI 0.98 to 1.24, 50 studies, 12,058 patients) which is identical to the HR reported in the previous IPD review (Bohlius 2009a; Bohlius 2009b). However, there were no statistically significant differences between this subgroup and the total patient sample in either the prior IPD meta-analysis or the current update and an increased risk in cancer patients undergoing chemotherapy and receiving ESAs cannot be excluded. FDA (FDA 2010) has recommended restricting the use of ESAs to cancer patients receiving chemotherapy with palliative intent. ESAs should not be used in patients receiving radiotherapy or no antic-cancer therapy. However, an increased risk for death in patients receiving chemotherapy cannot be excluded.

Several hypotheses have been proposed to explain the increased risk for death in patients receiving ESAs. One is that erythropoietin might directly influence tumour cell growth. In vitro studies have reported high levels of erythropoietin receptors in breast cancer cells and other malignancies (Acs 2001; Arcasoy 2002; Bennett 2010; Henke 2006; Jelkmann 2004; Jelkmann 2008; McKinney 2011;Yasuda 2003). Either endogenously produced or exogenously administered, erythropoietin may promote the proliferation and survival of cancer cells expressing erythropoietin receptor (Acs 2001; Acs 2002; Arcasoy 2002; Bennett 2010; Henke 2006; Jelkmann 2004; Jelkmann 2008; McKinney 2011; Yasuda 2003). However, conflicting evidence has been reported from preclinical studies on the effects of rHu erythropoietin on cultured cell lines (Bennett 2010). Tumour stimulation through erythropoietin has been suggested in some studies, whereas other studies have not observed a relationship between rHuEPO and tumour cell growth (Bennett 2010; McKinney 2011). An alternative hypothesis suggests that the efficacy of malignancy treatments, both radiotherapy and oxygen-dependent chemotherapy, can be enhanced by decreasing tumour hypoxia. Tumour tissue is often hypoxic and this hypoxia may increase if the patient is anaemic (Becker 2000; Henke 2000; Tatum 2006; Vaupel 2001; Vaupel 2008). This hypothesis suggests that tumour hypoxia diminishes the effectiveness of radiotherapy and oxygen-dependent chemotherapy (Tatum 2006; Vaupel 2001; Vaupel 2008). Evidence for this hypothesis comes from reports that tumour control and overall survival are better in solid tumour patients with better tumour oxygenation (Hockel 1993; Knocke 1999). In addition, some authors have reported that the effectiveness of oxygen-dependent radiotherapy is impaired in anaemic patients (Frommhold 1998; Grau 2000). Enhanced cytocidal efficacy in adequately oxygenated cells has been documented for a number of cytotoxic drugs, such as cyclophosphamide, carboplatin and doxorubicin (Teicher 1981; Teicher 1994). In animal models, cyclophosphamide (Thews 2001) and cisplatin (Silver 1999) have yielded better tumour control with improved tissue oxygenation. Given these observations, it seems plausible that increasing the Hb level with erythropoietin may improve tumour oxygenation and thus tumour control and eventually overall survival. This has been partly demonstrated in animal models (Kelleher 1998). However, other pre-clinical studies have demonstrated that experimental tumour cells acclimatize rapidly to acute anaemia and return to normal radio sensitivity despite continuing anaemia (Hirst 1984). Chronic anaemia does not necessarily produce radio-resistance of experimental tumours (Koong 1991) and the correction of anaemia by erythropoietin does not necessarily increase radio-sensitivity (Joiner 1993).

# AUTHORS' CONCLUSIONS

## Implications for practice

ESAs reduce the need for red blood cell transfusions but increase the risk for thromboembolic events and deaths. There is suggestive evidence that ESAs may improve QoL. Whether and how ESAs affects tumour control remains uncertain. The increased risk of death and thromboembolic events should be balanced against the potential benefits of ESA treatment taking into account each patient's clinical circumstances and preferences.

## Implications for research

More data are needed for the effect of these drugs on quality of life, tumour progression and other adverse effects. Further research is needed to clarify cellular and molecular mechanisms and pathways of the effects of ESAs on thrombogenesis and their potential effects on tumour growth.

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* *Indicates the major publication for the study*

# CHARACTERISTICS OF STUDIES

## Characteristics of included studies *[ordered by study ID]*

**Aapro 2008**

| | |
|---|---|
| Methods | randomised controlled trial, not placebo-controlled |
| Participants | N = 463 randomised: ESA = 231; control = 232<br>disease: breast cancer (M1)<br>treatment: chemotherapy<br>mean/median baseline Hb: 11.4 g/dL |
| Interventions | drug: Epoetin beta<br>dose: 30000 IU sc weekly<br>Hb-target: 13-15 g/dL<br>planned ESA duration: 24 weeks |
| Outcomes | primary: overall survival<br>secondary: progression free survival, tumour response rate, QoL |
| Notes | full text publication, additional unpublished data were obtained for an individual patient data meta-analysis study (Bohlius et al 2009, study number = 97413) |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | unclear - no description |
| Allocation concealment (selection bias) | Low risk | yes - central randomisation |

**Aapro 2008 IPD**

| | |
|---|---|
| Methods | see Aapro 2008 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | |

**Abels 1993**

| | |
|---|---|
| Methods | randomised controlled trial, placebo-controlled |
| Participants | N = 124 randomised: ESA = 65; control = 59<br>disease: hematological malignancies, genitourinary, gastrointestinal, and other cancer; except primary myeloid malignancy or acute leukaemia (category: mixed)<br>treatment: none<br>mean/median baseline Hb: 9.3 g/dL; |
| Interventions | drug: Epoetin alpha<br>dose: 100 IU/kg tiw s.c.<br>Hb-target: not reported<br>duration: 8 weeks |
| Outcomes | primary: transfusion, Hct<br>secondary: QoL, safety |
| Notes | full text publication, additional unpublished data were obtained for the first Cochrane review (1985-2001) and an individual patient data meta-analysis study (Bohlius et al 2009, study number = 98906) |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | yes - computer-generated |
| Allocation concealment (selection bias) | Unclear risk | unclear - each patient was assigned a random identification number and was assigned to a treatment group by a computerised randomisation schedule |

**Abels 1993 IPD**

| | |
|---|---|
| Methods | see Abels 1993 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | |

**Abels 1993 J&J 2004**

| | |
|---|---|
| Methods | see Abels 1993 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | Data presented by J&J at FDA/ODAC hearing in May 2004 |

**Antonadou 2001**

| | |
|---|---|
| Methods | randomised controlled trial, not placebo-controlled |
| Participants | N = 385, randomised: ESA = 190, control = 195<br>disease: pelvic malignancies<br>treatment: radiotherapy<br>baseline Hb: 9.95 g/dL , ESA 9.8, control 10.1, , categorized as < 10g/dL |
| Interventions | drug: Epoetin<br>dose: 10.000 U 5x/week s.c.<br>Hb-target: >= 13 g/dL<br>duration: 5-6 weeks |
| Outcomes | 4 years disease free survival, safety, Hb, tumour control, overall survival |
| Notes | abstract, poster, study number = 10176 |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | NR |
| Allocation concealment (selection bias) | Unclear risk | NR |

**Aravantinos 2003**

| | |
|---|---|
| Methods | randomised controlled trial, not placebo-controlled |
| Participants | N = 47 randomised: ESA = 24; control = 23<br>disease: ovarian, lung, stomach, other cancer (categorised as solid)<br>treatment: platinum-based chemotherapy<br>Hb baseline: 9.6 g/dL |

**Aravantinos 2003** (*Continued*)

| | |
|---|---|
| Interventions | drug: Epoetin alpha<br>dose: 150 IU/kg tiw sc<br>Hb target: 14 g/dL<br>duration: NR, approx. >9-12 weeks, categorized: 12-16 weeks |
| Outcomes | primary: transfusion requirements (secondary: ?) Hct, Hb, RBC number |
| Notes | full text publication, study number = 11595 |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Unclear |
| Allocation concealment (selection bias) | Unclear risk | Unclear |

**Bamias 2003**

| | |
|---|---|
| Methods | randomised controlled trial, not placebo-controlled |
| Participants | N = 144 randomised: ESA = 72; control = 72<br>disease: ovarian, NSCLC, SCLC, other cancer (categorized: solid)<br>treatment: platinum-based chemotherapy<br>Hb baseline: 11.5 g/dL |
| Interventions | drug: Epoetin alpha<br>dose: 10,000 IU tiw sc<br>Hb target: 13 - 15 g/dL<br>duration: 21 to 24 weeks (duration of chemotherapy) |
| Outcomes | primary: transfusions<br>secondary: Hb < 10 g/dL, predictors of response, optional: QoL |
| Notes | full text publication, study number = 16091 |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Unclear |
| Allocation concealment (selection bias) | Unclear risk | Unclear |

**Blohmer 2011**

| | |
|---|---|
| Methods | randomised controlled trial, not placebo-controlled |
| Participants | N = 257, randomised: ESA = 128, control = 129<br>disease: cervical cancer<br>treatment: platinum-containing chemotherapy in all patients and radiotherapy (categorized as radiochemotherapy)<br>baseline Hb: 11.9 g/dL , ESA 12.0 g/dL, control 11.8 g/dL, categorised as 10-12 g/dL |
| Interventions | drug: Epoetin alfa<br>dose: 10'000 IU sc. TIW<br>Hb-target: >14 g/dL<br>duration: >20 weeks |
| Outcomes | primary: relapse free survival |
| Notes | full text publication, additional unpublished data were obtained for the first Cochrane review (1985-2001), study number = 16218 |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Yes - computer random-numbers generator |
| Allocation concealment (selection bias) | Low risk | Yes - central registration of the patients for treatment allocation |

**Boogaerts 2003**

| | |
|---|---|
| Methods | randomised controlled trial, not placebo-controlled |
| Participants | N = 262 randomised: ESA = 133; control = 129<br>disease: multiple myeloma, Non-Hodgkin lymphoma, chronic lymphocytic leukaemia, Hodgkin disease, ovarian, bone, gastrointestinal, respiratory, other cancer<br>treatment: chemotherapy<br>baseline Hb: 9.0 g/dL |
| Interventions | drug: Epoetin beta<br>dose: 150 IU/kg sc TIW<br>Hb-target: 12-14 g/dL<br>planned ESA duration: 12 weeks |
| Outcomes | primary: QoL<br>secondary: hematologic response, hematopoietic response, Hb change, transfusions, PS, Hct |

**Boogaerts 2003** (*Continued*)

| | |
|---|---|
| Notes | full text publication of the study previously published as abstract Coiffier 2001, additional unpublished data were obtained for the first Cochrane review (1985-2001) and an individual patient data meta-analysis study (Bohlius et al 2009, study number = 36158) |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | unclear - no description |
| Allocation concealment (selection bias) | Low risk | yes - central randomisation |

**Boogaerts 2003 IPD**

| | |
|---|---|
| Methods | see Boogaerts 2003 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | |

**Boogaerts Coiffier 2001**

| | |
|---|---|
| Methods | see Boogaerts 2003 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | Abstract |

**Carabantes 1999**

| | |
|---|---|
| Methods | randomised controlled trial, not placebo-controlled |
| Participants | N = 35, randomised: ESA = 20, control = 15<br>disease: SCLC and ovarian carcinoma<br>treatment: platinum-containing chemotherapy<br>baseline Hb: (at randomisation): 10.5 g/dL |

**Carabantes 1999** (*Continued*)

| | |
|---|---|
| Interventions | drug: Epoetin alpha<br>dose: 150U/kg 3x/week s.c.<br>Hb target: NR<br>control: no treatment<br>duration: 18-24 weeks |
| Outcomes | haematologic response, transfusion requirements, QoL |
| Notes | abstract publication, study number = 17026 |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | unclear |
| Allocation concealment (selection bias) | Unclear risk | unclear |

**Cascinu 1994**

| | |
|---|---|
| Methods | randomised controlled trial, placebo-controlled |
| Participants | N = 100, randomised: ESA = 50; control = 50<br>disease: various solid tumours<br>treatment: concomitant platinum-based chemotherapy; some patients received G-CSF (n = 27)<br>mean/median baseline Hb: 8.7 g/dL |
| Interventions | drug: Epoetin alpha<br>dose: 100 U/kg 3x/week s.c.<br>Hb target: 10 - 12 g/dL<br>duration: 9 weeks |
| Outcomes | haematologic response, change in Hb values, transfusion requirement, adverse events |
| Notes | full text publication, additional unpublished data were obtained for the first Cochrane review (1985-2001), study number = 19548 |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Yes - computer random-number generator |
| Allocation concealment (selection bias) | Unclear risk | unclear - sealed envelopes |

**Case 1993**

| | |
|---|---|
| Methods | randomised controlled trial, placebo-controlled |
| Participants | N = 157, randomised: ESA = 81; control = 76<br>disease: non myeloid hematological malignancies, breast, lung, gynaecological, gastrointestinal, other cancer<br>treatment: non-cisplatin chemotherapy<br>mean/median baseline Hematocrit: 28.9% |
| Interventions | drug: Epoetin alpha<br>dose: 150U/kg 3x/week s.c.<br>Hb target: Hct 38%-40%<br>duration: 12 weeks |
| Outcomes | haematologic response, change in Hct, transfusion requirement, QoL, adverse events |
| Notes | full text publication, additional unpublished data were obtained for the first Cochrane review (1985-2001) and an individual patient data meta-analysis study (Bohlius et al 2009, study number = 34917) |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | yes - computer-generated |
| Allocation concealment (selection bias) | Unclear risk | unclear - description is unclear |

**Case 1993 IPD**

| | |
|---|---|
| Methods | see Case 1993 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | study number = 34917 |

**Case 1993 J&J 2004**

| | |
|---|---|
| Methods | see Case 1993 |
| Participants | |
| Interventions | |

**Case 1993 J&J 2004** (*Continued*)

| | |
|---|---|
| Outcomes | |
| Notes | |

**Cazzola 1995**

| | |
|---|---|
| Methods | randomised controlled trial, not placebo-controlled |
| Participants | N = 146, randomised: control = 29 (IPD: control:30, EPO: 116), evaluated EPO:114, control: 29<br>ESAa = 31; ESAb = 29; ESAc = 31; ESAd = 26; ESAtotal = 117<br>disease: multiple myeloma, Non-Hodgkin´ s Lymphoma<br>treatment: chemotherapy, assumed without platinum because of hematological disease<br>mean/median baseline Hb: 9.4 g/dL |
| Interventions | drug: Epoetin beta<br>dosages: a: 1000 IU sc 7x/week; b: 2000 IU sc 7x/week; c: 5000 IU sc 7x/ week; d: 10000 IU sc 7x/week<br>Hb-target: 11-13 g/dL (MM), 11-15 g/dL (NHL)<br>a: 1000 IU sc 7x/week, b: 2000 IU sc 7x/week; c: 5000 IU sc 7x/ week; d: 10000 IU sc 7x/week<br>duration: 8 weeks |
| Outcomes | primary: haematologic response<br>secondary: Hb, Hct, transfusions, reticulocytes, iron, ferritin, safety |
| Notes | full text publication, additional unpublished data obtained for first Cochrane Review and an individual patient data meta-analysis study (Bohlius et al 2009, study number = 37653) |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | unclear - randomisation list |
| Allocation concealment (selection bias) | Low risk | yes - central randomisation |

**Cazzola 1995 IPD**

| | |
|---|---|
| Methods | seeCazzola 1995 |
| Participants | |
| Interventions | |

**Cazzola 1995 IPD** (*Continued*)

| | |
|---|---|
| Outcomes | |
| Notes | |

**Cazzola 1995a**

| | |
|---|---|
| Methods | see Cazzola 1995 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | |

**Cazzola 1995b**

| | |
|---|---|
| Methods | see Cazzola 1995 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | |

**Cazzola 1995c**

| | |
|---|---|
| Methods | see Cazzola 1995 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | |

**Cazzola 1995d**

| | |
|---|---|
| Methods | see Cazzola 1995 |
| Participants | |
| Interventions | |

**Cazzola 1995d** (*Continued*)

| | |
|---|---|
| Outcomes | |
| Notes | |

**Chang 2005**

| | |
|---|---|
| Methods | randomised controlled trial, not placebo-controlled |
| Participants | N = 354, randomised: ESA = 176; control = 178<br>disease: breast cancer, stage I-IV<br>treatment: chemotherapy<br>baseline Hb: 11.3 g/dL |
| Interventions | drug: Epoetin alpha<br>dose: 40,000 IU qw sc<br>Hb target: 14 g/dL<br>duration: 16 weeks, max 28 weeks |
| Outcomes | primary: QoL<br>secondary: maintain Hb above 12 g/dL, tumour response, overall survival |
| Notes | full text publication, additional unpublished data were obtained for an individual patient data meta-analysis study (Bohlius et al 2009, study number = 99137) |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | unclear - no description |
| Allocation concealment (selection bias) | Low risk | yes - central randomisation |

**Chang 2005 IPD**

| | |
|---|---|
| Methods | see Chang 2005 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | study number = 99137 |

**Charu 2007**

| | |
|---|---|
| Methods | randomised controlled trial, not placebo-controlled |
| Participants | N = 287, randomised: ESA = 228, control = 59<br>disease: lymphoma, breast, lung, gastrointestinal, genitourinary, gynaecologic, other cancer<br>treatment: none<br>baseline Hb: 10.2 g/dL |
| Interventions | drug: Darbepoetin alpha<br>dose: 3.0 µg/kg sc Q2W<br>Hb-target: 13-14 g/dL (women), 13-15 g/dL (men)<br>duration: 12 weeks |
| Outcomes | primary: hospitalisation days<br>secondary: costs, QoL, transfusion, Hb, safety |
| Notes | full text publication, additional unpublished data were obtained for an individual patient data meta-analysis study (Bohlius et al 2009, study number = 53081) |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | unclear - no description |
| Allocation concealment (selection bias) | Low risk | yes - central randomisation |

**Charu 2007 Amgen 2007**

| | |
|---|---|
| Methods | see Charu 2007 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | |

**Charu 2007 IPD**

| | |
|---|---|
| Methods | see Charu 2007 |
| Participants | |
| Interventions | |

**Charu 2007 IPD** (*Continued*)

| | |
|---|---|
| Outcomes | |
| Notes | |

**Christodoulou 2009**

| | |
|---|---|
| Methods | randomised controlled trial, not placebo-controlled |
| Participants | N = 399, randomised: NR, evaluated: ESA 167, control = 170<br>disease: solid tumours<br>treatment: chemotherapy, platinum and non-platinum containing<br>baseline Hb: 10.2 g/dL |
| Interventions | drug: Epoetin alfa<br>dose: 10'000 IU TIW<br>Hb-target: 12 - 14 g/dL<br>duration: minimum anticipated duration 12 weeks. categorized 12-16 weeks |
| Outcomes | primary: QoL<br>secondary: transfusions, anaemia |
| Notes | full text publication, abstract in 2003 (Janinis), study number = 22108 |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | yes - block randomisation |
| Allocation concealment (selection bias) | Low risk | yes - centrally randomised |

**Dammacco 2001**

| | |
|---|---|
| Methods | randomised controlled trial, placebo-controlled |
| Participants | N = 145, randomised: ESA = 69; control = 76<br>disease: multiple myeloma<br>treatment: chemotherapy<br>mean/median baseline Hb: 9.5 g/dL |
| Interventions | drug: Epoetin alpha<br>dose: 150U/kg 3x/week s.c.<br>Hb target: 14 g/dL<br>duration: 12 weeks |

**Dammacco 2001** (*Continued*)

| | |
|---|---|
| Outcomes | primary: transfusion<br>secondary: haematologic response, Hb, Hct, reticulocytes, serum erythropoietin levels, QoL, adverse events |
| Notes | full text publication, additional unpublished data were obtained for the first Cochrane review (1985-2001) and an individual patient data meta-analysis study (Bohlius et al 2009, study number = 11220) |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | unclear - randomisation schedule prepared by RWJPRI |
| Allocation concealment (selection bias) | Unclear risk | unclear - two randomisation lists (pat. prev. transfused or not), when patient enters the study the next number was to be assigned |

**Dammacco 2001 IPD**

| | |
|---|---|
| Methods | see Dammacco 2001 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | |

**Dammacco 2001 J&J 2004**

| | |
|---|---|
| Methods | see Dammacco 2001 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | Data presented by J&J at FDA/ODAC hearing in May 2004 |

**Debus 2006 IPD**

| | |
|---|---|
| Methods | randomised controlled trial, not placebo-controlled |
| Participants | N = 385, randomised: ESA = 195, control = 190<br>disease: NSCLC (stage III, primarily inoperable)<br>treatment: radiochemotherapy<br>baseline Hb: not reported, unclear |
| Interventions | drug: Epoetin alpha<br>dose: 40'000 IU sc weekly<br>Hb-target: 12-14 g/dL, in 11/2003 reduced to 12-13 g/dL<br>duration: assumed to be 12-16 weeks |
| Outcomes | primary: 2-year-survival rate<br>secondary: tumour response, QoL, tolerance to epoetin alpha, Hb change, transfusion, safety |
| Notes | only unpublished data available, were obtained for an individual patient data meta-analysis study (Bohlius et al 2009, study number = 83322) |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | unclear - randomisation code provided by OrthoBiotech |
| Allocation concealment (selection bias) | Unclear risk | unclear - assigned envelopes, sequentially numbered, but it is unclear whether they were sealed and opaque |

**Debus 2006 J&J 2004**

| | |
|---|---|
| Methods | see Debus 2006 IPD |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | |

**Debus 2006 J&J 2007**

| | |
|---|---|
| Methods | see Debus 2006 IPD |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | |

**Del Mastro 1997**

| | |
|---|---|
| Methods | randomised controlled trial, not placebo-controlled |
| Participants | N = 62, randomised: ESA = 31, control = 31<br>disease: breast cancer<br>treatment: non-platinum based chemotherapy and G-CSF 5µg/kg d4-d11 s.c for all patients;<br>radiotherapy and Tamoxifen fore the majority<br>mean/median baseline Hb: 13.1 g/dL |
| Interventions | drug: Epoetin (?)<br>dose: 150U/kg 3x/week s.c.<br>Hb target: 13-15 g/dL<br>duration: 14 weeks |
| Outcomes | change in Hb values, transfusion requirement, QoL, adverse events |
| Notes | full text publication, additional unpublished data were obtained for the first Cochrane review (1985-2001), study number = 24367 |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Yes - computer random-number generator |
| Allocation concealment (selection bias) | Low risk | Yes - central allocation |

**Dunphy 1999**

| | |
|---|---|
| Methods | randomised controlled trial, not placebo-controlled |
| Participants | N = 30, randomised: ESA = 15, control = 15<br>disease: head and neck cancer, NSCLC<br>treatment: platinum-based chemotherapy<br>mean/median baseline Hb: 14.1 g/dL |

**Dunphy 1999** (*Continued*)

| | |
|---|---|
| Interventions | drug: Epoetin (?)<br>dose: 150U/kg 3x/week s.c.<br>Hb target: 16-18 g/dL<br>duration: 6 weeks |
| Outcomes | change in Hb values, transfusion requirement |
| Notes | full text publication, study number = 25455 |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Unclear |
| Allocation concealment (selection bias) | Unclear risk | Unclear |

**Engert 2009**

| | |
|---|---|
| Methods | See Engert 2010 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | |

**Engert 2010**

| | |
|---|---|
| Methods | randomised controlled trial, placebo-controlled |
| Participants | N = 1,379, randomised ESA: 685, placebo: 694<br>disease: advanced stage Hodgkin Lymphoma<br>treatment: chemotherapy without platinum<br>baseline Hb: 12.5 g/dL |
| Interventions | drug: Epoetin alpha<br>dose: 40,000 IU /week<br>Hb target: 12-13 g/dL<br>duration: > 20 weeks |
| Outcomes | primary: anaemia-related fatigue<br>secondary: other QoL, number of transfusions needed, Hb during and after treatment, safety, freedom from treatment failure, OS |

**Engert 2010** (*Continued*)

| | |
|---|---|
| Notes | full-text publication, additional unpublished data, study number = 27258 |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | unclear, not reported |
| Allocation concealment (selection bias) | Unclear risk | unclear, not reported |

**EPO-GER-20 IPD**

| | |
|---|---|
| Methods | randomised controlled trial, not placebo-controlled |
| Participants | n = 93, randomised: ESA = 45, control = 48<br>disease: SCLC (extensive stage)<br>treatment: chemotherapy<br>baseline Hb: not reported, unclear |
| Interventions | drug: Epoetin alpha<br>dose: 10000 IU sc TIW<br>Hb-target: 12-14 g/dL<br>duration: during chemotherapy |
| Outcomes | primary: rate of patients with anaemia<br>secondary: QoL, tolerability of ESA, transfusion, effectiveness of chemotherapy |
| Notes | only IPD data, study number = 31678 |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | unclear - patients were assigned with a randomisation code provided by Janssen-Cilag |
| Allocation concealment (selection bias) | Unclear risk | unclear - assigned envelopes, sequentially numbered, but it is unclear whether they were sealed and opaque |

**EPO-INT-1 IPD**

| | |
|---|---|
| Methods | see EPO-INT-1 J&J 2004 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | |

**EPO-INT-1 J&J 2004**

| | |
|---|---|
| Methods | randomised controlled trial, placebo-controlled |
| Participants | N = 246, randomised: ESA = 165, control = 81<br>disease: ovarian cancer (stage I-IV)<br>treatment: chemotherapy<br>baseline Hb: not reported, eligibility criterion Hb < 11 g/dL or Hb drop 1.5 g/dL, categorized as Hb 10-12 g/dL |
| Interventions | drug: Epoetin alpha<br>dose: a: 150, b: 300 IU/kg tiw sc<br>Hb-target: 14 g/dL<br>duration: 1 month |
| Outcomes | primary: transfusion<br>secondary: Hb change, Hct, QoL, survival |
| Notes | data presented by J&J at FDA/ODAC hearing in may 2004, additional unpublished data were obtained for an individual patient data meta-analysis study (Bohlius et al 2009, study number = 53915) |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | unclear - no description |
| Allocation concealment (selection bias) | Unclear risk | unclear - no description |

**EPO-INT-3 IPD**

| | |
|---|---|
| Methods | see EPO-INT-3 J&J 2004 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | |

**EPO-INT-3 J&J 2004**

| | |
|---|---|
| Methods | randomised controlled trial, placebo-controlled |
| Participants | N = 201, randomised: ESA = 136, control = 65<br>disease: breast, NHL, MM, ovarian, SCLC, other cancer<br>treatment: chemotherapy, < 70% platinum containing<br>baseline Hb: not reported, eligibility criterion Hb < 12 g/dL or Hb drop 1.5 g/dL, categorized as Hb 10-12 g/dL |
| Interventions | drug: Epoetin alpha<br>dose: 150-300 IU/kg tiw sc<br>Hb-target: 14 g/dL for women and 16 g/dL for men<br>duration: 12 weeks |
| Outcomes | primary: transfusions<br>secondary: mortality, disease progression, tumour response, adverse events, Hb, QoL |
| Notes | Data presented by J&J at FDA/ODAC hearing in May 2004, additional unpublished data were obtained for an individual patient data meta-analysis study (Bohlius et al 2009, study number = 36274), clinicaltrials.gov |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | unclear - according to randomisation schedule prepared by RWJPRI |
| Allocation concealment (selection bias) | Low risk | yes - central randomisation |

**Fujisaka 2011**

| | |
|---|---|
| Methods | randomised controlled trial, placebo-controlled |
| Participants | randomised N = 186, evaluated N = 181, ESA = 89, control = 92<br>disease: lung cancer, gynaecological cancer<br>treatment: platinum-based chemotherapy<br>baseline Hb: 9.4 g/dL<br>duration: 12 weeks |
| Interventions | drug: epoetin beta<br>dose: 36,000 IU/week<br>target Hb: 12.0g/dL<br>duration: 12 weeks |
| Outcomes | primary: proportion of patients receiving RBCTs and/or Hb<8.0 g/dL<br>secondary: need for transfusions, changes in Hb, QoL |
| Notes | full-text publication, study id: 15478 |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | not reported |
| Allocation concealment (selection bias) | Low risk | central randomisation system |

**Gebbia 2003**

| | |
|---|---|
| Methods | randomised controlled trial, not placebo-controlled |
| Participants | N = 45, randomised ESA = 22, control = 23<br>disease: squamous cell carcinoma of the head an neck<br>treatment: platinum-containing chemotherapy<br>baseline Hb: 12.1 g/dL |
| Interventions | drug: rhEpo<br>dose: 10'000IU tiw<br>Hb-target: 12-14 g/dL<br>duration: NR |
| Outcomes | primary: NR<br>secondary: transfusion, QoL, clinical outcome |
| Notes | full text publication, study number = 29327 |

***Risk of bias***

**Gebbia 2003** (*Continued*)

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | unclear |
| Allocation concealment (selection bias) | Unclear risk | unclear |

**Gordon 2008**

| | |
|---|---|
| Methods | randomised controlled trial, placebo-controlled |
| Participants | N = 220, randomised: ESA = 164, control = 56<br>disease: non-myeloid hematological malignancies, breast, gastrointestinal, genitourinary, lung, gynaecological, other cancer (stage I-IV)<br>therapy: none<br>baseline Hb: 10.2 g/dL |
| Interventions | drug: Darbepoetin alpha<br>dose: 6.75 µg/kg sc Q4W<br>Hb-target: 12-13 g/dL<br>duration: 16 weeks |
| Outcomes | primary: Hb response<br>secondary: transfusion, Hb change, QoL, safety |
| Notes | full text publication, additional unpublished data were obtained for an individual patient data meta-analysis study (Bohlius et al 2009, study number = 65772) |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | unclear - randomisation list will be centrally generated by Amgen |
| Allocation concealment (selection bias) | Low risk | yes - central randomisation |

**Gordon 2008 IPD**

| | |
|---|---|
| Methods | see Gordon 2008 |
| Participants | |
| Interventions | |
| Outcomes | |

| | |
|---|---|
| Notes | |

**Goss 2005**

| | |
|---|---|
| Methods | randomised controlled trial, placebo-controlled |
| Participants | N = 104, randomised: ESA = 52, control = 52<br>disease:SCLC (limited disease)<br>treatment: radiochemotherapy<br>baseline Hb: 13.5 g/dL |
| Interventions | drug: Epoetin alpha<br>dose: 40000 IU sc weekly<br>Hb-target: 14-16 g/dL, in 10/2002 reduced to 12-14 g/dL<br>duration: during chemotherapy and radiotherapy |
| Outcomes | disease progression free survival, tumour response, overall survival, local disease progression, Hb, transfusion, QoL |
| Notes | abstract publication, additional unpublished data obtained for an individual patient data meta-analysis study (Bohlius et al 2009, study number = 55703) |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | yes - computer-generated |
| Allocation concealment (selection bias) | Low risk | yes - central randomisation |

**Goss 2005 FDA 2004**

| | |
|---|---|
| Methods | see Goss 2005 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | |

**Goss 2005 IPD**

| | |
|---|---|
| Methods | see Goss 2005 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | |

**Goss 2005 J&J 2004**

| | |
|---|---|
| Methods | see Goss 2005 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | |

**Grote 2005**

| | |
|---|---|
| Methods | randomised controlled trial, placebo-controlled |
| Participants | N = 224, randomised: ESA = 109, control = 115<br>disease: SCLC (limited and extensive disease)<br>treatment: chemotherapy<br>baseline Hb: 12.9 g/dL |
| Interventions | drug: Epoetin alpha<br>dose: 150 IU/kg sc TIW<br>Hb-target: 14-16 g/dL<br>duration: NR, assumed to be 12 weeks (drug given during 3 x 3 weeks chemo plus 3 weeks) |
| Outcomes | primary: assess possible stimulatory effects of ESA on solid tumour growth, tumour response<br>secondary: overall survival, Hb, transfusion, safety |
| Notes | full text publication, additional unpublished data were obtained for an individual patient data meta-analysis study (Bohlius et al 2009, study number = 73807) |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|

**Grote 2005** (*Continued*)

| | | |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | yes - computer-generated |
| Allocation concealment (selection bias) | Unclear risk | unclear - description is unclear |

**Grote 2005 IPD**

| | |
|---|---|
| Methods | see Grote 2005 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | |

**Grote 2005 J&J 2004**

| | |
|---|---|
| Methods | see Grote 2005 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | |

**Gupta 2009**

| | |
|---|---|
| Methods | randomised controlled trial, not placebo-controlled |
| Participants | N = 120, randomised: ESA = 60, control = 60<br>disease: cervical cancer<br>treatment: platinum-containing in all patients plus radiotherapy<br>baseline Hb: 10.6 g/dL |
| Interventions | drug: Epoetin beta<br>dose: 30'000 IU TIW<br>Hb-target: unclear<br>duration: unclear |
| Outcomes | primary: Hb, energy level, QoL<br>secondary: response rate, survival, toxicities, adverse events |
| Notes | full text publication, study number = 30057 |

**Gupta 2009** (*Continued*)

| *Risk of bias* | | |
|---|---|---|
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Unclear risk | unclear |
| Allocation concealment (selection bias) | Unclear risk | unclear |

**Hedenus 2002**

| | |
|---|---|
| Methods | randomised controlled trial, placebo-controlled |
| Participants | N = 66, randomised: ESA = 55, control = 11<br>disease: lymphoma: HD, NHL, MM<br>treatment: NR, assumed to be chemotherapy without platinum<br>baseline Hb: 9.6 g/dL |
| Interventions | drug: Darbepoetin alpha<br>dosages: a: 1.0 µg/kg qw sc; b: 2.25 µg/kg qw sc; c:Darbepoetin 4.5 µg/kg qw sc<br>Hb target: 13-14 g/dL for women and 13-15 g/dL for men<br>duration: 12 weeks |
| Outcomes | primary: dose response relationship of darbepoetin in haemoglobin or haematopoietic response and overall survival<br>secondary: transfusion |
| Notes | full text publication, study number = 32213 |

| *Risk of bias* | | |
|---|---|---|
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Unclear risk | Unclear |
| Allocation concealment (selection bias) | Low risk | yes - central computerized system |

**Hedenus 2002a**

| | |
|---|---|
| Methods | see Hedenus 2002 |
| Participants | |
| Interventions | Darbepoetin 1.0 µg/kg qw sc |
| Outcomes | |

**Hedenus 2002a** (*Continued*)

| | |
|---|---|
| Notes | |

**Hedenus 2002b**

| | |
|---|---|
| Methods | see Hedenus 2002 |
| Participants | |
| Interventions | Darbepoetin 2.25 µg/kg qw sc |
| Outcomes | |
| Notes | |

**Hedenus 2002c**

| | |
|---|---|
| Methods | see Hedenus 2002 |
| Participants | |
| Interventions | Darbepoetin 4.5 µg/kg qw sc |
| Outcomes | |
| Notes | |

**Hedenus 2003**

| | |
|---|---|
| Methods | randomised controlled trial, placebo-controlled |
| Participants | N = 349, randomised: ESA = 176, control = 173<br>disease: lymphoma: Hodgkin disease, NHL, MM, CLL, Waldenstrom´ s disease<br>treatment: NR, assumed to be chemotherapy without platinum<br>Hb baseline: 9.5 g/dL |
| Interventions | drug: Darbepoetin alpha<br>dose: 2.25 mg/kg qw sc<br>Hb target: 13-14 g/dL (women), 13-15 g/dL (men)<br>duration: 12 weeks |
| Outcomes | primary: Hb response<br>secondary: transfusion, Hb change, QoL, safety |
| Notes | full text publication, additional unpublished data were obtained for an individual patient data meta-analysis study (Bohlius et al 2009, study number = 63455) |
| ***Risk of bias*** | |

**Hedenus 2003** (*Continued*)

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | unclear - based on a schedule specified by Amgen before the start of the study |
| Allocation concealment (selection bias) | Low risk | yes - central randomisation |

**Hedenus 2003 FDA 2007**

| | |
|---|---|
| Methods | see Hedenus 2003 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | |

**Hedenus 2003 IPD**

| | |
|---|---|
| Methods | see Hedenus 2003 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | 63455 |

**Henke 1999**

| | |
|---|---|
| Methods | randomised controlled trial, not placebo-controlled |
| Participants | N = 50, randomised: control = 11; ESAa = 19; ESAb = 14; ESAc = 6; ESAtotal = 39<br>disease: various solid tumours<br>treatment: radiotherapy<br>mean/median baseline Hb: 11.5 g/dL |
| Interventions | drug: Epoetin alpha or beta<br>dose: ESAa: 150U/kg 3x/week i.v., ESAb: 300U/kg 3x/week i.v., ESAc: 150U/kg 3x/week s.c.;<br>Hb target: 14 - 16 g/dL (men) or 13 - 15 g/dL (women)<br>duration: 8 weeks |
| Outcomes | haematologic response, change in Hb values |

**Henke 1999** (*Continued*)

| | |
|---|---|
| Notes | full text publication, study number = 39895 |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Unclear |
| Allocation concealment (selection bias) | Unclear risk | Unclear |

**Henke 1999a**

| | |
|---|---|
| Methods | see Henke 1999 |
| Participants | n = 19 |
| Interventions | Epoetin alpha or beta a: 150U/kg 3x/week i.v. |
| Outcomes | |
| Notes | |

**Henke 1999b**

| | |
|---|---|
| Methods | see Henke 1999 |
| Participants | n = 14 |
| Interventions | Epoetin alpha or beta b: 300U/kg 3x/week i.v.; |
| Outcomes | |
| Notes | |

**Henke 1999c**

| | |
|---|---|
| Methods | see Henke 1999 |
| Participants | n= 6 |
| Interventions | Epoetin alpha or beta c: 150U/kg 3x/week s.c. |
| Outcomes | |
| Notes | |

**Henke 2003**

| | |
|---|---|
| Methods | randomised controlled trial, placebo-controlled |
| Participants | N = 351, randomised: ESA = 180, control = 171<br>disease: advanced (stage III , IV) head and neck cancer<br>treatment: radiotherapy<br>baseline Hb: 11.8 g/dL |
| Interventions | drug: Epoetin beta<br>dose: 300 IU/kg tiw sc<br>Hb-target: 12-14 g/dL (women), 13-15 g/dL (men)<br>duration: 7-9 weeks |
| Outcomes | primary: efficacy of radiotherapy, measured as local progression free survival<br>secondary: survival, progression free survival, Hb, safety, tolerability |
| Notes | full text publication, additional unpublished data were obtained for an individual patient data meta-analysis study (Bohlius et al 2009, study number = 58106) |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | unclear - each centre had numbered packages per stratum, once randomised the lowest number had to be assigned. There was a randomisation list only the statistics centre had access to. In addition, there were sealed envelopes for emergencies |
| Allocation concealment (selection bias) | Low risk | yes - coded drug packs of identical appearance |

**Henke 2003 IPD**

| | |
|---|---|
| Methods | see Henke 2003 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | |

**Henke 2003 Roche 2004**

| | |
|---|---|
| Methods | See Henke 2003 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | Data presented by Roche at FDA/ODAC hearing in May 2004 |

**Henry 1995**

| | |
|---|---|
| Methods | randomised controlled trial, placebo-controlled |
| Participants | N = 132, randomised: ESA = 67, control = 65<br>disease: any type of cancer except primary myeloid malignancy or acute leukaemia<br>treatment: platinum-containing chemotherapy<br>baseline Hb: 9.5 g/dL |
| Interventions | drug: Epoetin alpha<br>dose: 150 IU/kg sc TIW<br>Hb-target: Hct 38%-40%<br>duration: 12 weeks |
| Outcomes | primary: Hct, transfusion, haematologic response<br>secondary: correction of anaemia, response, QoL, safety |
| Notes | full text publication, additional unpublished data were obtained for the first Cochrane review (1985-2001) and an individual patient data meta-analysis study (Bohlius et al 2009, study number = 70332) |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | yes - computer generated |
| Allocation concealment (selection bias) | Unclear risk | unclear - medication boxes were used, but without identical appearance |

**Henry 1995 IPD**

| | |
|---|---|
| Methods | see Henry 1995 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | study number = 70332 |

**Henry 1995 J&J 2004**

| | |
|---|---|
| Methods | see Henry 1995 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | Data presented by J&J at FDA/ODAC hearing in May 2004 |

**Hernandez 2009**

| | |
|---|---|
| Methods | randomised controlled trial, placebo-controlled |
| Participants | n = 391, randomised: ESA = 196, control = 195<br>disease: non-myeloid haematological malignancies, breast, lung, gastrointestinal, genitourinary, gynaecological, other cancer (stage I-IV)<br>treatment: chemotherapy, 36% receiving platinum<br>baseline Hb:10.1 g/dL |
| Interventions | drug: Darbepoetin alpha<br>dose: 300 µg sc Q3W<br>Hb-target: 12-13 g/dL<br>duration: 15 weeks |
| Outcomes | primary: transfusion<br>secondary: Hb target achieved, number of transfusions, safety, QoL |
| Notes | full text publication, additional unpublished data were obtained for an individual patient data meta-analysis study (Bohlius et al 2009, study number = 37476, Taylor 2005) |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|

| | | |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | unclear - no description |
| Allocation concealment (selection bias) | Low risk | yes - central randomisation |

**Hernandez 2009 IPD**

| | |
|---|---|
| Methods | see Hernandez 2009 was Taylor 2005 in IPD meta-analysis by Bohlius et al 2009 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | study number = 37476 |

**Hoskin 2009**

| | |
|---|---|
| Methods | randomised controlled trial, not placebo-controlled |
| Participants | N = 300, randomised: ESA = 151, control = 149<br>disease: head and neck cancer (stage I-IV)<br>treatment: radiotherapy, no chemotherapy<br>baseline Hb: 13.6 g/dL |
| Interventions | drug: Epoetin alpha<br>dose: if Hb < 12.5 10000 IU sc TIW; if Hb > 12.5 4000 IU sc TIW<br>Hb-target: 14.5 to 15 g/dL<br>duration: 12 weeks |
| Outcomes | primary: local disease free survival<br>secondary: overall survival, QoL, safety |
| Notes | full text publication, additional unpublished data were obtained for an individual patient data meta-analysis study (Bohlius et al 2009, study number = 81645) |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | unclear - central randomisation schedule stratified by the study site was generated by the sponsor |
| Allocation concealment (selection bias) | Unclear risk | unclear - no description |

**Hoskin 2009 GBR-7 FDA 04**

| | |
|---|---|
| Methods | see Hoskin 2009 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | unpublished study, data obtained from FDA report for the FDA/ODAC in hearing May 2004 |

**Hoskin 2009 IPD**

| | |
|---|---|
| Methods | see Hoskin 2009 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | study number = 81645 |

**Hoskin 2009 J&J 2004**

| | |
|---|---|
| Methods | see Hoskin 2009 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | |

**Huddart 2002**

| | |
|---|---|
| Methods | randomised controlled trial, not placebo-controlled |
| Participants | N = 95, randomised: ESA = 48, control = 47<br>disease: lung, gynaecological, genitourinary, other cancer<br>treatment: platinum-containing chemotherapy<br>baseline Hb: not reported, eligibility criterion Hb < 10.5 g/dL, categorized as Hb 10-12 g/dL |
| Interventions | drug: Epoetin alpha<br>dose: 10,000 IU tiw<br>Hb-target: 12-14 g/dL<br>duration: max 28 weeks |

**Huddart 2002** (*Continued*)

| | |
|---|---|
| Outcomes | Hb response, reticulocyte, survival, QoL, safety |
| Notes | abstract, additional unpublished data were obtained for an individual patient data meta-analysis study (Bohlius et al 2009, study number = 88443) |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | unclear - no description |
| Allocation concealment (selection bias) | Unclear risk | unclear - no description |

**Huddart 2002 IPD**

| | |
|---|---|
| Methods | see Huddart 2002 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | study number = 88443 |

**Iconomou 2003**

| | |
|---|---|
| Methods | randomised controlled trial, not placebo-controlled |
| Participants | N = 122, randomised: ESA = 57, control = 55<br>disease: lung, breast, colorectal, ovarian, unknown primary, kidney, stomach, other cancer<br>treatment: chemotherapy, platinum & non platinum<br>baseline Hb: 10.1 g/dL |
| Interventions | drug and dose: NR, assumed Epoetin alpha 10,000 IU tiw sc<br>Hb target: NR<br>duration: 12 weeks |
| Outcomes | primary: QoL<br>secondary: Hb, transfusions |
| Notes | full text publication, study number = 40799 |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|

| | | |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Unclear |
| Allocation concealment (selection bias) | Low risk | Randomisation was performed by a telephone call to the registry of the department of medicine |

**Italian 1998**

| | |
|---|---|
| Methods | randomised controlled trial, placebo-controlled |
| Participants | N = 87, randomised: ESA = 44, control = 43<br>disease: Myelodysplastic Syndromes<br>treatment: none<br>mean/median baseline Hb: 8.2 g/dL; |
| Interventions | drug: Epoetin alpha<br>dose: 150U/kg 3x/week s.c.<br>Hb target: not reported<br>duration: 8 weeks, thereafter Epo for all the patients |
| Outcomes | haematologic response, change in haemoglobin values, adverse events |
| Notes | full text publication, additional unpublished data were obtained for the first Cochrane review (1985-2001), study number = 46703 |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Yes - computer random number generator |
| Allocation concealment (selection bias) | Low risk | Yes - central registration by telephone before treatment assignment |

**Katakami 2008**

| | |
|---|---|
| Methods | randomised controlled trial, placebo-controlled |
| Participants | N = 207, ESA = 103, control = 104<br>disease: lung and gynaecologic cancer<br>treatment: platinum-containing chemotherapy<br>baseline Hb: not reported, eligibility criterion Hb <= 11 g/dL, categorized as Hb 10-12 g/dL |

**Katakami 2008** (*Continued*)

| | |
|---|---|
| Interventions | drug: darbepoetin alfa<br>dose: 2.25 ug/kg once per week sc<br>Hb target: 13.0 g/dL (amended to 12.0 g/dL)<br>duration: 12 weeks |
| Outcomes | proportion of patients reaching transfusion trigger or receiving RBCT, haematologic endpoints,<br>adverse events, survival |
| Notes | abstract publication (study id: 13567) additional study reporting exactly the same: Katsumata 2009 |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | unclear, not reported |
| Allocation concealment (selection bias) | Unclear risk | unclear, not reported |

**Kotasek 2002**

| | |
|---|---|
| Methods | randomised controlled trial, placebo-controlled |
| Participants | N = 161, randomised: ESA = 129, control = 32<br>disease: lung, breast, gastrointestinal, genitourinary, gynaecological, other cancer (stage I-IV)<br>treatment: chemotherapy<br>baseline Hb: not reported, eligibility criterion Hb <= 11 g/dL, categorized as Hb 10-12 g/dL |
| Interventions | drug: Darbepoetin alpha<br>dose: a: 9 µg/kg sc Q4W, b: 12 µg/kg sc Q4W, c: 15 µg/kg sc Q4W, d: 18 µg/kg sc Q4W<br>Hb-target: 13-14 g/dL (women), 13-15 g/dL (men)<br>duration: 12 weeks |
| Outcomes | primary: safety<br>secondary: determine effective dose, effect of ESA, QoL feasibility |
| Notes | additional unpublished data were obtained for an individual patient data meta-analysis study (Bohlius et al 2009, study number = 26117) |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|

**Kotasek 2002** (*Continued*)

| | | |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | unclear - no description |
| Allocation concealment (selection bias) | Low risk | yes - central randomisation |

**Kotasek 2002 IPD**

| | |
|---|---|
| Methods | see Kotasek 2002 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | |

**Kotasek 2003**

| | |
|---|---|
| Methods | randomised controlled trial, placebo-controlled |
| Participants | N = 259, randomised: ESA = 208, control = 51<br>disease: breast, gynaecological, gastrointestinal, lung, genitourinary, other cancer<br>treatment: chemotherapy, not reported whether with or without platinum, interpreted as some patients receiving platinum<br>baseline Hb: 9.9 g/dL |
| Interventions | drug = Darbepoetin alpha<br>dose = a: 4.5 µg/kg sc Q3W, b: 6.75 µg/kg sc Q3W, c: 9 µg/kg sc Q3W, d: 12 µg/kg sc Q3W, e: 13.5 µg/kg sc Q3W, f: 15 µg/kg sc Q3W<br>Hb-target = 13-14 g/dL (women), 13-15 g/dL (men)<br>duration = 12 weeks |
| Outcomes | primary: safety<br>secondary: determine effective dose, effect of ESA, QoL feasibility |
| Notes | full text publication, additional unpublished data were obtained for an individual patient data meta-analysis study (Bohlius et al 2009, study number = 35466) |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | unclear - no description |
| Allocation concealment (selection bias) | Low risk | yes - central randomisation |

**Kotasek 2003 IPD**

| | |
|---|---|
| Methods | see Kotasek 2003 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | study number = 35466 |

**Kotasek 2003a**

| | |
|---|---|
| Methods | see Kotasek 2003 |
| Participants | N = 32 |
| Interventions | Darbepoetin 4.5 µg/kg Q3W sc |
| Outcomes | |
| Notes | |

**Kotasek 2003b**

| | |
|---|---|
| Methods | see Kotasek 2003 |
| Participants | N = 17 |
| Interventions | Darbepoetin 6.75 µg/kg Q3W sc |
| Outcomes | |
| Notes | |

**Kotasek 2003c**

| | |
|---|---|
| Methods | see Kotasek 2003 |
| Participants | N = 46 |
| Interventions | Darbepoetin 9 µg/kg Q3W sc |
| Outcomes | |
| Notes | |

**Kotasek 2003d**

| | |
|---|---|
| Methods | see Kotasek 2003 |
| Participants | N = 28 |
| Interventions | Darbepoetin 12 µg/kg Q3W sc |
| Outcomes | |
| Notes | |

**Kotasek 2003e**

| | |
|---|---|
| Methods | see Kotasek 2003 |
| Participants | N = 35 |
| Interventions | Darbepeotin 13.5 µg/kg Q3W sc |
| Outcomes | |
| Notes | |

**Kotasek 2003f**

| | |
|---|---|
| Methods | see Kotasek 2003 |
| Participants | N = 40 |
| Interventions | Darbepoetin 15 µg/kg Q3W sc |
| Outcomes | |
| Notes | |

**Krzakowski 2008**

| | |
|---|---|
| Methods | randomised controlled trial, placebo-controlled |
| Participants | N = 313, randomised: ESA a = 104, ESA b = 105, control = 104<br>disease: lung cancer, gastrointestinal tumour, breast cancer, genitourinary, haematological and other cancer<br>treatment: platinum and non-platinum containing chemotherapy<br>baseline Hb: 9.4 g/dL |
| Interventions | drug: Epoetin delta<br>dose: a: 150 IU/kg tiw, b: 300 IU/kg tiw<br>Hb-target: 12 - 14 g/dL<br>duration: 12 weeks |

**Krzakowski 2008** (*Continued*)

| | |
|---|---|
| Outcomes | primary: Hb, RBC, transfusions<br>secondary: haematocrit, FACT-An, subgroup analysis for type of cancer/ chemotherapy |
| Notes | full text publication, study number = 49839 |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | unclear |
| Allocation concealment (selection bias) | Unclear risk | unclear |

**Krzakowski 2008a**

| | |
|---|---|
| Methods | see Krzakowski 2008 |
| Participants | ESA a = 104 |
| Interventions | dose: a: 150 IU/kg tiw |
| Outcomes | |
| Notes | |

**Krzakowski 2008b**

| | |
|---|---|
| Methods | see Krzakowski 2008 |
| Participants | ESA b = 105 |
| Interventions | dose: b: 300 IU/kg tiw |
| Outcomes | |
| Notes | |

**Kunikane 2001**

| | |
|---|---|
| Methods | randomised controlled trial, placebo-controlled |
| Participants | N = 72, evaluated: 53. randomisation is only given for those:<br>Epoetin a = 16, Epoetin b = 18, control = 19<br>disease: NSCLC<br>treatment: platinum based chemotherapy<br>baseline Hb: 12.3 g/dL |

**Kunikane 2001** (*Continued*)

| | |
|---|---|
| Interventions | drug: Epoetin beta<br>dose: 1: 100U/kg 3x/week s.c.; 2: 200U/kg 3x/week s.c.<br>Hb-target: 14 g/dL in women, 16 g/dL in men<br>duration: 6 weeks |
| Outcomes | change in Hb values, transfusion requirement, adverse events |
| Notes | full text publication, additional unpublished data obtained for first Cochrane Review, study number = 51164 |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | unclear |
| Allocation concealment (selection bias) | Low risk | yes - central registration before treatment assignment |

**Kunikane 2001a**

| | |
|---|---|
| Methods | see Kunikane 2001 |
| Participants | Epoetin 1: n = 16 |
| Interventions | Epoetin beta 1: 100U/kg 3x/week s.c. |
| Outcomes | |
| Notes | |

**Kunikane 2001b**

| | |
|---|---|
| Methods | see Kunikane 2001 |
| Participants | |
| Interventions | Epoetin beta 2: 200U/kg 3x/week s.c. |
| Outcomes | |
| Notes | |

**Kurz 1997**

| | |
|---|---|
| Methods | randomised controlled trial, placebo-controlled |
| Participants | N = 35, randomised: ESA = 23, control = 13<br>disease: gynaecologic tumours<br>treatment: platinum based chemotherapy<br>baseline Hb: 9.9 g/dL |
| Interventions | drug: Epoetin alpha<br>dose: 150U/kg 3x/week s.c.<br>Hb-target: no upper target reported<br>duration: 12 weeks |
| Outcomes | haematologic response, change in Haemoglobin values, transfusion requirement, Quality of Life, adverse events |
| Notes | full text publication, additional unpublished data were obtained for the first Cochrane review (1985-2001), study number = 54819 |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Yes - random permuted blocks and a corresponding randomisation list at the randomisation office |
| Allocation concealment (selection bias) | Low risk | Yes - registration of the patients with an institution seperate from the centre where patients were recruited before treatment assignment |

**Leyland-Jones 05 J&J 04**

| | |
|---|---|
| Methods | see Leyland-Jones 2005 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | Data presented by J&J at FDA/ODAC hearing in May 2004 |

**Leyland-Jones 2005**

| | |
|---|---|
| Methods | randomised controlled trial, placebo-controlled |
| Participants | N = 939, randomised: ESA = 469, control = 470<br>disease: metastatic breast cancer (stage IV, M1)<br>treatment: chemotherapy<br>baseline Hb: 12.5 g/dL |
| Interventions | drug: Epoetin alpha<br>dose: 40,000 IU qw sc<br>Hb-target = 12-14 g/dL<br>duration: 52 weeks |
| Outcomes | primary: overall survival<br>secondary: Hb, transfusion, tumour control, QoL, time to progression |
| Notes | full text publication, additional unpublished data were obtained for an individual patient data meta-analysis study (Bohlius et al 2009, study number = 17100) |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | yes - computer-generated |
| Allocation concealment (selection bias) | Low risk | yes - central randomisation |

**Leyland-Jones 2005 IPD**

| | |
|---|---|
| Methods | see Leyland-Jones 2005 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | study number = 17100 |

**Littlewood 2001**

| | |
|---|---|
| Methods | randomised controlled trial, placebo-controlled |
| Participants | N=375, randomised: ESA = 251, control = 124<br>disease: NHL, MM, HD, CLL, gastrointestinal, other cancer<br>treatment: chemotherapy without platinum<br>baseline Hb: 9.8 g/dL |

**Littlewood 2001** (*Continued*)

| | |
|---|---|
| Interventions | drug: Epoetin alpha<br>dose: 150 IU/kg sc TIW<br>Hb-target: 12-15 g/dL<br>duration: 28 weeks |
| Outcomes | primary: transfusion<br>secondary: haematologic response, Hb, Hct, reticulocytes, predictors for response, QoL, adverse events, after protocol amendment also survival |
| Notes | full text publication, additional unpublished data were obtained for the first Cochrane review (1985-2001) and an individual patient data meta-analysis study (Bohlius et al 2009, study number = 17123) |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | yes - computer-generated randomisation schedule prepared by RWJPRI |
| Allocation concealment (selection bias) | Low risk | yes - coded drug packs of identical appearance |

**Littlewood 2001 IPD**

| | |
|---|---|
| Methods | see Littlewood 2001 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | study number = 17123 |

**Littlewood 2001 J&J 2004**

| | |
|---|---|
| Methods | SeeLittlewood 2001 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | Data presented by J&J at FDA/ODAC hearing in May 2004 |

**Machtay 2007**

| | |
|---|---|
| Methods | randomised controlled trial, not placebo-controlled |
| Participants | N = 148, randomised: ESA = 77, control = 71<br>disease: head and neck cancer (stage I-IV)<br>treatment: radiotherapy, advanced stages received in addition platinum based chemo-therapy<br>baseline Hb: 12.1 g/dL |
| Interventions | drug: Epoetin alpha<br>dose: 40'000 IU sc weekly<br>Hb-target: 12.5-14 g/dL (women), 13.5-16 g/dL (men)<br>duration: 8-10 weeks |
| Outcomes | primary: local regional control tumour response<br>secondary: overall survival, patterns of failure, local-regional progression-free survival, Hb, toxicity, QoL |
| Notes | full text publication, additional unpublished data were obtained for an individual patient data meta-analysis study (Bohlius et al 2009, study number = 87660), old publication was Machtay 2004 |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | unclear - no description |
| Allocation concealment (selection bias) | Low risk | yes - central randomisation |

**Machtay 2007 IPD**

| | |
|---|---|
| Methods | see Machtay 2007 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | study number = 87660 |

**Milroy 2003 IPD**

| | |
|---|---|
| Methods | see Milroy 2011 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | |

**Milroy 2011**

| | |
|---|---|
| Methods | randomised controlled trial, not placebo-controlled |
| Participants | N = 424, randomised: ESA = 214, control = 210<br>disease: NSCLC (stage IIIb or IV, advanced)<br>treatment: platinum-based chemotherapy<br>baseline Hb: 12.7 g/dL |
| Interventions | drug: Epoetin alpha<br>dose: if body weight > 45 kg 10000 IU sc TIW, if body weight < 45 kg 5000 IU sc TIW<br>Hb-target: 12.5-14 g/dL (women), 13.5-15 g/dL (men)<br>duration = during chemotherapy |
| Outcomes | primary: QoL<br>secondary: Hb, tumour response, survival, transfusion |
| Notes | full text publication, additional unpublished data were obtained for an individual patient data meta-analysis study (Bohlius et al 2009, study number = 67954) |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | unclear - no description |
| Allocation concealment (selection bias) | Low risk | yes - central randomisation |

**ML17616 2006**

| | |
|---|---|
| Methods | randomised controlled trial, not placebo-controlled |
| Participants | N = 60<br>disease: MM, NHL and Cll<br>treatment: chemotherapy, assumed to be without platinum because of hematological disease |

| | |
|---|---|
| | baseline Hb: not reported, eligibility criterion Hb <10 g/dL, categorized as Hb baseline < 10 g/dL |
| Interventions | drug: epoetin beta<br>dose: 150 IU/kg TIW<br>Hb-target: NR<br>duration: 12 weeks |
| Outcomes | primary: hematologic response<br>secondary: Hb, transfusions, safety |
| Notes | clinical trial result information, study number = 99765 |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | unclear |
| Allocation concealment (selection bias) | Unclear risk | unclear |

**ML17620 2006**

| | |
|---|---|
| Methods | randomised controlled trial, not placebo-controlled |
| Participants | N = 121<br>disease: solid tumours<br>treatment: platinum-based chemotherapy<br>baseline Hb: not reported, unclear |
| Interventions | drug: epoetin beta<br>dose: 150 IU/kg TIW<br>Hb-target: NR<br>duration: 12 weeks |
| Outcomes | primary: hematologic response<br>secondary: Hb, transfusions, Hct, safety, blood pressure |
| Notes | clinical trial result information, study number = 10373 |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | unclear |

| | | |
|---|---|---|
| Allocation concealment (selection bias) | Unclear risk | unclear |

**Moebus 2007**

| | |
|---|---|
| Methods | randomised controlled trial, not placebo-controlled |
| Participants | N = 643, randomised: ESA = 324, control = 319<br>disease: breast cancer (high risk, stage II/IIIA; M0)<br>treatment: chemotherapy without platinum<br>baseline Hb: 12.6 g/dL |
| Interventions | drug: Epoetin alpha<br>dose: 150 IU/kg sc TIW<br>Hb-target: 13-14 g/dL<br>duration: 18 weeks |
| Outcomes | primary: transfusion, Hb<br>secondary: recurrence free survival, overall survival, relapse, QoL |
| Notes | abstract publication, additional unpublished data were obtained for the first Cochrane review (1985-2001) and an individual patient data meta-analysis study (Bohlius et al 2009, study number = 22515) |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | yes - computer random-number generator |
| Allocation concealment (selection bias) | Low risk | yes - central registration of patients before treatment allocation |

**Moebus 2007 IPD**

| | |
|---|---|
| Methods | see Moebus 2007 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | |

**Moebus 2007 J&J 2007**

| | |
|---|---|
| Methods | see Moebus 2007 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | |

**Mystakidou 2005**

| | |
|---|---|
| Methods | randomised controlled trial, placebo-controlled |
| Participants | N = 100, randomised: ESA = 50, control = 50<br>disease: pancreatic, genital, colon and lung cancer<br>treatment: none<br>baseline Hb: 10.01 g/dL; for ESA group 9.87g/dL for control group 10.15, categorized as 10-12 g/dL |
| Interventions | drug: Epoetin alfa<br>dose: 40'000 weekly<br>Hb-target: 15 g/dL<br>duration: 24 weeks |
| Outcomes | primary: Hb<br>secondary: QoL, safety |
| Notes | full text publication, was excluded in the IPD Review, study number = 61315 |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | unclear |
| Allocation concealment (selection bias) | Unclear risk | unclear |

**O'Shaughnessy 2005**

| | |
|---|---|
| Methods | randomised controlled trial, placebo-controlled |
| Participants | N = 100, randomised: ESA = 51, control = 49<br>disease: breast cancer, stages I-IIIB<br>treatment: chemotherapy<br>baseline Hb: 12.9 g/dL |

**O'Shaughnessy 2005** (*Continued*)

| | |
|---|---|
| Interventions | drug: Epoetin alpha<br>dose: 40,000 IU qw sc<br>Hb-target: 13-15 g/dL<br>duration: 12 weeks |
| Outcomes | primary: cognitive function, fatigue<br>secondary: QoL |
| Notes | full text publication, additional unpublished data were obtained for an individual patient data meta-analysis study (Bohlius et al 2009, study number = 40730) |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | yes - computer generated |
| Allocation concealment (selection bias) | Low risk | yes - coded drug packs of identical appearance |

**O'Shaugnessy 2005 IPD**

| | |
|---|---|
| Methods | see O'Shaughnessy 2005 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | study number = 40730 |

**OBE/EPO-INT-03 IPD**

| | |
|---|---|
| Methods | randomised controlled trial, not placebo-controlled |
| Participants | N = 72, randomised: ESA = 35, control = 37<br>disease: MM<br>treatment: chemotherapy, assumed to be without platinum because of hematological disease<br>baseline Hb: not reported, unclear |
| Interventions | drug: Epoetin alpha<br>dose: 40'000 IU sc weekly<br>Hb-target: 12-13 g/dL<br>duration: during chemotherapy |

**OBE/EPO-INT-03 IPD** (*Continued*)

| | |
|---|---|
| Outcomes | primary: Hb change<br>secondary: QoL, Hb response, transfusion, safety |
| Notes | unpublished data were obtained for an individual patient data meta-analysis study (Bohlius et al 2009, study number = 92503) |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | unclear - no description |
| Allocation concealment (selection bias) | Low risk | yes - central randomisation |

**Oberhoff 1998**

| | |
|---|---|
| Methods | randomised controlled trial, not placebo-controlled |
| Participants | N = 218, randomised: ESA = 114, control = 104<br>disease: ovarian, breast, lung, genitourinary, gastrointestinal, other cancer<br>treatment: platinum containing chemotherapy<br>baseline Hb: ESA arm 9.6 g/dL, control 10.3 g/dL, categorised as < 10 g/dL |
| Interventions | drug: Epoetin beta<br>dose: 5000U daily s.c.<br>Hb-target: 14 g/dL<br>duration: 12 weeks |
| Outcomes | primary: transfusion<br>secondary: haematologic response, Hb response, safety |
| Notes | full text publication, additional unpublished data were obtained for the first Cochrane review (1985-2001) and an individual patient data meta-analysis study (Bohlius et al 2009, study number = 45434) |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | unclear - no description |
| Allocation concealment (selection bias) | Low risk | yes - central randomisation |

**Oberhoff 1998 IPD**

| | |
|---|---|
| Methods | see Oberhoff 1998 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | study number = 45434 |

**Osterborg 1996**

| | |
|---|---|
| Methods | randomised controlled trial, not placebo-controlled |
| Participants | N = 144, randomised: ESA 1 = 47, ESA 2 = 48, control = 49<br>disease: MM, NHL, chronic lymphocytic lymphoma<br>treatment: chemotherapy, non-platinum containing<br>baseline Hb: 8.8 g/dL |
| Interventions | drug: Epoetin beta<br>dose: a: 10000 IU sc 7x/week, b: 2.000U daily s.c.; increased to 5.000U and 10.000U daily if no response<br>Hb-target: 12-13 g/dL (women), 13-14 g/dL (men)<br>duration: 24 weeks |
| Outcomes | primary: transfusion<br>secondary: safety, Hb, haematologic response |
| Notes | full text publication, additional unpublished data were obtained for the first Cochrane review (1985-2001) and an individual patient data meta-analysis study (Bohlius et al 2009, study number = 43680) |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | unclear - no description |
| Allocation concealment (selection bias) | Low risk | yes - central randomisation |

**Osterborg 1996 IPD**

| | |
|---|---|
| Methods | see Osterborg 1996 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | study number = 43680 |

**Osterborg 1996a**

| | |
|---|---|
| Methods | see Osterborg 1996 |
| Participants | |
| Interventions | dose a: 10'000 daily sc |
| Outcomes | |
| Notes | |

**Osterborg 1996b**

| | |
|---|---|
| Methods | see Osterborg 1996 |
| Participants | |
| Interventions | dose b: 2.000U daily s.c.; increased to 5.000U and 10.000U daily if no response |
| Outcomes | |
| Notes | |

**Osterborg 2002**

| | |
|---|---|
| Methods | randomised controlled trial, placebo-controlled |
| Participants | N = 349, randomised: ESA = 173, control = 176<br>disease: MM, NHL, CLL;<br>treatment: chemotherapy, assumed without platinum because of hematological disease<br>baseline Hb: 9.3 10g/dL |
| Interventions | drug: Epoetin beta<br>dose: 150U/kg 3x/week s.c.<br>Hb-target = 13-14 g/dL<br>duration: 16 weeks |

**Osterborg 2002** (*Continued*)

| | |
|---|---|
| Outcomes | primary: transfusion free survival<br>secondary: haematologic response, Hb change, time to response, number of blood transfusions, QoL, safety |
| Notes | full text publication, additional unpublished data were obtained for the first Cochrane review and an individual patient data meta-analysis study (Bohlius et al 2009, study number = 77914) |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | unclear - randomisation program |
| Allocation concealment (selection bias) | Low risk | yes - central randomisation |

**Osterborg 2002 IPD**

| | |
|---|---|
| Methods | see Osterborg 2002 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | study number = 77914 |

**Overgaard 2009**

| | |
|---|---|
| Methods | randomised controlled trial, not placebo-controlled |
| Participants | N = 515, randomised: ESA = 255, control = 260<br>disease: head and neck cancer<br>treatment: radiotherapy<br>baseline Hb: approximately 13 g/dL |
| Interventions | drug: darbepoetin<br>dose: 150 mg sc weekly<br>Hb target: > 15.5 g/dL<br>duration: 8 to 10 weeks |
| Outcomes | OS, DS, tumour control, adverse events |
| Notes | abstract publication, study number = 62913 |

**Overgaard 2009** (*Continued*)

| *Risk of bias* | | |
|---|---|---|
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Unclear risk | not reported |
| Allocation concealment (selection bias) | Low risk | central allocation method |

**P-174 IPD**

| | |
|---|---|
| Methods | see P-174 J&J 2004 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | |

**P-174 J&J 2004**

| | |
|---|---|
| Methods | randomised controlled trial, placebo-controlled |
| Participants | N = 45, randomised: ESA = 33, control = 12<br>disease: CLL (any stage)<br>treatment: NR 'other'<br>baseline Hb category: not reported, unclear |
| Interventions | drug: Epoetin alpha<br>dose: 150 IU/kg tiw sc<br>Hct-target: 38% to 40%<br>duration 12 weeks |
| Outcomes | primary: Hct<br>secondary: Hb, transfusion, QoL, safety |
| Notes | data presented by J&J at FDA/ODAC hearing in May 2004, additional unpublished data were obtained for an individual patient data meta-analysis (Bohlius et al, 2009 study number = 60584) |

| *Risk of bias* | | |
|---|---|---|
| **Bias** | **Authors' judgement** | **Support for judgement** |

| | | |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | yes - computer-generated |
| Allocation concealment (selection bias) | Unclear risk | unclear - no description |

**Pirker 2008**

| | |
|---|---|
| Methods | randomised controlled trial, placebo-controlled |
| Participants | N = 600, randomised: ESA = 299, control = 301<br>disease: SCLC (untreated, extensive stage)<br>treatment: platinum-containing chemotherapy<br>baseline Hb: 11.9 g/dL, ESA arm 12.03 g/dL, control 11.86 g/dL, categorised as 10-12 g/dL |
| Interventions | drug: Darbepoetin alpha<br>dose: 300 µg sc weekly for weeks 1-4 then 300 µg Q3W starting week 5 onwards<br>Hb-target: 13-14 g/dL<br>duration: 19 weeks |
| Outcomes | primary: Hb change, survival<br>secondary: QoL, progression-free-survival, tumour response, time to progression, transfusion |
| Notes | full text publication, additional unpublished data were obtained for an individual patient data meta-analysis study (Bohlius et al 2009, study number = 89335) |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | unclear - no description |
| Allocation concealment (selection bias) | Low risk | yes - central randomisation |

**Pirker 2008 IPD**

| | |
|---|---|
| Methods | see Pirker 2008 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | |

**Pronzato 2010**

| | |
|---|---|
| Methods | randomised controlled trial, not placebo-controlled |
| Participants | N = 223, randomised ESA=110, control =113<br>disease: breast cancer (stage I-IV)<br>treatment: chemotherapy<br>baseline Hb: 10.7 g/dL |
| Interventions | drug: epoetin alpha<br>dose: if body weight >45kg 10,000 IU sc TIW, if body weight <45kg 5,000 IU sc TIW<br>Hb target: 12-14 g/dL<br>duration: categorized: >20 weeks |
| Outcomes | Primary: QoL (anaemia)<br>Secondary: hematological response, other QoL, tumour response, OS, number of patients transfuse |
| Notes | Full-text publication, unpublished data were obtained for an individual patient data meta-analysis study (Bohlius et al 2009, study number = 22233) |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | unclear - no description |
| Allocation concealment (selection bias) | Low risk | yes - central randomisation |

**Pronzato 2010 IPD**

| | |
|---|---|
| Methods | see Pronzato 2010 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | |

**Quirt 1996**

| | |
|---|---|
| Methods | randomised controlled trial, placebo-controlled |
| Participants | N = 56, randomised: ESA = 28, control = 28<br>disease: lung, gynaecological, hematological malignancies, other cancer<br>treatment: chemotherapy<br>baseline Hb: 10.8 g/dL |

**Quirt 1996** (*Continued*)

| | |
|---|---|
| Interventions | drug: Epoetin alpha<br>dose: 150U/kg 3x/week s.c<br>Hb-target: 12.5-14 g/dL<br>duration: 16 weeks |
| Outcomes | primary: transfusion, Hb change<br>secondary: QoL, costs from societal perspective, tumour response |
| Notes | abstract publication, additional unpublished data were obtained for an individual patient data meta-analysis study (Bohlius et al 2009, study number = 80214) |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | unclear - no description |
| Allocation concealment (selection bias) | Unclear risk | unclear - no description |

**Quirt 1996 IPD**

| | |
|---|---|
| Methods | see Quirt 1996 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | study number = 80214 |

**Ray-Coquard 2009**

| | |
|---|---|
| Methods | randomised controlled trial, not placebo-controlled |
| Participants | N = 218, randomised: ESA = 110, control = 108<br>disease: breast, sarcoma, lung, ovarian, other solid cancer and hematological malignancies<br>treatment: chemotherapy (IPD) full text: NR<br>baseline Hb: 10.0 g/dL, categorised as 10-12 g/dL |
| Interventions | drug: Epoetin alpha<br>dose: if body weight < 45 kg 10000 IU sc 2x/week, if body weight 45 kg to < 89 kg 10000 IU sc TIW, if body weight > 89 kg 10000 IU sc 4x/week<br>Hb-target: 12-14 g/dL<br>planned ESA duration: 12 weeks |

**Ray-Coquard 2009** (*Continued*)

| | |
|---|---|
| Outcomes | primary: transfusion dependent anaemia<br>secondary: QoL, Hb response predictors, Hb, toxicity, survival, costs |
| Notes | full text publication, additional unpublished data were obtained for an individual patient data meta-analysis study (Bohlius et al 2009, study number = 37491) |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | yes |
| Allocation concealment (selection bias) | Low risk | yes |

**Ray-Coquard 2009 IPD**

| | |
|---|---|
| Methods | see Ray-Coquard 2009 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | abstract publication, IPD data |

**Razzouk 2004**

| | |
|---|---|
| Methods | see Razzouk 2006 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | |

**Razzouk 2006**

| | |
|---|---|
| Methods | randomised controlled trial, placebo-controlled |
| Participants | N = 224, randomised ESA: 112, Control: 112<br>disease: solid tumours, HD, NHL, ALL<br>treatment: chemotherapy<br>baseline Hb: 9.7 g/dL |

**Razzouk 2006** (*Continued*)

| | |
|---|---|
| Interventions | drug: epoetin alpha<br>dose: 600 IU/kg iv weekly<br>Hb target: 13-15 g/dL (age >12 years), 13-14 g/dL (age<12 years)<br>duration: 16 weeks |
| Outcomes | primary: QoL<br>secondary: Hb, transfusion |
| Notes | Full-text publication, additional unpublished data were obtained for an Individual Patient Data meta-analysis study (Bohlius et al 2009). Study number: 80515 |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | yes- computer generated |
| Allocation concealment (selection bias) | Low risk | yes- central randomisation and coded drug packages of identical appearance |

**Rose 1994**

| | |
|---|---|
| Methods | randomised controlled trial, placebo-controlled |
| Participants | N = 221, ESA = 142, control = 79<br>disease: CLL (stage III, IV)<br>treatment: chemo- and radiotherapy, without platinum<br>baseline Hb: 9.2 g/dL |
| Interventions | drug: Epoetin alpha<br>dose: 150U/kg 3x/week s.c.<br>Hb target: Hct 38%-40%<br>duration: 12 weeks |
| Outcomes | primary: Hct, haematologic response<br>secondary: transfusion, safety, QoL |
| Notes | Abstract publication, additional unpublished data were obtained for the this Cochrane review and an individual patient data meta-analysis study (Bohlius et al 2009, study number = 98358) |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|

| | | |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | yes - computer-generated |
| Allocation concealment (selection bias) | Unclear risk | unclear - no description |

**Rose 1994 IPD**

| | |
|---|---|
| Methods | see Rose 1994 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | study number = 98358 |

**Rose 1994 J&J 2004**

| | |
|---|---|
| Methods | see Rose 1994 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | Data presented by J&J at FDA/ODAC hearing in May 2004 |

**Rosen 2003**

| | |
|---|---|
| Methods | randomised controlled trial, not placebo-controlled |
| Participants | N = 90, randomised: ESA = 47, control = 43<br>disease: head and neck cancer<br>treatment: radiation therapy and non platinum-containing chemotherapy<br>baseline Hb: 12.2 g/dL at baseline |
| Interventions | drug: Epo<br>dose: 40'000 IU per week<br>Hb-target: NR<br>duration: 14 weeks |
| Outcomes | primary: response rate, toxicity, disease free and overall survival<br>secondary: response to Epo treatment |
| Notes | full text publication, was excluded in the IPD review: n = 90, study number = 72003 |

**Rosen 2003** (*Continued*)

| ***Risk of bias*** | | |
|---|---|---|
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Unclear risk | unclear |
| Allocation concealment (selection bias) | Unclear risk | unclear |

**Rosenzweig 2004**

| | |
|---|---|
| Methods | randomised controlled trial, not placebo-controlled |
| Participants | N = 27, randomised: ESA = 14, control = 13<br>disease: metastatic breast cancer<br>treatment: less than 50% of participants received chemotherapy, some received hormones, categorised as other<br>baseline Hb: not reported, eligibility criterion Hb < 12 g/dL, categorised as Hb 10-12 g/dL |
| Interventions | drug: Epoetin alpha<br>dose: 40,000 IU qw sc<br>Hb target: NR<br>duration: 12 weeks |
| Outcomes | primary: fatigue, QoL |
| Notes | full text publication, study number = 76065 |

| ***Risk of bias*** | | |
|---|---|---|
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Unclear risk | unclear |
| Allocation concealment (selection bias) | Low risk | Yes - using sequential, opaque, sealed envelopes with the order unknown to the investigators |

**Savonije 2005**

| | |
|---|---|
| Methods | randomised controlled trial, not placebo-controlled |
| Participants | N = 315, randomised: ESA = 211, control = 104<br>disease: NSCLC, gastrointestinal, gynaecological, colorectal, SCLC, other cancer<br>treatment: platinum based chemotherapy<br>baseline Hb: 10.7 g/dL |
| Interventions | drug: Epoetin alpha<br>dose: 10'000 IU sc TIW sc<br>Hb-target: 13-14 g/dL<br>duration: 14 weeks |
| Outcomes | primary: transfusion<br>secondary: Hb, tumour response, QoL, survival |
| Notes | full text publication, additional unpublished data were obtained for an individual patient data meta-analysis study (Bohlius et al 2009, study number = 70724) |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | unclear - randomisation centre generates a list of subject numbers and randomly allocate numbers to the two treatment groups using a block size of six |
| Allocation concealment (selection bias) | Low risk | Yes - central randomisation |

**Savonije 2005 IPD**

| | |
|---|---|
| Methods | see Savonije 2005 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | study number = 70724 |

**Silvestris 1995**

| | |
|---|---|
| Methods | randomised controlled trial, not placebo-controlled |
| Participants | N = 54, randomised: ESA = 30, control = 24<br>disease: MM<br>treatment: chemotherapy without platinum<br>baseline Hb: <=8 g/dL |
| Interventions | drug: Epoetin alpha<br>dose: 150U/kg 3x/week s.c.<br>Hb target: no target defined<br>duration: 24 weeks |
| Outcomes | haematologic response, adverse events |
| Notes | full text publication, study number = 76441 |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | unclear |
| Allocation concealment (selection bias) | Unclear risk | unclear |

**Smith 2003**

| | |
|---|---|
| Methods | randomised controlled trial, placebo-controlled |
| Participants | N = 86, randomised: ESA = 64, control = 22<br>disease: genitourinary, breast, gastrointestinal, lymphoma: myeloma, CLL, NHL<br>treatment: none<br>baseline Hb: 9.995; <10 g/dL for two groups and 10-12 g/dL for the other two, categorized as <10 g/dL |
| Interventions | drug: Darbepoetin alpha<br>dose: see below<br>Hb target: 13-14 g/L (women), 13-15 (men) g/dL<br>duration: 12 weeks |
| Outcomes | primary: haematopoietic response<br>secondary: time to response, Hb response, Hb change, transfusions, serum darbepoetin conc. in a subset of patients |
| Notes | full text publication, study number = 76561 |

***Risk of bias***

**Smith 2003** (*Continued*)

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | unclear |
| Allocation concealment (selection bias) | Unclear risk | unclear |

**Smith 2003 Amgen 2007**

| | |
|---|---|
| Methods | see Smith 2003 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | |

**Smith 2003a**

| | |
|---|---|
| Methods | See Smith 2003 |
| Participants | |
| Interventions | dose a: 6.75 µg/kg Q3W sc |
| Outcomes | |
| Notes | |

**Smith 2003b**

| | |
|---|---|
| Methods | See Smith 2003 |
| Participants | |
| Interventions | dose b: 6.75 µg/kg Q4W sc |
| Outcomes | |
| Notes | |

**Smith 2003c**

| | |
|---|---|
| Methods | See Smith 2003 |
| Participants | |
| Interventions | dose c: 10 µg/kg Q4W sc |
| Outcomes | |
| Notes | |

**Smith 2008**

| | |
|---|---|
| Methods | randomised controlled trial, placebo-controlled |
| Participants | N = 989, randomised: ESA = 517, control = 472<br>disease: lung, hematological malignancies, breast, gastrointestinal, genitourinary, other cancer (stage III-IV)<br>treatment: none<br>baseline Hb: 9.5 g/dL |
| Interventions | drug: Darbepoetin alpha<br>dose: 6.75 µg/kg sc Q4W<br>Hb-target: 12-13 g/dL<br>duration: 16 weeks |
| Outcomes | primary: transfusion<br>secondary: Hb, QoL, safety |
| Notes | full text publication, additional unpublished data were obtained for an individual patient data meta-analysis study (Bohlius et al 2009, study number = 81215) |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | unclear |
| Allocation concealment (selection bias) | Low risk | Yes, adequate |

**Smith 2008 IPD**

| | |
|---|---|
| Methods | see Smith 2008 |
| Participants | |
| Interventions | |

| | |
|---|---|
| Outcomes | |
| Notes | |

**Strauss 2008**

| | |
|---|---|
| Methods | randomised controlled trial, not placebo-controlled |
| Participants | n = 74, randomised: ESA = 34, control = 40<br>disease: cervical cancer (stage IIB-IVA)<br>treatment: radio- and platinum-containing chemotherapy<br>baseline Hb: 11.5 g/dL |
| Interventions | drug: Epoetin beta<br>dose: 150 IU/kg sc TIW<br>Hb-target: 14-15 g/dL<br>duration: 12 weeks |
| Outcomes | primary: tumour control failures<br>secondary: progression-free survival, overall response rate, relapses/metastases, overall survival, Hb change, QoL, safety |
| Notes | full text publication, additional unpublished data were obtained for an individual patient data meta-analysis study (Bohlius et al 2009, study number = 70404) |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | unclear - patient randomisation number were generated without reporting the method |
| Allocation concealment (selection bias) | Unclear risk | unclear - patient randomisation numbers were to be allocated sequentially in the order in which the patients are enrolled |

**Strauss 2008 IPD**

| | |
|---|---|
| Methods | see Strauss 2008 |
| Participants | |
| Interventions | |
| Outcomes | |

| | |
|---|---|
| Notes | |

**Suzuki 2008**

| | |
|---|---|
| Methods | randomised controlled trial, placebo-controlled |
| Participants | N=123: ESA: 81, control=42<br>disease: lymphoma, breast cancer<br>treatment: chemotherapy<br>baseline Hb: not reported, eligibility criterion Hb <= 11 g/dL, after amendment <= 10 g/dL, categorized as Hb 10-12 g/dL |
| Interventions | drug: darbepoetin alpha<br>dose: a) 4.5 ug/kg sc Q3W or b) 6.75 ug/kg sc Q3W<br>Hb target: <=13.0 g/dL, amended to <=12.0 g/dL<br>duration: 12 weeks |
| Outcomes | Hb response, safety, QoL, survival |
| Notes | abstract publication, study id: 14688 |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | unclear, not reported |
| Allocation concealment (selection bias) | Unclear risk | unclear, not reported |

**Suzuki 2008a**

| | |
|---|---|
| Methods | see Suzuki 2008 |
| Participants | darbepoetin: 40, placebo: 42 |
| Interventions | darbepoetin 4.5 ug/kg sc Q3W vs placebo |
| Outcomes | |
| Notes | |

**Suzuki 2008b**

| | |
|---|---|
| Methods | see Suzuki 2008 |
| Participants | darbepoetin: 41, placebo: 42 |
| Interventions | darbepoetin 6.75 ug/kg sc Q3W vs placebo |
| Outcomes | |
| Notes | |

**Sweeney 1998**

| | |
|---|---|
| Methods | randomised controlled trial, not placebo-controlled |
| Participants | N = 48, randomised: ESA = 24, control = 24<br>disease: breast, lung, prostate and cervix cancer<br>treatment: chemotherapy for 5 patients, radiotherapy for probably all of the patients<br>baseline Hb: ESA arm 12.07, control: 10.72 g/dL, categorized as 10-12 g/dL |
| Interventions | drug: Epoetin alfa<br>dose: 200 IU/kg/d<br>Hb target: 14 g/dL for women and 15 g/dL for men<br>duration: 7 weeks |
| Outcomes | Hb, total white blood cell count and platelets, QoL |
| Notes | full text publication, excluded for IPD-Review, study number = 77932 |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | computer-generated random numbers in blocks of 10 |
| Allocation concealment (selection bias) | Unclear risk | not reported, unclear |

**Ten Bokkel 1998**

| | |
|---|---|
| Methods | randomised controlled trial, not placebo-controlled |
| Participants | N = 122, randomised: ESA = 88, control = 34<br>disease: ovarian carcinoma (stage II-IV)<br>treatment: platinum-based chemotherapy<br>baseline Hb: 11.6 g/dL |

**Ten Bokkel 1998** (*Continued*)

| | |
|---|---|
| Interventions | drug: Epoetin beta<br>dose: a: 150 IU/kg sc TIW, b: 300 IU/kg sc TIW<br>Hb-target: 14-15 g/dL<br>duration = during chemotherapy, 24 weeks |
| Outcomes | primary: transfusion<br>secondary: Hb, reticulocytes, Hct, safety, tumour response, adverse events |
| Notes | full text publication, additional unpublished data were obtained for the first Cochrane review (1985-2001) and an individual patient data meta-analysis study (Bohlius et al 2009, study number = 47852) |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | unclear - no description |
| Allocation concealment (selection bias) | Low risk | yes - central randomisation |

**Ten Bokkel 1998a**

| | |
|---|---|
| Methods | see Ten Bokkel 1998 |
| Participants | Epoetin a: N = 45 |
| Interventions | dose a: 150U/kg 3x/week s.c. |
| Outcomes | |
| Notes | |

**Ten Bokkel 1998b**

| | |
|---|---|
| Methods | see Ten Bokkel 1998 |
| Participants | Epoetin 2: N = 42 |
| Interventions | dose b: 300U/kg 3x/week s.c. |
| Outcomes | |
| Notes | |

**Ten Bokkel1998 IPD**

| | |
|---|---|
| Methods | see Ten Bokkel 1998 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | study number = 47852 |

**Thatcher 1999**

| | |
|---|---|
| Methods | randomised controlled trial, not placebo-controlled |
| Participants | N = 130, randomised: ESA = 86, control = 44<br>disease: SCLC<br>treatment: platinum based chemotherapy<br>baseline Hb: 13.4 g/dL |
| Interventions | drug: Epoetin alpha<br>dose: ESA a: 150 IU/kg sc TIW; ESAb: 300 IU/kg sc TIW<br>Hb-target: 13-15 g/dL<br>duration: 26 weeks |
| Outcomes | change in Hb values, transfusion requirement, QoL, adverse events |
| Notes | full text publication, additional unpublished data were obtained for the first Cochrane review (1985-2001) and an individual patient data meta-analysis study (Bohlius et al 2009, study number = 65529) |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | unclear - upon study entry each patient was assigned a sequential identification number which had been randomly assigned to chemotherapy with or without ESA, blocks of 6, each investigator had to treat at least 6 patients, but preferably 12 patients |
| Allocation concealment (selection bias) | Unclear risk | unclear - see randomisation |

**Thatcher 1999 IPD**

| | |
|---|---|
| Methods | see Thatcher 1999 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | study number = 65529 |

**Thatcher 1999a**

| | |
|---|---|
| Methods | See Thatcher 1999 |
| Participants | Epoetin a: n = 42 |
| Interventions | Epoetin alpha a: 150U/kg 3x/week s.c. |
| Outcomes | |
| Notes | |

**Thatcher 1999b**

| | |
|---|---|
| Methods | See Thatcher 1999 |
| Participants | Epoetin b: N = 44 |
| Interventions | Epoetin alpha b: 300U/kg 3x/week s.c. |
| Outcomes | |
| Notes | |

**Thomas 2002**

| | |
|---|---|
| Methods | randomised controlled trial, not placebo-controlled |
| Participants | N = 130, randomised: ESA = 65, control = 65<br>disease: breast, gastrointestinal, gynaecological, other cancer<br>treatment: chemotherapy<br>baseline Hb: 10.6 g/dL |
| Interventions | drug: Epoetin alpha<br>dose: if body weight > 45 kg 10000 IU sc TIW, if body weight < 45 kg 5000 IU sc TIW<br>Hb-target: 12-14 g/dL<br>duration: 12 weeks |

**Thomas 2002** (*Continued*)

| | |
|---|---|
| Outcomes | Hb, QoL, transfusions |
| Notes | abstract publication, additional unpublished data were obtained for an individual patient data meta-analysis study (Bohlius et al 2009, study number = 84090) |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | unclear - no description |
| Allocation concealment (selection bias) | Low risk | yes - central randomisation |

**Thomas 2002 IPD**

| | |
|---|---|
| Methods | see Thomas 2002 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | study number = 84090 |

**Thomas 2008**

| | |
|---|---|
| Methods | randomised controlled trial, not placebo-controlled |
| Participants | N = 114 (from IPD), full-text: accrued: 114, 5 found subsequently not eligible randomised: ESA = 57, control = 52; planned were 460, vs IPD, vs 2006<br>disease: cervical cancer (stage IIB - IV A, M0)<br>treatment: platinum-based chemotherapy plus radiotherapy<br>baseline Hb: 10.7 g/dL |
| Interventions | drug: Epoetin alpha<br>dose: 40000 IU sc weekly<br>Hb-target: 13-14 g/dL<br>duration: 8 weeks max, categorised as 6-9 weeks |
| Outcomes | primary: progression-free survival<br>secondary: OS, local control, distant recurrences, thromboembolic events |
| Notes | full text publication, additional unpublished data were obtained for an individual patient data meta-analysis study (Bohlius et al 2009, study number = 21481) |

| *Risk of bias* | | |
|---|---|---|
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Unclear risk | unclear - no description "eligible patients were randomised..." |
| Allocation concealment (selection bias) | Low risk | yes - central randomisation |

**Thomas 2008 IPD**

| | |
|---|---|
| Methods | see Thomas 2008 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | |

**Thomas 2008 J&J 2004**

| | |
|---|---|
| Methods | see Thomas 2008 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | |

**Thompson 2000**

| | |
|---|---|
| Methods | randomised controlled trial, placebo-controlled |
| Participants | N = 66, randomised: ESA = 45, control = 21<br>disease: Myelodysplastic Syndromes<br>treatment: no chemotherapy, GM-CSF 0.3-5.0 mg/kg daily in both groups<br>mean/median baseline Hb: 9 g/dL |
| Interventions | drug: Epoetin alpha<br>dose: 150U/kg 3x/week s.c. +<br>Hb target: 12 - 13 g/dL<br>duration: 12 weeks |

**Thompson 2000** (*Continued*)

| | |
|---|---|
| Outcomes | haematologic response, change in Hb values, transfusion requirement, adverse events |
| Notes | full text publication, additional unpublished data were obtained for the first Cochrane review (1985-2001), study number = 82687 |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Yes - computer random-number generator |
| Allocation concealment (selection bias) | Low risk | Yes - adequate |

**Throuvalas 2000**

| | |
|---|---|
| Methods | randomised controlled trial, not placebo-controlled |
| Participants | N = 55, randomised: ESA = 28, control = 27<br>disease: cervix and bladder carcinoma<br>treatment: platinum-based radiochemotherapy<br>baseline Hb: 11.3 g/dL |
| Interventions | drug: Epoetin (?)<br>dose: 10,000U 5x/week s.c.<br>Hb target: NR<br>duration: 6 weeks |
| Outcomes | change in Hb values, transfusion requirement, tumour response |
| Notes | abstract publication, additional unpublished data were obtained for the first Cochrane review (1985-2001), study number = 83700 |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | yes - random-number generator |
| Allocation concealment (selection bias) | Low risk | yes - central allocation |

**Tjulandin 2010**

| | |
|---|---|
| Methods | randomised controlled trial, placebo-controlled |
| Participants | N = 223, randomised: Epo theta = 76, Epo beta = 73, control = 74<br>disease: ovarian cancer, gastric cancer, breast cancer, lung cancer. other solid cancers<br>treatment: platinum-based chemotherapy<br>baseline Hb: 9.5 g/dL |
| Interventions | drug a): Epoetin theta, dose: 20'000 IU weekly<br>drug b): Epoetin beta, dose: 150 IU/kg sc TIW<br>Hb-target: 13 g/dL<br>duration: 12 weeks |
| Outcomes | primary: haematological response<br>secondary: partial Hb response, RBCTs, number of bloods units transfused, safety, QoL |
| Notes | full-text publication, study number = 19632 |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | computer-generated allocation schedule |
| Allocation concealment (selection bias) | Unclear risk | not reported |

**Tjulandin 2010a**

| | |
|---|---|
| Methods | see Tjulandin 2010 |
| Participants | |
| Interventions | Epoetin theta, dose: 20'000 IU weekly |
| Outcomes | |
| Notes | |

**Tjulandin 2010b**

| | |
|---|---|
| Methods | see Tjulandin 2010 |
| Participants | |
| Interventions | Epoetin beta, dose: 150 IU/kg sc TIW |
| Outcomes | |

**Tjulandin 2010b** (*Continued*)

| | |
|---|---|
| Notes | |

**Tjulandin 2011**

| | |
|---|---|
| Methods | randomised controlled trial, placebo-controlled |
| Participants | N = 186, randomised: ESA = 95, control = 91<br>disease: hematological, breast and gastric cancer<br>treatment: chemotherapy without platinum<br>baseline Hb: 9.2 g/dL |
| Interventions | drug: Epoetin theta<br>dose: 20'000 IU weekly<br>Hb-target: 13 g/dL<br>duration: 12 weeks |
| Outcomes | primary: haematological response<br>secondary: partial Hb response, RBCTs, number of bloods units transfused, safety, QoL |
| Notes | full-text publication, study number = 18036 |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | computer-generated |
| Allocation concealment (selection bias) | Unclear risk | not reported |

**Tsuboi 2009**

| | |
|---|---|
| Methods | randomised controlled trial, placebo-controlled |
| Participants | N = 122, randomised: ESA = 63, control = 59<br>disease: lung cancer, malignant lymphoma (HL and NHL)<br>treatment: chemotherapy, both platinum and non-platinum containing, no numbers given<br>baseline Hb: 10.2 g/dL |
| Interventions | drug: Epoetin beta<br>dose: 36'000 IU sc weekly<br>Hb target: >= 14 g/dL<br>duration: 8 weeks |
| Outcomes | primary: Hb change<br>secondary: hematological response, transfusions, Hb, QoL, (survival, cave: retrospective) |

**Tsuboi 2009** (*Continued*)

| | |
|---|---|
| Notes | full text publication, abstract Watanabe 2006 was excluded for the IPD-Review, study number = 92759 |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | unclear |
| Allocation concealment (selection bias) | Low risk | yes - central randomisation system |

**Untch 2008 IPD**

| | |
|---|---|
| Methods | see Untch 2011˙1 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | |

**Untch 2011˙1**

| | |
|---|---|
| Methods | randomised controlled trial, not placebo-controlled |
| Participants | N = 733, randomised: ESA = 356, control = 377<br>disease: breast cancer (M0)<br>treatment: non platinum-containing chemotherapy<br>baseline Hb: 13.6 g/dL |
| Interventions | drug: Darbepoetin alpha<br>dose: 4.5 µg/kg sc Q2W<br>Hb-target: 12.5-13 g/dL<br>duration: during chemotherapy, approximately > 20 weeks |
| Outcomes | primary: relapse free survival time, OS<br>secondary: tumour control, safety and tolerability, transfusion, Hb level, QoL |
| Notes | two full text publications, in addition unpublished data were obtained for the individual patient data meta-analysis study (Bohlius et al 2009, study number = 66960) |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|

**Untch 2011˙1** (*Continued*)

| | | |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | unclear - no description |
| Allocation concealment (selection bias) | Unclear risk | unclear - description is unclear |

**Untch 2011˙2**

| | |
|---|---|
| Methods | see Untch 2011˙1 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | |

**Vansteenkiste 02 FDA 2004**

| | |
|---|---|
| Methods | see Vansteenkiste 2002 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | |

**Vansteenkiste 2002**

| | |
|---|---|
| Methods | randomised controlled trial, placebo-controlled |
| Participants | N = 320, randomised: ESA = 159, control = 161<br>disease: SCLC (limited and extensive), and NSCLC (stage I-IV)<br>treatment: platinum based chemotherapy<br>baseline Hb: 10.1 g/dL |
| Interventions | drug: Darbepoetin alpha<br>dose: 2.25 mg/kg sc weekly<br>Hb-target: 13-14 g/dL (women), 13-15 g/dL (men)<br>duration: 12 weeks |
| Outcomes | primary: transfusion<br>secondary: Hb response, Hb, transfusion timing and quantity, QoL |

**Vansteenkiste 2002** (*Continued*)

| | |
|---|---|
| Notes | full text publication, additional unpublished data were obtained for and an individual patient data meta-analysis study (Bohlius et al 2009, study number = 49684) |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | unclear - based on a schedule specified by Amgen before the start of the study |
| Allocation concealment (selection bias) | Low risk | yes - central randomisation |

**Vansteenkiste 2002 IPD**

| | |
|---|---|
| Methods | see Vansteenkiste 2002 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | study number = 49684 |

**Welch 1995**

| | |
|---|---|
| Methods | randomised controlled trial, not placebo-controlled |
| Participants | N = 30, randomised: ESA = 15, control = 15<br>disease: ovarian carcinoma<br>treatment: platinum-containing chemotherapy<br>mean/median baseline Hb: 12.9 g/dL |
| Interventions | drug: Epoetin alpha<br>dose: 300U/kg 3x/week s.c.<br>Hb - target: 12-15 g/dL<br>duration: 24 weeks |
| Outcomes | change in Hb values, transfusion requirement, adverse events |
| Notes | full text publication, study number = 97952 |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|

| | | |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | unclear |
| Allocation concealment (selection bias) | Unclear risk | unclear |

**Wilkinson 2006**

| | |
|---|---|
| Methods | randomised controlled trial, not placebo-controlled |
| Participants | N = 182, randomised: ESA = 121; control = 61<br>disease: ovarian cancer (stage I-IV)<br>treatment: chemotherapy<br>baseline Hb: 10.7 g/dL |
| Interventions | drug: Epoetin alpha<br>dose: if body weight > 45 kg 10000 IU sc TIW, if < 45 kg 5000 IU sc TIW<br>Hb-target: 12-14 g/dL<br>duration: max. 28 weeks |
| Outcomes | primary: Hb response<br>secondary: QoL, transfusion, tumour response |
| Notes | full text publication, additional unpublished data were obtained for an individual patient data meta-analysis study (Bohlius et al 2009, study number = 75688) |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | unclear - a prospective randomisation procedure will be employed |
| Allocation concealment (selection bias) | Unclear risk | unclear - assigned envelopes, but it is unclear whether they were opaque and sequentially numbered |

**Wilkinson 2006 IPD**

| | |
|---|---|
| Methods | seeWilkinson 2006 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | |

**Winquist 2009**

| | |
|---|---|
| Methods | randomised controlled trial, placebo-controlled |
| Participants | N = 56, randomised ESA: 26, control = 30<br>disease: prostate cancer<br>treatment: unclear<br>Baseline Hb: 10.4 g/dL |
| Interventions | drug: epoetin alpha<br>dose: 40,000 IU sc 3 times /week<br>Hb target: 14.0 g/dL<br>duration: 16 weeks |
| Outcomes | primary: QoL<br>secondary: Hb level, RBCTs, adverse events, survival |
| Notes | letter publication, study number 13321 |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | not reported, unclear |
| Allocation concealment (selection bias) | Low risk | central telephone |

**Witzig 2005**

| | |
|---|---|
| Methods | randomised controlled trial, placebo-controlled |
| Participants | N = 344, randomised: ESA = 174, control = 170<br>disease: lung, breast, other cancer (active incurable advanced stage)<br>treatment: chemotherapy, platinum & non platinum<br>Hb category: 9.5 g/dL |
| Interventions | drug: Epoetin alpha<br>dose: 40000 IU sc weekly<br>Hb-target: 13-15 g/dL<br>planned ESA duration: 16 weeks |
| Outcomes | primary: transfusions<br>secondary: Hb change, Hb over time, predictors for response, incidence of nephrotoxicity, OS, tumour response, QoL |
| Notes | full text publication, additional unpublished data were obtained for an individual patient data meta-analysis study (Bohlius et al 2009, study number = 36512) |

***Risk of bias***

**Witzig 2005** (*Continued*)

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | yes - computer-generated |
| Allocation concealment (selection bias) | Low risk | yes - central randomisation and coded drug packs of identical appearance |

**Witzig 2005 IPD**

| | |
|---|---|
| Methods | see Witzig 2005 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | |

**Witzig 2005 J&J 2004**

| | |
|---|---|
| Methods | see Witzig 2005 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | Data presented by J&J at FDA/ODAC hearing in May 2004 |

**Wright 2007**

| | |
|---|---|
| Methods | randomised controlled trial, placebo-controlled |
| Participants | N = 70, randomised: ESA = 33, control = 37<br>disease: NSCLC (advanced stage IIIA, B and IV, recurrent disease)<br>treatment: no anticancer therapy<br>baseline Hb: 10.3 g/dL |
| Interventions | drug: Epoetin alpha<br>dose: 40'000 IU sc weekly<br>Hb-target: 12-14 g/dL<br>duration = 12 weeks |

| | |
|---|---|
| Outcomes | primary: QoL<br>secondary: Hb, Hct, transfusion, safety |
| Notes | full text publication, additional unpublished data were obtained for an individual patient data meta-analysis study (Bohlius et al 2009, study number = 53572) |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | yes - computer-generated |
| Allocation concealment (selection bias) | Low risk | yes - central randomisation |

**Wright 2007 IPD**

| | |
|---|---|
| Methods | see Wright 2007 |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | |

**Wurnig 1996**

| | |
|---|---|
| Methods | randomised controlled trial, placebo-controlled |
| Participants | N = 30, randomised: ESA = 16, control = 14<br>disease: Ewing's or osteosarcoma<br>treatment: chemotherapy, some platinum-based<br>mean/median baseline Hb: 10.8 g/dL |
| Interventions | drug: Epoetin beta<br>dose: 600U/kg 2x/week i.v.<br>Hb-target: 11-13.5 g/dL<br>duration: 20 weeks |
| Outcomes | change in Hb values, transfusion requirement, adverse events |
| Notes | full text publication, no IPD data, study number = 97958 |

***Risk of bias***

**Wurnig 1996** (*Continued*)

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Yes - computer-generated randomisation code |
| Allocation concealment (selection bias) | Unclear risk | Unclear |

CLL: Chronic lymphatic leukaemia
D: day
ESA: erythropoiesis stimulating agent
FDA: Food and Drug Administration, USA
G-CSF: Granulocyte colony-stimulating factor
Hb: Haemoglobin
Hct: haematocrit
HD: Hodgkin's Disease
IPD: individual patient data
i.v.: intravenous
J&J: Johnson & Johnson Pharmaceuticals Ltd.
MM: multiple myeloma
NHL: non-Hodgkin's lymphoma
NSCLC: non-small cell lung cancer
NR: not reported
ODAC: Oncology Drug Advisory Committee
OS: overall survival
QoL: Quality of Life
qw: once per week
Q3W: once every three weeks
Q4W: once every four weeks
RBC: red blood cell
s.c.: subcutaneous
SCLC: small cell lung cancer
tiw: three times per week
TR: Tumour response
wk: week
wks: weeks

## Characteristics of excluded studies *[ordered by study ID]*

| Study | Reason for exclusion |
|---|---|
| Aagaard 2010 | nrct |
| Aapro 2009 | nrct |

(*Continued*)

| | |
|---|---|
| Abdelrazik 2007 | ineligible patient characteristics: ALL |
| Abraham 2011 | nrct |
| Adamson 2009 | no RCT |
| Alexopoulos 2004 | randomised comparison of epoetin alfa 10,000 IU tiw versus darbepoetin alfa 150 mcg qw, n = 50 |
| Anonymous 2007 | no RCT |
| Anthony 2011 | all arms ESAs |
| Arcasoy 2010 | nrct |
| Arslan 2004 | randomised comparison of different usage strategies |
| Auerbach 2004 | randomised comparison of different iron applications |
| Australian 2010 | nrct |
| Aziz 2001 | treatment allocation not concealed<br>IPD: too small for inclusion |
| Barosi 1998 | nrct |
| Barosi 2011 | nrct |
| Beggs 2003 | randomised comparison of 40,000 IU epoetin alfa versus placebo, study too small for inclusion: n = 21 |
| Bell 2008 | no RCT |
| Bessho 1997 | ineligible patient characteristics: only patients with aplastic anaemia included, N = 131 |
| Bindi 2004 | unclear whether this a randomised controlled trial, authors have been unsuccesfully contacted<br>IPD: too small for inclusion |
| Blayney 2003 | study stated to be randomised, experimental arms received darbepoetin alfa, treatment in the control group not documented, authors were contacted for clarification without success, n = 1173 |
| Boccia 2007 | no RCT |
| Borg 2008 | no RCT |
| Borget 2008 | no RCT |
| Bowen 2004 | G-CSF only in one arm |
| Brower 2008 | nrct |

(*Continued*)

| | |
|---|---|
| Buchler 2011 | nrct |
| Buyukpamukcu 2002 | follow-up study to Varan 1999, does not satisfy allocation concealment requirement |
| Cabanillas 2012 | acute leukaemia |
| Candelaria 2005 | no ESA was given |
| Canon 2006 | compared different ESA dosages |
| Canon 2011 | retrospective analysis of dose-fidning study |
| Caravita 2009 | nrct |
| Casadevall 2004 | randomised controlled study in patients with MDS, comparing erythropoietin PLUS G-CSF versus supportive care without erythropoietin and without G-CSF |
| Cazzola 2003 | randomised comparison of once weekly 30,000 IU epoetin beta versus three times weekly 10,000 IU epoetin beta |
| Chan 1995 | very small trial, only 10 evaluable patients per study arm |
| Cheng 2009 | yixuesheng capsule with ESA vs ESA alone |
| Christodoulakis 2005 | ESAs were given in context with surgery |
| Coiffier 2006 | nrct |
| Coleman 2009 | not randomised for epo |
| Crawford 1997 | randomised-controlled trial, placebo controlled, double-blind, included 25 patients with SCLC, as no sufficient data were available the study was excluded |
| Crawford 2003 | randomised comparison of epootin alfa 40,000 IU per week versus control; patients in the control group received epoetin alfa when the Hb level decreased below 10g/dL, n = 216 |
| Crawford 2007 | ESAs were given in context with surgery, stem cell transplantation, compared different ESA dosages or ESA products (epoetin versus darbepoetin), or trials were not randomised |
| Cremieux 2003 | nrct |
| Dahl 2008 | nrct |
| Daneryd 1998 | epoetin only given to the anaemic patients in the treatment arm |
| Dannemann 2004 | compared different ESA dosages |
| Demetri 1998 | community based, non randomised study including 2,370 patients with nonmyeloid malignancies |

(*Continued*)

| | |
|---|---|
| Dicato 2011 | nrct |
| Dronca 2008 | nrct |
| Dusenbery 1994 | mixed concurrent and historical controls |
| Elsaid 2001 | n too small |
| Fagnoni 2005 | retrospective study design |
| Ferrero 2009 | no RCT |
| Franchi 2008 | no RCT, dose comparing |
| Freeman 2006 | too small for inclusion, n = 14 |
| Fujisaka 2004 | single arm study, no RCT |
| Gabrilove 2001 | community based, nonrandomised study including 3,012 participants with nonmyeloid malignancies |
| Garton 1995 | very small trial, only 10 evaluable patrticipants per study arm |
| Gascon 2008 | nrct |
| Gebbia 1992 | n = 19, too small for inclusion |
| Glaser 1999 | no RCT, 37 participants with advanced oral squamous carcinoma receiving neoadjuvant radiochemotherapy |
| Glaser 2001 | no RCT, 191 patients with advanced oral squamous carcinoma receiving neoadjuvant radiochemotherapy |
| Glaspy 1997 | community study |
| Glaspy 2001 | dose finding study, not randomised |
| Glaspy 2002 | darbepoetin versus erythropoietin, related to Glaspy 2002b |
| Glaspy 2002b | darbepoetin versus erythropoietin, related to Glaspy 2002 |
| Glaspy 2003 | darbepoetin versus erythropoietin |
| Glaspy 2005 | ESAs were given in context with surgery, stem cell transplantation, compared different ESA dosages or ESA products (epoetin versus darbepoetin), or trials were not randomised |
| Glaspy 2006 | ESAs were given in context with surgery, stem cell transplantation, compared different ESA dosages or ESA products (epoetin versus darbepoetin), or trials were not randomised |
| Glaspy 2011 | nrct |

(*Continued*)

| | |
|---|---|
| Glimelius 1998 | randomised study with two different EPO groups: 2.000 U sc three times per week versus 10.000 U sc tree times per week |
| Glossmann 2003 | randomised controlled comparison in patietns with relapsed lymphoma undergoing stem-cell supported high-dose therapy with or without erythropoietin |
| Goldsmith 2011 | nrct |
| Granetto 2003 | randomised comparison of fixed versus weight-based dosing of epoetin alfa |
| Gregory 2005 | nrct |
| Grigorescu 2006 | probably not randomised |
| Hadland 2009 | nrct |
| Han 2008 | randomised trial of amifostine vs epo |
| Harousseau 2005 | nrct |
| Hellström-Lindberg 1998 | G-CSF supplementation only in the control arm |
| Hellstörm-Lindberg 2010 | nrct |
| Henry 2004 | ESAs were given in context with surgery, stem cell transplantation, compared different ESA dosages or ESA products (epoetin versus darbepoetin), or trials were not randomised |
| Henry 2006 | ESAs were given in context with surgery, stem cell transplantation, compared different ESA dosages or ESA products (epoetin versus darbepoetin), or trials were not randomised |
| Henry 2007 | ESAs were given in context with surgery, stem cell transplantation, compared different ESA dosages or ESA products (epoetin versus darbepoetin), or trials were not randomised |
| Henze 2002 | surgery |
| Hesketh 2004 | comparison of different darbepo dosages |
| Hirsh 2007 | CERA |
| Huggett 2011 | not relevant (listed as ”other reasons“ in prisma”) |
| Hyer 2011 | nrct |
| Itzykson 2009 | case report, no RCT |
| Jacubowski 2003 | comparisons of epo versus darbepo, ongoing |

(*Continued*)

| | |
|---|---|
| Jadersten 2008 | nrct |
| Jitnuyanont 2001 | randomised comparison of erythropoietin versus control in 24 anaemic cancer patients, study was split into three arms with 10 and less patients per study arm |
| Johansson 2001 | randomised comparison of epeotin beta 1,000 IU versus 5,000 IU three times per week |
| Jones 2011 | nrct |
| Juan 2006 | no RCT |
| Justice 2005 | compared different ESA products (sc vs iv) |
| Kara 2008 | nrct |
| Katodritou 2008 | nrct |
| Katodritou 2009 | nrct |
| Kettelhack 1998 | ESAs were given in context with surgery |
| Kim 2010 | no cancer |
| Kosmadakis 2003 | ESAs were given in context with surgery |
| Kotasek 2004 | compared different ESA dosages |
| Kotasek 2007 | compared different ESA dosages |
| Larsson 2008 | n = 18, too small for inclusion |
| Lastiri 2002 | nrct |
| Latagliata 2008 | nrct |
| Lavey 1993 | nrct |
| Lavey 2004 | nrct |
| Leitgeb 1994 | nrct |
| Leon 1998 | historical control group |
| Lichtin 2008 | nrct |
| Loibl 2006 | all patients received ESAs |
| Ludwig 1995 | nrct |

(*Continued*)

| | |
|---|---|
| Malik 1998 | nrct, N = 23 |
| Mangiameli 2002 | randomised controlled study with 5 patients per study arm |
| Mantovani 2000 | nrct |
| Marinaccio 2003 | randomised comparison of epoetin alfa versus control for patients with ovarian cancer undergoing surgery and chemotherapy, epoetin was administered BEFORE surgery, n = 22 |
| Markman 1993 | comparison of two non-randomised trials |
| Mel 2008 | nrct |
| Merchionne 2009 | nrct |
| Merlano 2001 | ESAs were given in context with surgery, stem cell transplantation, compared different ESA dosages or ESA products (epoetin versus darbepoetin), or trials were not randomised |
| MF4266 | ineligible patient characteristics AML |
| Miller 2004 | unclear wether this is a randomised trial |
| Morishima 2006 | compared different ESA dosages |
| Morrow 2007 | nrct |
| Muravyov 2009 | single arm study without control group |
| Muravyov 2010 | nrct |
| Mustacchi 2006 | nrct |
| Nagel 2011 | too many patients in experimental arm did not receive ESAs |
| NCT00364845 2011 | no cancer |
| Nonoguchi 2009 | nrct |
| Oberhoff 2005 | nrct |
| Olsson 2002 | randomised comparison of epeotin beta 1,000 IU versus 5,000 IU three times per week |
| Opie 2011 | nrct |
| Ots 2008 | epoetin vs darbepoetin |
| Pat 2009 | nrct |

(*Continued*)

| | |
|---|---|
| Pierelli 1999 | randomised-controlled trial, unblinded, not placebo controlled, 50 participants with ovarian carcinoma were included, as no sufficient data were available, the study was excluded |
| Poirier 2010 | nrct |
| Policarpo 2007 | ESAs were given in context with surgery, stem cell transplantation, compared different ESA dosages or ESA products (epoetin versus darbepoetin), or trials were not randomised |
| Popescu 2010 | nrct |
| Porter 1996 | too small for inclusion |
| Puglisi 2009 | subgroup analysis |
| Rades 2009 | nrct |
| Rath 2010 | nrct |
| Rau 1998 | ESAs were given in context with surgery, stem cell transplantation, compared different ESA dosages or ESA products (epoetin versus darbepoetin), or trials were not randomised |
| Rearden 2004 | randomised comparison of darbepoetin early and late initiating of treatment |
| Reed 2005 | compared different ESA products (epoetin versus darbepoetin) |
| Ribatti 2009 | nrct |
| Richardson 2011 | nrct |
| Rodgers 2008 | nrct |
| Sakai 2004 | ESAs were given in context with surgery, stem cell transplantation, compared different ESA dosages or ESA products (epoetin versus darbepoetin), or trials were not randomised |
| Samper 2002 | randomised comparison of erythropoetin alfa 10,000 IU three times per week versus 30,000 IU once per week |
| Schwartzberg 2004 | darbepo versus epo |
| Schwartzberg 2005 | ESAs were given in context with surgery, stem cell transplantation, compared different ESA dosages or ESA products (epoetin versus darbepoetin), or trials were not randomised |
| Schwartzberg 2007 | ESAs were given in context with surgery, stem cell transplantation, compared different ESA dosages or ESA products (epoetin versus darbepoetin), or trials were not randomised |
| Scott 2002 | randomised comparison of erythropoietin versus placebo in head and neck cancer patients undergoing surgery |

(*Continued*)

| | |
|---|---|
| Senecal 2005 | ESAs were given in context with surgery, stem cell transplantation, compared different ESA dosages or ESA products (epoetin versus darbepoetin), or trials were not randomised |
| Shasha 2003 | community study |
| Shi 2007 | ESAs were given in context with surgery, stem cell transplantation, compared different ESA dosages or ESA products (epoetin versus darbepoetin), or trials were not randomised |
| Shord 2009 | nrct |
| Spaeth 2010 | nrct |
| Spicka 2004 | ESAs were given in context with surgery, stem cell transplantation, compared different ESA dosages or ESA products (epoetin versus darbepoetin), or trials were not randomised |
| Steensma 2006 | ESAs were given in context with surgery, stem cell transplantation, compared different ESA dosages or ESA products (epoetin versus darbepoetin), or trials were not randomised |
| Steensma 2011 | all patients EPO |
| Stein 1991 | very small study, fewer than 10 participants per treatment arm<br>IPD: ineligible patient characteristics (e.g. with MDS or SAA) |
| Steinmetz 2011 | nrct |
| Stokoe 2009 | nrct |
| Stone 2008 | nrct |
| Straus 2002 | upfront epo compared to epo if Hb decreased below 9 g/dL |
| Straus 2006 | ESAs were given in context with surgery, stem cell transplantation, compared different ESA dosages or ESA products (epoetin versus darbepoetin), or trials were not randomised |
| Stull 2010 | nrct |
| Suzuki 2008ex | single arm study |
| Tsukuda 1998 | very small study, fewer than 10 participants in the study arms |
| Tzekova 2009 | nrct |
| Uhl 2007 | nrct |
| Vadhan-Raj 2003 | nrct |
| Vadhan-Raj 2004 | surgery |

(*Continued*)

| | |
|---|---|
| Varan 1999 | treatment allocation not concealed<br>IPD: too small for inclusion |
| Vekeman 2009 | nrct |
| Velilla Millan 2003 | randomised comparison of epeotin 10,000 IU tiw versus 40,000 IU qw |
| Vorvaud 2007 | nrct |
| Wagner 2004 | no usable data for any outcome |
| Walsh 2010 | nrct |
| Waltzman 2004 | comment to Glaspy 2003 study<br>IPD: Darbepoetin compared to erythropoietin |
| Waltzman 2005 | ESAs were given in context with surgery, stem cell transplantation, compared different ESA dosages or ESA products (epoetin versus darbepoetin), or trials were not randomised |
| Wauters 2006 | nrct |
| WHO 2011 | nrct |
| Yang 2008 | nrct |
| Yilmaz 2004 | application of different erythropoietin alfa dosages: 150 IU/kg tiw versus 250 IU/kg tiw in children with cancer |
| Yurut-Caloglu 2008 | nrct |
| Zagari 2003 | ESAs were given in context with surgery, stem cell transplantation, compared different ESA dosages or ESA products (epoetin versus darbepoetin), or trials were not randomised |
| Zaragoza 2004 | n = 17, too small for inclusion |
| Zhang 2003 | ESAs were given in context with surgery, stem cell transplantation, compared different ESA dosages or ESA products (epoetin versus darbepoetin), or trials were not randomised |
| Zhou 2006 | ESAs were given in context with surgery, stem cell transplantation, compared different ESA dosages or ESA products (epoetin versus darbepoetin), or trials were not randomised |

ALL: acute lymphatic leukaemia
AML: acute myeloid leukaemia
CERA: continuous erythropoietin receptor activator
ESAs: erythropoiesis stimulating agents
G-CSF: granulocyte colony-stimulating factor
Hb: haemoglobin

IPD: individual patient data
iv: intravenous
MDS: myelodysplastic syndrome
n: number
nrct: not a randomised controlled trial
RCT: randomised controlled trial
SAA: serum amyloid A
SCLC: small cell lung cancer
sc: subcutaneous
vs: versus

## Characteristics of ongoing studies *[ordered by study ID]*

**Blackstock**

| | |
|---|---|
| Trial name or title | 1CDR0000069148CCCWFU-62299; NCI-P01-0200; CCCWFU-BG01-193 |
| Methods | |
| Participants | Solid - NSCLC Chem + Rad |
| Interventions | Epo, unsure - Epo dose unknown |
| Outcomes | Hb levels, disease progression, tumour response rate, overall survival, QoL, number of RBCT |
| Starting date | January 2002 |
| Contact information | AR Blackstock |
| Notes | |

**Boehrer 2010**

| | |
|---|---|
| Trial name or title | GFMAzaEpo-2008-1 trial, NCT01015352 |
| Methods | Randomised phase-II trial |
| Participants | Lower Risk Myelodysplastic Syndrome (MDS) |
| Interventions | AZA vs AZA+Epoetin beta |
| Outcomes | Major erythroid responses (HI-E major) after 6 courses, according to IWG 2000 criteria. Secondary endpoints included overall IWG 2000 HI-E, including major and minor, after 4 and 6 courses, response duration, IPSS progression, survival and toxicity |
| Starting date | NR |
| Contact information | |

| | |
|---|---|
| Notes | http://abstracts.hematologylibrary.org/cgi/content/abstract/ashmtg<br>Unclear whether it should be included or not. |

**Broadley**

| | |
|---|---|
| Trial name or title | Double-blind randomised placebo controlled trial of the effect of epoetin alfa on symptomatic anaemia and fatigue in cancer patients receiving ongoing care without planned chemotherapy |
| Methods | |
| Participants | Disease: metastatic breast and prostate cancer;<br>Treatment: none |
| Interventions | Epoetin alfa vs placebo |
| Outcomes | Change in HB values;<br>QoL. |
| Starting date | October 1998 |
| Contact information | Dr K. Broadley<br>Palliative Medicine<br>The Royal Marsden NHS Trust<br>Fulham Road<br>Chelsea<br>London<br>SW3 6JJ<br>UK |
| Notes | |

**Chapman 2004**

| | |
|---|---|
| Trial name or title | NRR 2004 Issue 2 Study ID numbers: N0123138194, REC 01/05/53.C |
| Methods | |
| Participants | Haem - MM, Chemotherapy |
| Interventions | Epo alfa vs standard, epo dose unknown |
| Outcomes | Hb Respnse, QoL (FACT-An) |
| Starting date | Jan 2002, Finish date: June 05 |
| Contact information | Chapman C |

**Chapman 2004** (*Continued*)

| | |
|---|---|
| Notes | |

**Delarue 2009**

| | |
|---|---|
| Trial name or title | LNH03-6B GELA Study |
| Methods | Multicentric prospective randomised phase III study |
| Participants | Elderly patients with DLBCL treated by immunochemotherapy |
| Interventions | Darbepoetin vs usual treatment |
| Outcomes | The efficacy of DA in association with chemotherapy (R-CHOP) as measured by the EFS at 2 years, events being defined as death from any cause, relapse for complete responders and unconfirmed complete responders, progression during or after treatment and changes of therapy during allocated treatment. Secondary objectives were OS, PFS, DFS, response rate and analysis of toxicity |
| Starting date | NR |
| Contact information | NR |
| Notes | Interim analysis |

**EPO CAN 303**

| | |
|---|---|
| Trial name or title | EPO-CAN-303;NCT00083434R |
| Methods | |
| Participants | Not reported, no concomitant anticancer therapy |
| Interventions | Epo alfa? |
| Outcomes | NR |
| Starting date | NR |
| Contact information | NR |
| Notes | |

**Famoyin 2004**

| | |
|---|---|
| Trial name or title | A randomised phase II study of thalidomide with or without erythropoietin (EPO) in metastatic renal cell carcinoma (RCC) |
| Methods | Randomised phase II study |
| Participants | Metastatic renal cell carcinoma |
| Interventions | Thalidomide with or without EPO |
| Outcomes | Hb, QoL |
| Starting date | |
| Contact information | C. Famoyin, C. Byrnes, S. Roberts, J. Gollob, M. Atkins, J. Mier, Y.-J. Ko, S. Gautam and D. McDemott Beth Israel Deaconess Medical Center, Boston, MA |
| Notes | Journal of Clinical Oncology, 2004 ASCO Annual Meeting Proceedings (Post-Meeting Edition). Vol 22, No 14S (July 15 Supplement), 2004: 4747 |

**Fisch**

| | |
|---|---|
| Trial name or title | CDR0000069409; MDA-DM-02331; MDA-DM-0038; NCI-P02-0225; NCI00052221MJ |
| Methods | |
| Participants | Solid tumours, no concomitant anti- malignancy treatment |
| Interventions | Epo alfa vs Placebo |
| Outcomes | Hb response, QoL, Fatigue |
| Starting date | Feb 03 |
| Contact information | Fisch S |
| Notes | |

**Gallagher**

| | |
|---|---|
| Trial name or title | The role of epoetin alpha in anaemia and fatigue in cancer patients |
| Methods | |
| Participants | Disease: ovarian and cervical cancer<br>Treatment: concomitant cisplatin chemotherapy |
| Interventions | Epoetin alpha vs no treatment |

**Gallagher** (*Continued*)

| | |
|---|---|
| Outcomes | Changes in HB values;<br>QoL |
| Starting date | September 1998 |
| Contact information | Dr C Gallagher<br>Medical Oncology Department<br>St Bartholomew´ s Hospital<br>West Smithfield<br>London<br>EC1A 7BE<br>UK |
| Notes | |

**Gamucci 1993**

| | |
|---|---|
| Trial name or title | Erythropoietin for the prevention of anaemia in neoplastic patients treated with cisplatin |
| Methods | Randomised controlled study |
| Participants | Patients with advanced tumours |
| Interventions | Epoetin alpha versus control |
| Outcomes | Hb, serum epoetin levels |
| Starting date | NR |
| Contact information | T. Gamucci, Department of Medical Oncology, 1, Regina Elena Institute for Cancer Research, Rome, Italy, |
| Notes | Gamucci T, Thorel MF, Frasca AM, Giannarell D, Calabresi F. Erythropoietin for the prevention of anaemia in neoplastic patients treated with cisplatin. Eur J Cancer. 1993;29A Suppl 2:S13-4. PMID: 8398359 |

**Gascon 2010**

| | |
|---|---|
| Trial name or title | Amgen 20070782; ClinicalTrials.gov NCT00858364 |
| Methods | Randomized, placebo-controlled trial |
| Participants | Non-small cell lung cancer (NSCLC) patients (pts) with anaemia concomitant with chemotherapy (ACC) |
| Interventions | Darbepoetin vs placebo |
| Outcomes | Noninferiority of ESA to placebo for overall survival (primary endpoint) and progression-free survival (modified RECIST per investigator; secondary endpoint) will be examined when 2700 deaths occur. Other safety endpoints include tumour response and thromboembolic events. Transfusion rates are a key efficacy endpoint; |

| | |
|---|---|
| | Hb changes will also be reported |
| Starting date | NR |
| Contact information | NR |
| Notes | No results yet; to follow up |

**Ghavamzadeh 2010**

| | |
|---|---|
| Trial name or title | NR |
| Methods | Randomized, double blind, placebo-controlled phase III study |
| Participants | Anaemic patients with lung or gynaecologic cancer receiving platinum-containing chemotherapy |
| Interventions | Darbepoetin alpha |
| Outcomes | NR |
| Starting date | NR |
| Contact information | NR |
| Notes | Not retrievable from librarians. unclear whether it would be included or not |

**H Thomas 1997**

| | |
|---|---|
| Trial name or title | Open label comparative evaluation of the effect of epoetin on quality of life and burden of illness in anaemic patients receiving platinum-containing chemotherapy |
| Methods | |
| Participants | Disease: cancer;<br>Treatment: concomitant platinum-based chemotherapy |
| Interventions | |
| Outcomes | Changes in Hb values;<br>QoL |
| Starting date | July 1997 |
| Contact information | Dr Hilary Thomas<br>Department of Clinical Oncology<br>Imperial College School of Medicine<br>Hammersmith Hospital<br>Du Cane Road |

**H Thomas 1997** (*Continued*)

| | |
|---|---|
| | London<br>W12 0HS<br>UK |
| Notes | |

**Howell**

| | |
|---|---|
| Trial name or title | A double blind, randomised, placebo-controlled study to evaluate the impact of maintaining haemoglobin using epoetin alpha in stage IV breast cancer subjects receiving chemotherapy |
| Methods | |
| Participants | Disease: breast cancer;<br>Treatment: concomitant chemotherapy |
| Interventions | Epoetin alfa vs placebo |
| Outcomes | Change in Hb values;<br>Transfusion requirement;<br>AE;<br>OS;<br>QoL. |
| Starting date | August 2000 |
| Contact information | Prof A. Howell<br>Christie Hospital NHS Trust<br>Wilmslow Road<br>Withington<br>Manchester<br>M20 4BX<br>UK |
| Notes | |

**Koelbl**

| | |
|---|---|
| Trial name or title | CDR 0000257189;AGOSG-OVAR-MO16375-MARCH; EI20217; ROCHE-MO16375; ROCH-RO2053859 |
| Methods | |
| Participants | Solid cancers, Cervix ca, undergoing chemo - plat + Rad |
| Interventions | Epo beta vs Standard care , epo dose unknown |
| Outcomes | Hb, AE, TR, Hb response, QoL |

**Koelbl** (*Continued*)

| | |
|---|---|
| Starting date | |
| Contact information | H Koelbl |
| Notes | |

**Lambin 2006**

| | |
|---|---|
| Trial name or title | Lambin, was CDR0000068669 and EORTC 22996-24002 |
| Methods | A phase III double-blind, randomised, placebo-controlled study of Erythropoietin when used as an adjuvant to radiation therapy in patients with head and neck squamous cell carcinoma |
| Participants | Head and neck squamous cell carcinoma; Radiation |
| Interventions | Epo once a week +RT +/-chemotherapy versus placebo +RT +/-chemotherapy |
| Outcomes | Loco-regional control, overall survival, Hb levels during radiotherapy, adverse effects |
| Starting date | February 1999<br>designed for 762 patients |
| Contact information | Dr. P-. Lambin, EORTC, Maastricht/Heerlen, The Netherlands<br>Dr V. G. Budach<br>Arbeitsgemeinschaft Radiologische Onkologie<br>Dr J. Bernier<br>EORTC Head and Neck Cancer Group<br>Dr J.-H. Bourhis<br>Groupe d'Oncologie et Radiothérapie Tête et Cou<br>Dr J. Denham<br>Trans-Tasman Radiation Oncological Group Incorporated |
| Notes | |

**Liang 2009**

| | |
|---|---|
| Trial name or title | The clinical study on recombinant human erythropoietin for chemotherapy - related anaemia |
| Methods | Randomised controlled trial, not placebo-controlled |
| Participants | N = 62<br>Disease: NR<br>Treatment: chemotherapy<br>Baseline Hb: NR |

**Liang 2009** (*Continued*)

| | |
|---|---|
| Interventions | Drug: Epo<br>Dose: 12'000 IU tiw<br>Hb-target: NR<br>Duration: 6 weeks |
| Outcomes | NR |
| Starting date | |
| Contact information | |
| Notes | Liang J, Qing B, Shen L, Cheng H. The clinical study on recombinant human erythropoietin for chemotherapy - related anaemia. Clinical Research 2009;29(1):58-60; full text in Chinese, English abstract, study number = 54993 |

**Nitz 2008**

| | |
|---|---|
| Trial name or title | Adjuvant chemotherapy with or without darbepoetin in node-positive breast cancer: a safety analysis from the phase III ARA plus trial |
| Methods | Randomised controlled trial |
| Participants | Breast cancer patients |
| Interventions | Darbepoetin versus control |
| Outcomes | |
| Starting date | |
| Contact information | |
| Notes | Nitz U, Oberhoff C, Reimer T, Schumacher C, Hackmann J, Warm M, Uleer C, Runde V, Gluz O, Zuna I West German Study Group, Moenchengladbach, Germany; Marienhospital, Essen, Germany; Klinikum Suedstadt, Rostock, Germany; St. Elisabeth KH, Koeln, Germany; Uni Koeln, Koeln, Germany; HZM Pharmaservice, Wiesbaden, Germany; Praxis Gyn. Onko., Hildesheim, Germany; Wilhelm-Anton-H., Goch, Germany. Adjuvant chemotherapy with or without darbepoetin in node-positive breast cancer: a safety analysis from the phase III ARA plus trial. San Antonio Breast Cancer Symposium 2008:4100 |

**O′ Brien**

| | |
|---|---|
| Trial name or title | Open-label randomised group-comparative evaluation of the effect of epoetin on anaemia and fatigue in lung cancer patients receiving palliative platinum containing chemotherapy |
| Methods | |
| Participants | Disease: lung cancer<br>Treatment: concomitant platinum containing chemotherapy |

**O′ Brien** (*Continued*)

| | |
|---|---|
| Interventions | Epoetin vs standardised intervention |
| Outcomes | Change in HB values;<br>QoL;<br>Response and tolerance to chemotherapy. |
| Starting date | August 1998 |
| Contact information | Dr Mary O′ Brien<br>Medicine Section<br>The Royal Marsden NHS Trust<br>Downs Road<br>Sutton<br>Surrey<br>SM2 5PT<br>UK |
| Notes | |

**O′ Connell**

| | |
|---|---|
| Trial name or title | Phase III randomised study of epoetin alfa in anaemic patients with advanced cancer undergoing chemotherapy |
| Methods | |
| Participants | Disease: advanced cancer;<br>Treatment: concomitant chemotherapy |
| Interventions | Epoetin alfa vs placebo |
| Outcomes | Change in Hb values;<br>Transfusion requirement;<br>QoL. |
| Starting date | December 1998 |
| Contact information | Dr M. J. O′ Connell<br>North Central Cancer Treatment Group USA |
| Notes | |

**Park 1996**

| | |
|---|---|
| Trial name or title | Clinical evaluation of recombinant human erythropoietin (Eprex) in anaemic cancer patients receiving chemotherapy |
| Methods | Randomised controlled trial |
| Participants | Anaemic cancer patients (lung cancer, stomach cancer, colon cancer) |
| Interventions | Epeotin alpha |
| Outcomes | Haematocrit, RBC transfusion |
| Starting date | NR |
| Contact information | NR |
| Notes | Park HS, Hong DS, Lee SJ, Chung TJ, Choi YM. Clinical evaluation of recombinant human erythropoietin (Eprex) in anaemic cancer patients receiving chemotherapy. Ann Oncol 1996;7(Suppl 5) |

**Parliament**

| | |
|---|---|
| Trial name or title | Radiation therapy with or without Epoetin alfa in anaemic patients with head and neck cancer |
| Methods | |
| Participants | Disease: need and neck cancer;<br>Treatment: concomitant radiotherapy |
| Interventions | Epoetin:<br>Control: no treatment |
| Outcomes | Changes in Hb values; AEs; QoL; local tumour control rate; OS |
| Starting date | |
| Contact information | Cross Canada Institute<br>Edmonton, Alberta<br>T6G 1Z2<br>Canada |
| Notes | |

**R Thomas 2002**

| | |
|---|---|
| Trial name or title | EPREX trial: Open-label comparative-group evaluation of the effect of epoetin alfa on quality of life and burden of illness in anaemic cancer patients receiving platinum containing chemotherapy |
| Methods | |

**R Thomas 2002** (*Continued*)

| | |
|---|---|
| Participants | Disease: various malignancies;<br>Treatment: concomitant platinum-based chemotherapy |
| Interventions | Epoetin alfa vs no treatment |
| Outcomes | QoL;<br>Patient burden;<br>Transfusion requirements;<br>Change in Hb values. |
| Starting date | June 1997 |
| Contact information | Dr R. Thomas<br>Primrose Oncology Unit<br>Bedford South Wing Hospital<br>Kempston Road<br>Bedford<br>MK42 9DJ<br>UK |
| Notes | |

**Recasens 2003**

| | |
|---|---|
| Trial name or title | Randomised comparison of epoetin alfa versus control in patients with multiple myeloma, n=91, only interim analysis available so far, costs reported |
| Methods | Randomised controlled trial |
| Participants | Patients with multiple myeloma |
| Interventions | Epoetin alpha versus control |
| Outcomes | Costs |
| Starting date | |
| Contact information | pgiraldo@salud.aragon.es |
| Notes | Recasens V, Rubio-Martinez A, Gomez-Barrera M, Rubio-Felix D, Giralt M, Giraldo P. A pharmacoeconomical<br>analysis comparing Epoetin Alpha vs transfusion in patients with anaemia associated to multiple myeloma. Blood. 2003;<br>Vol. 102, issue 11. |

**Rexer 2006**

| | |
|---|---|
| Trial name or title | Prospektiv offene, randomisierte Phase III Studie zur Evaluation von Darbepoetin Alfa (Aranesp) als Supportivtherapie bei Paienten mit "good/intermediate prognosis" Keimzelltumoren: PEB versus PEB+ Darbepoetin alfa (Aranesp"), Leitung: Prof. Bokemeyer, University Hospital Eppendorf, Hamburg, Germany |
| Methods | Randomised controlled trial |
| Participants | Testicular cancer patients |
| Interventions | Darbepoetin versus control |
| Outcomes | Hb, RBC transfusion, QoL, disease progressions, OS. |
| Starting date | NR |
| Contact information | Ina Böhlke, i.boehlke@uke.uni-hamburg.de |
| Notes | Rexer H [Darbepoetin alfa (Aranesp) as supportive therapy in patients with germ cell tumours]. Urologe A. 2006 Aug;45(8):1017-8. MeckEvidence, Geschäftsstelle der AUO, Seestr. 11, 17252, Schwarz.<br>AUO@MeckEvidence.de |

**Rudd**

| | |
|---|---|
| Trial name or title | Evaluation of epoetin in lung cancer pts. receiving chemotherapy |
| Methods | |
| Participants | Disease: lung cancer;<br>Treatment: concomitant platinum-based chemotherapy |
| Interventions | Epoetin alpha vs no treatment |
| Outcomes | |
| Starting date | November 1998 |
| Contact information | Dr R. M. Rudd<br>Medical Oncology Department<br>St Bartholomew´ s Hospital<br>West Smithfield<br>London<br>EC1A 7BE<br>UK |
| Notes | |

**Stewart**

| | |
|---|---|
| Trial name or title | Open randomised comparative group evaluation of the effect of epoetin alfa on local disease free survival and quality of life in head and neck cancer patients receiving radical radiotherapy |
| Methods | |
| Participants | Disease: head and neck cancer;<br>Treatment: concomitant radiotherapy |
| Interventions | |
| Outcomes | Local tumour control;<br>Disease-free survival;<br>QoL;<br>OS. |
| Starting date | August 1999 |
| Contact information | Dr J. S. Stewart<br>Department of Radiotherapy<br>Charing Cross Hospital<br>Fulham Palace Road<br>London<br>W6 8RF<br>UK |
| Notes | |

**UKCCCR GN308**

| | |
|---|---|
| Trial name or title | A double-blind, placebo controlled study to assess the effects of early intervention and/or treatment with Epoetin alfa on anaemia in cancer patients receiving non platinum containing chemotherapy |
| Methods | |
| Participants | Disease: cancer<br>Treatment: concomitant chemotherapy |
| Interventions | Epoetin vs placebo |
| Outcomes | Transfusion requirement;<br>QoL. |
| Starting date | |
| Contact information | UKCCCR Register Co-ordinator<br>MRC Clinical Trials Unit<br>222 Euston Road<br>London NW1 2DA |

**UKCCCR GN308** (*Continued*)

| | |
|---|---|
| Notes | |

**Yousseff 2011**

| | |
|---|---|
| Trial name or title | The Effectiveness of a Fixed Low Dose of Erythropoietin (EPO) in Anemic Solid Tumor Patients Receiving Concomitant Chemotherapy: A Prospective, Randomized, Controlled Study |
| Methods | Randomised controlled trial |
| Participants | Anemic solid tumour patients |
| Interventions | Low dose Epoetin versus control |
| Outcomes | |
| Starting date | |
| Contact information | |
| Notes | Youssef Lama A, Hussien Dilman Haj, Sulaiman Siham. The Effectiveness of a Fixed Low Dose of Erythropoietin (EPO) in Anemic Solid Tumor Patients Receiving Concomitant Chemotherapy: A Prospective, Randomized, Controlled Study. ASH Annual Meeting Abstracts 2011;118(21):2092 |

**Ziras 2001**

| | |
|---|---|
| Trial name or title | Soluble transferrin receptor (sTFR) as a predictor of response to prophylactic epoetin alfa (EPO) treatment in non-anaemic cancer patients (pts) under chemotherapy (CT). Preliminary results |
| Methods | Randomised controlled trial |
| Participants | Non-anaemic cancer patients |
| Interventions | Epoetin alpha |
| Outcomes | Hb |
| Starting date | NR |
| Contact information | Agii Anargiri Cancer Hospital Athens, Metaxa Cancer Hosptial, Piraeus, Greece |
| Notes | Proc Am Soc Clin Oncol 20:2001 (abstr 2987) |

AE: adverse event
AZA: Azacitidine
DLBCL: diffuse large B-cell lymphoma.
EPO: Erythropoietin

ESA: erythropoiesis stimulating agent
G-CSF: granulocyte colony-stimulating factors
Hb: haemoglobin
IPSS: International Prognostic Scoring System
OS: overall survival
PFS: progression-free survival
Pts.: patients
QoL: quality of life
RBCS: Red blood cells
s.c.: subcutaneous
vs.: versus
NR: not reported
RBCT: red blood cell transfusions
RT: radiotherapy
TR: tumour response

## DATA AND ANALYSES

### Comparison 1. Haematologic response

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Haematological response - overall | 46 | 6413 | Risk Ratio (M-H, Fixed, 95% CI) | 3.39 [3.10, 3.71] |
| 2 Haematologic response - baseline Hb | 46 | 6413 | Risk Ratio (M-H, Fixed, 95% CI) | 3.39 [3.10, 3.71] |
| 2.1 Hb <= 10 g/dL | 36 | 4137 | Risk Ratio (M-H, Fixed, 95% CI) | 3.02 [2.72, 3.35] |
| 2.2 Hb 10 to 12 g/dL | 8 | 1775 | Risk Ratio (M-H, Fixed, 95% CI) | 4.60 [3.79, 5.58] |
| 2.3 Hb > 12 g/dL | 1 | 380 | Risk Ratio (M-H, Fixed, 95% CI) | 7.48 [3.00, 18.62] |
| 2.4 Hb category unclear | 1 | 121 | Risk Ratio (M-H, Fixed, 95% CI) | 2.04 [1.20, 3.46] |
| 3 Haematologic response - different malignancies | 46 | 6413 | Risk Ratio (M-H, Fixed, 95% CI) | 3.39 [3.10, 3.71] |
| 3.1 solid tumours | 18 | 3089 | Risk Ratio (M-H, Fixed, 95% CI) | 3.56 [3.12, 4.07] |
| 3.2 haematological malignancies | 15 | 1623 | Risk Ratio (M-H, Fixed, 95% CI) | 3.12 [2.64, 3.69] |
| 3.3 MDS | 2 | 151 | Risk Ratio (M-H, Fixed, 95% CI) | 4.27 [0.86, 21.19] |
| 3.4 mixed | 12 | 1550 | Risk Ratio (M-H, Fixed, 95% CI) | 3.38 [2.80, 4.08] |
| 3.5 not reported | 0 | 0 | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 4 Haematological response- age | 46 | 6413 | Risk Ratio (M-H, Fixed, 95% CI) | 3.39 [3.10, 3.71] |
| 4.1 children | 1 | 222 | Risk Ratio (M-H, Fixed, 95% CI) | 1.62 [1.20, 2.18] |
| 4.2 adults | 45 | 6191 | Risk Ratio (M-H, Fixed, 95% CI) | 3.55 [3.23, 3.90] |
| 5 Haematological response- age differentiated | 46 | 6413 | Risk Ratio (M-H, Fixed, 95% CI) | 3.39 [3.10, 3.71] |
| 5.1 only children <18 years | 1 | 222 | Risk Ratio (M-H, Fixed, 95% CI) | 1.62 [1.20, 2.18] |
| 5.2 adults ≥18 years | 43 | 5623 | Risk Ratio (M-H, Fixed, 95% CI) | 3.34 [3.03, 3.68] |
| 5.3 >70% non-elderly 18-65 years | 2 | 568 | Risk Ratio (M-H, Fixed, 95% CI) | 8.26 [5.22, 13.06] |
| 5.4 only non-elderly adults | 0 | 0 | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 5.5 >70% elderly >65 years | 0 | 0 | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 5.6 only elderly adults | 0 | 0 | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 6 Haematologic response - different therapies | 46 | 6413 | Risk Ratio (M-H, Fixed, 95% CI) | 3.39 [3.10, 3.71] |
| 6.1 chemotherapy | 38 | 5562 | Risk Ratio (M-H, Fixed, 95% CI) | 3.32 [3.02, 3.64] |
| 6.2 radiotherapy/ radiochemotherapy | 0 | 0 | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 6.3 no therapy | 7 | 630 | Risk Ratio (M-H, Fixed, 95% CI) | 5.50 [3.25, 9.31] |
| 6.4 other | 1 | 221 | Risk Ratio (M-H, Fixed, 95% CI) | 2.87 [1.69, 4.85] |
| 7 Haematologic response - different therapies differentiated | 46 | 6413 | Risk Ratio (M-H, Fixed, 95% CI) | 3.39 [3.10, 3.71] |
| 7.1 chemotherapy, >70% with platinum | 7 | 1301 | Risk Ratio (M-H, Fixed, 95% CI) | 3.12 [2.51, 3.87] |
| 7.2 chemotherapy, <70% platinum containing | 3 | 659 | Risk Ratio (M-H, Fixed, 95% CI) | 2.71 [2.16, 3.40] |

| | | | | |
|---|---|---|---|---|
| 7.3 chemotherapy without platinum (all patients) | 17 | 2614 | Risk Ratio (M-H, Fixed, 95% CI) | 3.73 [3.26, 4.26] |
| 7.4 chemotherapy, platinum and non-platinum containing, no numbers given | 8 | 643 | Risk Ratio (M-H, Fixed, 95% CI) | 4.05 [2.84, 5.77] |
| 7.5 chemotherapy no details given | 3 | 345 | Risk Ratio (M-H, Fixed, 95% CI) | 2.13 [1.59, 2.86] |
| 7.6 radiochemotherapy | 0 | 0 | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 7.7 radiotherapy | 0 | 0 | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 7.8 no therapy | 7 | 630 | Risk Ratio (M-H, Fixed, 95% CI) | 5.50 [3.25, 9.31] |
| 7.9 other | 1 | 221 | Risk Ratio (M-H, Fixed, 95% CI) | 2.87 [1.69, 4.85] |
| 8 Haematologic response - epoetin versus darbepoetin | 46 | 6413 | Risk Ratio (M-H, Fixed, 95% CI) | 3.39 [3.10, 3.71] |
| 8.1 Epoetin | 30 | 5270 | Risk Ratio (M-H, Fixed, 95% CI) | 3.27 [2.97, 3.59] |
| 8.2 Darbepoetin | 16 | 1143 | Risk Ratio (M-H, Fixed, 95% CI) | 4.22 [3.22, 5.55] |
| 9 Haematologic response - duration of ESA medication | 46 | 6413 | Risk Ratio (M-H, Fixed, 95% CI) | 3.39 [3.10, 3.71] |
| 9.1 6 to 9 weeks | 6 | 349 | Risk Ratio (M-H, Fixed, 95% CI) | 3.74 [1.94, 7.19] |
| 9.2 12 to 16 weeks | 34 | 4574 | Risk Ratio (M-H, Fixed, 95% CI) | 3.17 [2.87, 3.51] |
| 9.3 more than 17 weeks | 6 | 1490 | Risk Ratio (M-H, Fixed, 95% CI) | 4.41 [3.52, 5.52] |
| 10 Haematologic response - iron supplementation | 46 | 6413 | Risk Ratio (M-H, Fixed, 95% CI) | 3.39 [3.10, 3.71] |
| 10.1 fixed iron supplementation | 2 | 441 | Risk Ratio (M-H, Fixed, 95% CI) | 2.43 [1.92, 3.07] |
| 10.2 iron supplementation as necessary | 36 | 5265 | Risk Ratio (M-H, Fixed, 95% CI) | 3.63 [3.27, 4.03] |
| 10.3 no explicit statement on iron supplementation or no iron given | 7 | 399 | Risk Ratio (M-H, Fixed, 95% CI) | 4.82 [2.64, 8.81] |
| 10.4 explicitly stated NO IRON | 0 | 0 | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 10.5 iron given differently in both study arms | 1 | 308 | Risk Ratio (M-H, Fixed, 95% CI) | 2.22 [1.63, 3.01] |
| 11 Haematologic response - allocation concealment | 46 | 6413 | Risk Ratio (M-H, Fixed, 95% CI) | 3.39 [3.10, 3.71] |
| 11.1 adequate | 30 | 4721 | Risk Ratio (M-H, Fixed, 95% CI) | 3.35 [3.02, 3.72] |
| 11.2 unclear | 16 | 1692 | Risk Ratio (M-H, Fixed, 95% CI) | 3.50 [2.92, 4.19] |
| 12 Haematologic response - masking | 46 | 6413 | Risk Ratio (M-H, Fixed, 95% CI) | 3.39 [3.10, 3.71] |
| 12.1 double-blind | 29 | 3430 | Risk Ratio (M-H, Fixed, 95% CI) | 3.02 [2.70, 3.37] |
| 12.2 unblinded | 17 | 2983 | Risk Ratio (M-H, Fixed, 95% CI) | 4.07 [3.49, 4.74] |
| 13 Haematologic response - intention-to treat | 46 | 6413 | Risk Ratio (M-H, Fixed, 95% CI) | 3.39 [3.10, 3.71] |
| 13.1 ITT or less than 10% of participants per study arm excluded | 41 | 5657 | Risk Ratio (M-H, Fixed, 95% CI) | 3.32 [3.03, 3.65] |
| 13.2 more than 10% of participants per study arm excluded | 2 | 512 | Risk Ratio (M-H, Fixed, 95% CI) | 6.85 [3.76, 12.48] |
| 13.3 unclear | 3 | 244 | Risk Ratio (M-H, Fixed, 95% CI) | 3.04 [1.92, 4.80] |

| | | | | |
|---|---|---|---|---|
| 14 Haematologic response - publication | 46 | 6413 | Risk Ratio (M-H, Fixed, 95% CI) | 3.39 [3.10, 3.71] |
| 14.1 full text publication | 32 | 5229 | Risk Ratio (M-H, Fixed, 95% CI) | 3.44 [3.12, 3.80] |
| 14.2 abstract publication | 2 | 123 | Risk Ratio (M-H, Fixed, 95% CI) | 5.19 [2.23, 12.04] |
| 14.3 unpublished data | 10 | 880 | Risk Ratio (M-H, Fixed, 95% CI) | 3.44 [2.45, 4.82] |
| 14.4 FDA hearing | 0 | 0 | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 14.5 clinical trial result information | 2 | 181 | Risk Ratio (M-H, Fixed, 95% CI) | 1.98 [1.36, 2.89] |
| 15 Haematological response - merged experimental arms | 31 | 6413 | Risk Ratio (M-H, Fixed, 95% CI) | 3.42 [3.12, 3.74] |

## Comparison 2. Change of haemoglobin level

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Change in Hb values - overall | 75 | 11609 | Mean Difference (IV, Fixed, 95% CI) | 1.57 [1.51, 1.62] |
| 2 Change in Hb values - baseline Hb | 75 | 11609 | Mean Difference (IV, Fixed, 95% CI) | 1.57 [1.51, 1.62] |
| 2.1 Hb <=10g/dL | 41 | 5092 | Mean Difference (IV, Fixed, 95% CI) | 1.53 [1.43, 1.62] |
| 2.2 Hb 10 to 12 g/dL | 23 | 3572 | Mean Difference (IV, Fixed, 95% CI) | 1.79 [1.71, 1.88] |
| 2.3 Hb >12 g/dL | 10 | 2824 | Mean Difference (IV, Fixed, 95% CI) | 1.12 [0.99, 1.25] |
| 2.4 unclear | 1 | 121 | Mean Difference (IV, Fixed, 95% CI) | 1.53 [0.91, 2.15] |
| 3 Change in Hb values - different malignancies | 75 | 11609 | Mean Difference (IV, Fixed, 95% CI) | 1.57 [1.51, 1.62] |
| 3.1 solid tumours | 45 | 6262 | Mean Difference (IV, Fixed, 95% CI) | 1.76 [1.68, 1.83] |
| 3.2 haematological malignancies | 14 | 2391 | Mean Difference (IV, Fixed, 95% CI) | 1.05 [0.90, 1.19] |
| 3.3 MDS | 1 | 28 | Mean Difference (IV, Fixed, 95% CI) | 1.87 [0.89, 2.85] |
| 3.4 mixed | 15 | 2928 | Mean Difference (IV, Fixed, 95% CI) | 1.35 [1.21, 1.48] |
| 3.5 unclear | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 4 Change in Hb values - age | 75 | 11609 | Mean Difference (IV, Fixed, 95% CI) | 1.57 [1.51, 1.62] |
| 4.1 children | 1 | 222 | Mean Difference (IV, Fixed, 95% CI) | 0.30 [-0.27, 0.87] |
| 4.2 adults | 74 | 11387 | Mean Difference (IV, Fixed, 95% CI) | 1.58 [1.52, 1.64] |
| 5 Change in Hb values - age differentiated | 75 | 11609 | Mean Difference (IV, Fixed, 95% CI) | 1.57 [1.51, 1.62] |
| 5.1 only children <18 years | 1 | 222 | Mean Difference (IV, Fixed, 95% CI) | 0.30 [-0.27, 0.87] |
| 5.2 adults ≥18 years | 62 | 8214 | Mean Difference (IV, Fixed, 95% CI) | 1.57 [1.49, 1.64] |
| 5.3 > 70% non-elderly 18-65 years | 9 | 1136 | Mean Difference (IV, Fixed, 95% CI) | 1.99 [1.88, 2.10] |
| 5.4 only non-elderly adults | 2 | 1992 | Mean Difference (IV, Fixed, 95% CI) | 0.76 [0.60, 0.91] |
| 5.5 > 70% elderly >65 years | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 5.6 only elderly adults | 1 | 45 | Mean Difference (IV, Fixed, 95% CI) | 2.70 [1.87, 3.53] |
| 6 Change in Hb values - different therapies | 75 | 11609 | Mean Difference (IV, Fixed, 95% CI) | 1.57 [1.51, 1.62] |
| 6.1 chemotherapy | 58 | 8956 | Mean Difference (IV, Fixed, 95% CI) | 1.46 [1.39, 1.52] |
| 6.2 radiotherapy/ radiochemotherapy | 8 | 974 | Mean Difference (IV, Fixed, 95% CI) | 2.41 [2.24, 2.58] |
| 6.3 no therapy | 9 | 1679 | Mean Difference (IV, Fixed, 95% CI) | 1.42 [1.25, 1.60] |

| | | | | |
|---|---|---|---|---|
| 7 Change in Hb values - different therapies differentiated | 75 | 11609 | Mean Difference (IV, Fixed, 95% CI) | 1.57 [1.51, 1.62] |
| 7.1 chemotherapy, >70% with platinum | 19 | 2126 | Mean Difference (IV, Fixed, 95% CI) | 1.68 [1.55, 1.82] |
| 7.2 chemotherapy, <70% platinum containing | 7 | 1315 | Mean Difference (IV, Fixed, 95% CI) | 1.84 [1.62, 2.05] |
| 7.3 chemotherapy without platinum | 22 | 4511 | Mean Difference (IV, Fixed, 95% CI) | 1.33 [1.25, 1.42] |
| 7.4 chemotherapy, platinum and non-platinum containing, no numbers given | 9 | 782 | Mean Difference (IV, Fixed, 95% CI) | 1.37 [1.13, 1.61] |
| 7.5 chemotherapy, no details given | 1 | 222 | Mean Difference (IV, Fixed, 95% CI) | 0.30 [-0.27, 0.87] |
| 7.6 radiotherapy | 5 | 696 | Mean Difference (IV, Fixed, 95% CI) | 2.32 [2.01, 2.63] |
| 7.7 radiochemotherapy | 3 | 278 | Mean Difference (IV, Fixed, 95% CI) | 2.45 [2.25, 2.65] |
| 7.8 no therapy | 9 | 1679 | Mean Difference (IV, Fixed, 95% CI) | 1.42 [1.25, 1.60] |
| 8 Change in Hb values - epoetin vs darbepoetin | 75 | 11609 | Mean Difference (IV, Fixed, 95% CI) | 1.57 [1.51, 1.62] |
| 8.1 Epoetin | 57 | 8304 | Mean Difference (IV, Fixed, 95% CI) | 1.69 [1.62, 1.75] |
| 8.2 Darbepoetin | 18 | 3305 | Mean Difference (IV, Fixed, 95% CI) | 1.13 [1.00, 1.25] |
| 9 Change in Hb values - duration of ESA medication | 75 | 11609 | Mean Difference (IV, Fixed, 95% CI) | 1.57 [1.51, 1.62] |
| 9.1 6 to 9 weeks | 17 | 1235 | Mean Difference (IV, Fixed, 95% CI) | 2.30 [2.16, 2.44] |
| 9.2 12 to 16 weeks | 43 | 6393 | Mean Difference (IV, Fixed, 95% CI) | 1.62 [1.54, 1.70] |
| 9.3 more than 17 weeks | 15 | 3981 | Mean Difference (IV, Fixed, 95% CI) | 1.05 [0.95, 1.16] |
| 10 Change in Hb values - iron supplementation | 75 | 11609 | Mean Difference (IV, Fixed, 95% CI) | 1.57 [1.51, 1.62] |
| 10.1 fixed iron supplementation | 14 | 2483 | Mean Difference (IV, Fixed, 95% CI) | 1.94 [1.81, 2.07] |
| 10.2 iron supplementation as necessary | 53 | 8807 | Mean Difference (IV, Fixed, 95% CI) | 1.47 [1.40, 1.53] |
| 10.3 no explicit statement on iron supplementation or no iron given | 8 | 319 | Mean Difference (IV, Fixed, 95% CI) | 1.66 [1.34, 1.99] |
| 10.4 explicitly stated no iron new | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 10.5 iron given differently in both study arms new ongoing | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 11 Change in Hb values - allocation concealment | 75 | 11609 | Mean Difference (IV, Fixed, 95% CI) | 1.57 [1.51, 1.62] |
| 11.1 adequate | 45 | 6768 | Mean Difference (IV, Fixed, 95% CI) | 1.52 [1.45, 1.60] |
| 11.2 unclear | 30 | 4841 | Mean Difference (IV, Fixed, 95% CI) | 1.62 [1.53, 1.71] |
| 12 Change in Hb values - masking | 75 | 11609 | Mean Difference (IV, Fixed, 95% CI) | 1.57 [1.51, 1.62] |
| 12.1 double-blind | 42 | 7438 | Mean Difference (IV, Fixed, 95% CI) | 1.47 [1.40, 1.55] |
| 12.2 unblinded | 33 | 4171 | Mean Difference (IV, Fixed, 95% CI) | 1.67 [1.59, 1.75] |
| 13 Change in Hb values - intention-to-treat | 75 | 11609 | Mean Difference (IV, Fixed, 95% CI) | 1.57 [1.51, 1.62] |
| 13.1 ITT or less than 10% of participants per study arm excluded | 57 | 9137 | Mean Difference (IV, Fixed, 95% CI) | 1.61 [1.55, 1.68] |

| | | | | |
|---|---|---|---|---|
| 13.2 more than 10% of participants per study arm excluded | 18 | 2472 | Mean Difference (IV, Fixed, 95% CI) | 1.28 [1.13, 1.43] |
| 13.3 unclear | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 14 Change in Hb values - publication | 75 | 11609 | Mean Difference (IV, Fixed, 95% CI) | 1.57 [1.51, 1.62] |
| 14.1 full text publication | 59 | 10026 | Mean Difference (IV, Fixed, 95% CI) | 1.54 [1.47, 1.60] |
| 14.2 abstract publication | 3 | 252 | Mean Difference (IV, Fixed, 95% CI) | 1.70 [1.30, 2.09] |
| 14.3 unpublished data | 10 | 804 | Mean Difference (IV, Fixed, 95% CI) | 1.56 [1.36, 1.76] |
| 14.4 ODAC documents | 1 | 346 | Mean Difference (IV, Fixed, 95% CI) | 2.5 [2.14, 2.86] |
| 14.5 Clinical trials results | 2 | 181 | Mean Difference (IV, Fixed, 95% CI) | 1.48 [0.94, 2.02] |
| 15 Change in Hb values - experimental arms merged | 56 | 11609 | Mean Difference (IV, Fixed, 95% CI) | 1.56 [1.51, 1.62] |
| 16 Change in Hb values- sensitivity analysis | 65 | 8685 | Mean Difference (IV, Fixed, 95% CI) | 1.66 [1.59, 1.72] |
| 17 Change in Hb values - publication sensitivity analysis excluding Henke 2003 | 74 | 11263 | Mean Difference (IV, Fixed, 95% CI) | 1.54 [1.48, 1.60] |
| 17.1 full text publication | 58 | 8723 | Mean Difference (IV, Fixed, 95% CI) | 1.63 [1.57, 1.70] |
| 17.2 abstract publication | 4 | 1555 | Mean Difference (IV, Fixed, 95% CI) | 0.87 [0.69, 1.04] |
| 17.3 unpublished data | 10 | 804 | Mean Difference (IV, Fixed, 95% CI) | 1.56 [1.36, 1.76] |
| 17.4 ODAC documents | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 17.5 clinical study report | 2 | 181 | Mean Difference (IV, Fixed, 95% CI) | 1.48 [0.94, 2.02] |

**Comparison 3. Participants receiving red blood cell transfusions**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Participants receiving red blood cell transfusions - overall | 88 | 16093 | Risk Ratio (M-H, Fixed, 95% CI) | 0.65 [0.62, 0.68] |
| 2 Participants receiving red blood cell transfusions - baseline Hb | 88 | 16093 | Risk Ratio (M-H, Fixed, 95% CI) | 0.65 [0.62, 0.68] |
| 2.1 Hb <=10 g/dL | 42 | 5605 | Risk Ratio (M-H, Fixed, 95% CI) | 0.71 [0.67, 0.76] |
| 2.2 Hb 10 to 12 g/dL | 29 | 5669 | Risk Ratio (M-H, Fixed, 95% CI) | 0.50 [0.46, 0.55] |
| 2.3 Hb > 12 g/dL | 17 | 4819 | Risk Ratio (M-H, Fixed, 95% CI) | 0.73 [0.67, 0.78] |
| 2.4 unclear | 0 | 0 | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 3 Participants receiving red blood cell transfusions - different malignancies | 88 | 16093 | Risk Ratio (M-H, Fixed, 95% CI) | 0.65 [0.62, 0.68] |
| 3.1 solid tumours | 53 | 9305 | Risk Ratio (M-H, Fixed, 95% CI) | 0.50 [0.46, 0.54] |
| 3.2 haematological malignancies | 15 | 2852 | Risk Ratio (M-H, Fixed, 95% CI) | 0.80 [0.75, 0.86] |
| 3.3 MDS | 2 | 151 | Risk Ratio (M-H, Fixed, 95% CI) | 0.80 [0.68, 0.96] |
| 3.4 mixed | 19 | 3785 | Risk Ratio (M-H, Fixed, 95% CI) | 0.74 [0.68, 0.80] |
| 3.5 not reported | 0 | 0 | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 4 Participants receiving red blood cell transfusions - age | 88 | 16093 | Risk Ratio (M-H, Fixed, 95% CI) | 0.65 [0.62, 0.68] |
| 4.1 children | 1 | 222 | Risk Ratio (M-H, Fixed, 95% CI) | 0.84 [0.71, 0.99] |

| | | | | |
|---|---|---|---|---|
| 4.2 adults | 87 | 15871 | Risk Ratio (M-H, Fixed, 95% CI) | 0.64 [0.62, 0.67] |
| 5 Participants receiving red blood cell transfusions - age differentiated | 88 | 16093 | Risk Ratio (M-H, Fixed, 95% CI) | 0.65 [0.62, 0.68] |
| 5.1 only children <18 years | 1 | 222 | Risk Ratio (M-H, Fixed, 95% CI) | 0.84 [0.71, 0.99] |
| 5.2 adults ≥18 years | 70 | 11556 | Risk Ratio (M-H, Fixed, 95% CI) | 0.62 [0.59, 0.66] |
| 5.3 >68% non-elderly 18-65 years | 11 | 1343 | Risk Ratio (M-H, Fixed, 95% CI) | 0.49 [0.41, 0.60] |
| 5.4 only non-elderly adults | 5 | 2927 | Risk Ratio (M-H, Fixed, 95% CI) | 0.78 [0.72, 0.84] |
| 5.5 >68% elderly >65 years | 0 | 0 | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 5.6 only elderly adults | 1 | 45 | Risk Ratio (M-H, Fixed, 95% CI) | 0.40 [0.17, 0.94] |
| 6 Participants receiving red blood cell transfusions - different therapies | 88 | 16093 | Risk Ratio (M-H, Fixed, 95% CI) | 0.65 [0.62, 0.68] |
| 6.1 chemotherapy | 71 | 13405 | Risk Ratio (M-H, Fixed, 95% CI) | 0.64 [0.61, 0.67] |
| 6.2 radio/radiochemotherapy | 6 | 693 | Risk Ratio (M-H, Fixed, 95% CI) | 0.45 [0.34, 0.58] |
| 6.3 no therapy | 10 | 1774 | Risk Ratio (M-H, Fixed, 95% CI) | 0.81 [0.72, 0.91] |
| 6.4 unclear/other | 1 | 221 | Risk Ratio (M-H, Fixed, 95% CI) | 0.77 [0.60, 0.99] |
| 7 Participants receiving red blood cell transfusions - different therapies differentiated | 88 | 16093 | Risk Ratio (M-H, Fixed, 95% CI) | 0.65 [0.62, 0.68] |
| 7.1 chemotherapy, > 70% with platinum | 26 | 3592 | Risk Ratio (M-H, Fixed, 95% CI) | 0.49 [0.44, 0.54] |
| 7.2 chemotherapy, < 70% with platinum | 10 | 2043 | Risk Ratio (M-H, Fixed, 95% CI) | 0.63 [0.55, 0.73] |
| 7.3 chemotherapy without platinum (all patients) | 23 | 6509 | Risk Ratio (M-H, Fixed, 95% CI) | 0.73 [0.69, 0.78] |
| 7.4 chemotherapy, platinum and non-platinum containing, no numbers given | 9 | 772 | Risk Ratio (M-H, Fixed, 95% CI) | 0.53 [0.43, 0.65] |
| 7.5 chemotherapy no details given | 3 | 489 | Risk Ratio (M-H, Fixed, 95% CI) | 0.73 [0.63, 0.86] |
| 7.6 radiochemotherapy | 6 | 693 | Risk Ratio (M-H, Fixed, 95% CI) | 0.45 [0.34, 0.58] |
| 7.7 radiotherapy | 0 | 0 | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 7.8 no therapy | 10 | 1774 | Risk Ratio (M-H, Fixed, 95% CI) | 0.81 [0.72, 0.91] |
| 7.9 unclear/other | 1 | 221 | Risk Ratio (M-H, Fixed, 95% CI) | 0.77 [0.60, 0.99] |
| 8 Participants receiving red blood cell transfusions - epoetin versus darbepoetin | 88 | 16093 | Risk Ratio (M-H, Fixed, 95% CI) | 0.65 [0.62, 0.68] |
| 8.1 Epoetin | 67 | 11786 | Risk Ratio (M-H, Fixed, 95% CI) | 0.65 [0.62, 0.68] |
| 8.2 Darbepoetin | 21 | 4307 | Risk Ratio (M-H, Fixed, 95% CI) | 0.66 [0.60, 0.72] |
| 9 Participants receiving red blood cell transfusions - duration of ESA medication | 88 | 16093 | Risk Ratio (M-H, Fixed, 95% CI) | 0.65 [0.62, 0.68] |
| 9.1 6 to 9 weeks | 13 | 815 | Risk Ratio (M-H, Fixed, 95% CI) | 0.60 [0.49, 0.74] |
| 9.2 12 to 16 weeks | 52 | 8413 | Risk Ratio (M-H, Fixed, 95% CI) | 0.65 [0.61, 0.69] |
| 9.3 more than 17 weeks | 23 | 6865 | Risk Ratio (M-H, Fixed, 95% CI) | 0.65 [0.61, 0.70] |
| 10 Participants receiving red blood cell transfusions - iron supplementation | 88 | 16093 | Risk Ratio (M-H, Fixed, 95% CI) | 0.65 [0.62, 0.68] |

| | | | | |
|---|---|---|---|---|
| 10.1 fixed iron supplementation | 10 | 2104 | Risk Ratio (M-H, Fixed, 95% CI) | 0.58 [0.49, 0.70] |
| 10.2 iron supplementation as necessary | 63 | 12060 | Risk Ratio (M-H, Fixed, 95% CI) | 0.68 [0.65, 0.71] |
| 10.3 no explicit statement on iron supplementation or no iron given | 11 | 645 | Risk Ratio (M-H, Fixed, 95% CI) | 0.52 [0.42, 0.65] |
| 10.4 explicitly stated NO IRON | 0 | 0 | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 10.5 iron given differently in both study arms new | 4 | 1284 | Risk Ratio (M-H, Fixed, 95% CI) | 0.51 [0.43, 0.61] |
| 11 Participants receiving red blood cell transfusions - allocation concealment | 88 | 16093 | Risk Ratio (M-H, Fixed, 95% CI) | 0.65 [0.62, 0.68] |
| 11.1 adequate | 55 | 10898 | Risk Ratio (M-H, Fixed, 95% CI) | 0.61 [0.58, 0.65] |
| 11.2 unclear | 33 | 5195 | Risk Ratio (M-H, Fixed, 95% CI) | 0.71 [0.67, 0.76] |
| 12 Participants receiving red blood cell transfusions - masking | 88 | 16093 | Risk Ratio (M-H, Fixed, 95% CI) | 0.65 [0.62, 0.68] |
| 12.1 double-blind | 50 | 9677 | Risk Ratio (M-H, Fixed, 95% CI) | 0.71 [0.68, 0.75] |
| 12.2 unblinded | 38 | 6416 | Risk Ratio (M-H, Fixed, 95% CI) | 0.52 [0.47, 0.56] |
| 13 Participants receiving red blood cell transfusions - intention-to treat | 88 | 16093 | Risk Ratio (M-H, Fixed, 95% CI) | 0.65 [0.62, 0.68] |
| 13.1 ITT or less than 10% of participants per study arm excluded | 73 | 13772 | Risk Ratio (M-H, Fixed, 95% CI) | 0.66 [0.63, 0.69] |
| 13.2 more than 10% of participants per study arm excluded | 11 | 1035 | Risk Ratio (M-H, Fixed, 95% CI) | 0.48 [0.36, 0.63] |
| 13.3 unclear | 4 | 1286 | Risk Ratio (M-H, Fixed, 95% CI) | 0.45 [0.33, 0.62] |
| 14 Participants receiving red blood cell transfusions - publication | 88 | 16093 | Risk Ratio (M-H, Fixed, 95% CI) | 0.65 [0.62, 0.68] |
| 14.1 fulltext publication | 65 | 12678 | Risk Ratio (M-H, Fixed, 95% CI) | 0.66 [0.63, 0.70] |
| 14.2 abstract publication | 7 | 1242 | Risk Ratio (M-H, Fixed, 95% CI) | 0.40 [0.32, 0.49] |
| 14.3 unpublished data | 14 | 1658 | Risk Ratio (M-H, Fixed, 95% CI) | 0.73 [0.67, 0.80] |
| 14.4 FDA presented data | 1 | 314 | Risk Ratio (M-H, Fixed, 95% CI) | 0.60 [0.47, 0.78] |
| 14.5 Other | 1 | 201 | Risk Ratio (M-H, Fixed, 95% CI) | 0.44 [0.26, 0.73] |
| 15 Participants receiving red blood cell transfusions - first 4 weeks are... | 88 | 16093 | Risk Ratio (M-H, Fixed, 95% CI) | 0.65 [0.62, 0.68] |
| 15.1 included in the analysis | 32 | 5319 | Risk Ratio (M-H, Fixed, 95% CI) | 0.65 [0.61, 0.70] |
| 15.2 excluded from the analysis | 23 | 3288 | Risk Ratio (M-H, Fixed, 95% CI) | 0.68 [0.61, 0.75] |
| 15.3 unclear | 33 | 7486 | Risk Ratio (M-H, Fixed, 95% CI) | 0.64 [0.60, 0.68] |
| 16 Participants receiving red blood cell transfusions - experimental arms merged | 70 | 16093 | Risk Ratio (M-H, Fixed, 95% CI) | 0.65 [0.62, 0.68] |

**Comparison 4. Number of red blood cell units transfused per patient**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Number of RBC units transfused - overall | 25 | 4715 | Mean Difference (IV, Fixed, 95% CI) | -0.98 [-1.17, -0.78] |
| 2 Number of RBC units transfused - baseline Hb | 25 | 4715 | Mean Difference (IV, Fixed, 95% CI) | -0.98 [-1.17, -0.78] |
| 2.1 Hb < 10g/dL | 16 | 1996 | Mean Difference (IV, Fixed, 95% CI) | -1.02 [-1.35, -0.68] |
| 2.2 Hb 10 to 12g/dL | 5 | 1096 | Mean Difference (IV, Fixed, 95% CI) | -0.95 [-1.24, -0.65] |
| 2.3 Hb > 12g/dL | 4 | 1623 | Mean Difference (IV, Fixed, 95% CI) | -0.97 [-1.41, -0.54] |
| 3 Number of RBC units transfused - age differentiated | 25 | 4715 | Mean Difference (IV, Fixed, 95% CI) | -0.98 [-1.17, -0.78] |
| 3.1 only children <18 years | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 3.2 adults ≥18 years | 21 | 3093 | Mean Difference (IV, Fixed, 95% CI) | -0.81 [-1.04, -0.57] |
| 3.3 >68% non-elderly 18-65 years | 3 | 353 | Mean Difference (IV, Fixed, 95% CI) | -1.25 [-1.72, -0.77] |
| 3.4 only non-elderly adults | 1 | 1269 | Mean Difference (IV, Fixed, 95% CI) | -1.60 [-2.18, -1.02] |
| 3.5 >68% elderly >65 years | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 3.6 only elderly > 65 J | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 4 Number of RBC units transfused - age | 25 | 4715 | Mean Difference (IV, Fixed, 95% CI) | -0.98 [-1.17, -0.78] |
| 4.1 adults | 25 | 4715 | Mean Difference (IV, Fixed, 95% CI) | -0.98 [-1.17, -0.78] |
| 5 Number of RBC units transfused - different malignancies | 25 | 4715 | Mean Difference (IV, Fixed, 95% CI) | -0.98 [-1.17, -0.78] |
| 5.1 solid tumours | 10 | 1437 | Mean Difference (IV, Fixed, 95% CI) | -1.07 [-1.34, -0.80] |
| 5.2 haematological malignancies | 10 | 2254 | Mean Difference (IV, Fixed, 95% CI) | -1.19 [-1.63, -0.76] |
| 5.3 mixed | 5 | 1024 | Mean Difference (IV, Fixed, 95% CI) | -0.62 [-1.01, -0.24] |
| 6 Number of RBC units transfused - different therapies | 25 | 4715 | Mean Difference (IV, Fixed, 95% CI) | -0.98 [-1.17, -0.78] |
| 6.1 chemotherapy | 23 | 4376 | Mean Difference (IV, Fixed, 95% CI) | -0.98 [-1.18, -0.78] |
| 6.2 radiotherapy/ radiochemotherapy | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 6.3 no therapy | 1 | 118 | Mean Difference (IV, Fixed, 95% CI) | -0.67 [-1.81, 0.47] |
| 6.4 unclear/ other | 1 | 221 | Mean Difference (IV, Fixed, 95% CI) | -2.2 [-6.44, 2.04] |
| 7 Number of RBC units transfused - different therapies differentiated | 25 | 4715 | Mean Difference (IV, Fixed, 95% CI) | -0.98 [-1.17, -0.78] |
| 7.1 chemotherapy > 70% with platinum | 10 | 1344 | Mean Difference (IV, Fixed, 95% CI) | -1.11 [-1.40, -0.83] |
| 7.2 chemotherapy, <70% with platinum | 2 | 584 | Mean Difference (IV, Fixed, 95% CI) | -0.52 [-0.93, -0.12] |
| 7.3 chemotherapy without platinum | 9 | 2054 | Mean Difference (IV, Fixed, 95% CI) | -1.23 [-1.69, -0.78] |
| 7.4 chemotherapy, platinum and non-platinum containing, no numbers given | 2 | 394 | Mean Difference (IV, Fixed, 95% CI) | -1.01 [-1.80, -0.21] |
| 7.5 chemotherapy no details given | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |

| | | | | |
|---|---|---|---|---|
| 7.6 radiochemotherapy | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 7.7 radiotherapy | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 7.8 no therapy | 1 | 118 | Mean Difference (IV, Fixed, 95% CI) | -0.67 [-1.81, 0.47] |
| 7.9 unclear/other | 1 | 221 | Mean Difference (IV, Fixed, 95% CI) | -2.2 [-6.44, 2.04] |
| 8 Number of RBC units transfused - epoetin versus darbepoetin | 25 | 4715 | Mean Difference (IV, Fixed, 95% CI) | -0.98 [-1.17, -0.78] |
| 8.1 Epoetin | 23 | 4052 | Mean Difference (IV, Fixed, 95% CI) | -1.06 [-1.29, -0.82] |
| 8.2 Darbepoetin | 2 | 663 | Mean Difference (IV, Fixed, 95% CI) | -0.78 [-1.15, -0.42] |
| 9 Number of RBC units transfused - duration of ESA medication | 25 | 4715 | Mean Difference (IV, Fixed, 95% CI) | -0.98 [-1.17, -0.78] |
| 9.1 6 to 9 weeks | 6 | 364 | Mean Difference (IV, Fixed, 95% CI) | -1.25 [-1.75, -0.75] |
| 9.2 12 to 16 weeks | 12 | 2688 | Mean Difference (IV, Fixed, 95% CI) | -0.78 [-1.03, -0.54] |
| 9.3 more than 17 weeks | 7 | 1663 | Mean Difference (IV, Fixed, 95% CI) | -1.40 [-1.84, -0.95] |
| 10 Number of RBC units transfused - iron supplementation | 25 | 4715 | Mean Difference (IV, Fixed, 95% CI) | -0.98 [-1.17, -0.78] |
| 10.1 fixed iron supplementation | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 10.2 iron supplementation as necessary | 24 | 4402 | Mean Difference (IV, Fixed, 95% CI) | -0.92 [-1.13, -0.72] |
| 10.3 no explicit statement on iron supplementation or no iron given | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 10.4 explicitely stated NO IRON | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 10.5 iron given differently in both study arms | 1 | 313 | Mean Difference (IV, Fixed, 95% CI) | -1.6 [-2.30, -0.90] |
| 11 Number of RBC units transfused - allocation concealment | 25 | 4715 | Mean Difference (IV, Fixed, 95% CI) | -0.98 [-1.17, -0.78] |
| 11.1 adequate | 15 | 2243 | Mean Difference (IV, Fixed, 95% CI) | -0.93 [-1.19, -0.67] |
| 11.2 unclear | 10 | 2472 | Mean Difference (IV, Fixed, 95% CI) | -1.04 [-1.35, -0.74] |
| 12 Number of RBC units transfused - masking | 25 | 4715 | Mean Difference (IV, Fixed, 95% CI) | -0.98 [-1.17, -0.78] |
| 12.1 double-blind | 12 | 3382 | Mean Difference (IV, Fixed, 95% CI) | -0.91 [-1.14, -0.69] |
| 12.2 unblinded | 13 | 1333 | Mean Difference (IV, Fixed, 95% CI) | -1.16 [-1.55, -0.77] |
| 13 Number of RBC units transfused - intention-to-treat | 25 | 4715 | Mean Difference (IV, Fixed, 95% CI) | -0.98 [-1.17, -0.78] |
| 13.1 ITT or less than 10% of participants per study arm excluded | 24 | 4583 | Mean Difference (IV, Fixed, 95% CI) | -0.99 [-1.19, -0.79] |
| 13.2 more than 10% of participants per study arm excluded | 1 | 132 | Mean Difference (IV, Fixed, 95% CI) | -0.69 [-1.66, 0.28] |
| 14 Number of RBC units transfused - publication | 25 | 4715 | Mean Difference (IV, Fixed, 95% CI) | -0.98 [-1.17, -0.78] |
| 14.1 full text publication | 4 | 1200 | Mean Difference (IV, Fixed, 95% CI) | -0.77 [-1.06, -0.48] |
| 14.2 abstract publication | 1 | 1269 | Mean Difference (IV, Fixed, 95% CI) | -1.60 [-2.18, -1.02] |
| 14.3 unpublished data | 20 | 2246 | Mean Difference (IV, Fixed, 95% CI) | -1.03 [-1.33, -0.73] |
| 14.4 FDA presented data | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |

| | | | | |
|---|---|---|---|---|
| 15 Number of RBC units transfused - first 4 weeks are... | 25 | 4715 | Mean Difference (IV, Fixed, 95% CI) | -0.98 [-1.17, -0.78] |
| 15.1 included in the analysis | 18 | 2658 | Mean Difference (IV, Fixed, 95% CI) | -0.99 [-1.23, -0.74] |
| 15.2 excluded from the analysis | 3 | 623 | Mean Difference (IV, Fixed, 95% CI) | -0.53 [-0.94, -0.12] |
| 15.3 unclear | 4 | 1434 | Mean Difference (IV, Fixed, 95% CI) | -1.72 [-2.27, -1.18] |
| 16 Number of RBC units transfused - experimental arms merged | 19 | 4715 | Mean Difference (IV, Fixed, 95% CI) | -0.98 [-1.17, -0.78] |
| 17 Number of RBC units transfused - age differentiated sensitivity analysis | 25 | 4715 | Mean Difference (IV, Fixed, 95% CI) | -0.98 [-1.17, -0.78] |
| 17.1 only children <18 years | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 17.2 adults ≥18 years | 21 | 3093 | Mean Difference (IV, Fixed, 95% CI) | -0.81 [-1.04, -0.57] |
| 17.3 >68% non-elderly 18-65 years | 4 | 1622 | Mean Difference (IV, Fixed, 95% CI) | -1.39 [-1.75, -1.02] |
| 17.4 only non-elderly adults | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 17.5 >68% elderly >65 years | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 17.6 only elderly > 65 J | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |

## Comparison 5. Overall survival

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Overall survival - overall | 80 | 19003 | Peto Odds Ratio (95% CI) | 1.05 [1.00, 1.11] |
| 2 Overall survival updated review (adjusted results) | 80 | 19003 | Peto Odds Ratio (95% CI) | 1.05 [1.00, 1.11] |
| 3 Overall survival - baseline Hb | 80 | 19003 | Peto Odds Ratio (95% CI) | 1.05 [1.00, 1.11] |
| 3.1 Hb < 10 g/dL | 29 | 6144 | Peto Odds Ratio (95% CI) | 1.06 [0.96, 1.17] |
| 3.2 Hb 10 to 12 g/dL | 31 | 6418 | Peto Odds Ratio (95% CI) | 1.01 [0.93, 1.10] |
| 3.3 Hb > 12 g/dL | 15 | 5725 | Peto Odds Ratio (95% CI) | 1.17 [1.06, 1.29] |
| 3.4 unclear | 5 | 716 | Peto Odds Ratio (95% CI) | 0.83 [0.67, 1.03] |
| 4 Overall survival - different malignancies | 80 | 19003 | Peto Odds Ratio (95% CI) | 1.05 [1.00, 1.11] |
| 4.1 solid tumours | 50 | 11704 | Peto Odds Ratio (95% CI) | 1.06 [1.00, 1.13] |
| 4.2 haematological malignancies | 11 | 2901 | Peto Odds Ratio (95% CI) | 1.07 [0.90, 1.26] |
| 4.3 MDS | 1 | 66 | Peto Odds Ratio (95% CI) | 4.52 [0.38, 53.37] |
| 4.4 mixed | 18 | 4332 | Peto Odds Ratio (95% CI) | 1.02 [0.91, 1.15] |
| 4.5 not reported | 0 | 0 | Peto Odds Ratio (95% CI) | 0.0 [0.0, 0.0] |
| 5 Overall survival - age | 80 | 19003 | Peto Odds Ratio (95% CI) | 1.05 [1.00, 1.11] |
| 5.1 children | 1 | 222 | Peto Odds Ratio (95% CI) | 0.98 [0.14, 7.03] |
| 5.2 adults | 79 | 18781 | Peto Odds Ratio (95% CI) | 1.05 [1.00, 1.11] |
| 6 Overall survival - age differentiated | 80 | 19003 | Peto Odds Ratio (95% CI) | 1.05 [1.00, 1.11] |
| 6.1 only children < 18 | 1 | 222 | Peto Odds Ratio (95% CI) | 0.98 [0.14, 7.03] |
| 6.2 adults >= 18 | 62 | 13975 | Peto Odds Ratio (95% CI) | 1.07 [1.01, 1.13] |
| 6.3 > 68% non elderly 18-65 | 11 | 1611 | Peto Odds Ratio (95% CI) | 0.86 [0.67, 1.10] |

| | | | | |
|---|---|---|---|---|
| 6.4 only non-elderly adults | 4 | 2916 | Peto Odds Ratio (95% CI) | 1.02 [0.82, 1.26] |
| 6.5 > 68% elderly > 65 | 2 | 279 | Peto Odds Ratio (95% CI) | 0.77 [0.51, 1.17] |
| 6.6 only elderly > 65 | 0 | 0 | Peto Odds Ratio (95% CI) | 0.0 [0.0, 0.0] |
| 7 Overall survival - different therapies | 80 | 19003 | Peto Odds Ratio (95% CI) | 1.05 [1.00, 1.11] |
| 7.1 chemotherapy | 55 | 13800 | Peto Odds Ratio (95% CI) | 1.04 [0.98, 1.11] |
| 7.2 radiotherapy/ radiochemotherapy | 14 | 2939 | Peto Odds Ratio (95% CI) | 1.03 [0.92, 1.15] |
| 7.3 no therapy | 8 | 1942 | Peto Odds Ratio (95% CI) | 1.23 [1.04, 1.45] |
| 7.4 unclear/other | 3 | 322 | Peto Odds Ratio (95% CI) | 0.79 [0.49, 1.27] |
| 8 Overall survival - different therapies differentiated | 80 | 19003 | Peto Odds Ratio (95% CI) | 1.05 [1.00, 1.11] |
| 8.1 chemotherapy, > 70% with platinum | 19 | 3622 | Peto Odds Ratio (95% CI) | 1.01 [0.91, 1.12] |
| 8.2 chemotherapy, < 70% with platinum | 7 | 1812 | Peto Odds Ratio (95% CI) | 1.14 [0.95, 1.36] |
| 8.3 chemotherapy without platinum (all patients) | 19 | 6706 | Peto Odds Ratio (95% CI) | 1.08 [0.98, 1.19] |
| 8.4 chemotherapy, platinum and non platinum containing, no numbers given | 5 | 910 | Peto Odds Ratio (95% CI) | 0.94 [0.65, 1.37] |
| 8.5 chemotherapy no details given | 5 | 750 | Peto Odds Ratio (95% CI) | 0.82 [0.61, 1.10] |
| 8.6 radiochemotherapy | 8 | 1193 | Peto Odds Ratio (95% CI) | 0.92 [0.78, 1.09] |
| 8.7 radiotherapy | 6 | 1746 | Peto Odds Ratio (95% CI) | 1.12 [0.97, 1.30] |
| 8.8 no therapy | 8 | 1942 | Peto Odds Ratio (95% CI) | 1.23 [1.04, 1.45] |
| 8.9 unclear/other | 3 | 322 | Peto Odds Ratio (95% CI) | 0.79 [0.49, 1.27] |
| 9 Overall survival - epoetin vs darbepoetin | 80 | 19003 | Peto Odds Ratio (95% CI) | 1.05 [1.00, 1.11] |
| 9.1 Epoetin | 67 | 14047 | Peto Odds Ratio (95% CI) | 1.04 [0.98, 1.10] |
| 9.2 Darbepoetin | 13 | 4956 | Peto Odds Ratio (95% CI) | 1.09 [0.99, 1.20] |
| 10 Overall survival - duration of ESA medication | 80 | 19003 | Peto Odds Ratio (95% CI) | 1.05 [1.00, 1.11] |
| 10.1 6 to 9 weeks | 13 | 2244 | Peto Odds Ratio (95% CI) | 1.10 [0.95, 1.27] |
| 10.2 12 to 16 weeks | 46 | 9385 | Peto Odds Ratio (95% CI) | 1.05 [0.98, 1.13] |
| 10.3 more than 17 weeks | 18 | 6963 | Peto Odds Ratio (95% CI) | 1.04 [0.95, 1.14] |
| 10.4 not reported | 3 | 411 | Peto Odds Ratio (95% CI) | 1.10 [0.58, 2.07] |
| 11 Overall survival - iron supplementation | 80 | 19003 | Peto Odds Ratio (95% CI) | 1.05 [1.00, 1.11] |
| 11.1 fixed iron supplementation | 10 | 2348 | Peto Odds Ratio (95% CI) | 1.15 [0.99, 1.33] |
| 11.2 iron supplementation as necessary | 56 | 13888 | Peto Odds Ratio (95% CI) | 1.07 [1.01, 1.14] |
| 11.3 iron handled differently in the study arms | 9 | 2050 | Peto Odds Ratio (95% CI) | 0.96 [0.84, 1.11] |
| 11.4 no explicit statement on iron supplementation or no iron given | 5 | 717 | Peto Odds Ratio (95% CI) | 0.56 [0.38, 0.83] |
| 11.5 explicitly stated NO IRON | 0 | 0 | Peto Odds Ratio (95% CI) | 0.0 [0.0, 0.0] |
| 12 Overall survival - publication | 80 | 19003 | Peto Odds Ratio (95% CI) | 1.05 [1.00, 1.11] |

| | | | | |
|---|---|---|---|---|
| 12.1 full text publication | 20 | 4531 | Peto Odds Ratio (95% CI) | 1.07 [0.92, 1.24] |
| 12.2 abstract publication | 3 | 1020 | Peto Odds Ratio (95% CI) | 1.09 [0.87, 1.37] |
| 12.3 unpublished data | 5 | 318 | Peto Odds Ratio (95% CI) | 0.73 [0.17, 3.05] |
| 12.4 Data presented at FDA hearing | 0 | 0 | Peto Odds Ratio (95% CI) | 0.0 [0.0, 0.0] |
| 12.5 Data taken from IPD review (Bohlius 2009) | 50 | 13018 | Peto Odds Ratio (95% CI) | 1.06 [1.00, 1.12] |
| 12.6 clinical trial result information | 1 | 60 | Peto Odds Ratio (95% CI) | 7.39 [0.15, 372.38] |
| 12.7 other | 1 | 56 | Peto Odds Ratio (95% CI) | 0.58 [0.33, 1.03] |
| 13 Overall survival - time-to-event or binary mortality data | 80 | 19003 | Peto Odds Ratio (95% CI) | 1.05 [1.00, 1.11] |
| 13.1 binary mortality data at end of study | 19 | 1917 | Peto Odds Ratio (95% CI) | 1.02 [0.66, 1.60] |
| 13.2 Data from IPD review | 50 | 13018 | Peto Odds Ratio (95% CI) | 1.06 [1.00, 1.12] |
| 13.3 Cox regression analysis, Hazard ratio, log-rank test, p-value | 7 | 3141 | Peto Odds Ratio (95% CI) | 1.07 [0.92, 1.25] |
| 13.4 Survival curve and p-value | 4 | 927 | Peto Odds Ratio (95% CI) | 0.99 [0.78, 1.24] |
| 14 Overall survival - allocation concealment | 80 | 19003 | Peto Odds Ratio (95% CI) | 1.05 [1.00, 1.11] |
| 14.1 adequate | 47 | 12424 | Peto Odds Ratio (95% CI) | 1.08 [1.02, 1.14] |
| 14.2 unclear | 33 | 6579 | Peto Odds Ratio (95% CI) | 0.97 [0.87, 1.09] |
| 15 Overall survival - masking | 80 | 19003 | Peto Odds Ratio (95% CI) | 1.05 [1.00, 1.11] |
| 15.1 double-blind | 42 | 10525 | Peto Odds Ratio (95% CI) | 1.06 [0.99, 1.14] |
| 15.2 unblinded | 38 | 8478 | Peto Odds Ratio (95% CI) | 1.04 [0.96, 1.12] |
| 16 Overall survival - intention-to-treat | 80 | 19003 | Peto Odds Ratio (95% CI) | 1.05 [1.00, 1.11] |
| 16.1 ITT or less than 10% of participants per study arm excluded | 75 | 18052 | Peto Odds Ratio (95% CI) | 1.05 [1.00, 1.11] |
| 16.2 more than 10% of participants per study arm excluded | 2 | 385 | Peto Odds Ratio (95% CI) | 1.25 [0.92, 1.71] |
| 16.3 Unclear | 3 | 566 | Peto Odds Ratio (95% CI) | 0.49 [0.27, 0.89] |
| 17 Overall survival - follow up | 80 | 19003 | Peto Odds Ratio (95% CI) | 1.05 [1.00, 1.11] |
| 17.1 follow up longer than on-study mortality | 44 | 13224 | Peto Odds Ratio (95% CI) | 1.05 [0.99, 1.10] |
| 17.2 Short term follow up | 36 | 5779 | Peto Odds Ratio (95% CI) | 1.14 [0.95, 1.36] |
| 18 Overall survival - follow up and design | 80 | 19003 | Peto Odds Ratio (95% CI) | 1.05 [1.00, 1.11] |
| 18.1 Long term follow up and designed for long term follow up | 25 | 9704 | Peto Odds Ratio (95% CI) | 1.06 [0.99, 1.12] |
| 18.2 Long term follow up but not designed for long term follow up | 11 | 2197 | Peto Odds Ratio (95% CI) | 1.02 [0.89, 1.18] |
| 18.3 Long term follow up and design unclear | 7 | 1142 | Peto Odds Ratio (95% CI) | 0.96 [0.79, 1.16] |

| | | | | |
|---|---|---|---|---|
| 18.4 Short term follow up but designed for long term follow up | 3 | 1250 | Peto Odds Ratio (95% CI) | 1.32 [1.05, 1.66] |
| 18.5 Short term follow up and not designed for long term follow up | 34 | 4710 | Peto Odds Ratio (95% CI) | 0.97 [0.76, 1.23] |
| 18.6 short term follow up and design unclear | 0 | 0 | Peto Odds Ratio (95% CI) | 0.0 [0.0, 0.0] |
| 19 Overall survival- experimental arms merged | 78 | 19003 | Peto Odds Ratio (95% CI) | 1.05 [1.00, 1.11] |
| 20 Overall survival- experimental arms merged sens pos | 76 | 17551 | Peto Odds Ratio (95% CI) | 1.04 [0.98, 1.10] |
| 21 Overall survival- experimental arms merged sens neg | 76 | 18018 | Peto Odds Ratio (95% CI) | 1.08 [1.02, 1.14] |
| 22 Overall survival - sensitivity analysis baseline Hb | 75 | 18287 | Peto Odds Ratio (95% CI) | 1.07 [1.01, 1.13] |
| 22.1 Hb < 10 g/dL | 29 | 6144 | Peto Odds Ratio (95% CI) | 1.06 [0.96, 1.17] |
| 22.2 Hb 10 to 12 g/dL | 31 | 6418 | Peto Odds Ratio (95% CI) | 1.01 [0.93, 1.10] |
| 22.3 Hb > 12 g/dL | 15 | 5725 | Peto Odds Ratio (95% CI) | 1.17 [1.06, 1.29] |
| 23 Overall survival - sensitivity analysis iron supplementation | 75 | 18286 | Peto Odds Ratio (95% CI) | 1.07 [1.01, 1.12] |
| 23.1 fixed iron supplementation | 10 | 2348 | Peto Odds Ratio (95% CI) | 1.15 [0.99, 1.33] |
| 23.2 iron supplementation as necessary | 56 | 13888 | Peto Odds Ratio (95% CI) | 1.07 [1.01, 1.14] |
| 23.3 iron handled differently in the study arms | 9 | 2050 | Peto Odds Ratio (95% CI) | 0.96 [0.84, 1.11] |
| 23.4 explicitly stated NO IRON | 0 | 0 | Peto Odds Ratio (95% CI) | 0.0 [0.0, 0.0] |
| 24 Overall survival - sensitivity analysis intention-to-treat | 77 | 18437 | Peto Odds Ratio (95% CI) | 1.06 [1.01, 1.12] |
| 24.1 ITT or less than 10% of participants per study arm excluded | 75 | 18052 | Peto Odds Ratio (95% CI) | 1.05 [1.00, 1.11] |
| 24.2 more than 10% of participants per study arm excluded | 2 | 385 | Peto Odds Ratio (95% CI) | 1.25 [0.92, 1.71] |

## Comparison 6. On-study mortality

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 On-study mortality - overall | 72 | 15935 | Peto Odds Ratio (95% CI) | 1.17 [1.06, 1.29] |
| 2 On-study mortality - baseline Hb | 72 | 15935 | Peto Odds Ratio (95% CI) | 1.17 [1.06, 1.29] |
| 2.1 Hb < 10 g/dL | 28 | 5759 | Peto Odds Ratio (95% CI) | 1.12 [0.96, 1.32] |
| 2.2 Hb 10 to 12 g/dL | 26 | 5537 | Peto Odds Ratio (95% CI) | 1.09 [0.91, 1.29] |
| 2.3 Hb > 12 g/dL | 13 | 3923 | Peto Odds Ratio (95% CI) | 1.37 [1.12, 1.68] |

| | | | | |
|---|---|---|---|---|
| 2.4 unclear | 5 | 716 | Peto Odds Ratio (95% CI) | 1.20 [0.75, 1.93] |
| 3 On-study mortality - different malignancies | 72 | 15935 | Peto Odds Ratio (95% CI) | 1.17 [1.06, 1.29] |
| 3.1 solid tumours | 44 | 10056 | Peto Odds Ratio (95% CI) | 1.21 [1.06, 1.37] |
| 3.2 haematological malignancies | 10 | 1598 | Peto Odds Ratio (95% CI) | 1.13 [0.80, 1.59] |
| 3.3 MDS | 1 | 66 | Peto Odds Ratio (95% CI) | 4.52 [0.38, 53.37] |
| 3.4 mixed | 17 | 4215 | Peto Odds Ratio (95% CI) | 1.10 [0.92, 1.31] |
| 3.5 not reported | 0 | 0 | Peto Odds Ratio (95% CI) | 0.0 [0.0, 0.0] |
| 4 On-study mortality - age | 72 | 15935 | Peto Odds Ratio (95% CI) | 1.17 [1.06, 1.29] |
| 4.1 children | 1 | 222 | Peto Odds Ratio (95% CI) | 0.98 [0.14, 7.03] |
| 4.2 adults | 71 | 15713 | Peto Odds Ratio (95% CI) | 1.17 [1.06, 1.29] |
| 5 On-study mortality - age differentiated | 72 | 15935 | Peto Odds Ratio (95% CI) | 1.17 [1.06, 1.29] |
| 5.1 children | 1 | 222 | Peto Odds Ratio (95% CI) | 0.98 [0.14, 7.03] |
| 5.2 adults >= 18 | 59 | 13007 | Peto Odds Ratio (95% CI) | 1.18 [1.07, 1.31] |
| 5.3 > 68% non elderly, 18-65 | 10 | 1334 | Peto Odds Ratio (95% CI) | 0.76 [0.42, 1.35] |
| 5.4 only non elderly adults | 2 | 1372 | Peto Odds Ratio (95% CI) | 0.0 [0.0, 0.0] |
| 5.5 > 68% elderly > 65 years | 0 | 0 | Peto Odds Ratio (95% CI) | 0.0 [0.0, 0.0] |
| 5.6 only elderly | 0 | 0 | Peto Odds Ratio (95% CI) | 0.0 [0.0, 0.0] |
| 6 On-study mortality - different therapies | 72 | 15935 | Peto Odds Ratio (95% CI) | 1.17 [1.06, 1.29] |
| 6.1 chemotherapy | 52 | 12058 | Peto Odds Ratio (95% CI) | 1.10 [0.98, 1.24] |
| 6.2 radiotherapy/ radiochemotherapy | 10 | 1669 | Peto Odds Ratio (95% CI) | 1.48 [0.96, 2.27] |
| 6.3 no therapy | 8 | 1942 | Peto Odds Ratio (95% CI) | 1.34 [1.07, 1.66] |
| 6.4 unclear/other | 2 | 266 | Peto Odds Ratio (95% CI) | 1.48 [0.65, 3.37] |
| 7 On-study mortality - different therapies differentiated | 72 | 15935 | Peto Odds Ratio (95% CI) | 1.17 [1.06, 1.29] |
| 7.1 chemotherapy, > 70% with platinum | 19 | 3622 | Peto Odds Ratio (95% CI) | 1.04 [0.85, 1.27] |
| 7.2 chemotherapy, <70% with platinum | 6 | 1475 | Peto Odds Ratio (95% CI) | 1.06 [0.76, 1.49] |
| 7.3 chemotherapy without platinum, all patients | 18 | 5418 | Peto Odds Ratio (95% CI) | 1.24 [1.04, 1.47] |
| 7.4 chemotherapy, platinum and non-platinum containing, no numbers given | 4 | 793 | Peto Odds Ratio (95% CI) | 0.74 [0.40, 1.38] |
| 7.5 chemotherapy, no details reported | 5 | 750 | Peto Odds Ratio (95% CI) | 0.82 [0.50, 1.34] |
| 7.6 radiochemotherapy | 6 | 822 | Peto Odds Ratio (95% CI) | 1.46 [0.85, 2.51] |
| 7.7 radiotherapy | 4 | 847 | Peto Odds Ratio (95% CI) | 1.51 [0.75, 3.06] |
| 7.8 no therapy | 8 | 1942 | Peto Odds Ratio (95% CI) | 1.34 [1.07, 1.66] |
| 7.9 unclear/other | 2 | 266 | Peto Odds Ratio (95% CI) | 1.48 [0.65, 3.37] |
| 8 On-study mortality - duration of ESA medication | 72 | 15935 | Peto Odds Ratio (95% CI) | 1.17 [1.06, 1.29] |
| 8.1 6 to 9 weeks | 9 | 1113 | Peto Odds Ratio (95% CI) | 0.95 [0.57, 1.59] |
| 8.2 12 to 16 weeks | 44 | 8992 | Peto Odds Ratio (95% CI) | 1.16 [1.02, 1.33] |
| 8.3 more than 17 weeks | 16 | 5419 | Peto Odds Ratio (95% CI) | 1.22 [1.04, 1.42] |
| 8.4 not reported | 3 | 411 | Peto Odds Ratio (95% CI) | 0.82 [0.38, 1.78] |

| | | | | |
|---|---|---|---|---|
| 9 On-study mortality - epoetin vs darbepoetin | 72 | 15935 | Peto Odds Ratio (95% CI) | 1.17 [1.06, 1.29] |
| 9.1 Epoetin | 60 | 11478 | Peto Odds Ratio (95% CI) | 1.16 [1.03, 1.30] |
| 9.2 Darbepoetin | 12 | 4457 | Peto Odds Ratio (95% CI) | 1.20 [1.00, 1.44] |
| 10 On-study mortality - iron supplementation | 72 | 15935 | Peto Odds Ratio (95% CI) | 1.17 [1.06, 1.29] |
| 10.1 fixed iron supplementation | 8 | 1911 | Peto Odds Ratio (95% CI) | 1.20 [0.80, 1.81] |
| 10.2 iron supplementation as necessary | 53 | 11954 | Peto Odds Ratio (95% CI) | 1.17 [1.05, 1.30] |
| 10.3 no explicit statement on iron supplementation or no iron given | 3 | 276 | Peto Odds Ratio (95% CI) | 2.16 [0.72, 6.46] |
| 10.4 explicitly stated no iron | 0 | 0 | Peto Odds Ratio (95% CI) | 0.0 [0.0, 0.0] |
| 10.5 iron handled differently in the study arms | 8 | 1794 | Peto Odds Ratio (95% CI) | 1.09 [0.74, 1.60] |
| 11 On-study mortality - publication | 72 | 15935 | Peto Odds Ratio (95% CI) | 1.17 [1.06, 1.29] |
| 11.1 full text publication | 14 | 1689 | Peto Odds Ratio (95% CI) | 0.97 [0.60, 1.57] |
| 11.2 abstract publication | 2 | 181 | Peto Odds Ratio (95% CI) | 7.64 [1.29, 45.03] |
| 11.3 unpublished data | 5 | 318 | Peto Odds Ratio (95% CI) | 1.65 [0.20, 13.32] |
| 11.4 Data presented at FDA hearing | 0 | 0 | Peto Odds Ratio (95% CI) | 0.0 [0.0, 0.0] |
| 11.5 IPD Bohlius 2009 | 51 | 13747 | Peto Odds Ratio (95% CI) | 1.17 [1.06, 1.29] |
| 12 On-study mortality - time-to-event or binary mortality data | 72 | 15935 | Peto Odds Ratio (95% CI) | 1.17 [1.06, 1.29] |
| 12.1 binary mortality data at end of study | 21 | 2188 | Peto Odds Ratio (95% CI) | 1.14 [0.73, 1.79] |
| 12.2 Results from IPD review | 51 | 13747 | Peto Odds Ratio (95% CI) | 1.17 [1.06, 1.29] |
| 12.3 Cox regression analysis, Hazard ratio, log-rank test, p-value | 0 | 0 | Peto Odds Ratio (95% CI) | 0.0 [0.0, 0.0] |
| 12.4 Survival curve and p-value | 0 | 0 | Peto Odds Ratio (95% CI) | 0.0 [0.0, 0.0] |
| 13 On-study mortality - allocation concealment | 72 | 15935 | Peto Odds Ratio (95% CI) | 1.17 [1.06, 1.29] |
| 13.1 adequate | 42 | 11144 | Peto Odds Ratio (95% CI) | 1.20 [1.08, 1.34] |
| 13.2 unclear | 30 | 4791 | Peto Odds Ratio (95% CI) | 1.03 [0.82, 1.30] |
| 14 On-study mortality - masking | 72 | 15935 | Peto Odds Ratio (95% CI) | 1.17 [1.06, 1.29] |
| 14.1 double-blind | 39 | 9049 | Peto Odds Ratio (95% CI) | 1.19 [1.06, 1.34] |
| 14.2 unblinded | 33 | 6886 | Peto Odds Ratio (95% CI) | 1.12 [0.94, 1.34] |
| 15 On-study mortality - intention-to-treat | 72 | 15935 | Peto Odds Ratio (95% CI) | 1.17 [1.06, 1.29] |
| 15.1 ITT or less than 10% of participants per study arm excluded | 69 | 15706 | Peto Odds Ratio (95% CI) | 1.16 [1.05, 1.28] |
| 15.2 more than 10% of participants per study arm excluded | 1 | 48 | Peto Odds Ratio (95% CI) | 0.0 [0.0, 0.0] |
| 15.3 Unclear | 2 | 181 | Peto Odds Ratio (95% CI) | 7.64 [1.29, 45.03] |

| | | | | |
|---|---|---|---|---|
| 16 On-study mortality - sensitivity analysis - follow-up | 80 | 19018 | Peto Odds Ratio (95% CI) | 1.16 [1.05, 1.27] |
| 16.1 Short term follow subgroup | 72 | 15935 | Peto Odds Ratio (95% CI) | 1.17 [1.06, 1.29] |
| 16.2 Short term from Kaplan Meier curve | 7 | 2966 | Peto Odds Ratio (95% CI) | 1.06 [0.60, 1.86] |
| 16.3 Long term follow up | 1 | 117 | Peto Odds Ratio (95% CI) | 0.94 [0.57, 1.54] |
| 17 On-study mortality - sensitivity analysis experimental arms merged | 70 | 15935 | Peto Odds Ratio (95% CI) | 1.17 [1.06, 1.29] |
| 18 On-study mortality - sensitivity analysis intention-to-treat | 70 | 15754 | Peto Odds Ratio (95% CI) | 1.16 [1.05, 1.28] |
| 18.1 ITT or less than 10% of participants per study arm excluded | 69 | 15706 | Peto Odds Ratio (95% CI) | 1.16 [1.05, 1.28] |
| 18.2 more than 10% of participants per study arm excluded | 1 | 48 | Peto Odds Ratio (95% CI) | 0.0 [0.0, 0.0] |
| 19 On-study mortality - sensitivity analysis excluding Leyland and Smith | 70 | 14007 | Peto Odds Ratio (95% CI) | 1.09 [0.97, 1.23] |

**Comparison 7. Complete tumour response**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Complete tumour response | 19 | 5012 | Risk Ratio (M-H, Fixed, 95% CI) | 1.02 [0.98, 1.06] |
| 2 Tumour-response specific quality criteria | 19 | 5012 | Risk Ratio (M-H, Fixed, 95% CI) | 1.02 [0.98, 1.06] |
| 2.1 high quality | 5 | 2476 | Risk Ratio (M-H, Fixed, 95% CI) | 0.99 [0.95, 1.02] |
| 2.2 low quality | 14 | 2536 | Risk Ratio (M-H, Fixed, 95% CI) | 1.15 [0.98, 1.36] |
| 3 Complete tumour response - experimental study arms merged | 15 | 5012 | Risk Ratio (M-H, Fixed, 95% CI) | 1.02 [0.98, 1.06] |

**Comparison 8. Change in FACT-Fatigue 13**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Change in FACT-Fatigue (13 items) - overall | 18 | 4965 | Mean Difference (IV, Fixed, 95% CI) | 2.08 [1.43, 2.72] |
| 2 Change in FACT-Fatigue sensitivity analysis- Tsuboi | 18 | 4967 | Mean Difference (IV, Fixed, 95% CI) | 2.10 [1.46, 2.75] |

| | | | | |
|---|---|---|---|---|
| 3 Change in FACT-F 13 - baseline Hb | 18 | 4965 | Mean Difference (IV, Fixed, 95% CI) | 2.08 [1.43, 2.72] |
| 3.1 Hb <= 10 g/dL | 8 | 2484 | Mean Difference (IV, Fixed, 95% CI) | 1.66 [0.76, 2.55] |
| 3.2 Hb 10 to 12 g/dL | 9 | 2181 | Mean Difference (IV, Fixed, 95% CI) | 2.87 [1.89, 3.85] |
| 3.3 Hb > 12 g/dL | 1 | 300 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [-2.63, 2.63] |
| 3.4 Hb category unclear | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 4 Change in FACT-F 13 - different malignancies | 18 | 4965 | Mean Difference (IV, Fixed, 95% CI) | 2.08 [1.43, 2.72] |
| 4.1 solid tumours | 9 | 2459 | Mean Difference (IV, Fixed, 95% CI) | 2.29 [1.33, 3.25] |
| 4.2 haematological malignancies | 2 | 566 | Mean Difference (IV, Fixed, 95% CI) | 1.99 [0.28, 3.69] |
| 4.3 mixed | 7 | 1940 | Mean Difference (IV, Fixed, 95% CI) | 1.87 [0.87, 2.87] |
| 4.4 unclear | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 5 Change in FACT-F 13 - age | 18 | 4965 | Mean Difference (IV, Fixed, 95% CI) | 2.08 [1.43, 2.72] |
| 5.1 only children < 18 years | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 5.2 adults >= 18 years | 17 | 4627 | Mean Difference (IV, Fixed, 95% CI) | 1.82 [1.16, 2.49] |
| 5.3 >70% non elderly 18-65 years | 1 | 338 | Mean Difference (IV, Fixed, 95% CI) | 5.1 [2.79, 7.41] |
| 5.4 only non-elderly adults | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 5.5 >70% elderly >65 years | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 5.6 only elderly > 65 years | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 6 Change in FACT-F 13 - different therapies | 18 | 4965 | Mean Difference (IV, Fixed, 95% CI) | 2.08 [1.43, 2.72] |
| 6.1 chemotherapy | 14 | 3515 | Mean Difference (IV, Fixed, 95% CI) | 2.79 [2.03, 3.55] |
| 6.2 radiotherapy | 1 | 300 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [-2.63, 2.63] |
| 6.3 no therapy | 3 | 1150 | Mean Difference (IV, Fixed, 95% CI) | 0.42 [-0.91, 1.76] |
| 6.4 unclear | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 7 Change in FACT-F 13 - different therapies differentiated | 18 | 4965 | Mean Difference (IV, Fixed, 95% CI) | 2.07 [1.43, 2.72] |
| 7.1 chemotherapy, >70% with platinum | 4 | 1069 | Mean Difference (IV, Fixed, 95% CI) | 1.85 [0.41, 3.30] |
| 7.2 chemotherapy, <70% platinum containing | 2 | 411 | Mean Difference (IV, Fixed, 95% CI) | 2.53 [-0.01, 5.07] |
| 7.3 chemotherapy without platinum (all patients) | 6 | 1468 | Mean Difference (IV, Fixed, 95% CI) | 3.22 [2.12, 4.32] |
| 7.4 chemotherapy, platinum and non-platinum containing, no numbers given | 3 | 567 | Mean Difference (IV, Fixed, 95% CI) | 3.27 [1.30, 5.23] |
| 7.5 radiochemotherapy NEW | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 7.6 radiotherapy | 1 | 300 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [-2.63, 2.63] |
| 7.7 no therapy | 3 | 1150 | Mean Difference (IV, Fixed, 95% CI) | 0.42 [-0.91, 1.76] |
| 7.8 unclear | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 7.9 chemotherapy no details given | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 8 Change in FACT-F 13 - epoetin versus darbepoetin | 18 | 4965 | Mean Difference (IV, Fixed, 95% CI) | 2.08 [1.43, 2.72] |
| 8.1 Epoetin | 11 | 2475 | Mean Difference (IV, Fixed, 95% CI) | 3.25 [2.33, 4.16] |
| 8.2 Darbepoetin | 7 | 2490 | Mean Difference (IV, Fixed, 95% CI) | 0.94 [0.04, 1.84] |
| 9 Change in FACT-F 13 - duration of ESA medication | 18 | 4965 | Mean Difference (IV, Fixed, 95% CI) | 2.08 [1.43, 2.72] |
| 9.1 6 to 9 weeks | 1 | 115 | Mean Difference (IV, Fixed, 95% CI) | 3.10 [-0.27, 6.47] |
| 9.2 12 to 16 weeks | 15 | 4076 | Mean Difference (IV, Fixed, 95% CI) | 1.99 [1.30, 2.69] |

| | | | | |
|---|---|---|---|---|
| 9.3 more than 17 weeks | 2 | 774 | Mean Difference (IV, Fixed, 95% CI) | 2.35 [0.46, 4.25] |
| 9.4 unclear | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 10 Change in FACT-F 13 - iron supplementation | 18 | 4965 | Mean Difference (IV, Fixed, 95% CI) | 2.08 [1.43, 2.72] |
| 10.1 fixed iron supplementation | 4 | 863 | Mean Difference (IV, Fixed, 95% CI) | 1.64 [-0.01, 3.29] |
| 10.2 iron supplementation as necessary | 13 | 3881 | Mean Difference (IV, Fixed, 95% CI) | 2.03 [1.32, 2.74] |
| 10.3 no explicit statement on iron supplementation or no iron given | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 10.4 explicitly stated NO IRON | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 10.5 unclear | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 10.6 iron given differently in both study arms new | 1 | 221 | Mean Difference (IV, Fixed, 95% CI) | 5.15 [1.70, 8.60] |
| 11 Change in FACT-F 13 - allocation concealment | 18 | 4965 | Mean Difference (IV, Fixed, 95% CI) | 2.08 [1.43, 2.72] |
| 11.1 adequate | 16 | 4493 | Mean Difference (IV, Fixed, 95% CI) | 2.20 [1.51, 2.89] |
| 11.2 unclear | 2 | 472 | Mean Difference (IV, Fixed, 95% CI) | 1.20 [-0.61, 3.02] |
| 11.3 unclear wether adequate or unclear :) | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 12 Change in FACT-F 13 - masking | 18 | 4965 | Mean Difference (IV, Fixed, 95% CI) | 2.08 [1.43, 2.72] |
| 12.1 double-blind | 11 | 3384 | Mean Difference (IV, Fixed, 95% CI) | 1.33 [0.56, 2.10] |
| 12.2 unblinded | 7 | 1581 | Mean Difference (IV, Fixed, 95% CI) | 3.76 [2.60, 4.92] |
| 13 Change in FACT-F 13 - intention-to treat | 18 | 4965 | Mean Difference (IV, Fixed, 95% CI) | 2.08 [1.43, 2.72] |
| 13.1 ITT or less than 10% of participants per study arm excluded | 4 | 864 | Mean Difference (IV, Fixed, 95% CI) | 3.30 [1.89, 4.70] |
| 13.2 more than 10% of participants per study arm excluded | 12 | 3689 | Mean Difference (IV, Fixed, 95% CI) | 1.80 [1.04, 2.56] |
| 13.3 unclear | 2 | 412 | Mean Difference (IV, Fixed, 95% CI) | 1.34 [-0.95, 3.63] |
| 14 Change in FACT-F 13 - publication | 18 | 4965 | Mean Difference (IV, Fixed, 95% CI) | 2.08 [1.43, 2.72] |
| 14.1 full text publication | 16 | 4412 | Mean Difference (IV, Fixed, 95% CI) | 2.17 [1.49, 2.85] |
| 14.2 abstract publication | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 14.3 unpublished data | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 14.4 FDA hearing | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 14.5 clinical trial result information | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 14.6 other source | 2 | 553 | Mean Difference (IV, Fixed, 95% CI) | 1.32 [-0.63, 3.26] |
| 15 Change in FACT-F 13 - type of data | 18 | 4965 | Mean Difference (IV, Fixed, 95% CI) | 2.08 [1.43, 2.72] |
| 15.1 Not imputed data | 7 | 2298 | Mean Difference (IV, Fixed, 95% CI) | 1.88 [0.96, 2.80] |
| 15.2 Imputed data | 11 | 2667 | Mean Difference (IV, Fixed, 95% CI) | 2.26 [1.36, 3.15] |

## Comparison 9. Change in FACT-An 20

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Change in FACT-An (20 items) - overall | 6 | 1085 | Mean Difference (IV, Fixed, 95% CI) | 6.14 [4.55, 7.73] |
| 2 Change in FACT-An 20 - baseline Hb | 6 | 1085 | Mean Difference (IV, Fixed, 95% CI) | 6.14 [4.55, 7.73] |
| 2.1 Hb <= 10 g/dL | 1 | 290 | Mean Difference (IV, Fixed, 95% CI) | 6.6 [3.92, 9.28] |
| 2.2 Hb 10 to 12 g/dL | 4 | 713 | Mean Difference (IV, Fixed, 95% CI) | 5.82 [3.71, 7.93] |
| 2.3 Hb > 12 g/dL | 1 | 82 | Mean Difference (IV, Fixed, 95% CI) | 6.4 [0.83, 11.97] |
| 2.4 Hb category unclear | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 3 Change in FACT-An 20 - different malignancies | 6 | 1085 | Mean Difference (IV, Fixed, 95% CI) | 6.14 [4.55, 7.73] |
| 3.1 solid tumours | 5 | 795 | Mean Difference (IV, Fixed, 95% CI) | 5.90 [3.92, 7.87] |
| 3.2 haematological malignancies | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 3.3 mixed | 1 | 290 | Mean Difference (IV, Fixed, 95% CI) | 6.6 [3.92, 9.28] |
| 3.4 unclear | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 4 Change in FACT-An 20 - age | 6 | 1085 | Mean Difference (IV, Fixed, 95% CI) | 6.14 [4.55, 7.73] |
| 4.1 only children < 18 years | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 4.2 adults >= 18 years | 5 | 747 | Mean Difference (IV, Fixed, 95% CI) | 5.93 [4.00, 7.86] |
| 4.3 >70% non elderly 18-65 years | 1 | 338 | Mean Difference (IV, Fixed, 95% CI) | 6.59 [3.79, 9.39] |
| 4.4 only non-elderly adults | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 4.5 >70% elderly >65 years | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 4.6 only elderly > 65 years | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 5 Change in FACT-An 20 - different therapies | 6 | 1085 | Mean Difference (IV, Fixed, 95% CI) | 6.14 [4.55, 7.73] |
| 5.1 chemotherapy | 5 | 1051 | Mean Difference (IV, Fixed, 95% CI) | 6.21 [4.60, 7.82] |
| 5.2 radiotherapy | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 5.3 no therapy | 1 | 34 | Mean Difference (IV, Fixed, 95% CI) | 3.9 [-5.75, 13.55] |
| 5.4 unclear | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 6 Change in FACT-An 20 - different therapies differentiated | 6 | 1085 | Mean Difference (IV, Fixed, 95% CI) | 6.14 [4.55, 7.73] |
| 6.1 chemotherapy, >70% with platinum | 2 | 256 | Mean Difference (IV, Fixed, 95% CI) | 5.08 [1.12, 9.04] |
| 6.2 chemotherapy, <70% platinum containing | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 6.3 chemotherapy without platinum (all patients) | 4 | 795 | Mean Difference (IV, Fixed, 95% CI) | 6.43 [4.66, 8.19] |
| 6.4 chemotherapy, platinum and non-platinum containing, no numbers given | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 6.5 radiochemotherapy NEW | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 6.6 radiotherapy | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 6.7 no therapy | 1 | 34 | Mean Difference (IV, Fixed, 95% CI) | 3.9 [-5.75, 13.55] |
| 6.8 unclear | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |

| | | | | |
|---|---|---|---|---|
| 6.9 chemotherapy no details given | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 7 Change in FACT-An 20 - epoetin versus darbepoetin | 6 | 1085 | Mean Difference (IV, Fixed, 95% CI) | 6.14 [4.55, 7.73] |
| 7.1 Epoetin | 6 | 1085 | Mean Difference (IV, Fixed, 95% CI) | 6.14 [4.55, 7.73] |
| 7.2 Darbepoetin | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 8 Change in FACT-An 20 - duration of ESA medication | 6 | 1085 | Mean Difference (IV, Fixed, 95% CI) | 6.14 [4.55, 7.73] |
| 8.1 6 to 9 weeks | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 8.2 12 to 16 weeks | 5 | 795 | Mean Difference (IV, Fixed, 95% CI) | 5.90 [3.92, 7.87] |
| 8.3 more than 17 weeks | 1 | 290 | Mean Difference (IV, Fixed, 95% CI) | 6.6 [3.92, 9.28] |
| 8.4 unclear | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 9 Change in FACT-An 20 - iron supplementation | 6 | 1085 | Mean Difference (IV, Fixed, 95% CI) | 6.14 [4.55, 7.73] |
| 9.1 fixed iron supplementation | 1 | 126 | Mean Difference (IV, Fixed, 95% CI) | 3.53 [-1.90, 8.96] |
| 9.2 iron supplementation as necessary | 4 | 744 | Mean Difference (IV, Fixed, 95% CI) | 6.48 [4.68, 8.28] |
| 9.3 no explicit statement on iron supplementation or no iron given | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 9.4 explicitly stated NO IRON | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 9.5 unclear | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 9.6 iron given differently in both study arms new | 1 | 215 | Mean Difference (IV, Fixed, 95% CI) | 5.84 [1.47, 10.21] |
| 10 Change in FACT-An 20 - allocation concealment | 6 | 1085 | Mean Difference (IV, Fixed, 95% CI) | 6.14 [4.55, 7.73] |
| 10.1 adequate | 6 | 1085 | Mean Difference (IV, Fixed, 95% CI) | 6.14 [4.55, 7.73] |
| 10.2 unclear | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 10.3 unclear wether adequate or unclear :) | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 11 Change in FACT-An 20 - masking | 6 | 1085 | Mean Difference (IV, Fixed, 95% CI) | 6.14 [4.55, 7.73] |
| 11.1 double-blind | 3 | 406 | Mean Difference (IV, Fixed, 95% CI) | 6.41 [4.06, 8.75] |
| 11.2 unblinded | 3 | 679 | Mean Difference (IV, Fixed, 95% CI) | 5.92 [3.76, 8.08] |
| 12 Change in FACT-An 20 - intention-to treat | 6 | 1085 | Mean Difference (IV, Fixed, 95% CI) | 6.14 [4.55, 7.73] |
| 12.1 ITT or less than 10% of participants per study arm excluded | 1 | 338 | Mean Difference (IV, Fixed, 95% CI) | 6.59 [3.79, 9.39] |
| 12.2 more than 10% of participants per study arm excluded | 5 | 747 | Mean Difference (IV, Fixed, 95% CI) | 5.93 [4.00, 7.86] |
| 12.3 unclear | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 13 Change in FACT-An 20 - publication | 6 | 1085 | Mean Difference (IV, Fixed, 95% CI) | 6.14 [4.55, 7.73] |
| 13.1 full text publication | 6 | 1085 | Mean Difference (IV, Fixed, 95% CI) | 6.14 [4.55, 7.73] |
| 13.2 abstract publication | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 13.3 unpublished data | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 13.4 FDA hearing | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |

| | | | | |
|---|---|---|---|---|
| 13.5 clinical trial result information | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 14 Change in FACT-An 20 - data type | 6 | 1085 | Mean Difference (IV, Fixed, 95% CI) | 6.14 [4.55, 7.73] |
| 14.1 Not imputed data | 3 | 635 | Mean Difference (IV, Fixed, 95% CI) | 6.38 [4.20, 8.55] |
| 14.2 Imputed data | 3 | 450 | Mean Difference (IV, Fixed, 95% CI) | 5.88 [3.54, 8.21] |

**Comparison 10. Change in FACT-An Total 47**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Change in FACT-An Total (47 items) - overall | 10 | 1815 | Mean Difference (IV, Fixed, 95% CI) | 6.92 [4.59, 9.25] |
| 2 Change in FACT-An Total 47-sensitivity analysis | 9 | 1715 | Mean Difference (IV, Fixed, 95% CI) | 3.46 [0.96, 5.96] |
| 3 Change in FACT-An Total 47 - baseline Hb | 10 | 1815 | Mean Difference (IV, Fixed, 95% CI) | 6.92 [4.59, 9.25] |
| 3.1 Hb <= 10 g/dL | 5 | 978 | Mean Difference (IV, Fixed, 95% CI) | 2.57 [-0.63, 5.78] |
| 3.2 Hb 10 to 12 g/dL | 4 | 537 | Mean Difference (IV, Fixed, 95% CI) | 16.22 [12.14, 20.30] |
| 3.3 Hb > 12 g/dL | 1 | 300 | Mean Difference (IV, Fixed, 95% CI) | 1.90 [-4.19, 7.99] |
| 3.4 Hb category unclear | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 4 Change in FACT-An Total 47 - different malignancies | 10 | 1815 | Mean Difference (IV, Fixed, 95% CI) | 6.92 [4.59, 9.25] |
| 4.1 solid tumours | 8 | 1437 | Mean Difference (IV, Fixed, 95% CI) | 7.21 [4.58, 9.84] |
| 4.2 haematological malignancies | 1 | 206 | Mean Difference (IV, Fixed, 95% CI) | 6.10 [-1.67, 13.87] |
| 4.3 mixed | 1 | 172 | Mean Difference (IV, Fixed, 95% CI) | 5.7 [-0.83, 12.23] |
| 4.4 unclear | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 5 Change in FACT-An Total 47 - age | 10 | 1815 | Mean Difference (IV, Fixed, 95% CI) | 6.92 [4.59, 9.25] |
| 5.1 only children < 18 years | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 5.2 adults >= 18 years | 10 | 1815 | Mean Difference (IV, Fixed, 95% CI) | 6.92 [4.59, 9.25] |
| 5.3 >70% non elderly 18-65 years | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 5.4 only non-elderly adults | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 5.5 >70% elderly >65 years | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 5.6 only elderly > 65 years | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 6 Change in FACT-An Total 47 - different therapies | 10 | 1815 | Mean Difference (IV, Fixed, 95% CI) | 6.92 [4.59, 9.25] |
| 6.1 chemotherapy | 8 | 1415 | Mean Difference (IV, Fixed, 95% CI) | 3.77 [1.03, 6.51] |
| 6.2 radiotherapy | 1 | 300 | Mean Difference (IV, Fixed, 95% CI) | 1.90 [-4.19, 7.99] |
| 6.3 no therapy | 1 | 100 | Mean Difference (IV, Fixed, 95% CI) | 29.90 [23.46, 36.34] |
| 6.4 unclear | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 7 Change in FACT-An Total 47 - different therapies differentiated | 10 | 1815 | Mean Difference (IV, Fixed, 95% CI) | 6.92 [4.59, 9.25] |
| 7.1 chemotherapy, >70% with platinum | 3 | 352 | Mean Difference (IV, Fixed, 95% CI) | 6.91 [1.12, 12.70] |

| | | | | |
|---|---|---|---|---|
| 7.2 chemotherapy, <70% platinum containing | 3 | 600 | Mean Difference (IV, Fixed, 95% CI) | 0.28 [-3.90, 4.45] |
| 7.3 chemotherapy without platinum (all patients) | 3 | 463 | Mean Difference (IV, Fixed, 95% CI) | 6.10 [1.44, 10.76] |
| 7.4 chemotherapy, platinum and non-platinum containing, no numbers given | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 7.5 radiochemotherapy NEW | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 7.6 radiotherapy | 1 | 300 | Mean Difference (IV, Fixed, 95% CI) | 1.90 [-4.19, 7.99] |
| 7.7 no therapy | 1 | 100 | Mean Difference (IV, Fixed, 95% CI) | 29.90 [23.46, 36.34] |
| 7.8 unclear | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 7.9 chemotherapy no details given | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 8 Change in FACT-An Total 47 - epoetin versus darbepoetin | 10 | 1815 | Mean Difference (IV, Fixed, 95% CI) | 6.92 [4.59, 9.25] |
| 8.1 Epoetin | 10 | 1815 | Mean Difference (IV, Fixed, 95% CI) | 6.92 [4.59, 9.25] |
| 8.2 Darbepoetin | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 9 Change in FACT-An Total 47 - duration of ESA medication | 10 | 1815 | Mean Difference (IV, Fixed, 95% CI) | 6.92 [4.59, 9.25] |
| 9.1 6 to 9 weeks | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 9.2 12 to 16 weeks | 8 | 1625 | Mean Difference (IV, Fixed, 95% CI) | 3.39 [0.83, 5.96] |
| 9.3 more than 17 weeks | 2 | 190 | Mean Difference (IV, Fixed, 95% CI) | 23.64 [18.05, 29.22] |
| 9.4 unclear | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 10 Change in FACT-An Total 47 - iron supplementation | 10 | 1815 | Mean Difference (IV, Fixed, 95% CI) | 6.92 [4.59, 9.25] |
| 10.1 fixed iron supplementation | 7 | 1217 | Mean Difference (IV, Fixed, 95% CI) | 7.14 [4.31, 9.96] |
| 10.2 iron supplementation as necessary | 2 | 378 | Mean Difference (IV, Fixed, 95% CI) | 5.87 [0.86, 10.87] |
| 10.3 no explicit statement on iron supplementation or no iron given | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 10.4 explicitly stated NO IRON | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 10.5 unclear | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 10.6 iron given differently in both study arms new | 1 | 220 | Mean Difference (IV, Fixed, 95% CI) | 7.67 [0.40, 14.94] |
| 11 Change in FACT-An Total 47 - allocation concealment | 10 | 1815 | Mean Difference (IV, Fixed, 95% CI) | 6.92 [4.59, 9.25] |
| 11.1 adequate | 4 | 840 | Mean Difference (IV, Fixed, 95% CI) | 4.69 [0.92, 8.45] |
| 11.2 unclear | 6 | 975 | Mean Difference (IV, Fixed, 95% CI) | 8.30 [5.33, 11.26] |
| 12 Change in FACT-An Total 47 - masking | 10 | 1815 | Mean Difference (IV, Fixed, 95% CI) | 6.92 [4.59, 9.25] |
| 12.1 double-blind | 6 | 1078 | Mean Difference (IV, Fixed, 95% CI) | 8.00 [5.13, 10.87] |
| 12.2 unblinded | 4 | 737 | Mean Difference (IV, Fixed, 95% CI) | 4.83 [0.84, 8.82] |
| 13 Change in FACT-An Total 47 - intention-to treat | 10 | 1815 | Mean Difference (IV, Fixed, 95% CI) | 6.92 [4.59, 9.25] |
| 13.1 ITT or less than 10% of participants per study arm excluded | 4 | 585 | Mean Difference (IV, Fixed, 95% CI) | 10.85 [7.29, 14.41] |

| | | | | |
|---|---|---|---|---|
| 13.2 more than 10% of participants per study arm excluded | 4 | 840 | Mean Difference (IV, Fixed, 95% CI) | 4.69 [0.92, 8.45] |
| 13.3 unclear | 2 | 390 | Mean Difference (IV, Fixed, 95% CI) | 2.54 [-2.81, 7.90] |
| 14 Change in FACT-An Total 47 - publication | 10 | 1815 | Mean Difference (IV, Fixed, 95% CI) | 6.92 [4.59, 9.25] |
| 14.1 full text publication | 9 | 1725 | Mean Difference (IV, Fixed, 95% CI) | 7.02 [4.63, 9.40] |
| 14.2 abstract publication | 1 | 90 | Mean Difference (IV, Fixed, 95% CI) | 4.71 [-6.49, 15.91] |
| 14.3 unpublished data | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 14.4 FDA hearing | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 14.5 clinical trial result information | 0 | 0 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 15 Change in Fact-An Total 47 - data type | 10 | 1815 | Mean Difference (IV, Fixed, 95% CI) | 6.92 [4.59, 9.25] |
| 15.1 Not imputed data | 7 | 1101 | Mean Difference (IV, Fixed, 95% CI) | 9.31 [6.45, 12.17] |
| 15.2 Imputed data | 3 | 714 | Mean Difference (IV, Fixed, 95% CI) | 2.19 [-1.83, 6.20] |
| 16 FACT-An Total 47 - merged experimental study arms | 9 | 1815 | Mean Difference (IV, Fixed, 95% CI) | 6.92 [4.59, 9.25] |

## Comparison 11. Thrombotic events

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Thrombotic events - overall | 60 | 15498 | Risk Ratio (M-H, Fixed, 95% CI) | 1.52 [1.34, 1.74] |
| 2 Thrombotic events - baseline Hb | 60 | 15498 | Risk Ratio (M-H, Fixed, 95% CI) | 1.52 [1.34, 1.74] |
| 2.1 Hb < 10 g/dL | 19 | 4231 | Risk Ratio (M-H, Fixed, 95% CI) | 1.41 [1.06, 1.88] |
| 2.2 Hb 10 to 12 g/dL | 26 | 5491 | Risk Ratio (M-H, Fixed, 95% CI) | 1.64 [1.33, 2.03] |
| 2.3 Hb > 12 g/dL | 13 | 5348 | Risk Ratio (M-H, Fixed, 95% CI) | 1.44 [1.15, 1.80] |
| 2.4 Hb unclear | 2 | 428 | Risk Ratio (M-H, Fixed, 95% CI) | 1.64 [1.02, 2.65] |
| 3 Thrombotic events - different malignancies | 60 | 15498 | Risk Ratio (M-H, Fixed, 95% CI) | 1.52 [1.34, 1.74] |
| 3.1 solid tumours | 36 | 9121 | Risk Ratio (M-H, Fixed, 95% CI) | 1.67 [1.41, 1.96] |
| 3.2 haematological malignancies | 8 | 2531 | Risk Ratio (M-H, Fixed, 95% CI) | 1.33 [0.93, 1.90] |
| 3.3 mixed | 14 | 3693 | Risk Ratio (M-H, Fixed, 95% CI) | 1.29 [0.98, 1.69] |
| 3.4 MDS | 2 | 153 | Risk Ratio (M-H, Fixed, 95% CI) | 2.08 [0.23, 18.84] |
| 3.5 not reported | 0 | 0 | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 4 Thrombotic events - age | 60 | 15498 | Risk Ratio (M-H, Fixed, 95% CI) | 1.52 [1.34, 1.74] |
| 4.1 children | 1 | 222 | Risk Ratio (M-H, Fixed, 95% CI) | 2.95 [0.61, 14.28] |
| 4.2 adults | 59 | 15276 | Risk Ratio (M-H, Fixed, 95% CI) | 1.52 [1.33, 1.73] |
| 5 Thrombotic events - age differentiated | 60 | 15498 | Risk Ratio (M-H, Fixed, 95% CI) | 1.52 [1.34, 1.74] |
| 5.1 children | 1 | 222 | Risk Ratio (M-H, Fixed, 95% CI) | 2.95 [0.61, 14.28] |
| 5.2 adults >= 18 | 46 | 11310 | Risk Ratio (M-H, Fixed, 95% CI) | 1.60 [1.38, 1.86] |
| 5.3 > 68% non elderly, 18-65 | 7 | 1028 | Risk Ratio (M-H, Fixed, 95% CI) | 1.71 [1.02, 2.86] |
| 5.4 only non elderly | 5 | 2882 | Risk Ratio (M-H, Fixed, 95% CI) | 1.17 [0.86, 1.60] |
| 5.5 > 68% elderly > 65 years | 1 | 56 | Risk Ratio (M-H, Fixed, 95% CI) | 0.23 [0.01, 4.58] |
| 5.6 only elderly | 0 | 0 | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |

| | | | | |
|---|---|---|---|---|
| 6 Thrombotic events - different therapies | 60 | 15498 | Risk Ratio (M-H, Fixed, 95% CI) | 1.52 [1.34, 1.74] |
| 6.1 chemotherapy | 37 | 10844 | Risk Ratio (M-H, Fixed, 95% CI) | 1.48 [1.27, 1.73] |
| 6.2 radiotherapy/ radiochemotherapy | 11 | 2384 | Risk Ratio (M-H, Fixed, 95% CI) | 2.02 [1.44, 2.83] |
| 6.3 no therapy | 8 | 1921 | Risk Ratio (M-H, Fixed, 95% CI) | 1.25 [0.88, 1.78] |
| 6.4 unclear/other | 4 | 349 | Risk Ratio (M-H, Fixed, 95% CI) | 2.09 [0.74, 5.93] |
| 7 Thrombotic events - different therapies differentiated | 60 | 15498 | Risk Ratio (M-H, Fixed, 95% CI) | 1.52 [1.34, 1.74] |
| 7.1 chemotherapy, > 70% with platinum | 16 | 3136 | Risk Ratio (M-H, Fixed, 95% CI) | 1.46 [1.13, 1.89] |
| 7.2 chemotherapy, < 70% with platinum | 3 | 919 | Risk Ratio (M-H, Fixed, 95% CI) | 1.63 [0.92, 2.88] |
| 7.3 chemotherapy, without platinum, all patients | 14 | 6085 | Risk Ratio (M-H, Fixed, 95% CI) | 1.42 [1.14, 1.76] |
| 7.4 chemotherapy, platinum and non platinum containing, no numbers given | 2 | 265 | Risk Ratio (M-H, Fixed, 95% CI) | 4.56 [0.79, 26.20] |
| 7.5 chemotherapy no details given | 2 | 439 | Risk Ratio (M-H, Fixed, 95% CI) | 1.79 [0.67, 4.76] |
| 7.6 radiochemotherapy | 7 | 1097 | Risk Ratio (M-H, Fixed, 95% CI) | 2.01 [1.37, 2.96] |
| 7.7 radiotherapy | 4 | 1287 | Risk Ratio (M-H, Fixed, 95% CI) | 2.03 [1.02, 4.07] |
| 7.8 no therapy | 8 | 1921 | Risk Ratio (M-H, Fixed, 95% CI) | 1.25 [0.88, 1.78] |
| 7.9 unclear/other | 4 | 349 | Risk Ratio (M-H, Fixed, 95% CI) | 2.09 [0.74, 5.93] |
| 8 Thrombotic events - epoetin versus darbepoetin | 60 | 15498 | Risk Ratio (M-H, Fixed, 95% CI) | 1.52 [1.34, 1.74] |
| 8.1 Epoetin | 50 | 11055 | Risk Ratio (M-H, Fixed, 95% CI) | 1.57 [1.33, 1.85] |
| 8.2 Darbepoetin | 10 | 4443 | Risk Ratio (M-H, Fixed, 95% CI) | 1.44 [1.16, 1.79] |
| 9 Thrombotic events - duration of ESA treatment | 60 | 15498 | Risk Ratio (M-H, Fixed, 95% CI) | 1.52 [1.34, 1.74] |
| 9.1 6 to 9 weeks | 10 | 1719 | Risk Ratio (M-H, Fixed, 95% CI) | 2.06 [1.17, 3.64] |
| 9.2 12 to 16 weeks | 30 | 7223 | Risk Ratio (M-H, Fixed, 95% CI) | 1.46 [1.20, 1.77] |
| 9.3 more than 17 weeks | 19 | 6312 | Risk Ratio (M-H, Fixed, 95% CI) | 1.53 [1.27, 1.84] |
| 9.4 not reported | 1 | 244 | Risk Ratio (M-H, Fixed, 95% CI) | 1.46 [0.15, 13.85] |
| 10 Thrombotic events - iron supplementation | 60 | 15498 | Risk Ratio (M-H, Fixed, 95% CI) | 1.52 [1.34, 1.74] |
| 10.1 fixed iron supplementation | 4 | 1445 | Risk Ratio (M-H, Fixed, 95% CI) | 1.53 [0.92, 2.54] |
| 10.2 iron supplementation as necessary | 47 | 12073 | Risk Ratio (M-H, Fixed, 95% CI) | 1.51 [1.31, 1.74] |
| 10.3 no explicit statement on iron supplementation or no iron given | 4 | 293 | Risk Ratio (M-H, Fixed, 95% CI) | 1.26 [0.39, 4.06] |
| 10.4 iron handled differently in the study arms | 5 | 1687 | Risk Ratio (M-H, Fixed, 95% CI) | 1.69 [1.12, 2.54] |
| 10.5 explicitly stated NO IRON | 0 | 0 | Risk Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 11 Thrombotic events - concealment of allocation | 60 | 15498 | Risk Ratio (M-H, Fixed, 95% CI) | 1.52 [1.34, 1.74] |
| 11.1 adequate | 38 | 10494 | Risk Ratio (M-H, Fixed, 95% CI) | 1.64 [1.40, 1.92] |
| 11.2 unclear | 22 | 5004 | Risk Ratio (M-H, Fixed, 95% CI) | 1.31 [1.04, 1.65] |

| | | | | |
|---|---|---|---|---|
| 12 Thrombotic events - masking | 60 | 15498 | Risk Ratio (M-H, Fixed, 95% CI) | 1.52 [1.34, 1.74] |
| 12.1 double-blind | 32 | 9209 | Risk Ratio (M-H, Fixed, 95% CI) | 1.40 [1.19, 1.64] |
| 12.2 unblinded | 28 | 6289 | Risk Ratio (M-H, Fixed, 95% CI) | 1.78 [1.43, 2.23] |
| 13 Thrombotic events - intention-to-treat | 60 | 15498 | Risk Ratio (M-H, Fixed, 95% CI) | 1.52 [1.34, 1.74] |
| 13.1 ITT or less than 10% of participants per study arm excluded | 55 | 13182 | Risk Ratio (M-H, Fixed, 95% CI) | 1.50 [1.30, 1.72] |
| 13.2 more than 10% of participants per study arm excluded | 3 | 1589 | Risk Ratio (M-H, Fixed, 95% CI) | 1.59 [0.95, 2.66] |
| 13.3 unclear | 2 | 727 | Risk Ratio (M-H, Fixed, 95% CI) | 1.82 [1.15, 2.89] |
| 14 Thrombotic events - publication | 60 | 15498 | Risk Ratio (M-H, Fixed, 95% CI) | 1.52 [1.34, 1.74] |
| 14.1 full text publication | 35 | 8388 | Risk Ratio (M-H, Fixed, 95% CI) | 1.57 [1.32, 1.87] |
| 14.2 abstract publication | 2 | 1343 | Risk Ratio (M-H, Fixed, 95% CI) | 1.04 [0.70, 1.55] |
| 14.3 unpublished data | 1 | 66 | Risk Ratio (M-H, Fixed, 95% CI) | 1.43 [0.06, 33.82] |
| 14.4 data presented at ODAC hearing | 21 | 5645 | Risk Ratio (M-H, Fixed, 95% CI) | 1.66 [1.33, 2.08] |
| 14.5 other | 1 | 56 | Risk Ratio (M-H, Fixed, 95% CI) | 0.23 [0.01, 4.58] |
| 15 Thrombotic events - experimental arms merged | 57 | 15498 | Risk Ratio (M-H, Fixed, 95% CI) | 1.53 [1.34, 1.74] |

## Comparison 12. Hypertension

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Hypertension - overall | 37 | 7228 | Risk Ratio (M-H, Fixed, 95% CI) | 1.30 [1.08, 1.56] |
| 2 Hypertension - merged experimental study arms | 31 | 7228 | Risk Ratio (M-H, Fixed, 95% CI) | 1.31 [1.09, 1.58] |
| 3 Hypertension - sensitivity analysis Dammacco | 37 | 7228 | Risk Ratio (M-H, Fixed, 95% CI) | 1.29 [1.10, 1.52] |
| 4 Hypertension - sensitivity analysis random effects | 37 | 7228 | Risk Ratio (M-H, Random, 95% CI) | 1.12 [0.94, 1.33] |
| 5 Hypertension - sensitivity analysis without Rose | 36 | 7007 | Risk Ratio (M-H, Fixed, 95% CI) | 1.52 [1.18, 1.97] |

### Comparison 13. Thrombocytopenia or haemorrhage

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Thrombocytopenia - overall | 24 | 4507 | Risk Ratio (M-H, Fixed, 95% CI) | 1.21 [1.04, 1.42] |
| 2 Thrombocytopenia - merged experimental arms | 21 | 4507 | Risk Ratio (M-H, Fixed, 95% CI) | 1.21 [1.04, 1.41] |
| 3 Thrombocytopenia - sensitivity analysis random effects | 24 | 4507 | Risk Ratio (M-H, Random, 95% CI) | 1.18 [1.02, 1.36] |

### Comparison 14. Rash

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Rash - overall | 18 | 2485 | Risk Ratio (M-H, Fixed, 95% CI) | 1.49 [0.99, 2.24] |
| 2 Rash - merged experimental arms | 16 | 2485 | Risk Ratio (M-H, Fixed, 95% CI) | 1.50 [1.00, 2.27] |

### Comparison 15. Seizure

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Seizure - overall | 8 | 2890 | Risk Ratio (M-H, Fixed, 95% CI) | 0.77 [0.42, 1.41] |

## Analysis 1.1. Comparison 1 Haematologic response, Outcome 1 Haematological response - overall.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 1 Haematologic response

Outcome: 1 Haematological response - overall

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Aapro 2008 | 157/231 | 32/232 | | 6.6 % | 4.93 [ 3.53, 6.88 ] |
| Abels 1993 | 20/63 | 6/55 | | 1.3 % | 2.91 [ 1.26, 6.72 ] |
| Bamias 2003 | 15/72 | 2/72 | | 0.4 % | 7.50 [ 1.78, 31.62 ] |
| Boogaerts 2003 | 63/133 | 17/129 | | 3.6 % | 3.59 [ 2.23, 5.80 ] |
| Case 1993 | 46/79 | 10/74 | | 2.1 % | 4.31 [ 2.35, 7.90 ] |
| Cazzola 1995a | 2/31 | 0/7 | | 0.2 % | 1.25 [ 0.07, 23.55 ] |
| Cazzola 1995b | 9/29 | 1/8 | | 0.3 % | 2.48 [ 0.37, 16.80 ] |
| Cazzola 1995c | 19/31 | 0/7 | | 0.2 % | 9.75 [ 0.66, 144.80 ] |
| Cazzola 1995d | 16/26 | 1/7 | | 0.3 % | 4.31 [ 0.68, 27.12 ] |
| Chang 2005 | 115/175 | 11/175 | | 2.3 % | 10.45 [ 5.84, 18.71 ] |
| Charu 2007 | 150/220 | 5/55 | | 1.7 % | 7.50 [ 3.24, 17.38 ] |
| Dammacco 2001 | 38/66 | 6/66 | | 1.2 % | 6.33 [ 2.87, 13.96 ] |
| Hedenus 2002a | 5/11 | 1/3 | | 0.3 % | 1.36 [ 0.24, 7.66 ] |
| Hedenus 2002b | 12/22 | 0/4 | | 0.2 % | 5.43 [ 0.38, 77.40 ] |
| Hedenus 2002c | 14/22 | 0/4 | | 0.2 % | 6.30 [ 0.45, 89.06 ] |
| Hedenus 2003 | 104/174 | 31/170 | | 6.5 % | 3.28 [ 2.33, 4.61 ] |
| Henry 1995 | 31/64 | 4/61 | | 0.8 % | 7.39 [ 2.77, 19.69 ] |
| Iconomou 2003 | 25/57 | 7/55 | | 1.5 % | 3.45 [ 1.62, 7.31 ] |
| Italian 1998 | 5/43 | 0/42 | | 0.1 % | 10.75 [ 0.61, 188.54 ] |
| Kotasek 2003a | 8/32 | 1/8 | | 0.3 % | 2.00 [ 0.29, 13.77 ] |
| Kotasek 2003b | 8/17 | 1/8 | | 0.3 % | 3.76 [ 0.56, 25.21 ] |
| Kotasek 2003c | 23/46 | 2/9 | | 0.7 % | 2.25 [ 0.64, 7.90 ] |
| Kotasek 2003d | 17/28 | 1/8 | | 0.3 % | 4.86 [ 0.76, 31.12 ] |
| Kotasek 2003e | 20/35 | 1/9 | | 0.3 % | 5.14 [ 0.79, 33.37 ] |
| Kotasek 2003f | 20/40 | 1/9 | | 0.3 % | 4.50 [ 0.69, 29.30 ] |
| Littlewood 2001 | 172/244 | 22/115 | | 6.2 % | 3.68 [ 2.51, 5.41 ] |


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| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Milroy 2011 | 37/189 | 5/191 | | 1.0 % | 7.48 [ 3.00, 18.62 ] |
| ML17616 2006 | 21/30 | 11/30 | | 2.3 % | 1.91 [ 1.13, 3.23 ] |
| ML17620 2006 | 29/61 | 14/60 | | 2.9 % | 2.04 [ 1.20, 3.46 ] |
| Oberhoff 1998 | 38/114 | 7/104 | | 1.5 % | 4.95 [ 2.31, 10.60 ] |
| Osterborg 1996a | 21/47 | 4/24 | | 1.1 % | 2.68 [ 1.04, 6.93 ] |
| Osterborg 1996b | 23/48 | 4/25 | | 1.1 % | 2.99 [ 1.16, 7.71 ] |
| Osterborg 2002 | 114/170 | 46/173 | | 9.4 % | 2.52 [ 1.93, 3.30 ] |
| Razzouk 2006 | 63/111 | 39/111 | | 8.1 % | 1.62 [ 1.20, 2.18 ] |
| Rose 1994 | 67/142 | 13/79 | | 3.5 % | 2.87 [ 1.69, 4.85 ] |
| Savonije 2005 | 143/208 | 31/100 | | 8.7 % | 2.22 [ 1.63, 3.01 ] |
| Smith 2003a | 12/21 | 1/7 | | 0.3 % | 4.00 [ 0.63, 25.49 ] |
| Smith 2003b | 10/21 | 0/7 | | 0.2 % | 7.64 [ 0.50, 115.83 ] |
| Smith 2003c | 13/22 | 0/8 | | 0.1 % | 10.57 [ 0.70, 159.65 ] |
| Suzuki 2008a | 22/40 | 3/21 | | 0.8 % | 3.85 [ 1.30, 11.39 ] |
| Suzuki 2008b | 28/41 | 2/21 | | 0.5 % | 7.17 [ 1.89, 27.24 ] |
| Thompson 2000 | 4/45 | 1/21 | | 0.3 % | 1.87 [ 0.22, 15.70 ] |
| Tjulandin 2010a | 50/76 | 8/37 | | 2.2 % | 3.04 [ 1.61, 5.74 ] |
| Tjulandin 2010b | 52/73 | 7/37 | | 1.9 % | 3.77 [ 1.90, 7.45 ] |
| Tjulandin 2011 | 69/95 | 23/91 | | 4.9 % | 2.87 [ 1.98, 4.18 ] |
| Witzig 2005 | 120/165 | 52/164 | | 10.8 % | 2.29 [ 1.80, 2.93 ] |
| **Total (95% CI)** | **3710** | **2703** | | **100.0 %** | **3.39 [ 3.10, 3.71 ]** |

Total events: 2050 (Treatment), 434 (Control)

Heterogeneity: $Chi^2$ = 95.56, df = 45 (P = 0.00002); $I^2$ =53%

Test for overall effect: Z = 26.39 (P < 0.00001)

Test for subgroup differences: Not applicable

## Analysis 1.2. Comparison 1 Haematologic response, Outcome 2 Haematologic response - baseline Hb.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 1 Haematologic response

Outcome: 2 Haematologic response - baseline Hb

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 Hb <= 10 g/dL | | | | | |
| Abels 1993 | 20/63 | 6/55 | | 1.3 % | 2.91 [ 1.26, 6.72 ] |
| Boogaerts 2003 | 63/133 | 17/129 | | 3.6 % | 3.59 [ 2.23, 5.80 ] |
| Case 1993 | 46/79 | 10/74 | | 2.1 % | 4.31 [ 2.35, 7.90 ] |
| Cazzola 1995a | 2/31 | 0/7 | | 0.2 % | 1.25 [ 0.07, 23.55 ] |
| Cazzola 1995b | 9/29 | 1/8 | | 0.3 % | 2.48 [ 0.37, 16.80 ] |
| Cazzola 1995c | 19/31 | 0/7 | | 0.2 % | 9.75 [ 0.66, 144.80 ] |
| Cazzola 1995d | 16/26 | 1/7 | | 0.3 % | 4.31 [ 0.68, 27.12 ] |
| Dammacco 2001 | 38/66 | 6/66 | | 1.2 % | 6.33 [ 2.87, 13.96 ] |
| Hedenus 2002a | 5/11 | 1/3 | | 0.3 % | 1.36 [ 0.24, 7.66 ] |
| Hedenus 2002b | 12/22 | 0/4 | | 0.2 % | 5.43 [ 0.38, 77.40 ] |
| Hedenus 2002c | 14/22 | 0/4 | | 0.2 % | 6.30 [ 0.45, 89.06 ] |
| Hedenus 2003 | 104/174 | 31/170 | | 6.5 % | 3.28 [ 2.33, 4.61 ] |
| Henry 1995 | 31/64 | 4/61 | | 0.8 % | 7.39 [ 2.77, 19.69 ] |
| Italian 1998 | 5/43 | 0/42 | | 0.1 % | 10.75 [ 0.61, 188.54 ] |
| Kotasek 2003a | 8/32 | 1/8 | | 0.3 % | 2.00 [ 0.29, 13.77 ] |
| Kotasek 2003b | 8/17 | 1/8 | | 0.3 % | 3.76 [ 0.56, 25.21 ] |
| Kotasek 2003c | 23/46 | 2/9 | | 0.7 % | 2.25 [ 0.64, 7.90 ] |
| Kotasek 2003d | 17/28 | 1/8 | | 0.3 % | 4.86 [ 0.76, 31.12 ] |
| Kotasek 2003e | 20/35 | 1/9 | | 0.3 % | 5.14 [ 0.79, 33.37 ] |
| Kotasek 2003f | 20/40 | 1/9 | | 0.3 % | 4.50 [ 0.69, 29.30 ] |
| Littlewood 2001 | 172/244 | 22/115 | | 6.2 % | 3.68 [ 2.51, 5.41 ] |
| ML17616 2006 | 21/30 | 11/30 | | 2.3 % | 1.91 [ 1.13, 3.23 ] |
| Oberhoff 1998 | 38/114 | 7/104 | | 1.5 % | 4.95 [ 2.31, 10.60 ] |
| Osterborg 1996a | 21/47 | 4/24 | | 1.1 % | 2.68 [ 1.04, 6.93 ] |
| Osterborg 1996b | 23/48 | 4/25 | | 1.1 % | 2.99 [ 1.16, 7.71 ] |


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| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Osterborg 2002 | 114/170 | 46/173 | | 9.4 % | 2.52 [ 1.93, 3.30 ] |
| Razzouk 2006 | 63/111 | 39/111 | | 8.1 % | 1.62 [ 1.20, 2.18 ] |
| Rose 1994 | 67/142 | 13/79 | | 3.5 % | 2.87 [ 1.69, 4.85 ] |
| Smith 2003a | 12/21 | 1/7 | | 0.3 % | 4.00 [ 0.63, 25.49 ] |
| Smith 2003b | 10/21 | 0/7 | | 0.2 % | 7.64 [ 0.50, 115.83 ] |
| Smith 2003c | 13/22 | 0/8 | | 0.1 % | 10.57 [ 0.70, 159.65 ] |
| Thompson 2000 | 4/45 | 1/21 | | 0.3 % | 1.87 [ 0.22, 15.70 ] |
| Tjulandin 2010a | 50/76 | 8/37 | | 2.2 % | 3.04 [ 1.61, 5.74 ] |
| Tjulandin 2010b | 52/73 | 7/37 | | 1.9 % | 3.77 [ 1.90, 7.45 ] |
| Tjulandin 2011 | 69/95 | 23/91 | | 4.9 % | 2.87 [ 1.98, 4.18 ] |
| Witzig 2005 | 120/165 | 52/164 | | 10.8 % | 2.29 [ 1.80, 2.93 ] |
| **Subtotal (95% CI)** | **2416** | **1721** | | **73.6 %** | **3.02 [ 2.72, 3.35 ]** |
| Total events: 1329 (Treatment), 322 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 44.07, df = 35 (P = 0.14); $I^2$ =21% | | | | | |
| Test for overall effect: Z = 20.57 (P < 0.00001) | | | | | |
| 2 Hb 10 to 12 g/dL | | | | | |
| Aapro 2008 | 157/231 | 32/232 | | 6.6 % | 4.93 [ 3.53, 6.88 ] |
| Bamias 2003 | 15/72 | 2/72 | | 0.4 % | 7.50 [ 1.78, 31.62 ] |
| Chang 2005 | 115/175 | 11/175 | | 2.3 % | 10.45 [ 5.84, 18.71 ] |
| Charu 2007 | 150/220 | 5/55 | | 1.7 % | 7.50 [ 3.24, 17.38 ] |
| Iconomou 2003 | 25/57 | 7/55 | | 1.5 % | 3.45 [ 1.62, 7.31 ] |
| Savonije 2005 | 143/208 | 31/100 | | 8.7 % | 2.22 [ 1.63, 3.01 ] |
| Suzuki 2008a | 22/40 | 3/21 | | 0.8 % | 3.85 [ 1.30, 11.39 ] |
| Suzuki 2008b | 28/41 | 2/21 | | 0.5 % | 7.17 [ 1.89, 27.24 ] |
| **Subtotal (95% CI)** | **1044** | **731** | | **22.5 %** | **4.60 [ 3.79, 5.58 ]** |
| Total events: 655 (Treatment), 93 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 32.40, df = 7 (P = 0.00003); $I^2$ =78% | | | | | |
| Test for overall effect: Z = 15.51 (P < 0.00001) | | | | | |
| 3 Hb > 12 g/dL | | | | | |
| Milroy 2011 | 37/189 | 5/191 | | 1.0 % | 7.48 [ 3.00, 18.62 ] |
| **Subtotal (95% CI)** | **189** | **191** | | **1.0 %** | **7.48 [ 3.00, 18.62 ]** |
| Total events: 37 (Treatment), 5 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 4.32 (P = 0.000015) | | | | | |
| 4 Hb category unclear | | | | | |
| ML17620 2006 | 29/61 | 14/60 | | 2.9 % | 2.04 [ 1.20, 3.46 ] |


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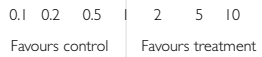
| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| **Subtotal (95% CI)** | **61** | **60** | | **2.9 %** | **2.04 [ 1.20, 3.46 ]** |
| Total events: 29 (Treatment), 14 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 2.64 (P = 0.0084) | | | | | |
| **Total (95% CI)** | **3710** | **2703** | | **100.0 %** | **3.39 [ 3.10, 3.71 ]** |
| Total events: 2050 (Treatment), 434 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 95.56, df = 45 (P = 0.00002); $I^2$ =53% | | | | | |
| Test for overall effect: Z = 26.39 (P < 0.00001) | | | | | |
| Test for subgroup differences: $Chi^2$ = 20.41, df = 3 (P = 0.00), $I^2$ =85% | | | | | |



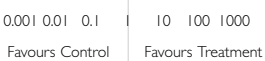

**Analysis 1.3. Comparison 1 Haematologic response, Outcome 3 Haematologic response - different malignancies.**

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 1 Haematologic response

Outcome: 3 Haematologic response - different malignancies

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 solid tumours | | | | | |
| Aapro 2008 | 157/231 | 32/232 | | 6.6 % | 4.93 [ 3.53, 6.88 ] |
| Bamias 2003 | 15/72 | 2/72 | | 0.4 % | 7.50 [ 1.78, 31.62 ] |
| Chang 2005 | 115/175 | 11/175 | | 2.3 % | 10.45 [ 5.84, 18.71 ] |
| Iconomou 2003 | 25/57 | 7/55 | | 1.5 % | 3.45 [ 1.62, 7.31 ] |
| Kotasek 2003a | 8/32 | 1/8 | | 0.3 % | 2.00 [ 0.29, 13.77 ] |
| Kotasek 2003b | 8/17 | 1/8 | | 0.3 % | 3.76 [ 0.56, 25.21 ] |
| Kotasek 2003c | 23/46 | 2/9 | | 0.7 % | 2.25 [ 0.64, 7.90 ] |
| Kotasek 2003d | 17/28 | 1/8 | | 0.3 % | 4.86 [ 0.76, 31.12 ] |

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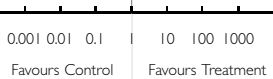
| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Kotasek 2003e | 20/35 | 1/9 | | 0.3 % | 5.14 [ 0.79, 33.37 ] |
| Kotasek 2003f | 20/40 | 1/9 | | 0.3 % | 4.50 [ 0.69, 29.30 ] |
| Littlewood 2001 | 87/131 | 13/61 | | 3.7 % | 3.12 [ 1.90, 5.12 ] |
| Milroy 2011 | 37/189 | 5/191 | | 1.0 % | 7.48 [ 3.00, 18.62 ] |
| ML17620 2006 | 29/61 | 14/60 | | 2.9 % | 2.04 [ 1.20, 3.46 ] |
| Oberhoff 1998 | 38/114 | 7/104 | | 1.5 % | 4.95 [ 2.31, 10.60 ] |
| Savonije 2005 | 143/208 | 31/100 | | 8.7 % | 2.22 [ 1.63, 3.01 ] |
| Tjulandin 2010a | 50/76 | 8/37 | | 2.2 % | 3.04 [ 1.61, 5.74 ] |
| Tjulandin 2010b | 52/73 | 7/37 | | 1.9 % | 3.77 [ 1.90, 7.45 ] |
| Witzig 2005 | 120/165 | 52/164 | | 10.8 % | 2.29 [ 1.80, 2.93 ] |
| **Subtotal (95% CI)** | **1750** | **1339** | | **45.9 %** | **3.56 [ 3.12, 4.07 ]** |
| Total events: 964 (Treatment), 196 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 48.84, df = 17 (P = 0.00006); $I^2$ =65% | | | | | |
| Test for overall effect: Z = 18.83 (P < 0.00001) | | | | | |
| 2 haematological malignancies | | | | | |
| Cazzola 1995a | 2/31 | 0/7 | | 0.2 % | 1.25 [ 0.07, 23.55 ] |
| Cazzola 1995b | 9/29 | 1/8 | | 0.3 % | 2.48 [ 0.37, 16.80 ] |
| Cazzola 1995c | 19/31 | 0/7 | | 0.2 % | 9.75 [ 0.66, 144.80 ] |
| Cazzola 1995d | 16/26 | 1/7 | | 0.3 % | 4.31 [ 0.68, 27.12 ] |
| Dammacco 2001 | 38/66 | 6/66 | | 1.2 % | 6.33 [ 2.87, 13.96 ] |
| Hedenus 2002a | 5/11 | 1/3 | | 0.3 % | 1.36 [ 0.24, 7.66 ] |
| Hedenus 2002b | 12/22 | 0/4 | | 0.2 % | 5.43 [ 0.38, 77.40 ] |
| Hedenus 2002c | 14/22 | 0/4 | | 0.2 % | 6.30 [ 0.45, 89.06 ] |
| Hedenus 2003 | 104/174 | 31/170 | | 6.5 % | 3.28 [ 2.33, 4.61 ] |
| Littlewood 2001 | 85/113 | 9/54 | | 2.5 % | 4.51 [ 2.46, 8.27 ] |
| ML17616 2006 | 21/30 | 11/30 | | 2.3 % | 1.91 [ 1.13, 3.23 ] |
| Osterborg 1996a | 21/47 | 4/24 | | 1.1 % | 2.68 [ 1.04, 6.93 ] |
| Osterborg 1996b | 23/48 | 4/25 | | 1.1 % | 2.99 [ 1.16, 7.71 ] |
| Osterborg 2002 | 114/170 | 46/173 | | 9.4 % | 2.52 [ 1.93, 3.30 ] |
| Rose 1994 | 67/142 | 13/79 | | 3.5 % | 2.87 [ 1.69, 4.85 ] |
| **Subtotal (95% CI)** | **962** | **661** | | **29.3 %** | **3.12 [ 2.64, 3.69 ]** |
| Total events: 550 (Treatment), 127 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 13.10, df = 14 (P = 0.52); $I^2$ =0.0% | | | | | |
| Test for overall effect: Z = 13.32 (P < 0.00001) | | | | | |

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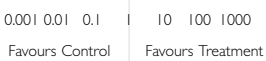
| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 3 MDS | | | | | |
| Italian 1998 | 5/43 | 0/42 | | 0.1 % | 10.75 [ 0.61, 188.54 ] |
| Thompson 2000 | 4/45 | 1/21 | | 0.3 % | 1.87 [ 0.22, 15.70 ] |
| **Subtotal (95% CI)** | **88** | **63** | | **0.4 %** | **4.27 [ 0.86, 21.19 ]** |
| Total events: 9 (Treatment), 1 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 0.98, df = 1 (P = 0.32); $I^2$ =0.0% | | | | | |
| Test for overall effect: Z = 1.78 (P = 0.076) | | | | | |
| 4 mixed | | | | | |
| Abels 1993 | 20/63 | 6/55 | | 1.3 % | 2.91 [ 1.26, 6.72 ] |
| Boogaerts 2003 | 63/133 | 17/129 | | 3.6 % | 3.59 [ 2.23, 5.80 ] |
| Case 1993 | 46/79 | 10/74 | | 2.1 % | 4.31 [ 2.35, 7.90 ] |
| Charu 2007 | 150/220 | 5/55 | | 1.7 % | 7.50 [ 3.24, 17.38 ] |
| Henry 1995 | 31/64 | 4/61 | | 0.8 % | 7.39 [ 2.77, 19.69 ] |
| Razzouk 2006 | 63/111 | 39/111 | | 8.1 % | 1.62 [ 1.20, 2.18 ] |
| Smith 2003a | 12/21 | 1/7 | | 0.3 % | 4.00 [ 0.63, 25.49 ] |
| Smith 2003b | 10/21 | 0/7 | | 0.2 % | 7.64 [ 0.50, 115.83 ] |
| Smith 2003c | 13/22 | 0/8 | | 0.1 % | 10.57 [ 0.70, 159.65 ] |
| Suzuki 2008a | 22/40 | 3/21 | | 0.8 % | 3.85 [ 1.30, 11.39 ] |
| Suzuki 2008b | 28/41 | 2/21 | | 0.5 % | 7.17 [ 1.89, 27.24 ] |
| Tjulandin 2011 | 69/95 | 23/91 | | 4.9 % | 2.87 [ 1.98, 4.18 ] |
| **Subtotal (95% CI)** | **910** | **640** | | **24.5 %** | **3.38 [ 2.80, 4.08 ]** |
| Total events: 527 (Treatment), 110 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 32.95, df = 11 (P = 0.00054); $I^2$ =67% | | | | | |
| Test for overall effect: Z = 12.72 (P < 0.00001) | | | | | |
| 5 not reported | | | | | |
| **Subtotal (95% CI)** | **0** | **0** | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Total events: 0 (Treatment), 0 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: not applicable | | | | | |
| **Total (95% CI)** | **3710** | **2703** | | **100.0 %** | **3.39 [ 3.10, 3.71 ]** |
| Total events: 2050 (Treatment), 434 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 96.35, df = 46 (P = 0.00002); $I^2$ =52% | | | | | |
| Test for overall effect: Z = 26.39 (P < 0.00001) | | | | | |
| Test for subgroup differences: $Chi^2$ = 1.57, df = 3 (P = 0.67), $I^2$ =0.0% | | | | | |



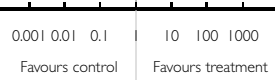
## Analysis 1.4. Comparison 1 Haematologic response, Outcome 4 Haematological response- age.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 1 Haematologic response

Outcome: 4 Haematological response- age

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 children | | | | | |
| Razzouk 2006 | 63/111 | 39/111 | | 8.1 % | 1.62 [ 1.20, 2.18 ] |
| **Subtotal (95% CI)** | **111** | **111** | | **8.1 %** | **1.62 [ 1.20, 2.18 ]** |
| Total events: 63 (Treatment), 39 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 3.13 (P = 0.0018) | | | | | |
| 2 adults | | | | | |
| Aapro 2008 | 157/231 | 32/232 | | 6.6 % | 4.93 [ 3.53, 6.88 ] |
| Abels 1993 | 20/63 | 6/55 | | 1.3 % | 2.91 [ 1.26, 6.72 ] |
| Bamias 2003 | 15/72 | 2/72 | | 0.4 % | 7.50 [ 1.78, 31.62 ] |
| Boogaerts 2003 | 63/133 | 17/129 | | 3.6 % | 3.59 [ 2.23, 5.80 ] |
| Case 1993 | 46/79 | 10/74 | | 2.1 % | 4.31 [ 2.35, 7.90 ] |
| Cazzola 1995a | 2/31 | 0/7 | | 0.2 % | 1.25 [ 0.07, 23.55 ] |
| Cazzola 1995b | 9/29 | 1/8 | | 0.3 % | 2.48 [ 0.37, 16.80 ] |
| Cazzola 1995c | 19/31 | 0/7 | | 0.2 % | 9.75 [ 0.66, 144.80 ] |
| Cazzola 1995d | 16/26 | 1/7 | | 0.3 % | 4.31 [ 0.68, 27.12 ] |
| Chang 2005 | 115/175 | 11/175 | | 2.3 % | 10.45 [ 5.84, 18.71 ] |
| Charu 2007 | 150/220 | 5/55 | | 1.7 % | 7.50 [ 3.24, 17.38 ] |
| Dammacco 2001 | 38/66 | 6/66 | | 1.2 % | 6.33 [ 2.87, 13.96 ] |
| Hedenus 2002a | 5/11 | 1/3 | | 0.3 % | 1.36 [ 0.24, 7.66 ] |
| Hedenus 2002b | 12/22 | 0/4 | | 0.2 % | 5.43 [ 0.38, 77.40 ] |
| Hedenus 2002c | 14/22 | 0/4 | | 0.2 % | 6.30 [ 0.45, 89.06 ] |
| Hedenus 2003 | 104/174 | 31/170 | | 6.5 % | 3.28 [ 2.33, 4.61 ] |
| Henry 1995 | 31/64 | 4/61 | | 0.8 % | 7.39 [ 2.77, 19.69 ] |
| Iconomou 2003 | 25/57 | 7/55 | | 1.5 % | 3.45 [ 1.62, 7.31 ] |
| Italian 1998 | 5/43 | 0/42 | | 0.1 % | 10.75 [ 0.61, 188.54 ] |
| Kotasek 2003a | 8/32 | 1/8 | | 0.3 % | 2.00 [ 0.29, 13.77 ] |

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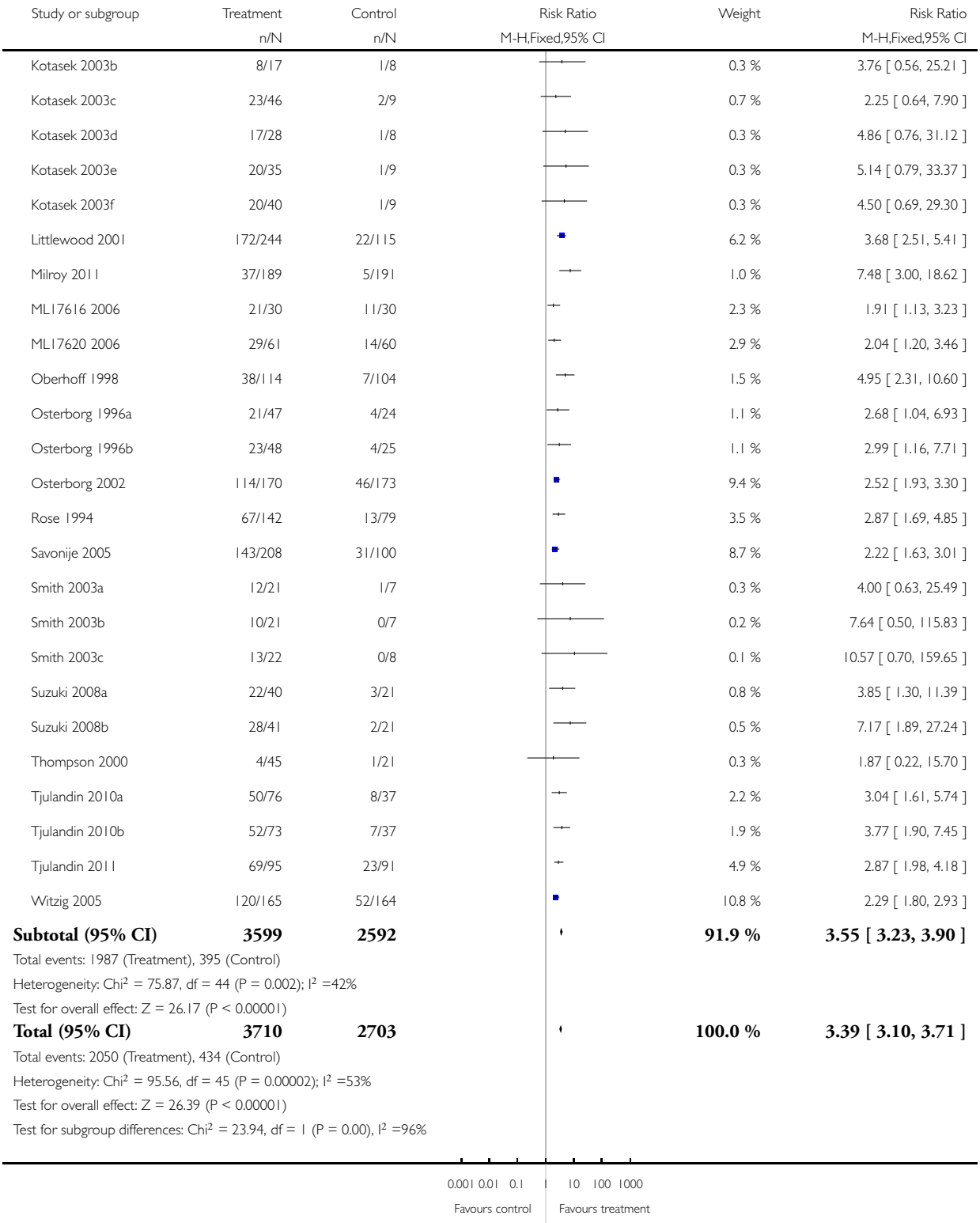


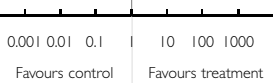
## Analysis 1.5. Comparison 1 Haematologic response, Outcome 5 Haematological response- age differentiated.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 1 Haematologic response

Outcome: 5 Haematological response- age differentiated

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 only children <18 years | | | | | |
| Razzouk 2006 | 63/111 | 39/111 | | 8.1 % | 1.62 [ 1.20, 2.18 ] |
| **Subtotal (95% CI)** | **111** | **111** | | **8.1 %** | **1.62 [ 1.20, 2.18 ]** |
| Total events: 63 (Treatment), 39 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 3.13 (P = 0.0018) | | | | | |
| 2 adults ≥18 years | | | | | |
| Aapro 2008 | 157/231 | 32/232 | | 6.6 % | 4.93 [ 3.53, 6.88 ] |
| Abels 1993 | 20/63 | 6/55 | | 1.3 % | 2.91 [ 1.26, 6.72 ] |
| Bamias 2003 | 15/72 | 2/72 | | 0.4 % | 7.50 [ 1.78, 31.62 ] |
| Boogaerts 2003 | 63/133 | 17/129 | | 3.6 % | 3.59 [ 2.23, 5.80 ] |
| Case 1993 | 46/79 | 10/74 | | 2.1 % | 4.31 [ 2.35, 7.90 ] |
| Cazzola 1995a | 2/31 | 0/7 | | 0.2 % | 1.25 [ 0.07, 23.55 ] |
| Cazzola 1995b | 9/29 | 1/8 | | 0.3 % | 2.48 [ 0.37, 16.80 ] |
| Cazzola 1995c | 19/31 | 0/7 | | 0.2 % | 9.75 [ 0.66, 144.80 ] |
| Cazzola 1995d | 16/26 | 1/7 | | 0.3 % | 4.31 [ 0.68, 27.12 ] |
| Charu 2007 | 150/220 | 5/55 | | 1.7 % | 7.50 [ 3.24, 17.38 ] |
| Dammacco 2001 | 38/66 | 6/66 | | 1.2 % | 6.33 [ 2.87, 13.96 ] |
| Hedenus 2002a | 5/11 | 1/3 | | 0.3 % | 1.36 [ 0.24, 7.66 ] |
| Hedenus 2002b | 12/22 | 0/4 | | 0.2 % | 5.43 [ 0.38, 77.40 ] |
| Hedenus 2002c | 14/22 | 0/4 | | 0.2 % | 6.30 [ 0.45, 89.06 ] |
| Hedenus 2003 | 104/174 | 31/170 | | 6.5 % | 3.28 [ 2.33, 4.61 ] |

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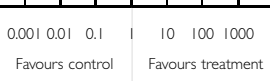
| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Henry 1995 | 31/64 | 4/61 | | 0.8 % | 7.39 [ 2.77, 19.69 ] |
| Iconomou 2003 | 25/57 | 7/55 | | 1.5 % | 3.45 [ 1.62, 7.31 ] |
| Italian 1998 | 5/43 | 0/42 | | 0.1 % | 10.75 [ 0.61, 188.54 ] |
| Kotasek 2003a | 8/32 | 1/8 | | 0.3 % | 2.00 [ 0.29, 13.77 ] |
| Kotasek 2003b | 8/17 | 1/8 | | 0.3 % | 3.76 [ 0.56, 25.21 ] |
| Kotasek 2003c | 23/46 | 2/9 | | 0.7 % | 2.25 [ 0.64, 7.90 ] |
| Kotasek 2003d | 17/28 | 1/8 | | 0.3 % | 4.86 [ 0.76, 31.12 ] |
| Kotasek 2003e | 20/35 | 1/9 | | 0.3 % | 5.14 [ 0.79, 33.37 ] |
| Kotasek 2003f | 20/40 | 1/9 | | 0.3 % | 4.50 [ 0.69, 29.30 ] |
| Littlewood 2001 | 172/244 | 22/115 | | 6.2 % | 3.68 [ 2.51, 5.41 ] |
| Milroy 2011 | 37/189 | 5/191 | | 1.0 % | 7.48 [ 3.00, 18.62 ] |
| ML17616 2006 | 21/30 | 11/30 | | 2.3 % | 1.91 [ 1.13, 3.23 ] |
| ML17620 2006 | 29/61 | 14/60 | | 2.9 % | 2.04 [ 1.20, 3.46 ] |
| Osterborg 1996a | 21/47 | 4/24 | | 1.1 % | 2.68 [ 1.04, 6.93 ] |
| Osterborg 1996b | 23/48 | 4/25 | | 1.1 % | 2.99 [ 1.16, 7.71 ] |
| Osterborg 2002 | 114/170 | 46/173 | | 9.4 % | 2.52 [ 1.93, 3.30 ] |
| Rose 1994 | 67/142 | 13/79 | | 3.5 % | 2.87 [ 1.69, 4.85 ] |
| Savonije 2005 | 143/208 | 31/100 | | 8.7 % | 2.22 [ 1.63, 3.01 ] |
| Smith 2003a | 12/21 | 1/7 | | 0.3 % | 4.00 [ 0.63, 25.49 ] |
| Smith 2003b | 10/21 | 0/7 | | 0.2 % | 7.64 [ 0.50, 115.83 ] |
| Smith 2003c | 13/22 | 0/8 | | 0.1 % | 10.57 [ 0.70, 159.65 ] |
| Suzuki 2008a | 22/40 | 3/21 | | 0.8 % | 3.85 [ 1.30, 11.39 ] |
| Suzuki 2008b | 28/41 | 2/21 | | 0.5 % | 7.17 [ 1.89, 27.24 ] |
| Thompson 2000 | 4/45 | 1/21 | | 0.3 % | 1.87 [ 0.22, 15.70 ] |
| Tjulandin 2010a | 50/76 | 8/37 | | 2.2 % | 3.04 [ 1.61, 5.74 ] |
| Tjulandin 2010b | 52/73 | 7/37 | | 1.9 % | 3.77 [ 1.90, 7.45 ] |
| Tjulandin 2011 | 69/95 | 23/91 | | 4.9 % | 2.87 [ 1.98, 4.18 ] |
| Witzig 2005 | 120/165 | 52/164 | | 10.8 % | 2.29 [ 1.80, 2.93 ] |
| **Subtotal (95% CI)** | **3310** | **2313** | | **88.1 %** | **3.34 [ 3.03, 3.68 ]** |
| Total events: 1834 (Treatment), 377 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 55.62, df = 42 (P = 0.08); $I^2$ =24% | | | | | |
| Test for overall effect: Z = 24.39 (P < 0.00001) | | | | | |
| 3 >70% non-elderly 18-65 years | | | | | |

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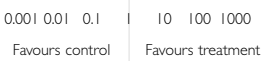
| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Chang 2005 | 115/175 | 11/175 | | 2.3 % | 10.45 [ 5.84, 18.71 ] |
| Oberhoff 1998 | 38/114 | 7/104 | | 1.5 % | 4.95 [ 2.31, 10.60 ] |
| **Subtotal (95% CI)** | **289** | **279** | | **3.8 %** | **8.26 [ 5.22, 13.06 ]** |
| Total events: 153 (Treatment), 18 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 2.36, df = 1 (P = 0.12); $I^2$ =58% | | | | | |
| Test for overall effect: Z = 9.03 (P < 0.00001) | | | | | |
| 4 only non-elderly adults | | | | | |
| **Subtotal (95% CI)** | **0** | **0** | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Total events: 0 (Treatment), 0 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: not applicable | | | | | |
| 5 >70% elderly >65 years | | | | | |
| **Subtotal (95% CI)** | **0** | **0** | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Total events: 0 (Treatment), 0 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: not applicable | | | | | |
| 6 only elderly adults | | | | | |
| **Subtotal (95% CI)** | **0** | **0** | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Total events: 0 (Treatment), 0 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: not applicable | | | | | |
| **Total (95% CI)** | **3710** | **2703** | | **100.0 %** | **3.39 [ 3.10, 3.71 ]** |
| Total events: 2050 (Treatment), 434 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 95.56, df = 45 (P = 0.00002); $I^2$ =53% | | | | | |
| Test for overall effect: Z = 26.39 (P < 0.00001) | | | | | |
| Test for subgroup differences: $Chi^2$ = 37.02, df = 2 (P = 0.00), $I^2$ =95% | | | | | |



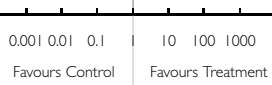
## Analysis 1.6. Comparison 1 Haematologic response, Outcome 6 Haematologic response - different therapies.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 1 Haematologic response

Outcome: 6 Haematologic response - different therapies

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 chemotherapy | | | | | |
| Aapro 2008 | 157/231 | 32/232 | | 6.6 % | 4.93 [ 3.53, 6.88 ] |
| Bamias 2003 | 15/72 | 2/72 | | 0.4 % | 7.50 [ 1.78, 31.62 ] |
| Boogaerts 2003 | 63/133 | 17/129 | | 3.6 % | 3.59 [ 2.23, 5.80 ] |
| Case 1993 | 46/79 | 10/74 | | 2.1 % | 4.31 [ 2.35, 7.90 ] |
| Cazzola 1995a | 2/31 | 0/7 | | 0.2 % | 1.25 [ 0.07, 23.55 ] |
| Cazzola 1995b | 9/29 | 1/8 | | 0.3 % | 2.48 [ 0.37, 16.80 ] |
| Cazzola 1995c | 19/31 | 0/7 | | 0.2 % | 9.75 [ 0.66, 144.80 ] |
| Cazzola 1995d | 16/26 | 1/7 | | 0.3 % | 4.31 [ 0.68, 27.12 ] |
| Chang 2005 | 115/175 | 11/175 | | 2.3 % | 10.45 [ 5.84, 18.71 ] |
| Dammacco 2001 | 38/66 | 6/66 | | 1.2 % | 6.33 [ 2.87, 13.96 ] |
| Hedenus 2002a | 5/11 | 1/3 | | 0.3 % | 1.36 [ 0.24, 7.66 ] |
| Hedenus 2002b | 12/22 | 0/4 | | 0.2 % | 5.43 [ 0.38, 77.40 ] |
| Hedenus 2002c | 14/22 | 0/4 | | 0.2 % | 6.30 [ 0.45, 89.06 ] |
| Hedenus 2003 | 104/174 | 31/170 | | 6.5 % | 3.28 [ 2.33, 4.61 ] |
| Henry 1995 | 31/64 | 4/61 | | 0.8 % | 7.39 [ 2.77, 19.69 ] |
| Iconomou 2003 | 25/57 | 7/55 | | 1.5 % | 3.45 [ 1.62, 7.31 ] |
| Kotasek 2003a | 8/32 | 1/8 | | 0.3 % | 2.00 [ 0.29, 13.77 ] |
| Kotasek 2003b | 8/17 | 1/8 | | 0.3 % | 3.76 [ 0.56, 25.21 ] |
| Kotasek 2003c | 23/46 | 2/9 | | 0.7 % | 2.25 [ 0.64, 7.90 ] |
| Kotasek 2003d | 17/28 | 1/8 | | 0.3 % | 4.86 [ 0.76, 31.12 ] |
| Kotasek 2003e | 20/35 | 1/9 | | 0.3 % | 5.14 [ 0.79, 33.37 ] |
| Kotasek 2003f | 20/40 | 1/9 | | 0.3 % | 4.50 [ 0.69, 29.30 ] |
| Littlewood 2001 | 172/244 | 22/115 | | 6.2 % | 3.68 [ 2.51, 5.41 ] |
| Milroy 2011 | 37/189 | 5/191 | | 1.0 % | 7.48 [ 3.00, 18.62 ] |

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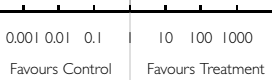
| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| ML17616 2006 | 21/30 | 11/30 | | 2.3 % | 1.91 [ 1.13, 3.23 ] |
| ML17620 2006 | 29/61 | 14/60 | | 2.9 % | 2.04 [ 1.20, 3.46 ] |
| Oberhoff 1998 | 38/114 | 7/104 | | 1.5 % | 4.95 [ 2.31, 10.60 ] |
| Osterborg 1996a | 21/47 | 4/24 | | 1.1 % | 2.68 [ 1.04, 6.93 ] |
| Osterborg 1996b | 23/48 | 4/25 | | 1.1 % | 2.99 [ 1.16, 7.71 ] |
| Osterborg 2002 | 114/170 | 46/173 | | 9.4 % | 2.52 [ 1.93, 3.30 ] |
| Razzouk 2006 | 63/111 | 39/111 | | 8.1 % | 1.62 [ 1.20, 2.18 ] |
| Savonije 2005 | 143/208 | 31/100 | | 8.7 % | 2.22 [ 1.63, 3.01 ] |
| Suzuki 2008a | 22/40 | 3/21 | | 0.8 % | 3.85 [ 1.30, 11.39 ] |
| Suzuki 2008b | 28/41 | 2/21 | | 0.5 % | 7.17 [ 1.89, 27.24 ] |
| Tjulandin 2010a | 50/76 | 8/37 | | 2.2 % | 3.04 [ 1.61, 5.74 ] |
| Tjulandin 2010b | 52/73 | 7/37 | | 1.9 % | 3.77 [ 1.90, 7.45 ] |
| Tjulandin 2011 | 69/95 | 23/91 | | 4.9 % | 2.87 [ 1.98, 4.18 ] |
| Witzig 2005 | 120/165 | 52/164 | | 10.8 % | 2.29 [ 1.80, 2.93 ] |
| **Subtotal (95% CI)** | **3133** | **2429** | | **92.6 %** | **3.32 [ 3.02, 3.64 ]** |
| Total events: 1769 (Treatment), 408 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 87.08, df = 37 (P<0.00001); $I^2$ =58% | | | | | |
| Test for overall effect: Z = 25.32 (P < 0.00001) | | | | | |
| 2 radiotherapy/radiochemotherapy | | | | | |
| **Subtotal (95% CI)** | **0** | **0** | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Total events: 0 (Treatment), 0 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: not applicable | | | | | |
| 3 no therapy | | | | | |
| Abels 1993 | 20/63 | 6/55 | | 1.3 % | 2.91 [ 1.26, 6.72 ] |
| Charu 2007 | 150/220 | 5/55 | | 1.7 % | 7.50 [ 3.24, 17.38 ] |
| Italian 1998 | 5/43 | 0/42 | | 0.1 % | 10.75 [ 0.61, 188.54 ] |
| Smith 2003a | 12/21 | 1/7 | | 0.3 % | 4.00 [ 0.63, 25.49 ] |
| Smith 2003b | 10/21 | 0/7 | | 0.2 % | 7.64 [ 0.50, 115.83 ] |
| Smith 2003c | 13/22 | 0/8 | | 0.1 % | 10.57 [ 0.70, 159.65 ] |
| Thompson 2000 | 4/45 | 1/21 | | 0.3 % | 1.87 [ 0.22, 15.70 ] |
| **Subtotal (95% CI)** | **435** | **195** | | **4.0 %** | **5.50 [ 3.25, 9.31 ]** |
| Total events: 214 (Treatment), 13 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 4.34, df = 6 (P = 0.63); $I^2$ =0.0% | | | | | |
| Test for overall effect: Z = 6.36 (P < 0.00001) | | | | | |
| 4 other | | | | | |

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| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Rose 1994 | 67/142 | 13/79 | | 3.5 % | 2.87 [ 1.69, 4.85 ] |
| **Subtotal (95% CI)** | **142** | **79** | | **3.5 %** | **2.87 [ 1.69, 4.85 ]** |
| Total events: 67 (Treatment), 13 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 3.92 (P = 0.000088) | | | | | |
| **Total (95% CI)** | **3710** | **2703** | | **100.0 %** | **3.39 [ 3.10, 3.71 ]** |
| Total events: 2050 (Treatment), 434 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 95.56, df = 45 (P = 0.00002); $I^2$ =53% | | | | | |
| Test for overall effect: Z = 26.39 (P < 0.00001) | | | | | |
| Test for subgroup differences: $Chi^2$ = 3.80, df = 2 (P = 0.15), $I^2$ =47% | | | | | |


**Analysis 1.7. Comparison 1 Haematologic response, Outcome 7 Haematologic response - different therapies differentiated.**

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 1 Haematologic response

Outcome: 7 Haematologic response - different therapies differentiated

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 chemotherapy, >70% with platinum | | | | | |
| Bamias 2003 | 15/72 | 2/72 | | 0.4 % | 7.50 [ 1.78, 31.62 ] |
| Henry 1995 | 31/64 | 4/61 | | 0.8 % | 7.39 [ 2.77, 19.69 ] |
| Milroy 2011 | 37/189 | 5/191 | | 1.0 % | 7.48 [ 3.00, 18.62 ] |
| ML17620 2006 | 29/61 | 14/60 | | 2.9 % | 2.04 [ 1.20, 3.46 ] |
| Savonije 2005 | 143/208 | 31/100 | | 8.7 % | 2.22 [ 1.63, 3.01 ] |
| Tjulandin 2010a | 50/76 | 8/37 | | 2.2 % | 3.04 [ 1.61, 5.74 ] |
| Tjulandin 2010b | 52/73 | 7/37 | | 1.9 % | 3.77 [ 1.90, 7.45 ] |


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| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| **Subtotal (95% CI)** | **743** | **558** | ♦ | **18.0 %** | **3.12 [ 2.51, 3.87 ]** |
| Total events: 357 (Treatment), 71 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 15.48, df = 6 (P = 0.02); $I^2$ =61% | | | | | |
| Test for overall effect: Z = 10.31 (P < 0.00001) | | | | | |
| 2 chemotherapy, <70% platinum containing | | | | | |
| Iconomou 2003 | 25/57 | 7/55 | | 1.5 % | 3.45 [ 1.62, 7.31 ] |
| Oberhoff 1998 | 38/114 | 7/104 | | 1.5 % | 4.95 [ 2.31, 10.60 ] |
| Witzig 2005 | 120/165 | 52/164 | | 10.8 % | 2.29 [ 1.80, 2.93 ] |
| **Subtotal (95% CI)** | **336** | **323** | ♦ | **13.8 %** | **2.71 [ 2.16, 3.40 ]** |
| Total events: 183 (Treatment), 66 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 4.61, df = 2 (P = 0.10); $I^2$ =57% | | | | | |
| Test for overall effect: Z = 8.59 (P < 0.00001) | | | | | |
| 3 chemotherapy without platinum (all patients) | | | | | |
| Aapro 2008 | 157/231 | 32/232 | | 6.6 % | 4.93 [ 3.53, 6.88 ] |
| Case 1993 | 46/79 | 10/74 | | 2.1 % | 4.31 [ 2.35, 7.90 ] |
| Cazzola 1995a | 2/31 | 0/7 | | 0.2 % | 1.25 [ 0.07, 23.55 ] |
| Cazzola 1995b | 9/29 | 1/8 | | 0.3 % | 2.48 [ 0.37, 16.80 ] |
| Cazzola 1995c | 19/31 | 0/7 | | 0.2 % | 9.75 [ 0.66, 144.80 ] |
| Cazzola 1995d | 16/26 | 1/7 | | 0.3 % | 4.31 [ 0.68, 27.12 ] |
| Chang 2005 | 115/175 | 11/175 | | 2.3 % | 10.45 [ 5.84, 18.71 ] |
| Hedenus 2002a | 5/11 | 1/3 | | 0.3 % | 1.36 [ 0.24, 7.66 ] |
| Hedenus 2002b | 12/22 | 0/4 | | 0.2 % | 5.43 [ 0.38, 77.40 ] |
| Hedenus 2002c | 14/22 | 0/4 | | 0.2 % | 6.30 [ 0.45, 89.06 ] |
| Hedenus 2003 | 104/174 | 31/170 | | 6.5 % | 3.28 [ 2.33, 4.61 ] |
| Littlewood 2001 | 172/244 | 22/115 | | 6.2 % | 3.68 [ 2.51, 5.41 ] |
| ML17616 2006 | 21/30 | 11/30 | | 2.3 % | 1.91 [ 1.13, 3.23 ] |
| Osterborg 1996a | 21/47 | 4/24 | | 1.1 % | 2.68 [ 1.04, 6.93 ] |
| Osterborg 1996b | 23/48 | 4/25 | | 1.1 % | 2.99 [ 1.16, 7.71 ] |
| Osterborg 2002 | 114/170 | 46/173 | | 9.4 % | 2.52 [ 1.93, 3.30 ] |
| Tjulandin 2011 | 69/95 | 23/91 | | 4.9 % | 2.87 [ 1.98, 4.18 ] |
| **Subtotal (95% CI)** | **1465** | **1149** | ♦ | **44.2 %** | **3.73 [ 3.26, 4.26 ]** |
| Total events: 919 (Treatment), 197 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 35.13, df = 16 (P = 0.004); $I^2$ =54% | | | | | |
| Test for overall effect: Z = 19.37 (P < 0.00001) | | | | | |
| 4 chemotherapy, platinum and non-platinum containing, no numbers given | | | | | |
| Boogaerts 2003 | 63/133 | 17/129 | | 3.6 % | 3.59 [ 2.23, 5.80 ] |

0.001 0.01 0.1 1 10 100 1000

Favours Control Favours Treatment

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| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Dammacco 2001 | 38/66 | 6/66 | | 1.2 % | 6.33 [ 2.87, 13.96 ] |
| Kotasek 2003a | 8/32 | 1/8 | | 0.3 % | 2.00 [ 0.29, 13.77 ] |
| Kotasek 2003b | 8/17 | 1/8 | | 0.3 % | 3.76 [ 0.56, 25.21 ] |
| Kotasek 2003c | 23/46 | 2/9 | | 0.7 % | 2.25 [ 0.64, 7.90 ] |
| Kotasek 2003d | 17/28 | 1/8 | | 0.3 % | 4.86 [ 0.76, 31.12 ] |
| Kotasek 2003e | 20/35 | 1/9 | | 0.3 % | 5.14 [ 0.79, 33.37 ] |
| Kotasek 2003f | 20/40 | 1/9 | | 0.3 % | 4.50 [ 0.69, 29.30 ] |
| **Subtotal (95% CI)** | **397** | **246** | | **7.1 %** | **4.05 [ 2.84, 5.77 ]** |
| Total events: 197 (Treatment), 30 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 2.94, df = 7 (P = 0.89); $I^2$ =0.0% | | | | | |
| Test for overall effect: Z = 7.73 (P < 0.00001) | | | | | |
| 5 chemotherapy no details given | | | | | |
| Razzouk 2006 | 63/111 | 39/111 | | 8.1 % | 1.62 [ 1.20, 2.18 ] |
| Suzuki 2008a | 22/40 | 3/21 | | 0.8 % | 3.85 [ 1.30, 11.39 ] |
| Suzuki 2008b | 28/41 | 2/21 | | 0.5 % | 7.17 [ 1.89, 27.24 ] |
| **Subtotal (95% CI)** | **192** | **153** | | **9.4 %** | **2.13 [ 1.59, 2.86 ]** |
| Total events: 113 (Treatment), 44 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 7.58, df = 2 (P = 0.02); $I^2$ =74% | | | | | |
| Test for overall effect: Z = 5.05 (P < 0.00001) | | | | | |
| 6 radiochemotherapy | | | | | |
| **Subtotal (95% CI)** | **0** | **0** | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Total events: 0 (Treatment), 0 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: not applicable | | | | | |
| 7 radiotherapy | | | | | |
| **Subtotal (95% CI)** | **0** | **0** | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Total events: 0 (Treatment), 0 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: not applicable | | | | | |
| 8 no therapy | | | | | |
| Abels 1993 | 20/63 | 6/55 | | 1.3 % | 2.91 [ 1.26, 6.72 ] |
| Charu 2007 | 150/220 | 5/55 | | 1.7 % | 7.50 [ 3.24, 17.38 ] |
| Italian 1998 | 5/43 | 0/42 | | 0.1 % | 10.75 [ 0.61, 188.54 ] |
| Smith 2003a | 12/21 | 1/7 | | 0.3 % | 4.00 [ 0.63, 25.49 ] |
| Smith 2003b | 10/21 | 0/7 | | 0.2 % | 7.64 [ 0.50, 115.83 ] |
| Smith 2003c | 13/22 | 0/8 | | 0.1 % | 10.57 [ 0.70, 159.65 ] |
| Thompson 2000 | 4/45 | 1/21 | | 0.3 % | 1.87 [ 0.22, 15.70 ] |
| **Subtotal (95% CI)** | **435** | **195** | | **4.0 %** | **5.50 [ 3.25, 9.31 ]** |


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| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Total events: 214 (Treatment), 13 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 4.34, df = 6 (P = 0.63); $I^2$ =0.0% | | | | | |
| Test for overall effect: Z = 6.36 (P < 0.00001) | | | | | |
| 9 other | | | | | |
| Rose 1994 | 67/142 | 13/79 | | 3.5 % | 2.87 [ 1.69, 4.85 ] |
| **Subtotal (95% CI)** | **142** | **79** | | **3.5 %** | **2.87 [ 1.69, 4.85 ]** |
| Total events: 67 (Treatment), 13 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 3.92 (P = 0.000088) | | | | | |
| **Total (95% CI)** | **3710** | **2703** | | **100.0 %** | **3.39 [ 3.10, 3.71 ]** |
| Total events: 2050 (Treatment), 434 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 95.56, df = 45 (P = 0.00002); $I^2$ =53% | | | | | |
| Test for overall effect: Z = 26.39 (P < 0.00001) | | | | | |
| Test for subgroup differences: $Chi^2$ = 20.08, df = 6 (P = 0.00), $I^2$ =70% | | | | | |

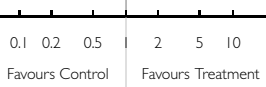
## Analysis 1.8. Comparison 1 Haematologic response, Outcome 8 Haematologic response - epoetin versus darbepoetin.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 1 Haematologic response

Outcome: 8 Haematologic response - epoetin versus darbepoetin

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 Epoetin | | | | | |
| Aapro 2008 | 157/231 | 32/232 | | 6.6 % | 4.93 [ 3.53, 6.88 ] |
| Abels 1993 | 20/63 | 6/55 | | 1.3 % | 2.91 [ 1.26, 6.72 ] |
| Bamias 2003 | 15/72 | 2/72 | | 0.4 % | 7.50 [ 1.78, 31.62 ] |
| Boogaerts 2003 | 63/133 | 17/129 | | 3.6 % | 3.59 [ 2.23, 5.80 ] |
| Case 1993 | 46/79 | 10/74 | | 2.1 % | 4.31 [ 2.35, 7.90 ] |
| Cazzola 1995a | 2/31 | 0/7 | | 0.2 % | 1.25 [ 0.07, 23.55 ] |
| Cazzola 1995b | 9/29 | 1/8 | | 0.3 % | 2.48 [ 0.37, 16.80 ] |
| Cazzola 1995c | 19/31 | 0/7 | | 0.2 % | 9.75 [ 0.66, 144.80 ] |
| Cazzola 1995d | 16/26 | 1/7 | | 0.3 % | 4.31 [ 0.68, 27.12 ] |
| Chang 2005 | 115/175 | 11/175 | | 2.3 % | 10.45 [ 5.84, 18.71 ] |
| Dammacco 2001 | 38/66 | 6/66 | | 1.2 % | 6.33 [ 2.87, 13.96 ] |
| Henry 1995 | 31/64 | 4/61 | | 0.8 % | 7.39 [ 2.77, 19.69 ] |
| Iconomou 2003 | 25/57 | 7/55 | | 1.5 % | 3.45 [ 1.62, 7.31 ] |
| Italian 1998 | 5/43 | 0/42 | | 0.1 % | 10.75 [ 0.61, 188.54 ] |
| Littlewood 2001 | 172/244 | 22/115 | | 6.2 % | 3.68 [ 2.51, 5.41 ] |
| Milroy 2011 | 37/189 | 5/191 | | 1.0 % | 7.48 [ 3.00, 18.62 ] |
| ML17616 2006 | 21/30 | 11/30 | | 2.3 % | 1.91 [ 1.13, 3.23 ] |
| ML17620 2006 | 29/61 | 14/60 | | 2.9 % | 2.04 [ 1.20, 3.46 ] |
| Oberhoff 1998 | 38/114 | 7/104 | | 1.5 % | 4.95 [ 2.31, 10.60 ] |
| Osterborg 1996a | 21/47 | 4/24 | | 1.1 % | 2.68 [ 1.04, 6.93 ] |
| Osterborg 1996b | 23/48 | 4/25 | | 1.1 % | 2.99 [ 1.16, 7.71 ] |
| Osterborg 2002 | 114/170 | 46/173 | | 9.4 % | 2.52 [ 1.93, 3.30 ] |
| Razzouk 2006 | 63/111 | 39/111 | | 8.1 % | 1.62 [ 1.20, 2.18 ] |
| Rose 1994 | 67/142 | 13/79 | | 3.5 % | 2.87 [ 1.69, 4.85 ] |

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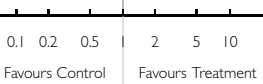
| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Savonije 2005 | 143/208 | 31/100 | | 8.7 % | 2.22 [ 1.63, 3.01 ] |
| Thompson 2000 | 4/45 | 1/21 | | 0.3 % | 1.87 [ 0.22, 15.70 ] |
| Tjulandin 2010a | 50/76 | 8/37 | | 2.2 % | 3.04 [ 1.61, 5.74 ] |
| Tjulandin 2010b | 52/73 | 7/37 | | 1.9 % | 3.77 [ 1.90, 7.45 ] |
| Tjulandin 2011 | 69/95 | 23/91 | | 4.9 % | 2.87 [ 1.98, 4.18 ] |
| Witzig 2005 | 120/165 | 52/164 | | 10.8 % | 2.29 [ 1.80, 2.93 ] |
| **Subtotal (95% CI)** | **2918** | **2352** | | **86.9 %** | **3.27 [ 2.97, 3.59 ]** |
| Total events: 1584 (Treatment), 384 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 82.73, df = 29 (P<0.00001); $I^2$ =65% | | | | | |
| Test for overall effect: Z = 24.28 (P < 0.00001) | | | | | |
| 2 Darbepoetin | | | | | |
| Charu 2007 | 150/220 | 5/55 | | 1.7 % | 7.50 [ 3.24, 17.38 ] |
| Hedenus 2002a | 5/11 | 1/3 | | 0.3 % | 1.36 [ 0.24, 7.66 ] |
| Hedenus 2002b | 12/22 | 0/4 | | 0.2 % | 5.43 [ 0.38, 77.40 ] |
| Hedenus 2002c | 14/22 | 0/4 | | 0.2 % | 6.30 [ 0.45, 89.06 ] |
| Hedenus 2003 | 104/174 | 31/170 | | 6.5 % | 3.28 [ 2.33, 4.61 ] |
| Kotasek 2003a | 8/32 | 1/8 | | 0.3 % | 2.00 [ 0.29, 13.77 ] |
| Kotasek 2003b | 8/17 | 1/8 | | 0.3 % | 3.76 [ 0.56, 25.21 ] |
| Kotasek 2003c | 23/46 | 2/9 | | 0.7 % | 2.25 [ 0.64, 7.90 ] |
| Kotasek 2003d | 17/28 | 1/8 | | 0.3 % | 4.86 [ 0.76, 31.12 ] |
| Kotasek 2003e | 20/35 | 1/9 | | 0.3 % | 5.14 [ 0.79, 33.37 ] |
| Kotasek 2003f | 20/40 | 1/9 | | 0.3 % | 4.50 [ 0.69, 29.30 ] |
| Smith 2003a | 12/21 | 1/7 | | 0.3 % | 4.00 [ 0.63, 25.49 ] |
| Smith 2003b | 10/21 | 0/7 | | 0.2 % | 7.64 [ 0.50, 115.83 ] |
| Smith 2003c | 13/22 | 0/8 | | 0.1 % | 10.57 [ 0.70, 159.65 ] |
| Suzuki 2008a | 22/40 | 3/21 | | 0.8 % | 3.85 [ 1.30, 11.39 ] |
| Suzuki 2008b | 28/41 | 2/21 | | 0.5 % | 7.17 [ 1.89, 27.24 ] |
| **Subtotal (95% CI)** | **792** | **351** | | **13.1 %** | **4.22 [ 3.22, 5.55 ]** |
| Total events: 466 (Treatment), 50 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 8.57, df = 15 (P = 0.90); $I^2$ =0.0% | | | | | |
| Test for overall effect: Z = 10.36 (P < 0.00001) | | | | | |
| **Total (95% CI)** | **3710** | **2703** | | **100.0 %** | **3.39 [ 3.10, 3.71 ]** |
| Total events: 2050 (Treatment), 434 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 95.56, df = 45 (P = 0.00002); $I^2$ =53% | | | | | |
| Test for overall effect: Z = 26.39 (P < 0.00001) | | | | | |

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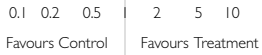
| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Test for subgroup differences: Chi² = 3.04, df = 1 (P = 0.08), I² =67% | | | | | |




**Analysis 1.9. Comparison 1 Haematologic response, Outcome 9 Haematologic response - duration of ESA medication.**

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 1 Haematologic response

Outcome: 9 Haematologic response - duration of ESA medication

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 6 to 9 weeks | | | | | |
| Abels 1993 | 20/63 | 6/55 | | 1.3 % | 2.91 [ 1.26, 6.72 ] |
| Cazzola 1995a | 2/31 | 0/7 | | 0.2 % | 1.25 [ 0.07, 23.55 ] |
| Cazzola 1995b | 9/29 | 1/8 | | 0.3 % | 2.48 [ 0.37, 16.80 ] |
| Cazzola 1995c | 19/31 | 0/7 | | 0.2 % | 9.75 [ 0.66, 144.80 ] |
| Cazzola 1995d | 16/26 | 1/7 | | 0.3 % | 4.31 [ 0.68, 27.12 ] |
| Italian 1998 | 5/43 | 0/42 | | 0.1 % | 10.75 [ 0.61, 188.54 ] |
| **Subtotal (95% CI)** | **223** | **126** | | **2.4 %** | **3.74 [ 1.94, 7.19 ]** |
| Total events: 71 (Treatment), 8 (Control) | | | | | |
| Heterogeneity: Chi² = 2.08, df = 5 (P = 0.84); I² =0.0% | | | | | |
| Test for overall effect: Z = 3.95 (P = 0.000078) | | | | | |
| 2 12 to 16 weeks | | | | | |
| Boogaerts 2003 | 63/133 | 17/129 | | 3.6 % | 3.59 [ 2.23, 5.80 ] |
| Case 1993 | 46/79 | 10/74 | | 2.1 % | 4.31 [ 2.35, 7.90 ] |
| Chang 2005 | 115/175 | 11/175 | | 2.3 % | 10.45 [ 5.84, 18.71 ] |
| Charu 2007 | 150/220 | 5/55 | | 1.7 % | 7.50 [ 3.24, 17.38 ] |
| Dammacco 2001 | 38/66 | 6/66 | | 1.2 % | 6.33 [ 2.87, 13.96 ] |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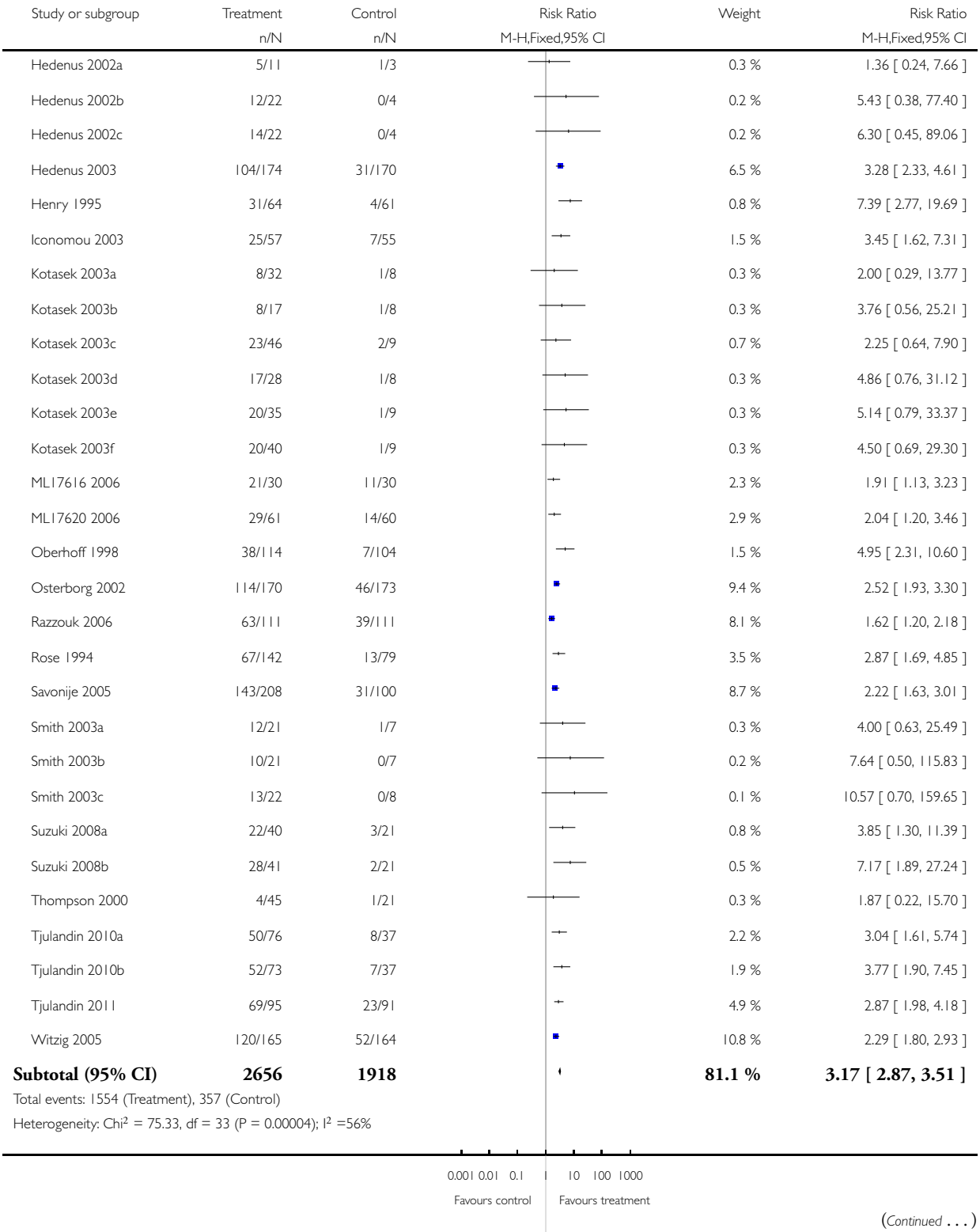

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Hedenus 2002a | 5/11 | 1/3 | | 0.3 % | 1.36 [ 0.24, 7.66 ] |
| Hedenus 2002b | 12/22 | 0/4 | | 0.2 % | 5.43 [ 0.38, 77.40 ] |
| Hedenus 2002c | 14/22 | 0/4 | | 0.2 % | 6.30 [ 0.45, 89.06 ] |
| Hedenus 2003 | 104/174 | 31/170 | | 6.5 % | 3.28 [ 2.33, 4.61 ] |
| Henry 1995 | 31/64 | 4/61 | | 0.8 % | 7.39 [ 2.77, 19.69 ] |
| Iconomou 2003 | 25/57 | 7/55 | | 1.5 % | 3.45 [ 1.62, 7.31 ] |
| Kotasek 2003a | 8/32 | 1/8 | | 0.3 % | 2.00 [ 0.29, 13.77 ] |
| Kotasek 2003b | 8/17 | 1/8 | | 0.3 % | 3.76 [ 0.56, 25.21 ] |
| Kotasek 2003c | 23/46 | 2/9 | | 0.7 % | 2.25 [ 0.64, 7.90 ] |
| Kotasek 2003d | 17/28 | 1/8 | | 0.3 % | 4.86 [ 0.76, 31.12 ] |
| Kotasek 2003e | 20/35 | 1/9 | | 0.3 % | 5.14 [ 0.79, 33.37 ] |
| Kotasek 2003f | 20/40 | 1/9 | | 0.3 % | 4.50 [ 0.69, 29.30 ] |
| ML17616 2006 | 21/30 | 11/30 | | 2.3 % | 1.91 [ 1.13, 3.23 ] |
| ML17620 2006 | 29/61 | 14/60 | | 2.9 % | 2.04 [ 1.20, 3.46 ] |
| Oberhoff 1998 | 38/114 | 7/104 | | 1.5 % | 4.95 [ 2.31, 10.60 ] |
| Osterborg 2002 | 114/170 | 46/173 | | 9.4 % | 2.52 [ 1.93, 3.30 ] |
| Razzouk 2006 | 63/111 | 39/111 | | 8.1 % | 1.62 [ 1.20, 2.18 ] |
| Rose 1994 | 67/142 | 13/79 | | 3.5 % | 2.87 [ 1.69, 4.85 ] |
| Savonije 2005 | 143/208 | 31/100 | | 8.7 % | 2.22 [ 1.63, 3.01 ] |
| Smith 2003a | 12/21 | 1/7 | | 0.3 % | 4.00 [ 0.63, 25.49 ] |
| Smith 2003b | 10/21 | 0/7 | | 0.2 % | 7.64 [ 0.50, 115.83 ] |
| Smith 2003c | 13/22 | 0/8 | | 0.1 % | 10.57 [ 0.70, 159.65 ] |
| Suzuki 2008a | 22/40 | 3/21 | | 0.8 % | 3.85 [ 1.30, 11.39 ] |
| Suzuki 2008b | 28/41 | 2/21 | | 0.5 % | 7.17 [ 1.89, 27.24 ] |
| Thompson 2000 | 4/45 | 1/21 | | 0.3 % | 1.87 [ 0.22, 15.70 ] |
| Tjulandin 2010a | 50/76 | 8/37 | | 2.2 % | 3.04 [ 1.61, 5.74 ] |
| Tjulandin 2010b | 52/73 | 7/37 | | 1.9 % | 3.77 [ 1.90, 7.45 ] |
| Tjulandin 2011 | 69/95 | 23/91 | | 4.9 % | 2.87 [ 1.98, 4.18 ] |
| Witzig 2005 | 120/165 | 52/164 | | 10.8 % | 2.29 [ 1.80, 2.93 ] |
| **Subtotal (95% CI)** | **2656** | **1918** | | **81.1 %** | **3.17 [ 2.87, 3.51 ]** |
| Total events: 1554 (Treatment), 357 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 75.33, df = 33 (P = 0.00004); $I^2$ =56% | | | | | |



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| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Test for overall effect: Z = 22.63 (P < 0.00001) | | | | | |
| 3 more than 17 weeks | | | | | |
| Aapro 2008 | 157/231 | 32/232 | | 6.6 % | 4.93 [ 3.53, 6.88 ] |
| Bamias 2003 | 15/72 | 2/72 | | 0.4 % | 7.50 [ 1.78, 31.62 ] |
| Littlewood 2001 | 172/244 | 22/115 | | 6.2 % | 3.68 [ 2.51, 5.41 ] |
| Milroy 2011 | 37/189 | 5/191 | | 1.0 % | 7.48 [ 3.00, 18.62 ] |
| Osterborg 1996a | 21/47 | 4/24 | | 1.1 % | 2.68 [ 1.04, 6.93 ] |
| Osterborg 1996b | 23/48 | 4/25 | | 1.1 % | 2.99 [ 1.16, 7.71 ] |
| **Subtotal (95% CI)** | **831** | **659** | | **16.4 %** | **4.41 [ 3.52, 5.52 ]** |
| Total events: 425 (Treatment), 69 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 4.77, df = 5 (P = 0.44); $I^2$ =0.0% | | | | | |
| Test for overall effect: Z = 12.92 (P < 0.00001) | | | | | |
| **Total (95% CI)** | **3710** | **2703** | | **100.0 %** | **3.39 [ 3.10, 3.71 ]** |
| Total events: 2050 (Treatment), 434 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 95.56, df = 45 (P = 0.00002); $I^2$ =53% | | | | | |
| Test for overall effect: Z = 26.39 (P < 0.00001) | | | | | |
| Test for subgroup differences: $Chi^2$ = 6.92, df = 2 (P = 0.03), $I^2$ =71% | | | | | |

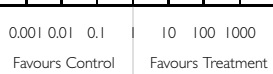
## Analysis 1.10. Comparison 1 Haematologic response, Outcome 10 Haematologic response - iron supplementation.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 1 Haematologic response

Outcome: 10 Haematologic response - iron supplementation

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 fixed iron supplementation | | | | | |
| Iconomou 2003 | 25/57 | 7/55 | | 1.5 % | 3.45 [ 1.62, 7.31 ] |
| Witzig 2005 | 120/165 | 52/164 | | 10.8 % | 2.29 [ 1.80, 2.93 ] |
| **Subtotal (95% CI)** | **222** | **219** | | **12.3 %** | **2.43 [ 1.92, 3.07 ]** |
| Total events: 145 (Treatment), 59 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 1.05, df = 1 (P = 0.31); $I^2$ =5% | | | | | |
| Test for overall effect: Z = 7.44 (P < 0.00001) | | | | | |
| 2 iron supplementation as necessary | | | | | |
| Aapro 2008 | 157/231 | 32/232 | | 6.6 % | 4.93 [ 3.53, 6.88 ] |
| Abels 1993 | 20/63 | 6/55 | | 1.3 % | 2.91 [ 1.26, 6.72 ] |
| Boogaerts 2003 | 63/133 | 17/129 | | 3.6 % | 3.59 [ 2.23, 5.80 ] |
| Case 1993 | 46/79 | 10/74 | | 2.1 % | 4.31 [ 2.35, 7.90 ] |
| Cazzola 1995a | 2/31 | 0/7 | | 0.2 % | 1.25 [ 0.07, 23.55 ] |
| Cazzola 1995b | 9/29 | 1/8 | | 0.3 % | 2.48 [ 0.37, 16.80 ] |
| Cazzola 1995c | 19/31 | 0/7 | | 0.2 % | 9.75 [ 0.66, 144.80 ] |
| Cazzola 1995d | 16/26 | 1/7 | | 0.3 % | 4.31 [ 0.68, 27.12 ] |
| Chang 2005 | 115/175 | 11/175 | | 2.3 % | 10.45 [ 5.84, 18.71 ] |
| Charu 2007 | 150/220 | 5/55 | | 1.7 % | 7.50 [ 3.24, 17.38 ] |
| Dammacco 2001 | 38/66 | 6/66 | | 1.2 % | 6.33 [ 2.87, 13.96 ] |
| Hedenus 2003 | 104/174 | 31/170 | | 6.5 % | 3.28 [ 2.33, 4.61 ] |
| Henry 1995 | 31/64 | 4/61 | | 0.8 % | 7.39 [ 2.77, 19.69 ] |
| Italian 1998 | 5/43 | 0/42 | | 0.1 % | 10.75 [ 0.61, 188.54 ] |
| Kotasek 2003a | 8/32 | 1/8 | | 0.3 % | 2.00 [ 0.29, 13.77 ] |
| Kotasek 2003b | 8/17 | 1/8 | | 0.3 % | 3.76 [ 0.56, 25.21 ] |
| Kotasek 2003c | 23/46 | 2/9 | | 0.7 % | 2.25 [ 0.64, 7.90 ] |
| Kotasek 2003d | 17/28 | 1/8 | | 0.3 % | 4.86 [ 0.76, 31.12 ] |
| Kotasek 2003e | 20/35 | 1/9 | | 0.3 % | 5.14 [ 0.79, 33.37 ] |

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| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Kotasek 2003f | 20/40 | 1/9 | | 0.3 % | 4.50 [ 0.69, 29.30 ] |
| Littlewood 2001 | 172/244 | 22/115 | | 6.2 % | 3.68 [ 2.51, 5.41 ] |
| Milroy 2011 | 37/189 | 5/191 | | 1.0 % | 7.48 [ 3.00, 18.62 ] |
| ML17616 2006 | 21/30 | 11/30 | | 2.3 % | 1.91 [ 1.13, 3.23 ] |
| ML17620 2006 | 29/61 | 14/60 | | 2.9 % | 2.04 [ 1.20, 3.46 ] |
| Oberhoff 1998 | 38/114 | 7/104 | | 1.5 % | 4.95 [ 2.31, 10.60 ] |
| Osterborg 1996a | 21/47 | 4/24 | | 1.1 % | 2.68 [ 1.04, 6.93 ] |
| Osterborg 1996b | 23/48 | 4/25 | | 1.1 % | 2.99 [ 1.16, 7.71 ] |
| Osterborg 2002 | 114/170 | 46/173 | | 9.4 % | 2.52 [ 1.93, 3.30 ] |
| Razzouk 2006 | 63/111 | 39/111 | | 8.1 % | 1.62 [ 1.20, 2.18 ] |
| Rose 1994 | 67/142 | 13/79 | | 3.5 % | 2.87 [ 1.69, 4.85 ] |
| Smith 2003a | 12/21 | 1/7 | | 0.3 % | 4.00 [ 0.63, 25.49 ] |
| Smith 2003b | 10/21 | 0/7 | | 0.2 % | 7.64 [ 0.50, 115.83 ] |
| Smith 2003c | 13/22 | 0/8 | | 0.1 % | 10.57 [ 0.70, 159.65 ] |
| Tjulandin 2010a | 50/76 | 8/37 | | 2.2 % | 3.04 [ 1.61, 5.74 ] |
| Tjulandin 2010b | 52/73 | 7/37 | | 1.9 % | 3.77 [ 1.90, 7.45 ] |
| Tjulandin 2011 | 69/95 | 23/91 | | 4.9 % | 2.87 [ 1.98, 4.18 ] |
| **Subtotal (95% CI)** | **3027** | **2238** | | **76.3 %** | **3.63 [ 3.27, 4.03 ]** |
| Total events: 1662 (Treatment), 335 (Control) | | | | | |
| Heterogeneity: Chi² = 78.84, df = 35 (P = 0.00003); I² =56% | | | | | |
| Test for overall effect: Z = 24.20 (P < 0.00001) | | | | | |
| 3 no explicit statement on iron supplementation or no iron given | | | | | |
| Bamias 2003 | 15/72 | 2/72 | | 0.4 % | 7.50 [ 1.78, 31.62 ] |
| Hedenus 2002a | 5/11 | 1/3 | | 0.3 % | 1.36 [ 0.24, 7.66 ] |
| Hedenus 2002b | 12/22 | 0/4 | | 0.2 % | 5.43 [ 0.38, 77.40 ] |
| Hedenus 2002c | 14/22 | 0/4 | | 0.2 % | 6.30 [ 0.45, 89.06 ] |
| Suzuki 2008a | 22/40 | 3/21 | | 0.8 % | 3.85 [ 1.30, 11.39 ] |
| Suzuki 2008b | 28/41 | 2/21 | | 0.5 % | 7.17 [ 1.89, 27.24 ] |
| Thompson 2000 | 4/45 | 1/21 | | 0.3 % | 1.87 [ 0.22, 15.70 ] |
| **Subtotal (95% CI)** | **253** | **146** | | **2.7 %** | **4.82 [ 2.64, 8.81 ]** |
| Total events: 100 (Treatment), 9 (Control) | | | | | |
| Heterogeneity: Chi² = 3.73, df = 6 (P = 0.71); I² =0.0% | | | | | |
| Test for overall effect: Z = 5.12 (P < 0.00001) | | | | | |
| 4 explicitly stated NO IRON | | | | | |


(*Continued* . . . )

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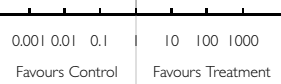
| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| **Subtotal (95% CI)** | **0** | **0** | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Total events: 0 (Treatment), 0 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: not applicable | | | | | |
| 5 iron given differently in both study arms | | | | | |
| Savonije 2005 | 143/208 | 31/100 | | 8.7 % | 2.22 [ 1.63, 3.01 ] |
| **Subtotal (95% CI)** | **208** | **100** | | **8.7 %** | **2.22 [ 1.63, 3.01 ]** |
| Total events: 143 (Treatment), 31 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 5.09 (P < 0.00001) | | | | | |
| **Total (95% CI)** | **3710** | **2703** | | **100.0 %** | **3.39 [ 3.10, 3.71 ]** |
| Total events: 2050 (Treatment), 434 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 95.56, df = 45 (P = 0.00002); $I^2$ =53% | | | | | |
| Test for overall effect: Z = 26.39 (P < 0.00001) | | | | | |
| Test for subgroup differences: $Chi^2$ = 17.66, df = 3 (P = 0.00), $I^2$ =83% | | | | | |



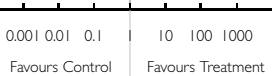
## Analysis 1.11. Comparison 1 Haematologic response, Outcome 11 Haematologic response - allocation concealment.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 1 Haematologic response

Outcome: 11 Haematologic response - allocation concealment

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 adequate | | | | | |
| Aapro 2008 | 157/231 | 32/232 | | 6.6 % | 4.93 [ 3.53, 6.88 ] |
| Boogaerts 2003 | 63/133 | 17/129 | | 3.6 % | 3.59 [ 2.23, 5.80 ] |
| Cazzola 1995a | 2/31 | 0/7 | | 0.2 % | 1.25 [ 0.07, 23.55 ] |
| Cazzola 1995b | 9/29 | 1/8 | | 0.3 % | 2.48 [ 0.37, 16.80 ] |
| Cazzola 1995c | 19/31 | 0/7 | | 0.2 % | 9.75 [ 0.66, 144.80 ] |
| Cazzola 1995d | 16/26 | 1/7 | | 0.3 % | 4.31 [ 0.68, 27.12 ] |
| Chang 2005 | 115/175 | 11/175 | | 2.3 % | 10.45 [ 5.84, 18.71 ] |
| Charu 2007 | 150/220 | 5/55 | | 1.7 % | 7.50 [ 3.24, 17.38 ] |
| Hedenus 2002a | 5/11 | 1/3 | | 0.3 % | 1.36 [ 0.24, 7.66 ] |
| Hedenus 2002b | 12/22 | 0/4 | | 0.2 % | 5.43 [ 0.38, 77.40 ] |
| Hedenus 2002c | 14/22 | 0/4 | | 0.2 % | 6.30 [ 0.45, 89.06 ] |
| Hedenus 2003 | 104/174 | 31/170 | | 6.5 % | 3.28 [ 2.33, 4.61 ] |
| Iconomou 2003 | 25/57 | 7/55 | | 1.5 % | 3.45 [ 1.62, 7.31 ] |
| Italian 1998 | 5/43 | 0/42 | | 0.1 % | 10.75 [ 0.61, 188.54 ] |
| Kotasek 2003a | 8/32 | 1/8 | | 0.3 % | 2.00 [ 0.29, 13.77 ] |
| Kotasek 2003b | 8/17 | 1/8 | | 0.3 % | 3.76 [ 0.56, 25.21 ] |
| Kotasek 2003c | 23/46 | 2/9 | | 0.7 % | 2.25 [ 0.64, 7.90 ] |
| Kotasek 2003d | 17/28 | 1/8 | | 0.3 % | 4.86 [ 0.76, 31.12 ] |
| Kotasek 2003e | 20/35 | 1/9 | | 0.3 % | 5.14 [ 0.79, 33.37 ] |
| Kotasek 2003f | 20/40 | 1/9 | | 0.3 % | 4.50 [ 0.69, 29.30 ] |
| Littlewood 2001 | 172/244 | 22/115 | | 6.2 % | 3.68 [ 2.51, 5.41 ] |
| Milroy 2011 | 37/189 | 5/191 | | 1.0 % | 7.48 [ 3.00, 18.62 ] |
| Oberhoff 1998 | 38/114 | 7/104 | | 1.5 % | 4.95 [ 2.31, 10.60 ] |
| Osterborg 1996a | 21/47 | 4/24 | | 1.1 % | 2.68 [ 1.04, 6.93 ] |

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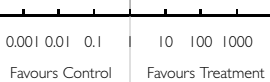
| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Osterborg 1996b | 23/48 | 4/25 | | 1.1 % | 2.99 [ 1.16, 7.71 ] |
| Osterborg 2002 | 114/170 | 46/173 | | 9.4 % | 2.52 [ 1.93, 3.30 ] |
| Razzouk 2006 | 63/111 | 39/111 | | 8.1 % | 1.62 [ 1.20, 2.18 ] |
| Savonije 2005 | 143/208 | 31/100 | | 8.7 % | 2.22 [ 1.63, 3.01 ] |
| Thompson 2000 | 4/45 | 1/21 | | 0.3 % | 1.87 [ 0.22, 15.70 ] |
| Witzig 2005 | 120/165 | 52/164 | | 10.8 % | 2.29 [ 1.80, 2.93 ] |
| **Subtotal (95% CI)** | **2744** | **1977** | | **74.4 %** | **3.35 [ 3.02, 3.72 ]** |
| Total events: 1527 (Treatment), 324 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 75.91, df = 29 (P<0.00001); $I^2$ =62% | | | | | |
| Test for overall effect: Z = 22.64 (P < 0.00001) | | | | | |
| 2 unclear | | | | | |
| Abels 1993 | 20/63 | 6/55 | | 1.3 % | 2.91 [ 1.26, 6.72 ] |
| Bamias 2003 | 15/72 | 2/72 | | 0.4 % | 7.50 [ 1.78, 31.62 ] |
| Case 1993 | 46/79 | 10/74 | | 2.1 % | 4.31 [ 2.35, 7.90 ] |
| Dammacco 2001 | 38/66 | 6/66 | | 1.2 % | 6.33 [ 2.87, 13.96 ] |
| Henry 1995 | 31/64 | 4/61 | | 0.8 % | 7.39 [ 2.77, 19.69 ] |
| ML17616 2006 | 21/30 | 11/30 | | 2.3 % | 1.91 [ 1.13, 3.23 ] |
| ML17620 2006 | 29/61 | 14/60 | | 2.9 % | 2.04 [ 1.20, 3.46 ] |
| Rose 1994 | 67/142 | 13/79 | | 3.5 % | 2.87 [ 1.69, 4.85 ] |
| Smith 2003a | 12/21 | 1/7 | | 0.3 % | 4.00 [ 0.63, 25.49 ] |
| Smith 2003b | 10/21 | 0/7 | | 0.2 % | 7.64 [ 0.50, 115.83 ] |
| Smith 2003c | 13/22 | 0/8 | | 0.1 % | 10.57 [ 0.70, 159.65 ] |
| Suzuki 2008a | 22/40 | 3/21 | | 0.8 % | 3.85 [ 1.30, 11.39 ] |
| Suzuki 2008b | 28/41 | 2/21 | | 0.5 % | 7.17 [ 1.89, 27.24 ] |
| Tjulandin 2010a | 50/76 | 8/37 | | 2.2 % | 3.04 [ 1.61, 5.74 ] |
| Tjulandin 2010b | 52/73 | 7/37 | | 1.9 % | 3.77 [ 1.90, 7.45 ] |
| Tjulandin 2011 | 69/95 | 23/91 | | 4.9 % | 2.87 [ 1.98, 4.18 ] |
| **Subtotal (95% CI)** | **966** | **726** | | **25.6 %** | **3.50 [ 2.92, 4.19 ]** |
| Total events: 523 (Treatment), 110 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 19.17, df = 15 (P = 0.21); $I^2$ =22% | | | | | |
| Test for overall effect: Z = 13.56 (P < 0.00001) | | | | | |
| **Total (95% CI)** | **3710** | **2703** | | **100.0 %** | **3.39 [ 3.10, 3.71 ]** |
| Total events: 2050 (Treatment), 434 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 95.56, df = 45 (P = 0.00002); $I^2$ =53% | | | | | |
| Test for overall effect: Z = 26.39 (P < 0.00001) | | | | | |

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| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Test for subgroup differences: $Chi^2$ = 0.15, df = 1 (P = 0.70), $I^2$ =0.0% | | | | | |


### Analysis 1.12. Comparison 1 Haematologic response, Outcome 12 Haematologic response - masking.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 1 Haematologic response

Outcome: 12 Haematologic response - masking

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 double-blind | | | | | |
| Abels 1993 | 20/63 | 6/55 | | 1.3 % | 2.91 [ 1.26, 6.72 ] |
| Case 1993 | 46/79 | 10/74 | | 2.1 % | 4.31 [ 2.35, 7.90 ] |
| Dammacco 2001 | 38/66 | 6/66 | | 1.2 % | 6.33 [ 2.87, 13.96 ] |
| Hedenus 2002a | 5/11 | 1/3 | | 0.3 % | 1.36 [ 0.24, 7.66 ] |
| Hedenus 2002b | 12/22 | 0/4 | | 0.2 % | 5.43 [ 0.38, 77.40 ] |
| Hedenus 2002c | 14/22 | 0/4 | | 0.2 % | 6.30 [ 0.45, 89.06 ] |
| Hedenus 2003 | 104/174 | 31/170 | | 6.5 % | 3.28 [ 2.33, 4.61 ] |
| Henry 1995 | 31/64 | 4/61 | | 0.8 % | 7.39 [ 2.77, 19.69 ] |
| Italian 1998 | 5/43 | 0/42 | | 0.1 % | 10.75 [ 0.61, 188.54 ] |
| Kotasek 2003a | 8/32 | 1/8 | | 0.3 % | 2.00 [ 0.29, 13.77 ] |
| Kotasek 2003b | 8/17 | 1/8 | | 0.3 % | 3.76 [ 0.56, 25.21 ] |
| Kotasek 2003c | 23/46 | 2/9 | | 0.7 % | 2.25 [ 0.64, 7.90 ] |
| Kotasek 2003d | 17/28 | 1/8 | | 0.3 % | 4.86 [ 0.76, 31.12 ] |
| Kotasek 2003e | 20/35 | 1/9 | | 0.3 % | 5.14 [ 0.79, 33.37 ] |
| Kotasek 2003f | 20/40 | 1/9 | | 0.3 % | 4.50 [ 0.69, 29.30 ] |


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| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Littlewood 2001 | 172/244 | 22/115 | | 6.2 % | 3.68 [ 2.51, 5.41 ] |
| Osterborg 2002 | 114/170 | 46/173 | | 9.4 % | 2.52 [ 1.93, 3.30 ] |
| Razzouk 2006 | 63/111 | 39/111 | | 8.1 % | 1.62 [ 1.20, 2.18 ] |
| Rose 1994 | 67/142 | 13/79 | | 3.5 % | 2.87 [ 1.69, 4.85 ] |
| Smith 2003a | 12/21 | 1/7 | | 0.3 % | 4.00 [ 0.63, 25.49 ] |
| Smith 2003b | 10/21 | 0/7 | | 0.2 % | 7.64 [ 0.50, 115.83 ] |
| Smith 2003c | 13/22 | 0/8 | | 0.1 % | 10.57 [ 0.70, 159.65 ] |
| Suzuki 2008a | 22/40 | 3/21 | | 0.8 % | 3.85 [ 1.30, 11.39 ] |
| Suzuki 2008b | 28/41 | 2/21 | | 0.5 % | 7.17 [ 1.89, 27.24 ] |
| Thompson 2000 | 4/45 | 1/21 | | 0.3 % | 1.87 [ 0.22, 15.70 ] |
| Tjulandin 2010a | 50/76 | 8/37 | | 2.2 % | 3.04 [ 1.61, 5.74 ] |
| Tjulandin 2010b | 52/73 | 7/37 | | 1.9 % | 3.77 [ 1.90, 7.45 ] |
| Tjulandin 2011 | 69/95 | 23/91 | | 4.9 % | 2.87 [ 1.98, 4.18 ] |
| Witzig 2005 | 120/165 | 52/164 | | 10.8 % | 2.29 [ 1.80, 2.93 ] |
| **Subtotal (95% CI)** | **2008** | **1422** | | **64.4 %** | **3.02 [ 2.70, 3.37 ]** |
| Total events: 1167 (Treatment), 282 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 39.44, df = 28 (P = 0.07); $I^2$ =29% | | | | | |
| Test for overall effect: Z = 19.30 (P < 0.00001) | | | | | |
| 2 unblinded | | | | | |
| Aapro 2008 | 157/231 | 32/232 | | 6.6 % | 4.93 [ 3.53, 6.88 ] |
| Bamias 2003 | 15/72 | 2/72 | | 0.4 % | 7.50 [ 1.78, 31.62 ] |
| Boogaerts 2003 | 63/133 | 17/129 | | 3.6 % | 3.59 [ 2.23, 5.80 ] |
| Cazzola 1995a | 2/31 | 0/7 | | 0.2 % | 1.25 [ 0.07, 23.55 ] |
| Cazzola 1995b | 9/29 | 1/8 | | 0.3 % | 2.48 [ 0.37, 16.80 ] |
| Cazzola 1995c | 19/31 | 0/7 | | 0.2 % | 9.75 [ 0.66, 144.80 ] |
| Cazzola 1995d | 16/26 | 1/7 | | 0.3 % | 4.31 [ 0.68, 27.12 ] |
| Chang 2005 | 115/175 | 11/175 | | 2.3 % | 10.45 [ 5.84, 18.71 ] |
| Charu 2007 | 150/220 | 5/55 | | 1.7 % | 7.50 [ 3.24, 17.38 ] |
| Iconomou 2003 | 25/57 | 7/55 | | 1.5 % | 3.45 [ 1.62, 7.31 ] |
| Milroy 2011 | 37/189 | 5/191 | | 1.0 % | 7.48 [ 3.00, 18.62 ] |
| ML17616 2006 | 21/30 | 11/30 | | 2.3 % | 1.91 [ 1.13, 3.23 ] |
| ML17620 2006 | 29/61 | 14/60 | | 2.9 % | 2.04 [ 1.20, 3.46 ] |
| Oberhoff 1998 | 38/114 | 7/104 | | 1.5 % | 4.95 [ 2.31, 10.60 ] |


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| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Osterborg 1996a | 21/47 | 4/24 | | 1.1 % | 2.68 [ 1.04, 6.93 ] |
| Osterborg 1996b | 23/48 | 4/25 | | 1.1 % | 2.99 [ 1.16, 7.71 ] |
| Savonije 2005 | 143/208 | 31/100 | | 8.7 % | 2.22 [ 1.63, 3.01 ] |
| **Subtotal (95% CI)** | **1702** | **1281** | | **35.6 %** | **4.07 [ 3.49, 4.74 ]** |
| Total events: 883 (Treatment), 152 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 48.54, df = 16 (P = 0.00004); $I^2$ =67% | | | | | |
| Test for overall effect: Z = 17.91 (P < 0.00001) | | | | | |
| **Total (95% CI)** | **3710** | **2703** | | **100.0 %** | **3.39 [ 3.10, 3.71 ]** |
| Total events: 2050 (Treatment), 434 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 95.56, df = 45 (P = 0.00002); $I^2$ =53% | | | | | |
| Test for overall effect: Z = 26.39 (P < 0.00001) | | | | | |
| Test for subgroup differences: $Chi^2$ = 9.54, df = 1 (P = 0.00), $I^2$ =90% | | | | | |

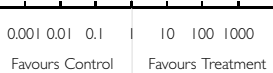
## Analysis 1.13. Comparison 1 Haematologic response, Outcome 13 Haematologic response - intention-to treat.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 1 Haematologic response

Outcome: 13 Haematologic response - intention-to treat

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 ITT or less than 10% of participants per study arm excluded | | | | | |
| Aapro 2008 | 157/231 | 32/232 | | 6.6 % | 4.93 [ 3.53, 6.88 ] |
| Abels 1993 | 20/63 | 6/55 | | 1.3 % | 2.91 [ 1.26, 6.72 ] |
| Bamias 2003 | 15/72 | 2/72 | | 0.4 % | 7.50 [ 1.78, 31.62 ] |
| Boogaerts 2003 | 63/133 | 17/129 | | 3.6 % | 3.59 [ 2.23, 5.80 ] |
| Case 1993 | 46/79 | 10/74 | | 2.1 % | 4.31 [ 2.35, 7.90 ] |
| Cazzola 1995a | 2/31 | 0/7 | | 0.2 % | 1.25 [ 0.07, 23.55 ] |
| Cazzola 1995b | 9/29 | 1/8 | | 0.3 % | 2.48 [ 0.37, 16.80 ] |
| Cazzola 1995c | 19/31 | 0/7 | | 0.2 % | 9.75 [ 0.66, 144.80 ] |
| Cazzola 1995d | 16/26 | 1/7 | | 0.3 % | 4.31 [ 0.68, 27.12 ] |
| Chang 2005 | 115/175 | 11/175 | | 2.3 % | 10.45 [ 5.84, 18.71 ] |
| Charu 2007 | 150/220 | 5/55 | | 1.7 % | 7.50 [ 3.24, 17.38 ] |
| Hedenus 2002a | 5/11 | 1/3 | | 0.3 % | 1.36 [ 0.24, 7.66 ] |
| Hedenus 2002b | 12/22 | 0/4 | | 0.2 % | 5.43 [ 0.38, 77.40 ] |
| Hedenus 2002c | 14/22 | 0/4 | | 0.2 % | 6.30 [ 0.45, 89.06 ] |
| Hedenus 2003 | 104/174 | 31/170 | | 6.5 % | 3.28 [ 2.33, 4.61 ] |
| Henry 1995 | 31/64 | 4/61 | | 0.8 % | 7.39 [ 2.77, 19.69 ] |
| Iconomou 2003 | 25/57 | 7/55 | | 1.5 % | 3.45 [ 1.62, 7.31 ] |
| Italian 1998 | 5/43 | 0/42 | | 0.1 % | 10.75 [ 0.61, 188.54 ] |
| Kotasek 2003a | 8/32 | 1/8 | | 0.3 % | 2.00 [ 0.29, 13.77 ] |
| Kotasek 2003b | 8/17 | 1/8 | | 0.3 % | 3.76 [ 0.56, 25.21 ] |
| Kotasek 2003c | 23/46 | 2/9 | | 0.7 % | 2.25 [ 0.64, 7.90 ] |
| Kotasek 2003d | 17/28 | 1/8 | | 0.3 % | 4.86 [ 0.76, 31.12 ] |
| Kotasek 2003e | 20/35 | 1/9 | | 0.3 % | 5.14 [ 0.79, 33.37 ] |
| Kotasek 2003f | 20/40 | 1/9 | | 0.3 % | 4.50 [ 0.69, 29.30 ] |

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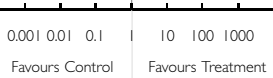
| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Littlewood 2001 | 172/244 | 22/115 | | 6.2 % | 3.68 [ 2.51, 5.41 ] |
| ML17616 2006 | 21/30 | 11/30 | | 2.3 % | 1.91 [ 1.13, 3.23 ] |
| Oberhoff 1998 | 38/114 | 7/104 | | 1.5 % | 4.95 [ 2.31, 10.60 ] |
| Osterborg 1996a | 21/47 | 4/24 | | 1.1 % | 2.68 [ 1.04, 6.93 ] |
| Osterborg 1996b | 23/48 | 4/25 | | 1.1 % | 2.99 [ 1.16, 7.71 ] |
| Osterborg 2002 | 114/170 | 46/173 | | 9.4 % | 2.52 [ 1.93, 3.30 ] |
| Razzouk 2006 | 63/111 | 39/111 | | 8.1 % | 1.62 [ 1.20, 2.18 ] |
| Rose 1994 | 67/142 | 13/79 | | 3.5 % | 2.87 [ 1.69, 4.85 ] |
| Savonije 2005 | 143/208 | 31/100 | | 8.7 % | 2.22 [ 1.63, 3.01 ] |
| Smith 2003a | 12/21 | 1/7 | | 0.3 % | 4.00 [ 0.63, 25.49 ] |
| Smith 2003b | 10/21 | 0/7 | | 0.2 % | 7.64 [ 0.50, 115.83 ] |
| Smith 2003c | 13/22 | 0/8 | | 0.1 % | 10.57 [ 0.70, 159.65 ] |
| Thompson 2000 | 4/45 | 1/21 | | 0.3 % | 1.87 [ 0.22, 15.70 ] |
| Tjulandin 2010a | 50/76 | 8/37 | | 2.2 % | 3.04 [ 1.61, 5.74 ] |
| Tjulandin 2010b | 52/73 | 7/37 | | 1.9 % | 3.77 [ 1.90, 7.45 ] |
| Tjulandin 2011 | 69/95 | 23/91 | | 4.9 % | 2.87 [ 1.98, 4.18 ] |
| Witzig 2005 | 120/165 | 52/164 | | 10.8 % | 2.29 [ 1.80, 2.93 ] |
| **Subtotal (95% CI)** | **3313** | **2344** | | **93.4 %** | **3.32 [ 3.03, 3.65 ]** |
| Total events: 1896 (Treatment), 404 (Control) | | | | | |
| Heterogeneity: Chi² = 82.99, df = 40 (P = 0.00008); I² =52% | | | | | |
| Test for overall effect: Z = 25.13 (P < 0.00001) | | | | | |
| 2 more than 10% of participants per study arm excluded | | | | | |
| Dammacco 2001 | 38/66 | 6/66 | | 1.2 % | 6.33 [ 2.87, 13.96 ] |
| Milroy 2011 | 37/189 | 5/191 | | 1.0 % | 7.48 [ 3.00, 18.62 ] |
| **Subtotal (95% CI)** | **255** | **257** | | **2.3 %** | **6.85 [ 3.76, 12.48 ]** |
| Total events: 75 (Treatment), 11 (Control) | | | | | |
| Heterogeneity: Chi² = 0.07, df = 1 (P = 0.79); I² =0.0% | | | | | |
| Test for overall effect: Z = 6.29 (P < 0.00001) | | | | | |
| 3 unclear | | | | | |
| ML17620 2006 | 29/61 | 14/60 | | 2.9 % | 2.04 [ 1.20, 3.46 ] |
| Suzuki 2008a | 22/40 | 3/21 | | 0.8 % | 3.85 [ 1.30, 11.39 ] |
| Suzuki 2008b | 28/41 | 2/21 | | 0.5 % | 7.17 [ 1.89, 27.24 ] |
| **Subtotal (95% CI)** | **142** | **102** | | **4.3 %** | **3.04 [ 1.92, 4.80 ]** |
| Total events: 79 (Treatment), 19 (Control) | | | | | |
| Heterogeneity: Chi² = 3.96, df = 2 (P = 0.14); I² =50% | | | | | |

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| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Test for overall effect: Z = 4.75 (P < 0.00001) | | | | | |
| **Total (95% CI)** | **3710** | **2703** | | **100.0 %** | **3.39 [ 3.10, 3.71 ]** |
| Total events: 2050 (Treatment), 434 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 95.56, df = 45 (P = 0.00002); $I^2$ =53% | | | | | |
| Test for overall effect: Z = 26.39 (P < 0.00001) | | | | | |
| Test for subgroup differences: $Chi^2$ = 5.67, df = 2 (P = 0.06), $I^2$ =65% | | | | | |

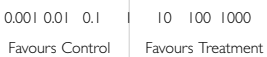

### Analysis 1.14. Comparison 1 Haematologic response, Outcome 14 Haematologic response - publication.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 1 Haematologic response

Outcome: 14 Haematologic response - publication

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 full text publication | | | | | |
| Aapro 2008 | 157/231 | 32/232 | | 6.6 % | 4.93 [ 3.53, 6.88 ] |
| Abels 1993 | 20/63 | 6/55 | | 1.3 % | 2.91 [ 1.26, 6.72 ] |
| Bamias 2003 | 15/72 | 2/72 | | 0.4 % | 7.50 [ 1.78, 31.62 ] |
| Boogaerts 2003 | 63/133 | 17/129 | | 3.6 % | 3.59 [ 2.23, 5.80 ] |
| Case 1993 | 46/79 | 10/74 | | 2.1 % | 4.31 [ 2.35, 7.90 ] |
| Chang 2005 | 115/175 | 11/175 | | 2.3 % | 10.45 [ 5.84, 18.71 ] |
| Charu 2007 | 150/220 | 5/55 | | 1.7 % | 7.50 [ 3.24, 17.38 ] |
| Dammacco 2001 | 38/66 | 6/66 | | 1.2 % | 6.33 [ 2.87, 13.96 ] |
| Hedenus 2002a | 5/11 | 1/3 | | 0.3 % | 1.36 [ 0.24, 7.66 ] |
| Hedenus 2002b | 12/22 | 0/4 | | 0.2 % | 5.43 [ 0.38, 77.40 ] |
| Hedenus 2002c | 14/22 | 0/4 | | 0.2 % | 6.30 [ 0.45, 89.06 ] |

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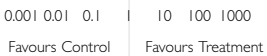
| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Hedenus 2003 | 104/174 | 31/170 | | 6.5 % | 3.28 [ 2.33, 4.61 ] |
| Henry 1995 | 31/64 | 4/61 | | 0.8 % | 7.39 [ 2.77, 19.69 ] |
| Iconomou 2003 | 25/57 | 7/55 | | 1.5 % | 3.45 [ 1.62, 7.31 ] |
| Kotasek 2003a | 8/32 | 1/8 | | 0.3 % | 2.00 [ 0.29, 13.77 ] |
| Kotasek 2003b | 8/17 | 1/8 | | 0.3 % | 3.76 [ 0.56, 25.21 ] |
| Kotasek 2003c | 23/46 | 2/9 | | 0.7 % | 2.25 [ 0.64, 7.90 ] |
| Kotasek 2003d | 17/28 | 1/8 | | 0.3 % | 4.86 [ 0.76, 31.12 ] |
| Kotasek 2003e | 20/35 | 1/9 | | 0.3 % | 5.14 [ 0.79, 33.37 ] |
| Kotasek 2003f | 20/40 | 1/9 | | 0.3 % | 4.50 [ 0.69, 29.30 ] |
| Littlewood 2001 | 172/244 | 22/115 | | 6.2 % | 3.68 [ 2.51, 5.41 ] |
| Milroy 2011 | 37/189 | 5/191 | | 1.0 % | 7.48 [ 3.00, 18.62 ] |
| Osterborg 2002 | 114/170 | 46/173 | | 9.4 % | 2.52 [ 1.93, 3.30 ] |
| Razzouk 2006 | 63/111 | 39/111 | | 8.1 % | 1.62 [ 1.20, 2.18 ] |
| Savonije 2005 | 143/208 | 31/100 | | 8.7 % | 2.22 [ 1.63, 3.01 ] |
| Smith 2003a | 12/21 | 1/7 | | 0.3 % | 4.00 [ 0.63, 25.49 ] |
| Smith 2003b | 10/21 | 0/7 | | 0.2 % | 7.64 [ 0.50, 115.83 ] |
| Smith 2003c | 13/22 | 0/8 | | 0.1 % | 10.57 [ 0.70, 159.65 ] |
| Tjulandin 2010a | 50/76 | 8/37 | | 2.2 % | 3.04 [ 1.61, 5.74 ] |
| Tjulandin 2010b | 52/73 | 7/37 | | 1.9 % | 3.77 [ 1.90, 7.45 ] |
| Tjulandin 2011 | 69/95 | 23/91 | | 4.9 % | 2.87 [ 1.98, 4.18 ] |
| Witzig 2005 | 120/165 | 52/164 | | 10.8 % | 2.29 [ 1.80, 2.93 ] |
| **Subtotal (95% CI)** | **2982** | **2247** | | **84.9 %** | **3.44 [ 3.12, 3.80 ]** |
| Total events: 1746 (Treatment), 373 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 83.98, df = 31 (P<0.00001); $I^2$ =63% | | | | | |
| Test for overall effect: Z = 24.87 (P < 0.00001) | | | | | |
| 2 abstract publication | | | | | |
| Suzuki 2008a | 22/40 | 3/21 | | 0.8 % | 3.85 [ 1.30, 11.39 ] |
| Suzuki 2008b | 28/41 | 2/21 | | 0.5 % | 7.17 [ 1.89, 27.24 ] |
| **Subtotal (95% CI)** | **81** | **42** | | **1.4 %** | **5.19 [ 2.23, 12.04 ]** |
| Total events: 50 (Treatment), 5 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 0.52, df = 1 (P = 0.47); $I^2$ =0.0% | | | | | |
| Test for overall effect: Z = 3.83 (P = 0.00013) | | | | | |
| 3 unpublished data | | | | | |
| Cazzola 1995a | 2/31 | 0/7 | | 0.2 % | 1.25 [ 0.07, 23.55 ] |

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| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Cazzola 1995b | 9/29 | 1/8 | | 0.3 % | 2.48 [ 0.37, 16.80 ] |
| Cazzola 1995c | 19/31 | 0/7 | | 0.2 % | 9.75 [ 0.66, 144.80 ] |
| Cazzola 1995d | 16/26 | 1/7 | | 0.3 % | 4.31 [ 0.68, 27.12 ] |
| Italian 1998 | 5/43 | 0/42 | | 0.1 % | 10.75 [ 0.61, 188.54 ] |
| Oberhoff 1998 | 38/114 | 7/104 | | 1.5 % | 4.95 [ 2.31, 10.60 ] |
| Osterborg 1996a | 21/47 | 4/24 | | 1.1 % | 2.68 [ 1.04, 6.93 ] |
| Osterborg 1996b | 23/48 | 4/25 | | 1.1 % | 2.99 [ 1.16, 7.71 ] |
| Rose 1994 | 67/142 | 13/79 | | 3.5 % | 2.87 [ 1.69, 4.85 ] |
| Thompson 2000 | 4/45 | 1/21 | | 0.3 % | 1.87 [ 0.22, 15.70 ] |
| **Subtotal (95% CI)** | **556** | **324** | | **8.5 %** | **3.44 [ 2.45, 4.82 ]** |
| Total events: 204 (Treatment), 31 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 3.81, df = 9 (P = 0.92); $I^2$ =0.0% | | | | | |
| Test for overall effect: Z = 7.16 (P < 0.00001) | | | | | |
| 4 FDA hearing | | | | | |
| **Subtotal (95% CI)** | **0** | **0** | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Total events: 0 (Treatment), 0 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: not applicable | | | | | |
| 5 clinical trial result information | | | | | |
| ML17616 2006 | 21/30 | 11/30 | | 2.3 % | 1.91 [ 1.13, 3.23 ] |
| ML17620 2006 | 29/61 | 14/60 | | 2.9 % | 2.04 [ 1.20, 3.46 ] |
| **Subtotal (95% CI)** | **91** | **90** | | **5.2 %** | **1.98 [ 1.36, 2.89 ]** |
| Total events: 50 (Treatment), 25 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 0.03, df = 1 (P = 0.86); $I^2$ =0.0% | | | | | |
| Test for overall effect: Z = 3.56 (P = 0.00038) | | | | | |
| **Total (95% CI)** | **3710** | **2703** | | **100.0 %** | **3.39 [ 3.10, 3.71 ]** |
| Total events: 2050 (Treatment), 434 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 95.56, df = 45 (P = 0.00002); $I^2$ =53% | | | | | |
| Test for overall effect: Z = 26.39 (P < 0.00001) | | | | | |
| Test for subgroup differences: $Chi^2$ = 8.83, df = 3 (P = 0.03), $I^2$ =66% | | | | | |

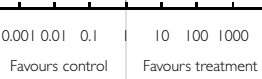
## Analysis 1.15. Comparison 1 Haematologic response, Outcome 15 Haematological response - merged experimental arms.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 1 Haematologic response

Outcome: 15 Haematological response - merged experimental arms

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Aapro 2008 | 157/231 | 32/232 | | 6.7 % | 4.93 [ 3.53, 6.88 ] |
| Abels 1993 | 20/63 | 6/55 | | 1.3 % | 2.91 [ 1.26, 6.72 ] |
| Bamias 2003 | 15/72 | 2/72 | | 0.4 % | 7.50 [ 1.78, 31.62 ] |
| Boogaerts 2003 | 63/133 | 17/129 | | 3.6 % | 3.59 [ 2.23, 5.80 ] |
| Case 1993 | 46/79 | 10/74 | | 2.2 % | 4.31 [ 2.35, 7.90 ] |
| Cazzola 1995 | 46/117 | 2/29 | | 0.7 % | 5.70 [ 1.47, 22.12 ] |
| Chang 2005 | 115/175 | 11/175 | | 2.3 % | 10.45 [ 5.84, 18.71 ] |
| Charu 2007 | 150/220 | 5/55 | | 1.7 % | 7.50 [ 3.24, 17.38 ] |
| Dammacco 2001 | 38/66 | 6/66 | | 1.3 % | 6.33 [ 2.87, 13.96 ] |
| Hedenus 2002 | 31/55 | 1/11 | | 0.3 % | 6.20 [ 0.94, 40.76 ] |
| Hedenus 2003 | 104/174 | 31/170 | | 6.6 % | 3.28 [ 2.33, 4.61 ] |
| Henry 1995 | 31/64 | 4/61 | | 0.9 % | 7.39 [ 2.77, 19.69 ] |
| Iconomou 2003 | 25/57 | 7/55 | | 1.5 % | 3.45 [ 1.62, 7.31 ] |
| Italian 1998 | 5/43 | 0/42 | | 0.1 % | 10.75 [ 0.61, 188.54 ] |
| Kotasek 2003 | 96/198 | 7/51 | | 2.3 % | 3.53 [ 1.75, 7.13 ] |
| Littlewood 2001 | 172/244 | 22/115 | | 6.3 % | 3.68 [ 2.51, 5.41 ] |
| Milroy 2011 | 37/189 | 5/191 | | 1.0 % | 7.48 [ 3.00, 18.62 ] |
| ML17616 2006 | 21/30 | 11/30 | | 2.3 % | 1.91 [ 1.13, 3.23 ] |
| ML17620 2006 | 29/61 | 14/60 | | 3.0 % | 2.04 [ 1.20, 3.46 ] |
| Oberhoff 1998 | 38/114 | 7/104 | | 1.5 % | 4.95 [ 2.31, 10.60 ] |
| Osterborg 1996 | 44/95 | 8/49 | | 2.2 % | 2.84 [ 1.45, 5.54 ] |
| Osterborg 2002 | 114/170 | 46/173 | | 9.5 % | 2.52 [ 1.93, 3.30 ] |
| Razzouk 2006 | 63/111 | 39/111 | | 8.2 % | 1.62 [ 1.20, 2.18 ] |
| Rose 1994 | 67/142 | 13/79 | | 3.5 % | 2.87 [ 1.69, 4.85 ] |
| Savonije 2005 | 143/208 | 31/100 | | 8.8 % | 2.22 [ 1.63, 3.01 ] |

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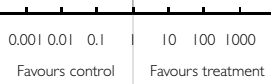
| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Smith 2003 | 35/64 | 1/22 | | 0.3 % | 12.03 [ 1.75, 82.71 ] |
| Suzuki 2008 | 50/81 | 5/42 | | 1.4 % | 5.19 [ 2.24, 12.02 ] |
| Thompson 2000 | 4/45 | 1/21 | | 0.3 % | 1.87 [ 0.22, 15.70 ] |
| Tjulandin 2010 | 102/149 | 15/74 | | 4.2 % | 3.38 [ 2.12, 5.38 ] |
| Tjulandin 2011 | 69/95 | 23/91 | | 4.9 % | 2.87 [ 1.98, 4.18 ] |
| Witzig 2005 | 120/165 | 52/164 | | 10.9 % | 2.29 [ 1.80, 2.93 ] |
| **Total (95% CI)** | **3710** | **2703** | | **100.0 %** | **3.42 [ 3.12, 3.74 ]** |

Total events: 2050 (Treatment), 434 (Control)

Heterogeneity: $Chi^2$ = 93.78, df = 30 (P<0.00001); $I^2$ =68%

Test for overall effect: Z = 26.41 (P < 0.00001)

Test for subgroup differences: Not applicable



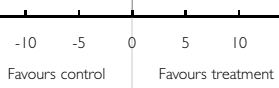
## Analysis 2.1. Comparison 2 Change of haemoglobin level, Outcome 1 Change in Hb values - overall.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 2 Change of haemoglobin level

Outcome: 1 Change in Hb values - overall

| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Abels 1993 | 63 | 0.952 (2.142) | 55 | -0.03 (1.36) | | 0.8 % | 0.99 [ 0.35, 1.63 ] |
| Aravantinos 2003 | 24 | 2.31 (1.22) | 23 | 1.23 (1.59) | | 0.5 % | 1.08 [ 0.27, 1.89 ] |
| Bamias 2003 | 72 | 0.57 (2.12) | 72 | -0.49 (1.36) | | 1.0 % | 1.06 [ 0.48, 1.64 ] |
| Boogaerts 2003 | 133 | 2.1 (1.83) | 129 | 0.9 (1.5) | | 2.0 % | 1.20 [ 0.80, 1.60 ] |
| Carabantes 1999 | 20 | 1 (1.56) | 15 | -1.7 (1.22) | | 0.4 % | 2.70 [ 1.78, 3.62 ] |
| Cascinu 1994 | 50 | 1.88 (0.83) | 49 | -0.61 (0.95) | | 2.7 % | 2.49 [ 2.14, 2.84 ] |
| Case 1993 | 79 | 2.346 (2.04) | 74 | 0.37 (1.46) | | 1.1 % | 1.97 [ 1.41, 2.53 ] |
| Cazzola 1995a | 31 | -0.1 (2.23) | 7 | -0.04 (2.05) | | 0.1 % | -0.06 [ -1.77, 1.65 ] |
| Cazzola 1995b | 29 | 0.17 (1.72) | 8 | -0.04 (2.05) | | 0.1 % | 0.21 [ -1.34, 1.76 ] |
| Cazzola 1995c | 31 | 0.3 (2.9) | 7 | -0.04 (2.05) | | 0.1 % | 0.34 [ -1.49, 2.17 ] |
| Cazzola 1995d | 26 | 0.44 (2.29) | 7 | -0.04 (2.05) | | 0.1 % | 0.48 [ -1.28, 2.24 ] |
| Chang 2005 | 175 | 1.14 (0.8) | 175 | -0.58 (0.73) | | 12.9 % | 1.72 [ 1.56, 1.88 ] |
| Charu 2007 | 220 | 2.1 (1.854) | 55 | 0.1 (0.927) | | 2.8 % | 2.00 [ 1.65, 2.35 ] |
| Christodoulou 2009 | 167 | 2.74 (13.62) | 170 | 0.52 (4.18) | | 0.1 % | 2.22 [ 0.06, 4.38 ] |
| Dammacco 2001 | 69 | 1.8 (2.11) | 76 | -0.2 (1.31) | | 1.0 % | 2.00 [ 1.42, 2.58 ] |
| Del Mastro 1997 | 28 | -0.8 (1.4) | 24 | -3.05 (1) | | 0.8 % | 2.25 [ 1.60, 2.90 ] |
| Engert 2009 | 648 | -1.88 (1.78) | 655 | -2.55 (1.78) | | 8.9 % | 0.67 [ 0.48, 0.86 ] |
| Fujisaka 2011 | 89 | 1.84 (1.33) | 92 | 0.02 (1.12) | | 2.6 % | 1.82 [ 1.46, 2.18 ] |
| Gebbia 2003 | 22 | -2.4 (1.5) | 23 | -5.1 (1.33) | | 0.5 % | 2.70 [ 1.87, 3.53 ] |
| Gordon 2008 | 139 | 1.3 (1.4) | 49 | 0.2 (1) | | 2.5 % | 1.10 [ 0.74, 1.46 ] |
| Grote 2005 | 64 | -0.2 (1.38) | 58 | -2.9 (1.53) | | 1.2 % | 2.70 [ 2.18, 3.22 ] |
| Gupta 2009 | 58 | 1.55 (0.74) | 57 | -1.5 (0.61) | | 5.4 % | 3.05 [ 2.80, 3.30 ] |
| Hedenus 2002a | 5 | 1.56 (1.93) | 2 | 1 (0.56) | | 0.1 % | 0.56 [ -1.30, 2.42 ] |
| Hedenus 2002b | 17 | 1.64 (1.25) | 2 | 1 (0.56) | | 0.3 % | 0.64 [ -0.34, 1.62 ] |
| Hedenus 2002c | 14 | 2.46 (1.49) | 2 | 1 (0.56) | | 0.3 % | 1.46 [ 0.36, 2.56 ] |

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| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Hedenus 2003 | 174 | 1.8 (2.24) | 170 | 0.19 (1.3) | | 2.2 % | 1.61 [ 1.22, 2.00 ] |
| Henke 1999a | 19 | 3.2 (1.6) | 3 | 0.6 (1.4) | | 0.1 % | 2.60 [ 0.86, 4.34 ] |
| Henke 1999b | 14 | 3.5 (1.2) | 4 | 0.6 (1.4) | | 0.1 % | 2.90 [ 1.39, 4.41 ] |
| Henke 1999c | 6 | 3.9 (2.1) | 4 | 0.6 (1.4) | | 0.1 % | 3.30 [ 1.13, 5.47 ] |
| Henke 2003 Roche 2004 | 178 | 3.4 (1.7) | 168 | 0.9 (1.7) | | 2.6 % | 2.50 [ 2.14, 2.86 ] |
| Henry 1995 | 63 | 2.04 (2.38) | 61 | 0.44 (1.7) | | 0.6 % | 1.60 [ 0.87, 2.33 ] |
| Hoskin 2009 | 151 | 0.625 (3.5) | 149 | -0.47 (3.48) | | 0.5 % | 1.09 [ 0.30, 1.88 ] |
| Huddart 2002 | 45 | 2.6 (2) | 45 | 1.2 (1.46) | | 0.6 % | 1.40 [ 0.68, 2.12 ] |
| Iconomou 2003 | 57 | 1.7 (1.6) | 55 | 0.3 (1.4) | | 1.1 % | 1.40 [ 0.84, 1.96 ] |
| Italian 1998 | 17 | 1.73 (1.56) | 11 | -0.14 (1.09) | | 0.3 % | 1.87 [ 0.89, 2.85 ] |
| Kotasek 2003a | 32 | 0.54 (1.24) | 8 | -0.02 (1.43) | | 0.3 % | 0.56 [ -0.52, 1.64 ] |
| Kotasek 2003b | 17 | 0.86 (1.57) | 8 | -0.02 (1.43) | | 0.2 % | 0.88 [ -0.36, 2.12 ] |
| Kotasek 2003c | 46 | 0.9 (1.63) | 9 | -0.02 (1.43) | | 0.3 % | 0.92 [ -0.13, 1.97 ] |
| Kotasek 2003d | 28 | 1.63 (2.01) | 8 | -0.02 (1.43) | | 0.2 % | 1.65 [ 0.41, 2.89 ] |
| Kotasek 2003e | 35 | 1.45 (1.42) | 8 | -0.02 (1.43) | | 0.3 % | 1.47 [ 0.37, 2.57 ] |
| Kotasek 2003f | 40 | 1.21 (1.9) | 9 | -0.02 (1.43) | | 0.3 % | 1.23 [ 0.13, 2.33 ] |
| Krzakowski 2008a | 104 | 2.5 (2.4) | 52 | 0.6 (1.7) | | 0.8 % | 1.90 [ 1.25, 2.55 ] |
| Krzakowski 2008b | 105 | 2.5 (2.6) | 52 | 0.6 (1.7) | | 0.7 % | 1.90 [ 1.22, 2.58 ] |
| Kunikane 2001a | 16 | 0.89 (1.72) | 10 | -0.65 (1.31) | | 0.2 % | 1.54 [ 0.37, 2.71 ] |
| Kunikane 2001b | 18 | 1.72 (1.1) | 9 | -0.65 (1.31) | | 0.3 % | 2.37 [ 1.37, 3.37 ] |
| Kurz 1997 | 23 | 3.26 (1.98) | 12 | 0.25 (1.66) | | 0.2 % | 3.01 [ 1.77, 4.25 ] |
| Leyland-Jones 2005 | 81 | 0.34 (1.73) | 86 | 0.14 (1.7) | | 1.2 % | 0.20 [ -0.32, 0.72 ] |
| Littlewood 2001 | 244 | 2.2 (2.18) | 115 | 0.5 (1.79) | | 1.8 % | 1.70 [ 1.27, 2.13 ] |
| ML17616 2006 | 30 | 3.09 (2.08) | 30 | 1.76 (2.28) | | 0.3 % | 1.33 [ 0.23, 2.43 ] |
| ML17620 2006 | 61 | 2.12 (1.64) | 60 | 0.59 (1.83) | | 0.9 % | 1.53 [ 0.91, 2.15 ] |
| Mystakidou 2005 | 50 | 2.4 (1.3) | 50 | -0.1 (1.02) | | 1.6 % | 2.50 [ 2.04, 2.96 ] |
| O'Shaughnessy 2005 | 47 | 0.8 (1.2) | 46 | -2.1 (1.4) | | 1.2 % | 2.90 [ 2.37, 3.43 ] |
| Oberhoff 1998 | 59 | 2.24 (2) | 47 | 0.6 (1.43) | | 0.8 % | 1.64 [ 0.99, 2.29 ] |
| Osterborg 1996a | 17 | 2.6 (1.74) | 13 | 1.02 (1.28) | | 0.3 % | 1.58 [ 0.50, 2.66 ] |
| Osterborg 1996b | 27 | 1.71 (1.67) | 14 | 1.02 (1.28) | | 0.4 % | 0.69 [ -0.23, 1.61 ] |
| Osterborg 2002 | 138 | 2.48 (1.74) | 142 | 0.82 (1.4) | | 2.4 % | 1.66 [ 1.29, 2.03 ] |

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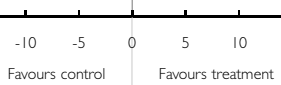
| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Pirker 2008 | 270 | -1.13 (1.93) | 279 | -1.98 (1.87) | | 3.3 % | 0.85 [ 0.53, 1.17 ] |
| Pronzato 2010 | 107 | 1.7 (1.35) | 109 | 0.4 (1.24) | | 2.8 % | 1.30 [ 0.95, 1.65 ] |
| Razzouk 2006 | 111 | 1.3 (2.38) | 111 | 1 (1.9) | | 1.0 % | 0.30 [ -0.27, 0.87 ] |
| Smith 2003a | 21 | 1.18 (2.01) | 7 | 0 (0.91) | | 0.3 % | 1.18 [ 0.09, 2.27 ] |
| Smith 2003b | 21 | 1.22 (1.62) | 7 | 0 (0.91) | | 0.4 % | 1.22 [ 0.25, 2.19 ] |
| Smith 2003c | 22 | 1.7 (1.93) | 8 | 0 (0.91) | | 0.3 % | 1.70 [ 0.68, 2.72 ] |
| Smith 2008 | 437 | 0.79 (2.83) | 447 | 0.29 (2.8) | | 2.4 % | 0.50 [ 0.13, 0.87 ] |
| Ten Bokkel 1998a | 34 | 0.66 (1.76) | 12 | -0.57 (1.16) | | 0.4 % | 1.23 [ 0.35, 2.11 ] |
| Ten Bokkel 1998b | 27 | 1.04 (1.73) | 12 | -0.57 (1.16) | | 0.4 % | 1.61 [ 0.68, 2.54 ] |
| Thomas 2002 | 62 | 1.9 (1.74) | 65 | 0.39 (1.38) | | 1.1 % | 1.51 [ 0.96, 2.06 ] |
| Thomas 2008 | 52 | 1.72 (1.79) | 57 | 0.09 (1.23) | | 1.0 % | 1.63 [ 1.05, 2.21 ] |
| Throuvalas 2000 | 28 | 0.7 (0.95) | 26 | -0.5 (0.56) | | 1.9 % | 1.20 [ 0.79, 1.61 ] |
| Tjulandin 2010a | 76 | 1.6 (1.42) | 37 | 0.2 (1.74) | | 0.8 % | 1.40 [ 0.75, 2.05 ] |
| Tjulandin 2010b | 73 | 1.9 (1.74) | 37 | 0.2 (1.74) | | 0.7 % | 1.70 [ 1.01, 2.39 ] |
| Tjulandin 2011 | 95 | 2.1 (1.3) | 91 | 0.65 (1.94) | | 1.5 % | 1.45 [ 0.97, 1.93 ] |
| Tsuboi 2009 | 61 | 1.4 (1.9) | 56 | -0.8 (1.5) | | 0.9 % | 2.20 [ 1.58, 2.82 ] |
| Untch 2011˙1 | 330 | -0.07 (2) | 359 | -0.98 (1.33) | | 5.1 % | 0.91 [ 0.65, 1.17 ] |
| Wilkinson 2006 | 114 | 1.6 (1.5) | 59 | 0.3 (1.3) | | 1.8 % | 1.30 [ 0.87, 1.73 ] |
| Witzig 2005 | 166 | 2.8 (1.62) | 164 | 0.9 (1.52) | | 2.9 % | 1.90 [ 1.56, 2.24 ] |
| **Total (95% CI)** | **6322** | | **5287** | | | **100.0 %** | **1.57 [ 1.51, 1.62 ]** |

Heterogeneity: $Chi^2$ = 564.37, df = 74 (P<0.00001); $I^2$ =87%

Test for overall effect: Z = 53.27 (P < 0.00001)

Test for subgroup differences: Not applicable



### Analysis 2.2. Comparison 2 Change of haemoglobin level, Outcome 2 Change in Hb values - baseline Hb.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 2 Change of haemoglobin level

Outcome: 2 Change in Hb values - baseline Hb

| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 Hb <=10g/dL | | | | | | | |
| Abels 1993 | 63 | 0.952 (2.142) | 55 | -0.03 (1.36) | | 0.8 % | 0.99 [ 0.35, 1.63 ] |
| Aravantinos 2003 | 24 | 2.31 (1.22) | 23 | 1.23 (1.59) | | 0.5 % | 1.08 [ 0.27, 1.89 ] |
| Boogaerts 2003 | 133 | 2.1 (1.83) | 129 | 0.9 (1.5) | | 2.0 % | 1.20 [ 0.80, 1.60 ] |
| Cascinu 1994 | 50 | 1.88 (0.83) | 49 | -0.61 (0.95) | | 2.7 % | 2.49 [ 2.14, 2.84 ] |
| Case 1993 | 79 | 2.346 (2.04) | 74 | 0.37 (1.46) | | 1.1 % | 1.97 [ 1.41, 2.53 ] |
| Cazzola 1995a | 31 | -0.1 (2.23) | 7 | -0.04 (2.05) | | 0.1 % | -0.06 [ -1.77, 1.65 ] |
| Cazzola 1995b | 29 | 0.17 (1.72) | 8 | -0.04 (2.05) | | 0.1 % | 0.21 [ -1.34, 1.76 ] |
| Cazzola 1995c | 31 | 0.3 (2.9) | 7 | -0.04 (2.05) | | 0.1 % | 0.34 [ -1.49, 2.17 ] |
| Cazzola 1995d | 26 | 0.44 (2.29) | 7 | -0.04 (2.05) | | 0.1 % | 0.48 [ -1.28, 2.24 ] |
| Dammacco 2001 | 69 | 1.8 (2.11) | 76 | -0.2 (1.31) | | 1.0 % | 2.00 [ 1.42, 2.58 ] |
| Fujisaka 2011 | 89 | 1.84 (1.33) | 92 | 0.02 (1.12) | | 2.6 % | 1.82 [ 1.46, 2.18 ] |
| Hedenus 2002a | 5 | 1.56 (1.93) | 2 | 1 (0.56) | | 0.1 % | 0.56 [ -1.30, 2.42 ] |
| Hedenus 2002b | 17 | 1.64 (1.25) | 2 | 1 (0.56) | | 0.3 % | 0.64 [ -0.34, 1.62 ] |
| Hedenus 2002c | 14 | 2.46 (1.49) | 2 | 1 (0.56) | | 0.3 % | 1.46 [ 0.36, 2.56 ] |
| Hedenus 2003 | 174 | 1.8 (2.24) | 170 | 0.19 (1.3) | | 2.2 % | 1.61 [ 1.22, 2.00 ] |
| Henry 1995 | 63 | 2.04 (2.38) | 61 | 0.44 (1.7) | | 0.6 % | 1.60 [ 0.87, 2.33 ] |
| Italian 1998 | 17 | 1.73 (1.56) | 11 | -0.14 (1.09) | | 0.3 % | 1.87 [ 0.89, 2.85 ] |
| Kotasek 2003a | 32 | 0.54 (1.24) | 8 | -0.02 (1.43) | | 0.3 % | 0.56 [ -0.52, 1.64 ] |
| Kotasek 2003b | 17 | 0.86 (1.57) | 8 | -0.02 (1.43) | | 0.2 % | 0.88 [ -0.36, 2.12 ] |
| Kotasek 2003c | 46 | 0.9 (1.63) | 9 | -0.02 (1.43) | | 0.3 % | 0.92 [ -0.13, 1.97 ] |
| Kotasek 2003d | 28 | 1.63 (2.01) | 8 | -0.02 (1.43) | | 0.2 % | 1.65 [ 0.41, 2.89 ] |
| Kotasek 2003e | 35 | 1.45 (1.42) | 8 | -0.02 (1.43) | | 0.3 % | 1.47 [ 0.37, 2.57 ] |
| Kotasek 2003f | 40 | 1.21 (1.9) | 9 | -0.02 (1.43) | | 0.3 % | 1.23 [ 0.13, 2.33 ] |
| Krzakowski 2008a | 104 | 2.5 (2.4) | 52 | 0.6 (1.7) | | 0.8 % | 1.90 [ 1.25, 2.55 ] |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| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Krzakowski 2008b | 105 | 2.5 (2.6) | 52 | 0.6 (1.7) | | 0.7 % | 1.90 [ 1.22, 2.58 ] |
| Kurz 1997 | 23 | 3.26 (1.98) | 12 | 0.25 (1.66) | | 0.2 % | 3.01 [ 1.77, 4.25 ] |
| Littlewood 2001 | 244 | 2.2 (2.18) | 115 | 0.5 (1.79) | | 1.8 % | 1.70 [ 1.27, 2.13 ] |
| ML17616 2006 | 30 | 3.09 (2.08) | 30 | 1.76 (2.28) | | 0.3 % | 1.33 [ 0.23, 2.43 ] |
| Oberhoff 1998 | 59 | 2.24 (2) | 47 | 0.6 (1.43) | | 0.8 % | 1.64 [ 0.99, 2.29 ] |
| Osterborg 1996a | 17 | 2.6 (1.74) | 13 | 1.02 (1.28) | | 0.3 % | 1.58 [ 0.50, 2.66 ] |
| Osterborg 1996b | 27 | 1.71 (1.67) | 14 | 1.02 (1.28) | | 0.4 % | 0.69 [ -0.23, 1.61 ] |
| Osterborg 2002 | 138 | 2.48 (1.74) | 142 | 0.82 (1.4) | | 2.4 % | 1.66 [ 1.29, 2.03 ] |
| Razzouk 2006 | 111 | 1.3 (2.38) | 111 | 1 (1.9) | | 1.0 % | 0.30 [ -0.27, 0.87 ] |
| Smith 2003a | 21 | 1.18 (2.01) | 7 | 0 (0.91) | | 0.3 % | 1.18 [ 0.09, 2.27 ] |
| Smith 2003b | 21 | 1.22 (1.62) | 7 | 0 (0.91) | | 0.4 % | 1.22 [ 0.25, 2.19 ] |
| Smith 2003c | 22 | 1.7 (1.93) | 8 | 0 (0.91) | | 0.3 % | 1.70 [ 0.68, 2.72 ] |
| Smith 2008 | 437 | 0.79 (2.83) | 447 | 0.29 (2.8) | | 2.4 % | 0.50 [ 0.13, 0.87 ] |
| Tjulandin 2010a | 76 | 1.6 (1.42) | 37 | 0.2 (1.74) | | 0.8 % | 1.40 [ 0.75, 2.05 ] |
| Tjulandin 2010b | 73 | 1.9 (1.74) | 37 | 0.2 (1.74) | | 0.7 % | 1.70 [ 1.01, 2.39 ] |
| Tjulandin 2011 | 95 | 2.1 (1.3) | 91 | 0.65 (1.94) | | 1.5 % | 1.45 [ 0.97, 1.93 ] |
| Witzig 2005 | 166 | 2.8 (1.62) | 164 | 0.9 (1.52) | | 2.9 % | 1.90 [ 1.56, 2.24 ] |
| **Subtotal (95% CI)** | **2881** | | **2211** | | | **34.5 %** | **1.53 [ 1.43, 1.62 ]** |
| Heterogeneity: $Chi^2$ = 128.41, df = 40 (P<0.00001); $I^2$ =69% | | | | | | | |
| Test for overall effect: Z = 30.50 (P < 0.00001) | | | | | | | |
| 2 Hb 10 to 12 g/dL | | | | | | | |
| Bamias 2003 | 72 | 0.57 (2.12) | 72 | -0.49 (1.36) | | 1.0 % | 1.06 [ 0.48, 1.64 ] |
| Carabantes 1999 | 20 | 1 (1.56) | 15 | -1.7 (1.22) | | 0.4 % | 2.70 [ 1.78, 3.62 ] |
| Chang 2005 | 175 | 1.14 (0.8) | 175 | -0.58 (0.73) | | 12.9 % | 1.72 [ 1.56, 1.88 ] |
| Charu 2007 | 220 | 2.1 (1.854) | 55 | 0.1 (0.927) | | 2.8 % | 2.00 [ 1.65, 2.35 ] |
| Christodoulou 2009 | 167 | 2.74 (13.62) | 170 | 0.52 (4.18) | | 0.1 % | 2.22 [ 0.06, 4.38 ] |
| Gordon 2008 | 139 | 1.3 (1.4) | 49 | 0.2 (1) | | 2.5 % | 1.10 [ 0.74, 1.46 ] |
| Gupta 2009 | 58 | 1.55 (0.74) | 57 | -1.5 (0.61) | | 5.4 % | 3.05 [ 2.80, 3.30 ] |
| Henke 1999a | 19 | 3.2 (1.6) | 3 | 0.6 (1.4) | | 0.1 % | 2.60 [ 0.86, 4.34 ] |
| Henke 1999b | 14 | 3.5 (1.2) | 4 | 0.6 (1.4) | | 0.1 % | 2.90 [ 1.39, 4.41 ] |
| Henke 1999c | 6 | 3.9 (2.1) | 4 | 0.6 (1.4) | | 0.1 % | 3.30 [ 1.13, 5.47 ] |
| Henke 2003 Roche 2004 | 178 | 3.4 (1.7) | 168 | 0.9 (1.7) | | 2.6 % | 2.50 [ 2.14, 2.86 ] |


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| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Huddart 2002 | 45 | 2.6 (2) | 45 | 1.2 (1.46) | | 0.6 % | 1.40 [ 0.68, 2.12 ] |
| Iconomou 2003 | 57 | 1.7 (1.6) | 55 | 0.3 (1.4) | | 1.1 % | 1.40 [ 0.84, 1.96 ] |
| Mystakidou 2005 | 50 | 2.4 (1.3) | 50 | -0.1 (1.02) | | 1.6 % | 2.50 [ 2.04, 2.96 ] |
| Pirker 2008 | 270 | -1.13 (1.93) | 279 | -1.98 (1.87) | | 3.3 % | 0.85 [ 0.53, 1.17 ] |
| Pronzato 2010 | 107 | 1.7 (1.35) | 109 | 0.4 (1.24) | | 2.8 % | 1.30 [ 0.95, 1.65 ] |
| Ten Bokkel 1998a | 34 | 0.66 (1.76) | 12 | -0.57 (1.16) | | 0.4 % | 1.23 [ 0.35, 2.11 ] |
| Ten Bokkel 1998b | 27 | 1.04 (1.73) | 12 | -0.57 (1.16) | | 0.4 % | 1.61 [ 0.68, 2.54 ] |
| Thomas 2002 | 62 | 1.9 (1.74) | 65 | 0.39 (1.38) | | 1.1 % | 1.51 [ 0.96, 2.06 ] |
| Thomas 2008 | 52 | 1.72 (1.79) | 57 | 0.09 (1.23) | | 1.0 % | 1.63 [ 1.05, 2.21 ] |
| Throuvalas 2000 | 28 | 0.7 (0.95) | 26 | -0.5 (0.56) | | 1.9 % | 1.20 [ 0.79, 1.61 ] |
| Tsuboi 2009 | 61 | 1.4 (1.9) | 56 | -0.8 (1.5) | | 0.9 % | 2.20 [ 1.58, 2.82 ] |
| Wilkinson 2006 | 114 | 1.6 (1.5) | 59 | 0.3 (1.3) | | 1.8 % | 1.30 [ 0.87, 1.73 ] |
| **Subtotal (95% CI)** | **1975** | | **1597** | | | **44.7 %** | **1.79 [ 1.71, 1.88 ]** |
| Heterogeneity: $Chi^2$ = 216.14, df = 22 (P<0.00001); $I^2$ =90% | | | | | | | |
| Test for overall effect: Z = 40.85 (P < 0.00001) | | | | | | | |
| 3 Hb >12 g/dL | | | | | | | |
| Del Mastro 1997 | 28 | -0.8 (1.4) | 24 | -3.05 (1) | | 0.8 % | 2.25 [ 1.60, 2.90 ] |
| Engert 2009 | 648 | -1.88 (1.78) | 655 | -2.55 (1.78) | | 8.9 % | 0.67 [ 0.48, 0.86 ] |
| Gebbia 2003 | 22 | -2.4 (1.5) | 23 | -5.1 (1.33) | | 0.5 % | 2.70 [ 1.87, 3.53 ] |
| Grote 2005 | 64 | -0.2 (1.38) | 58 | -2.9 (1.53) | | 1.2 % | 2.70 [ 2.18, 3.22 ] |
| Hoskin 2009 | 151 | 0.625 (3.5) | 149 | -0.47 (3.48) | | 0.5 % | 1.09 [ 0.30, 1.88 ] |
| Kunikane 2001a | 16 | 0.89 (1.72) | 10 | -0.65 (1.31) | | 0.2 % | 1.54 [ 0.37, 2.71 ] |
| Kunikane 2001b | 18 | 1.72 (1.1) | 9 | -0.65 (1.31) | | 0.3 % | 2.37 [ 1.37, 3.37 ] |
| Leyland-Jones 2005 | 81 | 0.34 (1.73) | 86 | 0.14 (1.7) | | 1.2 % | 0.20 [ -0.32, 0.72 ] |
| O'Shaughnessy 2005 | 47 | 0.8 (1.2) | 46 | -2.1 (1.4) | | 1.2 % | 2.90 [ 2.37, 3.43 ] |
| Untch 2011˙1 | 330 | -0.07 (2) | 359 | -0.98 (1.33) | | 5.1 % | 0.91 [ 0.65, 1.17 ] |
| **Subtotal (95% CI)** | **1405** | | **1419** | | | **19.9 %** | **1.12 [ 0.99, 1.25 ]** |
| Heterogeneity: $Chi^2$ = 146.19, df = 9 (P<0.00001); $I^2$ =94% | | | | | | | |
| Test for overall effect: Z = 17.02 (P < 0.00001) | | | | | | | |
| 4 unclear | | | | | | | |
| ML17620 2006 | 61 | 2.12 (1.64) | 60 | 0.59 (1.83) | | 0.9 % | 1.53 [ 0.91, 2.15 ] |
| **Subtotal (95% CI)** | **61** | | **60** | | | **0.9 %** | **1.53 [ 0.91, 2.15 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 4.84 (P < 0.00001) | | | | | | | |

-10 -5 0 5 10

Favours Control Favours Treatment

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| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| **Total (95% CI)** | **6322** | | **5287** | | | **100.0 %** | **1.57 [ 1.51, 1.62 ]** |
| Heterogeneity: $Chi^2$ = 564.37, df = 74 (P<0.00001); $I^2$ =87% | | | | | | | |
| Test for overall effect: Z = 53.27 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 73.63, df = 3 (P = 0.00), $I^2$ =96% | | | | | | | |


**Analysis 2.3. Comparison 2 Change of haemoglobin level, Outcome 3 Change in Hb values - different malignancies.**

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 2 Change of haemoglobin level

Outcome: 3 Change in Hb values - different malignancies

| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 solid tumours | | | | | | | |
| Aravantinos 2003 | 24 | 2.31 (1.22) | 23 | 1.23 (1.59) | | 0.5 % | 1.08 [ 0.27, 1.89 ] |
| Bamias 2003 | 72 | 0.57 (2.12) | 72 | -0.49 (1.36) | | 1.0 % | 1.06 [ 0.48, 1.64 ] |
| Carabantes 1999 | 20 | 1 (1.56) | 15 | -1.7 (1.22) | | 0.4 % | 2.70 [ 1.78, 3.62 ] |
| Cascinu 1994 | 50 | 1.88 (0.83) | 49 | -0.61 (0.95) | | 2.7 % | 2.49 [ 2.14, 2.84 ] |
| Chang 2005 | 175 | 1.14 (0.8) | 175 | -0.58 (0.73) | | 12.9 % | 1.72 [ 1.56, 1.88 ] |
| Christodoulou 2009 | 167 | 2.74 (13.62) | 170 | 0.52 (4.18) | | 0.1 % | 2.22 [ 0.06, 4.38 ] |
| Del Mastro 1997 | 28 | -0.8 (1.4) | 24 | -3.05 (1) | | 0.8 % | 2.25 [ 1.60, 2.90 ] |
| Fujisaka 2011 | 89 | 1.84 (1.33) | 92 | 0.02 (1.12) | | 2.6 % | 1.82 [ 1.46, 2.18 ] |
| Gebbia 2003 | 22 | -2.4 (1.5) | 23 | -5.1 (1.33) | | 0.5 % | 2.70 [ 1.87, 3.53 ] |
| Grote 2005 | 64 | -0.2 (1.38) | 58 | -2.9 (1.53) | | 1.2 % | 2.70 [ 2.18, 3.22 ] |
| Gupta 2009 | 58 | 1.55 (0.74) | 57 | -1.5 (0.61) | | 5.4 % | 3.05 [ 2.80, 3.30 ] |


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| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Henke 1999a | 19 | 3.2 (1.6) | 3 | 0.6 (1.4) | | 0.1 % | 2.60 [ 0.86, 4.34 ] |
| Henke 1999b | 14 | 3.5 (1.2) | 4 | 0.6 (1.4) | | 0.1 % | 2.90 [ 1.39, 4.41 ] |
| Henke 1999c | 6 | 3.9 (2.1) | 4 | 0.6 (1.4) | | 0.1 % | 3.30 [ 1.13, 5.47 ] |
| Henke 2003 Roche 2004 | 178 | 3.4 (1.7) | 168 | 0.9 (1.7) | | 2.6 % | 2.50 [ 2.14, 2.86 ] |
| Hoskin 2009 | 151 | 0.625 (3.5) | 149 | -0.47 (3.48) | | 0.5 % | 1.09 [ 0.30, 1.88 ] |
| Huddart 2002 | 45 | 2.6 (2) | 45 | 1.2 (1.46) | | 0.6 % | 1.40 [ 0.68, 2.12 ] |
| Iconomou 2003 | 57 | 1.7 (1.6) | 55 | 0.3 (1.4) | | 1.1 % | 1.40 [ 0.84, 1.96 ] |
| Kotasek 2003a | 32 | 0.54 (1.24) | 8 | -0.02 (1.43) | | 0.3 % | 0.56 [ -0.52, 1.64 ] |
| Kotasek 2003b | 17 | 0.86 (1.57) | 8 | -0.02 (1.43) | | 0.2 % | 0.88 [ -0.36, 2.12 ] |
| Kotasek 2003c | 46 | 0.9 (1.63) | 9 | -0.02 (1.43) | | 0.3 % | 0.92 [ -0.13, 1.97 ] |
| Kotasek 2003d | 28 | 1.63 (2.01) | 8 | -0.02 (1.43) | | 0.2 % | 1.65 [ 0.41, 2.89 ] |
| Kotasek 2003e | 35 | 1.45 (1.42) | 8 | -0.02 (1.43) | | 0.3 % | 1.47 [ 0.37, 2.57 ] |
| Kotasek 2003f | 40 | 1.21 (1.9) | 9 | -0.02 (1.43) | | 0.3 % | 1.23 [ 0.13, 2.33 ] |
| Kunikane 2001a | 16 | 0.89 (1.72) | 10 | -0.65 (1.31) | | 0.2 % | 1.54 [ 0.37, 2.71 ] |
| Kunikane 2001b | 18 | 1.72 (1.1) | 9 | -0.65 (1.31) | | 0.3 % | 2.37 [ 1.37, 3.37 ] |
| Kurz 1997 | 23 | 3.26 (1.98) | 12 | 0.25 (1.66) | | 0.2 % | 3.01 [ 1.77, 4.25 ] |
| Leyland-Jones 2005 | 81 | 0.34 (1.73) | 86 | 0.14 (1.7) | | 1.2 % | 0.20 [ -0.32, 0.72 ] |
| Littlewood 2001 | 244 | 2.2 (2.18) | 115 | 0.5 (1.79) | | 1.8 % | 1.70 [ 1.27, 2.13 ] |
| ML17620 2006 | 61 | 2.12 (1.64) | 60 | 0.59 (1.83) | | 0.9 % | 1.53 [ 0.91, 2.15 ] |
| Mystakidou 2005 | 50 | 2.4 (1.3) | 50 | -0.1 (1.02) | | 1.6 % | 2.50 [ 2.04, 2.96 ] |
| O'Shaughnessy 2005 | 47 | 0.8 (1.2) | 46 | -2.1 (1.4) | | 1.2 % | 2.90 [ 2.37, 3.43 ] |
| Oberhoff 1998 | 59 | 2.24 (2) | 47 | 0.6 (1.43) | | 0.8 % | 1.64 [ 0.99, 2.29 ] |
| Pirker 2008 | 270 | -1.13 (1.93) | 279 | -1.98 (1.87) | | 3.3 % | 0.85 [ 0.53, 1.17 ] |
| Pronzato 2010 | 107 | 1.7 (1.35) | 109 | 0.4 (1.24) | | 2.8 % | 1.30 [ 0.95, 1.65 ] |
| Ten Bokkel 1998a | 34 | 0.66 (1.76) | 12 | -0.57 (1.16) | | 0.4 % | 1.23 [ 0.35, 2.11 ] |
| Ten Bokkel 1998b | 27 | 1.04 (1.73) | 12 | -0.57 (1.16) | | 0.4 % | 1.61 [ 0.68, 2.54 ] |
| Thomas 2002 | 62 | 1.9 (1.74) | 65 | 0.39 (1.38) | | 1.1 % | 1.51 [ 0.96, 2.06 ] |
| Thomas 2008 | 52 | 1.72 (1.79) | 57 | 0.09 (1.23) | | 1.0 % | 1.63 [ 1.05, 2.21 ] |
| Throuvalas 2000 | 28 | 0.7 (0.95) | 26 | -0.5 (0.56) | | 1.9 % | 1.20 [ 0.79, 1.61 ] |
| Tjulandin 2010a | 76 | 1.6 (1.42) | 37 | 0.2 (1.74) | | 0.8 % | 1.40 [ 0.75, 2.05 ] |
| Tjulandin 2010b | 73 | 1.9 (1.74) | 37 | 0.2 (1.74) | | 0.7 % | 1.70 [ 1.01, 2.39 ] |


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(. . . *Continued*)

| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Untch 2011˙1 | 330 | -0.07 (2) | 359 | -0.98 (1.33) | | 5.1 % | 0.91 [ 0.65, 1.17 ] |
| Wilkinson 2006 | 114 | 1.6 (1.5) | 59 | 0.3 (1.3) | | 1.8 % | 1.30 [ 0.87, 1.73 ] |
| Witzig 2005 | 166 | 2.8 (1.62) | 164 | 0.9 (1.52) | | 2.9 % | 1.90 [ 1.56, 2.24 ] |
| **Subtotal (95% CI)** | **3375** | | **2887** | | | **65.0 %** | **1.76 [ 1.68, 1.83 ]** |
| Heterogeneity: $Chi^2$ = 355.14, df = 44 (P<0.00001); $I^2$ =88% | | | | | | | |
| Test for overall effect: Z = 48.21 (P < 0.00001) | | | | | | | |
| 2 haematological malignancies | | | | | | | |
| Cazzola 1995a | 31 | -0.1 (2.23) | 7 | -0.04 (2.05) | | 0.1 % | -0.06 [ -1.77, 1.65 ] |
| Cazzola 1995b | 29 | 0.17 (1.72) | 8 | -0.04 (2.05) | | 0.1 % | 0.21 [ -1.34, 1.76 ] |
| Cazzola 1995c | 31 | 0.3 (2.9) | 7 | -0.04 (2.05) | | 0.1 % | 0.34 [ -1.49, 2.17 ] |
| Cazzola 1995d | 26 | 0.44 (2.29) | 7 | -0.04 (2.05) | | 0.1 % | 0.48 [ -1.28, 2.24 ] |
| Dammacco 2001 | 69 | 1.8 (2.11) | 76 | -0.2 (1.31) | | 1.0 % | 2.00 [ 1.42, 2.58 ] |
| Engert 2009 | 648 | -1.88 (1.78) | 655 | -2.55 (1.78) | | 8.9 % | 0.67 [ 0.48, 0.86 ] |
| Hedenus 2002a | 5 | 1.56 (1.93) | 2 | 1 (0.56) | | 0.1 % | 0.56 [ -1.30, 2.42 ] |
| Hedenus 2002b | 17 | 1.64 (1.25) | 2 | 1 (0.56) | | 0.3 % | 0.64 [ -0.34, 1.62 ] |
| Hedenus 2002c | 14 | 2.46 (1.49) | 2 | 1 (0.56) | | 0.3 % | 1.46 [ 0.36, 2.56 ] |
| Hedenus 2003 | 174 | 1.8 (2.24) | 170 | 0.19 (1.3) | | 2.2 % | 1.61 [ 1.22, 2.00 ] |
| ML17616 2006 | 30 | 3.09 (2.08) | 30 | 1.76 (2.28) | | 0.3 % | 1.33 [ 0.23, 2.43 ] |
| Osterborg 1996a | 17 | 2.6 (1.74) | 13 | 1.02 (1.28) | | 0.3 % | 1.58 [ 0.50, 2.66 ] |
| Osterborg 1996b | 27 | 1.71 (1.67) | 14 | 1.02 (1.28) | | 0.4 % | 0.69 [ -0.23, 1.61 ] |
| Osterborg 2002 | 138 | 2.48 (1.74) | 142 | 0.82 (1.4) | | 2.4 % | 1.66 [ 1.29, 2.03 ] |
| **Subtotal (95% CI)** | **1256** | | **1135** | | | **16.6 %** | **1.05 [ 0.90, 1.19 ]** |
| Heterogeneity: $Chi^2$ = 50.66, df = 13 (P<0.00001); $I^2$ =74% | | | | | | | |
| Test for overall effect: Z = 14.51 (P < 0.00001) | | | | | | | |
| 3 MDS | | | | | | | |
| Italian 1998 | 17 | 1.73 (1.56) | 11 | -0.14 (1.09) | | 0.3 % | 1.87 [ 0.89, 2.85 ] |
| **Subtotal (95% CI)** | **17** | | **11** | | | **0.3 %** | **1.87 [ 0.89, 2.85 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 3.73 (P = 0.00019) | | | | | | | |
| 4 mixed | | | | | | | |
| Abels 1993 | 63 | 0.952 (2.142) | 55 | -0.03 (1.36) | | 0.8 % | 0.99 [ 0.35, 1.63 ] |
| Boogaerts 2003 | 133 | 2.1 (1.83) | 129 | 0.9 (1.5) | | 2.0 % | 1.20 [ 0.80, 1.60 ] |
| Case 1993 | 79 | 2.346 (2.04) | 74 | 0.37 (1.46) | | 1.1 % | 1.97 [ 1.41, 2.53 ] |
| Charu 2007 | 220 | 2.1 (1.854) | 55 | 0.1 (0.927) | | 2.8 % | 2.00 [ 1.65, 2.35 ] |


(*Continued* . . . )

(. . . *Continued*)

| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Gordon 2008 | 139 | 1.3 (1.4) | 49 | 0.2 (1) | | 2.5 % | 1.10 [ 0.74, 1.46 ] |
| Henry 1995 | 63 | 2.04 (2.38) | 61 | 0.44 (1.7) | | 0.6 % | 1.60 [ 0.87, 2.33 ] |
| Krzakowski 2008a | 104 | 2.5 (2.4) | 52 | 0.6 (1.7) | | 0.8 % | 1.90 [ 1.25, 2.55 ] |
| Krzakowski 2008b | 105 | 2.5 (2.6) | 52 | 0.6 (1.7) | | 0.7 % | 1.90 [ 1.22, 2.58 ] |
| Razzouk 2006 | 111 | 1.3 (2.38) | 111 | 1 (1.9) | | 1.0 % | 0.30 [ -0.27, 0.87 ] |
| Smith 2003a | 21 | 1.18 (2.01) | 7 | 0 (0.91) | | 0.3 % | 1.18 [ 0.09, 2.27 ] |
| Smith 2003b | 21 | 1.22 (1.62) | 7 | 0 (0.91) | | 0.4 % | 1.22 [ 0.25, 2.19 ] |
| Smith 2003c | 22 | 1.7 (1.93) | 8 | 0 (0.91) | | 0.3 % | 1.70 [ 0.68, 2.72 ] |
| Smith 2008 | 437 | 0.79 (2.83) | 447 | 0.29 (2.8) | | 2.4 % | 0.50 [ 0.13, 0.87 ] |
| Tjulandin 2011 | 95 | 2.1 (1.3) | 91 | 0.65 (1.94) | | 1.5 % | 1.45 [ 0.97, 1.93 ] |
| Tsuboi 2009 | 61 | 1.4 (1.9) | 56 | -0.8 (1.5) | | 0.9 % | 2.20 [ 1.58, 2.82 ] |
| **Subtotal (95% CI)** | **1674** | | **1254** | | | **18.0 %** | **1.35 [ 1.21, 1.48 ]** |
| Heterogeneity: $Chi^2$ = 68.95, df = 14 (P<0.00001); $I^2$ =80% | | | | | | | |
| Test for overall effect: Z = 19.48 (P < 0.00001) | | | | | | | |
| 5 unclear | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| **Total (95% CI)** | **6322** | | **5287** | | | **100.0 %** | **1.57 [ 1.51, 1.62 ]** |
| Heterogeneity: $Chi^2$ = 564.37, df = 74 (P<0.00001); $I^2$ =87% | | | | | | | |
| Test for overall effect: Z = 53.27 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 89.61, df = 3 (P = 0.00), $I^2$ =97% | | | | | | | |

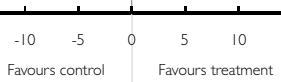
### Analysis 2.4. Comparison 2 Change of haemoglobin level, Outcome 4 Change in Hb values - age.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 2 Change of haemoglobin level

Outcome: 4 Change in Hb values - age

| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 children | | | | | | | |
| Razzouk 2006 | 111 | 1.3 (2.38) | 111 | 1 (1.9) | | 1.0 % | 0.30 [ -0.27, 0.87 ] |
| **Subtotal (95% CI)** | **111** | | **111** | | | **1.0 %** | **0.30 [ -0.27, 0.87 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 1.04 (P = 0.30) | | | | | | | |
| 2 adults | | | | | | | |
| Abels 1993 | 63 | 0.952 (2.142) | 55 | -0.03 (1.36) | | 0.8 % | 0.99 [ 0.35, 1.63 ] |
| Aravantinos 2003 | 24 | 2.31 (1.22) | 23 | 1.23 (1.59) | | 0.5 % | 1.08 [ 0.27, 1.89 ] |
| Bamias 2003 | 72 | 0.57 (2.12) | 72 | -0.49 (1.36) | | 1.0 % | 1.06 [ 0.48, 1.64 ] |
| Boogaerts 2003 | 133 | 2.1 (1.83) | 129 | 0.9 (1.5) | | 2.0 % | 1.20 [ 0.80, 1.60 ] |
| Carabantes 1999 | 20 | 1 (1.56) | 15 | -1.7 (1.22) | | 0.4 % | 2.70 [ 1.78, 3.62 ] |
| Cascinu 1994 | 50 | 1.88 (0.83) | 49 | -0.61 (0.95) | | 2.7 % | 2.49 [ 2.14, 2.84 ] |
| Case 1993 | 79 | 2.346 (2.04) | 74 | 0.37 (1.46) | | 1.1 % | 1.97 [ 1.41, 2.53 ] |
| Cazzola 1995a | 31 | -0.1 (2.23) | 7 | -0.04 (2.05) | | 0.1 % | -0.06 [ -1.77, 1.65 ] |
| Cazzola 1995b | 29 | 0.17 (1.72) | 8 | -0.04 (2.05) | | 0.1 % | 0.21 [ -1.34, 1.76 ] |
| Cazzola 1995c | 31 | 0.3 (2.9) | 7 | -0.04 (2.05) | | 0.1 % | 0.34 [ -1.49, 2.17 ] |
| Cazzola 1995d | 26 | 0.44 (2.29) | 7 | -0.04 (2.05) | | 0.1 % | 0.48 [ -1.28, 2.24 ] |
| Chang 2005 | 175 | 1.14 (0.8) | 175 | -0.58 (0.73) | | 12.9 % | 1.72 [ 1.56, 1.88 ] |
| Charu 2007 | 220 | 2.1 (1.854) | 55 | 0.1 (0.927) | | 2.8 % | 2.00 [ 1.65, 2.35 ] |
| Christodoulou 2009 | 167 | 2.74 (13.62) | 170 | 0.52 (4.18) | | 0.1 % | 2.22 [ 0.06, 4.38 ] |
| Dammacco 2001 | 69 | 1.8 (2.11) | 76 | -0.2 (1.31) | | 1.0 % | 2.00 [ 1.42, 2.58 ] |
| Del Mastro 1997 | 28 | -0.8 (1.4) | 24 | -3.05 (1) | | 0.8 % | 2.25 [ 1.60, 2.90 ] |
| Engert 2009 | 648 | -1.88 (1.78) | 655 | -2.55 (1.78) | | 8.9 % | 0.67 [ 0.48, 0.86 ] |
| Fujisaka 2011 | 89 | 1.84 (1.33) | 92 | 0.02 (1.12) | | 2.6 % | 1.82 [ 1.46, 2.18 ] |
| Gebbia 2003 | 22 | -2.4 (1.5) | 23 | -5.1 (1.33) | | 0.5 % | 2.70 [ 1.87, 3.53 ] |
| Gordon 2008 | 139 | 1.3 (1.4) | 49 | 0.2 (1) | | 2.5 % | 1.10 [ 0.74, 1.46 ] |




(*Continued . . .*)

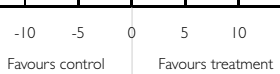
(. . . *Continued*)

| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Grote 2005 | 64 | -0.2 (1.38) | 58 | -2.9 (1.53) | | 1.2 % | 2.70 [ 2.18, 3.22 ] |
| Gupta 2009 | 58 | 1.55 (0.74) | 57 | -1.5 (0.61) | | 5.4 % | 3.05 [ 2.80, 3.30 ] |
| Hedenus 2002a | 5 | 1.56 (1.93) | 2 | 1 (0.56) | | 0.1 % | 0.56 [ -1.30, 2.42 ] |
| Hedenus 2002b | 17 | 1.64 (1.25) | 2 | 1 (0.56) | | 0.3 % | 0.64 [ -0.34, 1.62 ] |
| Hedenus 2002c | 14 | 2.46 (1.49) | 2 | 1 (0.56) | | 0.3 % | 1.46 [ 0.36, 2.56 ] |
| Hedenus 2003 | 174 | 1.8 (2.24) | 170 | 0.19 (1.3) | | 2.2 % | 1.61 [ 1.22, 2.00 ] |
| Henke 1999a | 19 | 3.2 (1.6) | 3 | 0.6 (1.4) | | 0.1 % | 2.60 [ 0.86, 4.34 ] |
| Henke 1999b | 14 | 3.5 (1.2) | 4 | 0.6 (1.4) | | 0.1 % | 2.90 [ 1.39, 4.41 ] |
| Henke 1999c | 6 | 3.9 (2.1) | 4 | 0.6 (1.4) | | 0.1 % | 3.30 [ 1.13, 5.47 ] |
| Henke 2003 Roche 2004 | 178 | 3.4 (1.7) | 168 | 0.9 (1.7) | | 2.6 % | 2.50 [ 2.14, 2.86 ] |
| Henry 1995 | 63 | 2.04 (2.38) | 61 | 0.44 (1.7) | | 0.6 % | 1.60 [ 0.87, 2.33 ] |
| Hoskin 2009 | 151 | 0.625 (3.5) | 149 | -0.47 (3.48) | | 0.5 % | 1.09 [ 0.30, 1.88 ] |
| Huddart 2002 | 45 | 2.6 (2) | 45 | 1.2 (1.46) | | 0.6 % | 1.40 [ 0.68, 2.12 ] |
| Iconomou 2003 | 57 | 1.7 (1.6) | 55 | 0.3 (1.4) | | 1.1 % | 1.40 [ 0.84, 1.96 ] |
| Italian 1998 | 17 | 1.73 (1.56) | 11 | -0.14 (1.09) | | 0.3 % | 1.87 [ 0.89, 2.85 ] |
| Kotasek 2003a | 32 | 0.54 (1.24) | 8 | -0.02 (1.43) | | 0.3 % | 0.56 [ -0.52, 1.64 ] |
| Kotasek 2003b | 17 | 0.86 (1.57) | 8 | -0.02 (1.43) | | 0.2 % | 0.88 [ -0.36, 2.12 ] |
| Kotasek 2003c | 46 | 0.9 (1.63) | 9 | -0.02 (1.43) | | 0.3 % | 0.92 [ -0.13, 1.97 ] |
| Kotasek 2003d | 28 | 1.63 (2.01) | 8 | -0.02 (1.43) | | 0.2 % | 1.65 [ 0.41, 2.89 ] |
| Kotasek 2003e | 35 | 1.45 (1.42) | 8 | -0.02 (1.43) | | 0.3 % | 1.47 [ 0.37, 2.57 ] |
| Kotasek 2003f | 40 | 1.21 (1.9) | 9 | -0.02 (1.43) | | 0.3 % | 1.23 [ 0.13, 2.33 ] |
| Krzakowski 2008a | 104 | 2.5 (2.4) | 52 | 0.6 (1.7) | | 0.8 % | 1.90 [ 1.25, 2.55 ] |
| Krzakowski 2008b | 105 | 2.5 (2.6) | 52 | 0.6 (1.7) | | 0.7 % | 1.90 [ 1.22, 2.58 ] |
| Kunikane 2001a | 16 | 0.89 (1.72) | 10 | -0.65 (1.31) | | 0.2 % | 1.54 [ 0.37, 2.71 ] |
| Kunikane 2001b | 18 | 1.72 (1.1) | 9 | -0.65 (1.31) | | 0.3 % | 2.37 [ 1.37, 3.37 ] |
| Kurz 1997 | 23 | 3.26 (1.98) | 12 | 0.25 (1.66) | | 0.2 % | 3.01 [ 1.77, 4.25 ] |
| Leyland-Jones 2005 | 81 | 0.34 (1.73) | 86 | 0.14 (1.7) | | 1.2 % | 0.20 [ -0.32, 0.72 ] |
| Littlewood 2001 | 244 | 2.2 (2.18) | 115 | 0.5 (1.79) | | 1.8 % | 1.70 [ 1.27, 2.13 ] |
| ML17616 2006 | 30 | 3.09 (2.08) | 30 | 1.76 (2.28) | | 0.3 % | 1.33 [ 0.23, 2.43 ] |
| ML17620 2006 | 61 | 2.12 (1.64) | 60 | 0.59 (1.83) | | 0.9 % | 1.53 [ 0.91, 2.15 ] |
| Mystakidou 2005 | 50 | 2.4 (1.3) | 50 | -0.1 (1.02) | | 1.6 % | 2.50 [ 2.04, 2.96 ] |


(*Continued* . . . )

(. . . *Continued*)

| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| O'Shaughnessy 2005 | 47 | 0.8 (1.2) | 46 | -2.1 (1.4) | | 1.2 % | 2.90 [ 2.37, 3.43 ] |
| Oberhoff 1998 | 59 | 2.24 (2) | 47 | 0.6 (1.43) | | 0.8 % | 1.64 [ 0.99, 2.29 ] |
| Osterborg 1996a | 17 | 2.6 (1.74) | 13 | 1.02 (1.28) | | 0.3 % | 1.58 [ 0.50, 2.66 ] |
| Osterborg 1996b | 27 | 1.71 (1.67) | 14 | 1.02 (1.28) | | 0.4 % | 0.69 [ -0.23, 1.61 ] |
| Osterborg 2002 | 138 | 2.48 (1.74) | 142 | 0.82 (1.4) | | 2.4 % | 1.66 [ 1.29, 2.03 ] |
| Pirker 2008 | 270 | -1.13 (1.93) | 279 | -1.98 (1.87) | | 3.3 % | 0.85 [ 0.53, 1.17 ] |
| Pronzato 2010 | 107 | 1.7 (1.35) | 109 | 0.4 (1.24) | | 2.8 % | 1.30 [ 0.95, 1.65 ] |
| Smith 2003a | 21 | 1.18 (2.01) | 7 | 0 (0.91) | | 0.3 % | 1.18 [ 0.09, 2.27 ] |
| Smith 2003b | 21 | 1.22 (1.62) | 7 | 0 (0.91) | | 0.4 % | 1.22 [ 0.25, 2.19 ] |
| Smith 2003c | 22 | 1.7 (1.93) | 8 | 0 (0.91) | | 0.3 % | 1.70 [ 0.68, 2.72 ] |
| Smith 2008 | 437 | 0.79 (2.83) | 447 | 0.29 (2.8) | | 2.4 % | 0.50 [ 0.13, 0.87 ] |
| Ten Bokkel 1998a | 34 | 0.66 (1.76) | 12 | -0.57 (1.16) | | 0.4 % | 1.23 [ 0.35, 2.11 ] |
| Ten Bokkel 1998b | 27 | 1.04 (1.73) | 12 | -0.57 (1.16) | | 0.4 % | 1.61 [ 0.68, 2.54 ] |
| Thomas 2002 | 62 | 1.9 (1.74) | 65 | 0.39 (1.38) | | 1.1 % | 1.51 [ 0.96, 2.06 ] |
| Thomas 2008 | 52 | 1.72 (1.79) | 57 | 0.09 (1.23) | | 1.0 % | 1.63 [ 1.05, 2.21 ] |
| Throuvalas 2000 | 28 | 0.7 (0.95) | 26 | -0.5 (0.56) | | 1.9 % | 1.20 [ 0.79, 1.61 ] |
| Tjulandin 2010a | 76 | 1.6 (1.42) | 37 | 0.2 (1.74) | | 0.8 % | 1.40 [ 0.75, 2.05 ] |
| Tjulandin 2010b | 73 | 1.9 (1.74) | 37 | 0.2 (1.74) | | 0.7 % | 1.70 [ 1.01, 2.39 ] |
| Tjulandin 2011 | 95 | 2.1 (1.3) | 91 | 0.65 (1.94) | | 1.5 % | 1.45 [ 0.97, 1.93 ] |
| Tsuboi 2009 | 61 | 1.4 (1.9) | 56 | -0.8 (1.5) | | 0.9 % | 2.20 [ 1.58, 2.82 ] |
| Untch 2011`1 | 330 | -0.07 (2) | 359 | -0.98 (1.33) | | 5.1 % | 0.91 [ 0.65, 1.17 ] |
| Wilkinson 2006 | 114 | 1.6 (1.5) | 59 | 0.3 (1.3) | | 1.8 % | 1.30 [ 0.87, 1.73 ] |
| Witzig 2005 | 166 | 2.8 (1.62) | 164 | 0.9 (1.52) | | 2.9 % | 1.90 [ 1.56, 2.24 ] |
| **Subtotal (95% CI)** | **6211** | | **5176** | | | **99.0 %** | **1.58 [ 1.52, 1.64 ]** |
| Heterogeneity: $Chi^2$ = 545.01, df = 73 (P<0.00001); $I^2$ =87% | | | | | | | |
| Test for overall effect: Z = 53.45 (P < 0.00001) | | | | | | | |
| **Total (95% CI)** | **6322** | | **5287** | | | **100.0 %** | **1.57 [ 1.51, 1.62 ]** |
| Heterogeneity: $Chi^2$ = 564.37, df = 74 (P<0.00001); $I^2$ =87% | | | | | | | |
| Test for overall effect: Z = 53.27 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 19.35, df = 1 (P = 0.00), $I^2$ =95% | | | | | | | |



### Analysis 2.5. Comparison 2 Change of haemoglobin level, Outcome 5 Change in Hb values - age differentiated.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 2 Change of haemoglobin level

Outcome: 5 Change in Hb values - age differentiated

| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 only children <18 years | | | | | | | |
| Razzouk 2006 | 111 | 1.3 (2.38) | 111 | 1 (1.9) | | 1.0 % | 0.30 [ -0.27, 0.87 ] |
| **Subtotal (95% CI)** | **111** | | **111** | | | **1.0 %** | **0.30 [ -0.27, 0.87 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 1.04 (P = 0.30) | | | | | | | |
| 2 adults ≥18 years | | | | | | | |
| Abels 1993 | 63 | 0.952 (2.142) | 55 | -0.03 (1.36) | | 0.8 % | 0.99 [ 0.35, 1.63 ] |
| Aravantinos 2003 | 24 | 2.31 (1.22) | 23 | 1.23 (1.59) | | 0.5 % | 1.08 [ 0.27, 1.89 ] |
| Bamias 2003 | 72 | 0.57 (2.12) | 72 | -0.49 (1.36) | | 1.0 % | 1.06 [ 0.48, 1.64 ] |
| Boogaerts 2003 | 133 | 2.1 (1.83) | 129 | 0.9 (1.5) | | 2.0 % | 1.20 [ 0.80, 1.60 ] |
| Carabantes 1999 | 20 | 1 (1.56) | 15 | -1.7 (1.22) | | 0.4 % | 2.70 [ 1.78, 3.62 ] |
| Case 1993 | 79 | 2.346 (2.04) | 74 | 0.37 (1.46) | | 1.1 % | 1.97 [ 1.41, 2.53 ] |
| Cazzola 1995a | 31 | -0.1 (2.23) | 7 | -0.04 (2.05) | | 0.1 % | -0.06 [ -1.77, 1.65 ] |
| Cazzola 1995b | 29 | 0.17 (1.72) | 8 | -0.04 (2.05) | | 0.1 % | 0.21 [ -1.34, 1.76 ] |
| Cazzola 1995c | 31 | 0.3 (2.9) | 7 | -0.04 (2.05) | | 0.1 % | 0.34 [ -1.49, 2.17 ] |
| Cazzola 1995d | 26 | 0.44 (2.29) | 7 | -0.04 (2.05) | | 0.1 % | 0.48 [ -1.28, 2.24 ] |
| Charu 2007 | 220 | 2.1 (1.854) | 55 | 0.1 (0.927) | | 2.8 % | 2.00 [ 1.65, 2.35 ] |
| Christodoulou 2009 | 167 | 2.74 (13.62) | 170 | 0.52 (4.18) | | 0.1 % | 2.22 [ 0.06, 4.38 ] |
| Dammacco 2001 | 69 | 1.8 (2.11) | 76 | -0.2 (1.31) | | 1.0 % | 2.00 [ 1.42, 2.58 ] |
| Fujisaka 2011 | 89 | 1.84 (1.33) | 92 | 0.02 (1.12) | | 2.6 % | 1.82 [ 1.46, 2.18 ] |
| Gordon 2008 | 139 | 1.3 (1.4) | 49 | 0.2 (1) | | 2.5 % | 1.10 [ 0.74, 1.46 ] |
| Grote 2005 | 64 | -0.2 (1.38) | 58 | -2.9 (1.53) | | 1.2 % | 2.70 [ 2.18, 3.22 ] |
| Hedenus 2002a | 5 | 1.56 (1.93) | 2 | 1 (0.56) | | 0.1 % | 0.56 [ -1.30, 2.42 ] |
| Hedenus 2002b | 17 | 1.64 (1.25) | 2 | 1 (0.56) | | 0.3 % | 0.64 [ -0.34, 1.62 ] |
| Hedenus 2002c | 14 | 2.46 (1.49) | 2 | 1 (0.56) | | 0.3 % | 1.46 [ 0.36, 2.56 ] |
| Hedenus 2003 | 174 | 1.8 (2.24) | 170 | 0.19 (1.3) | | 2.2 % | 1.61 [ 1.22, 2.00 ] |


(*Continued* . . . )

(. . . *Continued*)

| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Henke 1999a | 19 | 3.2 (1.6) | 3 | 0.6 (1.4) | | 0.1 % | 2.60 [ 0.86, 4.34 ] |
| Henke 1999b | 14 | 3.5 (1.2) | 4 | 0.6 (1.4) | | 0.1 % | 2.90 [ 1.39, 4.41 ] |
| Henke 1999c | 6 | 3.9 (2.1) | 4 | 0.6 (1.4) | | 0.1 % | 3.30 [ 1.13, 5.47 ] |
| Henke 2003 Roche 2004 | 178 | 3.4 (1.7) | 168 | 0.9 (1.7) | | 2.6 % | 2.50 [ 2.14, 2.86 ] |
| Henry 1995 | 63 | 2.04 (2.38) | 61 | 0.44 (1.7) | | 0.6 % | 1.60 [ 0.87, 2.33 ] |
| Hoskin 2009 | 151 | 0.625 (3.5) | 149 | -0.47 (3.48) | | 0.5 % | 1.09 [ 0.30, 1.88 ] |
| Huddart 2002 | 45 | 2.6 (2) | 45 | 1.2 (1.46) | | 0.6 % | 1.40 [ 0.68, 2.12 ] |
| Iconomou 2003 | 57 | 1.7 (1.6) | 55 | 0.3 (1.4) | | 1.1 % | 1.40 [ 0.84, 1.96 ] |
| Italian 1998 | 17 | 1.73 (1.56) | 11 | -0.14 (1.09) | | 0.3 % | 1.87 [ 0.89, 2.85 ] |
| Kotasek 2003a | 32 | 0.54 (1.24) | 8 | -0.02 (1.43) | | 0.3 % | 0.56 [ -0.52, 1.64 ] |
| Kotasek 2003b | 17 | 0.86 (1.57) | 8 | -0.02 (1.43) | | 0.2 % | 0.88 [ -0.36, 2.12 ] |
| Kotasek 2003c | 46 | 0.9 (1.63) | 9 | -0.02 (1.43) | | 0.3 % | 0.92 [ -0.13, 1.97 ] |
| Kotasek 2003d | 28 | 1.63 (2.01) | 8 | -0.02 (1.43) | | 0.2 % | 1.65 [ 0.41, 2.89 ] |
| Kotasek 2003e | 35 | 1.45 (1.42) | 8 | -0.02 (1.43) | | 0.3 % | 1.47 [ 0.37, 2.57 ] |
| Kotasek 2003f | 40 | 1.21 (1.9) | 9 | -0.02 (1.43) | | 0.3 % | 1.23 [ 0.13, 2.33 ] |
| Krzakowski 2008a | 104 | 2.5 (2.4) | 52 | 0.6 (1.7) | | 0.8 % | 1.90 [ 1.25, 2.55 ] |
| Krzakowski 2008b | 105 | 2.5 (2.6) | 52 | 0.6 (1.7) | | 0.7 % | 1.90 [ 1.22, 2.58 ] |
| Kunikane 2001a | 16 | 0.89 (1.72) | 10 | -0.65 (1.31) | | 0.2 % | 1.54 [ 0.37, 2.71 ] |
| Kunikane 2001b | 18 | 1.72 (1.1) | 9 | -0.65 (1.31) | | 0.3 % | 2.37 [ 1.37, 3.37 ] |
| Leyland-Jones 2005 | 81 | 0.34 (1.73) | 86 | 0.14 (1.7) | | 1.2 % | 0.20 [ -0.32, 0.72 ] |
| Littlewood 2001 | 244 | 2.2 (2.18) | 115 | 0.5 (1.79) | | 1.8 % | 1.70 [ 1.27, 2.13 ] |
| ML17616 2006 | 30 | 3.09 (2.08) | 30 | 1.76 (2.28) | | 0.3 % | 1.33 [ 0.23, 2.43 ] |
| ML17620 2006 | 61 | 2.12 (1.64) | 60 | 0.59 (1.83) | | 0.9 % | 1.53 [ 0.91, 2.15 ] |
| Mystakidou 2005 | 50 | 2.4 (1.3) | 50 | -0.1 (1.02) | | 1.6 % | 2.50 [ 2.04, 2.96 ] |
| O'Shaughnessy 2005 | 47 | 0.8 (1.2) | 46 | -2.1 (1.4) | | 1.2 % | 2.90 [ 2.37, 3.43 ] |
| Osterborg 1996a | 17 | 2.6 (1.74) | 13 | 1.02 (1.28) | | 0.3 % | 1.58 [ 0.50, 2.66 ] |
| Osterborg 1996b | 27 | 1.71 (1.67) | 14 | 1.02 (1.28) | | 0.4 % | 0.69 [ -0.23, 1.61 ] |
| Osterborg 2002 | 138 | 2.48 (1.74) | 142 | 0.82 (1.4) | | 2.4 % | 1.66 [ 1.29, 2.03 ] |
| Pirker 2008 | 270 | -1.13 (1.93) | 279 | -1.98 (1.87) | | 3.3 % | 0.85 [ 0.53, 1.17 ] |
| Smith 2003a | 21 | 1.18 (2.01) | 7 | 0 (0.91) | | 0.3 % | 1.18 [ 0.09, 2.27 ] |
| Smith 2003b | 21 | 1.22 (1.62) | 7 | 0 (0.91) | | 0.4 % | 1.22 [ 0.25, 2.19 ] |

-10 -5 0 5 10

Favours control Favours treatment

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| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Smith 2003c | 22 | 1.7 (1.93) | 8 | 0 (0.91) | | 0.3 % | 1.70 [ 0.68, 2.72 ] |
| Smith 2008 | 437 | 0.79 (2.83) | 447 | 0.29 (2.8) | | 2.4 % | 0.50 [ 0.13, 0.87 ] |
| Ten Bokkel 1998a | 34 | 0.66 (1.76) | 12 | -0.57 (1.16) | | 0.4 % | 1.23 [ 0.35, 2.11 ] |
| Ten Bokkel 1998b | 27 | 1.04 (1.73) | 12 | -0.57 (1.16) | | 0.4 % | 1.61 [ 0.68, 2.54 ] |
| Thomas 2002 | 62 | 1.9 (1.74) | 65 | 0.39 (1.38) | | 1.1 % | 1.51 [ 0.96, 2.06 ] |
| Tjulandin 2010a | 76 | 1.6 (1.42) | 37 | 0.2 (1.74) | | 0.8 % | 1.40 [ 0.75, 2.05 ] |
| Tjulandin 2010b | 73 | 1.9 (1.74) | 37 | 0.2 (1.74) | | 0.7 % | 1.70 [ 1.01, 2.39 ] |
| Tjulandin 2011 | 95 | 2.1 (1.3) | 91 | 0.65 (1.94) | | 1.5 % | 1.45 [ 0.97, 1.93 ] |
| Tsuboi 2009 | 61 | 1.4 (1.9) | 56 | -0.8 (1.5) | | 0.9 % | 2.20 [ 1.58, 2.82 ] |
| Wilkinson 2006 | 114 | 1.6 (1.5) | 59 | 0.3 (1.3) | | 1.8 % | 1.30 [ 0.87, 1.73 ] |
| Witzig 2005 | 166 | 2.8 (1.62) | 164 | 0.9 (1.52) | | 2.9 % | 1.90 [ 1.56, 2.24 ] |
| **Subtotal (95% CI)** | **4631** | | **3583** | | | **56.1 %** | **1.57 [ 1.49, 1.64 ]** |
| Heterogeneity: $Chi^2$ = 247.47, df = 61 (P<0.00001); $I^2$ =75% | | | | | | | |
| Test for overall effect: Z = 39.91 (P < 0.00001) | | | | | | | |
| 3 > 70% non-elderly 18-65 years | | | | | | | |
| Cascinu 1994 | 50 | 1.88 (0.83) | 49 | -0.61 (0.95) | | 2.7 % | 2.49 [ 2.14, 2.84 ] |
| Chang 2005 | 175 | 1.14 (0.8) | 175 | -0.58 (0.73) | | 12.9 % | 1.72 [ 1.56, 1.88 ] |
| Del Mastro 1997 | 28 | -0.8 (1.4) | 24 | -3.05 (1) | | 0.8 % | 2.25 [ 1.60, 2.90 ] |
| Gupta 2009 | 58 | 1.55 (0.74) | 57 | -1.5 (0.61) | | 5.4 % | 3.05 [ 2.80, 3.30 ] |
| Kurz 1997 | 23 | 3.26 (1.98) | 12 | 0.25 (1.66) | | 0.2 % | 3.01 [ 1.77, 4.25 ] |
| Oberhoff 1998 | 59 | 2.24 (2) | 47 | 0.6 (1.43) | | 0.8 % | 1.64 [ 0.99, 2.29 ] |
| Pronzato 2010 | 107 | 1.7 (1.35) | 109 | 0.4 (1.24) | | 2.8 % | 1.30 [ 0.95, 1.65 ] |
| Thomas 2008 | 52 | 1.72 (1.79) | 57 | 0.09 (1.23) | | 1.0 % | 1.63 [ 1.05, 2.21 ] |
| Throuvalas 2000 | 28 | 0.7 (0.95) | 26 | -0.5 (0.56) | | 1.9 % | 1.20 [ 0.79, 1.61 ] |
| **Subtotal (95% CI)** | **580** | | **556** | | | **28.4 %** | **1.99 [ 1.88, 2.10 ]** |
| Heterogeneity: $Chi^2$ = 124.16, df = 8 (P<0.00001); $I^2$ =94% | | | | | | | |
| Test for overall effect: Z = 36.07 (P < 0.00001) | | | | | | | |
| 4 only non-elderly adults | | | | | | | |
| Engert 2009 | 648 | -1.88 (1.78) | 655 | -2.55 (1.78) | | 8.9 % | 0.67 [ 0.48, 0.86 ] |
| Untch 2011˙1 | 330 | -0.07 (2) | 359 | -0.98 (1.33) | | 5.1 % | 0.91 [ 0.65, 1.17 ] |
| **Subtotal (95% CI)** | **978** | | **1014** | | | **13.9 %** | **0.76 [ 0.60, 0.91 ]** |
| Heterogeneity: $Chi^2$ = 2.15, df = 1 (P = 0.14); $I^2$ =54% | | | | | | | |
| Test for overall effect: Z = 9.62 (P < 0.00001) | | | | | | | |
| 5 > 70% elderly >65 years | | | | | | | |


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| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| 6 only elderly adults | | | | | | | |
| Gebbia 2003 | 22 | -2.4 (1.5) | 23 | -5.1 (1.33) | | 0.5 % | 2.70 [ 1.87, 3.53 ] |
| **Subtotal (95% CI)** | **22** | | **23** | | | **0.5 %** | **2.70 [ 1.87, 3.53 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 6.38 (P < 0.00001) | | | | | | | |
| **Total (95% CI)** | **6322** | | **5287** | | | **100.0 %** | **1.57 [ 1.51, 1.62 ]** |
| Heterogeneity: $Chi^2$ = 564.37, df = 74 (P<0.00001); $I^2$ =87% | | | | | | | |
| Test for overall effect: Z = 53.27 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 190.59, df = 4 (P = 0.00), $I^2$ =98% | | | | | | | |

## Analysis 2.6. Comparison 2 Change of haemoglobin level, Outcome 6 Change in Hb values - different therapies.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 2 Change of haemoglobin level

Outcome: 6 Change in Hb values - different therapies

| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 chemotherapy | | | | | | | |
| Aravantinos 2003 | 24 | 2.31 (1.22) | 23 | 1.23 (1.59) | | 0.5 % | 1.08 [ 0.27, 1.89 ] |
| Bamias 2003 | 72 | 0.57 (2.12) | 72 | -0.49 (1.36) | | 1.0 % | 1.06 [ 0.48, 1.64 ] |
| Boogaerts 2003 | 133 | 2.1 (1.83) | 129 | 0.9 (1.5) | | 2.0 % | 1.20 [ 0.80, 1.60 ] |
| Carabantes 1999 | 20 | 1 (1.56) | 15 | -1.7 (1.22) | | 0.4 % | 2.70 [ 1.78, 3.62 ] |
| Cascinu 1994 | 50 | 1.88 (0.83) | 49 | -0.61 (0.95) | | 2.7 % | 2.49 [ 2.14, 2.84 ] |
| Case 1993 | 79 | 2.346 (2.04) | 74 | 0.37 (1.46) | | 1.1 % | 1.97 [ 1.41, 2.53 ] |
| Cazzola 1995a | 31 | -0.1 (2.23) | 7 | -0.04 (2.05) | | 0.1 % | -0.06 [ -1.77, 1.65 ] |
| Cazzola 1995b | 29 | 0.17 (1.72) | 8 | -0.04 (2.05) | | 0.1 % | 0.21 [ -1.34, 1.76 ] |
| Cazzola 1995c | 31 | 0.3 (2.9) | 7 | -0.04 (2.05) | | 0.1 % | 0.34 [ -1.49, 2.17 ] |
| Cazzola 1995d | 26 | 0.44 (2.29) | 7 | -0.04 (2.05) | | 0.1 % | 0.48 [ -1.28, 2.24 ] |
| Chang 2005 | 175 | 1.14 (0.8) | 175 | -0.58 (0.73) | | 12.9 % | 1.72 [ 1.56, 1.88 ] |
| Christodoulou 2009 | 167 | 2.74 (13.62) | 170 | 0.52 (4.18) | | 0.1 % | 2.22 [ 0.06, 4.38 ] |
| Dammacco 2001 | 69 | 1.8 (2.11) | 76 | -0.2 (1.31) | | 1.0 % | 2.00 [ 1.42, 2.58 ] |
| Del Mastro 1997 | 28 | -0.8 (1.4) | 24 | -3.05 (1) | | 0.8 % | 2.25 [ 1.60, 2.90 ] |
| Engert 2009 | 648 | -1.88 (1.78) | 655 | -2.55 (1.78) | | 8.9 % | 0.67 [ 0.48, 0.86 ] |
| Fujisaka 2011 | 89 | 1.84 (1.33) | 92 | 0.02 (1.12) | | 2.6 % | 1.82 [ 1.46, 2.18 ] |
| Gebbia 2003 | 22 | -2.4 (1.5) | 23 | -5.1 (1.33) | | 0.5 % | 2.70 [ 1.87, 3.53 ] |
| Grote 2005 | 64 | -0.2 (1.38) | 58 | -2.9 (1.53) | | 1.2 % | 2.70 [ 2.18, 3.22 ] |
| Hedenus 2002a | 5 | 1.56 (1.93) | 2 | 1 (0.56) | | 0.1 % | 0.56 [ -1.30, 2.42 ] |
| Hedenus 2002b | 17 | 1.64 (1.25) | 2 | 1 (0.56) | | 0.3 % | 0.64 [ -0.34, 1.62 ] |
| Hedenus 2002c | 14 | 2.46 (1.49) | 2 | 1 (0.56) | | 0.3 % | 1.46 [ 0.36, 2.56 ] |
| Hedenus 2003 | 174 | 1.8 (2.24) | 170 | 0.19 (1.3) | | 2.2 % | 1.61 [ 1.22, 2.00 ] |
| Henry 1995 | 63 | 2.04 (2.38) | 61 | 0.44 (1.7) | | 0.6 % | 1.60 [ 0.87, 2.33 ] |


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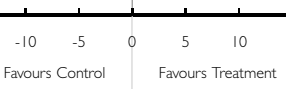
| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Huddart 2002 | 45 | 2.6 (2) | 45 | 1.2 (1.46) | | 0.6 % | 1.40 [ 0.68, 2.12 ] |
| Iconomou 2003 | 57 | 1.7 (1.6) | 55 | 0.3 (1.4) | | 1.1 % | 1.40 [ 0.84, 1.96 ] |
| Kotasek 2003a | 32 | 0.54 (1.24) | 8 | -0.02 (1.43) | | 0.3 % | 0.56 [ -0.52, 1.64 ] |
| Kotasek 2003b | 17 | 0.86 (1.57) | 8 | -0.02 (1.43) | | 0.2 % | 0.88 [ -0.36, 2.12 ] |
| Kotasek 2003c | 46 | 0.9 (1.63) | 9 | -0.02 (1.43) | | 0.3 % | 0.92 [ -0.13, 1.97 ] |
| Kotasek 2003d | 28 | 1.63 (2.01) | 8 | -0.02 (1.43) | | 0.2 % | 1.65 [ 0.41, 2.89 ] |
| Kotasek 2003e | 35 | 1.45 (1.42) | 8 | -0.02 (1.43) | | 0.3 % | 1.47 [ 0.37, 2.57 ] |
| Kotasek 2003f | 40 | 1.21 (1.9) | 9 | -0.02 (1.43) | | 0.3 % | 1.23 [ 0.13, 2.33 ] |
| Krzakowski 2008a | 104 | 2.5 (2.4) | 52 | 0.6 (1.7) | | 0.8 % | 1.90 [ 1.25, 2.55 ] |
| Krzakowski 2008b | 105 | 2.5 (2.6) | 52 | 0.6 (1.7) | | 0.7 % | 1.90 [ 1.22, 2.58 ] |
| Kunikane 2001a | 16 | 0.89 (1.72) | 10 | -0.65 (1.31) | | 0.2 % | 1.54 [ 0.37, 2.71 ] |
| Kunikane 2001b | 18 | 1.72 (1.1) | 9 | -0.65 (1.31) | | 0.3 % | 2.37 [ 1.37, 3.37 ] |
| Kurz 1997 | 23 | 3.26 (1.98) | 12 | 0.25 (1.66) | | 0.2 % | 3.01 [ 1.77, 4.25 ] |
| Leyland-Jones 2005 | 81 | 0.34 (1.73) | 86 | 0.14 (1.7) | | 1.2 % | 0.20 [ -0.32, 0.72 ] |
| Littlewood 2001 | 244 | 2.2 (2.18) | 115 | 0.5 (1.79) | | 1.8 % | 1.70 [ 1.27, 2.13 ] |
| ML17616 2006 | 30 | 3.09 (2.08) | 30 | 1.76 (2.28) | | 0.3 % | 1.33 [ 0.23, 2.43 ] |
| ML17620 2006 | 61 | 2.12 (1.64) | 60 | 0.59 (1.83) | | 0.9 % | 1.53 [ 0.91, 2.15 ] |
| O'Shaughnessy 2005 | 47 | 0.8 (1.2) | 46 | -2.1 (1.4) | | 1.2 % | 2.90 [ 2.37, 3.43 ] |
| Oberhoff 1998 | 59 | 2.24 (2) | 47 | 0.6 (1.43) | | 0.8 % | 1.64 [ 0.99, 2.29 ] |
| Osterborg 1996a | 17 | 2.6 (1.74) | 13 | 1.02 (1.28) | | 0.3 % | 1.58 [ 0.50, 2.66 ] |
| Osterborg 1996b | 27 | 1.71 (1.67) | 14 | 1.02 (1.28) | | 0.4 % | 0.69 [ -0.23, 1.61 ] |
| Osterborg 2002 | 138 | 2.48 (1.74) | 142 | 0.82 (1.4) | | 2.4 % | 1.66 [ 1.29, 2.03 ] |
| Pirker 2008 | 270 | -1.13 (1.93) | 279 | -1.98 (1.87) | | 3.3 % | 0.85 [ 0.53, 1.17 ] |
| Pronzato 2010 | 107 | 1.7 (1.35) | 109 | 0.4 (1.24) | | 2.8 % | 1.30 [ 0.95, 1.65 ] |
| Razzouk 2006 | 111 | 1.3 (2.38) | 111 | 1 (1.9) | | 1.0 % | 0.30 [ -0.27, 0.87 ] |
| Ten Bokkel 1998a | 34 | 0.66 (1.76) | 12 | -0.57 (1.16) | | 0.4 % | 1.23 [ 0.35, 2.11 ] |
| Ten Bokkel 1998b | 27 | 1.04 (1.73) | 12 | -0.57 (1.16) | | 0.4 % | 1.61 [ 0.68, 2.54 ] |
| Thomas 2002 | 62 | 1.9 (1.74) | 65 | 0.39 (1.38) | | 1.1 % | 1.51 [ 0.96, 2.06 ] |
| Tjulandin 2010a | 76 | 1.6 (1.42) | 37 | 0.2 (1.74) | | 0.8 % | 1.40 [ 0.75, 2.05 ] |
| Tjulandin 2010b | 73 | 1.9 (1.74) | 37 | 0.2 (1.74) | | 0.7 % | 1.70 [ 1.01, 2.39 ] |
| Tjulandin 2011 | 95 | 2.1 (1.3) | 91 | 0.65 (1.94) | | 1.5 % | 1.45 [ 0.97, 1.93 ] |

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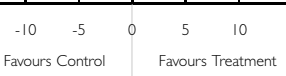
(. . . *Continued*)

| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Tsuboi 2009 | 61 | 1.4 (1.9) | 56 | -0.8 (1.5) | | 0.9 % | 2.20 [ 1.58, 2.82 ] |
| Untch 2011˙1 | 330 | -0.07 (2) | 359 | -0.98 (1.33) | | 5.1 % | 0.91 [ 0.65, 1.17 ] |
| Wilkinson 2006 | 114 | 1.6 (1.5) | 59 | 0.3 (1.3) | | 1.8 % | 1.30 [ 0.87, 1.73 ] |
| Witzig 2005 | 166 | 2.8 (1.62) | 164 | 0.9 (1.52) | | 2.9 % | 1.90 [ 1.56, 2.24 ] |
| **Subtotal (95% CI)** | **4826** | | **4130** | | | **76.9 %** | **1.46 [ 1.39, 1.52 ]** |
| Heterogeneity: Chi² = 313.83, df = 57 (P<0.00001); I² =82% | | | | | | | |
| Test for overall effect: Z = 43.46 (P < 0.00001) | | | | | | | |
| 2 radiotherapy/radiochemotherapy | | | | | | | |
| Gupta 2009 | 58 | 1.55 (0.74) | 57 | -1.5 (0.61) | | 5.4 % | 3.05 [ 2.80, 3.30 ] |
| Henke 1999a | 19 | 3.2 (1.6) | 3 | 0.6 (1.4) | | 0.1 % | 2.60 [ 0.86, 4.34 ] |
| Henke 1999b | 14 | 3.5 (1.2) | 4 | 0.6 (1.4) | | 0.1 % | 2.90 [ 1.39, 4.41 ] |
| Henke 1999c | 6 | 3.9 (2.1) | 4 | 0.6 (1.4) | | 0.1 % | 3.30 [ 1.13, 5.47 ] |
| Henke 2003 Roche 2004 | 178 | 3.4 (1.7) | 168 | 0.9 (1.7) | | 2.6 % | 2.50 [ 2.14, 2.86 ] |
| Hoskin 2009 | 151 | 0.625 (3.5) | 149 | -0.47 (3.48) | | 0.5 % | 1.09 [ 0.30, 1.88 ] |
| Thomas 2008 | 52 | 1.72 (1.79) | 57 | 0.09 (1.23) | | 1.0 % | 1.63 [ 1.05, 2.21 ] |
| Throuvalas 2000 | 28 | 0.7 (0.95) | 26 | -0.5 (0.56) | | 1.9 % | 1.20 [ 0.79, 1.61 ] |
| **Subtotal (95% CI)** | **506** | | **468** | | | **11.8 %** | **2.41 [ 2.24, 2.58 ]** |
| Heterogeneity: Chi² = 77.61, df = 7 (P<0.00001); I² =91% | | | | | | | |
| Test for overall effect: Z = 28.17 (P < 0.00001) | | | | | | | |
| 3 no therapy | | | | | | | |
| Abels 1993 | 63 | 0.952 (2.142) | 55 | -0.03 (1.36) | | 0.8 % | 0.99 [ 0.35, 1.63 ] |
| Charu 2007 | 220 | 2.1 (1.854) | 55 | 0.1 (0.927) | | 2.8 % | 2.00 [ 1.65, 2.35 ] |
| Gordon 2008 | 139 | 1.3 (1.4) | 49 | 0.2 (1) | | 2.5 % | 1.10 [ 0.74, 1.46 ] |
| Italian 1998 | 17 | 1.73 (1.56) | 11 | -0.14 (1.09) | | 0.3 % | 1.87 [ 0.89, 2.85 ] |
| Mystakidou 2005 | 50 | 2.4 (1.3) | 50 | -0.1 (1.02) | | 1.6 % | 2.50 [ 2.04, 2.96 ] |
| Smith 2003a | 21 | 1.18 (2.01) | 7 | 0 (0.91) | | 0.3 % | 1.18 [ 0.09, 2.27 ] |
| Smith 2003b | 21 | 1.22 (1.62) | 7 | 0 (0.91) | | 0.4 % | 1.22 [ 0.25, 2.19 ] |
| Smith 2003c | 22 | 1.7 (1.93) | 8 | 0 (0.91) | | 0.3 % | 1.70 [ 0.68, 2.72 ] |
| Smith 2008 | 437 | 0.79 (2.83) | 447 | 0.29 (2.8) | | 2.4 % | 0.50 [ 0.13, 0.87 ] |
| **Subtotal (95% CI)** | **990** | | **689** | | | **11.4 %** | **1.42 [ 1.25, 1.60 ]** |
| Heterogeneity: Chi² = 61.90, df = 8 (P<0.00001); I² =87% | | | | | | | |
| Test for overall effect: Z = 16.34 (P < 0.00001) | | | | | | | |
| **Total (95% CI)** | **6322** | | **5287** | | | **100.0 %** | **1.57 [ 1.51, 1.62 ]** |
| Heterogeneity: Chi² = 564.37, df = 74 (P<0.00001); I² =87% | | | | | | | |
| Test for overall effect: Z = 53.27 (P < 0.00001) | | | | | | | |

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| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Test for subgroup differences: $Chi^2$ = 111.03, df = 2 (P = 0.00), $I^2$ =98% | | | | | | | |

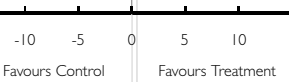

## Analysis 2.7. Comparison 2 Change of haemoglobin level, Outcome 7 Change in Hb values - different therapies differentiated.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 2 Change of haemoglobin level

Outcome: 7 Change in Hb values - different therapies differentiated

| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 chemotherapy, >70% with platinum | | | | | | | |
| Aravantinos 2003 | 24 | 2.31 (1.22) | 23 | 1.23 (1.59) | | 0.5 % | 1.08 [ 0.27, 1.89 ] |
| Bamias 2003 | 72 | 0.57 (2.12) | 72 | -0.49 (1.36) | | 1.0 % | 1.06 [ 0.48, 1.64 ] |
| Carabantes 1999 | 20 | 1 (1.56) | 15 | -1.7 (1.22) | | 0.4 % | 2.70 [ 1.78, 3.62 ] |
| Cascinu 1994 | 50 | 1.88 (0.83) | 49 | -0.61 (0.95) | | 2.7 % | 2.49 [ 2.14, 2.84 ] |
| Fujisaka 2011 | 89 | 1.84 (1.33) | 92 | 0.02 (1.12) | | 2.6 % | 1.82 [ 1.46, 2.18 ] |
| Gebbia 2003 | 22 | -2.4 (1.5) | 23 | -5.1 (1.33) | | 0.5 % | 2.70 [ 1.87, 3.53 ] |
| Grote 2005 | 64 | -0.2 (1.38) | 58 | -2.9 (1.53) | | 1.2 % | 2.70 [ 2.18, 3.22 ] |
| Henry 1995 | 63 | 2.04 (2.38) | 61 | 0.44 (1.7) | | 0.6 % | 1.60 [ 0.87, 2.33 ] |
| Huddart 2002 | 45 | 2.6 (2) | 45 | 1.2 (1.46) | | 0.6 % | 1.40 [ 0.68, 2.12 ] |
| Kunikane 2001a | 16 | 0.89 (1.72) | 10 | -0.65 (1.31) | | 0.2 % | 1.54 [ 0.37, 2.71 ] |
| Kunikane 2001b | 18 | 1.72 (1.1) | 9 | -0.65 (1.31) | | 0.3 % | 2.37 [ 1.37, 3.37 ] |
| Kurz 1997 | 23 | 3.26 (1.98) | 12 | 0.25 (1.66) | | 0.2 % | 3.01 [ 1.77, 4.25 ] |
| ML17620 2006 | 61 | 2.12 (1.64) | 60 | 0.59 (1.83) | | 0.9 % | 1.53 [ 0.91, 2.15 ] |

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| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Pirker 2008 | 270 | -1.13 (1.93) | 279 | -1.98 (1.87) | | 3.3 % | 0.85 [ 0.53, 1.17 ] |
| Ten Bokkel 1998a | 34 | 0.66 (1.76) | 12 | -0.57 (1.16) | | 0.4 % | 1.23 [ 0.35, 2.11 ] |
| Ten Bokkel 1998b | 27 | 1.04 (1.73) | 12 | -0.57 (1.16) | | 0.4 % | 1.61 [ 0.68, 2.54 ] |
| Tjulandin 2010a | 76 | 1.6 (1.42) | 37 | 0.2 (1.74) | | 0.8 % | 1.40 [ 0.75, 2.05 ] |
| Tjulandin 2010b | 73 | 1.9 (1.74) | 37 | 0.2 (1.74) | | 0.7 % | 1.70 [ 1.01, 2.39 ] |
| Wilkinson 2006 | 114 | 1.6 (1.5) | 59 | 0.3 (1.3) | | 1.8 % | 1.30 [ 0.87, 1.73 ] |
| **Subtotal (95% CI)** | **1161** | | **965** | | | **19.1 %** | **1.68 [ 1.55, 1.82 ]** |
| Heterogeneity: $Chi^2$ = 90.83, df = 18 (P<0.00001); $I^2$ =80% | | | | | | | |
| Test for overall effect: Z = 25.07 (P < 0.00001) | | | | | | | |
| 2 chemotherapy, <70% platinum containing | | | | | | | |
| Christodoulou 2009 | 167 | 2.74 (13.62) | 170 | 0.52 (4.18) | | 0.1 % | 2.22 [ 0.06, 4.38 ] |
| Iconomou 2003 | 57 | 1.7 (1.6) | 55 | 0.3 (1.4) | | 1.1 % | 1.40 [ 0.84, 1.96 ] |
| Krzakowski 2008a | 104 | 2.5 (2.4) | 52 | 0.6 (1.7) | | 0.8 % | 1.90 [ 1.25, 2.55 ] |
| Krzakowski 2008b | 105 | 2.5 (2.6) | 52 | 0.6 (1.7) | | 0.7 % | 1.90 [ 1.22, 2.58 ] |
| Oberhoff 1998 | 59 | 2.24 (2) | 47 | 0.6 (1.43) | | 0.8 % | 1.64 [ 0.99, 2.29 ] |
| Tsuboi 2009 | 61 | 1.4 (1.9) | 56 | -0.8 (1.5) | | 0.9 % | 2.20 [ 1.58, 2.82 ] |
| Witzig 2005 | 166 | 2.8 (1.62) | 164 | 0.9 (1.52) | | 2.9 % | 1.90 [ 1.56, 2.24 ] |
| **Subtotal (95% CI)** | **719** | | **596** | | | **7.2 %** | **1.84 [ 1.62, 2.05 ]** |
| Heterogeneity: $Chi^2$ = 4.37, df = 6 (P = 0.63); $I^2$ =0.0% | | | | | | | |
| Test for overall effect: Z = 16.74 (P < 0.00001) | | | | | | | |
| 3 chemotherapy without platinum | | | | | | | |
| Case 1993 | 79 | 2.346 (2.04) | 74 | 0.37 (1.46) | | 1.1 % | 1.97 [ 1.41, 2.53 ] |
| Cazzola 1995a | 31 | -0.1 (2.23) | 7 | -0.04 (2.05) | | 0.1 % | -0.06 [ -1.77, 1.65 ] |
| Cazzola 1995b | 29 | 0.17 (1.72) | 8 | -0.04 (2.05) | | 0.1 % | 0.21 [ -1.34, 1.76 ] |
| Cazzola 1995c | 31 | 0.3 (2.9) | 7 | -0.04 (2.05) | | 0.1 % | 0.34 [ -1.49, 2.17 ] |
| Cazzola 1995d | 26 | 0.44 (2.29) | 7 | -0.04 (2.05) | | 0.1 % | 0.48 [ -1.28, 2.24 ] |
| Chang 2005 | 175 | 1.14 (0.8) | 175 | -0.58 (0.73) | | 12.9 % | 1.72 [ 1.56, 1.88 ] |
| Del Mastro 1997 | 28 | -0.8 (1.4) | 24 | -3.05 (1) | | 0.8 % | 2.25 [ 1.60, 2.90 ] |
| Engert 2009 | 648 | -1.88 (1.78) | 655 | -2.55 (1.78) | | 8.9 % | 0.67 [ 0.48, 0.86 ] |
| Hedenus 2002a | 5 | 1.56 (1.93) | 2 | 1 (0.56) | | 0.1 % | 0.56 [ -1.30, 2.42 ] |
| Hedenus 2002b | 17 | 1.64 (1.25) | 2 | 1 (0.56) | | 0.3 % | 0.64 [ -0.34, 1.62 ] |
| Hedenus 2002c | 14 | 2.46 (1.49) | 2 | 1 (0.56) | | 0.3 % | 1.46 [ 0.36, 2.56 ] |
| Hedenus 2003 | 174 | 1.8 (2.24) | 170 | 0.19 (1.3) | | 2.2 % | 1.61 [ 1.22, 2.00 ] |

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Favours Control Favours Treatment

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| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Leyland-Jones 2005 | 81 | 0.34 (1.73) | 86 | 0.14 (1.7) | | 1.2 % | 0.20 [ -0.32, 0.72 ] |
| Littlewood 2001 | 244 | 2.2 (2.18) | 115 | 0.5 (1.79) | | 1.8 % | 1.70 [ 1.27, 2.13 ] |
| ML17616 2006 | 30 | 3.09 (2.08) | 30 | 1.76 (2.28) | | 0.3 % | 1.33 [ 0.23, 2.43 ] |
| O'Shaughnessy 2005 | 47 | 0.8 (1.2) | 46 | -2.1 (1.4) | | 1.2 % | 2.90 [ 2.37, 3.43 ] |
| Osterborg 1996a | 17 | 2.6 (1.74) | 13 | 1.02 (1.28) | | 0.3 % | 1.58 [ 0.50, 2.66 ] |
| Osterborg 1996b | 27 | 1.71 (1.67) | 14 | 1.02 (1.28) | | 0.4 % | 0.69 [ -0.23, 1.61 ] |
| Osterborg 2002 | 138 | 2.48 (1.74) | 142 | 0.82 (1.4) | | 2.4 % | 1.66 [ 1.29, 2.03 ] |
| Pronzato 2010 | 107 | 1.7 (1.35) | 109 | 0.4 (1.24) | | 2.8 % | 1.30 [ 0.95, 1.65 ] |
| Tjulandin 2011 | 95 | 2.1 (1.3) | 91 | 0.65 (1.94) | | 1.5 % | 1.45 [ 0.97, 1.93 ] |
| Untch 2011˙1 | 330 | -0.07 (2) | 359 | -0.98 (1.33) | | 5.1 % | 0.91 [ 0.65, 1.17 ] |
| **Subtotal (95% CI)** | **2373** | | **2138** | | | **43.9 %** | **1.33 [ 1.25, 1.42 ]** |
| Heterogeneity: $Chi^2$ = 161.70, df = 21 (P<0.00001); $I^2$ =87% | | | | | | | |
| Test for overall effect: Z = 30.05 (P < 0.00001) | | | | | | | |
| 4 chemotherapy, platinum and non-platinum containing, no numbers given | | | | | | | |
| Boogaerts 2003 | 133 | 2.1 (1.83) | 129 | 0.9 (1.5) | | 2.0 % | 1.20 [ 0.80, 1.60 ] |
| Dammacco 2001 | 69 | 1.8 (2.11) | 76 | -0.2 (1.31) | | 1.0 % | 2.00 [ 1.42, 2.58 ] |
| Kotasek 2003a | 32 | 0.54 (1.24) | 8 | -0.02 (1.43) | | 0.3 % | 0.56 [ -0.52, 1.64 ] |
| Kotasek 2003b | 17 | 0.86 (1.57) | 8 | -0.02 (1.43) | | 0.2 % | 0.88 [ -0.36, 2.12 ] |
| Kotasek 2003c | 46 | 0.9 (1.63) | 9 | -0.02 (1.43) | | 0.3 % | 0.92 [ -0.13, 1.97 ] |
| Kotasek 2003d | 28 | 1.63 (2.01) | 8 | -0.02 (1.43) | | 0.2 % | 1.65 [ 0.41, 2.89 ] |
| Kotasek 2003e | 35 | 1.45 (1.42) | 8 | -0.02 (1.43) | | 0.3 % | 1.47 [ 0.37, 2.57 ] |
| Kotasek 2003f | 40 | 1.21 (1.9) | 9 | -0.02 (1.43) | | 0.3 % | 1.23 [ 0.13, 2.33 ] |
| Thomas 2002 | 62 | 1.9 (1.74) | 65 | 0.39 (1.38) | | 1.1 % | 1.51 [ 0.96, 2.06 ] |
| **Subtotal (95% CI)** | **462** | | **320** | | | **5.7 %** | **1.37 [ 1.13, 1.61 ]** |
| Heterogeneity: $Chi^2$ = 9.25, df = 8 (P = 0.32); $I^2$ =13% | | | | | | | |
| Test for overall effect: Z = 11.14 (P < 0.00001) | | | | | | | |
| 5 chemotherapy, no details given | | | | | | | |
| Razzouk 2006 | 111 | 1.3 (2.38) | 111 | 1 (1.9) | | 1.0 % | 0.30 [ -0.27, 0.87 ] |
| **Subtotal (95% CI)** | **111** | | **111** | | | **1.0 %** | **0.30 [ -0.27, 0.87 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 1.04 (P = 0.30) | | | | | | | |
| 6 radiotherapy | | | | | | | |
| Henke 1999a | 19 | 3.2 (1.6) | 3 | 0.6 (1.4) | | 0.1 % | 2.60 [ 0.86, 4.34 ] |
| Henke 1999b | 14 | 3.5 (1.2) | 4 | 0.6 (1.4) | | 0.1 % | 2.90 [ 1.39, 4.41 ] |

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Favours Control Favours Treatment

(*Continued* . . . )

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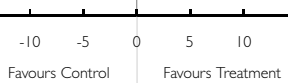
| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Henke 1999c | 6 | 3.9 (2.1) | 4 | 0.6 (1.4) | | 0.1 % | 3.30 [ 1.13, 5.47 ] |
| Henke 2003 Roche 2004 | 178 | 3.4 (1.7) | 168 | 0.9 (1.7) | | 2.6 % | 2.50 [ 2.14, 2.86 ] |
| Hoskin 2009 | 151 | 0.625 (3.5) | 149 | -0.47 (3.48) | | 0.5 % | 1.09 [ 0.30, 1.88 ] |
| **Subtotal (95% CI)** | **368** | | **328** | | | **3.4 %** | **2.32 [ 2.01, 2.63 ]** |
| Heterogeneity: $Chi^2$ = 11.68, df = 4 (P = 0.02); $I^2$ =66% | | | | | | | |
| Test for overall effect: Z = 14.64 (P < 0.00001) | | | | | | | |
| 7 radiochemotherapy | | | | | | | |
| Gupta 2009 | 58 | 1.55 (0.74) | 57 | -1.5 (0.61) | | 5.4 % | 3.05 [ 2.80, 3.30 ] |
| Thomas 2008 | 52 | 1.72 (1.79) | 57 | 0.09 (1.23) | | 1.0 % | 1.63 [ 1.05, 2.21 ] |
| Throuvalas 2000 | 28 | 0.7 (0.95) | 26 | -0.5 (0.56) | | 1.9 % | 1.20 [ 0.79, 1.61 ] |
| **Subtotal (95% CI)** | **138** | | **140** | | | **8.3 %** | **2.45 [ 2.25, 2.65 ]** |
| Heterogeneity: $Chi^2$ = 65.45, df = 2 (P<0.00001); $I^2$ =97% | | | | | | | |
| Test for overall effect: Z = 24.08 (P < 0.00001) | | | | | | | |
| 8 no therapy | | | | | | | |
| Abels 1993 | 63 | 0.952 (2.142) | 55 | -0.03 (1.36) | | 0.8 % | 0.99 [ 0.35, 1.63 ] |
| Charu 2007 | 220 | 2.1 (1.854) | 55 | 0.1 (0.927) | | 2.8 % | 2.00 [ 1.65, 2.35 ] |
| Gordon 2008 | 139 | 1.3 (1.4) | 49 | 0.2 (1) | | 2.5 % | 1.10 [ 0.74, 1.46 ] |
| Italian 1998 | 17 | 1.73 (1.56) | 11 | -0.14 (1.09) | | 0.3 % | 1.87 [ 0.89, 2.85 ] |
| Mystakidou 2005 | 50 | 2.4 (1.3) | 50 | -0.1 (1.02) | | 1.6 % | 2.50 [ 2.04, 2.96 ] |
| Smith 2003a | 21 | 1.18 (2.01) | 7 | 0 (0.91) | | 0.3 % | 1.18 [ 0.09, 2.27 ] |
| Smith 2003b | 21 | 1.22 (1.62) | 7 | 0 (0.91) | | 0.4 % | 1.22 [ 0.25, 2.19 ] |
| Smith 2003c | 22 | 1.7 (1.93) | 8 | 0 (0.91) | | 0.3 % | 1.70 [ 0.68, 2.72 ] |
| Smith 2008 | 437 | 0.79 (2.83) | 447 | 0.29 (2.8) | | 2.4 % | 0.50 [ 0.13, 0.87 ] |
| **Subtotal (95% CI)** | **990** | | **689** | | | **11.4 %** | **1.42 [ 1.25, 1.60 ]** |
| Heterogeneity: $Chi^2$ = 61.90, df = 8 (P<0.00001); $I^2$ =87% | | | | | | | |
| Test for overall effect: Z = 16.34 (P < 0.00001) | | | | | | | |
| **Total (95% CI)** | **6322** | | **5287** | | | **100.0 %** | **1.57 [ 1.51, 1.62 ]** |
| Heterogeneity: $Chi^2$ = 564.37, df = 74 (P<0.00001); $I^2$ =87% | | | | | | | |
| Test for overall effect: Z = 53.27 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 159.20, df = 7 (P = 0.00), $I^2$ =96% | | | | | | | |



### Analysis 2.8. Comparison 2 Change of haemoglobin level, Outcome 8 Change in Hb values - epoetin vs darbepoetin.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 2 Change of haemoglobin level

Outcome: 8 Change in Hb values - epoetin vs darbepoetin

| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 Epoetin | | | | | | | |
| Abels 1993 | 63 | 0.952 (2.142) | 55 | -0.03 (1.36) | | 0.8 % | 0.99 [ 0.35, 1.63 ] |
| Aravantinos 2003 | 24 | 2.31 (1.22) | 23 | 1.23 (1.59) | | 0.5 % | 1.08 [ 0.27, 1.89 ] |
| Bamias 2003 | 72 | 0.57 (2.12) | 72 | -0.49 (1.36) | | 1.0 % | 1.06 [ 0.48, 1.64 ] |
| Boogaerts 2003 | 133 | 2.1 (1.83) | 129 | 0.9 (1.5) | | 2.0 % | 1.20 [ 0.80, 1.60 ] |
| Carabantes 1999 | 20 | 1 (1.56) | 15 | -1.7 (1.22) | | 0.4 % | 2.70 [ 1.78, 3.62 ] |
| Cascinu 1994 | 50 | 1.88 (0.83) | 49 | -0.61 (0.95) | | 2.7 % | 2.49 [ 2.14, 2.84 ] |
| Case 1993 | 79 | 2.346 (2.04) | 74 | 0.37 (1.46) | | 1.1 % | 1.97 [ 1.41, 2.53 ] |
| Cazzola 1995a | 31 | -0.1 (2.23) | 7 | -0.04 (2.05) | | 0.1 % | -0.06 [ -1.77, 1.65 ] |
| Cazzola 1995b | 29 | 0.17 (1.72) | 8 | -0.04 (2.05) | | 0.1 % | 0.21 [ -1.34, 1.76 ] |
| Cazzola 1995c | 31 | 0.3 (2.9) | 7 | -0.04 (2.05) | | 0.1 % | 0.34 [ -1.49, 2.17 ] |
| Cazzola 1995d | 26 | 0.44 (2.29) | 7 | -0.04 (2.05) | | 0.1 % | 0.48 [ -1.28, 2.24 ] |
| Chang 2005 | 175 | 1.14 (0.8) | 175 | -0.58 (0.73) | | 12.9 % | 1.72 [ 1.56, 1.88 ] |
| Christodoulou 2009 | 167 | 2.74 (13.62) | 170 | 0.52 (4.18) | | 0.1 % | 2.22 [ 0.06, 4.38 ] |
| Dammacco 2001 | 69 | 1.8 (2.11) | 76 | -0.2 (1.31) | | 1.0 % | 2.00 [ 1.42, 2.58 ] |
| Del Mastro 1997 | 28 | -0.8 (1.4) | 24 | -3.05 (1) | | 0.8 % | 2.25 [ 1.60, 2.90 ] |
| Engert 2009 | 648 | -1.88 (1.78) | 655 | -2.55 (1.78) | | 8.9 % | 0.67 [ 0.48, 0.86 ] |
| Fujisaka 2011 | 89 | 1.84 (1.33) | 92 | 0.02 (1.12) | | 2.6 % | 1.82 [ 1.46, 2.18 ] |
| Gebbia 2003 | 22 | -2.4 (1.5) | 23 | -5.1 (1.33) | | 0.5 % | 2.70 [ 1.87, 3.53 ] |
| Grote 2005 | 64 | -0.2 (1.38) | 58 | -2.9 (1.53) | | 1.2 % | 2.70 [ 2.18, 3.22 ] |
| Gupta 2009 | 58 | 1.55 (0.74) | 57 | -1.5 (0.61) | | 5.4 % | 3.05 [ 2.80, 3.30 ] |
| Henke 1999a | 19 | 3.2 (1.6) | 3 | 0.6 (1.4) | | 0.1 % | 2.60 [ 0.86, 4.34 ] |
| Henke 1999b | 14 | 3.5 (1.2) | 4 | 0.6 (1.4) | | 0.1 % | 2.90 [ 1.39, 4.41 ] |
| Henke 1999c | 6 | 3.9 (2.1) | 4 | 0.6 (1.4) | | 0.1 % | 3.30 [ 1.13, 5.47 ] |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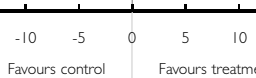
| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Henke 2003 Roche 2004 | 178 | 3.4 (1.7) | 168 | 0.9 (1.7) | | 2.6 % | 2.50 [ 2.14, 2.86 ] |
| Henry 1995 | 63 | 2.04 (2.38) | 61 | 0.44 (1.7) | | 0.6 % | 1.60 [ 0.87, 2.33 ] |
| Hoskin 2009 | 151 | 0.625 (3.5) | 149 | -0.47 (3.48) | | 0.5 % | 1.09 [ 0.30, 1.88 ] |
| Huddart 2002 | 45 | 2.6 (2) | 45 | 1.2 (1.46) | | 0.6 % | 1.40 [ 0.68, 2.12 ] |
| Iconomou 2003 | 57 | 1.7 (1.6) | 55 | 0.3 (1.4) | | 1.1 % | 1.40 [ 0.84, 1.96 ] |
| Italian 1998 | 17 | 1.73 (1.56) | 11 | -0.14 (1.09) | | 0.3 % | 1.87 [ 0.89, 2.85 ] |
| Krzakowski 2008a | 104 | 2.5 (2.4) | 52 | 0.6 (1.7) | | 0.8 % | 1.90 [ 1.25, 2.55 ] |
| Krzakowski 2008b | 105 | 2.5 (2.6) | 52 | 0.6 (1.7) | | 0.7 % | 1.90 [ 1.22, 2.58 ] |
| Kunikane 2001a | 16 | 0.89 (1.72) | 10 | -0.65 (1.31) | | 0.2 % | 1.54 [ 0.37, 2.71 ] |
| Kunikane 2001b | 18 | 1.72 (1.1) | 9 | -0.65 (1.31) | | 0.3 % | 2.37 [ 1.37, 3.37 ] |
| Kurz 1997 | 23 | 3.26 (1.98) | 12 | 0.25 (1.66) | | 0.2 % | 3.01 [ 1.77, 4.25 ] |
| Leyland-Jones 2005 | 81 | 0.34 (1.73) | 86 | 0.14 (1.7) | | 1.2 % | 0.20 [ -0.32, 0.72 ] |
| Littlewood 2001 | 244 | 2.2 (2.18) | 115 | 0.5 (1.79) | | 1.8 % | 1.70 [ 1.27, 2.13 ] |
| ML17616 2006 | 30 | 3.09 (2.08) | 30 | 1.76 (2.28) | | 0.3 % | 1.33 [ 0.23, 2.43 ] |
| ML17620 2006 | 61 | 2.12 (1.64) | 60 | 0.59 (1.83) | | 0.9 % | 1.53 [ 0.91, 2.15 ] |
| Mystakidou 2005 | 50 | 2.4 (1.3) | 50 | -0.1 (1.02) | | 1.6 % | 2.50 [ 2.04, 2.96 ] |
| O'Shaughnessy 2005 | 47 | 0.8 (1.2) | 46 | -2.1 (1.4) | | 1.2 % | 2.90 [ 2.37, 3.43 ] |
| Oberhoff 1998 | 59 | 2.24 (2) | 47 | 0.6 (1.43) | | 0.8 % | 1.64 [ 0.99, 2.29 ] |
| Osterborg 1996a | 17 | 2.6 (1.74) | 13 | 1.02 (1.28) | | 0.3 % | 1.58 [ 0.50, 2.66 ] |
| Osterborg 1996b | 27 | 1.71 (1.67) | 14 | 1.02 (1.28) | | 0.4 % | 0.69 [ -0.23, 1.61 ] |
| Osterborg 2002 | 138 | 2.48 (1.74) | 142 | 0.82 (1.4) | | 2.4 % | 1.66 [ 1.29, 2.03 ] |
| Pronzato 2010 | 107 | 1.7 (1.35) | 109 | 0.4 (1.24) | | 2.8 % | 1.30 [ 0.95, 1.65 ] |
| Razzouk 2006 | 111 | 1.3 (2.38) | 111 | 1 (1.9) | | 1.0 % | 0.30 [ -0.27, 0.87 ] |
| Ten Bokkel 1998a | 34 | 0.66 (1.76) | 12 | -0.57 (1.16) | | 0.4 % | 1.23 [ 0.35, 2.11 ] |
| Ten Bokkel 1998b | 27 | 1.04 (1.73) | 12 | -0.57 (1.16) | | 0.4 % | 1.61 [ 0.68, 2.54 ] |
| Thomas 2002 | 62 | 1.9 (1.74) | 65 | 0.39 (1.38) | | 1.1 % | 1.51 [ 0.96, 2.06 ] |
| Thomas 2008 | 52 | 1.72 (1.79) | 57 | 0.09 (1.23) | | 1.0 % | 1.63 [ 1.05, 2.21 ] |
| Throuvalas 2000 | 28 | 0.7 (0.95) | 26 | -0.5 (0.56) | | 1.9 % | 1.20 [ 0.79, 1.61 ] |
| Tjulandin 2010a | 76 | 1.6 (1.42) | 37 | 0.2 (1.74) | | 0.8 % | 1.40 [ 0.75, 2.05 ] |
| Tjulandin 2010b | 73 | 1.9 (1.74) | 37 | 0.2 (1.74) | | 0.7 % | 1.70 [ 1.01, 2.39 ] |
| Tjulandin 2011 | 95 | 2.1 (1.3) | 91 | 0.65 (1.94) | | 1.5 % | 1.45 [ 0.97, 1.93 ] |

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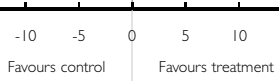
| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Tsuboi 2009 | 61 | 1.4 (1.9) | 56 | -0.8 (1.5) | | 0.9 % | 2.20 [ 1.58, 2.82 ] |
| Wilkinson 2006 | 114 | 1.6 (1.5) | 59 | 0.3 (1.3) | | 1.8 % | 1.30 [ 0.87, 1.73 ] |
| Witzig 2005 | 166 | 2.8 (1.62) | 164 | 0.9 (1.52) | | 2.9 % | 1.90 [ 1.56, 2.24 ] |
| **Subtotal (95% CI)** | **4454** | | **3850** | | | **78.5 %** | **1.69 [ 1.62, 1.75 ]** |
| Heterogeneity: $Chi^2$ = 450.63, df = 56 (P<0.00001); $I^2$ =88% | | | | | | | |
| Test for overall effect: Z = 50.84 (P < 0.00001) | | | | | | | |
| 2 Darbepoetin | | | | | | | |
| Charu 2007 | 220 | 2.1 (1.854) | 55 | 0.1 (0.927) | | 2.8 % | 2.00 [ 1.65, 2.35 ] |
| Gordon 2008 | 139 | 1.3 (1.4) | 49 | 0.2 (1) | | 2.5 % | 1.10 [ 0.74, 1.46 ] |
| Hedenus 2002a | 5 | 1.56 (1.93) | 2 | 1 (0.56) | | 0.1 % | 0.56 [ -1.30, 2.42 ] |
| Hedenus 2002b | 17 | 1.64 (1.25) | 2 | 1 (0.56) | | 0.3 % | 0.64 [ -0.34, 1.62 ] |
| Hedenus 2002c | 14 | 2.46 (1.49) | 2 | 1 (0.56) | | 0.3 % | 1.46 [ 0.36, 2.56 ] |
| Hedenus 2003 | 174 | 1.8 (2.24) | 170 | 0.19 (1.3) | | 2.2 % | 1.61 [ 1.22, 2.00 ] |
| Kotasek 2003a | 32 | 0.54 (1.24) | 8 | -0.02 (1.43) | | 0.3 % | 0.56 [ -0.52, 1.64 ] |
| Kotasek 2003b | 17 | 0.86 (1.57) | 8 | -0.02 (1.43) | | 0.2 % | 0.88 [ -0.36, 2.12 ] |
| Kotasek 2003c | 46 | 0.9 (1.63) | 9 | -0.02 (1.43) | | 0.3 % | 0.92 [ -0.13, 1.97 ] |
| Kotasek 2003d | 28 | 1.63 (2.01) | 8 | -0.02 (1.43) | | 0.2 % | 1.65 [ 0.41, 2.89 ] |
| Kotasek 2003e | 35 | 1.45 (1.42) | 8 | -0.02 (1.43) | | 0.3 % | 1.47 [ 0.37, 2.57 ] |
| Kotasek 2003f | 40 | 1.21 (1.9) | 9 | -0.02 (1.43) | | 0.3 % | 1.23 [ 0.13, 2.33 ] |
| Pirker 2008 | 270 | -1.13 (1.93) | 279 | -1.98 (1.87) | | 3.3 % | 0.85 [ 0.53, 1.17 ] |
| Smith 2003a | 21 | 1.18 (2.01) | 7 | 0 (0.91) | | 0.3 % | 1.18 [ 0.09, 2.27 ] |
| Smith 2003b | 21 | 1.22 (1.62) | 7 | 0 (0.91) | | 0.4 % | 1.22 [ 0.25, 2.19 ] |
| Smith 2003c | 22 | 1.7 (1.93) | 8 | 0 (0.91) | | 0.3 % | 1.70 [ 0.68, 2.72 ] |
| Smith 2008 | 437 | 0.79 (2.83) | 447 | 0.29 (2.8) | | 2.4 % | 0.50 [ 0.13, 0.87 ] |
| Untch 2011˙1 | 330 | -0.07 (2) | 359 | -0.98 (1.33) | | 5.1 % | 0.91 [ 0.65, 1.17 ] |
| **Subtotal (95% CI)** | **1868** | | **1437** | | | **21.5 %** | **1.13 [ 1.00, 1.25 ]** |
| Heterogeneity: $Chi^2$ = 52.43, df = 17 (P = 0.00002); $I^2$ =68% | | | | | | | |
| Test for overall effect: Z = 17.74 (P < 0.00001) | | | | | | | |
| **Total (95% CI)** | **6322** | | **5287** | | | **100.0 %** | **1.57 [ 1.51, 1.62 ]** |
| Heterogeneity: $Chi^2$ = 564.37, df = 74 (P<0.00001); $I^2$ =87% | | | | | | | |
| Test for overall effect: Z = 53.27 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 61.31, df = 1 (P = 0.00), $I^2$ =98% | | | | | | | |



## Analysis 2.9. Comparison 2 Change of haemoglobin level, Outcome 9 Change in Hb values - duration of ESA medication.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 2 Change of haemoglobin level

Outcome: 9 Change in Hb values - duration of ESA medication

| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 6 to 9 weeks | | | | | | | |
| Abels 1993 | 63 | 0.952 (2.142) | 55 | -0.03 (1.36) | | 0.8 % | 0.99 [ 0.35, 1.63 ] |
| Cascinu 1994 | 50 | 1.88 (0.83) | 49 | -0.61 (0.95) | | 2.7 % | 2.49 [ 2.14, 2.84 ] |
| Cazzola 1995a | 31 | -0.1 (2.23) | 7 | -0.04 (2.05) | | 0.1 % | -0.06 [ -1.77, 1.65 ] |
| Cazzola 1995b | 29 | 0.17 (1.72) | 8 | -0.04 (2.05) | | 0.1 % | 0.21 [ -1.34, 1.76 ] |
| Cazzola 1995c | 31 | 0.3 (2.9) | 7 | -0.04 (2.05) | | 0.1 % | 0.34 [ -1.49, 2.17 ] |
| Cazzola 1995d | 26 | 0.44 (2.29) | 7 | -0.04 (2.05) | | 0.1 % | 0.48 [ -1.28, 2.24 ] |
| Gupta 2009 | 58 | 1.55 (0.74) | 57 | -1.5 (0.61) | | 5.4 % | 3.05 [ 2.80, 3.30 ] |
| Henke 1999a | 19 | 3.2 (1.6) | 3 | 0.6 (1.4) | | 0.1 % | 2.60 [ 0.86, 4.34 ] |
| Henke 1999b | 14 | 3.5 (1.2) | 4 | 0.6 (1.4) | | 0.1 % | 2.90 [ 1.39, 4.41 ] |
| Henke 1999c | 6 | 3.9 (2.1) | 4 | 0.6 (1.4) | | 0.1 % | 3.30 [ 1.13, 5.47 ] |
| Henke 2003 Roche 2004 | 178 | 3.4 (1.7) | 168 | 0.9 (1.7) | | 2.6 % | 2.50 [ 2.14, 2.86 ] |
| Italian 1998 | 17 | 1.73 (1.56) | 11 | -0.14 (1.09) | | 0.3 % | 1.87 [ 0.89, 2.85 ] |
| Kunikane 2001a | 16 | 0.89 (1.72) | 10 | -0.65 (1.31) | | 0.2 % | 1.54 [ 0.37, 2.71 ] |
| Kunikane 2001b | 18 | 1.72 (1.1) | 9 | -0.65 (1.31) | | 0.3 % | 2.37 [ 1.37, 3.37 ] |
| Thomas 2008 | 52 | 1.72 (1.79) | 57 | 0.09 (1.23) | | 1.0 % | 1.63 [ 1.05, 2.21 ] |
| Throuvalas 2000 | 28 | 0.7 (0.95) | 26 | -0.5 (0.56) | | 1.9 % | 1.20 [ 0.79, 1.61 ] |
| Tsuboi 2009 | 61 | 1.4 (1.9) | 56 | -0.8 (1.5) | | 0.9 % | 2.20 [ 1.58, 2.82 ] |
| **Subtotal (95% CI)** | **697** | | **538** | | | **17.0 %** | **2.30 [ 2.16, 2.44 ]** |
| Heterogeneity: Chi² = 113.00, df = 16 (P<0.00001); I² =86% | | | | | | | |
| Test for overall effect: Z = 32.31 (P < 0.00001) | | | | | | | |
| 2 12 to 16 weeks | | | | | | | |
| Aravantinos 2003 | 24 | 2.31 (1.22) | 23 | 1.23 (1.59) | | 0.5 % | 1.08 [ 0.27, 1.89 ] |
| Boogaerts 2003 | 133 | 2.1 (1.83) | 129 | 0.9 (1.5) | | 2.0 % | 1.20 [ 0.80, 1.60 ] |
| Case 1993 | 79 | 2.346 (2.04) | 74 | 0.37 (1.46) | | 1.1 % | 1.97 [ 1.41, 2.53 ] |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| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Chang 2005 | 175 | 1.14 (0.8) | 175 | -0.58 (0.73) | | 12.9 % | 1.72 [ 1.56, 1.88 ] |
| Charu 2007 | 220 | 2.1 (1.854) | 55 | 0.1 (0.927) | | 2.8 % | 2.00 [ 1.65, 2.35 ] |
| Christodoulou 2009 | 167 | 2.74 (13.62) | 170 | 0.52 (4.18) | | 0.1 % | 2.22 [ 0.06, 4.38 ] |
| Dammacco 2001 | 69 | 1.8 (2.11) | 76 | -0.2 (1.31) | | 1.0 % | 2.00 [ 1.42, 2.58 ] |
| Del Mastro 1997 | 28 | -0.8 (1.4) | 24 | -3.05 (1) | | 0.8 % | 2.25 [ 1.60, 2.90 ] |
| Fujisaka 2011 | 89 | 1.84 (1.33) | 92 | 0.02 (1.12) | | 2.6 % | 1.82 [ 1.46, 2.18 ] |
| Gebbia 2003 | 22 | -2.4 (1.5) | 23 | -5.1 (1.33) | | 0.5 % | 2.70 [ 1.87, 3.53 ] |
| Gordon 2008 | 139 | 1.3 (1.4) | 49 | 0.2 (1) | | 2.5 % | 1.10 [ 0.74, 1.46 ] |
| Grote 2005 | 64 | -0.2 (1.38) | 58 | -2.9 (1.53) | | 1.2 % | 2.70 [ 2.18, 3.22 ] |
| Hedenus 2002a | 5 | 1.56 (1.93) | 2 | 1 (0.56) | | 0.1 % | 0.56 [ -1.30, 2.42 ] |
| Hedenus 2002b | 17 | 1.64 (1.25) | 2 | 1 (0.56) | | 0.3 % | 0.64 [ -0.34, 1.62 ] |
| Hedenus 2002c | 14 | 2.46 (1.49) | 2 | 1 (0.56) | | 0.3 % | 1.46 [ 0.36, 2.56 ] |
| Hedenus 2003 | 174 | 1.8 (2.24) | 170 | 0.19 (1.3) | | 2.2 % | 1.61 [ 1.22, 2.00 ] |
| Henry 1995 | 63 | 2.04 (2.38) | 61 | 0.44 (1.7) | | 0.6 % | 1.60 [ 0.87, 2.33 ] |
| Hoskin 2009 | 151 | 0.625 (3.5) | 149 | -0.47 (3.48) | | 0.5 % | 1.09 [ 0.30, 1.88 ] |
| Iconomou 2003 | 57 | 1.7 (1.6) | 55 | 0.3 (1.4) | | 1.1 % | 1.40 [ 0.84, 1.96 ] |
| Kotasek 2003a | 32 | 0.54 (1.24) | 8 | -0.02 (1.43) | | 0.3 % | 0.56 [ -0.52, 1.64 ] |
| Kotasek 2003b | 17 | 0.86 (1.57) | 8 | -0.02 (1.43) | | 0.2 % | 0.88 [ -0.36, 2.12 ] |
| Kotasek 2003c | 46 | 0.9 (1.63) | 9 | -0.02 (1.43) | | 0.3 % | 0.92 [ -0.13, 1.97 ] |
| Kotasek 2003d | 28 | 1.63 (2.01) | 8 | -0.02 (1.43) | | 0.2 % | 1.65 [ 0.41, 2.89 ] |
| Kotasek 2003e | 35 | 1.45 (1.42) | 8 | -0.02 (1.43) | | 0.3 % | 1.47 [ 0.37, 2.57 ] |
| Kotasek 2003f | 40 | 1.21 (1.9) | 9 | -0.02 (1.43) | | 0.3 % | 1.23 [ 0.13, 2.33 ] |
| Krzakowski 2008a | 104 | 2.5 (2.4) | 52 | 0.6 (1.7) | | 0.8 % | 1.90 [ 1.25, 2.55 ] |
| Krzakowski 2008b | 105 | 2.5 (2.6) | 52 | 0.6 (1.7) | | 0.7 % | 1.90 [ 1.22, 2.58 ] |
| Kurz 1997 | 23 | 3.26 (1.98) | 12 | 0.25 (1.66) | | 0.2 % | 3.01 [ 1.77, 4.25 ] |
| ML17616 2006 | 30 | 3.09 (2.08) | 30 | 1.76 (2.28) | | 0.3 % | 1.33 [ 0.23, 2.43 ] |
| ML17620 2006 | 61 | 2.12 (1.64) | 60 | 0.59 (1.83) | | 0.9 % | 1.53 [ 0.91, 2.15 ] |
| O'Shaughnessy 2005 | 47 | 0.8 (1.2) | 46 | -2.1 (1.4) | | 1.2 % | 2.90 [ 2.37, 3.43 ] |
| Oberhoff 1998 | 59 | 2.24 (2) | 47 | 0.6 (1.43) | | 0.8 % | 1.64 [ 0.99, 2.29 ] |
| Osterborg 2002 | 138 | 2.48 (1.74) | 142 | 0.82 (1.4) | | 2.4 % | 1.66 [ 1.29, 2.03 ] |
| Razzouk 2006 | 111 | 1.3 (2.38) | 111 | 1 (1.9) | | 1.0 % | 0.30 [ -0.27, 0.87 ] |

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Favours Control Favours Treatment

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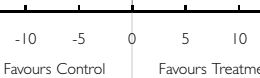
| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Smith 2003a | 21 | 1.18 (2.01) | 7 | 0 (0.91) | | 0.3 % | 1.18 [ 0.09, 2.27 ] |
| Smith 2003b | 21 | 1.22 (1.62) | 7 | 0 (0.91) | | 0.4 % | 1.22 [ 0.25, 2.19 ] |
| Smith 2003c | 22 | 1.7 (1.93) | 8 | 0 (0.91) | | 0.3 % | 1.70 [ 0.68, 2.72 ] |
| Smith 2008 | 437 | 0.79 (2.83) | 447 | 0.29 (2.8) | | 2.4 % | 0.50 [ 0.13, 0.87 ] |
| Thomas 2002 | 62 | 1.9 (1.74) | 65 | 0.39 (1.38) | | 1.1 % | 1.51 [ 0.96, 2.06 ] |
| Tjulandin 2010a | 76 | 1.6 (1.42) | 37 | 0.2 (1.74) | | 0.8 % | 1.40 [ 0.75, 2.05 ] |
| Tjulandin 2010b | 73 | 1.9 (1.74) | 37 | 0.2 (1.74) | | 0.7 % | 1.70 [ 1.01, 2.39 ] |
| Tjulandin 2011 | 95 | 2.1 (1.3) | 91 | 0.65 (1.94) | | 1.5 % | 1.45 [ 0.97, 1.93 ] |
| Witzig 2005 | 166 | 2.8 (1.62) | 164 | 0.9 (1.52) | | 2.9 % | 1.90 [ 1.56, 2.24 ] |
| **Subtotal (95% CI)** | **3539** | | **2854** | | | **53.1 %** | **1.62 [ 1.54, 1.70 ]** |
| Heterogeneity: Chi² = 155.84, df = 42 (P<0.00001); I² =73% | | | | | | | |
| Test for overall effect: Z = 40.16 (P < 0.00001) | | | | | | | |
| 3 more than 17 weeks | | | | | | | |
| Bamias 2003 | 72 | 0.57 (2.12) | 72 | -0.49 (1.36) | | 1.0 % | 1.06 [ 0.48, 1.64 ] |
| Carabantes 1999 | 20 | 1 (1.56) | 15 | -1.7 (1.22) | | 0.4 % | 2.70 [ 1.78, 3.62 ] |
| Engert 2009 | 648 | -1.88 (1.78) | 655 | -2.55 (1.78) | | 8.9 % | 0.67 [ 0.48, 0.86 ] |
| Huddart 2002 | 45 | 2.6 (2) | 45 | 1.2 (1.46) | | 0.6 % | 1.40 [ 0.68, 2.12 ] |
| Leyland-Jones 2005 | 81 | 0.34 (1.73) | 86 | 0.14 (1.7) | | 1.2 % | 0.20 [ -0.32, 0.72 ] |
| Littlewood 2001 | 244 | 2.2 (2.18) | 115 | 0.5 (1.79) | | 1.8 % | 1.70 [ 1.27, 2.13 ] |
| Mystakidou 2005 | 50 | 2.4 (1.3) | 50 | -0.1 (1.02) | | 1.6 % | 2.50 [ 2.04, 2.96 ] |
| Osterborg 1996a | 17 | 2.6 (1.74) | 13 | 1.02 (1.28) | | 0.3 % | 1.58 [ 0.50, 2.66 ] |
| Osterborg 1996b | 27 | 1.71 (1.67) | 14 | 1.02 (1.28) | | 0.4 % | 0.69 [ -0.23, 1.61 ] |
| Pirker 2008 | 270 | -1.13 (1.93) | 279 | -1.98 (1.87) | | 3.3 % | 0.85 [ 0.53, 1.17 ] |
| Pronzato 2010 | 107 | 1.7 (1.35) | 109 | 0.4 (1.24) | | 2.8 % | 1.30 [ 0.95, 1.65 ] |
| Ten Bokkel 1998a | 34 | 0.66 (1.76) | 12 | -0.57 (1.16) | | 0.4 % | 1.23 [ 0.35, 2.11 ] |
| Ten Bokkel 1998b | 27 | 1.04 (1.73) | 12 | -0.57 (1.16) | | 0.4 % | 1.61 [ 0.68, 2.54 ] |
| Untch 2011˙1 | 330 | -0.07 (2) | 359 | -0.98 (1.33) | | 5.1 % | 0.91 [ 0.65, 1.17 ] |
| Wilkinson 2006 | 114 | 1.6 (1.5) | 59 | 0.3 (1.3) | | 1.8 % | 1.30 [ 0.87, 1.73 ] |
| **Subtotal (95% CI)** | **2086** | | **1895** | | | **29.9 %** | **1.05 [ 0.95, 1.16 ]** |
| Heterogeneity: Chi² = 94.78, df = 14 (P<0.00001); I² =85% | | | | | | | |
| Test for overall effect: Z = 19.55 (P < 0.00001) | | | | | | | |
| **Total (95% CI)** | **6322** | | **5287** | | | **100.0 %** | **1.57 [ 1.51, 1.62 ]** |
| Heterogeneity: Chi² = 564.37, df = 74 (P<0.00001); I² =87% | | | | | | | |
| Test for overall effect: Z = 53.27 (P < 0.00001) | | | | | | | |

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| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Test for subgroup differences: $Chi^2$ = 200.75, df = 2 (P = 0.00), $I^2$ =99% | | | | | | | |

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Favours Control Favours Treatment

## Analysis 2.10. Comparison 2 Change of haemoglobin level, Outcome 10 Change in Hb values - iron supplementation.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 2 Change of haemoglobin level

Outcome: 10 Change in Hb values - iron supplementation

| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 fixed iron supplementation | | | | | | | |
| Aravantinos 2003 | 24 | 2.31 (1.22) | 23 | 1.23 (1.59) | | 0.5 % | 1.08 [ 0.27, 1.89 ] |
| Christodoulou 2009 | 167 | 2.74 (13.62) | 170 | 0.52 (4.18) | | 0.1 % | 2.22 [ 0.06, 4.38 ] |
| Gupta 2009 | 58 | 1.55 (0.74) | 57 | -1.5 (0.61) | | 5.4 % | 3.05 [ 2.80, 3.30 ] |
| Henke 1999a | 19 | 3.2 (1.6) | 3 | 0.6 (1.4) | | 0.1 % | 2.60 [ 0.86, 4.34 ] |
| Henke 1999b | 14 | 3.5 (1.2) | 4 | 0.6 (1.4) | | 0.1 % | 2.90 [ 1.39, 4.41 ] |
| Henke 1999c | 6 | 3.9 (2.1) | 4 | 0.6 (1.4) | | 0.1 % | 3.30 [ 1.13, 5.47 ] |
| Hoskin 2009 | 151 | 0.625 (3.5) | 149 | -0.47 (3.48) | | 0.5 % | 1.09 [ 0.30, 1.88 ] |
| Huddart 2002 | 45 | 2.6 (2) | 45 | 1.2 (1.46) | | 0.6 % | 1.40 [ 0.68, 2.12 ] |
| Iconomou 2003 | 57 | 1.7 (1.6) | 55 | 0.3 (1.4) | | 1.1 % | 1.40 [ 0.84, 1.96 ] |
| Krzakowski 2008a | 104 | 2.5 (2.4) | 52 | 0.6 (1.7) | | 0.8 % | 1.90 [ 1.25, 2.55 ] |
| Krzakowski 2008b | 105 | 2.5 (2.6) | 52 | 0.6 (1.7) | | 0.7 % | 1.90 [ 1.22, 2.58 ] |
| Mystakidou 2005 | 50 | 2.4 (1.3) | 50 | -0.1 (1.02) | | 1.6 % | 2.50 [ 2.04, 2.96 ] |
| Untch 2011˙1 | 330 | -0.07 (2) | 359 | -0.98 (1.33) | | 5.1 % | 0.91 [ 0.65, 1.17 ] |

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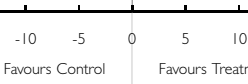
Favours Control Favours Treatment

(*Continued* . . . )

(. . . *Continued*)

| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Witzig 2005 | 166 | 2.8 (1.62) | 164 | 0.9 (1.52) | | 2.9 % | 1.90 [ 1.56, 2.24 ] |
| **Subtotal (95% CI)** | **1296** | | **1187** | | | **19.6 %** | **1.94 [ 1.81, 2.07 ]** |
| Heterogeneity: $Chi^2$ = 163.36, df = 13 (P<0.00001); $I^2$ =92% | | | | | | | |
| Test for overall effect: Z = 29.23 (P < 0.00001) | | | | | | | |
| 2 iron supplementation as necessary | | | | | | | |
| Abels 1993 | 63 | 0.952 (2.142) | 55 | -0.03 (1.36) | | 0.8 % | 0.99 [ 0.35, 1.63 ] |
| Boogaerts 2003 | 133 | 2.1 (1.83) | 129 | 0.9 (1.5) | | 2.0 % | 1.20 [ 0.80, 1.60 ] |
| Cascinu 1994 | 50 | 1.88 (0.83) | 49 | -0.61 (0.95) | | 2.7 % | 2.49 [ 2.14, 2.84 ] |
| Case 1993 | 79 | 2.346 (2.04) | 74 | 0.37 (1.46) | | 1.1 % | 1.97 [ 1.41, 2.53 ] |
| Cazzola 1995a | 31 | -0.1 (2.23) | 7 | -0.04 (2.05) | | 0.1 % | -0.06 [ -1.77, 1.65 ] |
| Cazzola 1995b | 29 | 0.17 (1.72) | 8 | -0.04 (2.05) | | 0.1 % | 0.21 [ -1.34, 1.76 ] |
| Cazzola 1995c | 31 | 0.3 (2.9) | 7 | -0.04 (2.05) | | 0.1 % | 0.34 [ -1.49, 2.17 ] |
| Cazzola 1995d | 26 | 0.44 (2.29) | 7 | -0.04 (2.05) | | 0.1 % | 0.48 [ -1.28, 2.24 ] |
| Chang 2005 | 175 | 1.14 (0.8) | 175 | -0.58 (0.73) | | 12.9 % | 1.72 [ 1.56, 1.88 ] |
| Charu 2007 | 220 | 2.1 (1.854) | 55 | 0.1 (0.927) | | 2.8 % | 2.00 [ 1.65, 2.35 ] |
| Dammacco 2001 | 69 | 1.8 (2.11) | 76 | -0.2 (1.31) | | 1.0 % | 2.00 [ 1.42, 2.58 ] |
| Del Mastro 1997 | 28 | -0.8 (1.4) | 24 | -3.05 (1) | | 0.8 % | 2.25 [ 1.60, 2.90 ] |
| Engert 2009 | 648 | -1.88 (1.78) | 655 | -2.55 (1.78) | | 8.9 % | 0.67 [ 0.48, 0.86 ] |
| Fujisaka 2011 | 89 | 1.84 (1.33) | 92 | 0.02 (1.12) | | 2.6 % | 1.82 [ 1.46, 2.18 ] |
| Gordon 2008 | 139 | 1.3 (1.4) | 49 | 0.2 (1) | | 2.5 % | 1.10 [ 0.74, 1.46 ] |
| Grote 2005 | 64 | -0.2 (1.38) | 58 | -2.9 (1.53) | | 1.2 % | 2.70 [ 2.18, 3.22 ] |
| Hedenus 2003 | 174 | 1.8 (2.24) | 170 | 0.19 (1.3) | | 2.2 % | 1.61 [ 1.22, 2.00 ] |
| Henke 2003 Roche 2004 | 178 | 3.4 (1.7) | 168 | 0.9 (1.7) | | 2.6 % | 2.50 [ 2.14, 2.86 ] |
| Henry 1995 | 63 | 2.04 (2.38) | 61 | 0.44 (1.7) | | 0.6 % | 1.60 [ 0.87, 2.33 ] |
| Italian 1998 | 17 | 1.73 (1.56) | 11 | -0.14 (1.09) | | 0.3 % | 1.87 [ 0.89, 2.85 ] |
| Kotasek 2003a | 32 | 0.54 (1.24) | 8 | -0.02 (1.43) | | 0.3 % | 0.56 [ -0.52, 1.64 ] |
| Kotasek 2003b | 17 | 0.86 (1.57) | 8 | -0.02 (1.43) | | 0.2 % | 0.88 [ -0.36, 2.12 ] |
| Kotasek 2003c | 46 | 0.9 (1.63) | 9 | -0.02 (1.43) | | 0.3 % | 0.92 [ -0.13, 1.97 ] |
| Kotasek 2003d | 28 | 1.63 (2.01) | 8 | -0.02 (1.43) | | 0.2 % | 1.65 [ 0.41, 2.89 ] |
| Kotasek 2003e | 35 | 1.45 (1.42) | 8 | -0.02 (1.43) | | 0.3 % | 1.47 [ 0.37, 2.57 ] |
| Kotasek 2003f | 40 | 1.21 (1.9) | 9 | -0.02 (1.43) | | 0.3 % | 1.23 [ 0.13, 2.33 ] |
| Kurz 1997 | 23 | 3.26 (1.98) | 12 | 0.25 (1.66) | | 0.2 % | 3.01 [ 1.77, 4.25 ] |




(*Continued* . . . )

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| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Leyland-Jones 2005 | 81 | 0.34 (1.73) | 86 | 0.14 (1.7) | | 1.2 % | 0.20 [ -0.32, 0.72 ] |
| Littlewood 2001 | 244 | 2.2 (2.18) | 115 | 0.5 (1.79) | | 1.8 % | 1.70 [ 1.27, 2.13 ] |
| ML17616 2006 | 30 | 3.09 (2.08) | 30 | 1.76 (2.28) | | 0.3 % | 1.33 [ 0.23, 2.43 ] |
| ML17620 2006 | 61 | 2.12 (1.64) | 60 | 0.59 (1.83) | | 0.9 % | 1.53 [ 0.91, 2.15 ] |
| O'Shaughnessy 2005 | 47 | 0.8 (1.2) | 46 | -2.1 (1.4) | | 1.2 % | 2.90 [ 2.37, 3.43 ] |
| Oberhoff 1998 | 59 | 2.24 (2) | 47 | 0.6 (1.43) | | 0.8 % | 1.64 [ 0.99, 2.29 ] |
| Osterborg 1996a | 17 | 2.6 (1.74) | 13 | 1.02 (1.28) | | 0.3 % | 1.58 [ 0.50, 2.66 ] |
| Osterborg 1996b | 27 | 1.71 (1.67) | 14 | 1.02 (1.28) | | 0.4 % | 0.69 [ -0.23, 1.61 ] |
| Osterborg 2002 | 138 | 2.48 (1.74) | 142 | 0.82 (1.4) | | 2.4 % | 1.66 [ 1.29, 2.03 ] |
| Pirker 2008 | 270 | -1.13 (1.93) | 279 | -1.98 (1.87) | | 3.3 % | 0.85 [ 0.53, 1.17 ] |
| Pronzato 2010 | 107 | 1.7 (1.35) | 109 | 0.4 (1.24) | | 2.8 % | 1.30 [ 0.95, 1.65 ] |
| Razzouk 2006 | 111 | 1.3 (2.38) | 111 | 1 (1.9) | | 1.0 % | 0.30 [ -0.27, 0.87 ] |
| Smith 2003a | 21 | 1.18 (2.01) | 7 | 0 (0.91) | | 0.3 % | 1.18 [ 0.09, 2.27 ] |
| Smith 2003b | 21 | 1.22 (1.62) | 7 | 0 (0.91) | | 0.4 % | 1.22 [ 0.25, 2.19 ] |
| Smith 2003c | 22 | 1.7 (1.93) | 8 | 0 (0.91) | | 0.3 % | 1.70 [ 0.68, 2.72 ] |
| Smith 2008 | 437 | 0.79 (2.83) | 447 | 0.29 (2.8) | | 2.4 % | 0.50 [ 0.13, 0.87 ] |
| Ten Bokkel 1998a | 34 | 0.66 (1.76) | 12 | -0.57 (1.16) | | 0.4 % | 1.23 [ 0.35, 2.11 ] |
| Ten Bokkel 1998b | 27 | 1.04 (1.73) | 12 | -0.57 (1.16) | | 0.4 % | 1.61 [ 0.68, 2.54 ] |
| Thomas 2002 | 62 | 1.9 (1.74) | 65 | 0.39 (1.38) | | 1.1 % | 1.51 [ 0.96, 2.06 ] |
| Thomas 2008 | 52 | 1.72 (1.79) | 57 | 0.09 (1.23) | | 1.0 % | 1.63 [ 1.05, 2.21 ] |
| Throuvalas 2000 | 28 | 0.7 (0.95) | 26 | -0.5 (0.56) | | 1.9 % | 1.20 [ 0.79, 1.61 ] |
| Tjulandin 2010a | 76 | 1.6 (1.42) | 37 | 0.2 (1.74) | | 0.8 % | 1.40 [ 0.75, 2.05 ] |
| Tjulandin 2010b | 73 | 1.9 (1.74) | 37 | 0.2 (1.74) | | 0.7 % | 1.70 [ 1.01, 2.39 ] |
| Tjulandin 2011 | 95 | 2.1 (1.3) | 91 | 0.65 (1.94) | | 1.5 % | 1.45 [ 0.97, 1.93 ] |
| Tsuboi 2009 | 61 | 1.4 (1.9) | 56 | -0.8 (1.5) | | 0.9 % | 2.20 [ 1.58, 2.82 ] |
| Wilkinson 2006 | 114 | 1.6 (1.5) | 59 | 0.3 (1.3) | | 1.8 % | 1.30 [ 0.87, 1.73 ] |
| **Subtotal (95% CI)** | **4842** | | **3965** | | | **77.3 %** | **1.47 [ 1.40, 1.53 ]** |
| Heterogeneity: $Chi^2$ = 337.12, df = 52 (P<0.00001); $I^2$ =85% | | | | | | | |
| Test for overall effect: Z = 43.87 (P < 0.00001) | | | | | | | |
| 3 no explicit statement on iron supplementation or no iron given | | | | | | | |
| Bamias 2003 | 72 | 0.57 (2.12) | 72 | -0.49 (1.36) | | 1.0 % | 1.06 [ 0.48, 1.64 ] |
| Carabantes 1999 | 20 | 1 (1.56) | 15 | -1.7 (1.22) | | 0.4 % | 2.70 [ 1.78, 3.62 ] |

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Favours Control Favours Treatment

(*Continued* . . . )

(. . . *Continued*)

| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Gebbia 2003 | 22 | -2.4 (1.5) | 23 | -5.1 (1.33) | | 0.5 % | 2.70 [ 1.87, 3.53 ] |
| Hedenus 2002a | 5 | 1.56 (1.93) | 2 | 1 (0.56) | | 0.1 % | 0.56 [ -1.30, 2.42 ] |
| Hedenus 2002b | 17 | 1.64 (1.25) | 2 | 1 (0.56) | | 0.3 % | 0.64 [ -0.34, 1.62 ] |
| Hedenus 2002c | 14 | 2.46 (1.49) | 2 | 1 (0.56) | | 0.3 % | 1.46 [ 0.36, 2.56 ] |
| Kunikane 2001a | 16 | 0.89 (1.72) | 10 | -0.65 (1.31) | | 0.2 % | 1.54 [ 0.37, 2.71 ] |
| Kunikane 2001b | 18 | 1.72 (1.1) | 9 | -0.65 (1.31) | | 0.3 % | 2.37 [ 1.37, 3.37 ] |
| **Subtotal (95% CI)** | **184** | | **135** | | | **3.1 %** | **1.66 [ 1.34, 1.99 ]** |
| Heterogeneity: $Chi^2$ = 22.66, df = 7 (P = 0.002); $I^2$ =69% | | | | | | | |
| Test for overall effect: Z = 10.05 (P < 0.00001) | | | | | | | |
| 4 explicitly stated no iron new | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| 5 iron given differently in both study arms new ongoing | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| **Total (95% CI)** | **6322** | | **5287** | | | **100.0 %** | **1.57 [ 1.51, 1.62 ]** |
| Heterogeneity: $Chi^2$ = 564.37, df = 74 (P<0.00001); $I^2$ =87% | | | | | | | |
| Test for overall effect: Z = 53.27 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 41.22, df = 2 (P = 0.00), $I^2$ =95% | | | | | | | |

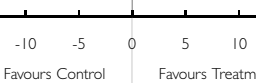
## Analysis 2.11. Comparison 2 Change of haemoglobin level, Outcome 11 Change in Hb values - allocation concealment.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 2 Change of haemoglobin level

Outcome: 11 Change in Hb values - allocation concealment

| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 adequate | | | | | | | |
| Boogaerts 2003 | 133 | 2.1 (1.83) | 129 | 0.9 (1.5) | | 2.0 % | 1.20 [ 0.80, 1.60 ] |
| Cazzola 1995a | 31 | -0.1 (2.23) | 7 | -0.04 (2.05) | | 0.1 % | -0.06 [ -1.77, 1.65 ] |
| Cazzola 1995b | 29 | 0.17 (1.72) | 8 | -0.04 (2.05) | | 0.1 % | 0.21 [ -1.34, 1.76 ] |
| Cazzola 1995c | 31 | 0.3 (2.9) | 7 | -0.04 (2.05) | | 0.1 % | 0.34 [ -1.49, 2.17 ] |
| Cazzola 1995d | 26 | 0.44 (2.29) | 7 | -0.04 (2.05) | | 0.1 % | 0.48 [ -1.28, 2.24 ] |
| Chang 2005 | 175 | 1.14 (0.8) | 175 | -0.58 (0.73) | | 12.9 % | 1.72 [ 1.56, 1.88 ] |
| Charu 2007 | 220 | 2.1 (1.854) | 55 | 0.1 (0.927) | | 2.8 % | 2.00 [ 1.65, 2.35 ] |
| Christodoulou 2009 | 167 | 2.74 (13.62) | 170 | 0.52 (4.18) | | 0.1 % | 2.22 [ 0.06, 4.38 ] |
| Del Mastro 1997 | 28 | -0.8 (1.4) | 24 | -3.05 (1) | | 0.8 % | 2.25 [ 1.60, 2.90 ] |
| Fujisaka 2011 | 89 | 1.84 (1.33) | 92 | 0.02 (1.12) | | 2.6 % | 1.82 [ 1.46, 2.18 ] |
| Gordon 2008 | 139 | 1.3 (1.4) | 49 | 0.2 (1) | | 2.5 % | 1.10 [ 0.74, 1.46 ] |
| Hedenus 2002a | 5 | 1.56 (1.93) | 2 | 1 (0.56) | | 0.1 % | 0.56 [ -1.30, 2.42 ] |
| Hedenus 2002b | 17 | 1.64 (1.25) | 2 | 1 (0.56) | | 0.3 % | 0.64 [ -0.34, 1.62 ] |
| Hedenus 2002c | 14 | 2.46 (1.49) | 2 | 1 (0.56) | | 0.3 % | 1.46 [ 0.36, 2.56 ] |
| Hedenus 2003 | 174 | 1.8 (2.24) | 170 | 0.19 (1.3) | | 2.2 % | 1.61 [ 1.22, 2.00 ] |
| Henke 2003 Roche 2004 | 178 | 3.4 (1.7) | 168 | 0.9 (1.7) | | 2.6 % | 2.50 [ 2.14, 2.86 ] |
| Iconomou 2003 | 57 | 1.7 (1.6) | 55 | 0.3 (1.4) | | 1.1 % | 1.40 [ 0.84, 1.96 ] |
| Italian 1998 | 17 | 1.73 (1.56) | 11 | -0.14 (1.09) | | 0.3 % | 1.87 [ 0.89, 2.85 ] |
| Kotasek 2003a | 32 | 0.54 (1.24) | 8 | -0.02 (1.43) | | 0.3 % | 0.56 [ -0.52, 1.64 ] |
| Kotasek 2003b | 17 | 0.86 (1.57) | 8 | -0.02 (1.43) | | 0.2 % | 0.88 [ -0.36, 2.12 ] |
| Kotasek 2003c | 46 | 0.9 (1.63) | 9 | -0.02 (1.43) | | 0.3 % | 0.92 [ -0.13, 1.97 ] |
| Kotasek 2003d | 28 | 1.63 (2.01) | 8 | -0.02 (1.43) | | 0.2 % | 1.65 [ 0.41, 2.89 ] |
| Kotasek 2003e | 35 | 1.45 (1.42) | 8 | -0.02 (1.43) | | 0.3 % | 1.47 [ 0.37, 2.57 ] |
| Kotasek 2003f | 40 | 1.21 (1.9) | 9 | -0.02 (1.43) | | 0.3 % | 1.23 [ 0.13, 2.33 ] |

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(. . . *Continued*)

| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Kunikane 2001a | 16 | 0.89 (1.72) | 10 | -0.65 (1.31) | | 0.2 % | 1.54 [ 0.37, 2.71 ] |
| Kunikane 2001b | 18 | 1.72 (1.1) | 9 | -0.65 (1.31) | | 0.3 % | 2.37 [ 1.37, 3.37 ] |
| Kurz 1997 | 23 | 3.26 (1.98) | 12 | 0.25 (1.66) | | 0.2 % | 3.01 [ 1.77, 4.25 ] |
| Leyland-Jones 2005 | 81 | 0.34 (1.73) | 86 | 0.14 (1.7) | | 1.2 % | 0.20 [ -0.32, 0.72 ] |
| Littlewood 2001 | 244 | 2.2 (2.18) | 115 | 0.5 (1.79) | | 1.8 % | 1.70 [ 1.27, 2.13 ] |
| O'Shaughnessy 2005 | 47 | 0.8 (1.2) | 46 | -2.1 (1.4) | | 1.2 % | 2.90 [ 2.37, 3.43 ] |
| Oberhoff 1998 | 59 | 2.24 (2) | 47 | 0.6 (1.43) | | 0.8 % | 1.64 [ 0.99, 2.29 ] |
| Osterborg 1996a | 17 | 2.6 (1.74) | 13 | 1.02 (1.28) | | 0.3 % | 1.58 [ 0.50, 2.66 ] |
| Osterborg 1996b | 27 | 1.71 (1.67) | 14 | 1.02 (1.28) | | 0.4 % | 0.69 [ -0.23, 1.61 ] |
| Osterborg 2002 | 138 | 2.48 (1.74) | 142 | 0.82 (1.4) | | 2.4 % | 1.66 [ 1.29, 2.03 ] |
| Pirker 2008 | 270 | -1.13 (1.93) | 279 | -1.98 (1.87) | | 3.3 % | 0.85 [ 0.53, 1.17 ] |
| Pronzato 2010 | 107 | 1.7 (1.35) | 109 | 0.4 (1.24) | | 2.8 % | 1.30 [ 0.95, 1.65 ] |
| Razzouk 2006 | 111 | 1.3 (2.38) | 111 | 1 (1.9) | | 1.0 % | 0.30 [ -0.27, 0.87 ] |
| Smith 2008 | 437 | 0.79 (2.83) | 447 | 0.29 (2.8) | | 2.4 % | 0.50 [ 0.13, 0.87 ] |
| Ten Bokkel 1998a | 34 | 0.66 (1.76) | 12 | -0.57 (1.16) | | 0.4 % | 1.23 [ 0.35, 2.11 ] |
| Ten Bokkel 1998b | 27 | 1.04 (1.73) | 12 | -0.57 (1.16) | | 0.4 % | 1.61 [ 0.68, 2.54 ] |
| Thomas 2002 | 62 | 1.9 (1.74) | 65 | 0.39 (1.38) | | 1.1 % | 1.51 [ 0.96, 2.06 ] |
| Thomas 2008 | 52 | 1.72 (1.79) | 57 | 0.09 (1.23) | | 1.0 % | 1.63 [ 1.05, 2.21 ] |
| Throuvalas 2000 | 28 | 0.7 (0.95) | 26 | -0.5 (0.56) | | 1.9 % | 1.20 [ 0.79, 1.61 ] |
| Tsuboi 2009 | 61 | 1.4 (1.9) | 56 | -0.8 (1.5) | | 0.9 % | 2.20 [ 1.58, 2.82 ] |
| Witzig 2005 | 166 | 2.8 (1.62) | 164 | 0.9 (1.52) | | 2.9 % | 1.90 [ 1.56, 2.24 ] |
| **Subtotal (95% CI)** | **3753** | | **3015** | | | **59.5 %** | **1.52 [ 1.45, 1.60 ]** |
| Heterogeneity: $Chi^2$ = 218.40, df = 44 (P<0.00001); $I^2$ =80% | | | | | | | |
| Test for overall effect: Z = 40.04 (P < 0.00001) | | | | | | | |
| 2 unclear | | | | | | | |
| Abels 1993 | 63 | 0.952 (2.142) | 55 | -0.03 (1.36) | | 0.8 % | 0.99 [ 0.35, 1.63 ] |
| Aravantinos 2003 | 24 | 2.31 (1.22) | 23 | 1.23 (1.59) | | 0.5 % | 1.08 [ 0.27, 1.89 ] |
| Bamias 2003 | 72 | 0.57 (2.12) | 72 | -0.49 (1.36) | | 1.0 % | 1.06 [ 0.48, 1.64 ] |
| Carabantes 1999 | 20 | 1 (1.56) | 15 | -1.7 (1.22) | | 0.4 % | 2.70 [ 1.78, 3.62 ] |
| Cascinu 1994 | 50 | 1.88 (0.83) | 49 | -0.61 (0.95) | | 2.7 % | 2.49 [ 2.14, 2.84 ] |
| Case 1993 | 79 | 2.346 (2.04) | 74 | 0.37 (1.46) | | 1.1 % | 1.97 [ 1.41, 2.53 ] |
| Dammacco 2001 | 69 | 1.8 (2.11) | 76 | -0.2 (1.31) | | 1.0 % | 2.00 [ 1.42, 2.58 ] |

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Favours Control Favours Treatment

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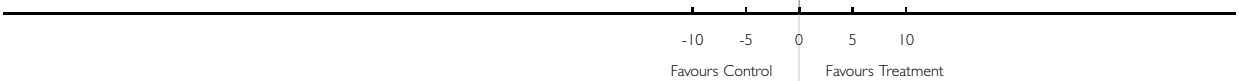
| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Engert 2009 | 648 | -1.88 (1.78) | 655 | -2.55 (1.78) | | 8.9 % | 0.67 [ 0.48, 0.86 ] |
| Gebbia 2003 | 22 | -2.4 (1.5) | 23 | -5.1 (1.33) | | 0.5 % | 2.70 [ 1.87, 3.53 ] |
| Grote 2005 | 64 | -0.2 (1.38) | 58 | -2.9 (1.53) | | 1.2 % | 2.70 [ 2.18, 3.22 ] |
| Gupta 2009 | 58 | 1.55 (0.74) | 57 | -1.5 (0.61) | | 5.4 % | 3.05 [ 2.80, 3.30 ] |
| Henke 1999a | 19 | 3.2 (1.6) | 3 | 0.6 (1.4) | | 0.1 % | 2.60 [ 0.86, 4.34 ] |
| Henke 1999b | 14 | 3.5 (1.2) | 4 | 0.6 (1.4) | | 0.1 % | 2.90 [ 1.39, 4.41 ] |
| Henke 1999c | 6 | 3.9 (2.1) | 4 | 0.6 (1.4) | | 0.1 % | 3.30 [ 1.13, 5.47 ] |
| Henry 1995 | 63 | 2.04 (2.38) | 61 | 0.44 (1.7) | | 0.6 % | 1.60 [ 0.87, 2.33 ] |
| Hoskin 2009 | 151 | 0.625 (3.5) | 149 | -0.47 (3.48) | | 0.5 % | 1.09 [ 0.30, 1.88 ] |
| Huddart 2002 | 45 | 2.6 (2) | 45 | 1.2 (1.46) | | 0.6 % | 1.40 [ 0.68, 2.12 ] |
| Krzakowski 2008a | 104 | 2.5 (2.4) | 52 | 0.6 (1.7) | | 0.8 % | 1.90 [ 1.25, 2.55 ] |
| Krzakowski 2008b | 105 | 2.5 (2.6) | 52 | 0.6 (1.7) | | 0.7 % | 1.90 [ 1.22, 2.58 ] |
| ML17616 2006 | 30 | 3.09 (2.08) | 30 | 1.76 (2.28) | | 0.3 % | 1.33 [ 0.23, 2.43 ] |
| ML17620 2006 | 61 | 2.12 (1.64) | 60 | 0.59 (1.83) | | 0.9 % | 1.53 [ 0.91, 2.15 ] |
| Mystakidou 2005 | 50 | 2.4 (1.3) | 50 | -0.1 (1.02) | | 1.6 % | 2.50 [ 2.04, 2.96 ] |
| Smith 2003a | 21 | 1.18 (2.01) | 7 | 0 (0.91) | | 0.3 % | 1.18 [ 0.09, 2.27 ] |
| Smith 2003b | 21 | 1.22 (1.62) | 7 | 0 (0.91) | | 0.4 % | 1.22 [ 0.25, 2.19 ] |
| Smith 2003c | 22 | 1.7 (1.93) | 8 | 0 (0.91) | | 0.3 % | 1.70 [ 0.68, 2.72 ] |
| Tjulandin 2010a | 76 | 1.6 (1.42) | 37 | 0.2 (1.74) | | 0.8 % | 1.40 [ 0.75, 2.05 ] |
| Tjulandin 2010b | 73 | 1.9 (1.74) | 37 | 0.2 (1.74) | | 0.7 % | 1.70 [ 1.01, 2.39 ] |
| Tjulandin 2011 | 95 | 2.1 (1.3) | 91 | 0.65 (1.94) | | 1.5 % | 1.45 [ 0.97, 1.93 ] |
| Untch 2011˙1 | 330 | -0.07 (2) | 359 | -0.98 (1.33) | | 5.1 % | 0.91 [ 0.65, 1.17 ] |
| Wilkinson 2006 | 114 | 1.6 (1.5) | 59 | 0.3 (1.3) | | 1.8 % | 1.30 [ 0.87, 1.73 ] |
| **Subtotal (95% CI)** | **2569** | | **2272** | | | **40.5 %** | **1.62 [ 1.53, 1.71 ]** |
| Heterogeneity: $Chi^2$ = 343.18, df = 29 (P<0.00001); $I^2$ =92% | | | | | | | |
| Test for overall effect: Z = 35.18 (P < 0.00001) | | | | | | | |
| **Total (95% CI)** | **6322** | | **5287** | | | **100.0 %** | **1.57 [ 1.51, 1.62 ]** |
| Heterogeneity: $Chi^2$ = 564.37, df = 74 (P<0.00001); $I^2$ =87% | | | | | | | |
| Test for overall effect: Z = 53.27 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 2.78, df = 1 (P = 0.10), $I^2$ =64% | | | | | | | |



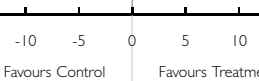
## Analysis 2.12. Comparison 2 Change of haemoglobin level, Outcome 12 Change in Hb values - masking.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 2 Change of haemoglobin level

Outcome: 12 Change in Hb values - masking

| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 double-blind | | | | | | | |
| Abels 1993 | 63 | 0.952 (2.142) | 55 | -0.03 (1.36) | | 0.8 % | 0.99 [ 0.35, 1.63 ] |
| Cascinu 1994 | 50 | 1.88 (0.83) | 49 | -0.61 (0.95) | | 2.7 % | 2.49 [ 2.14, 2.84 ] |
| Case 1993 | 79 | 2.346 (2.04) | 74 | 0.37 (1.46) | | 1.1 % | 1.97 [ 1.41, 2.53 ] |
| Dammacco 2001 | 69 | 1.8 (2.11) | 76 | -0.2 (1.31) | | 1.0 % | 2.00 [ 1.42, 2.58 ] |
| Engert 2009 | 648 | -1.88 (1.78) | 655 | -2.55 (1.78) | | 8.9 % | 0.67 [ 0.48, 0.86 ] |
| Fujisaka 2011 | 89 | 1.84 (1.33) | 92 | 0.02 (1.12) | | 2.6 % | 1.82 [ 1.46, 2.18 ] |
| Gordon 2008 | 139 | 1.3 (1.4) | 49 | 0.2 (1) | | 2.5 % | 1.10 [ 0.74, 1.46 ] |
| Grote 2005 | 64 | -0.2 (1.38) | 58 | -2.9 (1.53) | | 1.2 % | 2.70 [ 2.18, 3.22 ] |
| Hedenus 2002a | 5 | 1.56 (1.93) | 2 | 1 (0.56) | | 0.1 % | 0.56 [ -1.30, 2.42 ] |
| Hedenus 2002b | 17 | 1.64 (1.25) | 2 | 1 (0.56) | | 0.3 % | 0.64 [ -0.34, 1.62 ] |
| Hedenus 2002c | 14 | 2.46 (1.49) | 2 | 1 (0.56) | | 0.3 % | 1.46 [ 0.36, 2.56 ] |
| Hedenus 2003 | 174 | 1.8 (2.24) | 170 | 0.19 (1.3) | | 2.2 % | 1.61 [ 1.22, 2.00 ] |
| Henke 2003 Roche 2004 | 178 | 3.4 (1.7) | 168 | 0.9 (1.7) | | 2.6 % | 2.50 [ 2.14, 2.86 ] |
| Henry 1995 | 63 | 2.04 (2.38) | 61 | 0.44 (1.7) | | 0.6 % | 1.60 [ 0.87, 2.33 ] |
| Italian 1998 | 17 | 1.73 (1.56) | 11 | -0.14 (1.09) | | 0.3 % | 1.87 [ 0.89, 2.85 ] |
| Kotasek 2003a | 32 | 0.54 (1.24) | 8 | -0.02 (1.43) | | 0.3 % | 0.56 [ -0.52, 1.64 ] |
| Kotasek 2003b | 17 | 0.86 (1.57) | 8 | -0.02 (1.43) | | 0.2 % | 0.88 [ -0.36, 2.12 ] |
| Kotasek 2003c | 46 | 0.9 (1.63) | 9 | -0.02 (1.43) | | 0.3 % | 0.92 [ -0.13, 1.97 ] |
| Kotasek 2003d | 28 | 1.63 (2.01) | 8 | -0.02 (1.43) | | 0.2 % | 1.65 [ 0.41, 2.89 ] |
| Kotasek 2003e | 35 | 1.45 (1.42) | 8 | -0.02 (1.43) | | 0.3 % | 1.47 [ 0.37, 2.57 ] |
| Kotasek 2003f | 40 | 1.21 (1.9) | 9 | -0.02 (1.43) | | 0.3 % | 1.23 [ 0.13, 2.33 ] |
| Krzakowski 2008a | 104 | 2.5 (2.4) | 52 | 0.6 (1.7) | | 0.8 % | 1.90 [ 1.25, 2.55 ] |
| Krzakowski 2008b | 105 | 2.5 (2.6) | 52 | 0.6 (1.7) | | 0.7 % | 1.90 [ 1.22, 2.58 ] |
| Kunikane 2001a | 16 | 0.89 (1.72) | 10 | -0.65 (1.31) | | 0.2 % | 1.54 [ 0.37, 2.71 ] |

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| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Kunikane 2001b | 18 | 1.72 (1.1) | 9 | -0.65 (1.31) | | 0.3 % | 2.37 [ 1.37, 3.37 ] |
| Kurz 1997 | 23 | 3.26 (1.98) | 12 | 0.25 (1.66) | | 0.2 % | 3.01 [ 1.77, 4.25 ] |
| Leyland-Jones 2005 | 81 | 0.34 (1.73) | 86 | 0.14 (1.7) | | 1.2 % | 0.20 [ -0.32, 0.72 ] |
| Littlewood 2001 | 244 | 2.2 (2.18) | 115 | 0.5 (1.79) | | 1.8 % | 1.70 [ 1.27, 2.13 ] |
| Mystakidou 2005 | 50 | 2.4 (1.3) | 50 | -0.1 (1.02) | | 1.6 % | 2.50 [ 2.04, 2.96 ] |
| O'Shaughnessy 2005 | 47 | 0.8 (1.2) | 46 | -2.1 (1.4) | | 1.2 % | 2.90 [ 2.37, 3.43 ] |
| Osterborg 2002 | 138 | 2.48 (1.74) | 142 | 0.82 (1.4) | | 2.4 % | 1.66 [ 1.29, 2.03 ] |
| Pirker 2008 | 270 | -1.13 (1.93) | 279 | -1.98 (1.87) | | 3.3 % | 0.85 [ 0.53, 1.17 ] |
| Razzouk 2006 | 111 | 1.3 (2.38) | 111 | 1 (1.9) | | 1.0 % | 0.30 [ -0.27, 0.87 ] |
| Smith 2003a | 21 | 1.18 (2.01) | 7 | 0 (0.91) | | 0.3 % | 1.18 [ 0.09, 2.27 ] |
| Smith 2003b | 21 | 1.22 (1.62) | 7 | 0 (0.91) | | 0.4 % | 1.22 [ 0.25, 2.19 ] |
| Smith 2003c | 22 | 1.7 (1.93) | 8 | 0 (0.91) | | 0.3 % | 1.70 [ 0.68, 2.72 ] |
| Smith 2008 | 437 | 0.79 (2.83) | 447 | 0.29 (2.8) | | 2.4 % | 0.50 [ 0.13, 0.87 ] |
| Tjulandin 2010a | 76 | 1.6 (1.42) | 37 | 0.2 (1.74) | | 0.8 % | 1.40 [ 0.75, 2.05 ] |
| Tjulandin 2010b | 73 | 1.9 (1.74) | 37 | 0.2 (1.74) | | 0.7 % | 1.70 [ 1.01, 2.39 ] |
| Tjulandin 2011 | 95 | 2.1 (1.3) | 91 | 0.65 (1.94) | | 1.5 % | 1.45 [ 0.97, 1.93 ] |
| Tsuboi 2009 | 61 | 1.4 (1.9) | 56 | -0.8 (1.5) | | 0.9 % | 2.20 [ 1.58, 2.82 ] |
| Witzig 2005 | 166 | 2.8 (1.62) | 164 | 0.9 (1.52) | | 2.9 % | 1.90 [ 1.56, 2.24 ] |
| **Subtotal (95% CI)** | **4046** | | **3392** | | | **53.7 %** | **1.47 [ 1.40, 1.55 ]** |
| Heterogeneity: $Chi^2$ = 332.01, df = 41 (P<0.00001); $I^2$ =88% | | | | | | | |
| Test for overall effect: Z = 36.77 (P < 0.00001) | | | | | | | |
| 2 unblinded | | | | | | | |
| Aravantinos 2003 | 24 | 2.31 (1.22) | 23 | 1.23 (1.59) | | 0.5 % | 1.08 [ 0.27, 1.89 ] |
| Bamias 2003 | 72 | 0.57 (2.12) | 72 | -0.49 (1.36) | | 1.0 % | 1.06 [ 0.48, 1.64 ] |
| Boogaerts 2003 | 133 | 2.1 (1.83) | 129 | 0.9 (1.5) | | 2.0 % | 1.20 [ 0.80, 1.60 ] |
| Carabantes 1999 | 20 | 1 (1.56) | 15 | -1.7 (1.22) | | 0.4 % | 2.70 [ 1.78, 3.62 ] |
| Cazzola 1995a | 31 | -0.1 (2.23) | 7 | -0.04 (2.05) | | 0.1 % | -0.06 [ -1.77, 1.65 ] |
| Cazzola 1995b | 29 | 0.17 (1.72) | 8 | -0.04 (2.05) | | 0.1 % | 0.21 [ -1.34, 1.76 ] |
| Cazzola 1995c | 31 | 0.3 (2.9) | 7 | -0.04 (2.05) | | 0.1 % | 0.34 [ -1.49, 2.17 ] |
| Cazzola 1995d | 26 | 0.44 (2.29) | 7 | -0.04 (2.05) | | 0.1 % | 0.48 [ -1.28, 2.24 ] |
| Chang 2005 | 175 | 1.14 (0.8) | 175 | -0.58 (0.73) | | 12.9 % | 1.72 [ 1.56, 1.88 ] |
| Charu 2007 | 220 | 2.1 (1.854) | 55 | 0.1 (0.927) | | 2.8 % | 2.00 [ 1.65, 2.35 ] |


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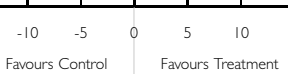
| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Christodoulou 2009 | 167 | 2.74 (13.62) | 170 | 0.52 (4.18) | | 0.1 % | 2.22 [ 0.06, 4.38 ] |
| Del Mastro 1997 | 28 | -0.8 (1.4) | 24 | -3.05 (1) | | 0.8 % | 2.25 [ 1.60, 2.90 ] |
| Gebbia 2003 | 22 | -2.4 (1.5) | 23 | -5.1 (1.33) | | 0.5 % | 2.70 [ 1.87, 3.53 ] |
| Gupta 2009 | 58 | 1.55 (0.74) | 57 | -1.5 (0.61) | | 5.4 % | 3.05 [ 2.80, 3.30 ] |
| Henke 1999a | 19 | 3.2 (1.6) | 3 | 0.6 (1.4) | | 0.1 % | 2.60 [ 0.86, 4.34 ] |
| Henke 1999b | 14 | 3.5 (1.2) | 4 | 0.6 (1.4) | | 0.1 % | 2.90 [ 1.39, 4.41 ] |
| Henke 1999c | 6 | 3.9 (2.1) | 4 | 0.6 (1.4) | | 0.1 % | 3.30 [ 1.13, 5.47 ] |
| Hoskin 2009 | 151 | 0.625 (3.5) | 149 | -0.47 (3.48) | | 0.5 % | 1.09 [ 0.30, 1.88 ] |
| Huddart 2002 | 45 | 2.6 (2) | 45 | 1.2 (1.46) | | 0.6 % | 1.40 [ 0.68, 2.12 ] |
| Iconomou 2003 | 57 | 1.7 (1.6) | 55 | 0.3 (1.4) | | 1.1 % | 1.40 [ 0.84, 1.96 ] |
| ML17616 2006 | 30 | 3.09 (2.08) | 30 | 1.76 (2.28) | | 0.3 % | 1.33 [ 0.23, 2.43 ] |
| ML17620 2006 | 61 | 2.12 (1.64) | 60 | 0.59 (1.83) | | 0.9 % | 1.53 [ 0.91, 2.15 ] |
| Oberhoff 1998 | 59 | 2.24 (2) | 47 | 0.6 (1.43) | | 0.8 % | 1.64 [ 0.99, 2.29 ] |
| Osterborg 1996a | 17 | 2.6 (1.74) | 13 | 1.02 (1.28) | | 0.3 % | 1.58 [ 0.50, 2.66 ] |
| Osterborg 1996b | 27 | 1.71 (1.67) | 14 | 1.02 (1.28) | | 0.4 % | 0.69 [ -0.23, 1.61 ] |
| Pronzato 2010 | 107 | 1.7 (1.35) | 109 | 0.4 (1.24) | | 2.8 % | 1.30 [ 0.95, 1.65 ] |
| Ten Bokkel 1998a | 34 | 0.66 (1.76) | 12 | -0.57 (1.16) | | 0.4 % | 1.23 [ 0.35, 2.11 ] |
| Ten Bokkel 1998b | 27 | 1.04 (1.73) | 12 | -0.57 (1.16) | | 0.4 % | 1.61 [ 0.68, 2.54 ] |
| Thomas 2002 | 62 | 1.9 (1.74) | 65 | 0.39 (1.38) | | 1.1 % | 1.51 [ 0.96, 2.06 ] |
| Thomas 2008 | 52 | 1.72 (1.79) | 57 | 0.09 (1.23) | | 1.0 % | 1.63 [ 1.05, 2.21 ] |
| Throuvalas 2000 | 28 | 0.7 (0.95) | 26 | -0.5 (0.56) | | 1.9 % | 1.20 [ 0.79, 1.61 ] |
| Untch 2011˙1 | 330 | -0.07 (2) | 359 | -0.98 (1.33) | | 5.1 % | 0.91 [ 0.65, 1.17 ] |
| Wilkinson 2006 | 114 | 1.6 (1.5) | 59 | 0.3 (1.3) | | 1.8 % | 1.30 [ 0.87, 1.73 ] |
| **Subtotal (95% CI)** | **2276** | | **1895** | | | **46.3 %** | **1.67 [ 1.59, 1.75 ]** |
| Heterogeneity: $Chi^2$ = 221.32, df = 32 (P<0.00001); $I^2$ =86% | | | | | | | |
| Test for overall effect: Z = 38.70 (P < 0.00001) | | | | | | | |
| **Total (95% CI)** | **6322** | | **5287** | | | **100.0 %** | **1.57 [ 1.51, 1.62 ]** |
| Heterogeneity: $Chi^2$ = 564.37, df = 74 (P<0.00001); $I^2$ =87% | | | | | | | |
| Test for overall effect: Z = 53.27 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 11.04, df = 1 (P = 0.00), $I^2$ =91% | | | | | | | |



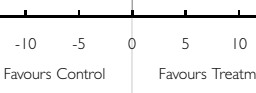
## Analysis 2.13. Comparison 2 Change of haemoglobin level, Outcome 13 Change in Hb values - intention-to-treat.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 2 Change of haemoglobin level

Outcome: 13 Change in Hb values - intention-to-treat

| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 ITT or less than 10% of participants per study arm excluded | | | | | | | |
| Abels 1993 | 63 | 0.952 (2.142) | 55 | -0.03 (1.36) | | 0.8 % | 0.99 [ 0.35, 1.63 ] |
| Aravantinos 2003 | 24 | 2.31 (1.22) | 23 | 1.23 (1.59) | | 0.5 % | 1.08 [ 0.27, 1.89 ] |
| Bamias 2003 | 72 | 0.57 (2.12) | 72 | -0.49 (1.36) | | 1.0 % | 1.06 [ 0.48, 1.64 ] |
| Boogaerts 2003 | 133 | 2.1 (1.83) | 129 | 0.9 (1.5) | | 2.0 % | 1.20 [ 0.80, 1.60 ] |
| Carabantes 1999 | 20 | 1 (1.56) | 15 | -1.7 (1.22) | | 0.4 % | 2.70 [ 1.78, 3.62 ] |
| Cascinu 1994 | 50 | 1.88 (0.83) | 49 | -0.61 (0.95) | | 2.7 % | 2.49 [ 2.14, 2.84 ] |
| Case 1993 | 79 | 2.346 (2.04) | 74 | 0.37 (1.46) | | 1.1 % | 1.97 [ 1.41, 2.53 ] |
| Cazzola 1995a | 31 | -0.1 (2.23) | 7 | -0.04 (2.05) | | 0.1 % | -0.06 [ -1.77, 1.65 ] |
| Cazzola 1995b | 29 | 0.17 (1.72) | 8 | -0.04 (2.05) | | 0.1 % | 0.21 [ -1.34, 1.76 ] |
| Cazzola 1995c | 31 | 0.3 (2.9) | 7 | -0.04 (2.05) | | 0.1 % | 0.34 [ -1.49, 2.17 ] |
| Cazzola 1995d | 26 | 0.44 (2.29) | 7 | -0.04 (2.05) | | 0.1 % | 0.48 [ -1.28, 2.24 ] |
| Chang 2005 | 175 | 1.14 (0.8) | 175 | -0.58 (0.73) | | 12.9 % | 1.72 [ 1.56, 1.88 ] |
| Charu 2007 | 220 | 2.1 (1.854) | 55 | 0.1 (0.927) | | 2.8 % | 2.00 [ 1.65, 2.35 ] |
| Dammacco 2001 | 69 | 1.8 (2.11) | 76 | -0.2 (1.31) | | 1.0 % | 2.00 [ 1.42, 2.58 ] |
| Del Mastro 1997 | 28 | -0.8 (1.4) | 24 | -3.05 (1) | | 0.8 % | 2.25 [ 1.60, 2.90 ] |
| Engert 2009 | 648 | -1.88 (1.78) | 655 | -2.55 (1.78) | | 8.9 % | 0.67 [ 0.48, 0.86 ] |
| Fujisaka 2011 | 89 | 1.84 (1.33) | 92 | 0.02 (1.12) | | 2.6 % | 1.82 [ 1.46, 2.18 ] |
| Gebbia 2003 | 22 | -2.4 (1.5) | 23 | -5.1 (1.33) | | 0.5 % | 2.70 [ 1.87, 3.53 ] |
| Gupta 2009 | 58 | 1.55 (0.74) | 57 | -1.5 (0.61) | | 5.4 % | 3.05 [ 2.80, 3.30 ] |
| Hedenus 2003 | 174 | 1.8 (2.24) | 170 | 0.19 (1.3) | | 2.2 % | 1.61 [ 1.22, 2.00 ] |
| Henke 1999a | 19 | 3.2 (1.6) | 3 | 0.6 (1.4) | | 0.1 % | 2.60 [ 0.86, 4.34 ] |
| Henke 1999b | 14 | 3.5 (1.2) | 4 | 0.6 (1.4) | | 0.1 % | 2.90 [ 1.39, 4.41 ] |
| Henke 1999c | 6 | 3.9 (2.1) | 4 | 0.6 (1.4) | | 0.1 % | 3.30 [ 1.13, 5.47 ] |
| Henke 2003 Roche 2004 | 178 | 3.4 (1.7) | 168 | 0.9 (1.7) | | 2.6 % | 2.50 [ 2.14, 2.86 ] |

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(. . . *Continued*)

| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Henry 1995 | 63 | 2.04 (2.38) | 61 | 0.44 (1.7) | | 0.6 % | 1.60 [ 0.87, 2.33 ] |
| Hoskin 2009 | 151 | 0.625 (3.5) | 149 | -0.47 (3.48) | | 0.5 % | 1.09 [ 0.30, 1.88 ] |
| Huddart 2002 | 45 | 2.6 (2) | 45 | 1.2 (1.46) | | 0.6 % | 1.40 [ 0.68, 2.12 ] |
| Iconomou 2003 | 57 | 1.7 (1.6) | 55 | 0.3 (1.4) | | 1.1 % | 1.40 [ 0.84, 1.96 ] |
| Kotasek 2003a | 32 | 0.54 (1.24) | 8 | -0.02 (1.43) | | 0.3 % | 0.56 [ -0.52, 1.64 ] |
| Kotasek 2003b | 17 | 0.86 (1.57) | 8 | -0.02 (1.43) | | 0.2 % | 0.88 [ -0.36, 2.12 ] |
| Kotasek 2003c | 46 | 0.9 (1.63) | 9 | -0.02 (1.43) | | 0.3 % | 0.92 [ -0.13, 1.97 ] |
| Kotasek 2003d | 28 | 1.63 (2.01) | 8 | -0.02 (1.43) | | 0.2 % | 1.65 [ 0.41, 2.89 ] |
| Kotasek 2003e | 35 | 1.45 (1.42) | 8 | -0.02 (1.43) | | 0.3 % | 1.47 [ 0.37, 2.57 ] |
| Kotasek 2003f | 40 | 1.21 (1.9) | 9 | -0.02 (1.43) | | 0.3 % | 1.23 [ 0.13, 2.33 ] |
| Krzakowski 2008a | 104 | 2.5 (2.4) | 52 | 0.6 (1.7) | | 0.8 % | 1.90 [ 1.25, 2.55 ] |
| Krzakowski 2008b | 105 | 2.5 (2.6) | 52 | 0.6 (1.7) | | 0.7 % | 1.90 [ 1.22, 2.58 ] |
| Kurz 1997 | 23 | 3.26 (1.98) | 12 | 0.25 (1.66) | | 0.2 % | 3.01 [ 1.77, 4.25 ] |
| Littlewood 2001 | 244 | 2.2 (2.18) | 115 | 0.5 (1.79) | | 1.8 % | 1.70 [ 1.27, 2.13 ] |
| ML17616 2006 | 30 | 3.09 (2.08) | 30 | 1.76 (2.28) | | 0.3 % | 1.33 [ 0.23, 2.43 ] |
| ML17620 2006 | 61 | 2.12 (1.64) | 60 | 0.59 (1.83) | | 0.9 % | 1.53 [ 0.91, 2.15 ] |
| Mystakidou 2005 | 50 | 2.4 (1.3) | 50 | -0.1 (1.02) | | 1.6 % | 2.50 [ 2.04, 2.96 ] |
| O'Shaughnessy 2005 | 47 | 0.8 (1.2) | 46 | -2.1 (1.4) | | 1.2 % | 2.90 [ 2.37, 3.43 ] |
| Pirker 2008 | 270 | -1.13 (1.93) | 279 | -1.98 (1.87) | | 3.3 % | 0.85 [ 0.53, 1.17 ] |
| Pronzato 2010 | 107 | 1.7 (1.35) | 109 | 0.4 (1.24) | | 2.8 % | 1.30 [ 0.95, 1.65 ] |
| Razzouk 2006 | 111 | 1.3 (2.38) | 111 | 1 (1.9) | | 1.0 % | 0.30 [ -0.27, 0.87 ] |
| Smith 2003a | 21 | 1.18 (2.01) | 7 | 0 (0.91) | | 0.3 % | 1.18 [ 0.09, 2.27 ] |
| Smith 2003b | 21 | 1.22 (1.62) | 7 | 0 (0.91) | | 0.4 % | 1.22 [ 0.25, 2.19 ] |
| Smith 2003c | 22 | 1.7 (1.93) | 8 | 0 (0.91) | | 0.3 % | 1.70 [ 0.68, 2.72 ] |
| Thomas 2002 | 62 | 1.9 (1.74) | 65 | 0.39 (1.38) | | 1.1 % | 1.51 [ 0.96, 2.06 ] |
| Throuvalas 2000 | 28 | 0.7 (0.95) | 26 | -0.5 (0.56) | | 1.9 % | 1.20 [ 0.79, 1.61 ] |
| Tjulandin 2010a | 76 | 1.6 (1.42) | 37 | 0.2 (1.74) | | 0.8 % | 1.40 [ 0.75, 2.05 ] |
| Tjulandin 2010b | 73 | 1.9 (1.74) | 37 | 0.2 (1.74) | | 0.7 % | 1.70 [ 1.01, 2.39 ] |
| Tjulandin 2011 | 95 | 2.1 (1.3) | 91 | 0.65 (1.94) | | 1.5 % | 1.45 [ 0.97, 1.93 ] |
| Tsuboi 2009 | 61 | 1.4 (1.9) | 56 | -0.8 (1.5) | | 0.9 % | 2.20 [ 1.58, 2.82 ] |
| Untch 2011˙1 | 330 | -0.07 (2) | 359 | -0.98 (1.33) | | 5.1 % | 0.91 [ 0.65, 1.17 ] |


(*Continued* . . . )

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| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Wilkinson 2006 | 114 | 1.6 (1.5) | 59 | 0.3 (1.3) | | 1.8 % | 1.30 [ 0.87, 1.73 ] |
| Witzig 2005 | 166 | 2.8 (1.62) | 164 | 0.9 (1.52) | | 2.9 % | 1.90 [ 1.56, 2.24 ] |
| **Subtotal (95% CI)** | **4993** | | **4144** | | | **85.3 %** | **1.61 [ 1.55, 1.68 ]** |
| Heterogeneity: Chi² = 467.14, df = 56 (P<0.00001); I² =88% | | | | | | | |
| Test for overall effect: Z = 50.72 (P < 0.00001) | | | | | | | |
| 2 more than 10% of participants per study arm excluded | | | | | | | |
| Christodoulou 2009 | 167 | 2.74 (13.62) | 170 | 0.52 (4.18) | | 0.1 % | 2.22 [ 0.06, 4.38 ] |
| Gordon 2008 | 139 | 1.3 (1.4) | 49 | 0.2 (1) | | 2.5 % | 1.10 [ 0.74, 1.46 ] |
| Grote 2005 | 64 | -0.2 (1.38) | 58 | -2.9 (1.53) | | 1.2 % | 2.70 [ 2.18, 3.22 ] |
| Hedenus 2002a | 5 | 1.56 (1.93) | 2 | 1 (0.56) | | 0.1 % | 0.56 [ -1.30, 2.42 ] |
| Hedenus 2002b | 17 | 1.64 (1.25) | 2 | 1 (0.56) | | 0.3 % | 0.64 [ -0.34, 1.62 ] |
| Hedenus 2002c | 14 | 2.46 (1.49) | 2 | 1 (0.56) | | 0.3 % | 1.46 [ 0.36, 2.56 ] |
| Italian 1998 | 17 | 1.73 (1.56) | 11 | -0.14 (1.09) | | 0.3 % | 1.87 [ 0.89, 2.85 ] |
| Kunikane 2001a | 16 | 0.89 (1.72) | 10 | -0.65 (1.31) | | 0.2 % | 1.54 [ 0.37, 2.71 ] |
| Kunikane 2001b | 18 | 1.72 (1.1) | 9 | -0.65 (1.31) | | 0.3 % | 2.37 [ 1.37, 3.37 ] |
| Leyland-Jones 2005 | 81 | 0.34 (1.73) | 86 | 0.14 (1.7) | | 1.2 % | 0.20 [ -0.32, 0.72 ] |
| Oberhoff 1998 | 59 | 2.24 (2) | 47 | 0.6 (1.43) | | 0.8 % | 1.64 [ 0.99, 2.29 ] |
| Osterborg 1996a | 17 | 2.6 (1.74) | 13 | 1.02 (1.28) | | 0.3 % | 1.58 [ 0.50, 2.66 ] |
| Osterborg 1996b | 27 | 1.71 (1.67) | 14 | 1.02 (1.28) | | 0.4 % | 0.69 [ -0.23, 1.61 ] |
| Osterborg 2002 | 138 | 2.48 (1.74) | 142 | 0.82 (1.4) | | 2.4 % | 1.66 [ 1.29, 2.03 ] |
| Smith 2008 | 437 | 0.79 (2.83) | 447 | 0.29 (2.8) | | 2.4 % | 0.50 [ 0.13, 0.87 ] |
| Ten Bokkel 1998a | 34 | 0.66 (1.76) | 12 | -0.57 (1.16) | | 0.4 % | 1.23 [ 0.35, 2.11 ] |
| Ten Bokkel 1998b | 27 | 1.04 (1.73) | 12 | -0.57 (1.16) | | 0.4 % | 1.61 [ 0.68, 2.54 ] |
| Thomas 2008 | 52 | 1.72 (1.79) | 57 | 0.09 (1.23) | | 1.0 % | 1.63 [ 1.05, 2.21 ] |
| **Subtotal (95% CI)** | **1329** | | **1143** | | | **14.7 %** | **1.28 [ 1.13, 1.43 ]** |
| Heterogeneity: Chi² = 81.39, df = 17 (P<0.00001); I² =79% | | | | | | | |
| Test for overall effect: Z = 16.77 (P < 0.00001) | | | | | | | |
| 3 unclear | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| **Total (95% CI)** | **6322** | | **5287** | | | **100.0 %** | **1.57 [ 1.51, 1.62 ]** |
| Heterogeneity: Chi² = 564.37, df = 74 (P<0.00001); I² =87% | | | | | | | |
| Test for overall effect: Z = 53.27 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: Chi² = 15.84, df = 1 (P = 0.00), I² =94% | | | | | | | |

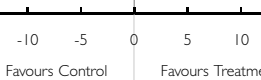
### Analysis 2.14. Comparison 2 Change of haemoglobin level, Outcome 14 Change in Hb values - publication.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 2 Change of haemoglobin level

Outcome: 14 Change in Hb values - publication

| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 full text publication | | | | | | | |
| Abels 1993 | 63 | 0.952 (2.142) | 55 | -0.03 (1.36) | | 0.8 % | 0.99 [ 0.35, 1.63 ] |
| Aravantinos 2003 | 24 | 2.31 (1.22) | 23 | 1.23 (1.59) | | 0.5 % | 1.08 [ 0.27, 1.89 ] |
| Bamias 2003 | 72 | 0.57 (2.12) | 72 | -0.49 (1.36) | | 1.0 % | 1.06 [ 0.48, 1.64 ] |
| Boogaerts 2003 | 133 | 2.1 (1.83) | 129 | 0.9 (1.5) | | 2.0 % | 1.20 [ 0.80, 1.60 ] |
| Cascinu 1994 | 50 | 1.88 (0.83) | 49 | -0.61 (0.95) | | 2.7 % | 2.49 [ 2.14, 2.84 ] |
| Case 1993 | 79 | 2.346 (2.04) | 74 | 0.37 (1.46) | | 1.1 % | 1.97 [ 1.41, 2.53 ] |
| Cazzola 1995a | 31 | -0.1 (2.23) | 7 | -0.04 (2.05) | | 0.1 % | -0.06 [ -1.77, 1.65 ] |
| Cazzola 1995b | 29 | 0.17 (1.72) | 8 | -0.04 (2.05) | | 0.1 % | 0.21 [ -1.34, 1.76 ] |
| Cazzola 1995c | 31 | 0.3 (2.9) | 7 | -0.04 (2.05) | | 0.1 % | 0.34 [ -1.49, 2.17 ] |
| Cazzola 1995d | 26 | 0.44 (2.29) | 7 | -0.04 (2.05) | | 0.1 % | 0.48 [ -1.28, 2.24 ] |
| Chang 2005 | 175 | 1.14 (0.8) | 175 | -0.58 (0.73) | | 12.9 % | 1.72 [ 1.56, 1.88 ] |
| Charu 2007 | 220 | 2.1 (1.854) | 55 | 0.1 (0.927) | | 2.8 % | 2.00 [ 1.65, 2.35 ] |
| Christodoulou 2009 | 167 | 2.74 (13.62) | 170 | 0.52 (4.18) | | 0.1 % | 2.22 [ 0.06, 4.38 ] |
| Del Mastro 1997 | 28 | -0.8 (1.4) | 24 | -3.05 (1) | | 0.8 % | 2.25 [ 1.60, 2.90 ] |
| Engert 2009 | 648 | -1.88 (1.78) | 655 | -2.55 (1.78) | | 8.9 % | 0.67 [ 0.48, 0.86 ] |
| Fujisaka 2011 | 89 | 1.84 (1.33) | 92 | 0.02 (1.12) | | 2.6 % | 1.82 [ 1.46, 2.18 ] |
| Gebbia 2003 | 22 | -2.4 (1.5) | 23 | -5.1 (1.33) | | 0.5 % | 2.70 [ 1.87, 3.53 ] |
| Gordon 2008 | 139 | 1.3 (1.4) | 49 | 0.2 (1) | | 2.5 % | 1.10 [ 0.74, 1.46 ] |
| Grote 2005 | 64 | -0.2 (1.38) | 58 | -2.9 (1.53) | | 1.2 % | 2.70 [ 2.18, 3.22 ] |
| Gupta 2009 | 58 | 1.55 (0.74) | 57 | -1.5 (0.61) | | 5.4 % | 3.05 [ 2.80, 3.30 ] |
| Hedenus 2002a | 5 | 1.56 (1.93) | 2 | 1 (0.56) | | 0.1 % | 0.56 [ -1.30, 2.42 ] |




(*Continued . . .*)

(. . . *Continued*)

| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Hedenus 2002b | 17 | 1.64 (1.25) | 2 | 1 (0.56) | | 0.3 % | 0.64 [ -0.34, 1.62 ] |
| Hedenus 2002c | 14 | 2.46 (1.49) | 2 | 1 (0.56) | | 0.3 % | 1.46 [ 0.36, 2.56 ] |
| Hedenus 2003 | 174 | 1.8 (2.24) | 170 | 0.19 (1.3) | | 2.2 % | 1.61 [ 1.22, 2.00 ] |
| Henke 1999a | 19 | 3.2 (1.6) | 3 | 0.6 (1.4) | | 0.1 % | 2.60 [ 0.86, 4.34 ] |
| Henke 1999b | 14 | 3.5 (1.2) | 4 | 0.6 (1.4) | | 0.1 % | 2.90 [ 1.39, 4.41 ] |
| Henke 1999c | 6 | 3.9 (2.1) | 4 | 0.6 (1.4) | | 0.1 % | 3.30 [ 1.13, 5.47 ] |
| Henry 1995 | 63 | 2.04 (2.38) | 61 | 0.44 (1.7) | | 0.6 % | 1.60 [ 0.87, 2.33 ] |
| Hoskin 2009 | 151 | 0.625 (3.5) | 149 | -0.47 (3.48) | | 0.5 % | 1.09 [ 0.30, 1.88 ] |
| Iconomou 2003 | 57 | 1.7 (1.6) | 55 | 0.3 (1.4) | | 1.1 % | 1.40 [ 0.84, 1.96 ] |
| Kotasek 2003a | 32 | 0.54 (1.24) | 8 | -0.02 (1.43) | | 0.3 % | 0.56 [ -0.52, 1.64 ] |
| Kotasek 2003b | 17 | 0.86 (1.57) | 8 | -0.02 (1.43) | | 0.2 % | 0.88 [ -0.36, 2.12 ] |
| Kotasek 2003c | 46 | 0.9 (1.63) | 9 | -0.02 (1.43) | | 0.3 % | 0.92 [ -0.13, 1.97 ] |
| Kotasek 2003d | 28 | 1.63 (2.01) | 8 | -0.02 (1.43) | | 0.2 % | 1.65 [ 0.41, 2.89 ] |
| Kotasek 2003e | 35 | 1.45 (1.42) | 8 | -0.02 (1.43) | | 0.3 % | 1.47 [ 0.37, 2.57 ] |
| Kotasek 2003f | 40 | 1.21 (1.9) | 9 | -0.02 (1.43) | | 0.3 % | 1.23 [ 0.13, 2.33 ] |
| Krzakowski 2008a | 104 | 2.5 (2.4) | 52 | 0.6 (1.7) | | 0.8 % | 1.90 [ 1.25, 2.55 ] |
| Krzakowski 2008b | 105 | 2.5 (2.6) | 52 | 0.6 (1.7) | | 0.7 % | 1.90 [ 1.22, 2.58 ] |
| Kunikane 2001a | 16 | 0.89 (1.72) | 10 | -0.65 (1.31) | | 0.2 % | 1.54 [ 0.37, 2.71 ] |
| Kunikane 2001b | 18 | 1.72 (1.1) | 9 | -0.65 (1.31) | | 0.3 % | 2.37 [ 1.37, 3.37 ] |
| Leyland-Jones 2005 | 81 | 0.34 (1.73) | 86 | 0.14 (1.7) | | 1.2 % | 0.20 [ -0.32, 0.72 ] |
| Littlewood 2001 | 244 | 2.2 (2.18) | 115 | 0.5 (1.79) | | 1.8 % | 1.70 [ 1.27, 2.13 ] |
| Mystakidou 2005 | 50 | 2.4 (1.3) | 50 | -0.1 (1.02) | | 1.6 % | 2.50 [ 2.04, 2.96 ] |
| O'Shaughnessy 2005 | 47 | 0.8 (1.2) | 46 | -2.1 (1.4) | | 1.2 % | 2.90 [ 2.37, 3.43 ] |
| Pirker 2008 | 270 | -1.13 (1.93) | 279 | -1.98 (1.87) | | 3.3 % | 0.85 [ 0.53, 1.17 ] |
| Pronzato 2010 | 107 | 1.7 (1.35) | 109 | 0.4 (1.24) | | 2.8 % | 1.30 [ 0.95, 1.65 ] |
| Razzouk 2006 | 111 | 1.3 (2.38) | 111 | 1 (1.9) | | 1.0 % | 0.30 [ -0.27, 0.87 ] |
| Smith 2003a | 21 | 1.18 (2.01) | 7 | 0 (0.91) | | 0.3 % | 1.18 [ 0.09, 2.27 ] |
| Smith 2003b | 21 | 1.22 (1.62) | 7 | 0 (0.91) | | 0.4 % | 1.22 [ 0.25, 2.19 ] |
| Smith 2003c | 22 | 1.7 (1.93) | 8 | 0 (0.91) | | 0.3 % | 1.70 [ 0.68, 2.72 ] |
| Smith 2008 | 437 | 0.79 (2.83) | 447 | 0.29 (2.8) | | 2.4 % | 0.50 [ 0.13, 0.87 ] |
| Thomas 2008 | 52 | 1.72 (1.79) | 57 | 0.09 (1.23) | | 1.0 % | 1.63 [ 1.05, 2.21 ] |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| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Tjulandin 2010a | 76 | 1.6 (1.42) | 37 | 0.2 (1.74) | | 0.8 % | 1.40 [ 0.75, 2.05 ] |
| Tjulandin 2010b | 73 | 1.9 (1.74) | 37 | 0.2 (1.74) | | 0.7 % | 1.70 [ 1.01, 2.39 ] |
| Tjulandin 2011 | 95 | 2.1 (1.3) | 91 | 0.65 (1.94) | | 1.5 % | 1.45 [ 0.97, 1.93 ] |
| Tsuboi 2009 | 61 | 1.4 (1.9) | 56 | -0.8 (1.5) | | 0.9 % | 2.20 [ 1.58, 2.82 ] |
| Untch 2011˙1 | 330 | -0.07 (2) | 359 | -0.98 (1.33) | | 5.1 % | 0.91 [ 0.65, 1.17 ] |
| Wilkinson 2006 | 114 | 1.6 (1.5) | 59 | 0.3 (1.3) | | 1.8 % | 1.30 [ 0.87, 1.73 ] |
| Witzig 2005 | 166 | 2.8 (1.62) | 164 | 0.9 (1.52) | | 2.9 % | 1.90 [ 1.56, 2.24 ] |
| **Subtotal (95% CI)** | **5487** | | **4539** | | | **86.0 %** | **1.54 [ 1.47, 1.60 ]** |
| Heterogeneity: $Chi^2$ = 515.98, df = 58 (P<0.00001); $I^2$ =89% | | | | | | | |
| Test for overall effect: Z = 48.46 (P < 0.00001) | | | | | | | |
| 2 abstract publication | | | | | | | |
| Carabantes 1999 | 20 | 1 (1.56) | 15 | -1.7 (1.22) | | 0.4 % | 2.70 [ 1.78, 3.62 ] |
| Huddart 2002 | 45 | 2.6 (2) | 45 | 1.2 (1.46) | | 0.6 % | 1.40 [ 0.68, 2.12 ] |
| Thomas 2002 | 62 | 1.9 (1.74) | 65 | 0.39 (1.38) | | 1.1 % | 1.51 [ 0.96, 2.06 ] |
| **Subtotal (95% CI)** | **127** | | **125** | | | **2.1 %** | **1.70 [ 1.30, 2.09 ]** |
| Heterogeneity: $Chi^2$ = 5.65, df = 2 (P = 0.06); $I^2$ =65% | | | | | | | |
| Test for overall effect: Z = 8.42 (P < 0.00001) | | | | | | | |
| 3 unpublished data | | | | | | | |
| Dammacco 2001 | 69 | 1.8 (2.11) | 76 | -0.2 (1.31) | | 1.0 % | 2.00 [ 1.42, 2.58 ] |
| Italian 1998 | 17 | 1.73 (1.56) | 11 | -0.14 (1.09) | | 0.3 % | 1.87 [ 0.89, 2.85 ] |
| Kurz 1997 | 23 | 3.26 (1.98) | 12 | 0.25 (1.66) | | 0.2 % | 3.01 [ 1.77, 4.25 ] |
| Oberhoff 1998 | 59 | 2.24 (2) | 47 | 0.6 (1.43) | | 0.8 % | 1.64 [ 0.99, 2.29 ] |
| Osterborg 1996a | 17 | 2.6 (1.74) | 13 | 1.02 (1.28) | | 0.3 % | 1.58 [ 0.50, 2.66 ] |
| Osterborg 1996b | 27 | 1.71 (1.67) | 14 | 1.02 (1.28) | | 0.4 % | 0.69 [ -0.23, 1.61 ] |
| Osterborg 2002 | 138 | 2.48 (1.74) | 142 | 0.82 (1.4) | | 2.4 % | 1.66 [ 1.29, 2.03 ] |
| Ten Bokkel 1998a | 34 | 0.66 (1.76) | 12 | -0.57 (1.16) | | 0.4 % | 1.23 [ 0.35, 2.11 ] |
| Ten Bokkel 1998b | 27 | 1.04 (1.73) | 12 | -0.57 (1.16) | | 0.4 % | 1.61 [ 0.68, 2.54 ] |
| Throuvalas 2000 | 28 | 0.7 (0.95) | 26 | -0.5 (0.56) | | 1.9 % | 1.20 [ 0.79, 1.61 ] |
| **Subtotal (95% CI)** | **439** | | **365** | | | **8.2 %** | **1.56 [ 1.36, 1.76 ]** |
| Heterogeneity: $Chi^2$ = 15.11, df = 9 (P = 0.09); $I^2$ =40% | | | | | | | |
| Test for overall effect: Z = 15.19 (P < 0.00001) | | | | | | | |
| 4 ODAC documents | | | | | | | |
| Henke 2003 Roche 2004 | 178 | 3.4 (1.7) | 168 | 0.9 (1.7) | | 2.6 % | 2.50 [ 2.14, 2.86 ] |
| **Subtotal (95% CI)** | **178** | | **168** | | | **2.6 %** | **2.50 [ 2.14, 2.86 ]** |
| Heterogeneity: not applicable | | | | | | | |

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Favours Control Favours Treatment

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| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Test for overall effect: Z = 13.67 (P < 0.00001) | | | | | | | |
| 5 Clinical trials results | | | | | | | |
| ML17616 2006 | 30 | 3.09 (2.08) | 30 | 1.76 (2.28) | | 0.3 % | 1.33 [ 0.23, 2.43 ] |
| ML17620 2006 | 61 | 2.12 (1.64) | 60 | 0.59 (1.83) | | 0.9 % | 1.53 [ 0.91, 2.15 ] |
| **Subtotal (95% CI)** | **91** | | **90** | | | **1.1 %** | **1.48 [ 0.94, 2.02 ]** |
| Heterogeneity: $Chi^2$ = 0.10, df = 1 (P = 0.76); $I^2$ =0.0% | | | | | | | |
| Test for overall effect: Z = 5.38 (P < 0.00001) | | | | | | | |
| **Total (95% CI)** | **6322** | | **5287** | | | **100.0 %** | **1.57 [ 1.51, 1.62 ]** |
| Heterogeneity: $Chi^2$ = 564.37, df = 74 (P<0.00001); $I^2$ =87% | | | | | | | |
| Test for overall effect: Z = 53.27 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 27.54, df = 4 (P = 0.00), $I^2$ =85% | | | | | | | |

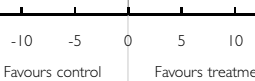
## Analysis 2.15. Comparison 2 Change of haemoglobin level, Outcome 15 Change in Hb values - experimental arms merged.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 2 Change of haemoglobin level

Outcome: 15 Change in Hb values - experimental arms merged

| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Abels 1993 | 63 | 0.952 (2.142) | 55 | -0.03 (1.36) | | 0.8 % | 0.99 [ 0.35, 1.63 ] |
| Aravantinos 2003 | 24 | 2.31 (1.22) | 23 | 1.23 (1.59) | | 0.5 % | 1.08 [ 0.27, 1.89 ] |
| Bamias 2003 | 72 | 0.57 (2.12) | 72 | -0.49 (1.36) | | 1.0 % | 1.06 [ 0.48, 1.64 ] |
| Boogaerts 2003 | 133 | 2.1 (1.83) | 129 | 0.9 (1.5) | | 2.0 % | 1.20 [ 0.80, 1.60 ] |
| Carabantes 1999 | 20 | 1 (1.56) | 15 | -1.7 (1.22) | | 0.4 % | 2.70 [ 1.78, 3.62 ] |
| Cascinu 1994 | 50 | 1.88 (0.83) | 49 | -0.61 (0.95) | | 2.7 % | 2.49 [ 2.14, 2.84 ] |
| Case 1993 | 79 | 2.346 (2.04) | 74 | 0.37 (1.46) | | 1.1 % | 1.97 [ 1.41, 2.53 ] |
| Cazzola 1995 | 117 | 0.19 (2.31) | 29 | -0.04 (2.05) | | 0.5 % | 0.23 [ -0.63, 1.09 ] |
| Chang 2005 | 175 | 1.14 (0.8) | 175 | -0.58 (0.73) | | 12.9 % | 1.72 [ 1.56, 1.88 ] |
| Charu 2007 | 220 | 2.1 (1.854) | 55 | 0.1 (0.927) | | 2.8 % | 2.00 [ 1.65, 2.35 ] |
| Christodoulou 2009 | 167 | 2.74 (13.62) | 170 | 0.52 (4.18) | | 0.1 % | 2.22 [ 0.06, 4.38 ] |
| Dammacco 2001 | 69 | 1.8 (2.11) | 76 | -0.2 (1.31) | | 1.0 % | 2.00 [ 1.42, 2.58 ] |
| Del Mastro 1997 | 28 | -0.8 (1.4) | 24 | -3.05 (1) | | 0.8 % | 2.25 [ 1.60, 2.90 ] |
| Engert 2009 | 648 | -1.88 (1.78) | 655 | -2.55 (1.78) | | 8.9 % | 0.67 [ 0.48, 0.86 ] |
| Fujisaka 2011 | 89 | 1.84 (1.33) | 92 | 0.02 (1.12) | | 2.6 % | 1.82 [ 1.46, 2.18 ] |
| Gebbia 2003 | 22 | -2.4 (1.5) | 23 | -5.1 (1.33) | | 0.5 % | 2.70 [ 1.87, 3.53 ] |
| Gordon 2008 | 139 | 1.3 (1.4) | 49 | 0.2 (1) | | 2.5 % | 1.10 [ 0.74, 1.46 ] |
| Grote 2005 | 64 | -0.2 (1.38) | 58 | -2.9 (1.53) | | 1.2 % | 2.70 [ 2.18, 3.22 ] |
| Gupta 2009 | 58 | 1.55 (0.74) | 57 | -1.5 (0.61) | | 5.4 % | 3.05 [ 2.80, 3.30 ] |
| Hedenus 2002 | 36 | 1.94 (1.46) | 6 | 1 (0.56) | | 0.8 % | 0.94 [ 0.29, 1.59 ] |
| Hedenus 2003 | 174 | 1.8 (2.24) | 170 | 0.19 (1.3) | | 2.2 % | 1.61 [ 1.22, 2.00 ] |
| Henke 1999 | 39 | 3.42 (1.53) | 11 | 0.6 (1.4) | | 0.4 % | 2.82 [ 1.86, 3.78 ] |
| Henke 2003 Roche 2004 | 178 | 3.4 (1.7) | 168 | 0.9 (1.7) | | 2.6 % | 2.50 [ 2.14, 2.86 ] |
| Henry 1995 | 63 | 2.04 (2.38) | 61 | 0.44 (1.7) | | 0.6 % | 1.60 [ 0.87, 2.33 ] |

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| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Hoskin 2009 | 151 | 0.625 (3.5) | 149 | -0.47 (3.48) | | 0.5 % | 1.09 [ 0.30, 1.88 ] |
| Huddart 2002 | 45 | 2.6 (2) | 45 | 1.2 (1.46) | | 0.6 % | 1.40 [ 0.68, 2.12 ] |
| Iconomou 2003 | 57 | 1.7 (1.6) | 55 | 0.3 (1.4) | | 1.1 % | 1.40 [ 0.84, 1.96 ] |
| Italian 1998 | 17 | 1.73 (1.56) | 11 | -0.14 (1.09) | | 0.3 % | 1.87 [ 0.89, 2.85 ] |
| Kotasek 2003 | 198 | 1.1 (1.67) | 50 | -0.02 (1.43) | | 1.6 % | 1.12 [ 0.66, 1.58 ] |
| Krzakowski 2008 | 209 | 2.5 (2.5) | 104 | 0.6 (1.7) | | 1.5 % | 1.90 [ 1.43, 2.37 ] |
| Kunikane 2001 | 34 | 1.33 (1.46) | 19 | -0.65 (1.31) | | 0.6 % | 1.98 [ 1.21, 2.75 ] |
| Kurz 1997 | 23 | 3.26 (1.98) | 12 | 0.25 (1.66) | | 0.2 % | 3.01 [ 1.77, 4.25 ] |
| Leyland-Jones 2005 | 81 | 0.34 (1.73) | 86 | 0.14 (1.7) | | 1.2 % | 0.20 [ -0.32, 0.72 ] |
| Littlewood 2001 | 244 | 2.2 (2.18) | 115 | 0.5 (1.79) | | 1.8 % | 1.70 [ 1.27, 2.13 ] |
| ML17616 2006 | 30 | 3.09 (2.08) | 30 | 1.76 (2.28) | | 0.3 % | 1.33 [ 0.23, 2.43 ] |
| ML17620 2006 | 61 | 2.12 (1.64) | 60 | 0.59 (1.83) | | 0.9 % | 1.53 [ 0.91, 2.15 ] |
| Mystakidou 2005 | 50 | 2.4 (1.3) | 50 | -0.1 (1.02) | | 1.6 % | 2.50 [ 2.04, 2.96 ] |
| O'Shaughnessy 2005 | 47 | 0.8 (1.2) | 46 | -2.1 (1.4) | | 1.2 % | 2.90 [ 2.37, 3.43 ] |
| Oberhoff 1998 | 59 | 2.24 (2) | 47 | 0.6 (1.43) | | 0.8 % | 1.64 [ 0.99, 2.29 ] |
| Osterborg 1996 | 44 | 2.05 (1.73) | 27 | 1.02 (1.28) | | 0.7 % | 1.03 [ 0.33, 1.73 ] |
| Osterborg 2002 | 138 | 2.48 (1.74) | 142 | 0.82 (1.4) | | 2.4 % | 1.66 [ 1.29, 2.03 ] |
| Pirker 2008 | 270 | -1.13 (1.93) | 279 | -1.98 (1.87) | | 3.3 % | 0.85 [ 0.53, 1.17 ] |
| Pronzato 2010 | 107 | 1.7 (1.35) | 109 | 0.4 (1.24) | | 2.8 % | 1.30 [ 0.95, 1.65 ] |
| Razzouk 2006 | 111 | 1.3 (2.38) | 111 | 1 (1.9) | | 1.0 % | 0.30 [ -0.27, 0.87 ] |
| Smith 2003 | 64 | 1.37 (1.75) | 22 | 0 (0.91) | | 1.0 % | 1.37 [ 0.80, 1.94 ] |
| Smith 2008 | 437 | 0.79 (2.83) | 447 | 0.29 (2.8) | | 2.4 % | 0.50 [ 0.13, 0.87 ] |
| Ten Bokkel 1998 | 61 | 0.83 (1.74) | 24 | -0.57 (1.16) | | 0.8 % | 1.40 [ 0.76, 2.04 ] |
| Thomas 2002 | 62 | 1.9 (1.74) | 65 | 0.39 (1.38) | | 1.1 % | 1.51 [ 0.96, 2.06 ] |
| Thomas 2008 | 52 | 1.72 (1.79) | 57 | 0.09 (1.23) | | 1.0 % | 1.63 [ 1.05, 2.21 ] |
| Throuvalas 2000 | 28 | 0.7 (0.95) | 26 | -0.5 (0.56) | | 1.9 % | 1.20 [ 0.79, 1.61 ] |
| Tjulandin 2010 | 149 | 1.75 (1.59) | 74 | 0.2 (1.74) | | 1.5 % | 1.55 [ 1.08, 2.02 ] |
| Tjulandin 2011 | 95 | 2.1 (1.3) | 91 | 0.65 (1.94) | | 1.5 % | 1.45 [ 0.97, 1.93 ] |
| Tsuboi 2009 | 61 | 1.4 (1.9) | 56 | -0.8 (1.5) | | 0.9 % | 2.20 [ 1.58, 2.82 ] |
| Untch 2011`1 | 330 | -0.07 (2) | 359 | -0.98 (1.33) | | 5.1 % | 0.91 [ 0.65, 1.17 ] |
| Wilkinson 2006 | 114 | 1.6 (1.5) | 59 | 0.3 (1.3) | | 1.8 % | 1.30 [ 0.87, 1.73 ] |

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| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Witzig 2005 | 166 | 2.8 (1.62) | 164 | 0.9 (1.52) | + | 2.9 % | 1.90 [ 1.56, 2.24 ] |
| **Total (95% CI)** | **6322** | | **5287** | | ◆ | **100.0 %** | **1.56 [ 1.51, 1.62 ]** |

Heterogeneity: $Chi^2$ = 556.15, df = 55 (P<0.00001); $I^2$ =90%

Test for overall effect: Z = 53.30 (P < 0.00001)

Test for subgroup differences: Not applicable

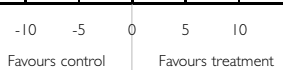

## Analysis 2.16. Comparison 2 Change of haemoglobin level, Outcome 16 Change in Hb values- sensitivity analysis.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 2 Change of haemoglobin level

Outcome: 16 Change in Hb values- sensitivity analysis

| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Abels 1993 | 63 | 0.952 (2.142) | 55 | -0.03 (1.36) | + | 1.1 % | 0.99 [ 0.35, 1.63 ] |
| Boogaerts 2003 | 133 | 2.1 (1.83) | 129 | 0.9 (1.5) | + | 2.8 % | 1.20 [ 0.80, 1.60 ] |
| Carabantes 1999 | 20 | 1 (1.56) | 15 | -1.7 (1.22) | + | 0.5 % | 2.70 [ 1.78, 3.62 ] |
| Cascinu 1994 | 50 | 1.88 (0.83) | 49 | -0.61 (0.95) | + | 3.7 % | 2.49 [ 2.14, 2.84 ] |
| Case 1993 | 79 | 2.346 (2.04) | 74 | 0.37 (1.46) | + | 1.5 % | 1.97 [ 1.41, 2.53 ] |
| Cazzola 1995a | 31 | -0.1 (2.23) | 7 | -0.04 (2.05) | + | 0.2 % | -0.06 [ -1.77, 1.65 ] |
| Cazzola 1995b | 29 | 0.17 (1.72) | 8 | -0.04 (2.05) | + | 0.2 % | 0.21 [ -1.34, 1.76 ] |
| Cazzola 1995c | 31 | 0.3 (2.9) | 7 | -0.04 (2.05) | + | 0.1 % | 0.34 [ -1.49, 2.17 ] |
| Cazzola 1995d | 26 | 0.44 (2.29) | 7 | -0.04 (2.05) | + | 0.1 % | 0.48 [ -1.28, 2.24 ] |
| Charu 2007 | 220 | 2.1 (1.854) | 55 | 0.1 (0.927) | + | 3.8 % | 2.00 [ 1.65, 2.35 ] |
| Dammacco 2001 | 69 | 1.8 (2.11) | 76 | -0.2 (1.31) | + | 1.4 % | 2.00 [ 1.42, 2.58 ] |

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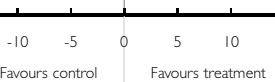
| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Del Mastro 1997 | 28 | -0.8 (1.4) | 24 | -3.05 (1) | | 1.1 % | 2.25 [ 1.60, 2.90 ] |
| Fujisaka 2011 | 89 | 1.84 (1.33) | 92 | 0.02 (1.12) | | 3.6 % | 1.82 [ 1.46, 2.18 ] |
| Gordon 2008 | 139 | 1.3 (1.4) | 49 | 0.2 (1) | | 3.5 % | 1.10 [ 0.74, 1.46 ] |
| Gupta 2009 | 58 | 1.55 (0.74) | 57 | -1.5 (0.61) | | 7.5 % | 3.05 [ 2.80, 3.30 ] |
| Hedenus 2002a | 5 | 1.56 (1.93) | 2 | 1 (0.56) | | 0.1 % | 0.56 [ -1.30, 2.42 ] |
| Hedenus 2002b | 17 | 1.64 (1.25) | 2 | 1 (0.56) | | 0.5 % | 0.64 [ -0.34, 1.62 ] |
| Hedenus 2002c | 14 | 2.46 (1.49) | 2 | 1 (0.56) | | 0.4 % | 1.46 [ 0.36, 2.56 ] |
| Hedenus 2003 | 174 | 1.8 (2.24) | 170 | 0.19 (1.3) | | 3.1 % | 1.61 [ 1.22, 2.00 ] |
| Henke 1999a | 19 | 3.2 (1.6) | 3 | 0.6 (1.4) | | 0.2 % | 2.60 [ 0.86, 4.34 ] |
| Henke 1999b | 14 | 3.5 (1.2) | 4 | 0.6 (1.4) | | 0.2 % | 2.90 [ 1.39, 4.41 ] |
| Henke 1999c | 6 | 3.9 (2.1) | 4 | 0.6 (1.4) | | 0.1 % | 3.30 [ 1.13, 5.47 ] |
| Henke 2003 Roche 2004 | 178 | 3.4 (1.7) | 168 | 0.9 (1.7) | | 3.6 % | 2.50 [ 2.14, 2.86 ] |
| Henry 1995 | 63 | 2.04 (2.38) | 61 | 0.44 (1.7) | | 0.9 % | 1.60 [ 0.87, 2.33 ] |
| Huddart 2002 | 45 | 2.6 (2) | 45 | 1.2 (1.46) | | 0.9 % | 1.40 [ 0.68, 2.12 ] |
| Iconomou 2003 | 57 | 1.7 (1.6) | 55 | 0.3 (1.4) | | 1.5 % | 1.40 [ 0.84, 1.96 ] |
| Italian 1998 | 17 | 1.73 (1.56) | 11 | -0.14 (1.09) | | 0.5 % | 1.87 [ 0.89, 2.85 ] |
| Kotasek 2003a | 32 | 0.54 (1.24) | 8 | -0.02 (1.43) | | 0.4 % | 0.56 [ -0.52, 1.64 ] |
| Kotasek 2003b | 17 | 0.86 (1.57) | 8 | -0.02 (1.43) | | 0.3 % | 0.88 [ -0.36, 2.12 ] |
| Kotasek 2003c | 46 | 0.9 (1.63) | 9 | -0.02 (1.43) | | 0.4 % | 0.92 [ -0.13, 1.97 ] |
| Kotasek 2003d | 28 | 1.63 (2.01) | 8 | -0.02 (1.43) | | 0.3 % | 1.65 [ 0.41, 2.89 ] |
| Kotasek 2003e | 35 | 1.45 (1.42) | 8 | -0.02 (1.43) | | 0.4 % | 1.47 [ 0.37, 2.57 ] |
| Kotasek 2003f | 40 | 1.21 (1.9) | 9 | -0.02 (1.43) | | 0.4 % | 1.23 [ 0.13, 2.33 ] |
| Krzakowski 2008a | 104 | 2.5 (2.4) | 52 | 0.6 (1.7) | | 1.1 % | 1.90 [ 1.25, 2.55 ] |
| Krzakowski 2008b | 105 | 2.5 (2.6) | 52 | 0.6 (1.7) | | 1.0 % | 1.90 [ 1.22, 2.58 ] |
| Kunikane 2001a | 16 | 0.89 (1.72) | 10 | -0.65 (1.31) | | 0.3 % | 1.54 [ 0.37, 2.71 ] |
| Kunikane 2001b | 18 | 1.72 (1.1) | 9 | -0.65 (1.31) | | 0.5 % | 2.37 [ 1.37, 3.37 ] |
| Kurz 1997 | 23 | 3.26 (1.98) | 12 | 0.25 (1.66) | | 0.3 % | 3.01 [ 1.77, 4.25 ] |
| Littlewood 2001 | 244 | 2.2 (2.18) | 115 | 0.5 (1.79) | | 2.5 % | 1.70 [ 1.27, 2.13 ] |
| ML17616 2006 | 30 | 3.09 (2.08) | 30 | 1.76 (2.28) | | 0.4 % | 1.33 [ 0.23, 2.43 ] |
| ML17620 2006 | 61 | 2.12 (1.64) | 60 | 0.59 (1.83) | | 1.2 % | 1.53 [ 0.91, 2.15 ] |
| Mystakidou 2005 | 50 | 2.4 (1.3) | 50 | -0.1 (1.02) | | 2.2 % | 2.50 [ 2.04, 2.96 ] |

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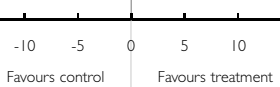
| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| O'Shaughnessy 2005 | 47 | 0.8 (1.2) | 46 | -2.1 (1.4) | | 1.6 % | 2.90 [ 2.37, 3.43 ] |
| Oberhoff 1998 | 59 | 2.24 (2) | 47 | 0.6 (1.43) | | 1.1 % | 1.64 [ 0.99, 2.29 ] |
| Osterborg 1996a | 17 | 2.6 (1.74) | 13 | 1.02 (1.28) | | 0.4 % | 1.58 [ 0.50, 2.66 ] |
| Osterborg 1996b | 27 | 1.71 (1.67) | 14 | 1.02 (1.28) | | 0.5 % | 0.69 [ -0.23, 1.61 ] |
| Osterborg 2002 | 138 | 2.48 (1.74) | 142 | 0.82 (1.4) | | 3.3 % | 1.66 [ 1.29, 2.03 ] |
| Pirker 2008 | 270 | -1.13 (1.93) | 279 | -1.98 (1.87) | | 4.5 % | 0.85 [ 0.53, 1.17 ] |
| Pronzato 2010 | 107 | 1.7 (1.35) | 109 | 0.4 (1.24) | | 3.8 % | 1.30 [ 0.95, 1.65 ] |
| Razzouk 2006 | 111 | 1.3 (2.38) | 111 | 1 (1.9) | | 1.4 % | 0.30 [ -0.27, 0.87 ] |
| Smith 2003a | 21 | 1.18 (2.01) | 7 | 0 (0.91) | | 0.4 % | 1.18 [ 0.09, 2.27 ] |
| Smith 2003b | 21 | 1.22 (1.62) | 7 | 0 (0.91) | | 0.5 % | 1.22 [ 0.25, 2.19 ] |
| Smith 2003c | 22 | 1.7 (1.93) | 8 | 0 (0.91) | | 0.4 % | 1.70 [ 0.68, 2.72 ] |
| Smith 2008 | 437 | 0.79 (2.83) | 447 | 0.29 (2.8) | | 3.3 % | 0.50 [ 0.13, 0.87 ] |
| Ten Bokkel 1998a | 34 | 0.66 (1.76) | 12 | -0.57 (1.16) | | 0.6 % | 1.23 [ 0.35, 2.11 ] |
| Ten Bokkel 1998b | 27 | 1.04 (1.73) | 12 | -0.57 (1.16) | | 0.5 % | 1.61 [ 0.68, 2.54 ] |
| Thomas 2002 | 62 | 1.9 (1.74) | 65 | 0.39 (1.38) | | 1.5 % | 1.51 [ 0.96, 2.06 ] |
| Throuvalas 2000 | 28 | 0.7 (0.95) | 26 | -0.5 (0.56) | | 2.7 % | 1.20 [ 0.79, 1.61 ] |
| Tjulandin 2010a | 76 | 1.6 (1.42) | 37 | 0.2 (1.74) | | 1.1 % | 1.40 [ 0.75, 2.05 ] |
| Tjulandin 2010b | 73 | 1.9 (1.74) | 37 | 0.2 (1.74) | | 1.0 % | 1.70 [ 1.01, 2.39 ] |
| Tjulandin 2011 | 95 | 2.1 (1.3) | 91 | 0.65 (1.94) | | 2.0 % | 1.45 [ 0.97, 1.93 ] |
| Tsuboi 2009 | 61 | 1.4 (1.9) | 56 | -0.8 (1.5) | | 1.2 % | 2.20 [ 1.58, 2.82 ] |
| Untch 2011˙1 | 330 | -0.07 (2) | 359 | -0.98 (1.33) | | 7.0 % | 0.91 [ 0.65, 1.17 ] |
| Wilkinson 2006 | 114 | 1.6 (1.5) | 59 | 0.3 (1.3) | | 2.5 % | 1.30 [ 0.87, 1.73 ] |
| Witzig 2005 | 166 | 2.8 (1.62) | 164 | 0.9 (1.52) | | 4.0 % | 1.90 [ 1.56, 2.24 ] |
| **Total (95% CI)** | **4866** | | **3819** | | | **100.0 %** | **1.66 [ 1.59, 1.72 ]** |

Heterogeneity: $Chi^2$ = 413.54, df = 64 (P<0.00001); $I^2$ =85%

Test for overall effect: Z = 47.91 (P < 0.00001)

Test for subgroup differences: Not applicable



## Analysis 2.17. Comparison 2 Change of haemoglobin level, Outcome 17 Change in Hb values - publication sensitivity analysis excluding Henke 2003.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 2 Change of haemoglobin level

Outcome: 17 Change in Hb values - publication sensitivity analysis excluding Henke 2003

| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 full text publication | | | | | | | |
| Abels 1993 | 63 | 0.952 (2.142) | 55 | -0.03 (1.36) | | 0.8 % | 0.99 [ 0.35, 1.63 ] |
| Aravantinos 2003 | 24 | 2.31 (1.22) | 23 | 1.23 (1.59) | | 0.5 % | 1.08 [ 0.27, 1.89 ] |
| Bamias 2003 | 72 | 0.57 (2.12) | 72 | -0.49 (1.36) | | 1.0 % | 1.06 [ 0.48, 1.64 ] |
| Boogaerts 2003 | 133 | 2.1 (1.83) | 129 | 0.9 (1.5) | | 2.1 % | 1.20 [ 0.80, 1.60 ] |
| Cascinu 1994 | 50 | 1.88 (0.83) | 49 | -0.61 (0.95) | | 2.8 % | 2.49 [ 2.14, 2.84 ] |
| Case 1993 | 79 | 2.346 (2.04) | 74 | 0.37 (1.46) | | 1.1 % | 1.97 [ 1.41, 2.53 ] |
| Cazzola 1995a | 31 | -0.1 (2.23) | 7 | -0.04 (2.05) | | 0.1 % | -0.06 [ -1.77, 1.65 ] |
| Cazzola 1995b | 29 | 0.17 (1.72) | 8 | -0.04 (2.05) | | 0.1 % | 0.21 [ -1.34, 1.76 ] |
| Cazzola 1995c | 31 | 0.3 (2.9) | 7 | -0.04 (2.05) | | 0.1 % | 0.34 [ -1.49, 2.17 ] |
| Cazzola 1995d | 26 | 0.44 (2.29) | 7 | -0.04 (2.05) | | 0.1 % | 0.48 [ -1.28, 2.24 ] |
| Chang 2005 | 175 | 1.14 (0.8) | 175 | -0.58 (0.73) | | 13.2 % | 1.72 [ 1.56, 1.88 ] |
| Charu 2007 | 220 | 2.1 (1.854) | 55 | 0.1 (0.927) | | 2.8 % | 2.00 [ 1.65, 2.35 ] |
| Christodoulou 2009 | 167 | 2.74 (13.62) | 170 | 0.52 (4.18) | | 0.1 % | 2.22 [ 0.06, 4.38 ] |
| Del Mastro 1997 | 28 | -0.8 (1.4) | 24 | -3.05 (1) | | 0.8 % | 2.25 [ 1.60, 2.90 ] |
| Fujisaka 2011 | 89 | 1.84 (1.33) | 92 | 0.02 (1.12) | | 2.6 % | 1.82 [ 1.46, 2.18 ] |
| Gebbia 2003 | 22 | -2.4 (1.5) | 23 | -5.1 (1.33) | | 0.5 % | 2.70 [ 1.87, 3.53 ] |
| Gordon 2008 | 139 | 1.3 (1.4) | 49 | 0.2 (1) | | 2.6 % | 1.10 [ 0.74, 1.46 ] |
| Grote 2005 | 64 | -0.2 (1.38) | 58 | -2.9 (1.53) | | 1.3 % | 2.70 [ 2.18, 3.22 ] |
| Gupta 2009 | 58 | 1.55 (0.74) | 57 | -1.5 (0.61) | | 5.5 % | 3.05 [ 2.80, 3.30 ] |
| Hedenus 2002a | 5 | 1.56 (1.93) | 2 | 1 (0.56) | | 0.1 % | 0.56 [ -1.30, 2.42 ] |
| Hedenus 2002b | 17 | 1.64 (1.25) | 2 | 1 (0.56) | | 0.4 % | 0.64 [ -0.34, 1.62 ] |
| Hedenus 2002c | 14 | 2.46 (1.49) | 2 | 1 (0.56) | | 0.3 % | 1.46 [ 0.36, 2.56 ] |
| Hedenus 2003 | 174 | 1.8 (2.24) | 170 | 0.19 (1.3) | | 2.3 % | 1.61 [ 1.22, 2.00 ] |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| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Henke 1999a | 19 | 3.2 (1.6) | 3 | 0.6 (1.4) | | 0.1 % | 2.60 [ 0.86, 4.34 ] |
| Henke 1999b | 14 | 3.5 (1.2) | 4 | 0.6 (1.4) | | 0.1 % | 2.90 [ 1.39, 4.41 ] |
| Henke 1999c | 6 | 3.9 (2.1) | 4 | 0.6 (1.4) | | 0.1 % | 3.30 [ 1.13, 5.47 ] |
| Henry 1995 | 63 | 2.04 (2.38) | 61 | 0.44 (1.7) | | 0.6 % | 1.60 [ 0.87, 2.33 ] |
| Hoskin 2009 | 151 | 0.625 (3.5) | 149 | -0.47 (3.48) | | 0.5 % | 1.09 [ 0.30, 1.88 ] |
| Iconomou 2003 | 57 | 1.7 (1.6) | 55 | 0.3 (1.4) | | 1.1 % | 1.40 [ 0.84, 1.96 ] |
| Kotasek 2003a | 32 | 0.54 (1.24) | 8 | -0.02 (1.43) | | 0.3 % | 0.56 [ -0.52, 1.64 ] |
| Kotasek 2003b | 17 | 0.86 (1.57) | 8 | -0.02 (1.43) | | 0.2 % | 0.88 [ -0.36, 2.12 ] |
| Kotasek 2003c | 46 | 0.9 (1.63) | 9 | -0.02 (1.43) | | 0.3 % | 0.92 [ -0.13, 1.97 ] |
| Kotasek 2003d | 28 | 1.63 (2.01) | 8 | -0.02 (1.43) | | 0.2 % | 1.65 [ 0.41, 2.89 ] |
| Kotasek 2003e | 35 | 1.45 (1.42) | 8 | -0.02 (1.43) | | 0.3 % | 1.47 [ 0.37, 2.57 ] |
| Kotasek 2003f | 40 | 1.21 (1.9) | 9 | -0.02 (1.43) | | 0.3 % | 1.23 [ 0.13, 2.33 ] |
| Krzakowski 2008a | 104 | 2.5 (2.4) | 52 | 0.6 (1.7) | | 0.8 % | 1.90 [ 1.25, 2.55 ] |
| Krzakowski 2008b | 105 | 2.5 (2.6) | 52 | 0.6 (1.7) | | 0.7 % | 1.90 [ 1.22, 2.58 ] |
| Kunikane 2001a | 16 | 0.89 (1.72) | 10 | -0.65 (1.31) | | 0.2 % | 1.54 [ 0.37, 2.71 ] |
| Kunikane 2001b | 18 | 1.72 (1.1) | 9 | -0.65 (1.31) | | 0.3 % | 2.37 [ 1.37, 3.37 ] |
| Leyland-Jones 2005 | 81 | 0.34 (1.73) | 86 | 0.14 (1.7) | | 1.3 % | 0.20 [ -0.32, 0.72 ] |
| Littlewood 2001 | 244 | 2.2 (2.18) | 115 | 0.5 (1.79) | | 1.9 % | 1.70 [ 1.27, 2.13 ] |
| Mystakidou 2005 | 50 | 2.4 (1.3) | 50 | -0.1 (1.02) | | 1.6 % | 2.50 [ 2.04, 2.96 ] |
| O'Shaughnessy 2005 | 47 | 0.8 (1.2) | 46 | -2.1 (1.4) | | 1.2 % | 2.90 [ 2.37, 3.43 ] |
| Pirker 2008 | 270 | -1.13 (1.93) | 279 | -1.98 (1.87) | | 3.4 % | 0.85 [ 0.53, 1.17 ] |
| Pronzato 2010 | 107 | 1.7 (1.35) | 109 | 0.4 (1.24) | | 2.8 % | 1.30 [ 0.95, 1.65 ] |
| Razzouk 2006 | 111 | 1.3 (2.38) | 111 | 1 (1.9) | | 1.1 % | 0.30 [ -0.27, 0.87 ] |
| Smith 2003a | 21 | 1.18 (2.01) | 7 | 0 (0.91) | | 0.3 % | 1.18 [ 0.09, 2.27 ] |
| Smith 2003b | 21 | 1.22 (1.62) | 7 | 0 (0.91) | | 0.4 % | 1.22 [ 0.25, 2.19 ] |
| Smith 2003c | 22 | 1.7 (1.93) | 8 | 0 (0.91) | | 0.3 % | 1.70 [ 0.68, 2.72 ] |
| Smith 2008 | 437 | 0.79 (2.83) | 447 | 0.29 (2.8) | | 2.5 % | 0.50 [ 0.13, 0.87 ] |
| Thomas 2008 | 52 | 1.72 (1.79) | 57 | 0.09 (1.23) | | 1.0 % | 1.63 [ 1.05, 2.21 ] |
| Tjulandin 2010a | 76 | 1.6 (1.42) | 37 | 0.2 (1.74) | | 0.8 % | 1.40 [ 0.75, 2.05 ] |
| Tjulandin 2010b | 73 | 1.9 (1.74) | 37 | 0.2 (1.74) | | 0.7 % | 1.70 [ 1.01, 2.39 ] |
| Tjulandin 2011 | 95 | 2.1 (1.3) | 91 | 0.65 (1.94) | | 1.5 % | 1.45 [ 0.97, 1.93 ] |

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Favours Control Favours Treatment

(*Continued* . . . )

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| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Tsuboi 2009 | 61 | 1.4 (1.9) | 56 | -0.8 (1.5) | | 0.9 % | 2.20 [ 1.58, 2.82 ] |
| Untch 2011˙1 | 330 | -0.07 (2) | 359 | -0.98 (1.33) | | 5.2 % | 0.91 [ 0.65, 1.17 ] |
| Wilkinson 2006 | 114 | 1.6 (1.5) | 59 | 0.3 (1.3) | | 1.8 % | 1.30 [ 0.87, 1.73 ] |
| Witzig 2005 | 166 | 2.8 (1.62) | 164 | 0.9 (1.52) | | 3.0 % | 1.90 [ 1.56, 2.24 ] |
| **Subtotal (95% CI)** | **4839** | | **3884** | | | **79.1 %** | **1.63 [ 1.57, 1.70 ]** |
| Heterogeneity: $Chi^2$ = 430.14, df = 57 (P<0.00001); $I^2$ =87% | | | | | | | |
| Test for overall effect: Z = 48.87 (P < 0.00001) | | | | | | | |
| 2 abstract publication | | | | | | | |
| Carabantes 1999 | 20 | 1 (1.56) | 15 | -1.7 (1.22) | | 0.4 % | 2.70 [ 1.78, 3.62 ] |
| Engert 2009 | 648 | -1.88 (1.78) | 655 | -2.55 (1.78) | | 9.1 % | 0.67 [ 0.48, 0.86 ] |
| Huddart 2002 | 45 | 2.6 (2) | 45 | 1.2 (1.46) | | 0.7 % | 1.40 [ 0.68, 2.12 ] |
| Thomas 2002 | 62 | 1.9 (1.74) | 65 | 0.39 (1.38) | | 1.1 % | 1.51 [ 0.96, 2.06 ] |
| **Subtotal (95% CI)** | **775** | | **780** | | | **11.3 %** | **0.87 [ 0.69, 1.04 ]** |
| Heterogeneity: $Chi^2$ = 26.58, df = 3 (P<0.00001); $I^2$ =89% | | | | | | | |
| Test for overall effect: Z = 9.81 (P < 0.00001) | | | | | | | |
| 3 unpublished data | | | | | | | |
| Dammacco 2001 | 69 | 1.8 (2.11) | 76 | -0.2 (1.31) | | 1.0 % | 2.00 [ 1.42, 2.58 ] |
| Italian 1998 | 17 | 1.73 (1.56) | 11 | -0.14 (1.09) | | 0.4 % | 1.87 [ 0.89, 2.85 ] |
| Kurz 1997 | 23 | 3.26 (1.98) | 12 | 0.25 (1.66) | | 0.2 % | 3.01 [ 1.77, 4.25 ] |
| Oberhoff 1998 | 59 | 2.24 (2) | 47 | 0.6 (1.43) | | 0.8 % | 1.64 [ 0.99, 2.29 ] |
| Osterborg 1996a | 17 | 2.6 (1.74) | 13 | 1.02 (1.28) | | 0.3 % | 1.58 [ 0.50, 2.66 ] |
| Osterborg 1996b | 27 | 1.71 (1.67) | 14 | 1.02 (1.28) | | 0.4 % | 0.69 [ -0.23, 1.61 ] |
| Osterborg 2002 | 138 | 2.48 (1.74) | 142 | 0.82 (1.4) | | 2.5 % | 1.66 [ 1.29, 2.03 ] |
| Ten Bokkel 1998a | 34 | 0.66 (1.76) | 12 | -0.57 (1.16) | | 0.4 % | 1.23 [ 0.35, 2.11 ] |
| Ten Bokkel 1998b | 27 | 1.04 (1.73) | 12 | -0.57 (1.16) | | 0.4 % | 1.61 [ 0.68, 2.54 ] |
| Throuvalas 2000 | 28 | 0.7 (0.95) | 26 | -0.5 (0.56) | | 2.0 % | 1.20 [ 0.79, 1.61 ] |
| **Subtotal (95% CI)** | **439** | | **365** | | | **8.4 %** | **1.56 [ 1.36, 1.76 ]** |
| Heterogeneity: $Chi^2$ = 15.11, df = 9 (P = 0.09); $I^2$ =40% | | | | | | | |
| Test for overall effect: Z = 15.19 (P < 0.00001) | | | | | | | |
| 4 ODAC documents | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| 5 clinical study report | | | | | | | |
| ML17616 2006 | 30 | 3.09 (2.08) | 30 | 1.76 (2.28) | | 0.3 % | 1.33 [ 0.23, 2.43 ] |
| ML17620 2006 | 61 | 2.12 (1.64) | 60 | 0.59 (1.83) | | 0.9 % | 1.53 [ 0.91, 2.15 ] |

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Favours Control Favours Treatment

(*Continued* . . . )

(. . . *Continued*)

| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| **Subtotal (95% CI)** | **91** | | **90** | | ◆ | **1.2 %** | **1.48 [ 0.94, 2.02 ]** |
| Heterogeneity: $Chi^2$ = 0.10, df = 1 (P = 0.76); $I^2$ =0.0% | | | | | | | |
| Test for overall effect: Z = 5.38 (P < 0.00001) | | | | | | | |
| **Total (95% CI)** | **6144** | | **5119** | | | **100.0 %** | **1.54 [ 1.48, 1.60 ]** |
| Heterogeneity: $Chi^2$ = 537.53, df = 73 (P<0.00001); $I^2$ =86% | | | | | | | |
| Test for overall effect: Z = 51.75 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 65.62, df = 3 (P = 0.00), $I^2$ =95% | | | | | | | |


**Analysis 3.1. Comparison 3 Participants receiving red blood cell transfusions, Outcome 1 Participants receiving red blood cell transfusions - overall.**

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 3 Participants receiving red blood cell transfusions

Outcome: 1 Participants receiving red blood cell transfusions - overall

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Aapro 2008 | 33/231 | 63/232 | | 2.1 % | 0.53 [ 0.36, 0.77 ] |
| Abels 1993 | 21/63 | 21/55 | | 0.7 % | 0.87 [ 0.54, 1.42 ] |
| Aravantinos 2003 | 9/24 | 23/23 | | 0.8 % | 0.39 [ 0.23, 0.64 ] |
| Bamias 2003 | 11/72 | 24/72 | | 0.8 % | 0.46 [ 0.24, 0.86 ] |
| Blohmer 2011 | 14/127 | 38/129 | | 1.2 % | 0.37 [ 0.21, 0.66 ] |
| Boogaerts 2003 | 43/133 | 67/129 | | 2.2 % | 0.62 [ 0.46, 0.84 ] |
| Carabantes 1999 | 4/20 | 13/15 | | 0.5 % | 0.23 [ 0.09, 0.57 ] |
| Cascinu 1994 | 10/50 | 28/50 | | 0.9 % | 0.36 [ 0.19, 0.65 ] |
| Case 1993 | 32/79 | 36/74 | | 1.2 % | 0.83 [ 0.58, 1.19 ] |
| Cazzola 1995a | 7/31 | 2/7 | | 0.1 % | 0.79 [ 0.21, 3.02 ] |


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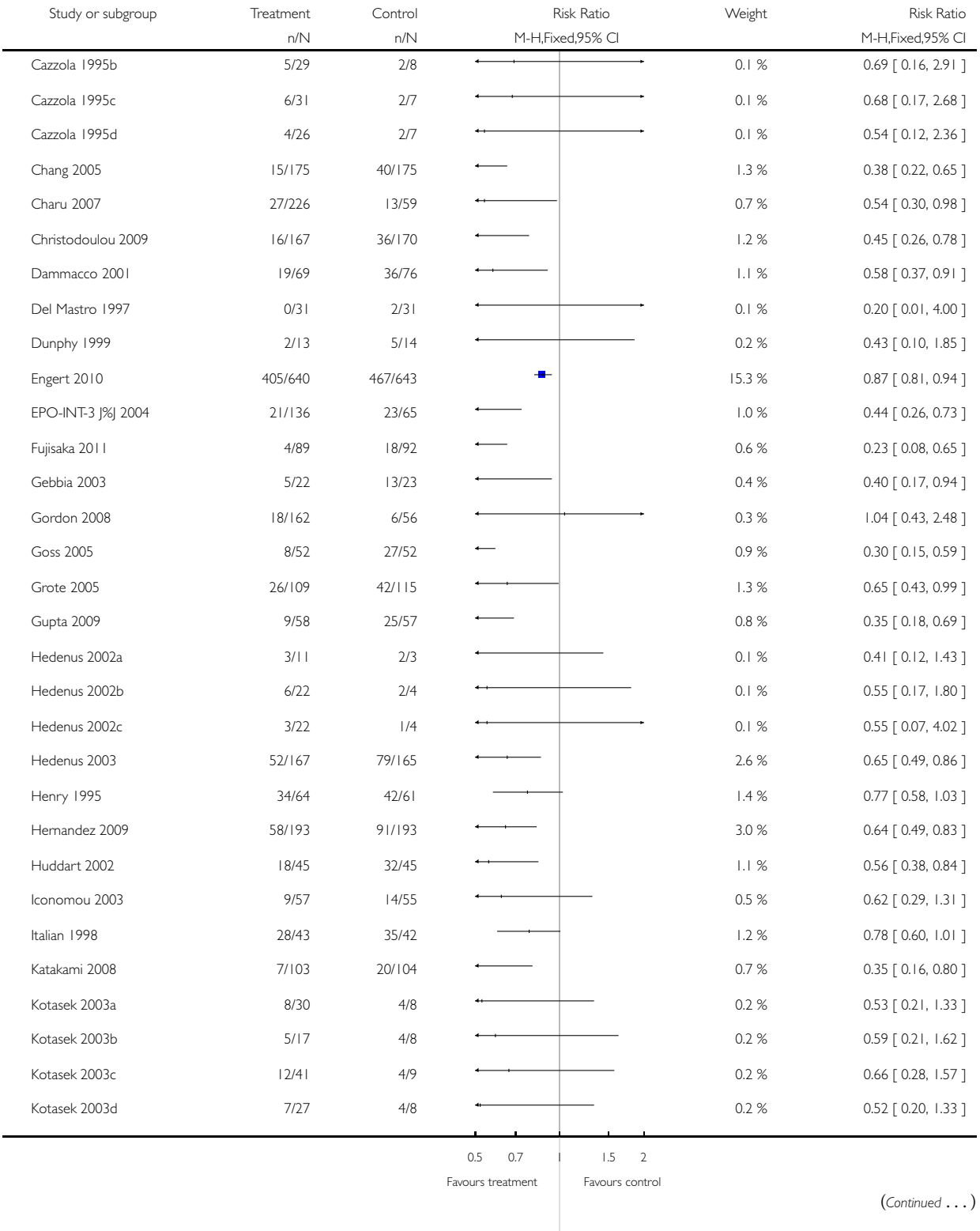


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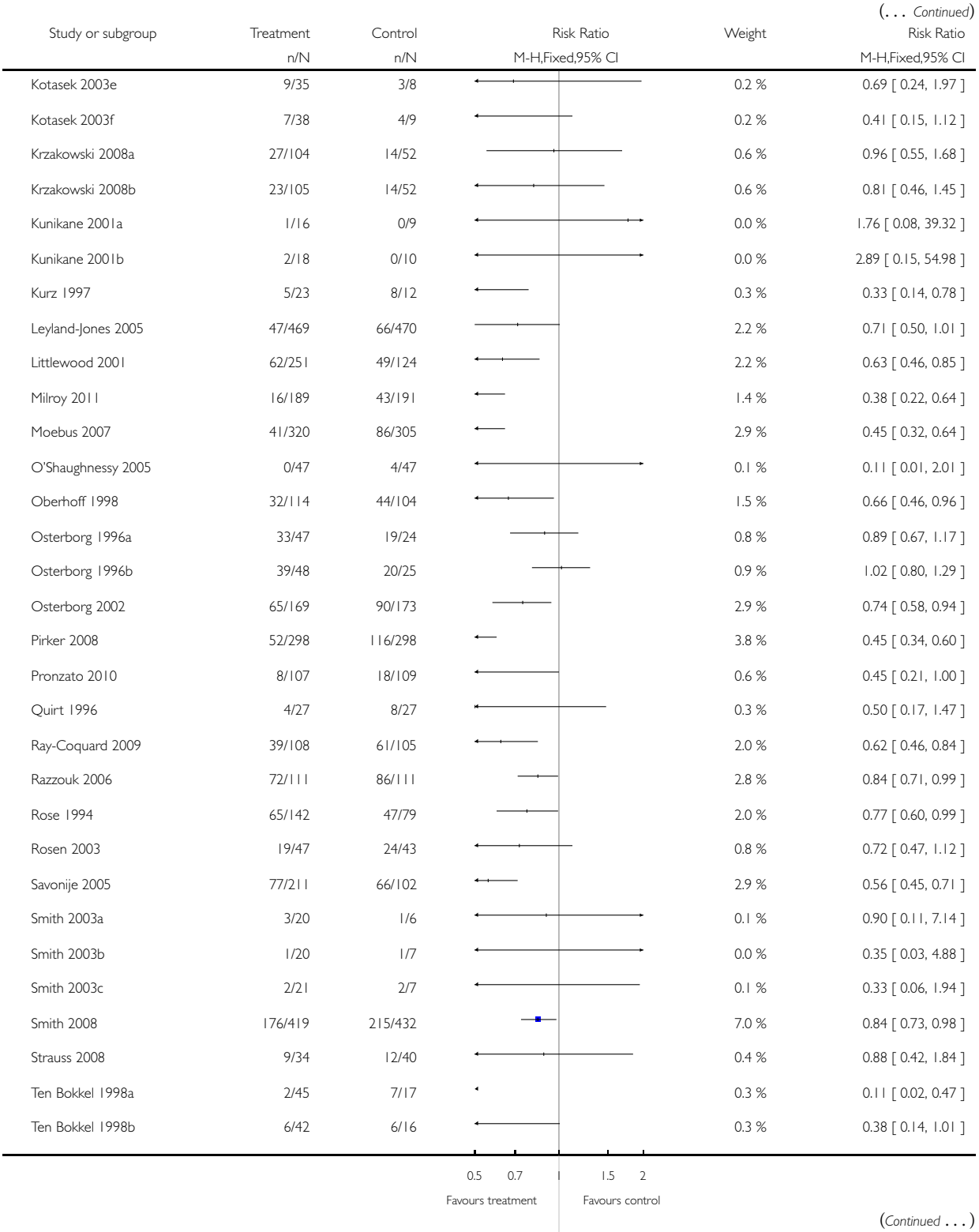

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Kotasek 2003e | 9/35 | 3/8 | | 0.2 % | 0.69 [ 0.24, 1.97 ] |
| Kotasek 2003f | 7/38 | 4/9 | | 0.2 % | 0.41 [ 0.15, 1.12 ] |
| Krzakowski 2008a | 27/104 | 14/52 | | 0.6 % | 0.96 [ 0.55, 1.68 ] |
| Krzakowski 2008b | 23/105 | 14/52 | | 0.6 % | 0.81 [ 0.46, 1.45 ] |
| Kunikane 2001a | 1/16 | 0/9 | | 0.0 % | 1.76 [ 0.08, 39.32 ] |
| Kunikane 2001b | 2/18 | 0/10 | | 0.0 % | 2.89 [ 0.15, 54.98 ] |
| Kurz 1997 | 5/23 | 8/12 | | 0.3 % | 0.33 [ 0.14, 0.78 ] |
| Leyland-Jones 2005 | 47/469 | 66/470 | | 2.2 % | 0.71 [ 0.50, 1.01 ] |
| Littlewood 2001 | 62/251 | 49/124 | | 2.2 % | 0.63 [ 0.46, 0.85 ] |
| Milroy 2011 | 16/189 | 43/191 | | 1.4 % | 0.38 [ 0.22, 0.64 ] |
| Moebus 2007 | 41/320 | 86/305 | | 2.9 % | 0.45 [ 0.32, 0.64 ] |
| O'Shaughnessy 2005 | 0/47 | 4/47 | | 0.1 % | 0.11 [ 0.01, 2.01 ] |
| Oberhoff 1998 | 32/114 | 44/104 | | 1.5 % | 0.66 [ 0.46, 0.96 ] |
| Osterborg 1996a | 33/47 | 19/24 | | 0.8 % | 0.89 [ 0.67, 1.17 ] |
| Osterborg 1996b | 39/48 | 20/25 | | 0.9 % | 1.02 [ 0.80, 1.29 ] |
| Osterborg 2002 | 65/169 | 90/173 | | 2.9 % | 0.74 [ 0.58, 0.94 ] |
| Pirker 2008 | 52/298 | 116/298 | | 3.8 % | 0.45 [ 0.34, 0.60 ] |
| Pronzato 2010 | 8/107 | 18/109 | | 0.6 % | 0.45 [ 0.21, 1.00 ] |
| Quirt 1996 | 4/27 | 8/27 | | 0.3 % | 0.50 [ 0.17, 1.47 ] |
| Ray-Coquard 2009 | 39/108 | 61/105 | | 2.0 % | 0.62 [ 0.46, 0.84 ] |
| Razzouk 2006 | 72/111 | 86/111 | | 2.8 % | 0.84 [ 0.71, 0.99 ] |
| Rose 1994 | 65/142 | 47/79 | | 2.0 % | 0.77 [ 0.60, 0.99 ] |
| Rosen 2003 | 19/47 | 24/43 | | 0.8 % | 0.72 [ 0.47, 1.12 ] |
| Savonije 2005 | 77/211 | 66/102 | | 2.9 % | 0.56 [ 0.45, 0.71 ] |
| Smith 2003a | 3/20 | 1/6 | | 0.1 % | 0.90 [ 0.11, 7.14 ] |
| Smith 2003b | 1/20 | 1/7 | | 0.0 % | 0.35 [ 0.03, 4.88 ] |
| Smith 2003c | 2/21 | 2/7 | | 0.1 % | 0.33 [ 0.06, 1.94 ] |
| Smith 2008 | 176/419 | 215/432 | | 7.0 % | 0.84 [ 0.73, 0.98 ] |
| Strauss 2008 | 9/34 | 12/40 | | 0.4 % | 0.88 [ 0.42, 1.84 ] |
| Ten Bokkel 1998a | 2/45 | 7/17 | | 0.3 % | 0.11 [ 0.02, 0.47 ] |
| Ten Bokkel 1998b | 6/42 | 6/16 | | 0.3 % | 0.38 [ 0.14, 1.01 ] |



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| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Thatcher 1999a | 19/42 | 13/22 | | 0.6 % | 0.77 [ 0.47, 1.24 ] |
| Thatcher 1999b | 9/44 | 13/22 | | 0.6 % | 0.35 [ 0.18, 0.68 ] |
| Thomas 2002 | 7/62 | 31/65 | | 1.0 % | 0.24 [ 0.11, 0.50 ] |
| Thompson 2000 | 34/45 | 19/21 | | 0.9 % | 0.84 [ 0.67, 1.04 ] |
| Throuvalas 2000 | 2/28 | 10/26 | | 0.3 % | 0.19 [ 0.04, 0.77 ] |
| Tjulandin 2010a | 8/76 | 9/37 | | 0.4 % | 0.43 [ 0.18, 1.03 ] |
| Tjulandin 2010b | 9/73 | 9/37 | | 0.4 % | 0.51 [ 0.22, 1.17 ] |
| Tjulandin 2011 | 13/95 | 23/91 | | 0.8 % | 0.54 [ 0.29, 1.00 ] |
| Tsuboi 2009 | 7/61 | 7/56 | | 0.2 % | 0.92 [ 0.34, 2.45 ] |
| Untch 2011˙1 | 1/356 | 0/377 | | 0.0 % | 3.18 [ 0.13, 77.72 ] |
| Vansteenkiste 02 FDA 2004 | 53/156 | 89/158 | | 2.9 % | 0.60 [ 0.47, 0.78 ] |
| Welch 1995 | 4/15 | 8/15 | | 0.3 % | 0.50 [ 0.19, 1.31 ] |
| Wilkinson 2006 | 9/114 | 18/59 | | 0.8 % | 0.26 [ 0.12, 0.54 ] |
| Witzig 2005 | 42/166 | 65/164 | | 2.2 % | 0.64 [ 0.46, 0.88 ] |
| Wright 2007 | 5/33 | 10/37 | | 0.3 % | 0.56 [ 0.21, 1.47 ] |
| Wurnig 1996 | 8/15 | 14/14 | | 0.5 % | 0.55 [ 0.34, 0.88 ] |
| **Total (95% CI)** | **8733** | **7360** | | **100.0 %** | **0.65 [ 0.62, 0.68 ]** |

Total events: 2198 (Treatment), 2880 (Control)

Heterogeneity: $Chi^2$ = 217.08, df = 87 (P<0.00001); $I^2$ =60%

Test for overall effect: Z = 19.89 (P < 0.00001)

Test for subgroup differences: Not applicable

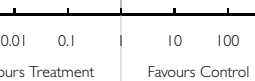
### Analysis 3.2. Comparison 3 Participants receiving red blood cell transfusions, Outcome 2 Participants receiving red blood cell transfusions - baseline Hb.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 3 Participants receiving red blood cell transfusions

Outcome: 2 Participants receiving red blood cell transfusions - baseline Hb

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 Hb <=10 g/dL | | | | | |
| Abels 1993 | 21/63 | 21/55 | | 0.7 % | 0.87 [ 0.54, 1.42 ] |
| Aravantinos 2003 | 9/24 | 23/23 | | 0.8 % | 0.39 [ 0.23, 0.64 ] |
| Boogaerts 2003 | 43/133 | 67/129 | | 2.2 % | 0.62 [ 0.46, 0.84 ] |
| Cascinu 1994 | 10/50 | 28/50 | | 0.9 % | 0.36 [ 0.19, 0.65 ] |
| Case 1993 | 32/79 | 36/74 | | 1.2 % | 0.83 [ 0.58, 1.19 ] |
| Cazzola 1995a | 7/31 | 2/7 | | 0.1 % | 0.79 [ 0.21, 3.02 ] |
| Cazzola 1995b | 5/29 | 2/8 | | 0.1 % | 0.69 [ 0.16, 2.91 ] |
| Cazzola 1995c | 6/31 | 2/7 | | 0.1 % | 0.68 [ 0.17, 2.68 ] |
| Cazzola 1995d | 4/26 | 2/7 | | 0.1 % | 0.54 [ 0.12, 2.36 ] |
| Dammacco 2001 | 19/69 | 36/76 | | 1.1 % | 0.58 [ 0.37, 0.91 ] |
| Fujisaka 2011 | 4/89 | 18/92 | | 0.6 % | 0.23 [ 0.08, 0.65 ] |
| Hedenus 2002a | 3/11 | 2/3 | | 0.1 % | 0.41 [ 0.12, 1.43 ] |
| Hedenus 2002b | 6/22 | 2/4 | | 0.1 % | 0.55 [ 0.17, 1.80 ] |
| Hedenus 2002c | 3/22 | 1/4 | | 0.1 % | 0.55 [ 0.07, 4.02 ] |
| Hedenus 2003 | 52/167 | 79/165 | | 2.6 % | 0.65 [ 0.49, 0.86 ] |
| Henry 1995 | 34/64 | 42/61 | | 1.4 % | 0.77 [ 0.58, 1.03 ] |
| Italian 1998 | 28/43 | 35/42 | | 1.2 % | 0.78 [ 0.60, 1.01 ] |
| Kotasek 2003a | 8/30 | 4/8 | | 0.2 % | 0.53 [ 0.21, 1.33 ] |
| Kotasek 2003b | 5/17 | 4/8 | | 0.2 % | 0.59 [ 0.21, 1.62 ] |
| Kotasek 2003c | 12/41 | 4/9 | | 0.2 % | 0.66 [ 0.28, 1.57 ] |
| Kotasek 2003d | 7/27 | 4/8 | | 0.2 % | 0.52 [ 0.20, 1.33 ] |
| Kotasek 2003e | 9/35 | 3/8 | | 0.2 % | 0.69 [ 0.24, 1.97 ] |
| Kotasek 2003f | 7/38 | 4/9 | | 0.2 % | 0.41 [ 0.15, 1.12 ] |
| Krzakowski 2008a | 27/104 | 14/52 | | 0.6 % | 0.96 [ 0.55, 1.68 ] |

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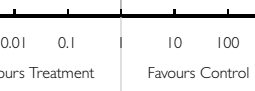
| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Krzakowski 2008b | 23/105 | 14/52 | | 0.6 % | 0.81 [ 0.46, 1.45 ] |
| Kurz 1997 | 5/23 | 8/12 | | 0.3 % | 0.33 [ 0.14, 0.78 ] |
| Littlewood 2001 | 62/251 | 49/124 | | 2.2 % | 0.63 [ 0.46, 0.85 ] |
| Oberhoff 1998 | 32/114 | 44/104 | | 1.5 % | 0.66 [ 0.46, 0.96 ] |
| Osterborg 1996a | 33/47 | 19/24 | | 0.8 % | 0.89 [ 0.67, 1.17 ] |
| Osterborg 1996b | 39/48 | 20/25 | | 0.9 % | 1.02 [ 0.80, 1.29 ] |
| Osterborg 2002 | 65/169 | 90/173 | | 2.9 % | 0.74 [ 0.58, 0.94 ] |
| Razzouk 2006 | 72/111 | 86/111 | | 2.8 % | 0.84 [ 0.71, 0.99 ] |
| Rose 1994 | 65/142 | 47/79 | | 2.0 % | 0.77 [ 0.60, 0.99 ] |
| Smith 2003a | 3/20 | 1/6 | | 0.1 % | 0.90 [ 0.11, 7.14 ] |
| Smith 2003b | 1/20 | 1/7 | | 0.0 % | 0.35 [ 0.03, 4.88 ] |
| Smith 2003c | 2/21 | 2/7 | | 0.1 % | 0.33 [ 0.06, 1.94 ] |
| Smith 2008 | 176/419 | 215/432 | | 7.0 % | 0.84 [ 0.73, 0.98 ] |
| Thompson 2000 | 34/45 | 19/21 | | 0.9 % | 0.84 [ 0.67, 1.04 ] |
| Tjulandin 2010a | 8/76 | 9/37 | | 0.4 % | 0.43 [ 0.18, 1.03 ] |
| Tjulandin 2010b | 9/73 | 9/37 | | 0.4 % | 0.51 [ 0.22, 1.17 ] |
| Tjulandin 2011 | 13/95 | 23/91 | | 0.8 % | 0.54 [ 0.29, 1.00 ] |
| Witzig 2005 | 42/166 | 65/164 | | 2.2 % | 0.64 [ 0.46, 0.88 ] |
| **Subtotal (95% CI)** | **3190** | **2415** | | **41.1 %** | **0.71 [ 0.67, 0.76 ]** |
| Total events: 1045 (Treatment), 1156 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 53.76, df = 41 (P = 0.09); $I^2$ =24% | | | | | |
| Test for overall effect: Z = 10.54 (P < 0.00001) | | | | | |
| 2 Hb 10 to 12 g/dL | | | | | |
| Aapro 2008 | 33/231 | 63/232 | | 2.1 % | 0.53 [ 0.36, 0.77 ] |
| Bamias 2003 | 11/72 | 24/72 | | 0.8 % | 0.46 [ 0.24, 0.86 ] |
| Blohmer 2011 | 14/127 | 38/129 | | 1.2 % | 0.37 [ 0.21, 0.66 ] |
| Carabantes 1999 | 4/20 | 13/15 | | 0.5 % | 0.23 [ 0.09, 0.57 ] |
| Chang 2005 | 15/175 | 40/175 | | 1.3 % | 0.38 [ 0.22, 0.65 ] |
| Charu 2007 | 27/226 | 13/59 | | 0.7 % | 0.54 [ 0.30, 0.98 ] |
| Christodoulou 2009 | 16/167 | 36/170 | | 1.2 % | 0.45 [ 0.26, 0.78 ] |
| EPO-INT-3 J%J 2004 | 21/136 | 23/65 | | 1.0 % | 0.44 [ 0.26, 0.73 ] |
| Gordon 2008 | 18/162 | 6/56 | | 0.3 % | 1.04 [ 0.43, 2.48 ] |
| Gupta 2009 | 9/58 | 25/57 | | 0.8 % | 0.35 [ 0.18, 0.69 ] |

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(. . . *Continued*)

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Hernandez 2009 | 58/193 | 91/193 | | 3.0 % | 0.64 [ 0.49, 0.83 ] |
| Huddart 2002 | 18/45 | 32/45 | | 1.1 % | 0.56 [ 0.38, 0.84 ] |
| Iconomou 2003 | 9/57 | 14/55 | | 0.5 % | 0.62 [ 0.29, 1.31 ] |
| Katakami 2008 | 7/103 | 20/104 | | 0.7 % | 0.35 [ 0.16, 0.80 ] |
| Pirker 2008 | 52/298 | 116/298 | | 3.8 % | 0.45 [ 0.34, 0.60 ] |
| Pronzato 2010 | 8/107 | 18/109 | | 0.6 % | 0.45 [ 0.21, 1.00 ] |
| Quirt 1996 | 4/27 | 8/27 | | 0.3 % | 0.50 [ 0.17, 1.47 ] |
| Ray-Coquard 2009 | 39/108 | 61/105 | | 2.0 % | 0.62 [ 0.46, 0.84 ] |
| Savonije 2005 | 77/211 | 66/102 | | 2.9 % | 0.56 [ 0.45, 0.71 ] |
| Strauss 2008 | 9/34 | 12/40 | | 0.4 % | 0.88 [ 0.42, 1.84 ] |
| Ten Bokkel 1998a | 2/45 | 7/17 | | 0.3 % | 0.11 [ 0.02, 0.47 ] |
| Ten Bokkel 1998b | 6/42 | 6/16 | | 0.3 % | 0.38 [ 0.14, 1.01 ] |
| Thomas 2002 | 7/62 | 31/65 | | 1.0 % | 0.24 [ 0.11, 0.50 ] |
| Throuvalas 2000 | 2/28 | 10/26 | | 0.3 % | 0.19 [ 0.04, 0.77 ] |
| Tsuboi 2009 | 7/61 | 7/56 | | 0.2 % | 0.92 [ 0.34, 2.45 ] |
| Vansteenkiste 02 FDA 2004 | 53/156 | 89/158 | | 2.9 % | 0.60 [ 0.47, 0.78 ] |
| Wilkinson 2006 | 9/114 | 18/59 | | 0.8 % | 0.26 [ 0.12, 0.54 ] |
| Wright 2007 | 5/33 | 10/37 | | 0.3 % | 0.56 [ 0.21, 1.47 ] |
| Wurnig 1996 | 8/15 | 14/14 | | 0.5 % | 0.55 [ 0.34, 0.88 ] |
| **Subtotal (95% CI)** | **3113** | **2556** | | **31.8 %** | **0.50 [ 0.46, 0.55 ]** |
| Total events: 548 (Treatment), 911 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 36.86, df = 28 (P = 0.12); $I^2$ =24% | | | | | |
| Test for overall effect: Z = 15.03 (P < 0.00001) | | | | | |
| 3 Hb > 12 g/dL | | | | | |
| Del Mastro 1997 | 0/31 | 2/31 | | 0.1 % | 0.20 [ 0.01, 4.00 ] |
| Dunphy 1999 | 2/13 | 5/14 | | 0.2 % | 0.43 [ 0.10, 1.85 ] |
| Engert 2010 | 405/640 | 467/643 | | 15.3 % | 0.87 [ 0.81, 0.94 ] |
| Gebbia 2003 | 5/22 | 13/23 | | 0.4 % | 0.40 [ 0.17, 0.94 ] |
| Goss 2005 | 8/52 | 27/52 | | 0.9 % | 0.30 [ 0.15, 0.59 ] |
| Grote 2005 | 26/109 | 42/115 | | 1.3 % | 0.65 [ 0.43, 0.99 ] |
| Kunikane 2001a | 1/16 | 0/9 | | 0.0 % | 1.76 [ 0.08, 39.32 ] |
| Kunikane 2001b | 2/18 | 0/10 | | 0.0 % | 2.89 [ 0.15, 54.98 ] |
| Leyland-Jones 2005 | 47/469 | 66/470 | | 2.2 % | 0.71 [ 0.50, 1.01 ] |


(*Continued* . . . )

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| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Milroy 2011 | 16/189 | 43/191 | | 1.4 % | 0.38 [ 0.22, 0.64 ] |
| Moebus 2007 | 41/320 | 86/305 | | 2.9 % | 0.45 [ 0.32, 0.64 ] |
| O'Shaughnessy 2005 | 0/47 | 4/47 | | 0.1 % | 0.11 [ 0.01, 2.01 ] |
| Rosen 2003 | 19/47 | 24/43 | | 0.8 % | 0.72 [ 0.47, 1.12 ] |
| Thatcher 1999a | 19/42 | 13/22 | | 0.6 % | 0.77 [ 0.47, 1.24 ] |
| Thatcher 1999b | 9/44 | 13/22 | | 0.6 % | 0.35 [ 0.18, 0.68 ] |
| Untch 2011˙1 | 1/356 | 0/377 | | 0.0 % | 3.18 [ 0.13, 77.72 ] |
| Welch 1995 | 4/15 | 8/15 | | 0.3 % | 0.50 [ 0.19, 1.31 ] |
| **Subtotal (95% CI)** | **2430** | **2389** | | **27.1 %** | **0.73 [ 0.67, 0.78 ]** |
| Total events: 605 (Treatment), 813 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 54.28, df = 16 (P<0.00001); $I^2$ =71% | | | | | |
| Test for overall effect: Z = 8.52 (P < 0.00001) | | | | | |
| 4 unclear | | | | | |
| **Subtotal (95% CI)** | **0** | **0** | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Total events: 0 (Treatment), 0 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: not applicable | | | | | |
| **Total (95% CI)** | **8733** | **7360** | | **100.0 %** | **0.65 [ 0.62, 0.68 ]** |
| Total events: 2198 (Treatment), 2880 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 217.08, df = 87 (P<0.00001); $I^2$ =60% | | | | | |
| Test for overall effect: Z = 19.89 (P < 0.00001) | | | | | |
| Test for subgroup differences: $Chi^2$ = 48.26, df = 2 (P = 0.00), $I^2$ =96% | | | | | |

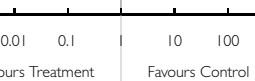
### Analysis 3.3. Comparison 3 Participants receiving red blood cell transfusions, Outcome 3 Participants receiving red blood cell transfusions - different malignancies.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 3 Participants receiving red blood cell transfusions

Outcome: 3 Participants receiving red blood cell transfusions - different malignancies

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 solid tumours | | | | | |
| Aapro 2008 | 33/231 | 63/232 | | 2.1 % | 0.53 [ 0.36, 0.77 ] |
| Aravantinos 2003 | 9/24 | 23/23 | | 0.8 % | 0.39 [ 0.23, 0.64 ] |
| Bamias 2003 | 11/72 | 24/72 | | 0.8 % | 0.46 [ 0.24, 0.86 ] |
| Blohmer 2011 | 14/127 | 38/129 | | 1.2 % | 0.37 [ 0.21, 0.66 ] |
| Carabantes 1999 | 4/20 | 13/15 | | 0.5 % | 0.23 [ 0.09, 0.57 ] |
| Cascinu 1994 | 10/50 | 28/50 | | 0.9 % | 0.36 [ 0.19, 0.65 ] |
| Chang 2005 | 15/175 | 40/175 | | 1.3 % | 0.38 [ 0.22, 0.65 ] |
| Christodoulou 2009 | 16/167 | 36/170 | | 1.2 % | 0.45 [ 0.26, 0.78 ] |
| Del Mastro 1997 | 0/31 | 2/31 | | 0.1 % | 0.20 [ 0.01, 4.00 ] |
| Dunphy 1999 | 2/13 | 5/14 | | 0.2 % | 0.43 [ 0.10, 1.85 ] |
| Fujisaka 2011 | 4/89 | 18/92 | | 0.6 % | 0.23 [ 0.08, 0.65 ] |
| Gebbia 2003 | 5/22 | 13/23 | | 0.4 % | 0.40 [ 0.17, 0.94 ] |
| Goss 2005 | 8/52 | 27/52 | | 0.9 % | 0.30 [ 0.15, 0.59 ] |
| Grote 2005 | 26/109 | 42/115 | | 1.3 % | 0.65 [ 0.43, 0.99 ] |
| Gupta 2009 | 9/58 | 25/57 | | 0.8 % | 0.35 [ 0.18, 0.69 ] |
| Huddart 2002 | 18/45 | 32/45 | | 1.1 % | 0.56 [ 0.38, 0.84 ] |
| Iconomou 2003 | 9/57 | 14/55 | | 0.5 % | 0.62 [ 0.29, 1.31 ] |
| Katakami 2008 | 7/103 | 20/104 | | 0.7 % | 0.35 [ 0.16, 0.80 ] |
| Kotasek 2003a | 8/30 | 4/8 | | 0.2 % | 0.53 [ 0.21, 1.33 ] |
| Kotasek 2003b | 5/17 | 4/8 | | 0.2 % | 0.59 [ 0.21, 1.62 ] |
| Kotasek 2003c | 12/41 | 4/9 | | 0.2 % | 0.66 [ 0.28, 1.57 ] |
| Kotasek 2003d | 7/27 | 4/8 | | 0.2 % | 0.52 [ 0.20, 1.33 ] |
| Kotasek 2003e | 9/35 | 3/8 | | 0.2 % | 0.69 [ 0.24, 1.97 ] |
| Kotasek 2003f | 7/38 | 4/9 | | 0.2 % | 0.41 [ 0.15, 1.12 ] |




(*Continued* . . . )

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| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Kunikane 2001a | 1/16 | 0/9 | | 0.0 % | 1.76 [ 0.08, 39.32 ] |
| Kunikane 2001b | 2/18 | 0/10 | | 0.0 % | 2.89 [ 0.15, 54.98 ] |
| Kurz 1997 | 5/23 | 8/12 | | 0.3 % | 0.33 [ 0.14, 0.78 ] |
| Leyland-Jones 2005 | 47/469 | 66/470 | | 2.2 % | 0.71 [ 0.50, 1.01 ] |
| Littlewood 2001 | 33/136 | 24/66 | | 1.1 % | 0.67 [ 0.43, 1.03 ] |
| Milroy 2011 | 16/189 | 43/191 | | 1.4 % | 0.38 [ 0.22, 0.64 ] |
| Moebus 2007 | 41/320 | 86/305 | | 2.9 % | 0.45 [ 0.32, 0.64 ] |
| O'Shaughnessy 2005 | 0/47 | 4/47 | | 0.1 % | 0.11 [ 0.01, 2.01 ] |
| Oberhoff 1998 | 32/114 | 44/104 | | 1.5 % | 0.66 [ 0.46, 0.96 ] |
| Pirker 2008 | 52/298 | 116/298 | | 3.8 % | 0.45 [ 0.34, 0.60 ] |
| Pronzato 2010 | 8/107 | 18/109 | | 0.6 % | 0.45 [ 0.21, 1.00 ] |
| Rosen 2003 | 19/47 | 24/43 | | 0.8 % | 0.72 [ 0.47, 1.12 ] |
| Savonije 2005 | 77/211 | 66/102 | | 2.9 % | 0.56 [ 0.45, 0.71 ] |
| Strauss 2008 | 9/34 | 12/40 | | 0.4 % | 0.88 [ 0.42, 1.84 ] |
| Ten Bokkel 1998a | 2/45 | 7/17 | | 0.3 % | 0.11 [ 0.02, 0.47 ] |
| Ten Bokkel 1998b | 6/42 | 6/16 | | 0.3 % | 0.38 [ 0.14, 1.01 ] |
| Thatcher 1999a | 19/42 | 13/22 | | 0.6 % | 0.77 [ 0.47, 1.24 ] |
| Thatcher 1999b | 9/44 | 13/22 | | 0.6 % | 0.35 [ 0.18, 0.68 ] |
| Thomas 2002 | 7/62 | 31/65 | | 1.0 % | 0.24 [ 0.11, 0.50 ] |
| Throuvalas 2000 | 2/28 | 10/26 | | 0.3 % | 0.19 [ 0.04, 0.77 ] |
| Tjulandin 2010a | 8/76 | 9/37 | | 0.4 % | 0.43 [ 0.18, 1.03 ] |
| Tjulandin 2010b | 9/73 | 9/37 | | 0.4 % | 0.51 [ 0.22, 1.17 ] |
| Untch 2011˙1 | 1/356 | 0/377 | | 0.0 % | 3.18 [ 0.13, 77.72 ] |
| Vansteenkiste 02 FDA 2004 | 53/156 | 89/158 | | 2.9 % | 0.60 [ 0.47, 0.78 ] |
| Welch 1995 | 4/15 | 8/15 | | 0.3 % | 0.50 [ 0.19, 1.31 ] |
| Wilkinson 2006 | 9/114 | 18/59 | | 0.8 % | 0.26 [ 0.12, 0.54 ] |
| Witzig 2005 | 42/166 | 65/164 | | 2.2 % | 0.64 [ 0.46, 0.88 ] |
| Wright 2007 | 5/33 | 10/37 | | 0.3 % | 0.56 [ 0.21, 1.47 ] |
| Wurnig 1996 | 8/15 | 14/14 | | 0.5 % | 0.55 [ 0.34, 0.88 ] |
| **Subtotal (95% CI)** | **4929** | **4376** | | **45.4 %** | **0.50 [ 0.46, 0.54 ]** |
| Total events: 774 (Treatment), 1299 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 60.78, df = 52 (P = 0.19); $I^2$ =14% | | | | | |


(*Continued* . . . )

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| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Test for overall effect: Z = 17.82 (P < 0.00001) | | | | | |
| 2 haematological malignancies | | | | | |
| Cazzola 1995a | 7/31 | 2/7 | | 0.1 % | 0.79 [ 0.21, 3.02 ] |
| Cazzola 1995b | 5/29 | 2/8 | | 0.1 % | 0.69 [ 0.16, 2.91 ] |
| Cazzola 1995c | 6/31 | 2/7 | | 0.1 % | 0.68 [ 0.17, 2.68 ] |
| Cazzola 1995d | 4/26 | 2/7 | | 0.1 % | 0.54 [ 0.12, 2.36 ] |
| Dammacco 2001 | 19/69 | 36/76 | | 1.1 % | 0.58 [ 0.37, 0.91 ] |
| Engert 2010 | 405/640 | 467/643 | | 15.3 % | 0.87 [ 0.81, 0.94 ] |
| Hedenus 2002a | 3/11 | 2/3 | | 0.1 % | 0.41 [ 0.12, 1.43 ] |
| Hedenus 2002b | 6/22 | 2/4 | | 0.1 % | 0.55 [ 0.17, 1.80 ] |
| Hedenus 2002c | 3/22 | 1/4 | | 0.1 % | 0.55 [ 0.07, 4.02 ] |
| Hedenus 2003 | 52/167 | 79/165 | | 2.6 % | 0.65 [ 0.49, 0.86 ] |
| Littlewood 2001 | 29/115 | 25/58 | | 1.1 % | 0.59 [ 0.38, 0.90 ] |
| Osterborg 1996a | 33/47 | 19/24 | | 0.8 % | 0.89 [ 0.67, 1.17 ] |
| Osterborg 1996b | 39/48 | 20/25 | | 0.9 % | 1.02 [ 0.80, 1.29 ] |
| Osterborg 2002 | 65/169 | 90/173 | | 2.9 % | 0.74 [ 0.58, 0.94 ] |
| Rose 1994 | 65/142 | 47/79 | | 2.0 % | 0.77 [ 0.60, 0.99 ] |
| **Subtotal (95% CI)** | **1569** | **1283** | | **27.5 %** | **0.80 [ 0.75, 0.86 ]** |
| Total events: 741 (Treatment), 796 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 17.50, df = 14 (P = 0.23); $I^2$ =20% | | | | | |
| Test for overall effect: Z = 6.64 (P < 0.00001) | | | | | |
| 3 MDS | | | | | |
| Italian 1998 | 28/43 | 35/42 | | 1.2 % | 0.78 [ 0.60, 1.01 ] |
| Thompson 2000 | 34/45 | 19/21 | | 0.9 % | 0.84 [ 0.67, 1.04 ] |
| **Subtotal (95% CI)** | **88** | **63** | | **2.0 %** | **0.80 [ 0.68, 0.96 ]** |
| Total events: 62 (Treatment), 54 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 0.16, df = 1 (P = 0.68); $I^2$ =0.0% | | | | | |
| Test for overall effect: Z = 2.46 (P = 0.014) | | | | | |
| 4 mixed | | | | | |
| Abels 1993 | 21/63 | 21/55 | | 0.7 % | 0.87 [ 0.54, 1.42 ] |
| Boogaerts 2003 | 43/133 | 67/129 | | 2.2 % | 0.62 [ 0.46, 0.84 ] |
| Case 1993 | 32/79 | 36/74 | | 1.2 % | 0.83 [ 0.58, 1.19 ] |
| Charu 2007 | 27/226 | 13/59 | | 0.7 % | 0.54 [ 0.30, 0.98 ] |
| EPO-INT-3 J%J 2004 | 21/136 | 23/65 | | 1.0 % | 0.44 [ 0.26, 0.73 ] |
| Gordon 2008 | 18/162 | 6/56 | | 0.3 % | 1.04 [ 0.43, 2.48 ] |


(*Continued* . . . )

(. . . *Continued*)

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Henry 1995 | 34/64 | 42/61 | | 1.4 % | 0.77 [ 0.58, 1.03 ] |
| Hernandez 2009 | 58/193 | 91/193 | | 3.0 % | 0.64 [ 0.49, 0.83 ] |
| Krzakowski 2008a | 27/104 | 14/52 | | 0.6 % | 0.96 [ 0.55, 1.68 ] |
| Krzakowski 2008b | 23/105 | 14/52 | | 0.6 % | 0.81 [ 0.46, 1.45 ] |
| Quirt 1996 | 4/27 | 8/27 | | 0.3 % | 0.50 [ 0.17, 1.47 ] |
| Ray-Coquard 2009 | 39/108 | 61/105 | | 2.0 % | 0.62 [ 0.46, 0.84 ] |
| Razzouk 2006 | 72/111 | 86/111 | | 2.8 % | 0.84 [ 0.71, 0.99 ] |
| Smith 2003a | 3/20 | 1/6 | | 0.1 % | 0.90 [ 0.11, 7.14 ] |
| Smith 2003b | 1/20 | 1/7 | | 0.0 % | 0.35 [ 0.03, 4.88 ] |
| Smith 2003c | 2/21 | 2/7 | | 0.1 % | 0.33 [ 0.06, 1.94 ] |
| Smith 2008 | 176/419 | 215/432 | | 7.0 % | 0.84 [ 0.73, 0.98 ] |
| Tjulandin 2011 | 13/95 | 23/91 | | 0.8 % | 0.54 [ 0.29, 1.00 ] |
| Tsuboi 2009 | 7/61 | 7/56 | | 0.2 % | 0.92 [ 0.34, 2.45 ] |
| **Subtotal (95% CI)** | **2147** | **1638** | | **25.1 %** | **0.74 [ 0.68, 0.80 ]** |
| Total events: 621 (Treatment), 731 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 19.35, df = 18 (P = 0.37); $I^2$ =7% | | | | | |
| Test for overall effect: Z = 7.20 (P < 0.00001) | | | | | |
| 5 not reported | | | | | |
| **Subtotal (95% CI)** | **0** | **0** | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Total events: 0 (Treatment), 0 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: not applicable | | | | | |
| **Total (95% CI)** | **8733** | **7360** | | **100.0 %** | **0.65 [ 0.62, 0.68 ]** |
| Total events: 2198 (Treatment), 2880 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 217.26, df = 88 (P<0.00001); $I^2$ =59% | | | | | |
| Test for overall effect: Z = 19.89 (P < 0.00001) | | | | | |
| Test for subgroup differences: $Chi^2$ = 97.22, df = 3 (P = 0.0), $I^2$ =97% | | | | | |

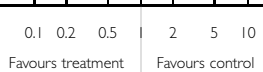
## Analysis 3.4. Comparison 3 Participants receiving red blood cell transfusions, Outcome 4 Participants receiving red blood cell transfusions - age.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 3 Participants receiving red blood cell transfusions

Outcome: 4 Participants receiving red blood cell transfusions - age

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 children | | | | | |
| Razzouk 2006 | 72/111 | 86/111 | | 2.8 % | 0.84 [ 0.71, 0.99 ] |
| **Subtotal (95% CI)** | **111** | **111** | | **2.8 %** | **0.84 [ 0.71, 0.99 ]** |
| Total events: 72 (Treatment), 86 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 2.05 (P = 0.040) | | | | | |
| 2 adults | | | | | |
| Aapro 2008 | 33/231 | 63/232 | | 2.1 % | 0.53 [ 0.36, 0.77 ] |
| Abels 1993 | 21/63 | 21/55 | | 0.7 % | 0.87 [ 0.54, 1.42 ] |
| Aravantinos 2003 | 9/24 | 23/23 | | 0.8 % | 0.39 [ 0.23, 0.64 ] |
| Bamias 2003 | 11/72 | 24/72 | | 0.8 % | 0.46 [ 0.24, 0.86 ] |
| Blohmer 2011 | 14/127 | 38/129 | | 1.2 % | 0.37 [ 0.21, 0.66 ] |
| Boogaerts 2003 | 43/133 | 67/129 | | 2.2 % | 0.62 [ 0.46, 0.84 ] |
| Carabantes 1999 | 4/20 | 13/15 | | 0.5 % | 0.23 [ 0.09, 0.57 ] |
| Cascinu 1994 | 10/50 | 28/50 | | 0.9 % | 0.36 [ 0.19, 0.65 ] |
| Case 1993 | 32/79 | 36/74 | | 1.2 % | 0.83 [ 0.58, 1.19 ] |
| Cazzola 1995a | 7/31 | 2/7 | | 0.1 % | 0.79 [ 0.21, 3.02 ] |
| Cazzola 1995b | 5/29 | 2/8 | | 0.1 % | 0.69 [ 0.16, 2.91 ] |
| Cazzola 1995c | 6/31 | 2/7 | | 0.1 % | 0.68 [ 0.17, 2.68 ] |
| Cazzola 1995d | 4/26 | 2/7 | | 0.1 % | 0.54 [ 0.12, 2.36 ] |
| Chang 2005 | 15/175 | 40/175 | | 1.3 % | 0.38 [ 0.22, 0.65 ] |
| Charu 2007 | 27/226 | 13/59 | | 0.7 % | 0.54 [ 0.30, 0.98 ] |
| Christodoulou 2009 | 16/167 | 36/170 | | 1.2 % | 0.45 [ 0.26, 0.78 ] |
| Dammacco 2001 | 19/69 | 36/76 | | 1.1 % | 0.58 [ 0.37, 0.91 ] |
| Del Mastro 1997 | 0/31 | 2/31 | | 0.1 % | 0.20 [ 0.01, 4.00 ] |
| Dunphy 1999 | 2/13 | 5/14 | | 0.2 % | 0.43 [ 0.10, 1.85 ] |
| Engert 2010 | 405/640 | 467/643 | | 15.3 % | 0.87 [ 0.81, 0.94 ] |

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| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| EPO-INT-3 J%J 2004 | 21/136 | 23/65 | | 1.0 % | 0.44 [ 0.26, 0.73 ] |
| Fujisaka 2011 | 4/89 | 18/92 | | 0.6 % | 0.23 [ 0.08, 0.65 ] |
| Gebbia 2003 | 5/22 | 13/23 | | 0.4 % | 0.40 [ 0.17, 0.94 ] |
| Gordon 2008 | 18/162 | 6/56 | | 0.3 % | 1.04 [ 0.43, 2.48 ] |
| Goss 2005 | 8/52 | 27/52 | | 0.9 % | 0.30 [ 0.15, 0.59 ] |
| Grote 2005 | 26/109 | 42/115 | | 1.3 % | 0.65 [ 0.43, 0.99 ] |
| Gupta 2009 | 9/58 | 25/57 | | 0.8 % | 0.35 [ 0.18, 0.69 ] |
| Hedenus 2002a | 3/11 | 2/3 | | 0.1 % | 0.41 [ 0.12, 1.43 ] |
| Hedenus 2002b | 6/22 | 2/4 | | 0.1 % | 0.55 [ 0.17, 1.80 ] |
| Hedenus 2002c | 3/22 | 1/4 | | 0.1 % | 0.55 [ 0.07, 4.02 ] |
| Hedenus 2003 | 52/167 | 79/165 | | 2.6 % | 0.65 [ 0.49, 0.86 ] |
| Henry 1995 | 34/64 | 42/61 | | 1.4 % | 0.77 [ 0.58, 1.03 ] |
| Hernandez 2009 | 58/193 | 91/193 | | 3.0 % | 0.64 [ 0.49, 0.83 ] |
| Huddart 2002 | 18/45 | 32/45 | | 1.1 % | 0.56 [ 0.38, 0.84 ] |
| Iconomou 2003 | 9/57 | 14/55 | | 0.5 % | 0.62 [ 0.29, 1.31 ] |
| Italian 1998 | 28/43 | 35/42 | | 1.2 % | 0.78 [ 0.60, 1.01 ] |
| Katakami 2008 | 7/103 | 20/104 | | 0.7 % | 0.35 [ 0.16, 0.80 ] |
| Kotasek 2003a | 8/30 | 4/8 | | 0.2 % | 0.53 [ 0.21, 1.33 ] |
| Kotasek 2003b | 5/17 | 4/8 | | 0.2 % | 0.59 [ 0.21, 1.62 ] |
| Kotasek 2003c | 12/41 | 4/9 | | 0.2 % | 0.66 [ 0.28, 1.57 ] |
| Kotasek 2003d | 7/27 | 4/8 | | 0.2 % | 0.52 [ 0.20, 1.33 ] |
| Kotasek 2003e | 9/35 | 3/8 | | 0.2 % | 0.69 [ 0.24, 1.97 ] |
| Kotasek 2003f | 7/38 | 4/9 | | 0.2 % | 0.41 [ 0.15, 1.12 ] |
| Krzakowski 2008a | 27/104 | 14/52 | | 0.6 % | 0.96 [ 0.55, 1.68 ] |
| Krzakowski 2008b | 23/105 | 14/52 | | 0.6 % | 0.81 [ 0.46, 1.45 ] |
| Kunikane 2001a | 1/16 | 0/9 | | 0.0 % | 1.76 [ 0.08, 39.32 ] |
| Kunikane 2001b | 2/18 | 0/10 | | 0.0 % | 2.89 [ 0.15, 54.98 ] |
| Kurz 1997 | 5/23 | 8/12 | | 0.3 % | 0.33 [ 0.14, 0.78 ] |
| Leyland-Jones 2005 | 47/469 | 66/470 | | 2.2 % | 0.71 [ 0.50, 1.01 ] |
| Littlewood 2001 | 62/251 | 49/124 | | 2.2 % | 0.63 [ 0.46, 0.85 ] |
| Milroy 2011 | 16/189 | 43/191 | | 1.4 % | 0.38 [ 0.22, 0.64 ] |


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| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Moebus 2007 | 41/320 | 86/305 | | 2.9 % | 0.45 [ 0.32, 0.64 ] |
| O'Shaughnessy 2005 | 0/47 | 4/47 | | 0.1 % | 0.11 [ 0.01, 2.01 ] |
| Oberhoff 1998 | 32/114 | 44/104 | | 1.5 % | 0.66 [ 0.46, 0.96 ] |
| Osterborg 1996a | 33/47 | 19/24 | | 0.8 % | 0.89 [ 0.67, 1.17 ] |
| Osterborg 1996b | 39/48 | 20/25 | | 0.9 % | 1.02 [ 0.80, 1.29 ] |
| Osterborg 2002 | 65/169 | 90/173 | | 2.9 % | 0.74 [ 0.58, 0.94 ] |
| Pirker 2008 | 52/298 | 116/298 | | 3.8 % | 0.45 [ 0.34, 0.60 ] |
| Pronzato 2010 | 8/107 | 18/109 | | 0.6 % | 0.45 [ 0.21, 1.00 ] |
| Quirt 1996 | 4/27 | 8/27 | | 0.3 % | 0.50 [ 0.17, 1.47 ] |
| Ray-Coquard 2009 | 39/108 | 61/105 | | 2.0 % | 0.62 [ 0.46, 0.84 ] |
| Rose 1994 | 65/142 | 47/79 | | 2.0 % | 0.77 [ 0.60, 0.99 ] |
| Rosen 2003 | 19/47 | 24/43 | | 0.8 % | 0.72 [ 0.47, 1.12 ] |
| Savonije 2005 | 77/211 | 66/102 | | 2.9 % | 0.56 [ 0.45, 0.71 ] |
| Smith 2003a | 3/20 | 1/6 | | 0.1 % | 0.90 [ 0.11, 7.14 ] |
| Smith 2003b | 1/20 | 1/7 | | 0.0 % | 0.35 [ 0.03, 4.88 ] |
| Smith 2003c | 2/21 | 2/7 | | 0.1 % | 0.33 [ 0.06, 1.94 ] |
| Smith 2008 | 176/419 | 215/432 | | 7.0 % | 0.84 [ 0.73, 0.98 ] |
| Strauss 2008 | 9/34 | 12/40 | | 0.4 % | 0.88 [ 0.42, 1.84 ] |
| Ten Bokkel 1998a | 2/45 | 7/17 | | 0.3 % | 0.11 [ 0.02, 0.47 ] |
| Ten Bokkel 1998b | 6/42 | 6/16 | | 0.3 % | 0.38 [ 0.14, 1.01 ] |
| Thatcher 1999a | 19/42 | 13/22 | | 0.6 % | 0.77 [ 0.47, 1.24 ] |
| Thatcher 1999b | 9/44 | 13/22 | | 0.6 % | 0.35 [ 0.18, 0.68 ] |
| Thomas 2002 | 7/62 | 31/65 | | 1.0 % | 0.24 [ 0.11, 0.50 ] |
| Thompson 2000 | 34/45 | 19/21 | | 0.9 % | 0.84 [ 0.67, 1.04 ] |
| Throuvalas 2000 | 2/28 | 10/26 | | 0.3 % | 0.19 [ 0.04, 0.77 ] |
| Tjulandin 2010a | 8/76 | 9/37 | | 0.4 % | 0.43 [ 0.18, 1.03 ] |
| Tjulandin 2010b | 9/73 | 9/37 | | 0.4 % | 0.51 [ 0.22, 1.17 ] |
| Tjulandin 2011 | 13/95 | 23/91 | | 0.8 % | 0.54 [ 0.29, 1.00 ] |
| Tsuboi 2009 | 7/61 | 7/56 | | 0.2 % | 0.92 [ 0.34, 2.45 ] |
| Untch 2011˙1 | 1/356 | 0/377 | | 0.0 % | 3.18 [ 0.13, 77.72 ] |
| Vansteenkiste 02 FDA 2004 | 53/156 | 89/158 | | 2.9 % | 0.60 [ 0.47, 0.78 ] |


(*Continued* . . . )

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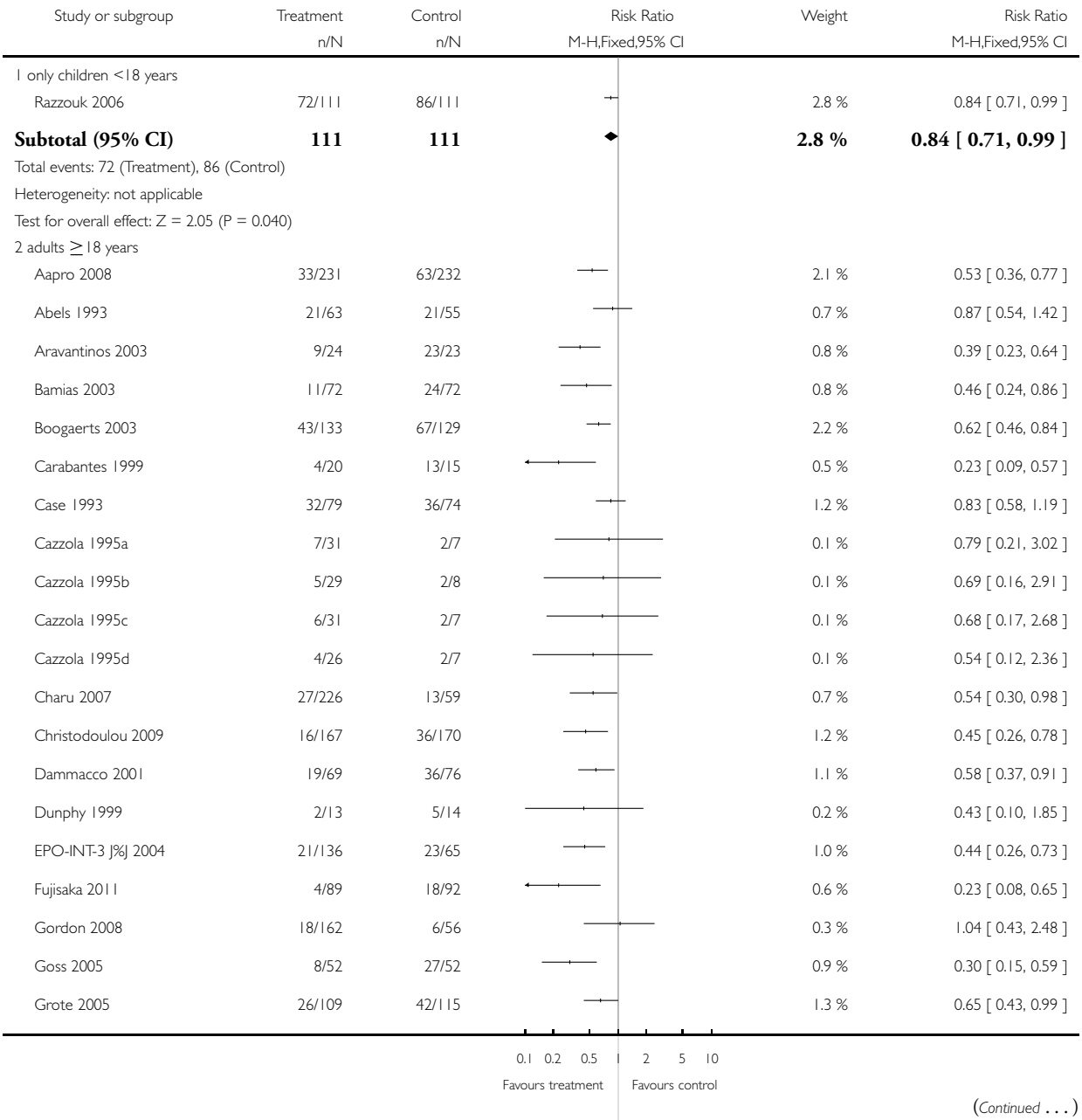
| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Welch 1995 | 4/15 | 8/15 | | 0.3 % | 0.50 [ 0.19, 1.31 ] |
| Wilkinson 2006 | 9/114 | 18/59 | | 0.8 % | 0.26 [ 0.12, 0.54 ] |
| Witzig 2005 | 42/166 | 65/164 | | 2.2 % | 0.64 [ 0.46, 0.88 ] |
| Wright 2007 | 5/33 | 10/37 | | 0.3 % | 0.56 [ 0.21, 1.47 ] |
| Wurnig 1996 | 8/15 | 14/14 | | 0.5 % | 0.55 [ 0.34, 0.88 ] |
| **Subtotal (95% CI)** | **8622** | **7249** | | **97.2 %** | **0.64 [ 0.62, 0.67 ]** |
| Total events: 2126 (Treatment), 2794 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 211.91, df = 86 (P<0.00001); $I^2$ =59% | | | | | |
| Test for overall effect: Z = 19.79 (P < 0.00001) | | | | | |
| **Total (95% CI)** | **8733** | **7360** | | **100.0 %** | **0.65 [ 0.62, 0.68 ]** |
| Total events: 2198 (Treatment), 2880 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 217.08, df = 87 (P<0.00001); $I^2$ =60% | | | | | |
| Test for overall effect: Z = 19.89 (P < 0.00001) | | | | | |
| Test for subgroup differences: $Chi^2$ = 8.64, df = 1 (P = 0.00), $I^2$ =88% | | | | | |

### Analysis 3.5. Comparison 3 Participants receiving red blood cell transfusions, Outcome 5 Participants receiving red blood cell transfusions - age differentiated.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 3 Participants receiving red blood cell transfusions

Outcome: 5 Participants receiving red blood cell transfusions - age differentiated

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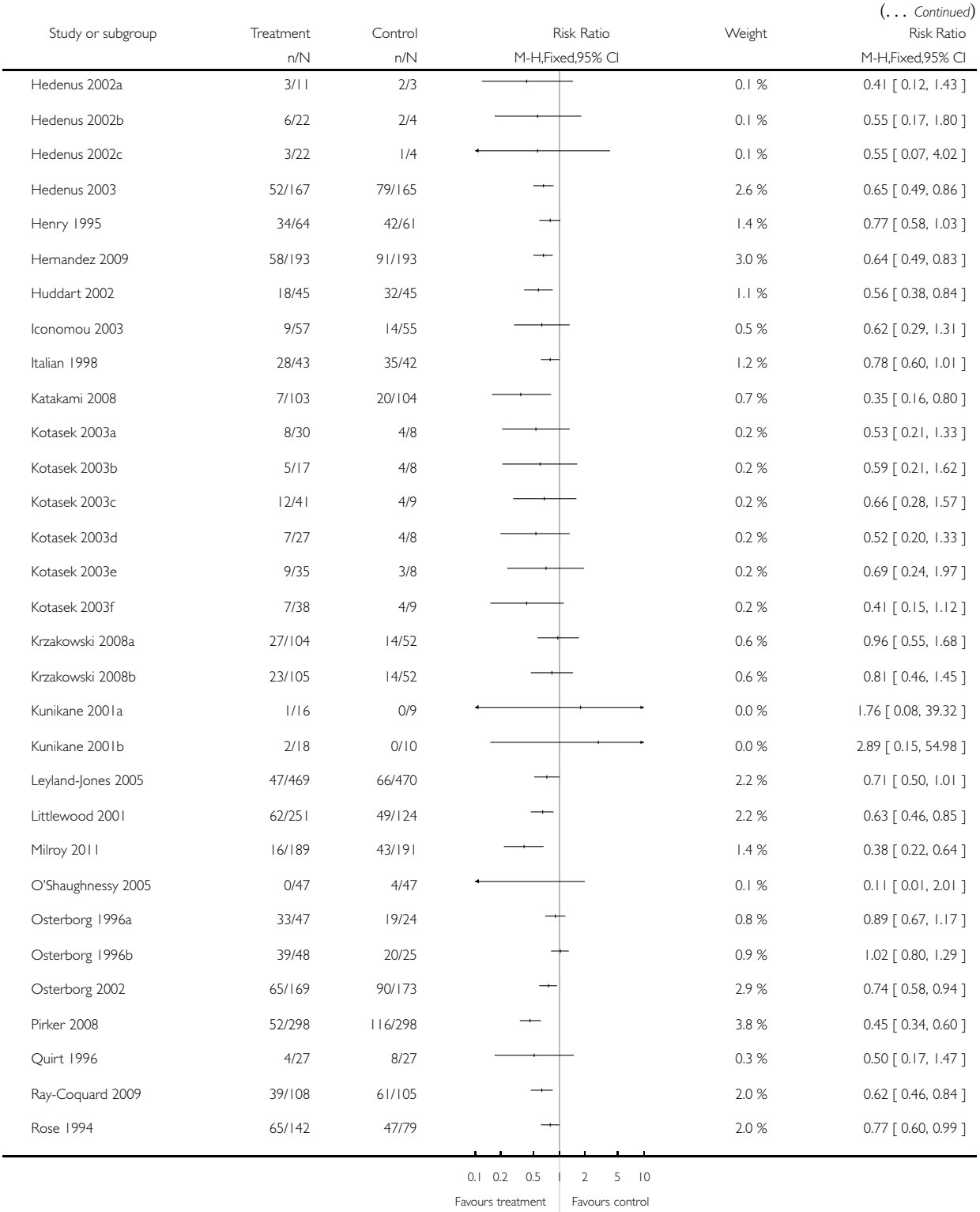

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Hedenus 2002a | 3/11 | 2/3 | | 0.1 % | 0.41 [ 0.12, 1.43 ] |
| Hedenus 2002b | 6/22 | 2/4 | | 0.1 % | 0.55 [ 0.17, 1.80 ] |
| Hedenus 2002c | 3/22 | 1/4 | | 0.1 % | 0.55 [ 0.07, 4.02 ] |
| Hedenus 2003 | 52/167 | 79/165 | | 2.6 % | 0.65 [ 0.49, 0.86 ] |
| Henry 1995 | 34/64 | 42/61 | | 1.4 % | 0.77 [ 0.58, 1.03 ] |
| Hernandez 2009 | 58/193 | 91/193 | | 3.0 % | 0.64 [ 0.49, 0.83 ] |
| Huddart 2002 | 18/45 | 32/45 | | 1.1 % | 0.56 [ 0.38, 0.84 ] |
| Iconomou 2003 | 9/57 | 14/55 | | 0.5 % | 0.62 [ 0.29, 1.31 ] |
| Italian 1998 | 28/43 | 35/42 | | 1.2 % | 0.78 [ 0.60, 1.01 ] |
| Katakami 2008 | 7/103 | 20/104 | | 0.7 % | 0.35 [ 0.16, 0.80 ] |
| Kotasek 2003a | 8/30 | 4/8 | | 0.2 % | 0.53 [ 0.21, 1.33 ] |
| Kotasek 2003b | 5/17 | 4/8 | | 0.2 % | 0.59 [ 0.21, 1.62 ] |
| Kotasek 2003c | 12/41 | 4/9 | | 0.2 % | 0.66 [ 0.28, 1.57 ] |
| Kotasek 2003d | 7/27 | 4/8 | | 0.2 % | 0.52 [ 0.20, 1.33 ] |
| Kotasek 2003e | 9/35 | 3/8 | | 0.2 % | 0.69 [ 0.24, 1.97 ] |
| Kotasek 2003f | 7/38 | 4/9 | | 0.2 % | 0.41 [ 0.15, 1.12 ] |
| Krzakowski 2008a | 27/104 | 14/52 | | 0.6 % | 0.96 [ 0.55, 1.68 ] |
| Krzakowski 2008b | 23/105 | 14/52 | | 0.6 % | 0.81 [ 0.46, 1.45 ] |
| Kunikane 2001a | 1/16 | 0/9 | | 0.0 % | 1.76 [ 0.08, 39.32 ] |
| Kunikane 2001b | 2/18 | 0/10 | | 0.0 % | 2.89 [ 0.15, 54.98 ] |
| Leyland-Jones 2005 | 47/469 | 66/470 | | 2.2 % | 0.71 [ 0.50, 1.01 ] |
| Littlewood 2001 | 62/251 | 49/124 | | 2.2 % | 0.63 [ 0.46, 0.85 ] |
| Milroy 2011 | 16/189 | 43/191 | | 1.4 % | 0.38 [ 0.22, 0.64 ] |
| O'Shaughnessy 2005 | 0/47 | 4/47 | | 0.1 % | 0.11 [ 0.01, 2.01 ] |
| Osterborg 1996a | 33/47 | 19/24 | | 0.8 % | 0.89 [ 0.67, 1.17 ] |
| Osterborg 1996b | 39/48 | 20/25 | | 0.9 % | 1.02 [ 0.80, 1.29 ] |
| Osterborg 2002 | 65/169 | 90/173 | | 2.9 % | 0.74 [ 0.58, 0.94 ] |
| Pirker 2008 | 52/298 | 116/298 | | 3.8 % | 0.45 [ 0.34, 0.60 ] |
| Quirt 1996 | 4/27 | 8/27 | | 0.3 % | 0.50 [ 0.17, 1.47 ] |
| Ray-Coquard 2009 | 39/108 | 61/105 | | 2.0 % | 0.62 [ 0.46, 0.84 ] |
| Rose 1994 | 65/142 | 47/79 | | 2.0 % | 0.77 [ 0.60, 0.99 ] |



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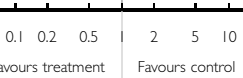
| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Savonije 2005 | 77/211 | 66/102 | | 2.9 % | 0.56 [ 0.45, 0.71 ] |
| Smith 2003a | 3/20 | 1/6 | | 0.1 % | 0.90 [ 0.11, 7.14 ] |
| Smith 2003b | 1/20 | 1/7 | | 0.0 % | 0.35 [ 0.03, 4.88 ] |
| Smith 2003c | 2/21 | 2/7 | | 0.1 % | 0.33 [ 0.06, 1.94 ] |
| Smith 2008 | 176/419 | 215/432 | | 7.0 % | 0.84 [ 0.73, 0.98 ] |
| Ten Bokkel 1998a | 2/45 | 7/17 | | 0.3 % | 0.11 [ 0.02, 0.47 ] |
| Ten Bokkel 1998b | 6/42 | 6/16 | | 0.3 % | 0.38 [ 0.14, 1.01 ] |
| Thatcher 1999a | 19/42 | 13/22 | | 0.6 % | 0.77 [ 0.47, 1.24 ] |
| Thatcher 1999b | 9/44 | 13/22 | | 0.6 % | 0.35 [ 0.18, 0.68 ] |
| Thomas 2002 | 7/62 | 31/65 | | 1.0 % | 0.24 [ 0.11, 0.50 ] |
| Thompson 2000 | 34/45 | 19/21 | | 0.9 % | 0.84 [ 0.67, 1.04 ] |
| Tjulandin 2010a | 8/76 | 9/37 | | 0.4 % | 0.43 [ 0.18, 1.03 ] |
| Tjulandin 2010b | 9/73 | 9/37 | | 0.4 % | 0.51 [ 0.22, 1.17 ] |
| Tjulandin 2011 | 13/95 | 23/91 | | 0.8 % | 0.54 [ 0.29, 1.00 ] |
| Tsuboi 2009 | 7/61 | 7/56 | | 0.2 % | 0.92 [ 0.34, 2.45 ] |
| Vansteenkiste 02 FDA 2004 | 53/156 | 89/158 | | 2.9 % | 0.60 [ 0.47, 0.78 ] |
| Wilkinson 2006 | 9/114 | 18/59 | | 0.8 % | 0.26 [ 0.12, 0.54 ] |
| Witzig 2005 | 42/166 | 65/164 | | 2.2 % | 0.64 [ 0.46, 0.88 ] |
| Wright 2007 | 5/33 | 10/37 | | 0.3 % | 0.56 [ 0.21, 1.47 ] |
| **Subtotal (95% CI)** | **6460** | **5096** | | **69.4 %** | **0.62 [ 0.59, 0.66 ]** |
| Total events: 1539 (Treatment), 1957 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 126.97, df = 69 (P = 0.00003); $I^2$ =46% | | | | | |
| Test for overall effect: Z = 17.19 (P < 0.00001) | | | | | |
| 3 >68% non-elderly 18-65 years | | | | | |
| Cascinu 1994 | 10/50 | 28/50 | | 0.9 % | 0.36 [ 0.19, 0.65 ] |
| Chang 2005 | 15/175 | 40/175 | | 1.3 % | 0.38 [ 0.22, 0.65 ] |
| Del Mastro 1997 | 0/31 | 2/31 | | 0.1 % | 0.20 [ 0.01, 4.00 ] |
| Gupta 2009 | 9/58 | 25/57 | | 0.8 % | 0.35 [ 0.18, 0.69 ] |
| Kurz 1997 | 5/23 | 8/12 | | 0.3 % | 0.33 [ 0.14, 0.78 ] |
| Oberhoff 1998 | 32/114 | 44/104 | | 1.5 % | 0.66 [ 0.46, 0.96 ] |
| Pronzato 2010 | 8/107 | 18/109 | | 0.6 % | 0.45 [ 0.21, 1.00 ] |
| Rosen 2003 | 19/47 | 24/43 | | 0.8 % | 0.72 [ 0.47, 1.12 ] |
| Strauss 2008 | 9/34 | 12/40 | | 0.4 % | 0.88 [ 0.42, 1.84 ] |

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| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Throuvalas 2000 | 2/28 | 10/26 | | 0.3 % | 0.19 [ 0.04, 0.77 ] |
| Wurnig 1996 | 8/15 | 14/14 | | 0.5 % | 0.55 [ 0.34, 0.88 ] |
| **Subtotal (95% CI)** | **682** | **661** | | **7.6 %** | **0.49 [ 0.41, 0.60 ]** |
| Total events: 117 (Treatment), 225 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 14.06, df = 10 (P = 0.17); $I^2$ =29% | | | | | |
| Test for overall effect: Z = 7.40 (P < 0.00001) | | | | | |
| 4 only non-elderly adults | | | | | |
| Blohmer 2011 | 14/127 | 38/129 | | 1.2 % | 0.37 [ 0.21, 0.66 ] |
| Engert 2010 | 405/640 | 467/643 | | 15.3 % | 0.87 [ 0.81, 0.94 ] |
| Moebus 2007 | 41/320 | 86/305 | | 2.9 % | 0.45 [ 0.32, 0.64 ] |
| Untch 2011˙1 | 1/356 | 0/377 | | 0.0 % | 3.18 [ 0.13, 77.72 ] |
| Welch 1995 | 4/15 | 8/15 | | 0.3 % | 0.50 [ 0.19, 1.31 ] |
| **Subtotal (95% CI)** | **1458** | **1469** | | **19.8 %** | **0.78 [ 0.72, 0.84 ]** |
| Total events: 465 (Treatment), 599 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 26.71, df = 4 (P = 0.00002); $I^2$ =85% | | | | | |
| Test for overall effect: Z = 6.40 (P < 0.00001) | | | | | |
| 5 >68% elderly >65 years | | | | | |
| **Subtotal (95% CI)** | **0** | **0** | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Total events: 0 (Treatment), 0 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: not applicable | | | | | |
| 6 only elderly adults | | | | | |
| Gebbia 2003 | 5/22 | 13/23 | | 0.4 % | 0.40 [ 0.17, 0.94 ] |
| **Subtotal (95% CI)** | **22** | **23** | | **0.4 %** | **0.40 [ 0.17, 0.94 ]** |
| Total events: 5 (Treatment), 13 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 2.10 (P = 0.036) | | | | | |
| **Total (95% CI)** | **8733** | **7360** | | **100.0 %** | **0.65 [ 0.62, 0.68 ]** |
| Total events: 2198 (Treatment), 2880 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 217.08, df = 87 (P<0.00001); $I^2$ =60% | | | | | |
| Test for overall effect: Z = 19.89 (P < 0.00001) | | | | | |
| Test for subgroup differences: $Chi^2$ = 38.54, df = 4 (P = 0.00), $I^2$ =90% | | | | | |

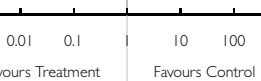
## Analysis 3.6. Comparison 3 Participants receiving red blood cell transfusions, Outcome 6 Participants receiving red blood cell transfusions - different therapies.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 3 Participants receiving red blood cell transfusions

Outcome: 6 Participants receiving red blood cell transfusions - different therapies

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 chemotherapy | | | | | |
| Aapro 2008 | 33/231 | 63/232 | | 2.1 % | 0.53 [ 0.36, 0.77 ] |
| Aravantinos 2003 | 9/24 | 23/23 | | 0.8 % | 0.39 [ 0.23, 0.64 ] |
| Bamias 2003 | 11/72 | 24/72 | | 0.8 % | 0.46 [ 0.24, 0.86 ] |
| Boogaerts 2003 | 43/133 | 67/129 | | 2.2 % | 0.62 [ 0.46, 0.84 ] |
| Carabantes 1999 | 4/20 | 13/15 | | 0.5 % | 0.23 [ 0.09, 0.57 ] |
| Cascinu 1994 | 10/50 | 28/50 | | 0.9 % | 0.36 [ 0.19, 0.65 ] |
| Case 1993 | 32/79 | 36/74 | | 1.2 % | 0.83 [ 0.58, 1.19 ] |
| Cazzola 1995a | 7/31 | 2/7 | | 0.1 % | 0.79 [ 0.21, 3.02 ] |
| Cazzola 1995b | 5/29 | 2/8 | | 0.1 % | 0.69 [ 0.16, 2.91 ] |
| Cazzola 1995c | 6/31 | 2/7 | | 0.1 % | 0.68 [ 0.17, 2.68 ] |
| Cazzola 1995d | 4/26 | 2/7 | | 0.1 % | 0.54 [ 0.12, 2.36 ] |
| Chang 2005 | 15/175 | 40/175 | | 1.3 % | 0.38 [ 0.22, 0.65 ] |
| Christodoulou 2009 | 16/167 | 36/170 | | 1.2 % | 0.45 [ 0.26, 0.78 ] |
| Dammacco 2001 | 19/69 | 36/76 | | 1.1 % | 0.58 [ 0.37, 0.91 ] |
| Del Mastro 1997 | 0/31 | 2/31 | | 0.1 % | 0.20 [ 0.01, 4.00 ] |
| Dunphy 1999 | 2/13 | 5/14 | | 0.2 % | 0.43 [ 0.10, 1.85 ] |
| Engert 2010 | 405/640 | 467/643 | | 15.3 % | 0.87 [ 0.81, 0.94 ] |
| EPO-INT-3 J%J 2004 | 21/136 | 23/65 | | 1.0 % | 0.44 [ 0.26, 0.73 ] |
| Fujisaka 2011 | 4/89 | 18/92 | | 0.6 % | 0.23 [ 0.08, 0.65 ] |
| Gebbia 2003 | 5/22 | 13/23 | | 0.4 % | 0.40 [ 0.17, 0.94 ] |
| Grote 2005 | 26/109 | 42/115 | | 1.3 % | 0.65 [ 0.43, 0.99 ] |
| Hedenus 2002a | 3/11 | 2/3 | | 0.1 % | 0.41 [ 0.12, 1.43 ] |
| Hedenus 2002b | 6/22 | 2/4 | | 0.1 % | 0.55 [ 0.17, 1.80 ] |
| Hedenus 2002c | 3/22 | 1/4 | | 0.1 % | 0.55 [ 0.07, 4.02 ] |

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| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Hedenus 2003 | 52/167 | 79/165 | | 2.6 % | 0.65 [ 0.49, 0.86 ] |
| Henry 1995 | 34/64 | 42/61 | | 1.4 % | 0.77 [ 0.58, 1.03 ] |
| Hernandez 2009 | 58/193 | 91/193 | | 3.0 % | 0.64 [ 0.49, 0.83 ] |
| Huddart 2002 | 18/45 | 32/45 | | 1.1 % | 0.56 [ 0.38, 0.84 ] |
| Iconomou 2003 | 9/57 | 14/55 | | 0.5 % | 0.62 [ 0.29, 1.31 ] |
| Katakami 2008 | 7/103 | 20/104 | | 0.7 % | 0.35 [ 0.16, 0.80 ] |
| Kotasek 2003a | 8/30 | 4/8 | | 0.2 % | 0.53 [ 0.21, 1.33 ] |
| Kotasek 2003b | 5/17 | 4/8 | | 0.2 % | 0.59 [ 0.21, 1.62 ] |
| Kotasek 2003c | 12/41 | 4/9 | | 0.2 % | 0.66 [ 0.28, 1.57 ] |
| Kotasek 2003d | 7/27 | 4/8 | | 0.2 % | 0.52 [ 0.20, 1.33 ] |
| Kotasek 2003e | 9/35 | 3/8 | | 0.2 % | 0.69 [ 0.24, 1.97 ] |
| Kotasek 2003f | 7/38 | 4/9 | | 0.2 % | 0.41 [ 0.15, 1.12 ] |
| Krzakowski 2008a | 27/104 | 14/52 | | 0.6 % | 0.96 [ 0.55, 1.68 ] |
| Krzakowski 2008b | 23/105 | 14/52 | | 0.6 % | 0.81 [ 0.46, 1.45 ] |
| Kunikane 2001a | 1/16 | 0/9 | | 0.0 % | 1.76 [ 0.08, 39.32 ] |
| Kunikane 2001b | 2/18 | 0/10 | | 0.0 % | 2.89 [ 0.15, 54.98 ] |
| Kurz 1997 | 5/23 | 8/12 | | 0.3 % | 0.33 [ 0.14, 0.78 ] |
| Leyland-Jones 2005 | 47/469 | 66/470 | | 2.2 % | 0.71 [ 0.50, 1.01 ] |
| Littlewood 2001 | 62/251 | 49/124 | | 2.2 % | 0.63 [ 0.46, 0.85 ] |
| Milroy 2011 | 16/189 | 43/191 | | 1.4 % | 0.38 [ 0.22, 0.64 ] |
| Moebus 2007 | 41/320 | 86/305 | | 2.9 % | 0.45 [ 0.32, 0.64 ] |
| O'Shaughnessy 2005 | 0/47 | 4/47 | | 0.1 % | 0.11 [ 0.01, 2.01 ] |
| Oberhoff 1998 | 32/114 | 44/104 | | 1.5 % | 0.66 [ 0.46, 0.96 ] |
| Osterborg 1996a | 33/47 | 19/24 | | 0.8 % | 0.89 [ 0.67, 1.17 ] |
| Osterborg 1996b | 39/48 | 20/25 | | 0.9 % | 1.02 [ 0.80, 1.29 ] |
| Osterborg 2002 | 65/169 | 90/173 | | 2.9 % | 0.74 [ 0.58, 0.94 ] |
| Pirker 2008 | 52/298 | 116/298 | | 3.8 % | 0.45 [ 0.34, 0.60 ] |
| Pronzato 2010 | 8/107 | 18/109 | | 0.6 % | 0.45 [ 0.21, 1.00 ] |
| Quirt 1996 | 4/27 | 8/27 | | 0.3 % | 0.50 [ 0.17, 1.47 ] |
| Ray-Coquard 2009 | 39/108 | 61/105 | | 2.0 % | 0.62 [ 0.46, 0.84 ] |
| Razzouk 2006 | 72/111 | 86/111 | | 2.8 % | 0.84 [ 0.71, 0.99 ] |


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| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Savonije 2005 | 77/211 | 66/102 | | 2.9 % | 0.56 [ 0.45, 0.71 ] |
| Ten Bokkel 1998a | 2/45 | 7/17 | | 0.3 % | 0.11 [ 0.02, 0.47 ] |
| Ten Bokkel 1998b | 6/42 | 6/16 | | 0.3 % | 0.38 [ 0.14, 1.01 ] |
| Thatcher 1999a | 19/42 | 13/22 | | 0.6 % | 0.77 [ 0.47, 1.24 ] |
| Thatcher 1999b | 9/44 | 13/22 | | 0.6 % | 0.35 [ 0.18, 0.68 ] |
| Thomas 2002 | 7/62 | 31/65 | | 1.0 % | 0.24 [ 0.11, 0.50 ] |
| Tjulandin 2010a | 8/76 | 9/37 | | 0.4 % | 0.43 [ 0.18, 1.03 ] |
| Tjulandin 2010b | 9/73 | 9/37 | | 0.4 % | 0.51 [ 0.22, 1.17 ] |
| Tjulandin 2011 | 13/95 | 23/91 | | 0.8 % | 0.54 [ 0.29, 1.00 ] |
| Tsuboi 2009 | 7/61 | 7/56 | | 0.2 % | 0.92 [ 0.34, 2.45 ] |
| Untch 2011˙1 | 1/356 | 0/377 | | 0.0 % | 3.18 [ 0.13, 77.72 ] |
| Vansteenkiste 02 FDA 2004 | 53/156 | 89/158 | | 2.9 % | 0.60 [ 0.47, 0.78 ] |
| Welch 1995 | 4/15 | 8/15 | | 0.3 % | 0.50 [ 0.19, 1.31 ] |
| Wilkinson 2006 | 9/114 | 18/59 | | 0.8 % | 0.26 [ 0.12, 0.54 ] |
| Witzig 2005 | 42/166 | 65/164 | | 2.2 % | 0.64 [ 0.46, 0.88 ] |
| Wurnig 1996 | 8/15 | 14/14 | | 0.5 % | 0.55 [ 0.34, 0.88 ] |
| **Subtotal (95% CI)** | **7193** | **6212** | | **82.3 %** | **0.64 [ 0.61, 0.67 ]** |
| Total events: 1757 (Treatment), 2374 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 183.91, df = 70 (P<0.00001); $I^2$ =62% | | | | | |
| Test for overall effect: Z = 18.80 (P < 0.00001) | | | | | |
| 2 radio/radiochemotherapy | | | | | |
| Blohmer 2011 | 14/127 | 38/129 | | 1.2 % | 0.37 [ 0.21, 0.66 ] |
| Goss 2005 | 8/52 | 27/52 | | 0.9 % | 0.30 [ 0.15, 0.59 ] |
| Gupta 2009 | 9/58 | 25/57 | | 0.8 % | 0.35 [ 0.18, 0.69 ] |
| Rosen 2003 | 19/47 | 24/43 | | 0.8 % | 0.72 [ 0.47, 1.12 ] |
| Strauss 2008 | 9/34 | 12/40 | | 0.4 % | 0.88 [ 0.42, 1.84 ] |
| Throuvalas 2000 | 2/28 | 10/26 | | 0.3 % | 0.19 [ 0.04, 0.77 ] |
| **Subtotal (95% CI)** | **346** | **347** | | **4.5 %** | **0.45 [ 0.34, 0.58 ]** |
| Total events: 61 (Treatment), 136 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 11.69, df = 5 (P = 0.04); $I^2$ =57% | | | | | |
| Test for overall effect: Z = 6.11 (P < 0.00001) | | | | | |
| 3 no therapy | | | | | |
| Abels 1993 | 21/63 | 21/55 | | 0.7 % | 0.87 [ 0.54, 1.42 ] |
| Charu 2007 | 27/226 | 13/59 | | 0.7 % | 0.54 [ 0.30, 0.98 ] |


(*Continued* . . . )

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| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Gordon 2008 | 18/162 | 6/56 | | 0.3 % | 1.04 [ 0.43, 2.48 ] |
| Italian 1998 | 28/43 | 35/42 | | 1.2 % | 0.78 [ 0.60, 1.01 ] |
| Smith 2003a | 3/20 | 1/6 | | 0.1 % | 0.90 [ 0.11, 7.14 ] |
| Smith 2003b | 1/20 | 1/7 | | 0.0 % | 0.35 [ 0.03, 4.88 ] |
| Smith 2003c | 2/21 | 2/7 | | 0.1 % | 0.33 [ 0.06, 1.94 ] |
| Smith 2008 | 176/419 | 215/432 | | 7.0 % | 0.84 [ 0.73, 0.98 ] |
| Thompson 2000 | 34/45 | 19/21 | | 0.9 % | 0.84 [ 0.67, 1.04 ] |
| Wright 2007 | 5/33 | 10/37 | | 0.3 % | 0.56 [ 0.21, 1.47 ] |
| **Subtotal (95% CI)** | **1052** | **722** | | **11.2 %** | **0.81 [ 0.72, 0.91 ]** |
| Total events: 315 (Treatment), 323 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 4.51, df = 9 (P = 0.87); $I^2$ =0.0% | | | | | |
| Test for overall effect: Z = 3.59 (P = 0.00033) | | | | | |
| 4 unclear/other | | | | | |
| Rose 1994 | 65/142 | 47/79 | | 2.0 % | 0.77 [ 0.60, 0.99 ] |
| **Subtotal (95% CI)** | **142** | **79** | | **2.0 %** | **0.77 [ 0.60, 0.99 ]** |
| Total events: 65 (Treatment), 47 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 2.01 (P = 0.044) | | | | | |
| **Total (95% CI)** | **8733** | **7360** | | **100.0 %** | **0.65 [ 0.62, 0.68 ]** |
| Total events: 2198 (Treatment), 2880 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 217.08, df = 87 (P<0.00001); $I^2$ =60% | | | | | |
| Test for overall effect: Z = 19.89 (P < 0.00001) | | | | | |
| Test for subgroup differences: $Chi^2$ = 25.04, df = 3 (P = 0.00), $I^2$ =88% | | | | | |

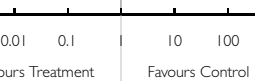
### Analysis 3.7. Comparison 3 Participants receiving red blood cell transfusions, Outcome 7 Participants receiving red blood cell transfusions - different therapies differentiated.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 3 Participants receiving red blood cell transfusions

Outcome: 7 Participants receiving red blood cell transfusions - different therapies differentiated

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 chemotherapy, > 70% with platinum | | | | | |
| Aravantinos 2003 | 9/24 | 23/23 | | 0.8 % | 0.39 [ 0.23, 0.64 ] |
| Bamias 2003 | 11/72 | 24/72 | | 0.8 % | 0.46 [ 0.24, 0.86 ] |
| Carabantes 1999 | 4/20 | 13/15 | | 0.5 % | 0.23 [ 0.09, 0.57 ] |
| Cascinu 1994 | 10/50 | 28/50 | | 0.9 % | 0.36 [ 0.19, 0.65 ] |
| Dunphy 1999 | 2/13 | 5/14 | | 0.2 % | 0.43 [ 0.10, 1.85 ] |
| Fujisaka 2011 | 4/89 | 18/92 | | 0.6 % | 0.23 [ 0.08, 0.65 ] |
| Gebbia 2003 | 5/22 | 13/23 | | 0.4 % | 0.40 [ 0.17, 0.94 ] |
| Grote 2005 | 26/109 | 42/115 | | 1.3 % | 0.65 [ 0.43, 0.99 ] |
| Henry 1995 | 34/64 | 42/61 | | 1.4 % | 0.77 [ 0.58, 1.03 ] |
| Huddart 2002 | 18/45 | 32/45 | | 1.1 % | 0.56 [ 0.38, 0.84 ] |
| Katakami 2008 | 7/103 | 20/104 | | 0.7 % | 0.35 [ 0.16, 0.80 ] |
| Kunikane 2001a | 1/16 | 0/9 | | 0.0 % | 1.76 [ 0.08, 39.32 ] |
| Kunikane 2001b | 2/18 | 0/10 | | 0.0 % | 2.89 [ 0.15, 54.98 ] |
| Kurz 1997 | 5/23 | 8/12 | | 0.3 % | 0.33 [ 0.14, 0.78 ] |
| Milroy 2011 | 16/189 | 43/191 | | 1.4 % | 0.38 [ 0.22, 0.64 ] |
| Pirker 2008 | 52/298 | 116/298 | | 3.8 % | 0.45 [ 0.34, 0.60 ] |
| Savonije 2005 | 77/211 | 66/102 | | 2.9 % | 0.56 [ 0.45, 0.71 ] |
| Ten Bokkel 1998a | 2/45 | 7/17 | | 0.3 % | 0.11 [ 0.02, 0.47 ] |
| Ten Bokkel 1998b | 6/42 | 6/16 | | 0.3 % | 0.38 [ 0.14, 1.01 ] |
| Thatcher 1999a | 19/42 | 13/22 | | 0.6 % | 0.77 [ 0.47, 1.24 ] |
| Thatcher 1999b | 9/44 | 13/22 | | 0.6 % | 0.35 [ 0.18, 0.68 ] |
| Tjulandin 2010a | 8/76 | 9/37 | | 0.4 % | 0.43 [ 0.18, 1.03 ] |
| Tjulandin 2010b | 9/73 | 9/37 | | 0.4 % | 0.51 [ 0.22, 1.17 ] |
| Vansteenkiste 02 FDA 2004 | 53/156 | 89/158 | | 2.9 % | 0.60 [ 0.47, 0.78 ] |

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(. . . *Continued*)

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Welch 1995 | 4/15 | 8/15 | | 0.3 % | 0.50 [ 0.19, 1.31 ] |
| Wilkinson 2006 | 9/114 | 18/59 | | 0.8 % | 0.26 [ 0.12, 0.54 ] |
| **Subtotal (95% CI)** | **1973** | **1619** | | **23.7 %** | **0.49 [ 0.44, 0.54 ]** |
| Total events: 402 (Treatment), 665 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 39.20, df = 25 (P = 0.04); $I^2$ =36% | | | | | |
| Test for overall effect: Z = 13.83 (P < 0.00001) | | | | | |
| 2 chemotherapy, < 70% with platinum | | | | | |
| Christodoulou 2009 | 16/167 | 36/170 | | 1.2 % | 0.45 [ 0.26, 0.78 ] |
| EPO-INT-3 J%J 2004 | 21/136 | 23/65 | | 1.0 % | 0.44 [ 0.26, 0.73 ] |
| Hernandez 2009 | 58/193 | 91/193 | | 3.0 % | 0.64 [ 0.49, 0.83 ] |
| Iconomou 2003 | 9/57 | 14/55 | | 0.5 % | 0.62 [ 0.29, 1.31 ] |
| Krzakowski 2008a | 27/104 | 14/52 | | 0.6 % | 0.96 [ 0.55, 1.68 ] |
| Krzakowski 2008b | 23/105 | 14/52 | | 0.6 % | 0.81 [ 0.46, 1.45 ] |
| Oberhoff 1998 | 32/114 | 44/104 | | 1.5 % | 0.66 [ 0.46, 0.96 ] |
| Tsuboi 2009 | 7/61 | 7/56 | | 0.2 % | 0.92 [ 0.34, 2.45 ] |
| Witzig 2005 | 42/166 | 65/164 | | 2.2 % | 0.64 [ 0.46, 0.88 ] |
| Wurnig 1996 | 8/15 | 14/14 | | 0.5 % | 0.55 [ 0.34, 0.88 ] |
| **Subtotal (95% CI)** | **1118** | **925** | | **11.3 %** | **0.63 [ 0.55, 0.73 ]** |
| Total events: 243 (Treatment), 322 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 7.39, df = 9 (P = 0.60); $I^2$ =0.0% | | | | | |
| Test for overall effect: Z = 6.40 (P < 0.00001) | | | | | |
| 3 chemotherapy without platinum (all patients) | | | | | |
| Aapro 2008 | 33/231 | 63/232 | | 2.1 % | 0.53 [ 0.36, 0.77 ] |
| Case 1993 | 32/79 | 36/74 | | 1.2 % | 0.83 [ 0.58, 1.19 ] |
| Cazzola 1995a | 7/31 | 2/7 | | 0.1 % | 0.79 [ 0.21, 3.02 ] |
| Cazzola 1995b | 5/29 | 2/8 | | 0.1 % | 0.69 [ 0.16, 2.91 ] |
| Cazzola 1995c | 6/31 | 2/7 | | 0.1 % | 0.68 [ 0.17, 2.68 ] |
| Cazzola 1995d | 4/26 | 2/7 | | 0.1 % | 0.54 [ 0.12, 2.36 ] |
| Chang 2005 | 15/175 | 40/175 | | 1.3 % | 0.38 [ 0.22, 0.65 ] |
| Del Mastro 1997 | 0/31 | 2/31 | | 0.1 % | 0.20 [ 0.01, 4.00 ] |
| Engert 2010 | 405/640 | 467/643 | | 15.3 % | 0.87 [ 0.81, 0.94 ] |
| Hedenus 2002a | 3/11 | 2/3 | | 0.1 % | 0.41 [ 0.12, 1.43 ] |
| Hedenus 2002b | 6/22 | 2/4 | | 0.1 % | 0.55 [ 0.17, 1.80 ] |
| Hedenus 2002c | 3/22 | 1/4 | | 0.1 % | 0.55 [ 0.07, 4.02 ] |


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(. . . *Continued*)

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Hedenus 2003 | 52/167 | 79/165 | | 2.6 % | 0.65 [ 0.49, 0.86 ] |
| Leyland-Jones 2005 | 47/469 | 66/470 | | 2.2 % | 0.71 [ 0.50, 1.01 ] |
| Littlewood 2001 | 62/251 | 49/124 | | 2.2 % | 0.63 [ 0.46, 0.85 ] |
| Moebus 2007 | 41/320 | 86/305 | | 2.9 % | 0.45 [ 0.32, 0.64 ] |
| O'Shaughnessy 2005 | 0/47 | 4/47 | | 0.1 % | 0.11 [ 0.01, 2.01 ] |
| Osterborg 1996a | 33/47 | 19/24 | | 0.8 % | 0.89 [ 0.67, 1.17 ] |
| Osterborg 1996b | 39/48 | 20/25 | | 0.9 % | 1.02 [ 0.80, 1.29 ] |
| Osterborg 2002 | 65/169 | 90/173 | | 2.9 % | 0.74 [ 0.58, 0.94 ] |
| Pronzato 2010 | 8/107 | 18/109 | | 0.6 % | 0.45 [ 0.21, 1.00 ] |
| Tjulandin 2011 | 13/95 | 23/91 | | 0.8 % | 0.54 [ 0.29, 1.00 ] |
| Untch 2011˙1 | 1/356 | 0/377 | | 0.0 % | 3.18 [ 0.13, 77.72 ] |
| **Subtotal (95% CI)** | **3404** | **3105** | | **36.7 %** | **0.73 [ 0.69, 0.78 ]** |
| Total events: 880 (Treatment), 1075 (Control) | | | | | |
| Heterogeneity: Chi² = 54.87, df = 22 (P = 0.00012); I² =60% | | | | | |
| Test for overall effect: Z = 9.49 (P < 0.00001) | | | | | |
| 4 chemotherapy, platinum and non-platinum containing, no numbers given | | | | | |
| Boogaerts 2003 | 43/133 | 67/129 | | 2.2 % | 0.62 [ 0.46, 0.84 ] |
| Dammacco 2001 | 19/69 | 36/76 | | 1.1 % | 0.58 [ 0.37, 0.91 ] |
| Kotasek 2003a | 8/30 | 4/8 | | 0.2 % | 0.53 [ 0.21, 1.33 ] |
| Kotasek 2003b | 5/17 | 4/8 | | 0.2 % | 0.59 [ 0.21, 1.62 ] |
| Kotasek 2003c | 12/41 | 4/9 | | 0.2 % | 0.66 [ 0.28, 1.57 ] |
| Kotasek 2003d | 7/27 | 4/8 | | 0.2 % | 0.52 [ 0.20, 1.33 ] |
| Kotasek 2003e | 9/35 | 3/8 | | 0.2 % | 0.69 [ 0.24, 1.97 ] |
| Kotasek 2003f | 7/38 | 4/9 | | 0.2 % | 0.41 [ 0.15, 1.12 ] |
| Thomas 2002 | 7/62 | 31/65 | | 1.0 % | 0.24 [ 0.11, 0.50 ] |
| **Subtotal (95% CI)** | **452** | **320** | | **5.5 %** | **0.53 [ 0.43, 0.65 ]** |
| Total events: 117 (Treatment), 157 (Control) | | | | | |
| Heterogeneity: Chi² = 6.53, df = 8 (P = 0.59); I² =0.0% | | | | | |
| Test for overall effect: Z = 6.10 (P < 0.00001) | | | | | |
| 5 chemotherapy no details given | | | | | |
| Quirt 1996 | 4/27 | 8/27 | | 0.3 % | 0.50 [ 0.17, 1.47 ] |
| Ray-Coquard 2009 | 39/108 | 61/105 | | 2.0 % | 0.62 [ 0.46, 0.84 ] |
| Razzouk 2006 | 72/111 | 86/111 | | 2.8 % | 0.84 [ 0.71, 0.99 ] |
| **Subtotal (95% CI)** | **246** | **243** | | **5.1 %** | **0.73 [ 0.63, 0.86 ]** |
| Total events: 115 (Treatment), 155 (Control) | | | | | |


(*Continued* . . . )

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| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Heterogeneity: Chi² = 3.98, df = 2 (P = 0.14); I² =50% | | | | | |
| Test for overall effect: Z = 3.91 (P = 0.000093) | | | | | |
| 6 radiochemotherapy | | | | | |
| Blohmer 2011 | 14/127 | 38/129 | | 1.2 % | 0.37 [ 0.21, 0.66 ] |
| Goss 2005 | 8/52 | 27/52 | | 0.9 % | 0.30 [ 0.15, 0.59 ] |
| Gupta 2009 | 9/58 | 25/57 | | 0.8 % | 0.35 [ 0.18, 0.69 ] |
| Rosen 2003 | 19/47 | 24/43 | | 0.8 % | 0.72 [ 0.47, 1.12 ] |
| Strauss 2008 | 9/34 | 12/40 | | 0.4 % | 0.88 [ 0.42, 1.84 ] |
| Throuvalas 2000 | 2/28 | 10/26 | | 0.3 % | 0.19 [ 0.04, 0.77 ] |
| **Subtotal (95% CI)** | **346** | **347** | | **4.5 %** | **0.45 [ 0.34, 0.58 ]** |
| Total events: 61 (Treatment), 136 (Control) | | | | | |
| Heterogeneity: Chi² = 11.69, df = 5 (P = 0.04); I² =57% | | | | | |
| Test for overall effect: Z = 6.11 (P < 0.00001) | | | | | |
| 7 radiotherapy | | | | | |
| **Subtotal (95% CI)** | **0** | **0** | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Total events: 0 (Treatment), 0 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: not applicable | | | | | |
| 8 no therapy | | | | | |
| Abels 1993 | 21/63 | 21/55 | | 0.7 % | 0.87 [ 0.54, 1.42 ] |
| Charu 2007 | 27/226 | 13/59 | | 0.7 % | 0.54 [ 0.30, 0.98 ] |
| Gordon 2008 | 18/162 | 6/56 | | 0.3 % | 1.04 [ 0.43, 2.48 ] |
| Italian 1998 | 28/43 | 35/42 | | 1.2 % | 0.78 [ 0.60, 1.01 ] |
| Smith 2003a | 3/20 | 1/6 | | 0.1 % | 0.90 [ 0.11, 7.14 ] |
| Smith 2003b | 1/20 | 1/7 | | 0.0 % | 0.35 [ 0.03, 4.88 ] |
| Smith 2003c | 2/21 | 2/7 | | 0.1 % | 0.33 [ 0.06, 1.94 ] |
| Smith 2008 | 176/419 | 215/432 | | 7.0 % | 0.84 [ 0.73, 0.98 ] |
| Thompson 2000 | 34/45 | 19/21 | | 0.9 % | 0.84 [ 0.67, 1.04 ] |
| Wright 2007 | 5/33 | 10/37 | | 0.3 % | 0.56 [ 0.21, 1.47 ] |
| **Subtotal (95% CI)** | **1052** | **722** | | **11.2 %** | **0.81 [ 0.72, 0.91 ]** |
| Total events: 315 (Treatment), 323 (Control) | | | | | |
| Heterogeneity: Chi² = 4.51, df = 9 (P = 0.87); I² =0.0% | | | | | |
| Test for overall effect: Z = 3.59 (P = 0.00033) | | | | | |
| 9 unclear/other | | | | | |
| Rose 1994 | 65/142 | 47/79 | | 2.0 % | 0.77 [ 0.60, 0.99 ] |
| **Subtotal (95% CI)** | **142** | **79** | | **2.0 %** | **0.77 [ 0.60, 0.99 ]** |
| Total events: 65 (Treatment), 47 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |


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| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Test for overall effect: Z = 2.01 (P = 0.044) | | | | | |
| **Total (95% CI)** | **8733** | **7360** | | **100.0 %** | **0.65 [ 0.62, 0.68 ]** |
| Total events: 2198 (Treatment), 2880 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 217.08, df = 87 (P<0.00001); $I^2$ =60% | | | | | |
| Test for overall effect: Z = 19.89 (P < 0.00001) | | | | | |
| Test for subgroup differences: $Chi^2$ = 71.88, df = 7 (P = 0.00), $I^2$ =90% | | | | | |

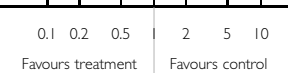

**Analysis 3.8. Comparison 3 Participants receiving red blood cell transfusions, Outcome 8 Participants receiving red blood cell transfusions - epoetin versus darbepoetin.**

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 3 Participants receiving red blood cell transfusions

Outcome: 8 Participants receiving red blood cell transfusions - epoetin versus darbepoetin

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 Epoetin | | | | | |
| Aapro 2008 | 33/231 | 63/232 | | 2.1 % | 0.53 [ 0.36, 0.77 ] |
| Abels 1993 | 21/63 | 21/55 | | 0.7 % | 0.87 [ 0.54, 1.42 ] |
| Aravantinos 2003 | 9/24 | 23/23 | | 0.8 % | 0.39 [ 0.23, 0.64 ] |
| Bamias 2003 | 11/72 | 24/72 | | 0.8 % | 0.46 [ 0.24, 0.86 ] |
| Blohmer 2011 | 14/127 | 38/129 | | 1.2 % | 0.37 [ 0.21, 0.66 ] |
| Boogaerts 2003 | 43/133 | 67/129 | | 2.2 % | 0.62 [ 0.46, 0.84 ] |
| Carabantes 1999 | 4/20 | 13/15 | | 0.5 % | 0.23 [ 0.09, 0.57 ] |
| Cascinu 1994 | 10/50 | 28/50 | | 0.9 % | 0.36 [ 0.19, 0.65 ] |
| Case 1993 | 32/79 | 36/74 | | 1.2 % | 0.83 [ 0.58, 1.19 ] |
| Cazzola 1995a | 7/31 | 2/7 | | 0.1 % | 0.79 [ 0.21, 3.02 ] |

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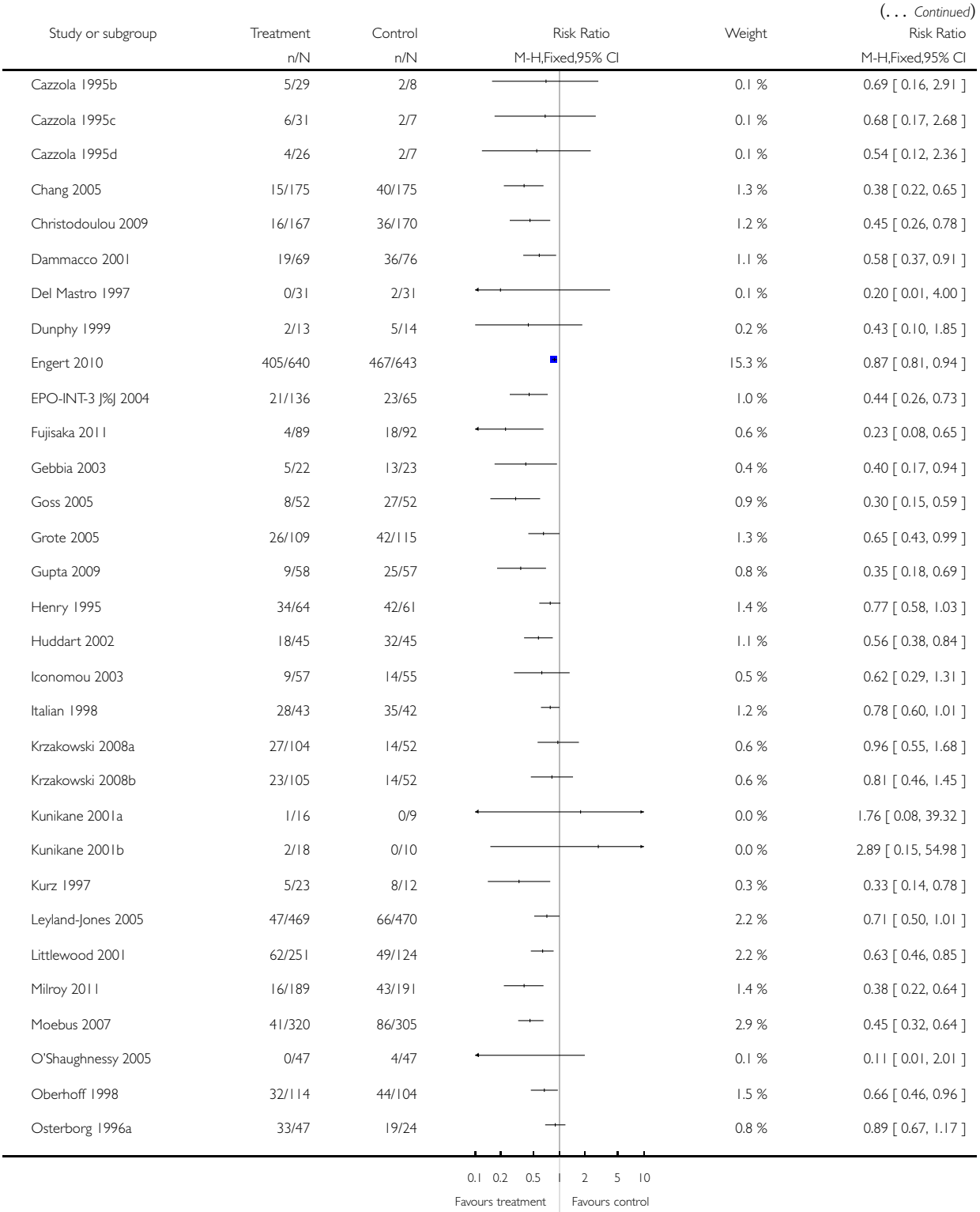


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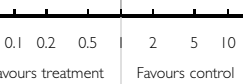
| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Osterborg 1996b | 39/48 | 20/25 | | 0.9 % | 1.02 [ 0.80, 1.29 ] |
| Osterborg 2002 | 65/169 | 90/173 | | 2.9 % | 0.74 [ 0.58, 0.94 ] |
| Pronzato 2010 | 8/107 | 18/109 | | 0.6 % | 0.45 [ 0.21, 1.00 ] |
| Quirt 1996 | 4/27 | 8/27 | | 0.3 % | 0.50 [ 0.17, 1.47 ] |
| Ray-Coquard 2009 | 39/108 | 61/105 | | 2.0 % | 0.62 [ 0.46, 0.84 ] |
| Razzouk 2006 | 72/111 | 86/111 | | 2.8 % | 0.84 [ 0.71, 0.99 ] |
| Rose 1994 | 65/142 | 47/79 | | 2.0 % | 0.77 [ 0.60, 0.99 ] |
| Rosen 2003 | 19/47 | 24/43 | | 0.8 % | 0.72 [ 0.47, 1.12 ] |
| Savonije 2005 | 77/211 | 66/102 | | 2.9 % | 0.56 [ 0.45, 0.71 ] |
| Strauss 2008 | 9/34 | 12/40 | | 0.4 % | 0.88 [ 0.42, 1.84 ] |
| Ten Bokkel 1998a | 2/45 | 7/17 | | 0.3 % | 0.11 [ 0.02, 0.47 ] |
| Ten Bokkel 1998b | 6/42 | 6/16 | | 0.3 % | 0.38 [ 0.14, 1.01 ] |
| Thatcher 1999a | 19/42 | 13/22 | | 0.6 % | 0.77 [ 0.47, 1.24 ] |
| Thatcher 1999b | 9/44 | 13/22 | | 0.6 % | 0.35 [ 0.18, 0.68 ] |
| Thomas 2002 | 7/62 | 31/65 | | 1.0 % | 0.24 [ 0.11, 0.50 ] |
| Thompson 2000 | 34/45 | 19/21 | | 0.9 % | 0.84 [ 0.67, 1.04 ] |
| Throuvalas 2000 | 2/28 | 10/26 | | 0.3 % | 0.19 [ 0.04, 0.77 ] |
| Tjulandin 2010a | 8/76 | 9/37 | | 0.4 % | 0.43 [ 0.18, 1.03 ] |
| Tjulandin 2010b | 9/73 | 9/37 | | 0.4 % | 0.51 [ 0.22, 1.17 ] |
| Tjulandin 2011 | 13/95 | 23/91 | | 0.8 % | 0.54 [ 0.29, 1.00 ] |
| Tsuboi 2009 | 7/61 | 7/56 | | 0.2 % | 0.92 [ 0.34, 2.45 ] |
| Welch 1995 | 4/15 | 8/15 | | 0.3 % | 0.50 [ 0.19, 1.31 ] |
| Wilkinson 2006 | 9/114 | 18/59 | | 0.8 % | 0.26 [ 0.12, 0.54 ] |
| Witzig 2005 | 42/166 | 65/164 | | 2.2 % | 0.64 [ 0.46, 0.88 ] |
| Wright 2007 | 5/33 | 10/37 | | 0.3 % | 0.56 [ 0.21, 1.47 ] |
| Wurnig 1996 | 8/15 | 14/14 | | 0.5 % | 0.55 [ 0.34, 0.88 ] |
| **Subtotal (95% CI)** | **6349** | **5437** | | **77.4 %** | **0.65 [ 0.62, 0.68 ]** |
| Total events: 1688 (Treatment), 2219 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 191.91, df = 66 (P<0.00001); $I^2$ =66% | | | | | |
| Test for overall effect: Z = 17.85 (P < 0.00001) | | | | | |
| 2 Darbepoetin | | | | | |
| Charu 2007 | 27/226 | 13/59 | | 0.7 % | 0.54 [ 0.30, 0.98 ] |
| Gordon 2008 | 18/162 | 6/56 | | 0.3 % | 1.04 [ 0.43, 2.48 ] |

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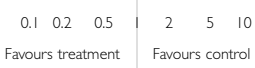
| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Hedenus 2002a | 3/11 | 2/3 | | 0.1 % | 0.41 [ 0.12, 1.43 ] |
| Hedenus 2002b | 6/22 | 2/4 | | 0.1 % | 0.55 [ 0.17, 1.80 ] |
| Hedenus 2002c | 3/22 | 1/4 | | 0.1 % | 0.55 [ 0.07, 4.02 ] |
| Hedenus 2003 | 52/167 | 79/165 | | 2.6 % | 0.65 [ 0.49, 0.86 ] |
| Hernandez 2009 | 58/193 | 91/193 | | 3.0 % | 0.64 [ 0.49, 0.83 ] |
| Katakami 2008 | 7/103 | 20/104 | | 0.7 % | 0.35 [ 0.16, 0.80 ] |
| Kotasek 2003a | 8/30 | 4/8 | | 0.2 % | 0.53 [ 0.21, 1.33 ] |
| Kotasek 2003b | 5/17 | 4/8 | | 0.2 % | 0.59 [ 0.21, 1.62 ] |
| Kotasek 2003c | 12/41 | 4/9 | | 0.2 % | 0.66 [ 0.28, 1.57 ] |
| Kotasek 2003d | 7/27 | 4/8 | | 0.2 % | 0.52 [ 0.20, 1.33 ] |
| Kotasek 2003e | 9/35 | 3/8 | | 0.2 % | 0.69 [ 0.24, 1.97 ] |
| Kotasek 2003f | 7/38 | 4/9 | | 0.2 % | 0.41 [ 0.15, 1.12 ] |
| Pirker 2008 | 52/298 | 116/298 | | 3.8 % | 0.45 [ 0.34, 0.60 ] |
| Smith 2003a | 3/20 | 1/6 | | 0.1 % | 0.90 [ 0.11, 7.14 ] |
| Smith 2003b | 1/20 | 1/7 | | 0.0 % | 0.35 [ 0.03, 4.88 ] |
| Smith 2003c | 2/21 | 2/7 | | 0.1 % | 0.33 [ 0.06, 1.94 ] |
| Smith 2008 | 176/419 | 215/432 | | 7.0 % | 0.84 [ 0.73, 0.98 ] |
| Untch 2011˙1 | 1/356 | 0/377 | | 0.0 % | 3.18 [ 0.13, 77.72 ] |
| Vansteenkiste 02 FDA 2004 | 53/156 | 89/158 | | 2.9 % | 0.60 [ 0.47, 0.78 ] |
| **Subtotal (95% CI)** | **2384** | **1923** | | **22.6 %** | **0.66 [ 0.60, 0.72 ]** |
| Total events: 510 (Treatment), 661 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 26.07, df = 20 (P = 0.16); $I^2$ =23% | | | | | |
| Test for overall effect: Z = 8.87 (P < 0.00001) | | | | | |
| **Total (95% CI)** | **8733** | **7360** | | **100.0 %** | **0.65 [ 0.62, 0.68 ]** |
| Total events: 2198 (Treatment), 2880 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 217.08, df = 87 (P<0.00001); $I^2$ =60% | | | | | |
| Test for overall effect: Z = 19.89 (P < 0.00001) | | | | | |
| Test for subgroup differences: $Chi^2$ = 0.05, df = 1 (P = 0.83), $I^2$ =0.0% | | | | | |



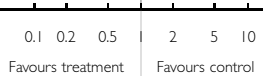
### Analysis 3.9. Comparison 3 Participants receiving red blood cell transfusions, Outcome 9 Participants receiving red blood cell transfusions - duration of ESA medication.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 3 Participants receiving red blood cell transfusions

Outcome: 9 Participants receiving red blood cell transfusions - duration of ESA medication

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 6 to 9 weeks | | | | | |
| Abels 1993 | 21/63 | 21/55 | | 0.7 % | 0.87 [ 0.54, 1.42 ] |
| Cascinu 1994 | 10/50 | 28/50 | | 0.9 % | 0.36 [ 0.19, 0.65 ] |
| Cazzola 1995a | 7/31 | 2/7 | | 0.1 % | 0.79 [ 0.21, 3.02 ] |
| Cazzola 1995b | 5/29 | 2/8 | | 0.1 % | 0.69 [ 0.16, 2.91 ] |
| Cazzola 1995c | 6/31 | 2/7 | | 0.1 % | 0.68 [ 0.17, 2.68 ] |
| Cazzola 1995d | 4/26 | 2/7 | | 0.1 % | 0.54 [ 0.12, 2.36 ] |
| Dunphy 1999 | 2/13 | 5/14 | | 0.2 % | 0.43 [ 0.10, 1.85 ] |
| Gupta 2009 | 9/58 | 25/57 | | 0.8 % | 0.35 [ 0.18, 0.69 ] |
| Italian 1998 | 28/43 | 35/42 | | 1.2 % | 0.78 [ 0.60, 1.01 ] |
| Kunikane 2001a | 1/16 | 0/9 | | 0.0 % | 1.76 [ 0.08, 39.32 ] |
| Kunikane 2001b | 2/18 | 0/10 | | 0.0 % | 2.89 [ 0.15, 54.98 ] |
| Throuvalas 2000 | 2/28 | 10/26 | | 0.3 % | 0.19 [ 0.04, 0.77 ] |
| Tsuboi 2009 | 7/61 | 7/56 | | 0.2 % | 0.92 [ 0.34, 2.45 ] |
| **Subtotal (95% CI)** | **467** | **348** | | **4.9 %** | **0.60 [ 0.49, 0.74 ]** |
| Total events: 104 (Treatment), 139 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 16.94, df = 12 (P = 0.15); $I^2$ =29% | | | | | |
| Test for overall effect: Z = 4.88 (P < 0.00001) | | | | | |
| 2 12 to 16 weeks | | | | | |
| Aravantinos 2003 | 9/24 | 23/23 | | 0.8 % | 0.39 [ 0.23, 0.64 ] |
| Boogaerts 2003 | 43/133 | 67/129 | | 2.2 % | 0.62 [ 0.46, 0.84 ] |
| Case 1993 | 32/79 | 36/74 | | 1.2 % | 0.83 [ 0.58, 1.19 ] |
| Chang 2005 | 15/175 | 40/175 | | 1.3 % | 0.38 [ 0.22, 0.65 ] |
| Charu 2007 | 27/226 | 13/59 | | 0.7 % | 0.54 [ 0.30, 0.98 ] |
| Christodoulou 2009 | 16/167 | 36/170 | | 1.2 % | 0.45 [ 0.26, 0.78 ] |
| Dammacco 2001 | 19/69 | 36/76 | | 1.1 % | 0.58 [ 0.37, 0.91 ] |
| Del Mastro 1997 | 0/31 | 2/31 | | 0.1 % | 0.20 [ 0.01, 4.00 ] |

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| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| EPO-INT-3 J%J 2004 | 21/136 | 23/65 | | 1.0 % | 0.44 [ 0.26, 0.73 ] |
| Fujisaka 2011 | 4/89 | 18/92 | | 0.6 % | 0.23 [ 0.08, 0.65 ] |
| Gebbia 2003 | 5/22 | 13/23 | | 0.4 % | 0.40 [ 0.17, 0.94 ] |
| Gordon 2008 | 18/162 | 6/56 | | 0.3 % | 1.04 [ 0.43, 2.48 ] |
| Grote 2005 | 26/109 | 42/115 | | 1.3 % | 0.65 [ 0.43, 0.99 ] |
| Hedenus 2002a | 3/11 | 2/3 | | 0.1 % | 0.41 [ 0.12, 1.43 ] |
| Hedenus 2002b | 6/22 | 2/4 | | 0.1 % | 0.55 [ 0.17, 1.80 ] |
| Hedenus 2002c | 3/22 | 1/4 | | 0.1 % | 0.55 [ 0.07, 4.02 ] |
| Hedenus 2003 | 52/167 | 79/165 | | 2.6 % | 0.65 [ 0.49, 0.86 ] |
| Henry 1995 | 34/64 | 42/61 | | 1.4 % | 0.77 [ 0.58, 1.03 ] |
| Hernandez 2009 | 58/193 | 91/193 | | 3.0 % | 0.64 [ 0.49, 0.83 ] |
| Iconomou 2003 | 9/57 | 14/55 | | 0.5 % | 0.62 [ 0.29, 1.31 ] |
| Katakami 2008 | 7/103 | 20/104 | | 0.7 % | 0.35 [ 0.16, 0.80 ] |
| Kotasek 2003a | 8/30 | 4/8 | | 0.2 % | 0.53 [ 0.21, 1.33 ] |
| Kotasek 2003b | 5/17 | 4/8 | | 0.2 % | 0.59 [ 0.21, 1.62 ] |
| Kotasek 2003c | 12/41 | 4/9 | | 0.2 % | 0.66 [ 0.28, 1.57 ] |
| Kotasek 2003d | 7/27 | 4/8 | | 0.2 % | 0.52 [ 0.20, 1.33 ] |
| Kotasek 2003e | 9/35 | 3/8 | | 0.2 % | 0.69 [ 0.24, 1.97 ] |
| Kotasek 2003f | 7/38 | 4/9 | | 0.2 % | 0.41 [ 0.15, 1.12 ] |
| Krzakowski 2008a | 27/104 | 14/52 | | 0.6 % | 0.96 [ 0.55, 1.68 ] |
| Krzakowski 2008b | 23/105 | 14/52 | | 0.6 % | 0.81 [ 0.46, 1.45 ] |
| Kurz 1997 | 5/23 | 8/12 | | 0.3 % | 0.33 [ 0.14, 0.78 ] |
| O'Shaughnessy 2005 | 0/47 | 4/47 | | 0.1 % | 0.11 [ 0.01, 2.01 ] |
| Oberhoff 1998 | 32/114 | 44/104 | | 1.5 % | 0.66 [ 0.46, 0.96 ] |
| Osterborg 2002 | 65/169 | 90/173 | | 2.9 % | 0.74 [ 0.58, 0.94 ] |
| Quirt 1996 | 4/27 | 8/27 | | 0.3 % | 0.50 [ 0.17, 1.47 ] |
| Ray-Coquard 2009 | 39/108 | 61/105 | | 2.0 % | 0.62 [ 0.46, 0.84 ] |
| Razzouk 2006 | 72/111 | 86/111 | | 2.8 % | 0.84 [ 0.71, 0.99 ] |
| Rose 1994 | 65/142 | 47/79 | | 2.0 % | 0.77 [ 0.60, 0.99 ] |
| Rosen 2003 | 19/47 | 24/43 | | 0.8 % | 0.72 [ 0.47, 1.12 ] |
| Savonije 2005 | 77/211 | 66/102 | | 2.9 % | 0.56 [ 0.45, 0.71 ] |




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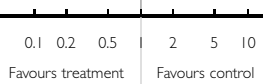
| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Smith 2003a | 3/20 | 1/6 | | 0.1 % | 0.90 [ 0.11, 7.14 ] |
| Smith 2003b | 1/20 | 1/7 | | 0.0 % | 0.35 [ 0.03, 4.88 ] |
| Smith 2003c | 2/21 | 2/7 | | 0.1 % | 0.33 [ 0.06, 1.94 ] |
| Smith 2008 | 176/419 | 215/432 | | 7.0 % | 0.84 [ 0.73, 0.98 ] |
| Strauss 2008 | 9/34 | 12/40 | | 0.4 % | 0.88 [ 0.42, 1.84 ] |
| Thomas 2002 | 7/62 | 31/65 | | 1.0 % | 0.24 [ 0.11, 0.50 ] |
| Thompson 2000 | 34/45 | 19/21 | | 0.9 % | 0.84 [ 0.67, 1.04 ] |
| Tjulandin 2010a | 8/76 | 9/37 | | 0.4 % | 0.43 [ 0.18, 1.03 ] |
| Tjulandin 2010b | 9/73 | 9/37 | | 0.4 % | 0.51 [ 0.22, 1.17 ] |
| Tjulandin 2011 | 13/95 | 23/91 | | 0.8 % | 0.54 [ 0.29, 1.00 ] |
| Vansteenkiste 02 FDA 2004 | 53/156 | 89/158 | | 2.9 % | 0.60 [ 0.47, 0.78 ] |
| Witzig 2005 | 42/166 | 65/164 | | 2.2 % | 0.64 [ 0.46, 0.88 ] |
| Wright 2007 | 5/33 | 10/37 | | 0.3 % | 0.56 [ 0.21, 1.47 ] |
| **Subtotal (95% CI)** | **4677** | **3736** | | **55.2 %** | **0.65 [ 0.61, 0.69 ]** |
| Total events: 1245 (Treatment), 1581 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 73.75, df = 51 (P = 0.02); $I^2$ =31% | | | | | |
| Test for overall effect: Z = 14.42 (P < 0.00001) | | | | | |
| 3 more than 17 weeks | | | | | |
| Aapro 2008 | 33/231 | 63/232 | | 2.1 % | 0.53 [ 0.36, 0.77 ] |
| Bamias 2003 | 11/72 | 24/72 | | 0.8 % | 0.46 [ 0.24, 0.86 ] |
| Blohmer 2011 | 14/127 | 38/129 | | 1.2 % | 0.37 [ 0.21, 0.66 ] |
| Carabantes 1999 | 4/20 | 13/15 | | 0.5 % | 0.23 [ 0.09, 0.57 ] |
| Engert 2010 | 405/640 | 467/643 | | 15.3 % | 0.87 [ 0.81, 0.94 ] |
| Goss 2005 | 8/52 | 27/52 | | 0.9 % | 0.30 [ 0.15, 0.59 ] |
| Huddart 2002 | 18/45 | 32/45 | | 1.1 % | 0.56 [ 0.38, 0.84 ] |
| Leyland-Jones 2005 | 47/469 | 66/470 | | 2.2 % | 0.71 [ 0.50, 1.01 ] |
| Littlewood 2001 | 62/251 | 49/124 | | 2.2 % | 0.63 [ 0.46, 0.85 ] |
| Milroy 2011 | 16/189 | 43/191 | | 1.4 % | 0.38 [ 0.22, 0.64 ] |
| Moebus 2007 | 41/320 | 86/305 | | 2.9 % | 0.45 [ 0.32, 0.64 ] |
| Osterborg 1996a | 33/47 | 19/24 | | 0.8 % | 0.89 [ 0.67, 1.17 ] |
| Osterborg 1996b | 39/48 | 20/25 | | 0.9 % | 1.02 [ 0.80, 1.29 ] |
| Pirker 2008 | 52/298 | 116/298 | | 3.8 % | 0.45 [ 0.34, 0.60 ] |
| Pronzato 2010 | 8/107 | 18/109 | | 0.6 % | 0.45 [ 0.21, 1.00 ] |

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| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Ten Bokkel 1998a | 2/45 | 7/17 | | 0.3 % | 0.11 [ 0.02, 0.47 ] |
| Ten Bokkel 1998b | 6/42 | 6/16 | | 0.3 % | 0.38 [ 0.14, 1.01 ] |
| Thatcher 1999a | 19/42 | 13/22 | | 0.6 % | 0.77 [ 0.47, 1.24 ] |
| Thatcher 1999b | 9/44 | 13/22 | | 0.6 % | 0.35 [ 0.18, 0.68 ] |
| Untch 2011˙1 | 1/356 | 0/377 | | 0.0 % | 3.18 [ 0.13, 77.72 ] |
| Welch 1995 | 4/15 | 8/15 | | 0.3 % | 0.50 [ 0.19, 1.31 ] |
| Wilkinson 2006 | 9/114 | 18/59 | | 0.8 % | 0.26 [ 0.12, 0.54 ] |
| Wurnig 1996 | 8/15 | 14/14 | | 0.5 % | 0.55 [ 0.34, 0.88 ] |
| **Subtotal (95% CI)** | **3589** | **3276** | | **39.9 %** | **0.65 [ 0.61, 0.70 ]** |
| Total events: 849 (Treatment), 1160 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 126.00, df = 22 (P<0.00001); $I^2$ =83% | | | | | |
| Test for overall effect: Z = 12.84 (P < 0.00001) | | | | | |
| **Total (95% CI)** | **8733** | **7360** | | **100.0 %** | **0.65 [ 0.62, 0.68 ]** |
| Total events: 2198 (Treatment), 2880 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 217.08, df = 87 (P<0.00001); $I^2$ =60% | | | | | |
| Test for overall effect: Z = 19.89 (P < 0.00001) | | | | | |
| Test for subgroup differences: $Chi^2$ = 0.61, df = 2 (P = 0.74), $I^2$ =0.0% | | | | | |

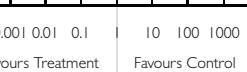
## Analysis 3.10. Comparison 3 Participants receiving red blood cell transfusions, Outcome 10 Participants receiving red blood cell transfusions - iron supplementation.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 3 Participants receiving red blood cell transfusions

Outcome: 10 Participants receiving red blood cell transfusions - iron supplementation

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 fixed iron supplementation | | | | | |
| Aravantinos 2003 | 9/24 | 23/23 | | 0.8 % | 0.39 [ 0.23, 0.64 ] |
| Christodoulou 2009 | 16/167 | 36/170 | | 1.2 % | 0.45 [ 0.26, 0.78 ] |
| Dunphy 1999 | 2/13 | 5/14 | | 0.2 % | 0.43 [ 0.10, 1.85 ] |
| Gupta 2009 | 9/58 | 25/57 | | 0.8 % | 0.35 [ 0.18, 0.69 ] |
| Huddart 2002 | 18/45 | 32/45 | | 1.1 % | 0.56 [ 0.38, 0.84 ] |
| Iconomou 2003 | 9/57 | 14/55 | | 0.5 % | 0.62 [ 0.29, 1.31 ] |
| Krzakowski 2008a | 27/104 | 14/52 | | 0.6 % | 0.96 [ 0.55, 1.68 ] |
| Krzakowski 2008b | 23/105 | 14/52 | | 0.6 % | 0.81 [ 0.46, 1.45 ] |
| Untch 2011˙1 | 1/356 | 0/377 | | 0.0 % | 3.18 [ 0.13, 77.72 ] |
| Witzig 2005 | 42/166 | 65/164 | | 2.2 % | 0.64 [ 0.46, 0.88 ] |
| **Subtotal (95% CI)** | **1095** | **1009** | | **7.9 %** | **0.58 [ 0.49, 0.70 ]** |
| Total events: 156 (Treatment), 228 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 11.55, df = 9 (P = 0.24); $I^2$ =22% | | | | | |
| Test for overall effect: Z = 6.07 (P < 0.00001) | | | | | |
| 2 iron supplementation as necessary | | | | | |
| Aapro 2008 | 33/231 | 63/232 | | 2.1 % | 0.53 [ 0.36, 0.77 ] |
| Abels 1993 | 21/63 | 21/55 | | 0.7 % | 0.87 [ 0.54, 1.42 ] |
| Boogaerts 2003 | 43/133 | 67/129 | | 2.2 % | 0.62 [ 0.46, 0.84 ] |
| Cascinu 1994 | 10/50 | 28/50 | | 0.9 % | 0.36 [ 0.19, 0.65 ] |
| Case 1993 | 32/79 | 36/74 | | 1.2 % | 0.83 [ 0.58, 1.19 ] |
| Cazzola 1995a | 7/31 | 2/7 | | 0.1 % | 0.79 [ 0.21, 3.02 ] |
| Cazzola 1995b | 5/29 | 2/8 | | 0.1 % | 0.69 [ 0.16, 2.91 ] |
| Cazzola 1995c | 6/31 | 2/7 | | 0.1 % | 0.68 [ 0.17, 2.68 ] |
| Cazzola 1995d | 4/26 | 2/7 | | 0.1 % | 0.54 [ 0.12, 2.36 ] |
| Chang 2005 | 15/175 | 40/175 | | 1.3 % | 0.38 [ 0.22, 0.65 ] |
| Charu 2007 | 27/226 | 13/59 | | 0.7 % | 0.54 [ 0.30, 0.98 ] |

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| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Dammacco 2001 | 19/69 | 36/76 | | 1.1 % | 0.58 [ 0.37, 0.91 ] |
| Del Mastro 1997 | 0/31 | 2/31 | | 0.1 % | 0.20 [ 0.01, 4.00 ] |
| Engert 2010 | 405/640 | 467/643 | | 15.3 % | 0.87 [ 0.81, 0.94 ] |
| EPO-INT-3 J%J 2004 | 21/136 | 23/65 | | 1.0 % | 0.44 [ 0.26, 0.73 ] |
| Fujisaka 2011 | 4/89 | 18/92 | | 0.6 % | 0.23 [ 0.08, 0.65 ] |
| Gordon 2008 | 18/162 | 6/56 | | 0.3 % | 1.04 [ 0.43, 2.48 ] |
| Goss 2005 | 8/52 | 27/52 | | 0.9 % | 0.30 [ 0.15, 0.59 ] |
| Grote 2005 | 26/109 | 42/115 | | 1.3 % | 0.65 [ 0.43, 0.99 ] |
| Hedenus 2003 | 52/167 | 79/165 | | 2.6 % | 0.65 [ 0.49, 0.86 ] |
| Henry 1995 | 34/64 | 42/61 | | 1.4 % | 0.77 [ 0.58, 1.03 ] |
| Hernandez 2009 | 58/193 | 91/193 | | 3.0 % | 0.64 [ 0.49, 0.83 ] |
| Italian 1998 | 28/43 | 35/42 | | 1.2 % | 0.78 [ 0.60, 1.01 ] |
| Kotasek 2003a | 8/30 | 4/8 | | 0.2 % | 0.53 [ 0.21, 1.33 ] |
| Kotasek 2003b | 5/17 | 4/8 | | 0.2 % | 0.59 [ 0.21, 1.62 ] |
| Kotasek 2003c | 12/41 | 4/9 | | 0.2 % | 0.66 [ 0.28, 1.57 ] |
| Kotasek 2003d | 7/27 | 4/8 | | 0.2 % | 0.52 [ 0.20, 1.33 ] |
| Kotasek 2003e | 9/35 | 3/8 | | 0.2 % | 0.69 [ 0.24, 1.97 ] |
| Kotasek 2003f | 7/38 | 4/9 | | 0.2 % | 0.41 [ 0.15, 1.12 ] |
| Kurz 1997 | 5/23 | 8/12 | | 0.3 % | 0.33 [ 0.14, 0.78 ] |
| Leyland-Jones 2005 | 47/469 | 66/470 | | 2.2 % | 0.71 [ 0.50, 1.01 ] |
| Littlewood 2001 | 62/251 | 49/124 | | 2.2 % | 0.63 [ 0.46, 0.85 ] |
| Milroy 2011 | 16/189 | 43/191 | | 1.4 % | 0.38 [ 0.22, 0.64 ] |
| O'Shaughnessy 2005 | 0/47 | 4/47 | | 0.1 % | 0.11 [ 0.01, 2.01 ] |
| Oberhoff 1998 | 32/114 | 44/104 | | 1.5 % | 0.66 [ 0.46, 0.96 ] |
| Osterborg 1996a | 33/47 | 19/24 | | 0.8 % | 0.89 [ 0.67, 1.17 ] |
| Osterborg 1996b | 39/48 | 20/25 | | 0.9 % | 1.02 [ 0.80, 1.29 ] |
| Osterborg 2002 | 65/169 | 90/173 | | 2.9 % | 0.74 [ 0.58, 0.94 ] |
| Pirker 2008 | 52/298 | 116/298 | | 3.8 % | 0.45 [ 0.34, 0.60 ] |
| Pronzato 2010 | 8/107 | 18/109 | | 0.6 % | 0.45 [ 0.21, 1.00 ] |
| Quirt 1996 | 4/27 | 8/27 | | 0.3 % | 0.50 [ 0.17, 1.47 ] |
| Ray-Coquard 2009 | 39/108 | 61/105 | | 2.0 % | 0.62 [ 0.46, 0.84 ] |




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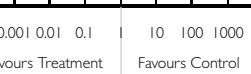
| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Razzouk 2006 | 72/111 | 86/111 | | 2.8 % | 0.84 [ 0.71, 0.99 ] |
| Rose 1994 | 65/142 | 47/79 | | 2.0 % | 0.77 [ 0.60, 0.99 ] |
| Smith 2003a | 3/20 | 1/6 | | 0.1 % | 0.90 [ 0.11, 7.14 ] |
| Smith 2003b | 1/20 | 1/7 | | 0.0 % | 0.35 [ 0.03, 4.88 ] |
| Smith 2003c | 2/21 | 2/7 | | 0.1 % | 0.33 [ 0.06, 1.94 ] |
| Smith 2008 | 176/419 | 215/432 | | 7.0 % | 0.84 [ 0.73, 0.98 ] |
| Strauss 2008 | 9/34 | 12/40 | | 0.4 % | 0.88 [ 0.42, 1.84 ] |
| Ten Bokkel 1998a | 2/45 | 7/17 | | 0.3 % | 0.11 [ 0.02, 0.47 ] |
| Ten Bokkel 1998b | 6/42 | 6/16 | | 0.3 % | 0.38 [ 0.14, 1.01 ] |
| Thatcher 1999a | 19/42 | 13/22 | | 0.6 % | 0.77 [ 0.47, 1.24 ] |
| Thatcher 1999b | 9/44 | 13/22 | | 0.6 % | 0.35 [ 0.18, 0.68 ] |
| Thomas 2002 | 7/62 | 31/65 | | 1.0 % | 0.24 [ 0.11, 0.50 ] |
| Throuvalas 2000 | 2/28 | 10/26 | | 0.3 % | 0.19 [ 0.04, 0.77 ] |
| Tjulandin 2010a | 8/76 | 9/37 | | 0.4 % | 0.43 [ 0.18, 1.03 ] |
| Tjulandin 2010b | 9/73 | 9/37 | | 0.4 % | 0.51 [ 0.22, 1.17 ] |
| Tjulandin 2011 | 13/95 | 23/91 | | 0.8 % | 0.54 [ 0.29, 1.00 ] |
| Tsuboi 2009 | 7/61 | 7/56 | | 0.2 % | 0.92 [ 0.34, 2.45 ] |
| Vansteenkiste 02 FDA 2004 | 53/156 | 89/158 | | 2.9 % | 0.60 [ 0.47, 0.78 ] |
| Welch 1995 | 4/15 | 8/15 | | 0.3 % | 0.50 [ 0.19, 1.31 ] |
| Wilkinson 2006 | 9/114 | 18/59 | | 0.8 % | 0.26 [ 0.12, 0.54 ] |
| Wright 2007 | 5/33 | 10/37 | | 0.3 % | 0.56 [ 0.21, 1.47 ] |
| **Subtotal (95% CI)** | **6567** | **5493** | | **80.2 %** | **0.68 [ 0.65, 0.71 ]** |
| Total events: 1807 (Treatment), 2330 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 158.97, df = 62 (P<0.00001); $I^2$ =61% | | | | | |
| Test for overall effect: Z = 16.62 (P < 0.00001) | | | | | |
| 3 no explicit statement on iron supplementation or no iron given | | | | | |
| Bamias 2003 | 11/72 | 24/72 | | 0.8 % | 0.46 [ 0.24, 0.86 ] |
| Carabantes 1999 | 4/20 | 13/15 | | 0.5 % | 0.23 [ 0.09, 0.57 ] |
| Gebbia 2003 | 5/22 | 13/23 | | 0.4 % | 0.40 [ 0.17, 0.94 ] |
| Hedenus 2002a | 3/11 | 2/3 | | 0.1 % | 0.41 [ 0.12, 1.43 ] |
| Hedenus 2002b | 6/22 | 2/4 | | 0.1 % | 0.55 [ 0.17, 1.80 ] |
| Hedenus 2002c | 3/22 | 1/4 | | 0.1 % | 0.55 [ 0.07, 4.02 ] |
| Katakami 2008 | 7/103 | 20/104 | | 0.7 % | 0.35 [ 0.16, 0.80 ] |

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| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Kunikane 2001a | 1/16 | 0/9 | | 0.0 % | 1.76 [ 0.08, 39.32 ] |
| Kunikane 2001b | 2/18 | 0/10 | | 0.0 % | 2.89 [ 0.15, 54.98 ] |
| Thompson 2000 | 34/45 | 19/21 | | 0.9 % | 0.84 [ 0.67, 1.04 ] |
| Wurnig 1996 | 8/15 | 14/14 | | 0.5 % | 0.55 [ 0.34, 0.88 ] |
| **Subtotal (95% CI)** | **366** | **279** | | **4.0 %** | **0.52 [ 0.42, 0.65 ]** |
| Total events: 84 (Treatment), 108 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 24.91, df = 10 (P = 0.01); $I^2$ =60% | | | | | |
| Test for overall effect: Z = 5.77 (P < 0.00001) | | | | | |
| 4 explicitly stated NO IRON | | | | | |
| **Subtotal (95% CI)** | **0** | **0** | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Total events: 0 (Treatment), 0 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: not applicable | | | | | |
| 5 iron given differently in both study arms new | | | | | |
| Blohmer 2011 | 14/127 | 38/129 | | 1.2 % | 0.37 [ 0.21, 0.66 ] |
| Moebus 2007 | 41/320 | 86/305 | | 2.9 % | 0.45 [ 0.32, 0.64 ] |
| Rosen 2003 | 19/47 | 24/43 | | 0.8 % | 0.72 [ 0.47, 1.12 ] |
| Savonije 2005 | 77/211 | 66/102 | | 2.9 % | 0.56 [ 0.45, 0.71 ] |
| **Subtotal (95% CI)** | **705** | **579** | | **7.9 %** | **0.51 [ 0.43, 0.61 ]** |
| Total events: 151 (Treatment), 214 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 4.82, df = 3 (P = 0.19); $I^2$ =38% | | | | | |
| Test for overall effect: Z = 7.57 (P < 0.00001) | | | | | |
| **Total (95% CI)** | **8733** | **7360** | | **100.0 %** | **0.65 [ 0.62, 0.68 ]** |
| Total events: 2198 (Treatment), 2880 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 217.08, df = 87 (P<0.00001); $I^2$ =60% | | | | | |
| Test for overall effect: Z = 19.89 (P < 0.00001) | | | | | |
| Test for subgroup differences: $Chi^2$ = 15.34, df = 3 (P = 0.00), $I^2$ =80% | | | | | |

## Analysis 3.11. Comparison 3 Participants receiving red blood cell transfusions, Outcome 11 Participants receiving red blood cell transfusions - allocation concealment.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 3 Participants receiving red blood cell transfusions

Outcome: 11 Participants receiving red blood cell transfusions - allocation concealment

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 adequate | | | | | |
| Aapro 2008 | 33/231 | 63/232 | | 2.1 % | 0.53 [ 0.36, 0.77 ] |
| Blohmer 2011 | 14/127 | 38/129 | | 1.2 % | 0.37 [ 0.21, 0.66 ] |
| Boogaerts 2003 | 43/133 | 67/129 | | 2.2 % | 0.62 [ 0.46, 0.84 ] |
| Cazzola 1995a | 7/31 | 2/7 | | 0.1 % | 0.79 [ 0.21, 3.02 ] |
| Cazzola 1995b | 5/29 | 2/8 | | 0.1 % | 0.69 [ 0.16, 2.91 ] |
| Cazzola 1995c | 6/31 | 2/7 | | 0.1 % | 0.68 [ 0.17, 2.68 ] |
| Cazzola 1995d | 4/26 | 2/7 | | 0.1 % | 0.54 [ 0.12, 2.36 ] |
| Chang 2005 | 15/175 | 40/175 | | 1.3 % | 0.38 [ 0.22, 0.65 ] |
| Charu 2007 | 27/226 | 13/59 | | 0.7 % | 0.54 [ 0.30, 0.98 ] |
| Christodoulou 2009 | 16/167 | 36/170 | | 1.2 % | 0.45 [ 0.26, 0.78 ] |
| Del Mastro 1997 | 0/31 | 2/31 | | 0.1 % | 0.20 [ 0.01, 4.00 ] |
| EPO-INT-3 J%J 2004 | 21/136 | 23/65 | | 1.0 % | 0.44 [ 0.26, 0.73 ] |
| Fujisaka 2011 | 4/89 | 18/92 | | 0.6 % | 0.23 [ 0.08, 0.65 ] |
| Gordon 2008 | 18/162 | 6/56 | | 0.3 % | 1.04 [ 0.43, 2.48 ] |
| Goss 2005 | 8/52 | 27/52 | | 0.9 % | 0.30 [ 0.15, 0.59 ] |
| Hedenus 2002a | 3/11 | 2/3 | | 0.1 % | 0.41 [ 0.12, 1.43 ] |
| Hedenus 2002b | 6/22 | 2/4 | | 0.1 % | 0.55 [ 0.17, 1.80 ] |
| Hedenus 2002c | 3/22 | 1/4 | | 0.1 % | 0.55 [ 0.07, 4.02 ] |
| Hedenus 2003 | 52/167 | 79/165 | | 2.6 % | 0.65 [ 0.49, 0.86 ] |
| Hernandez 2009 | 58/193 | 91/193 | | 3.0 % | 0.64 [ 0.49, 0.83 ] |
| Iconomou 2003 | 9/57 | 14/55 | | 0.5 % | 0.62 [ 0.29, 1.31 ] |
| Italian 1998 | 28/43 | 35/42 | | 1.2 % | 0.78 [ 0.60, 1.01 ] |
| Kotasek 2003a | 8/30 | 4/8 | | 0.2 % | 0.53 [ 0.21, 1.33 ] |
| Kotasek 2003b | 5/17 | 4/8 | | 0.2 % | 0.59 [ 0.21, 1.62 ] |


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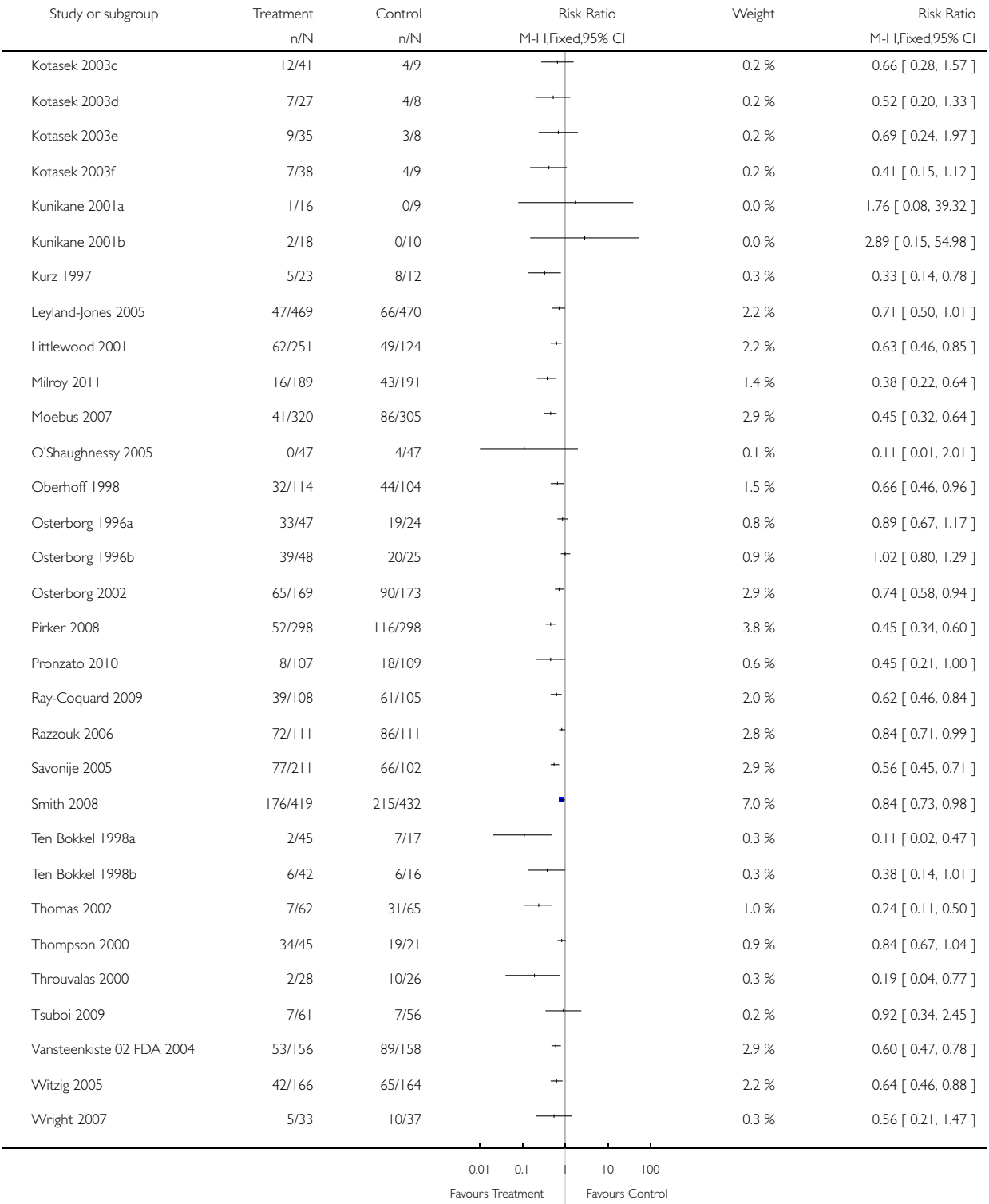


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| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| **Subtotal (95% CI)** | **5952** | **4946** | | **63.6 %** | **0.61 [ 0.58, 0.65 ]** |
| Total events: 1353 (Treatment), 1823 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 123.69, df = 54 (P<0.00001); $I^2$ =56% | | | | | |
| Test for overall effect: Z = 16.90 (P < 0.00001) | | | | | |
| 2 unclear | | | | | |
| Abels 1993 | 21/63 | 21/55 | | 0.7 % | 0.87 [ 0.54, 1.42 ] |
| Aravantinos 2003 | 9/24 | 23/23 | | 0.8 % | 0.39 [ 0.23, 0.64 ] |
| Bamias 2003 | 11/72 | 24/72 | | 0.8 % | 0.46 [ 0.24, 0.86 ] |
| Carabantes 1999 | 4/20 | 13/15 | | 0.5 % | 0.23 [ 0.09, 0.57 ] |
| Cascinu 1994 | 10/50 | 28/50 | | 0.9 % | 0.36 [ 0.19, 0.65 ] |
| Case 1993 | 32/79 | 36/74 | | 1.2 % | 0.83 [ 0.58, 1.19 ] |
| Dammacco 2001 | 19/69 | 36/76 | | 1.1 % | 0.58 [ 0.37, 0.91 ] |
| Dunphy 1999 | 2/13 | 5/14 | | 0.2 % | 0.43 [ 0.10, 1.85 ] |
| Engert 2010 | 405/640 | 467/643 | | 15.3 % | 0.87 [ 0.81, 0.94 ] |
| Gebbia 2003 | 5/22 | 13/23 | | 0.4 % | 0.40 [ 0.17, 0.94 ] |
| Grote 2005 | 26/109 | 42/115 | | 1.3 % | 0.65 [ 0.43, 0.99 ] |
| Gupta 2009 | 9/58 | 25/57 | | 0.8 % | 0.35 [ 0.18, 0.69 ] |
| Henry 1995 | 34/64 | 42/61 | | 1.4 % | 0.77 [ 0.58, 1.03 ] |
| Huddart 2002 | 18/45 | 32/45 | | 1.1 % | 0.56 [ 0.38, 0.84 ] |
| Katakami 2008 | 7/103 | 20/104 | | 0.7 % | 0.35 [ 0.16, 0.80 ] |
| Krzakowski 2008a | 27/104 | 14/52 | | 0.6 % | 0.96 [ 0.55, 1.68 ] |
| Krzakowski 2008b | 23/105 | 14/52 | | 0.6 % | 0.81 [ 0.46, 1.45 ] |
| Quirt 1996 | 4/27 | 8/27 | | 0.3 % | 0.50 [ 0.17, 1.47 ] |
| Rose 1994 | 65/142 | 47/79 | | 2.0 % | 0.77 [ 0.60, 0.99 ] |
| Rosen 2003 | 19/47 | 24/43 | | 0.8 % | 0.72 [ 0.47, 1.12 ] |
| Smith 2003a | 3/20 | 1/6 | | 0.1 % | 0.90 [ 0.11, 7.14 ] |
| Smith 2003b | 1/20 | 1/7 | | 0.0 % | 0.35 [ 0.03, 4.88 ] |
| Smith 2003c | 2/21 | 2/7 | | 0.1 % | 0.33 [ 0.06, 1.94 ] |
| Strauss 2008 | 9/34 | 12/40 | | 0.4 % | 0.88 [ 0.42, 1.84 ] |
| Thatcher 1999a | 19/42 | 13/22 | | 0.6 % | 0.77 [ 0.47, 1.24 ] |
| Thatcher 1999b | 9/44 | 13/22 | | 0.6 % | 0.35 [ 0.18, 0.68 ] |
| Tjulandin 2010a | 8/76 | 9/37 | | 0.4 % | 0.43 [ 0.18, 1.03 ] |
| Tjulandin 2010b | 9/73 | 9/37 | | 0.4 % | 0.51 [ 0.22, 1.17 ] |


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| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Tjulandin 2011 | 13/95 | 23/91 | | 0.8 % | 0.54 [ 0.29, 1.00 ] |
| Untch 2011˙1 | 1/356 | 0/377 | | 0.0 % | 3.18 [ 0.13, 77.72 ] |
| Welch 1995 | 4/15 | 8/15 | | 0.3 % | 0.50 [ 0.19, 1.31 ] |
| Wilkinson 2006 | 9/114 | 18/59 | | 0.8 % | 0.26 [ 0.12, 0.54 ] |
| Wurnig 1996 | 8/15 | 14/14 | | 0.5 % | 0.55 [ 0.34, 0.88 ] |
| **Subtotal (95% CI)** | **2781** | **2414** | | **36.4 %** | **0.71 [ 0.67, 0.76 ]** |
| Total events: 845 (Treatment), 1057 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 79.13, df = 32 (P<0.00001); $I^2$ =60% | | | | | |
| Test for overall effect: Z = 10.50 (P < 0.00001) | | | | | |
| **Total (95% CI)** | **8733** | **7360** | | **100.0 %** | **0.65 [ 0.62, 0.68 ]** |
| Total events: 2198 (Treatment), 2880 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 217.08, df = 87 (P<0.00001); $I^2$ =60% | | | | | |
| Test for overall effect: Z = 19.89 (P < 0.00001) | | | | | |
| Test for subgroup differences: $Chi^2$ = 12.21, df = 1 (P = 0.00), $I^2$ =92% | | | | | |

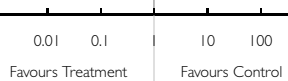
## Analysis 3.12. Comparison 3 Participants receiving red blood cell transfusions, Outcome 12 Participants receiving red blood cell transfusions - masking.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 3 Participants receiving red blood cell transfusions

Outcome: 12 Participants receiving red blood cell transfusions - masking

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 double-blind | | | | | |
| Abels 1993 | 21/63 | 21/55 | | 0.7 % | 0.87 [ 0.54, 1.42 ] |
| Cascinu 1994 | 10/50 | 28/50 | | 0.9 % | 0.36 [ 0.19, 0.65 ] |
| Case 1993 | 32/79 | 36/74 | | 1.2 % | 0.83 [ 0.58, 1.19 ] |
| Dammacco 2001 | 19/69 | 36/76 | | 1.1 % | 0.58 [ 0.37, 0.91 ] |
| Engert 2010 | 405/640 | 467/643 | | 15.3 % | 0.87 [ 0.81, 0.94 ] |
| EPO-INT-3 J%J 2004 | 21/136 | 23/65 | | 1.0 % | 0.44 [ 0.26, 0.73 ] |
| Fujisaka 2011 | 4/89 | 18/92 | | 0.6 % | 0.23 [ 0.08, 0.65 ] |
| Gordon 2008 | 18/162 | 6/56 | | 0.3 % | 1.04 [ 0.43, 2.48 ] |
| Goss 2005 | 8/52 | 27/52 | | 0.9 % | 0.30 [ 0.15, 0.59 ] |
| Grote 2005 | 26/109 | 42/115 | | 1.3 % | 0.65 [ 0.43, 0.99 ] |
| Hedenus 2002a | 3/11 | 2/3 | | 0.1 % | 0.41 [ 0.12, 1.43 ] |
| Hedenus 2002b | 6/22 | 2/4 | | 0.1 % | 0.55 [ 0.17, 1.80 ] |
| Hedenus 2002c | 3/22 | 1/4 | | 0.1 % | 0.55 [ 0.07, 4.02 ] |
| Hedenus 2003 | 52/167 | 79/165 | | 2.6 % | 0.65 [ 0.49, 0.86 ] |
| Henry 1995 | 34/64 | 42/61 | | 1.4 % | 0.77 [ 0.58, 1.03 ] |
| Hernandez 2009 | 58/193 | 91/193 | | 3.0 % | 0.64 [ 0.49, 0.83 ] |
| Italian 1998 | 28/43 | 35/42 | | 1.2 % | 0.78 [ 0.60, 1.01 ] |
| Katakami 2008 | 7/103 | 20/104 | | 0.7 % | 0.35 [ 0.16, 0.80 ] |
| Kotasek 2003a | 8/30 | 4/8 | | 0.2 % | 0.53 [ 0.21, 1.33 ] |
| Kotasek 2003b | 5/17 | 4/8 | | 0.2 % | 0.59 [ 0.21, 1.62 ] |
| Kotasek 2003c | 12/41 | 4/9 | | 0.2 % | 0.66 [ 0.28, 1.57 ] |
| Kotasek 2003d | 7/27 | 4/8 | | 0.2 % | 0.52 [ 0.20, 1.33 ] |
| Kotasek 2003e | 9/35 | 3/8 | | 0.2 % | 0.69 [ 0.24, 1.97 ] |
| Kotasek 2003f | 7/38 | 4/9 | | 0.2 % | 0.41 [ 0.15, 1.12 ] |

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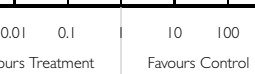
| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Krzakowski 2008a | 27/104 | 14/52 | | 0.6 % | 0.96 [ 0.55, 1.68 ] |
| Krzakowski 2008b | 23/105 | 14/52 | | 0.6 % | 0.81 [ 0.46, 1.45 ] |
| Kunikane 2001a | 1/16 | 0/9 | | 0.0 % | 1.76 [ 0.08, 39.32 ] |
| Kunikane 2001b | 2/18 | 0/10 | | 0.0 % | 2.89 [ 0.15, 54.98 ] |
| Kurz 1997 | 5/23 | 8/12 | | 0.3 % | 0.33 [ 0.14, 0.78 ] |
| Leyland-Jones 2005 | 47/469 | 66/470 | | 2.2 % | 0.71 [ 0.50, 1.01 ] |
| Littlewood 2001 | 62/251 | 49/124 | | 2.2 % | 0.63 [ 0.46, 0.85 ] |
| O'Shaughnessy 2005 | 0/47 | 4/47 | | 0.1 % | 0.11 [ 0.01, 2.01 ] |
| Osterborg 2002 | 65/169 | 90/173 | | 2.9 % | 0.74 [ 0.58, 0.94 ] |
| Pirker 2008 | 52/298 | 116/298 | | 3.8 % | 0.45 [ 0.34, 0.60 ] |
| Quirt 1996 | 4/27 | 8/27 | | 0.3 % | 0.50 [ 0.17, 1.47 ] |
| Razzouk 2006 | 72/111 | 86/111 | | 2.8 % | 0.84 [ 0.71, 0.99 ] |
| Rose 1994 | 65/142 | 47/79 | | 2.0 % | 0.77 [ 0.60, 0.99 ] |
| Smith 2003a | 3/20 | 1/6 | | 0.1 % | 0.90 [ 0.11, 7.14 ] |
| Smith 2003b | 1/20 | 1/7 | | 0.0 % | 0.35 [ 0.03, 4.88 ] |
| Smith 2003c | 2/21 | 2/7 | | 0.1 % | 0.33 [ 0.06, 1.94 ] |
| Smith 2008 | 176/419 | 215/432 | | 7.0 % | 0.84 [ 0.73, 0.98 ] |
| Thompson 2000 | 34/45 | 19/21 | | 0.9 % | 0.84 [ 0.67, 1.04 ] |
| Tjulandin 2010a | 8/76 | 9/37 | | 0.4 % | 0.43 [ 0.18, 1.03 ] |
| Tjulandin 2010b | 9/73 | 9/37 | | 0.4 % | 0.51 [ 0.22, 1.17 ] |
| Tjulandin 2011 | 13/95 | 23/91 | | 0.8 % | 0.54 [ 0.29, 1.00 ] |
| Tsuboi 2009 | 7/61 | 7/56 | | 0.2 % | 0.92 [ 0.34, 2.45 ] |
| Vansteenkiste 02 FDA 2004 | 53/156 | 89/158 | | 2.9 % | 0.60 [ 0.47, 0.78 ] |
| Witzig 2005 | 42/166 | 65/164 | | 2.2 % | 0.64 [ 0.46, 0.88 ] |
| Wright 2007 | 5/33 | 10/37 | | 0.3 % | 0.56 [ 0.21, 1.47 ] |
| Wurnig 1996 | 8/15 | 14/14 | | 0.5 % | 0.55 [ 0.34, 0.88 ] |
| **Subtotal (95% CI)** | **5242** | **4435** | | **67.4 %** | **0.71 [ 0.68, 0.75 ]** |
| Total events: 1589 (Treatment), 1965 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 94.05, df = 49 (P = 0.00012); $I^2$ =48% | | | | | |
| Test for overall effect: Z = 13.57 (P < 0.00001) | | | | | |
| 2 unblinded | | | | | |
| Aapro 2008 | 33/231 | 63/232 | | 2.1 % | 0.53 [ 0.36, 0.77 ] |
| Aravantinos 2003 | 9/24 | 23/23 | | 0.8 % | 0.39 [ 0.23, 0.64 ] |

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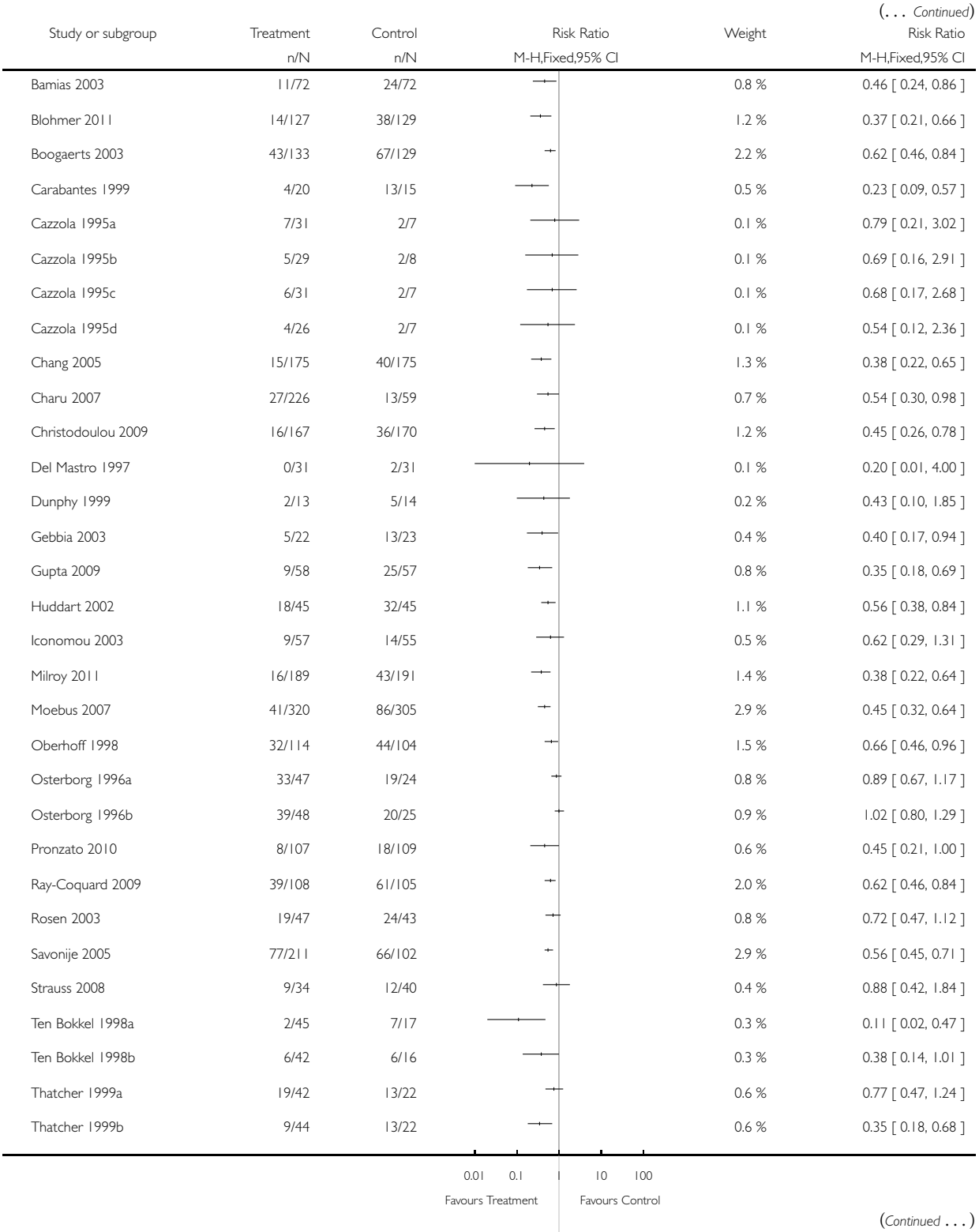


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| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Thomas 2002 | 7/62 | 31/65 | | 1.0 % | 0.24 [ 0.11, 0.50 ] |
| Throuvalas 2000 | 2/28 | 10/26 | | 0.3 % | 0.19 [ 0.04, 0.77 ] |
| Untch 2011˙1 | 1/356 | 0/377 | | 0.0 % | 3.18 [ 0.13, 77.72 ] |
| Welch 1995 | 4/15 | 8/15 | | 0.3 % | 0.50 [ 0.19, 1.31 ] |
| Wilkinson 2006 | 9/114 | 18/59 | | 0.8 % | 0.26 [ 0.12, 0.54 ] |
| **Subtotal (95% CI)** | **3491** | **2925** | | **32.6 %** | **0.52 [ 0.47, 0.56 ]** |
| Total events: 609 (Treatment), 915 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 86.98, df = 37 (P<0.00001); $I^2$ =57% | | | | | |
| Test for overall effect: Z = 15.06 (P < 0.00001) | | | | | |
| **Total (95% CI)** | **8733** | **7360** | | **100.0 %** | **0.65 [ 0.62, 0.68 ]** |
| Total events: 2198 (Treatment), 2880 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 217.08, df = 87 (P<0.00001); $I^2$ =60% | | | | | |
| Test for overall effect: Z = 19.89 (P < 0.00001) | | | | | |
| Test for subgroup differences: $Chi^2$ = 40.95, df = 1 (P = 0.00), $I^2$ =98% | | | | | |

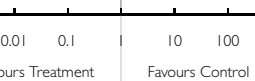
## Analysis 3.13. Comparison 3 Participants receiving red blood cell transfusions, Outcome 13 Participants receiving red blood cell transfusions - intention-to treat.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 3 Participants receiving red blood cell transfusions

Outcome: 13 Participants receiving red blood cell transfusions - intention-to treat

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 ITT or less than 10% of participants per study arm excluded | | | | | |
| Aapro 2008 | 33/231 | 63/232 | | 2.1 % | 0.53 [ 0.36, 0.77 ] |
| Abels 1993 | 21/63 | 21/55 | | 0.7 % | 0.87 [ 0.54, 1.42 ] |
| Aravantinos 2003 | 9/24 | 23/23 | | 0.8 % | 0.39 [ 0.23, 0.64 ] |
| Bamias 2003 | 11/72 | 24/72 | | 0.8 % | 0.46 [ 0.24, 0.86 ] |
| Boogaerts 2003 | 43/133 | 67/129 | | 2.2 % | 0.62 [ 0.46, 0.84 ] |
| Carabantes 1999 | 4/20 | 13/15 | | 0.5 % | 0.23 [ 0.09, 0.57 ] |
| Cascinu 1994 | 10/50 | 28/50 | | 0.9 % | 0.36 [ 0.19, 0.65 ] |
| Case 1993 | 32/79 | 36/74 | | 1.2 % | 0.83 [ 0.58, 1.19 ] |
| Cazzola 1995a | 7/31 | 2/7 | | 0.1 % | 0.79 [ 0.21, 3.02 ] |
| Cazzola 1995b | 5/29 | 2/8 | | 0.1 % | 0.69 [ 0.16, 2.91 ] |
| Cazzola 1995c | 6/31 | 2/7 | | 0.1 % | 0.68 [ 0.17, 2.68 ] |
| Cazzola 1995d | 4/26 | 2/7 | | 0.1 % | 0.54 [ 0.12, 2.36 ] |
| Chang 2005 | 15/175 | 40/175 | | 1.3 % | 0.38 [ 0.22, 0.65 ] |
| Charu 2007 | 27/226 | 13/59 | | 0.7 % | 0.54 [ 0.30, 0.98 ] |
| Dammacco 2001 | 19/69 | 36/76 | | 1.1 % | 0.58 [ 0.37, 0.91 ] |
| Del Mastro 1997 | 0/31 | 2/31 | | 0.1 % | 0.20 [ 0.01, 4.00 ] |
| Engert 2010 | 405/640 | 467/643 | | 15.3 % | 0.87 [ 0.81, 0.94 ] |
| EPO-INT-3 J%J 2004 | 21/136 | 23/65 | | 1.0 % | 0.44 [ 0.26, 0.73 ] |
| Fujisaka 2011 | 4/89 | 18/92 | | 0.6 % | 0.23 [ 0.08, 0.65 ] |
| Gebbia 2003 | 5/22 | 13/23 | | 0.4 % | 0.40 [ 0.17, 0.94 ] |
| Gordon 2008 | 18/162 | 6/56 | | 0.3 % | 1.04 [ 0.43, 2.48 ] |
| Goss 2005 | 8/52 | 27/52 | | 0.9 % | 0.30 [ 0.15, 0.59 ] |
| Grote 2005 | 26/109 | 42/115 | | 1.3 % | 0.65 [ 0.43, 0.99 ] |
| Gupta 2009 | 9/58 | 25/57 | | 0.8 % | 0.35 [ 0.18, 0.69 ] |

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| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Hedenus 2002a | 3/11 | 2/3 | | 0.1 % | 0.41 [ 0.12, 1.43 ] |
| Hedenus 2002b | 6/22 | 2/4 | | 0.1 % | 0.55 [ 0.17, 1.80 ] |
| Hedenus 2002c | 3/22 | 1/4 | | 0.1 % | 0.55 [ 0.07, 4.02 ] |
| Hedenus 2003 | 52/167 | 79/165 | | 2.6 % | 0.65 [ 0.49, 0.86 ] |
| Henry 1995 | 34/64 | 42/61 | | 1.4 % | 0.77 [ 0.58, 1.03 ] |
| Hernandez 2009 | 58/193 | 91/193 | | 3.0 % | 0.64 [ 0.49, 0.83 ] |
| Iconomou 2003 | 9/57 | 14/55 | | 0.5 % | 0.62 [ 0.29, 1.31 ] |
| Italian 1998 | 28/43 | 35/42 | | 1.2 % | 0.78 [ 0.60, 1.01 ] |
| Krzakowski 2008a | 27/104 | 14/52 | | 0.6 % | 0.96 [ 0.55, 1.68 ] |
| Krzakowski 2008b | 23/105 | 14/52 | | 0.6 % | 0.81 [ 0.46, 1.45 ] |
| Kurz 1997 | 5/23 | 8/12 | | 0.3 % | 0.33 [ 0.14, 0.78 ] |
| Leyland-Jones 2005 | 47/469 | 66/470 | | 2.2 % | 0.71 [ 0.50, 1.01 ] |
| Littlewood 2001 | 62/251 | 49/124 | | 2.2 % | 0.63 [ 0.46, 0.85 ] |
| Moebus 2007 | 41/320 | 86/305 | | 2.9 % | 0.45 [ 0.32, 0.64 ] |
| O'Shaughnessy 2005 | 0/47 | 4/47 | | 0.1 % | 0.11 [ 0.01, 2.01 ] |
| Oberhoff 1998 | 32/114 | 44/104 | | 1.5 % | 0.66 [ 0.46, 0.96 ] |
| Osterborg 1996a | 33/47 | 19/24 | | 0.8 % | 0.89 [ 0.67, 1.17 ] |
| Osterborg 1996b | 39/48 | 20/25 | | 0.9 % | 1.02 [ 0.80, 1.29 ] |
| Osterborg 2002 | 65/169 | 90/173 | | 2.9 % | 0.74 [ 0.58, 0.94 ] |
| Pirker 2008 | 52/298 | 116/298 | | 3.8 % | 0.45 [ 0.34, 0.60 ] |
| Pronzato 2010 | 8/107 | 18/109 | | 0.6 % | 0.45 [ 0.21, 1.00 ] |
| Quirt 1996 | 4/27 | 8/27 | | 0.3 % | 0.50 [ 0.17, 1.47 ] |
| Ray-Coquard 2009 | 39/108 | 61/105 | | 2.0 % | 0.62 [ 0.46, 0.84 ] |
| Razzouk 2006 | 72/111 | 86/111 | | 2.8 % | 0.84 [ 0.71, 0.99 ] |
| Rose 1994 | 65/142 | 47/79 | | 2.0 % | 0.77 [ 0.60, 0.99 ] |
| Rosen 2003 | 19/47 | 24/43 | | 0.8 % | 0.72 [ 0.47, 1.12 ] |
| Savonije 2005 | 77/211 | 66/102 | | 2.9 % | 0.56 [ 0.45, 0.71 ] |
| Smith 2003a | 3/20 | 1/6 | | 0.1 % | 0.90 [ 0.11, 7.14 ] |
| Smith 2003b | 1/20 | 1/7 | | 0.0 % | 0.35 [ 0.03, 4.88 ] |
| Smith 2003c | 2/21 | 2/7 | | 0.1 % | 0.33 [ 0.06, 1.94 ] |
| Smith 2008 | 176/419 | 215/432 | | 7.0 % | 0.84 [ 0.73, 0.98 ] |


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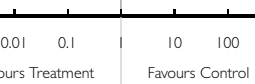
| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Strauss 2008 | 9/34 | 12/40 | | 0.4 % | 0.88 [ 0.42, 1.84 ] |
| Ten Bokkel 1998a | 2/45 | 7/17 | | 0.3 % | 0.11 [ 0.02, 0.47 ] |
| Ten Bokkel 1998b | 6/42 | 6/16 | | 0.3 % | 0.38 [ 0.14, 1.01 ] |
| Thatcher 1999a | 19/42 | 13/22 | | 0.6 % | 0.77 [ 0.47, 1.24 ] |
| Thatcher 1999b | 9/44 | 13/22 | | 0.6 % | 0.35 [ 0.18, 0.68 ] |
| Thomas 2002 | 7/62 | 31/65 | | 1.0 % | 0.24 [ 0.11, 0.50 ] |
| Thompson 2000 | 34/45 | 19/21 | | 0.9 % | 0.84 [ 0.67, 1.04 ] |
| Throuvalas 2000 | 2/28 | 10/26 | | 0.3 % | 0.19 [ 0.04, 0.77 ] |
| Tjulandin 2010a | 8/76 | 9/37 | | 0.4 % | 0.43 [ 0.18, 1.03 ] |
| Tjulandin 2010b | 9/73 | 9/37 | | 0.4 % | 0.51 [ 0.22, 1.17 ] |
| Tjulandin 2011 | 13/95 | 23/91 | | 0.8 % | 0.54 [ 0.29, 1.00 ] |
| Tsuboi 2009 | 7/61 | 7/56 | | 0.2 % | 0.92 [ 0.34, 2.45 ] |
| Vansteenkiste 02 FDA 2004 | 53/156 | 89/158 | | 2.9 % | 0.60 [ 0.47, 0.78 ] |
| Welch 1995 | 4/15 | 8/15 | | 0.3 % | 0.50 [ 0.19, 1.31 ] |
| Wilkinson 2006 | 9/114 | 18/59 | | 0.8 % | 0.26 [ 0.12, 0.54 ] |
| Witzig 2005 | 42/166 | 65/164 | | 2.2 % | 0.64 [ 0.46, 0.88 ] |
| Wright 2007 | 5/33 | 10/37 | | 0.3 % | 0.56 [ 0.21, 1.47 ] |
| Wurnig 1996 | 8/15 | 14/14 | | 0.5 % | 0.55 [ 0.34, 0.88 ] |
| **Subtotal (95% CI)** | **7511** | **6261** | | **93.1 %** | **0.66 [ 0.63, 0.69 ]** |
| Total events: 2073 (Treatment), 2683 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 191.64, df = 72 (P<0.00001); $I^2$ =62% | | | | | |
| Test for overall effect: Z = 18.58 (P < 0.00001) | | | | | |
| 2 more than 10% of participants per study arm excluded | | | | | |
| Christodoulou 2009 | 16/167 | 36/170 | | 1.2 % | 0.45 [ 0.26, 0.78 ] |
| Dunphy 1999 | 2/13 | 5/14 | | 0.2 % | 0.43 [ 0.10, 1.85 ] |
| Kotasek 2003a | 8/30 | 4/8 | | 0.2 % | 0.53 [ 0.21, 1.33 ] |
| Kotasek 2003b | 5/17 | 4/8 | | 0.2 % | 0.59 [ 0.21, 1.62 ] |
| Kotasek 2003c | 12/41 | 4/9 | | 0.2 % | 0.66 [ 0.28, 1.57 ] |
| Kotasek 2003d | 7/27 | 4/8 | | 0.2 % | 0.52 [ 0.20, 1.33 ] |
| Kotasek 2003e | 9/35 | 3/8 | | 0.2 % | 0.69 [ 0.24, 1.97 ] |
| Kotasek 2003f | 7/38 | 4/9 | | 0.2 % | 0.41 [ 0.15, 1.12 ] |
| Kunikane 2001a | 1/16 | 0/9 | | 0.0 % | 1.76 [ 0.08, 39.32 ] |
| Kunikane 2001b | 2/18 | 0/10 | | 0.0 % | 2.89 [ 0.15, 54.98 ] |

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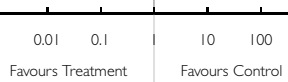
| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Milroy 2011 | 16/189 | 43/191 | | 1.4 % | 0.38 [ 0.22, 0.64 ] |
| **Subtotal (95% CI)** | **591** | **444** | | **4.0 %** | **0.48 [ 0.36, 0.63 ]** |
| Total events: 85 (Treatment), 107 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 4.24, df = 10 (P = 0.94); $I^2$ =0.0% | | | | | |
| Test for overall effect: Z = 5.29 (P < 0.00001) | | | | | |
| 3 unclear | | | | | |
| Blohmer 2011 | 14/127 | 38/129 | | 1.2 % | 0.37 [ 0.21, 0.66 ] |
| Huddart 2002 | 18/45 | 32/45 | | 1.1 % | 0.56 [ 0.38, 0.84 ] |
| Katakami 2008 | 7/103 | 20/104 | | 0.7 % | 0.35 [ 0.16, 0.80 ] |
| Untch 2011˙1 | 1/356 | 0/377 | | 0.0 % | 3.18 [ 0.13, 77.72 ] |
| **Subtotal (95% CI)** | **631** | **655** | | **3.0 %** | **0.45 [ 0.33, 0.62 ]** |
| Total events: 40 (Treatment), 90 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 3.34, df = 3 (P = 0.34); $I^2$ =10% | | | | | |
| Test for overall effect: Z = 4.95 (P < 0.00001) | | | | | |
| **Total (95% CI)** | **8733** | **7360** | | **100.0 %** | **0.65 [ 0.62, 0.68 ]** |
| Total events: 2198 (Treatment), 2880 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 217.08, df = 87 (P<0.00001); $I^2$ =60% | | | | | |
| Test for overall effect: Z = 19.89 (P < 0.00001) | | | | | |
| Test for subgroup differences: $Chi^2$ = 10.80, df = 2 (P = 0.00), $I^2$ =81% | | | | | |



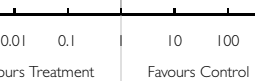
## Analysis 3.14. Comparison 3 Participants receiving red blood cell transfusions, Outcome 14 Participants receiving red blood cell transfusions - publication.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 3 Participants receiving red blood cell transfusions

Outcome: 14 Participants receiving red blood cell transfusions - publication

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 fulltext publication | | | | | |
| Aapro 2008 | 33/231 | 63/232 | | 2.1 % | 0.53 [ 0.36, 0.77 ] |
| Abels 1993 | 21/63 | 21/55 | | 0.7 % | 0.87 [ 0.54, 1.42 ] |
| Aravantinos 2003 | 9/24 | 23/23 | | 0.8 % | 0.39 [ 0.23, 0.64 ] |
| Bamias 2003 | 11/72 | 24/72 | | 0.8 % | 0.46 [ 0.24, 0.86 ] |
| Blohmer 2011 | 14/127 | 38/129 | | 1.2 % | 0.37 [ 0.21, 0.66 ] |
| Boogaerts 2003 | 43/133 | 67/129 | | 2.2 % | 0.62 [ 0.46, 0.84 ] |
| Cascinu 1994 | 10/50 | 28/50 | | 0.9 % | 0.36 [ 0.19, 0.65 ] |
| Cazzola 1995a | 7/31 | 2/7 | | 0.1 % | 0.79 [ 0.21, 3.02 ] |
| Cazzola 1995b | 5/29 | 2/8 | | 0.1 % | 0.69 [ 0.16, 2.91 ] |
| Cazzola 1995c | 6/31 | 2/7 | | 0.1 % | 0.68 [ 0.17, 2.68 ] |
| Cazzola 1995d | 4/26 | 2/7 | | 0.1 % | 0.54 [ 0.12, 2.36 ] |
| Chang 2005 | 15/175 | 40/175 | | 1.3 % | 0.38 [ 0.22, 0.65 ] |
| Charu 2007 | 27/226 | 13/59 | | 0.7 % | 0.54 [ 0.30, 0.98 ] |
| Christodoulou 2009 | 16/167 | 36/170 | | 1.2 % | 0.45 [ 0.26, 0.78 ] |
| Dammacco 2001 | 19/69 | 36/76 | | 1.1 % | 0.58 [ 0.37, 0.91 ] |
| Del Mastro 1997 | 0/31 | 2/31 | | 0.1 % | 0.20 [ 0.01, 4.00 ] |
| Dunphy 1999 | 2/13 | 5/14 | | 0.2 % | 0.43 [ 0.10, 1.85 ] |
| Engert 2010 | 405/640 | 467/643 | | 15.3 % | 0.87 [ 0.81, 0.94 ] |
| Fujisaka 2011 | 4/89 | 18/92 | | 0.6 % | 0.23 [ 0.08, 0.65 ] |
| Gebbia 2003 | 5/22 | 13/23 | | 0.4 % | 0.40 [ 0.17, 0.94 ] |
| Gordon 2008 | 18/162 | 6/56 | | 0.3 % | 1.04 [ 0.43, 2.48 ] |
| Grote 2005 | 26/109 | 42/115 | | 1.3 % | 0.65 [ 0.43, 0.99 ] |
| Gupta 2009 | 9/58 | 25/57 | | 0.8 % | 0.35 [ 0.18, 0.69 ] |
| Hedenus 2002a | 3/11 | 2/3 | | 0.1 % | 0.41 [ 0.12, 1.43 ] |

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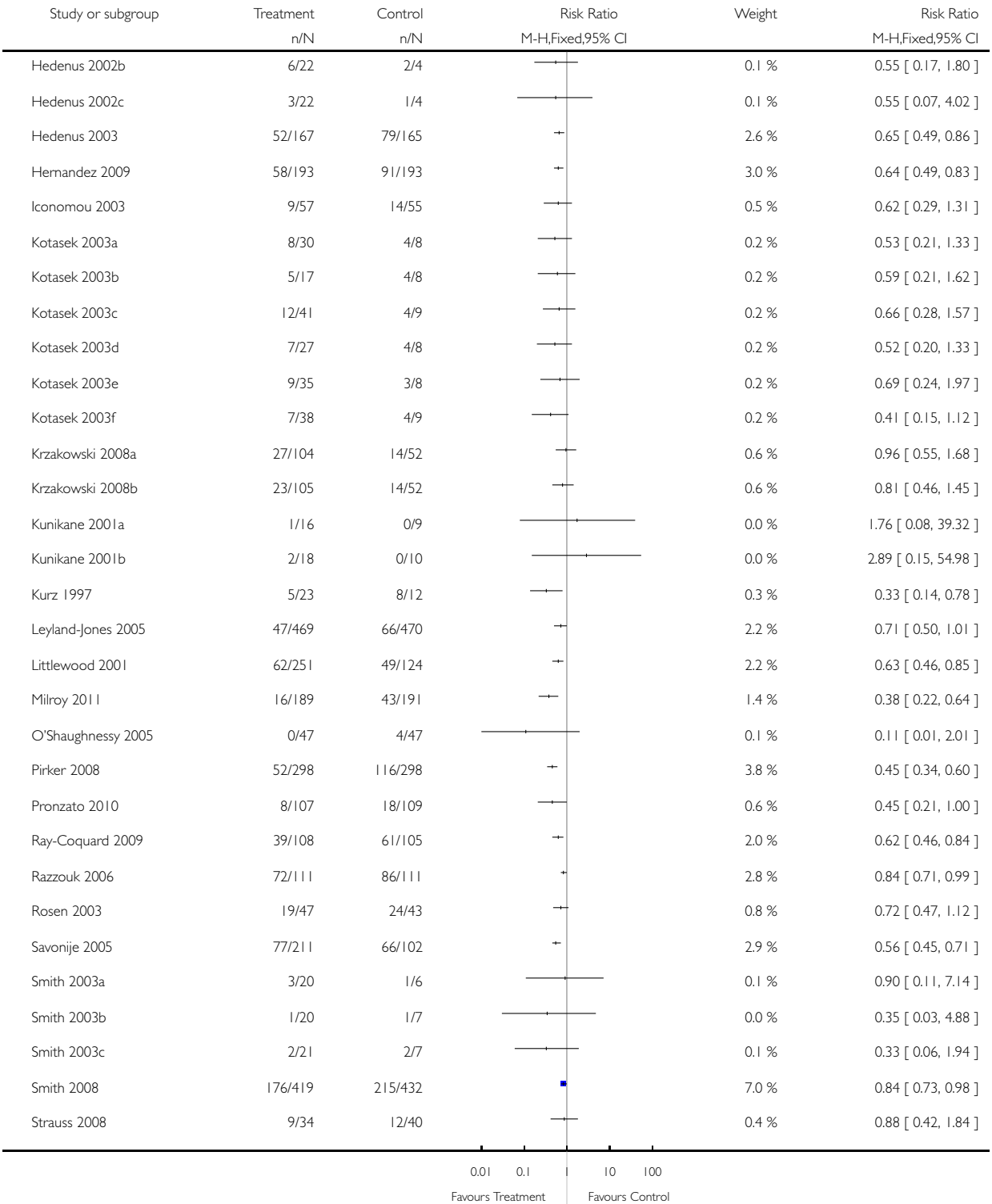


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| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Tjulandin 2010a | 8/76 | 9/37 | | 0.4 % | 0.43 [ 0.18, 1.03 ] |
| Tjulandin 2010b | 9/73 | 9/37 | | 0.4 % | 0.51 [ 0.22, 1.17 ] |
| Tjulandin 2011 | 13/95 | 23/91 | | 0.8 % | 0.54 [ 0.29, 1.00 ] |
| Tsuboi 2009 | 7/61 | 7/56 | | 0.2 % | 0.92 [ 0.34, 2.45 ] |
| Untch 2011˙1 | 1/356 | 0/377 | | 0.0 % | 3.18 [ 0.13, 77.72 ] |
| Welch 1995 | 4/15 | 8/15 | | 0.3 % | 0.50 [ 0.19, 1.31 ] |
| Wilkinson 2006 | 9/114 | 18/59 | | 0.8 % | 0.26 [ 0.12, 0.54 ] |
| Witzig 2005 | 42/166 | 65/164 | | 2.2 % | 0.64 [ 0.46, 0.88 ] |
| Wright 2007 | 5/33 | 10/37 | | 0.3 % | 0.56 [ 0.21, 1.47 ] |
| Wurnig 1996 | 8/15 | 14/14 | | 0.5 % | 0.55 [ 0.34, 0.88 ] |
| **Subtotal (95% CI)** | **6860** | **5818** | | **73.9 %** | **0.66 [ 0.63, 0.70 ]** |
| Total events: 1635 (Treatment), 2150 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 138.73, df = 64 (P<0.00001); $I^2$ =54% | | | | | |
| Test for overall effect: Z = 16.31 (P < 0.00001) | | | | | |
| 2 abstract publication | | | | | |
| Carabantes 1999 | 4/20 | 13/15 | | 0.5 % | 0.23 [ 0.09, 0.57 ] |
| Goss 2005 | 8/52 | 27/52 | | 0.9 % | 0.30 [ 0.15, 0.59 ] |
| Huddart 2002 | 18/45 | 32/45 | | 1.1 % | 0.56 [ 0.38, 0.84 ] |
| Katakami 2008 | 7/103 | 20/104 | | 0.7 % | 0.35 [ 0.16, 0.80 ] |
| Moebus 2007 | 41/320 | 86/305 | | 2.9 % | 0.45 [ 0.32, 0.64 ] |
| Quirt 1996 | 4/27 | 8/27 | | 0.3 % | 0.50 [ 0.17, 1.47 ] |
| Thomas 2002 | 7/62 | 31/65 | | 1.0 % | 0.24 [ 0.11, 0.50 ] |
| **Subtotal (95% CI)** | **629** | **613** | | **7.2 %** | **0.40 [ 0.32, 0.49 ]** |
| Total events: 89 (Treatment), 217 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 7.67, df = 6 (P = 0.26); $I^2$ =22% | | | | | |
| Test for overall effect: Z = 8.41 (P < 0.00001) | | | | | |
| 3 unpublished data | | | | | |
| Case 1993 | 32/79 | 36/74 | | 1.2 % | 0.83 [ 0.58, 1.19 ] |
| Henry 1995 | 34/64 | 42/61 | | 1.4 % | 0.77 [ 0.58, 1.03 ] |
| Italian 1998 | 28/43 | 35/42 | | 1.2 % | 0.78 [ 0.60, 1.01 ] |
| Oberhoff 1998 | 32/114 | 44/104 | | 1.5 % | 0.66 [ 0.46, 0.96 ] |
| Osterborg 1996a | 33/47 | 19/24 | | 0.8 % | 0.89 [ 0.67, 1.17 ] |
| Osterborg 1996b | 39/48 | 20/25 | | 0.9 % | 1.02 [ 0.80, 1.29 ] |
| Osterborg 2002 | 65/169 | 90/173 | | 2.9 % | 0.74 [ 0.58, 0.94 ] |


(*Continued* . . . )

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| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Rose 1994 | 65/142 | 47/79 | | 2.0 % | 0.77 [ 0.60, 0.99 ] |
| Ten Bokkel 1998a | 2/45 | 7/17 | | 0.3 % | 0.11 [ 0.02, 0.47 ] |
| Ten Bokkel 1998b | 6/42 | 6/16 | | 0.3 % | 0.38 [ 0.14, 1.01 ] |
| Thatcher 1999a | 19/42 | 13/22 | | 0.6 % | 0.77 [ 0.47, 1.24 ] |
| Thatcher 1999b | 9/44 | 13/22 | | 0.6 % | 0.35 [ 0.18, 0.68 ] |
| Thompson 2000 | 34/45 | 19/21 | | 0.9 % | 0.84 [ 0.67, 1.04 ] |
| Throuvalas 2000 | 2/28 | 10/26 | | 0.3 % | 0.19 [ 0.04, 0.77 ] |
| **Subtotal (95% CI)** | **952** | **706** | | **14.9 %** | **0.73 [ 0.67, 0.80 ]** |
| Total events: 400 (Treatment), 401 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 28.40, df = 13 (P = 0.01); $I^2$ =54% | | | | | |
| Test for overall effect: Z = 6.48 (P < 0.00001) | | | | | |
| 4 FDA presented data | | | | | |
| Vansteenkiste 02 FDA 2004 | 53/156 | 89/158 | | 2.9 % | 0.60 [ 0.47, 0.78 ] |
| **Subtotal (95% CI)** | **156** | **158** | | **2.9 %** | **0.60 [ 0.47, 0.78 ]** |
| Total events: 53 (Treatment), 89 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 3.84 (P = 0.00012) | | | | | |
| 5 Other | | | | | |
| EPO-INT-3 J%J 2004 | 21/136 | 23/65 | | 1.0 % | 0.44 [ 0.26, 0.73 ] |
| **Subtotal (95% CI)** | **136** | **65** | | **1.0 %** | **0.44 [ 0.26, 0.73 ]** |
| Total events: 21 (Treatment), 23 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 3.17 (P = 0.0015) | | | | | |
| **Total (95% CI)** | **8733** | **7360** | | **100.0 %** | **0.65 [ 0.62, 0.68 ]** |
| Total events: 2198 (Treatment), 2880 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 217.08, df = 87 (P<0.00001); $I^2$ =60% | | | | | |
| Test for overall effect: Z = 19.89 (P < 0.00001) | | | | | |
| Test for subgroup differences: $Chi^2$ = 28.83, df = 4 (P = 0.00), $I^2$ =86% | | | | | |

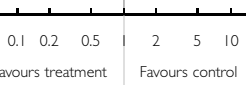
### Analysis 3.15. Comparison 3 Participants receiving red blood cell transfusions, Outcome 15 Participants receiving red blood cell transfusions - first 4 weeks are....

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 3 Participants receiving red blood cell transfusions

Outcome: 15 Participants receiving red blood cell transfusions - first 4 weeks are...

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 included in the analysis | | | | | |
| Abels 1993 | 21/63 | 21/55 | | 0.7 % | 0.87 [ 0.54, 1.42 ] |
| Aravantinos 2003 | 9/24 | 23/23 | | 0.8 % | 0.39 [ 0.23, 0.64 ] |
| Bamias 2003 | 11/72 | 24/72 | | 0.8 % | 0.46 [ 0.24, 0.86 ] |
| Boogaerts 2003 | 43/133 | 67/129 | | 2.2 % | 0.62 [ 0.46, 0.84 ] |
| Cascinu 1994 | 10/50 | 28/50 | | 0.9 % | 0.36 [ 0.19, 0.65 ] |
| Case 1993 | 32/79 | 36/74 | | 1.2 % | 0.83 [ 0.58, 1.19 ] |
| Cazzola 1995a | 7/31 | 2/7 | | 0.1 % | 0.79 [ 0.21, 3.02 ] |
| Cazzola 1995b | 5/29 | 2/8 | | 0.1 % | 0.69 [ 0.16, 2.91 ] |
| Cazzola 1995c | 6/31 | 2/7 | | 0.1 % | 0.68 [ 0.17, 2.68 ] |
| Cazzola 1995d | 4/26 | 2/7 | | 0.1 % | 0.54 [ 0.12, 2.36 ] |
| Charu 2007 | 27/226 | 13/59 | | 0.7 % | 0.54 [ 0.30, 0.98 ] |
| Dunphy 1999 | 2/13 | 5/14 | | 0.2 % | 0.43 [ 0.10, 1.85 ] |
| Gordon 2008 | 18/162 | 6/56 | | 0.3 % | 1.04 [ 0.43, 2.48 ] |
| Grote 2005 | 26/109 | 42/115 | | 1.3 % | 0.65 [ 0.43, 0.99 ] |
| Hernandez 2009 | 58/193 | 91/193 | | 3.0 % | 0.64 [ 0.49, 0.83 ] |
| Huddart 2002 | 18/45 | 32/45 | | 1.1 % | 0.56 [ 0.38, 0.84 ] |
| Iconomou 2003 | 9/57 | 14/55 | | 0.5 % | 0.62 [ 0.29, 1.31 ] |
| Milroy 2011 | 16/189 | 43/191 | | 1.4 % | 0.38 [ 0.22, 0.64 ] |
| Oberhoff 1998 | 32/114 | 44/104 | | 1.5 % | 0.66 [ 0.46, 0.96 ] |
| Osterborg 1996a | 33/47 | 19/24 | | 0.8 % | 0.89 [ 0.67, 1.17 ] |
| Osterborg 1996b | 39/48 | 20/25 | | 0.9 % | 1.02 [ 0.80, 1.29 ] |
| Osterborg 2002 | 65/169 | 90/173 | | 2.9 % | 0.74 [ 0.58, 0.94 ] |
| Pronzato 2010 | 8/107 | 18/109 | | 0.6 % | 0.45 [ 0.21, 1.00 ] |
| Razzouk 2006 | 72/111 | 86/111 | | 2.8 % | 0.84 [ 0.71, 0.99 ] |

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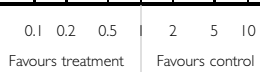
| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Rose 1994 | 65/142 | 47/79 | | 2.0 % | 0.77 [ 0.60, 0.99 ] |
| Savonije 2005 | 77/211 | 66/102 | | 2.9 % | 0.56 [ 0.45, 0.71 ] |
| Ten Bokkel 1998a | 2/45 | 7/17 | | 0.3 % | 0.11 [ 0.02, 0.47 ] |
| Ten Bokkel 1998b | 6/42 | 6/16 | | 0.3 % | 0.38 [ 0.14, 1.01 ] |
| Tsuboi 2009 | 7/61 | 7/56 | | 0.2 % | 0.92 [ 0.34, 2.45 ] |
| Vansteenkiste 02 FDA 2004 | 53/156 | 89/158 | | 2.9 % | 0.60 [ 0.47, 0.78 ] |
| Witzig 2005 | 42/166 | 65/164 | | 2.2 % | 0.64 [ 0.46, 0.88 ] |
| Wright 2007 | 5/33 | 10/37 | | 0.3 % | 0.56 [ 0.21, 1.47 ] |
| **Subtotal (95% CI)** | **2984** | **2335** | | **36.2 %** | **0.65 [ 0.61, 0.70 ]** |
| Total events: 828 (Treatment), 1027 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 58.44, df = 31 (P = 0.002); $I^2$ =47% | | | | | |
| Test for overall effect: Z = 11.94 (P < 0.00001) | | | | | |
| 2 excluded from the analysis | | | | | |
| Dammacco 2001 | 19/69 | 36/76 | | 1.1 % | 0.58 [ 0.37, 0.91 ] |
| EPO-INT-3 J%J 2004 | 21/136 | 23/65 | | 1.0 % | 0.44 [ 0.26, 0.73 ] |
| Fujisaka 2011 | 4/89 | 18/92 | | 0.6 % | 0.23 [ 0.08, 0.65 ] |
| Hedenus 2002a | 3/11 | 2/3 | | 0.1 % | 0.41 [ 0.12, 1.43 ] |
| Hedenus 2002b | 6/22 | 2/4 | | 0.1 % | 0.55 [ 0.17, 1.80 ] |
| Hedenus 2002c | 3/22 | 1/4 | | 0.1 % | 0.55 [ 0.07, 4.02 ] |
| Hedenus 2003 | 52/167 | 79/165 | | 2.6 % | 0.65 [ 0.49, 0.86 ] |
| Henry 1995 | 34/64 | 42/61 | | 1.4 % | 0.77 [ 0.58, 1.03 ] |
| Katakami 2008 | 7/103 | 20/104 | | 0.7 % | 0.35 [ 0.16, 0.80 ] |
| Kotasek 2003a | 8/30 | 4/8 | | 0.2 % | 0.53 [ 0.21, 1.33 ] |
| Kotasek 2003b | 5/17 | 4/8 | | 0.2 % | 0.59 [ 0.21, 1.62 ] |
| Kotasek 2003c | 12/41 | 4/9 | | 0.2 % | 0.66 [ 0.28, 1.57 ] |
| Kotasek 2003d | 7/27 | 4/8 | | 0.2 % | 0.52 [ 0.20, 1.33 ] |
| Kotasek 2003e | 9/35 | 3/8 | | 0.2 % | 0.69 [ 0.24, 1.97 ] |
| Kotasek 2003f | 7/38 | 4/9 | | 0.2 % | 0.41 [ 0.15, 1.12 ] |
| Krzakowski 2008a | 27/104 | 14/52 | | 0.6 % | 0.96 [ 0.55, 1.68 ] |
| Krzakowski 2008b | 23/105 | 14/52 | | 0.6 % | 0.81 [ 0.46, 1.45 ] |
| Littlewood 2001 | 62/251 | 49/124 | | 2.2 % | 0.63 [ 0.46, 0.85 ] |
| Smith 2003a | 3/20 | 1/6 | | 0.1 % | 0.90 [ 0.11, 7.14 ] |
| Smith 2003b | 1/20 | 1/7 | | 0.0 % | 0.35 [ 0.03, 4.88 ] |

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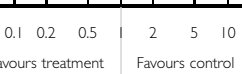
| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Smith 2003c | 2/21 | 2/7 | | 0.1 % | 0.33 [ 0.06, 1.94 ] |
| Smith 2008 | 176/419 | 215/432 | | 7.0 % | 0.84 [ 0.73, 0.98 ] |
| Wilkinson 2006 | 9/114 | 18/59 | | 0.8 % | 0.26 [ 0.12, 0.54 ] |
| **Subtotal (95% CI)** | **1925** | **1363** | | **20.2 %** | **0.68 [ 0.61, 0.75 ]** |
| Total events: 500 (Treatment), 560 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 31.44, df = 22 (P = 0.09); $I^2$ =30% | | | | | |
| Test for overall effect: Z = 7.96 (P < 0.00001) | | | | | |
| 3 unclear | | | | | |
| Aapro 2008 | 33/231 | 63/232 | | 2.1 % | 0.53 [ 0.36, 0.77 ] |
| Blohmer 2011 | 14/127 | 38/129 | | 1.2 % | 0.37 [ 0.21, 0.66 ] |
| Carabantes 1999 | 4/20 | 13/15 | | 0.5 % | 0.23 [ 0.09, 0.57 ] |
| Chang 2005 | 15/175 | 40/175 | | 1.3 % | 0.38 [ 0.22, 0.65 ] |
| Christodoulou 2009 | 16/167 | 36/170 | | 1.2 % | 0.45 [ 0.26, 0.78 ] |
| Del Mastro 1997 | 0/31 | 2/31 | | 0.1 % | 0.20 [ 0.01, 4.00 ] |
| Engert 2010 | 405/640 | 467/643 | | 15.3 % | 0.87 [ 0.81, 0.94 ] |
| Gebbia 2003 | 5/22 | 13/23 | | 0.4 % | 0.40 [ 0.17, 0.94 ] |
| Goss 2005 | 8/52 | 27/52 | | 0.9 % | 0.30 [ 0.15, 0.59 ] |
| Gupta 2009 | 9/58 | 25/57 | | 0.8 % | 0.35 [ 0.18, 0.69 ] |
| Italian 1998 | 28/43 | 35/42 | | 1.2 % | 0.78 [ 0.60, 1.01 ] |
| Kunikane 2001a | 1/16 | 0/9 | | 0.0 % | 1.76 [ 0.08, 39.32 ] |
| Kunikane 2001b | 2/18 | 0/10 | | 0.0 % | 2.89 [ 0.15, 54.98 ] |
| Kurz 1997 | 5/23 | 8/12 | | 0.3 % | 0.33 [ 0.14, 0.78 ] |
| Leyland-Jones 2005 | 47/469 | 66/470 | | 2.2 % | 0.71 [ 0.50, 1.01 ] |
| Moebus 2007 | 41/320 | 86/305 | | 2.9 % | 0.45 [ 0.32, 0.64 ] |
| O'Shaughnessy 2005 | 0/47 | 4/47 | | 0.1 % | 0.11 [ 0.01, 2.01 ] |
| Pirker 2008 | 52/298 | 116/298 | | 3.8 % | 0.45 [ 0.34, 0.60 ] |
| Quirt 1996 | 4/27 | 8/27 | | 0.3 % | 0.50 [ 0.17, 1.47 ] |
| Ray-Coquard 2009 | 39/108 | 61/105 | | 2.0 % | 0.62 [ 0.46, 0.84 ] |
| Rosen 2003 | 19/47 | 24/43 | | 0.8 % | 0.72 [ 0.47, 1.12 ] |
| Strauss 2008 | 9/34 | 12/40 | | 0.4 % | 0.88 [ 0.42, 1.84 ] |
| Thatcher 1999a | 19/42 | 13/22 | | 0.6 % | 0.77 [ 0.47, 1.24 ] |
| Thatcher 1999b | 9/44 | 13/22 | | 0.6 % | 0.35 [ 0.18, 0.68 ] |
| Thomas 2002 | 7/62 | 31/65 | | 1.0 % | 0.24 [ 0.11, 0.50 ] |

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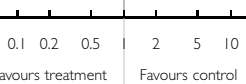
| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Thompson 2000 | 34/45 | 19/21 | | 0.9 % | 0.84 [ 0.67, 1.04 ] |
| Throuvalas 2000 | 2/28 | 10/26 | | 0.3 % | 0.19 [ 0.04, 0.77 ] |
| Tjulandin 2010a | 8/76 | 9/37 | | 0.4 % | 0.43 [ 0.18, 1.03 ] |
| Tjulandin 2010b | 9/73 | 9/37 | | 0.4 % | 0.51 [ 0.22, 1.17 ] |
| Tjulandin 2011 | 13/95 | 23/91 | | 0.8 % | 0.54 [ 0.29, 1.00 ] |
| Untch 2011˙1 | 1/356 | 0/377 | | 0.0 % | 3.18 [ 0.13, 77.72 ] |
| Welch 1995 | 4/15 | 8/15 | | 0.3 % | 0.50 [ 0.19, 1.31 ] |
| Wurnig 1996 | 8/15 | 14/14 | | 0.5 % | 0.55 [ 0.34, 0.88 ] |
| **Subtotal (95% CI)** | **3824** | **3662** | | **43.6 %** | **0.64 [ 0.60, 0.68 ]** |
| Total events: 870 (Treatment), 1293 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 131.29, df = 32 (P<0.00001); $I^2$ =76% | | | | | |
| Test for overall effect: Z = 13.86 (P < 0.00001) | | | | | |
| **Total (95% CI)** | **8733** | **7360** | | **100.0 %** | **0.65 [ 0.62, 0.68 ]** |
| Total events: 2198 (Treatment), 2880 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 217.08, df = 87 (P<0.00001); $I^2$ =60% | | | | | |
| Test for overall effect: Z = 19.89 (P < 0.00001) | | | | | |
| Test for subgroup differences: $Chi^2$ = 1.14, df = 2 (P = 0.57), $I^2$ =0.0% | | | | | |



### Analysis 3.16. Comparison 3 Participants receiving red blood cell transfusions, Outcome 16 Participants receiving red blood cell transfusions - experimental arms merged.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 3 Participants receiving red blood cell transfusions

Outcome: 16 Participants receiving red blood cell transfusions - experimental arms merged

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Aapro 2008 | 33/231 | 63/232 | | 2.1 % | 0.53 [ 0.36, 0.77 ] |
| Abels 1993 | 21/63 | 21/55 | | 0.7 % | 0.87 [ 0.54, 1.42 ] |
| Aravantinos 2003 | 9/24 | 23/23 | | 0.8 % | 0.39 [ 0.23, 0.64 ] |
| Bamias 2003 | 11/72 | 24/72 | | 0.8 % | 0.46 [ 0.24, 0.86 ] |
| Blohmer 2011 | 14/127 | 38/129 | | 1.2 % | 0.37 [ 0.21, 0.66 ] |
| Boogaerts 2003 | 43/133 | 67/129 | | 2.2 % | 0.62 [ 0.46, 0.84 ] |
| Carabantes 1999 | 4/20 | 13/15 | | 0.5 % | 0.23 [ 0.09, 0.57 ] |
| Cascinu 1994 | 10/50 | 28/50 | | 0.9 % | 0.36 [ 0.19, 0.65 ] |
| Case 1993 | 32/79 | 36/74 | | 1.2 % | 0.83 [ 0.58, 1.19 ] |
| Cazzola 1995 | 22/117 | 8/29 | | 0.4 % | 0.68 [ 0.34, 1.37 ] |
| Chang 2005 | 15/175 | 40/175 | | 1.3 % | 0.38 [ 0.22, 0.65 ] |
| Charu 2007 | 27/226 | 13/59 | | 0.7 % | 0.54 [ 0.30, 0.98 ] |
| Christodoulou 2009 | 16/167 | 36/170 | | 1.2 % | 0.45 [ 0.26, 0.78 ] |
| Dammacco 2001 | 19/69 | 36/76 | | 1.1 % | 0.58 [ 0.37, 0.91 ] |
| Del Mastro 1997 | 0/31 | 2/31 | | 0.1 % | 0.20 [ 0.01, 4.00 ] |
| Dunphy 1999 | 2/13 | 5/14 | | 0.2 % | 0.43 [ 0.10, 1.85 ] |
| Engert 2010 | 405/640 | 467/643 | | 15.3 % | 0.87 [ 0.81, 0.94 ] |
| EPO-INT-3 J%J 2004 | 21/136 | 23/65 | | 1.0 % | 0.44 [ 0.26, 0.73 ] |
| Fujisaka 2011 | 4/89 | 18/92 | | 0.6 % | 0.23 [ 0.08, 0.65 ] |
| Gebbia 2003 | 5/22 | 13/23 | | 0.4 % | 0.40 [ 0.17, 0.94 ] |
| Gordon 2008 | 18/162 | 6/56 | | 0.3 % | 1.04 [ 0.43, 2.48 ] |
| Goss 2005 | 8/52 | 27/52 | | 0.9 % | 0.30 [ 0.15, 0.59 ] |
| Grote 2005 | 26/109 | 42/115 | | 1.3 % | 0.65 [ 0.43, 0.99 ] |
| Gupta 2009 | 9/58 | 25/57 | | 0.8 % | 0.35 [ 0.18, 0.69 ] |
| Hedenus 2002 | 12/55 | 5/11 | | 0.3 % | 0.48 [ 0.21, 1.09 ] |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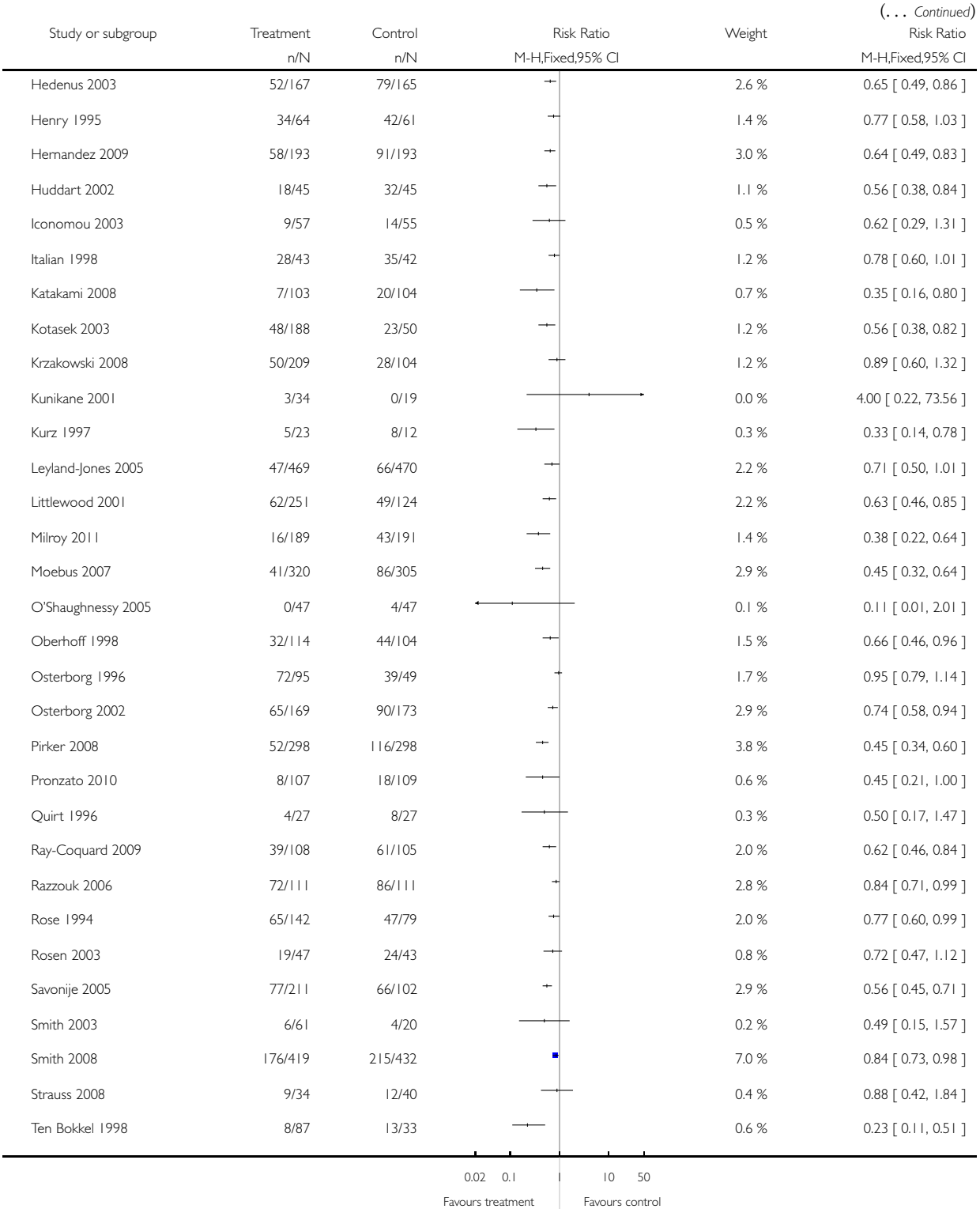


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| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Thatcher 1999 | 28/86 | 26/44 | | 1.1 % | 0.55 [ 0.37, 0.81 ] |
| Thomas 2002 | 7/62 | 31/65 | | 1.0 % | 0.24 [ 0.11, 0.50 ] |
| Thompson 2000 | 34/45 | 19/21 | | 0.9 % | 0.84 [ 0.67, 1.04 ] |
| Throuvalas 2000 | 2/28 | 10/26 | | 0.3 % | 0.19 [ 0.04, 0.77 ] |
| Tjulandin 2010 | 17/149 | 18/74 | | 0.8 % | 0.47 [ 0.26, 0.86 ] |
| Tjulandin 2011 | 13/95 | 23/91 | | 0.8 % | 0.54 [ 0.29, 1.00 ] |
| Tsuboi 2009 | 7/61 | 7/56 | | 0.2 % | 0.92 [ 0.34, 2.45 ] |
| Untch 2011˙1 | 1/356 | 0/377 | | 0.0 % | 3.18 [ 0.13, 77.72 ] |
| Vansteenkiste 02 FDA 2004 | 53/156 | 89/158 | | 2.9 % | 0.60 [ 0.47, 0.78 ] |
| Welch 1995 | 4/15 | 8/15 | | 0.3 % | 0.50 [ 0.19, 1.31 ] |
| Wilkinson 2006 | 9/114 | 18/59 | | 0.8 % | 0.26 [ 0.12, 0.54 ] |
| Witzig 2005 | 42/166 | 65/164 | | 2.2 % | 0.64 [ 0.46, 0.88 ] |
| Wright 2007 | 5/33 | 10/37 | | 0.3 % | 0.56 [ 0.21, 1.47 ] |
| Wurnig 1996 | 8/15 | 14/14 | | 0.5 % | 0.55 [ 0.34, 0.88 ] |
| **Total (95% CI)** | **8733** | **7360** | | **100.0 %** | **0.65 [ 0.62, 0.68 ]** |

Total events: 2198 (Treatment), 2880 (Control)

Heterogeneity: $Chi^2$ = 210.83, df = 69 (P<0.00001); $I^2$ =67%

Test for overall effect: Z = 19.90 (P < 0.00001)

Test for subgroup differences: Not applicable

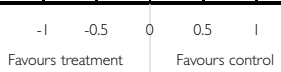
## Analysis 4.1. Comparison 4 Number of red blood cell units transfused per patient, Outcome 1 Number of RBC units transfused - overall.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 4 Number of red blood cell units transfused per patient

Outcome: 1 Number of RBC units transfused - overall

| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Abels 1993 | 63 | 1.52 (2.61) | 55 | 2.19 (3.57) | | 3.0 % | -0.67 [ -1.81, 0.47 ] |
| Boogaerts 2003 | 133 | 2.11 (4.97) | 129 | 3.78 (6.53) | | 2.0 % | -1.67 [ -3.08, -0.26 ] |
| Cascinu 1994 | 50 | 0.3 (0.07) | 50 | 1.8 (2.12) | | 11.3 % | -1.50 [ -2.09, -0.91 ] |
| Case 1993 | 79 | 2.03 (3.88) | 74 | 2.75 (4.15) | | 2.4 % | -0.72 [ -2.00, 0.56 ] |
| Cazzola 1995a | 31 | 1.19 (2.69) | 7 | 1.55 (4.31) | | 0.4 % | -0.36 [ -3.69, 2.97 ] |
| Cazzola 1995b | 29 | 1.45 (4.57) | 8 | 1.55 (4.31) | | 0.3 % | -0.10 [ -3.52, 3.32 ] |
| Cazzola 1995c | 31 | 0.97 (2.64) | 7 | 1.55 (4.31) | | 0.4 % | -0.58 [ -3.91, 2.75 ] |
| Cazzola 1995d | 26 | 0.81 (2.3) | 7 | 1.55 (4.31) | | 0.4 % | -0.74 [ -4.05, 2.57 ] |
| Dammacco 2001 | 66 | 1.49 (2.73) | 66 | 2.18 (2.95) | | 4.2 % | -0.69 [ -1.66, 0.28 ] |
| Engert 2009 | 637 | 3.7 (4.8) | 632 | 5.3 (5.7) | | 11.6 % | -1.60 [ -2.18, -1.02 ] |
| Grote 2005 | 109 | 0.5 (3.6) | 115 | 0.4 (0.7) | | 8.2 % | 0.10 [ -0.59, 0.79 ] |
| Henry 1995 | 64 | 3.56 (7.01) | 61 | 4.01 (4.87) | | 0.9 % | -0.45 [ -2.56, 1.66 ] |
| Hernandez 2009 | 181 | 1 (2) | 185 | 1.5 (2.5) | | 18.2 % | -0.50 [ -0.96, -0.04 ] |
| Kurz 1997 | 23 | 1.43 (3.8) | 12 | 3.7 (3.09) | | 0.7 % | -2.27 [ -4.61, 0.07 ] |
| Oberhoff 1998 | 114 | 1.32 (3.04) | 104 | 1.91 (3.28) | | 5.5 % | -0.59 [ -1.43, 0.25 ] |
| Osterborg 1996a | 47 | 6.8 (10.1) | 24 | 9.3 (9.2) | | 0.2 % | -2.50 [ -7.18, 2.18 ] |
| Osterborg 1996b | 48 | 8.7 (9.6) | 25 | 9.3 (9.2) | | 0.2 % | -0.60 [ -5.11, 3.91 ] |
| Osterborg 2002 | 169 | 2.66 (5.56) | 173 | 3.22 (5.17) | | 3.0 % | -0.56 [ -1.70, 0.58 ] |
| Rose 1994 | 142 | 5.8 (10.7) | 79 | 8 (17.5) | | 0.2 % | -2.20 [ -6.44, 2.04 ] |
| Savonije 2005 | 211 | 1.5 (2.6) | 102 | 3.1 (3.1) | | 8.0 % | -1.60 [ -2.30, -0.90 ] |
| Ten Bokkel 1998a | 45 | 0.33 (1.6) | 17 | 1.27 (1.97) | | 3.6 % | -0.94 [ -1.99, 0.11 ] |
| Ten Bokkel 1998b | 42 | 0.43 (1.23) | 16 | 1.27 (1.97) | | 3.6 % | -0.84 [ -1.87, 0.19 ] |
| Thatcher 1999a | 42 | 3.8 (5.58) | 22 | 6.13 (7.13) | | 0.3 % | -2.33 [ -5.75, 1.09 ] |
| Thatcher 1999b | 44 | 2.1 (4.6) | 22 | 6.13 (7.13) | | 0.4 % | -4.03 [ -7.30, -0.76 ] |

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| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Vansteenkiste 2002 | 148 | 0.67 (1.7) | 149 | 1.92 (3.27) | ← | 11.1 % | -1.25 [ -1.84, -0.66 ] |
| **Total (95% CI)** | **2574** | | **2141** | | ◆ | **100.0 %** | **-0.98 [ -1.17, -0.78 ]** |

Heterogeneity: $Chi^2$ = 34.52, df = 24 (P = 0.08); $I^2$ =30%

Test for overall effect: Z = 9.69 (P < 0.00001)

Test for subgroup differences: Not applicable

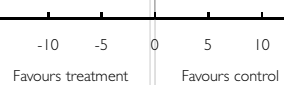

**Analysis 4.2. Comparison 4 Number of red blood cell units transfused per patient, Outcome 2 Number of RBC units transfused - baseline Hb.**

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 4 Number of red blood cell units transfused per patient

Outcome: 2 Number of RBC units transfused - baseline Hb

| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 Hb < 10g/dL | | | | | | | |
| Abels 1993 | 63 | 1.52 (2.61) | 55 | 2.19 (3.57) | | 3.0 % | -0.67 [ -1.81, 0.47 ] |
| Boogaerts 2003 | 133 | 2.11 (4.97) | 129 | 3.78 (6.53) | | 2.0 % | -1.67 [ -3.08, -0.26 ] |
| Cascinu 1994 | 50 | 0.3 (0.07) | 50 | 1.8 (2.12) | | 11.3 % | -1.50 [ -2.09, -0.91 ] |
| Case 1993 | 79 | 2.03 (3.88) | 74 | 2.75 (4.15) | | 2.4 % | -0.72 [ -2.00, 0.56 ] |
| Cazzola 1995a | 31 | 1.19 (2.69) | 7 | 1.55 (4.31) | | 0.4 % | -0.36 [ -3.69, 2.97 ] |
| Cazzola 1995b | 29 | 1.45 (4.57) | 8 | 1.55 (4.31) | | 0.3 % | -0.10 [ -3.52, 3.32 ] |
| Cazzola 1995c | 31 | 0.97 (2.64) | 7 | 1.55 (4.31) | | 0.4 % | -0.58 [ -3.91, 2.75 ] |
| Cazzola 1995d | 26 | 0.81 (2.3) | 7 | 1.55 (4.31) | | 0.4 % | -0.74 [ -4.05, 2.57 ] |
| Dammacco 2001 | 66 | 1.49 (2.73) | 66 | 2.18 (2.95) | | 4.2 % | -0.69 [ -1.66, 0.28 ] |
| Henry 1995 | 64 | 3.56 (7.01) | 61 | 4.01 (4.87) | | 0.9 % | -0.45 [ -2.56, 1.66 ] |

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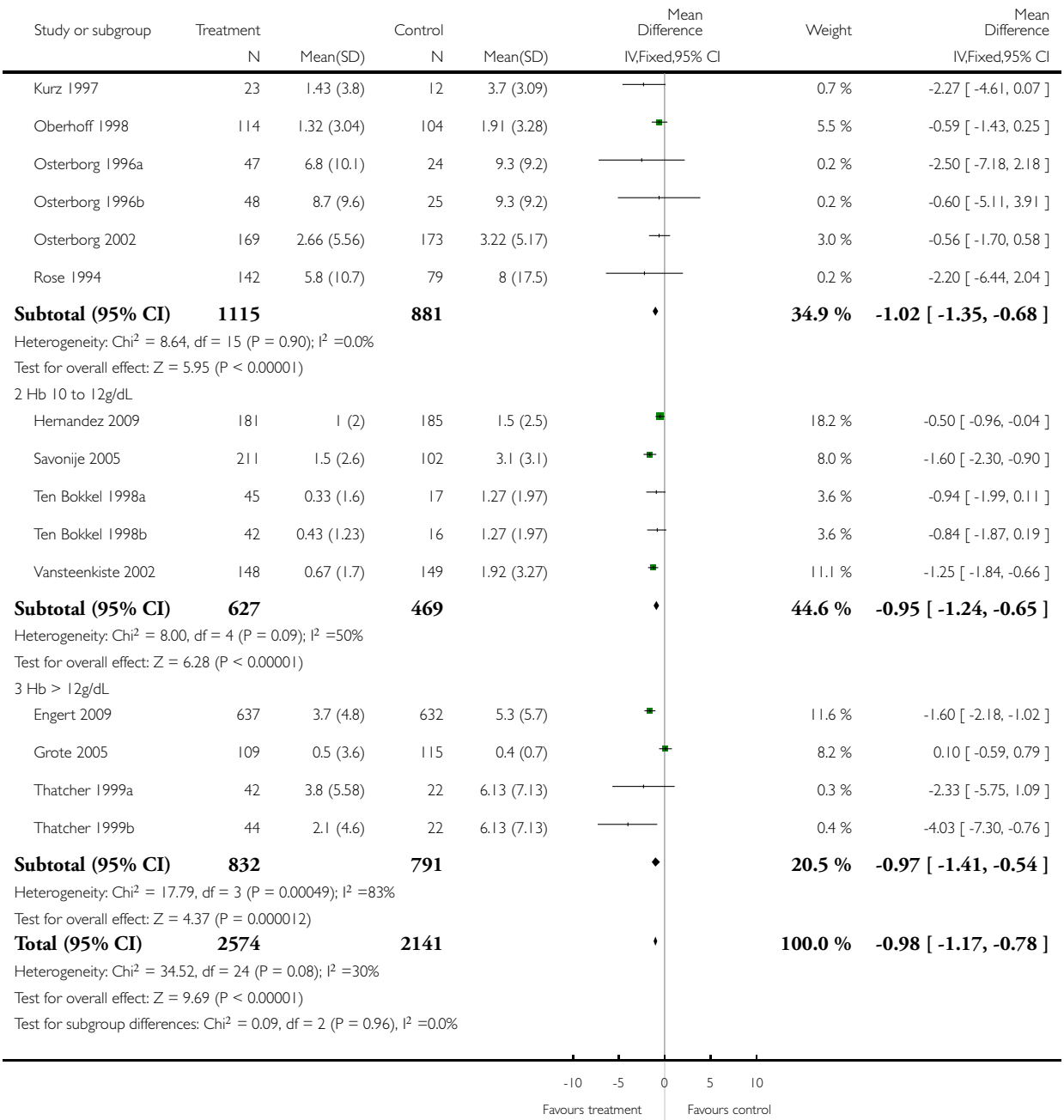


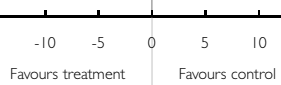
## Analysis 4.3. Comparison 4 Number of red blood cell units transfused per patient, Outcome 3 Number of RBC units transfused - age differentiated.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 4 Number of red blood cell units transfused per patient

Outcome: 3 Number of RBC units transfused - age differentiated

| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 only children <18 years | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| 2 adults ≥18 years | | | | | | | |
| Abels 1993 | 63 | 1.52 (2.61) | 55 | 2.19 (3.57) | | 3.0 % | -0.67 [ -1.81, 0.47 ] |
| Boogaerts 2003 | 133 | 2.11 (4.97) | 129 | 3.78 (6.53) | | 2.0 % | -1.67 [ -3.08, -0.26 ] |
| Case 1993 | 79 | 2.03 (3.88) | 74 | 2.75 (4.15) | | 2.4 % | -0.72 [ -2.00, 0.56 ] |
| Cazzola 1995a | 31 | 1.19 (2.69) | 7 | 1.55 (4.31) | | 0.4 % | -0.36 [ -3.69, 2.97 ] |
| Cazzola 1995b | 29 | 1.45 (4.57) | 8 | 1.55 (4.31) | | 0.3 % | -0.10 [ -3.52, 3.32 ] |
| Cazzola 1995c | 31 | 0.97 (2.64) | 7 | 1.55 (4.31) | | 0.4 % | -0.58 [ -3.91, 2.75 ] |
| Cazzola 1995d | 26 | 0.81 (2.3) | 7 | 1.55 (4.31) | | 0.4 % | -0.74 [ -4.05, 2.57 ] |
| Dammacco 2001 | 66 | 1.49 (2.73) | 66 | 2.18 (2.95) | | 4.2 % | -0.69 [ -1.66, 0.28 ] |
| Grote 2005 | 109 | 0.5 (3.6) | 115 | 0.4 (0.7) | | 8.2 % | 0.10 [ -0.59, 0.79 ] |
| Henry 1995 | 64 | 3.56 (7.01) | 61 | 4.01 (4.87) | | 0.9 % | -0.45 [ -2.56, 1.66 ] |
| Hernandez 2009 | 181 | 1 (2) | 185 | 1.5 (2.5) | | 18.2 % | -0.50 [ -0.96, -0.04 ] |
| Osterborg 1996a | 47 | 6.8 (10.1) | 24 | 9.3 (9.2) | | 0.2 % | -2.50 [ -7.18, 2.18 ] |
| Osterborg 1996b | 48 | 8.7 (9.6) | 25 | 9.3 (9.2) | | 0.2 % | -0.60 [ -5.11, 3.91 ] |
| Osterborg 2002 | 169 | 2.66 (5.56) | 173 | 3.22 (5.17) | | 3.0 % | -0.56 [ -1.70, 0.58 ] |
| Rose 1994 | 142 | 5.8 (10.7) | 79 | 8 (17.5) | | 0.2 % | -2.20 [ -6.44, 2.04 ] |
| Savonije 2005 | 211 | 1.5 (2.6) | 102 | 3.1 (3.1) | | 8.0 % | -1.60 [ -2.30, -0.90 ] |
| Ten Bokkel 1998a | 45 | 0.33 (1.6) | 17 | 1.27 (1.97) | | 3.6 % | -0.94 [ -1.99, 0.11 ] |
| Ten Bokkel 1998b | 42 | 0.43 (1.23) | 16 | 1.27 (1.97) | | 3.6 % | -0.84 [ -1.87, 0.19 ] |
| Thatcher 1999a | 42 | 3.8 (5.58) | 22 | 6.13 (7.13) | | 0.3 % | -2.33 [ -5.75, 1.09 ] |
| Thatcher 1999b | 44 | 2.1 (4.6) | 22 | 6.13 (7.13) | | 0.4 % | -4.03 [ -7.30, -0.76 ] |
| Vansteenkiste 2002 | 148 | 0.67 (1.7) | 149 | 1.92 (3.27) | | 11.1 % | -1.25 [ -1.84, -0.66 ] |

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| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| **Subtotal (95% CI)** | **1750** | | **1343** | | | **70.9 %** | **-0.81 [ -1.04, -0.57 ]** |
| Heterogeneity: Chi² = 23.08, df = 20 (P = 0.28); I² =13% | | | | | | | |
| Test for overall effect: Z = 6.76 (P < 0.00001) | | | | | | | |
| 3 >68% non-elderly 18-65 years | | | | | | | |
| Cascinu 1994 | 50 | 0.3 (0.07) | 50 | 1.8 (2.12) | | 11.3 % | -1.50 [ -2.09, -0.91 ] |
| Kurz 1997 | 23 | 1.43 (3.8) | 12 | 3.7 (3.09) | | 0.7 % | -2.27 [ -4.61, 0.07 ] |
| Oberhoff 1998 | 114 | 1.32 (3.04) | 104 | 1.91 (3.28) | | 5.5 % | -0.59 [ -1.43, 0.25 ] |
| **Subtotal (95% CI)** | **187** | | **166** | | | **17.5 %** | **-1.25 [ -1.72, -0.77 ]** |
| Heterogeneity: Chi² = 3.79, df = 2 (P = 0.15); I² =47% | | | | | | | |
| Test for overall effect: Z = 5.17 (P < 0.00001) | | | | | | | |
| 4 only non-elderly adults | | | | | | | |
| Engert 2009 | 637 | 3.7 (4.8) | 632 | 5.3 (5.7) | | 11.6 % | -1.60 [ -2.18, -1.02 ] |
| **Subtotal (95% CI)** | **637** | | **632** | | | **11.6 %** | **-1.60 [ -2.18, -1.02 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 5.41 (P < 0.00001) | | | | | | | |
| 5 >68% elderly >65 years | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| 6 only elderly > 65 J | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| **Total (95% CI)** | **2574** | | **2141** | | | **100.0 %** | **-0.98 [ -1.17, -0.78 ]** |
| Heterogeneity: Chi² = 34.52, df = 24 (P = 0.08); I² =30% | | | | | | | |
| Test for overall effect: Z = 9.69 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: Chi² = 7.65, df = 2 (P = 0.02), I² =74% | | | | | | | |

## Analysis 4.4. Comparison 4 Number of red blood cell units transfused per patient, Outcome 4 Number of RBC units transfused - age.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 4 Number of red blood cell units transfused per patient

Outcome: 4 Number of RBC units transfused - age

| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 adults | | | | | | | |
| Abels 1993 | 63 | 1.52 (2.61) | 55 | 2.19 (3.57) | | 3.0 % | -0.67 [ -1.81, 0.47 ] |
| Boogaerts 2003 | 133 | 2.11 (4.97) | 129 | 3.78 (6.53) | | 2.0 % | -1.67 [ -3.08, -0.26 ] |
| Cascinu 1994 | 50 | 0.3 (0.07) | 50 | 1.8 (2.12) | | 11.3 % | -1.50 [ -2.09, -0.91 ] |
| Case 1993 | 79 | 2.03 (3.88) | 74 | 2.75 (4.15) | | 2.4 % | -0.72 [ -2.00, 0.56 ] |
| Cazzola 1995a | 31 | 1.19 (2.69) | 7 | 1.55 (4.31) | | 0.4 % | -0.36 [ -3.69, 2.97 ] |
| Cazzola 1995b | 29 | 1.45 (4.57) | 8 | 1.55 (4.31) | | 0.3 % | -0.10 [ -3.52, 3.32 ] |
| Cazzola 1995c | 31 | 0.97 (2.64) | 7 | 1.55 (4.31) | | 0.4 % | -0.58 [ -3.91, 2.75 ] |
| Cazzola 1995d | 26 | 0.81 (2.3) | 7 | 1.55 (4.31) | | 0.4 % | -0.74 [ -4.05, 2.57 ] |
| Dammacco 2001 | 66 | 1.49 (2.73) | 66 | 2.18 (2.95) | | 4.2 % | -0.69 [ -1.66, 0.28 ] |
| Engert 2009 | 637 | 3.7 (4.8) | 632 | 5.3 (5.7) | | 11.6 % | -1.60 [ -2.18, -1.02 ] |
| Grote 2005 | 109 | 0.5 (3.6) | 115 | 0.4 (0.7) | | 8.2 % | 0.10 [ -0.59, 0.79 ] |
| Henry 1995 | 64 | 3.56 (7.01) | 61 | 4.01 (4.87) | | 0.9 % | -0.45 [ -2.56, 1.66 ] |
| Hernandez 2009 | 181 | 1 (2) | 185 | 1.5 (2.5) | | 18.2 % | -0.50 [ -0.96, -0.04 ] |
| Kurz 1997 | 23 | 1.43 (3.8) | 12 | 3.7 (3.09) | | 0.7 % | -2.27 [ -4.61, 0.07 ] |
| Oberhoff 1998 | 114 | 1.32 (3.04) | 104 | 1.91 (3.28) | | 5.5 % | -0.59 [ -1.43, 0.25 ] |
| Osterborg 1996a | 47 | 6.8 (10.1) | 24 | 9.3 (9.2) | | 0.2 % | -2.50 [ -7.18, 2.18 ] |
| Osterborg 1996b | 48 | 8.7 (9.6) | 25 | 9.3 (9.2) | | 0.2 % | -0.60 [ -5.11, 3.91 ] |
| Osterborg 2002 | 169 | 2.66 (5.56) | 173 | 3.22 (5.17) | | 3.0 % | -0.56 [ -1.70, 0.58 ] |
| Rose 1994 | 142 | 5.8 (10.7) | 79 | 8 (17.5) | | 0.2 % | -2.20 [ -6.44, 2.04 ] |
| Savonije 2005 | 211 | 1.5 (2.6) | 102 | 3.1 (3.1) | | 8.0 % | -1.60 [ -2.30, -0.90 ] |
| Ten Bokkel 1998a | 45 | 0.33 (1.6) | 17 | 1.27 (1.97) | | 3.6 % | -0.94 [ -1.99, 0.11 ] |
| Ten Bokkel 1998b | 42 | 0.43 (1.23) | 16 | 1.27 (1.97) | | 3.6 % | -0.84 [ -1.87, 0.19 ] |
| Thatcher 1999a | 42 | 3.8 (5.58) | 22 | 6.13 (7.13) | | 0.3 % | -2.33 [ -5.75, 1.09 ] |


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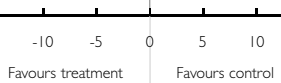
| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Thatcher 1999b | 44 | 2.1 (4.6) | 22 | 6.13 (7.13) | | 0.4 % | -4.03 [ -7.30, -0.76 ] |
| Vansteenkiste 2002 | 148 | 0.67 (1.7) | 149 | 1.92 (3.27) | | 11.1 % | -1.25 [ -1.84, -0.66 ] |
| **Total (95% CI)** | **2574** | | **2141** | | | **100.0 %** | **-0.98 [ -1.17, -0.78 ]** |

Heterogeneity: Chi$^2$ = 34.52, df = 24 (P = 0.08); I$^2$ =30%

Test for overall effect: Z = 9.69 (P < 0.00001)

Test for subgroup differences: Not applicable



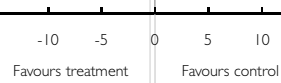

**Analysis 4.5. Comparison 4 Number of red blood cell units transfused per patient, Outcome 5 Number of RBC units transfused - different malignancies.**

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 4 Number of red blood cell units transfused per patient

Outcome: 5 Number of RBC units transfused - different malignancies

| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 solid tumours | | | | | | | |
| Cascinu 1994 | 50 | 0.3 (0.07) | 50 | 1.8 (2.12) | | 11.3 % | -1.50 [ -2.09, -0.91 ] |
| Grote 2005 | 109 | 0.5 (3.6) | 115 | 0.4 (0.7) | | 8.2 % | 0.10 [ -0.59, 0.79 ] |
| Kurz 1997 | 23 | 1.43 (3.8) | 12 | 3.7 (3.09) | | 0.7 % | -2.27 [ -4.61, 0.07 ] |
| Oberhoff 1998 | 114 | 1.32 (3.04) | 104 | 1.91 (3.28) | | 5.5 % | -0.59 [ -1.43, 0.25 ] |
| Savonije 2005 | 211 | 1.5 (2.6) | 102 | 3.1 (3.1) | | 8.0 % | -1.60 [ -2.30, -0.90 ] |
| Ten Bokkel 1998a | 45 | 0.33 (1.6) | 17 | 1.27 (1.97) | | 3.6 % | -0.94 [ -1.99, 0.11 ] |
| Ten Bokkel 1998b | 42 | 0.43 (1.23) | 16 | 1.27 (1.97) | | 3.6 % | -0.84 [ -1.87, 0.19 ] |
| Thatcher 1999a | 42 | 3.8 (5.58) | 22 | 6.13 (7.13) | | 0.3 % | -2.33 [ -5.75, 1.09 ] |
| Thatcher 1999b | 44 | 2.1 (4.6) | 22 | 6.13 (7.13) | | 0.4 % | -4.03 [ -7.30, -0.76 ] |

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| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Vansteenkiste 2002 | 148 | 0.67 (1.7) | 149 | 1.92 (3.27) | | 11.1 % | -1.25 [ -1.84, -0.66 ] |
| **Subtotal (95% CI)** | **828** | | **609** | | | **52.8 %** | **-1.07 [ -1.34, -0.80 ]** |
| Heterogeneity: Chi² = 21.92, df = 9 (P = 0.01); I² =59% | | | | | | | |
| Test for overall effect: Z = 7.70 (P < 0.00001) | | | | | | | |
| 2 haematological malignancies | | | | | | | |
| Cazzola 1995a | 31 | 1.19 (2.69) | 7 | 1.55 (4.31) | | 0.4 % | -0.36 [ -3.69, 2.97 ] |
| Cazzola 1995b | 29 | 1.45 (4.57) | 8 | 1.55 (4.31) | | 0.3 % | -0.10 [ -3.52, 3.32 ] |
| Cazzola 1995c | 31 | 0.97 (2.64) | 7 | 1.55 (4.31) | | 0.4 % | -0.58 [ -3.91, 2.75 ] |
| Cazzola 1995d | 26 | 0.81 (2.3) | 7 | 1.55 (4.31) | | 0.4 % | -0.74 [ -4.05, 2.57 ] |
| Dammacco 2001 | 66 | 1.49 (2.73) | 66 | 2.18 (2.95) | | 4.2 % | -0.69 [ -1.66, 0.28 ] |
| Engert 2009 | 637 | 3.7 (4.8) | 632 | 5.3 (5.7) | | 11.6 % | -1.60 [ -2.18, -1.02 ] |
| Osterborg 1996a | 47 | 6.8 (10.1) | 24 | 9.3 (9.2) | | 0.2 % | -2.50 [ -7.18, 2.18 ] |
| Osterborg 1996b | 48 | 8.7 (9.6) | 25 | 9.3 (9.2) | | 0.2 % | -0.60 [ -5.11, 3.91 ] |
| Osterborg 2002 | 169 | 2.66 (5.56) | 173 | 3.22 (5.17) | | 3.0 % | -0.56 [ -1.70, 0.58 ] |
| Rose 1994 | 142 | 5.8 (10.7) | 79 | 8 (17.5) | | 0.2 % | -2.20 [ -6.44, 2.04 ] |
| **Subtotal (95% CI)** | **1226** | | **1028** | | | **20.7 %** | **-1.19 [ -1.63, -0.76 ]** |
| Heterogeneity: Chi² = 5.53, df = 9 (P = 0.79); I² =0.0% | | | | | | | |
| Test for overall effect: Z = 5.40 (P < 0.00001) | | | | | | | |
| 3 mixed | | | | | | | |
| Abels 1993 | 63 | 1.52 (2.61) | 55 | 2.19 (3.57) | | 3.0 % | -0.67 [ -1.81, 0.47 ] |
| Boogaerts 2003 | 133 | 2.11 (4.97) | 129 | 3.78 (6.53) | | 2.0 % | -1.67 [ -3.08, -0.26 ] |
| Case 1993 | 79 | 2.03 (3.88) | 74 | 2.75 (4.15) | | 2.4 % | -0.72 [ -2.00, 0.56 ] |
| Henry 1995 | 64 | 3.56 (7.01) | 61 | 4.01 (4.87) | | 0.9 % | -0.45 [ -2.56, 1.66 ] |
| Hernandez 2009 | 181 | 1 (2) | 185 | 1.5 (2.5) | | 18.2 % | -0.50 [ -0.96, -0.04 ] |
| **Subtotal (95% CI)** | **520** | | **504** | | | **26.4 %** | **-0.62 [ -1.01, -0.24 ]** |
| Heterogeneity: Chi² = 2.45, df = 4 (P = 0.65); I² =0.0% | | | | | | | |
| Test for overall effect: Z = 3.19 (P = 0.0014) | | | | | | | |
| **Total (95% CI)** | **2574** | | **2141** | | | **100.0 %** | **-0.98 [ -1.17, -0.78 ]** |
| Heterogeneity: Chi² = 34.52, df = 24 (P = 0.08); I² =30% | | | | | | | |
| Test for overall effect: Z = 9.69 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: Chi² = 4.62, df = 2 (P = 0.10), I² =57% | | | | | | | |

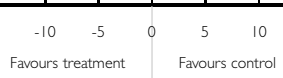
## Analysis 4.6. Comparison 4 Number of red blood cell units transfused per patient, Outcome 6 Number of RBC units transfused - different therapies.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 4 Number of red blood cell units transfused per patient

Outcome: 6 Number of RBC units transfused - different therapies

| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 chemotherapy | | | | | | | |
| Boogaerts 2003 | 133 | 2.11 (4.97) | 129 | 3.78 (6.53) | | 2.0 % | -1.67 [ -3.08, -0.26 ] |
| Cascinu 1994 | 50 | 0.3 (0.07) | 50 | 1.8 (2.12) | | 11.3 % | -1.50 [ -2.09, -0.91 ] |
| Case 1993 | 79 | 2.03 (3.88) | 74 | 2.75 (4.15) | | 2.4 % | -0.72 [ -2.00, 0.56 ] |
| Cazzola 1995a | 31 | 1.19 (2.69) | 7 | 1.55 (4.31) | | 0.4 % | -0.36 [ -3.69, 2.97 ] |
| Cazzola 1995b | 29 | 1.45 (4.57) | 8 | 1.55 (4.31) | | 0.3 % | -0.10 [ -3.52, 3.32 ] |
| Cazzola 1995c | 31 | 0.97 (2.64) | 7 | 1.55 (4.31) | | 0.4 % | -0.58 [ -3.91, 2.75 ] |
| Cazzola 1995d | 26 | 0.81 (2.3) | 7 | 1.55 (4.31) | | 0.4 % | -0.74 [ -4.05, 2.57 ] |
| Dammacco 2001 | 66 | 1.49 (2.73) | 66 | 2.18 (2.95) | | 4.2 % | -0.69 [ -1.66, 0.28 ] |
| Engert 2009 | 637 | 3.7 (4.8) | 632 | 5.3 (5.7) | | 11.6 % | -1.60 [ -2.18, -1.02 ] |
| Grote 2005 | 109 | 0.5 (3.6) | 115 | 0.4 (0.7) | | 8.2 % | 0.10 [ -0.59, 0.79 ] |
| Henry 1995 | 64 | 3.56 (7.01) | 61 | 4.01 (4.87) | | 0.9 % | -0.45 [ -2.56, 1.66 ] |
| Hernandez 2009 | 181 | 1 (2) | 185 | 1.5 (2.5) | | 18.2 % | -0.50 [ -0.96, -0.04 ] |
| Kurz 1997 | 23 | 1.43 (3.8) | 12 | 3.7 (3.09) | | 0.7 % | -2.27 [ -4.61, 0.07 ] |
| Oberhoff 1998 | 114 | 1.32 (3.04) | 104 | 1.91 (3.28) | | 5.5 % | -0.59 [ -1.43, 0.25 ] |
| Osterborg 1996a | 47 | 6.8 (10.1) | 24 | 9.3 (9.2) | | 0.2 % | -2.50 [ -7.18, 2.18 ] |
| Osterborg 1996b | 48 | 8.7 (9.6) | 25 | 9.3 (9.2) | | 0.2 % | -0.60 [ -5.11, 3.91 ] |
| Osterborg 2002 | 169 | 2.66 (5.56) | 173 | 3.22 (5.17) | | 3.0 % | -0.56 [ -1.70, 0.58 ] |
| Savonije 2005 | 211 | 1.5 (2.6) | 102 | 3.1 (3.1) | | 8.0 % | -1.60 [ -2.30, -0.90 ] |
| Ten Bokkel 1998a | 45 | 0.33 (1.6) | 17 | 1.27 (1.97) | | 3.6 % | -0.94 [ -1.99, 0.11 ] |
| Ten Bokkel 1998b | 42 | 0.43 (1.23) | 16 | 1.27 (1.97) | | 3.6 % | -0.84 [ -1.87, 0.19 ] |
| Thatcher 1999a | 42 | 3.8 (5.58) | 22 | 6.13 (7.13) | | 0.3 % | -2.33 [ -5.75, 1.09 ] |
| Thatcher 1999b | 44 | 2.1 (4.6) | 22 | 6.13 (7.13) | | 0.4 % | -4.03 [ -7.30, -0.76 ] |
| Vansteenkiste 2002 | 148 | 0.67 (1.7) | 149 | 1.92 (3.27) | | 11.1 % | -1.25 [ -1.84, -0.66 ] |

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| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| **Subtotal (95% CI)** | **2369** | | **2007** | | | **96.8 %** | **-0.98 [ -1.18, -0.78 ]** |
| Heterogeneity: Chi² = 33.92, df = 22 (P = 0.05); I² =35% | | | | | | | |
| Test for overall effect: Z = 9.60 (P < 0.00001) | | | | | | | |
| 2 radiotherapy/radiochemotherapy | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| 3 no therapy | | | | | | | |
| Abels 1993 | 63 | 1.52 (2.61) | 55 | 2.19 (3.57) | | 3.0 % | -0.67 [ -1.81, 0.47 ] |
| **Subtotal (95% CI)** | **63** | | **55** | | | **3.0 %** | **-0.67 [ -1.81, 0.47 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 1.15 (P = 0.25) | | | | | | | |
| 4 unclear/ other | | | | | | | |
| Rose 1994 | 142 | 5.8 (10.7) | 79 | 8 (17.5) | | 0.2 % | -2.20 [ -6.44, 2.04 ] |
| **Subtotal (95% CI)** | **142** | | **79** | | | **0.2 %** | **-2.20 [ -6.44, 2.04 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 1.02 (P = 0.31) | | | | | | | |
| **Total (95% CI)** | **2574** | | **2141** | | | **100.0 %** | **-0.98 [ -1.17, -0.78 ]** |
| Heterogeneity: Chi² = 34.52, df = 24 (P = 0.08); I² =30% | | | | | | | |
| Test for overall effect: Z = 9.69 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: Chi² = 0.60, df = 2 (P = 0.74), I² =0.0% | | | | | | | |

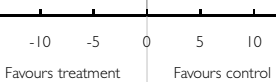
## Analysis 4.7. Comparison 4 Number of red blood cell units transfused per patient, Outcome 7 Number of RBC units transfused - different therapies differentiated.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 4 Number of red blood cell units transfused per patient

Outcome: 7 Number of RBC units transfused - different therapies differentiated

| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 chemotherapy > 70% with platinum | | | | | | | |
| Cascinu 1994 | 50 | 0.3 (0.07) | 50 | 1.8 (2.12) | | 11.3 % | -1.50 [ -2.09, -0.91 ] |
| Grote 2005 | 109 | 0.5 (3.6) | 115 | 0.4 (0.7) | | 8.2 % | 0.10 [ -0.59, 0.79 ] |
| Henry 1995 | 64 | 3.56 (7.01) | 61 | 4.01 (4.87) | | 0.9 % | -0.45 [ -2.56, 1.66 ] |
| Kurz 1997 | 23 | 1.43 (3.8) | 12 | 3.7 (3.09) | | 0.7 % | -2.27 [ -4.61, 0.07 ] |
| Savonije 2005 | 211 | 1.5 (2.6) | 102 | 3.1 (3.1) | | 8.0 % | -1.60 [ -2.30, -0.90 ] |
| Ten Bokkel 1998a | 45 | 0.33 (1.6) | 17 | 1.27 (1.97) | | 3.6 % | -0.94 [ -1.99, 0.11 ] |
| Ten Bokkel 1998b | 42 | 0.43 (1.23) | 16 | 1.27 (1.97) | | 3.6 % | -0.84 [ -1.87, 0.19 ] |
| Thatcher 1999a | 42 | 3.8 (5.58) | 22 | 6.13 (7.13) | | 0.3 % | -2.33 [ -5.75, 1.09 ] |
| Thatcher 1999b | 44 | 2.1 (4.6) | 22 | 6.13 (7.13) | | 0.4 % | -4.03 [ -7.30, -0.76 ] |
| Vansteenkiste 2002 | 148 | 0.67 (1.7) | 149 | 1.92 (3.27) | | 11.1 % | -1.25 [ -1.84, -0.66 ] |
| **Subtotal (95% CI)** | **778** | | **566** | | | **48.2 %** | **-1.11 [ -1.40, -0.83 ]** |
| Heterogeneity: Chi² = 20.92, df = 9 (P = 0.01); I² =57% | | | | | | | |
| Test for overall effect: Z = 7.65 (P < 0.00001) | | | | | | | |
| 2 chemotherapy, <70% with platinum | | | | | | | |
| Hernandez 2009 | 181 | 1 (2) | 185 | 1.5 (2.5) | | 18.2 % | -0.50 [ -0.96, -0.04 ] |
| Oberhoff 1998 | 114 | 1.32 (3.04) | 104 | 1.91 (3.28) | | 5.5 % | -0.59 [ -1.43, 0.25 ] |
| **Subtotal (95% CI)** | **295** | | **289** | | | **23.7 %** | **-0.52 [ -0.93, -0.12 ]** |
| Heterogeneity: Chi² = 0.03, df = 1 (P = 0.85); I² =0.0% | | | | | | | |
| Test for overall effect: Z = 2.52 (P = 0.012) | | | | | | | |
| 3 chemotherapy without platinum | | | | | | | |
| Case 1993 | 79 | 2.03 (3.88) | 74 | 2.75 (4.15) | | 2.4 % | -0.72 [ -2.00, 0.56 ] |
| Cazzola 1995a | 31 | 1.19 (2.69) | 7 | 1.55 (4.31) | | 0.4 % | -0.36 [ -3.69, 2.97 ] |
| Cazzola 1995b | 29 | 1.45 (4.57) | 8 | 1.55 (4.31) | | 0.3 % | -0.10 [ -3.52, 3.32 ] |
| Cazzola 1995c | 31 | 0.97 (2.64) | 7 | 1.55 (4.31) | | 0.4 % | -0.58 [ -3.91, 2.75 ] |
| Cazzola 1995d | 26 | 0.81 (2.3) | 7 | 1.55 (4.31) | | 0.4 % | -0.74 [ -4.05, 2.57 ] |
| Engert 2009 | 637 | 3.7 (4.8) | 632 | 5.3 (5.7) | | 11.6 % | -1.60 [ -2.18, -1.02 ] |

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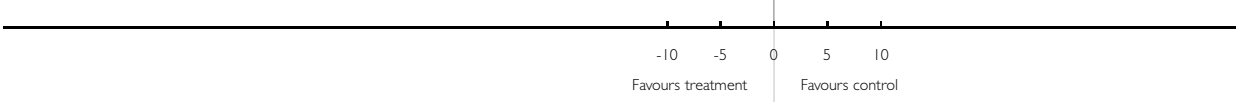
| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Osterborg 1996a | 47 | 6.8 (10.1) | 24 | 9.3 (9.2) | | 0.2 % | -2.50 [ -7.18, 2.18 ] |
| Osterborg 1996b | 48 | 8.7 (9.6) | 25 | 9.3 (9.2) | | 0.2 % | -0.60 [ -5.11, 3.91 ] |
| Osterborg 2002 | 169 | 2.66 (5.56) | 173 | 3.22 (5.17) | | 3.0 % | -0.56 [ -1.70, 0.58 ] |
| **Subtotal (95% CI)** | **1097** | | **957** | | | **18.8 %** | **-1.23 [ -1.69, -0.78 ]** |
| Heterogeneity: $Chi^2$ = 4.78, df = 8 (P = 0.78); $I^2$ =0.0% | | | | | | | |
| Test for overall effect: Z = 5.30 (P < 0.00001) | | | | | | | |
| 4 chemotherapy, platinum and non-platinum containing, no numbers given | | | | | | | |
| Boogaerts 2003 | 133 | 2.11 (4.97) | 129 | 3.78 (6.53) | | 2.0 % | -1.67 [ -3.08, -0.26 ] |
| Dammacco 2001 | 66 | 1.49 (2.73) | 66 | 2.18 (2.95) | | 4.2 % | -0.69 [ -1.66, 0.28 ] |
| **Subtotal (95% CI)** | **199** | | **195** | | | **6.1 %** | **-1.01 [ -1.80, -0.21 ]** |
| Heterogeneity: $Chi^2$ = 1.26, df = 1 (P = 0.26); $I^2$ =21% | | | | | | | |
| Test for overall effect: Z = 2.47 (P = 0.014) | | | | | | | |
| 5 chemotherapy no details given | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| 6 radiochemotherapy | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| 7 radiotherapy | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| 8 no therapy | | | | | | | |
| Abels 1993 | 63 | 1.52 (2.61) | 55 | 2.19 (3.57) | | 3.0 % | -0.67 [ -1.81, 0.47 ] |
| **Subtotal (95% CI)** | **63** | | **55** | | | **3.0 %** | **-0.67 [ -1.81, 0.47 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 1.15 (P = 0.25) | | | | | | | |
| 9 unclear/other | | | | | | | |
| Rose 1994 | 142 | 5.8 (10.7) | 79 | 8 (17.5) | | 0.2 % | -2.20 [ -6.44, 2.04 ] |
| **Subtotal (95% CI)** | **142** | | **79** | | | **0.2 %** | **-2.20 [ -6.44, 2.04 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 1.02 (P = 0.31) | | | | | | | |
| **Total (95% CI)** | **2574** | | **2141** | | | **100.0 %** | **-0.98 [ -1.17, -0.78 ]** |
| Heterogeneity: $Chi^2$ = 34.52, df = 24 (P = 0.08); $I^2$ =30% | | | | | | | |
| Test for overall effect: Z = 9.69 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 7.52, df = 5 (P = 0.18), $I^2$ =34% | | | | | | | |



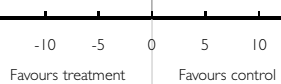
## Analysis 4.8. Comparison 4 Number of red blood cell units transfused per patient, Outcome 8 Number of RBC units transfused - epoetin versus darbepoetin.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 4 Number of red blood cell units transfused per patient

Outcome: 8 Number of RBC units transfused - epoetin versus darbepoetin

| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 Epoetin | | | | | | | |
| Abels 1993 | 63 | 1.52 (2.61) | 55 | 2.19 (3.57) | | 3.0 % | -0.67 [ -1.81, 0.47 ] |
| Boogaerts 2003 | 133 | 2.11 (4.97) | 129 | 3.78 (6.53) | | 2.0 % | -1.67 [ -3.08, -0.26 ] |
| Cascinu 1994 | 50 | 0.3 (0.07) | 50 | 1.8 (2.12) | | 11.3 % | -1.50 [ -2.09, -0.91 ] |
| Case 1993 | 79 | 2.03 (3.88) | 74 | 2.75 (4.15) | | 2.4 % | -0.72 [ -2.00, 0.56 ] |
| Cazzola 1995a | 31 | 1.19 (2.69) | 7 | 1.55 (4.31) | | 0.4 % | -0.36 [ -3.69, 2.97 ] |
| Cazzola 1995b | 29 | 1.45 (4.57) | 8 | 1.55 (4.31) | | 0.3 % | -0.10 [ -3.52, 3.32 ] |
| Cazzola 1995c | 31 | 0.97 (2.64) | 7 | 1.55 (4.31) | | 0.4 % | -0.58 [ -3.91, 2.75 ] |
| Cazzola 1995d | 26 | 0.81 (2.3) | 7 | 1.55 (4.31) | | 0.4 % | -0.74 [ -4.05, 2.57 ] |
| Dammacco 2001 | 66 | 1.49 (2.73) | 66 | 2.18 (2.95) | | 4.2 % | -0.69 [ -1.66, 0.28 ] |
| Engert 2009 | 637 | 3.7 (4.8) | 632 | 5.3 (5.7) | | 11.6 % | -1.60 [ -2.18, -1.02 ] |
| Grote 2005 | 109 | 0.5 (3.6) | 115 | 0.4 (0.7) | | 8.2 % | 0.10 [ -0.59, 0.79 ] |
| Henry 1995 | 64 | 3.56 (7.01) | 61 | 4.01 (4.87) | | 0.9 % | -0.45 [ -2.56, 1.66 ] |
| Kurz 1997 | 23 | 1.43 (3.8) | 12 | 3.7 (3.09) | | 0.7 % | -2.27 [ -4.61, 0.07 ] |
| Oberhoff 1998 | 114 | 1.32 (3.04) | 104 | 1.91 (3.28) | | 5.5 % | -0.59 [ -1.43, 0.25 ] |
| Osterborg 1996a | 47 | 6.8 (10.1) | 24 | 9.3 (9.2) | | 0.2 % | -2.50 [ -7.18, 2.18 ] |
| Osterborg 1996b | 48 | 8.7 (9.6) | 25 | 9.3 (9.2) | | 0.2 % | -0.60 [ -5.11, 3.91 ] |
| Osterborg 2002 | 169 | 2.66 (5.56) | 173 | 3.22 (5.17) | | 3.0 % | -0.56 [ -1.70, 0.58 ] |
| Rose 1994 | 142 | 5.8 (10.7) | 79 | 8 (17.5) | | 0.2 % | -2.20 [ -6.44, 2.04 ] |
| Savonije 2005 | 211 | 1.5 (2.6) | 102 | 3.1 (3.1) | | 8.0 % | -1.60 [ -2.30, -0.90 ] |
| Ten Bokkel 1998a | 45 | 0.33 (1.6) | 17 | 1.27 (1.97) | | 3.6 % | -0.94 [ -1.99, 0.11 ] |
| Ten Bokkel 1998b | 42 | 0.43 (1.23) | 16 | 1.27 (1.97) | | 3.6 % | -0.84 [ -1.87, 0.19 ] |
| Thatcher 1999a | 42 | 3.8 (5.58) | 22 | 6.13 (7.13) | | 0.3 % | -2.33 [ -5.75, 1.09 ] |

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| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Thatcher 1999b | 44 | 2.1 (4.6) | 22 | 6.13 (7.13) | | 0.4 % | -4.03 [ -7.30, -0.76 ] |
| **Subtotal (95% CI)** | **2245** | | **1807** | | | **70.7 %** | **-1.06 [ -1.29, -0.82 ]** |
| Heterogeneity: $Chi^2$ = 29.19, df = 22 (P = 0.14); $I^2$ =25% | | | | | | | |
| Test for overall effect: Z = 8.81 (P < 0.00001) | | | | | | | |
| 2 Darbepoetin | | | | | | | |
| Hernandez 2009 | 181 | 1 (2) | 185 | 1.5 (2.5) | | 18.2 % | -0.50 [ -0.96, -0.04 ] |
| Vansteenkiste 2002 | 148 | 0.67 (1.7) | 149 | 1.92 (3.27) | | 11.1 % | -1.25 [ -1.84, -0.66 ] |
| **Subtotal (95% CI)** | **329** | | **334** | | | **29.3 %** | **-0.78 [ -1.15, -0.42 ]** |
| Heterogeneity: $Chi^2$ = 3.82, df = 1 (P = 0.05); $I^2$ =74% | | | | | | | |
| Test for overall effect: Z = 4.22 (P = 0.000025) | | | | | | | |
| **Total (95% CI)** | **2574** | | **2141** | | | **100.0 %** | **-0.98 [ -1.17, -0.78 ]** |
| Heterogeneity: $Chi^2$ = 34.52, df = 24 (P = 0.08); $I^2$ =30% | | | | | | | |
| Test for overall effect: Z = 9.69 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 1.51, df = 1 (P = 0.22), $I^2$ =34% | | | | | | | |

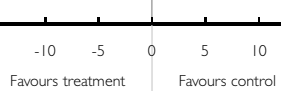
## Analysis 4.9. Comparison 4 Number of red blood cell units transfused per patient, Outcome 9 Number of RBC units transfused - duration of ESA medication.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 4 Number of red blood cell units transfused per patient

Outcome: 9 Number of RBC units transfused - duration of ESA medication

| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 6 to 9 weeks | | | | | | | |
| Abels 1993 | 63 | 1.52 (2.61) | 55 | 2.19 (3.57) | | 3.0 % | -0.67 [ -1.81, 0.47 ] |
| Cascinu 1994 | 50 | 0.3 (0.07) | 50 | 1.8 (2.12) | | 11.3 % | -1.50 [ -2.09, -0.91 ] |
| Cazzola 1995a | 31 | 1.19 (2.69) | 7 | 1.55 (4.31) | | 0.4 % | -0.36 [ -3.69, 2.97 ] |
| Cazzola 1995b | 29 | 1.45 (4.57) | 8 | 1.55 (4.31) | | 0.3 % | -0.10 [ -3.52, 3.32 ] |
| Cazzola 1995c | 31 | 0.97 (2.64) | 7 | 1.55 (4.31) | | 0.4 % | -0.58 [ -3.91, 2.75 ] |
| Cazzola 1995d | 26 | 0.81 (2.3) | 7 | 1.55 (4.31) | | 0.4 % | -0.74 [ -4.05, 2.57 ] |
| **Subtotal (95% CI)** | **230** | | **134** | | | **15.7 %** | **-1.25 [ -1.75, -0.75 ]** |
| Heterogeneity: Chi² = 2.64, df = 5 (P = 0.76); I² =0.0% | | | | | | | |
| Test for overall effect: Z = 4.90 (P < 0.00001) | | | | | | | |
| 2 12 to 16 weeks | | | | | | | |
| Boogaerts 2003 | 133 | 2.11 (4.97) | 129 | 3.78 (6.53) | | 2.0 % | -1.67 [ -3.08, -0.26 ] |
| Case 1993 | 79 | 2.03 (3.88) | 74 | 2.75 (4.15) | | 2.4 % | -0.72 [ -2.00, 0.56 ] |
| Dammacco 2001 | 66 | 1.49 (2.73) | 66 | 2.18 (2.95) | | 4.2 % | -0.69 [ -1.66, 0.28 ] |
| Grote 2005 | 109 | 0.5 (3.6) | 115 | 0.4 (0.7) | | 8.2 % | 0.10 [ -0.59, 0.79 ] |
| Henry 1995 | 64 | 3.56 (7.01) | 61 | 4.01 (4.87) | | 0.9 % | -0.45 [ -2.56, 1.66 ] |
| Hernandez 2009 | 181 | 1 (2) | 185 | 1.5 (2.5) | | 18.2 % | -0.50 [ -0.96, -0.04 ] |
| Kurz 1997 | 23 | 1.43 (3.8) | 12 | 3.7 (3.09) | | 0.7 % | -2.27 [ -4.61, 0.07 ] |
| Oberhoff 1998 | 114 | 1.32 (3.04) | 104 | 1.91 (3.28) | | 5.5 % | -0.59 [ -1.43, 0.25 ] |
| Osterborg 2002 | 169 | 2.66 (5.56) | 173 | 3.22 (5.17) | | 3.0 % | -0.56 [ -1.70, 0.58 ] |
| Rose 1994 | 142 | 5.8 (10.7) | 79 | 8 (17.5) | | 0.2 % | -2.20 [ -6.44, 2.04 ] |
| Savonije 2005 | 211 | 1.5 (2.6) | 102 | 3.1 (3.1) | | 8.0 % | -1.60 [ -2.30, -0.90 ] |
| Vansteenkiste 2002 | 148 | 0.67 (1.7) | 149 | 1.92 (3.27) | | 11.1 % | -1.25 [ -1.84, -0.66 ] |
| **Subtotal (95% CI)** | **1439** | | **1249** | | | **64.4 %** | **-0.78 [ -1.03, -0.54 ]** |
| Heterogeneity: Chi² = 19.44, df = 11 (P = 0.05); I² =43% | | | | | | | |
| Test for overall effect: Z = 6.22 (P < 0.00001) | | | | | | | |
| 3 more than 17 weeks | | | | | | | |

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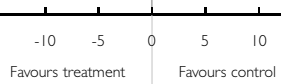
| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Engert 2009 | 637 | 3.7 (4.8) | 632 | 5.3 (5.7) | | 11.6 % | -1.60 [ -2.18, -1.02 ] |
| Osterborg 1996a | 47 | 6.8 (10.1) | 24 | 9.3 (9.2) | | 0.2 % | -2.50 [ -7.18, 2.18 ] |
| Osterborg 1996b | 48 | 8.7 (9.6) | 25 | 9.3 (9.2) | | 0.2 % | -0.60 [ -5.11, 3.91 ] |
| Ten Bokkel 1998a | 45 | 0.33 (1.6) | 17 | 1.27 (1.97) | | 3.6 % | -0.94 [ -1.99, 0.11 ] |
| Ten Bokkel 1998b | 42 | 0.43 (1.23) | 16 | 1.27 (1.97) | | 3.6 % | -0.84 [ -1.87, 0.19 ] |
| Thatcher 1999a | 42 | 3.8 (5.58) | 22 | 6.13 (7.13) | | 0.3 % | -2.33 [ -5.75, 1.09 ] |
| Thatcher 1999b | 44 | 2.1 (4.6) | 22 | 6.13 (7.13) | | 0.4 % | -4.03 [ -7.30, -0.76 ] |
| **Subtotal (95% CI)** | **905** | | **758** | | | **19.9 %** | **-1.40 [ -1.84, -0.95 ]** |
| Heterogeneity: $Chi^2$ = 5.42, df = 6 (P = 0.49); $I^2$ =0.0% | | | | | | | |
| Test for overall effect: Z = 6.18 (P < 0.00001) | | | | | | | |
| **Total (95% CI)** | **2574** | | **2141** | | | **100.0 %** | **-0.98 [ -1.17, -0.78 ]** |
| Heterogeneity: $Chi^2$ = 34.52, df = 24 (P = 0.08); $I^2$ =30% | | | | | | | |
| Test for overall effect: Z = 9.69 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 7.02, df = 2 (P = 0.03), $I^2$ =72% | | | | | | | |



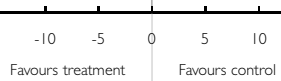
## Analysis 4.10. Comparison 4 Number of red blood cell units transfused per patient, Outcome 10 Number of RBC units transfused - iron supplementation.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 4 Number of red blood cell units transfused per patient

Outcome: 10 Number of RBC units transfused - iron supplementation

| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 fixed iron supplementation | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| 2 iron supplementation as necessary | | | | | | | |
| Abels 1993 | 63 | 1.52 (2.61) | 55 | 2.19 (3.57) | | 3.0 % | -0.67 [ -1.81, 0.47 ] |
| Boogaerts 2003 | 133 | 2.11 (4.97) | 129 | 3.78 (6.53) | | 2.0 % | -1.67 [ -3.08, -0.26 ] |
| Cascinu 1994 | 50 | 0.3 (0.07) | 50 | 1.8 (2.12) | | 11.3 % | -1.50 [ -2.09, -0.91 ] |
| Case 1993 | 79 | 2.03 (3.88) | 74 | 2.75 (4.15) | | 2.4 % | -0.72 [ -2.00, 0.56 ] |
| Cazzola 1995a | 31 | 1.19 (2.69) | 7 | 1.55 (4.31) | | 0.4 % | -0.36 [ -3.69, 2.97 ] |
| Cazzola 1995b | 29 | 1.45 (4.57) | 8 | 1.55 (4.31) | | 0.3 % | -0.10 [ -3.52, 3.32 ] |
| Cazzola 1995c | 31 | 0.97 (2.64) | 7 | 1.55 (4.31) | | 0.4 % | -0.58 [ -3.91, 2.75 ] |
| Cazzola 1995d | 26 | 0.81 (2.3) | 7 | 1.55 (4.31) | | 0.4 % | -0.74 [ -4.05, 2.57 ] |
| Dammacco 2001 | 66 | 1.49 (2.73) | 66 | 2.18 (2.95) | | 4.2 % | -0.69 [ -1.66, 0.28 ] |
| Engert 2009 | 637 | 3.7 (4.8) | 632 | 5.3 (5.7) | | 11.6 % | -1.60 [ -2.18, -1.02 ] |
| Grote 2005 | 109 | 0.5 (3.6) | 115 | 0.4 (0.7) | | 8.2 % | 0.10 [ -0.59, 0.79 ] |
| Henry 1995 | 64 | 3.56 (7.01) | 61 | 4.01 (4.87) | | 0.9 % | -0.45 [ -2.56, 1.66 ] |
| Hernandez 2009 | 181 | 1 (2) | 185 | 1.5 (2.5) | | 18.2 % | -0.50 [ -0.96, -0.04 ] |
| Kurz 1997 | 23 | 1.43 (3.8) | 12 | 3.7 (3.09) | | 0.7 % | -2.27 [ -4.61, 0.07 ] |
| Oberhoff 1998 | 114 | 1.32 (3.04) | 104 | 1.91 (3.28) | | 5.5 % | -0.59 [ -1.43, 0.25 ] |
| Osterborg 1996a | 47 | 6.8 (10.1) | 24 | 9.3 (9.2) | | 0.2 % | -2.50 [ -7.18, 2.18 ] |
| Osterborg 1996b | 48 | 8.7 (9.6) | 25 | 9.3 (9.2) | | 0.2 % | -0.60 [ -5.11, 3.91 ] |
| Osterborg 2002 | 169 | 2.66 (5.56) | 173 | 3.22 (5.17) | | 3.0 % | -0.56 [ -1.70, 0.58 ] |
| Rose 1994 | 142 | 5.8 (10.7) | 79 | 8 (17.5) | | 0.2 % | -2.20 [ -6.44, 2.04 ] |
| Ten Bokkel 1998a | 45 | 0.33 (1.6) | 17 | 1.27 (1.97) | | 3.6 % | -0.94 [ -1.99, 0.11 ] |
| Ten Bokkel 1998b | 42 | 0.43 (1.23) | 16 | 1.27 (1.97) | | 3.6 % | -0.84 [ -1.87, 0.19 ] |

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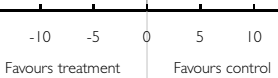
| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Thatcher 1999a | 42 | 3.8 (5.58) | 22 | 6.13 (7.13) | | 0.3 % | -2.33 [ -5.75, 1.09 ] |
| Thatcher 1999b | 44 | 2.1 (4.6) | 22 | 6.13 (7.13) | | 0.4 % | -4.03 [ -7.30, -0.76 ] |
| Vansteenkiste 2002 | 148 | 0.67 (1.7) | 149 | 1.92 (3.27) | | 11.1 % | -1.25 [ -1.84, -0.66 ] |
| **Subtotal (95% CI)** | **2363** | | **2039** | | | **92.0 %** | **-0.92 [ -1.13, -0.72 ]** |
| Heterogeneity: $Chi^2$ = 31.17, df = 23 (P = 0.12); $I^2$ =26% | | | | | | | |
| Test for overall effect: Z = 8.78 (P < 0.00001) | | | | | | | |
| 3 no explicit statement on iron supplementation or no iron given | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| 4 explicitely stated NO IRON | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| 5 iron given differently in both study arms | | | | | | | |
| Savonije 2005 | 211 | 1.5 (2.6) | 102 | 3.1 (3.1) | | 8.0 % | -1.60 [ -2.30, -0.90 ] |
| **Subtotal (95% CI)** | **211** | | **102** | | | **8.0 %** | **-1.60 [ -2.30, -0.90 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 4.50 (P < 0.00001) | | | | | | | |
| **Total (95% CI)** | **2574** | | **2141** | | | **100.0 %** | **-0.98 [ -1.17, -0.78 ]** |
| Heterogeneity: $Chi^2$ = 34.52, df = 24 (P = 0.08); $I^2$ =30% | | | | | | | |
| Test for overall effect: Z = 9.69 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 3.34, df = 1 (P = 0.07), $I^2$ =70% | | | | | | | |



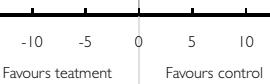
## Analysis 4.11. Comparison 4 Number of red blood cell units transfused per patient, Outcome 11 Number of RBC units transfused - allocation concealment.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 4 Number of red blood cell units transfused per patient

Outcome: 11 Number of RBC units transfused - allocation concealment

| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 adequate | | | | | | | |
| Boogaerts 2003 | 133 | 2.11 (4.97) | 129 | 3.78 (6.53) | | 2.0 % | -1.67 [ -3.08, -0.26 ] |
| Cazzola 1995a | 31 | 1.19 (2.69) | 7 | 1.55 (4.31) | | 0.4 % | -0.36 [ -3.69, 2.97 ] |
| Cazzola 1995b | 29 | 1.45 (4.57) | 8 | 1.55 (4.31) | | 0.3 % | -0.10 [ -3.52, 3.32 ] |
| Cazzola 1995c | 31 | 0.97 (2.64) | 7 | 1.55 (4.31) | | 0.4 % | -0.58 [ -3.91, 2.75 ] |
| Cazzola 1995d | 26 | 0.81 (2.3) | 7 | 1.55 (4.31) | | 0.4 % | -0.74 [ -4.05, 2.57 ] |
| Hernandez 2009 | 181 | 1 (2) | 185 | 1.5 (2.5) | | 18.2 % | -0.50 [ -0.96, -0.04 ] |
| Kurz 1997 | 23 | 1.43 (3.8) | 12 | 3.7 (3.09) | | 0.7 % | -2.27 [ -4.61, 0.07 ] |
| Oberhoff 1998 | 114 | 1.32 (3.04) | 104 | 1.91 (3.28) | | 5.5 % | -0.59 [ -1.43, 0.25 ] |
| Osterborg 1996a | 47 | 6.8 (10.1) | 24 | 9.3 (9.2) | | 0.2 % | -2.50 [ -7.18, 2.18 ] |
| Osterborg 1996b | 48 | 8.7 (9.6) | 25 | 9.3 (9.2) | | 0.2 % | -0.60 [ -5.11, 3.91 ] |
| Osterborg 2002 | 169 | 2.66 (5.56) | 173 | 3.22 (5.17) | | 3.0 % | -0.56 [ -1.70, 0.58 ] |
| Savonije 2005 | 211 | 1.5 (2.6) | 102 | 3.1 (3.1) | | 8.0 % | -1.60 [ -2.30, -0.90 ] |
| Ten Bokkel 1998a | 45 | 0.33 (1.6) | 17 | 1.27 (1.97) | | 3.6 % | -0.94 [ -1.99, 0.11 ] |
| Ten Bokkel 1998b | 42 | 0.43 (1.23) | 16 | 1.27 (1.97) | | 3.6 % | -0.84 [ -1.87, 0.19 ] |
| Vansteenkiste 2002 | 148 | 0.67 (1.7) | 149 | 1.92 (3.27) | | 11.1 % | -1.25 [ -1.84, -0.66 ] |
| **Subtotal (95% CI)** | **1278** | | **965** | | | **57.5 %** | **-0.93 [ -1.19, -0.67 ]** |
| Heterogeneity: $Chi^2$ = 12.22, df = 14 (P = 0.59); $I^2$ =0.0% | | | | | | | |
| Test for overall effect: Z = 6.97 (P < 0.00001) | | | | | | | |
| 2 unclear | | | | | | | |
| Abels 1993 | 63 | 1.52 (2.61) | 55 | 2.19 (3.57) | | 3.0 % | -0.67 [ -1.81, 0.47 ] |
| Cascinu 1994 | 50 | 0.3 (0.07) | 50 | 1.8 (2.12) | | 11.3 % | -1.50 [ -2.09, -0.91 ] |
| Case 1993 | 79 | 2.03 (3.88) | 74 | 2.75 (4.15) | | 2.4 % | -0.72 [ -2.00, 0.56 ] |
| Dammacco 2001 | 66 | 1.49 (2.73) | 66 | 2.18 (2.95) | | 4.2 % | -0.69 [ -1.66, 0.28 ] |
| Engert 2009 | 637 | 3.7 (4.8) | 632 | 5.3 (5.7) | | 11.6 % | -1.60 [ -2.18, -1.02 ] |
| Grote 2005 | 109 | 0.5 (3.6) | 115 | 0.4 (0.7) | | 8.2 % | 0.10 [ -0.59, 0.79 ] |

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| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Henry 1995 | 64 | 3.56 (7.01) | 61 | 4.01 (4.87) | | 0.9 % | -0.45 [ -2.56, 1.66 ] |
| Rose 1994 | 142 | 5.8 (10.7) | 79 | 8 (17.5) | | 0.2 % | -2.20 [ -6.44, 2.04 ] |
| Thatcher 1999a | 42 | 3.8 (5.58) | 22 | 6.13 (7.13) | | 0.3 % | -2.33 [ -5.75, 1.09 ] |
| Thatcher 1999b | 44 | 2.1 (4.6) | 22 | 6.13 (7.13) | | 0.4 % | -4.03 [ -7.30, -0.76 ] |
| **Subtotal (95% CI)** | **1296** | | **1176** | | | **42.5 %** | **-1.04 [ -1.35, -0.74 ]** |
| Heterogeneity: $Chi^2$ = 21.96, df = 9 (P = 0.01); $I^2$ =59% | | | | | | | |
| Test for overall effect: Z = 6.76 (P < 0.00001) | | | | | | | |
| **Total (95% CI)** | **2574** | | **2141** | | | **100.0 %** | **-0.98 [ -1.17, -0.78 ]** |
| Heterogeneity: $Chi^2$ = 34.52, df = 24 (P = 0.08); $I^2$ =30% | | | | | | | |
| Test for overall effect: Z = 9.69 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 0.34, df = 1 (P = 0.56), $I^2$ =0.0% | | | | | | | |

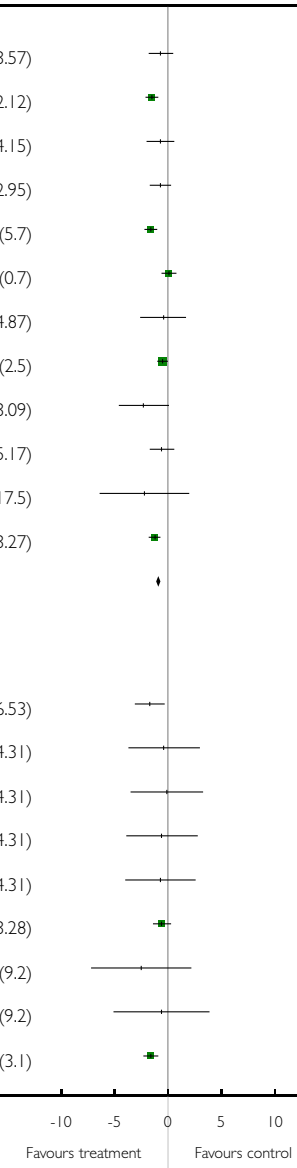
## Analysis 4.12. Comparison 4 Number of red blood cell units transfused per patient, Outcome 12 Number of RBC units transfused - masking.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 4 Number of red blood cell units transfused per patient

Outcome: 12 Number of RBC units transfused - masking

| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 double-blind | | | | | | | |
| Abels 1993 | 63 | 1.52 (2.61) | 55 | 2.19 (3.57) | | 3.0 % | -0.67 [ -1.81, 0.47 ] |
| Cascinu 1994 | 50 | 0.3 (0.07) | 50 | 1.8 (2.12) | | 11.3 % | -1.50 [ -2.09, -0.91 ] |
| Case 1993 | 79 | 2.03 (3.88) | 74 | 2.75 (4.15) | | 2.4 % | -0.72 [ -2.00, 0.56 ] |
| Dammacco 2001 | 66 | 1.49 (2.73) | 66 | 2.18 (2.95) | | 4.2 % | -0.69 [ -1.66, 0.28 ] |
| Engert 2009 | 637 | 3.7 (4.8) | 632 | 5.3 (5.7) | | 11.6 % | -1.60 [ -2.18, -1.02 ] |
| Grote 2005 | 109 | 0.5 (3.6) | 115 | 0.4 (0.7) | | 8.2 % | 0.10 [ -0.59, 0.79 ] |
| Henry 1995 | 64 | 3.56 (7.01) | 61 | 4.01 (4.87) | | 0.9 % | -0.45 [ -2.56, 1.66 ] |
| Hernandez 2009 | 181 | 1 (2) | 185 | 1.5 (2.5) | | 18.2 % | -0.50 [ -0.96, -0.04 ] |
| Kurz 1997 | 23 | 1.43 (3.8) | 12 | 3.7 (3.09) | | 0.7 % | -2.27 [ -4.61, 0.07 ] |
| Osterborg 2002 | 169 | 2.66 (5.56) | 173 | 3.22 (5.17) | | 3.0 % | -0.56 [ -1.70, 0.58 ] |
| Rose 1994 | 142 | 5.8 (10.7) | 79 | 8 (17.5) | | 0.2 % | -2.20 [ -6.44, 2.04 ] |
| Vansteenkiste 2002 | 148 | 0.67 (1.7) | 149 | 1.92 (3.27) | | 11.1 % | -1.25 [ -1.84, -0.66 ] |
| **Subtotal (95% CI)** | **1731** | | **1651** | | | **74.8 %** | **-0.91 [ -1.14, -0.69 ]** |
| Heterogeneity: Chi² = 24.51, df = 11 (P = 0.01); I² =55% | | | | | | | |
| Test for overall effect: Z = 7.85 (P < 0.00001) | | | | | | | |
| 2 unblinded | | | | | | | |
| Boogaerts 2003 | 133 | 2.11 (4.97) | 129 | 3.78 (6.53) | | 2.0 % | -1.67 [ -3.08, -0.26 ] |
| Cazzola 1995a | 31 | 1.19 (2.69) | 7 | 1.55 (4.31) | | 0.4 % | -0.36 [ -3.69, 2.97 ] |
| Cazzola 1995b | 29 | 1.45 (4.57) | 8 | 1.55 (4.31) | | 0.3 % | -0.10 [ -3.52, 3.32 ] |
| Cazzola 1995c | 31 | 0.97 (2.64) | 7 | 1.55 (4.31) | | 0.4 % | -0.58 [ -3.91, 2.75 ] |
| Cazzola 1995d | 26 | 0.81 (2.3) | 7 | 1.55 (4.31) | | 0.4 % | -0.74 [ -4.05, 2.57 ] |
| Oberhoff 1998 | 114 | 1.32 (3.04) | 104 | 1.91 (3.28) | | 5.5 % | -0.59 [ -1.43, 0.25 ] |
| Osterborg 1996a | 47 | 6.8 (10.1) | 24 | 9.3 (9.2) | | 0.2 % | -2.50 [ -7.18, 2.18 ] |
| Osterborg 1996b | 48 | 8.7 (9.6) | 25 | 9.3 (9.2) | | 0.2 % | -0.60 [ -5.11, 3.91 ] |
| Savonije 2005 | 211 | 1.5 (2.6) | 102 | 3.1 (3.1) | | 8.0 % | -1.60 [ -2.30, -0.90 ] |

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| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Ten Bokkel 1998a | 45 | 0.33 (1.6) | 17 | 1.27 (1.97) | | 3.6 % | -0.94 [ -1.99, 0.11 ] |
| Ten Bokkel 1998b | 42 | 0.43 (1.23) | 16 | 1.27 (1.97) | | 3.6 % | -0.84 [ -1.87, 0.19 ] |
| Thatcher 1999a | 42 | 3.8 (5.58) | 22 | 6.13 (7.13) | | 0.3 % | -2.33 [ -5.75, 1.09 ] |
| Thatcher 1999b | 44 | 2.1 (4.6) | 22 | 6.13 (7.13) | | 0.4 % | -4.03 [ -7.30, -0.76 ] |
| **Subtotal (95% CI)** | **843** | | **490** | | | **25.2 %** | **-1.16 [ -1.55, -0.77 ]** |
| Heterogeneity: $Chi^2$ = 8.88, df = 12 (P = 0.71); $I^2$ =0.0% | | | | | | | |
| Test for overall effect: Z = 5.78 (P < 0.00001) | | | | | | | |
| **Total (95% CI)** | **2574** | | **2141** | | | **100.0 %** | **-0.98 [ -1.17, -0.78 ]** |
| Heterogeneity: $Chi^2$ = 34.52, df = 24 (P = 0.08); $I^2$ =30% | | | | | | | |
| Test for overall effect: Z = 9.69 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 1.13, df = 1 (P = 0.29), $I^2$ =11% | | | | | | | |

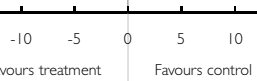
## Analysis 4.13. Comparison 4 Number of red blood cell units transfused per patient, Outcome 13 Number of RBC units transfused - intention-to-treat.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 4 Number of red blood cell units transfused per patient

Outcome: 13 Number of RBC units transfused - intention-to-treat

| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 ITT or less than 10% of participants per study arm excluded | | | | | | | |
| Abels 1993 | 63 | 1.52 (2.61) | 55 | 2.19 (3.57) | | 3.0 % | -0.67 [ -1.81, 0.47 ] |
| Boogaerts 2003 | 133 | 2.11 (4.97) | 129 | 3.78 (6.53) | | 2.0 % | -1.67 [ -3.08, -0.26 ] |
| Cascinu 1994 | 50 | 0.3 (0.07) | 50 | 1.8 (2.12) | | 11.3 % | -1.50 [ -2.09, -0.91 ] |
| Case 1993 | 79 | 2.03 (3.88) | 74 | 2.75 (4.15) | | 2.4 % | -0.72 [ -2.00, 0.56 ] |
| Cazzola 1995a | 31 | 1.19 (2.69) | 7 | 1.55 (4.31) | | 0.4 % | -0.36 [ -3.69, 2.97 ] |
| Cazzola 1995b | 29 | 1.45 (4.57) | 8 | 1.55 (4.31) | | 0.3 % | -0.10 [ -3.52, 3.32 ] |
| Cazzola 1995c | 31 | 0.97 (2.64) | 7 | 1.55 (4.31) | | 0.4 % | -0.58 [ -3.91, 2.75 ] |
| Cazzola 1995d | 26 | 0.81 (2.3) | 7 | 1.55 (4.31) | | 0.4 % | -0.74 [ -4.05, 2.57 ] |
| Engert 2009 | 637 | 3.7 (4.8) | 632 | 5.3 (5.7) | | 11.6 % | -1.60 [ -2.18, -1.02 ] |
| Grote 2005 | 109 | 0.5 (3.6) | 115 | 0.4 (0.7) | | 8.2 % | 0.10 [ -0.59, 0.79 ] |
| Henry 1995 | 64 | 3.56 (7.01) | 61 | 4.01 (4.87) | | 0.9 % | -0.45 [ -2.56, 1.66 ] |
| Hernandez 2009 | 181 | 1 (2) | 185 | 1.5 (2.5) | | 18.2 % | -0.50 [ -0.96, -0.04 ] |
| Kurz 1997 | 23 | 1.43 (3.8) | 12 | 3.7 (3.09) | | 0.7 % | -2.27 [ -4.61, 0.07 ] |
| Oberhoff 1998 | 114 | 1.32 (3.04) | 104 | 1.91 (3.28) | | 5.5 % | -0.59 [ -1.43, 0.25 ] |
| Osterborg 1996a | 47 | 6.8 (10.1) | 24 | 9.3 (9.2) | | 0.2 % | -2.50 [ -7.18, 2.18 ] |
| Osterborg 1996b | 48 | 8.7 (9.6) | 25 | 9.3 (9.2) | | 0.2 % | -0.60 [ -5.11, 3.91 ] |
| Osterborg 2002 | 169 | 2.66 (5.56) | 173 | 3.22 (5.17) | | 3.0 % | -0.56 [ -1.70, 0.58 ] |
| Rose 1994 | 142 | 5.8 (10.7) | 79 | 8 (17.5) | | 0.2 % | -2.20 [ -6.44, 2.04 ] |
| Savonije 2005 | 211 | 1.5 (2.6) | 102 | 3.1 (3.1) | | 8.0 % | -1.60 [ -2.30, -0.90 ] |
| Ten Bokkel 1998a | 45 | 0.33 (1.6) | 17 | 1.27 (1.97) | | 3.6 % | -0.94 [ -1.99, 0.11 ] |
| Ten Bokkel 1998b | 42 | 0.43 (1.23) | 16 | 1.27 (1.97) | | 3.6 % | -0.84 [ -1.87, 0.19 ] |
| Thatcher 1999a | 42 | 3.8 (5.58) | 22 | 6.13 (7.13) | | 0.3 % | -2.33 [ -5.75, 1.09 ] |
| Thatcher 1999b | 44 | 2.1 (4.6) | 22 | 6.13 (7.13) | | 0.4 % | -4.03 [ -7.30, -0.76 ] |
| Vansteenkiste 2002 | 148 | 0.67 (1.7) | 149 | 1.92 (3.27) | | 11.1 % | -1.25 [ -1.84, -0.66 ] |

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| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| **Subtotal (95% CI)** | **2508** | | **2075** | | | **95.8 %** | **-0.99 [ -1.19, -0.79 ]** |
| Heterogeneity: $Chi^2$ = 34.17, df = 23 (P = 0.06); $I^2$ =33% | | | | | | | |
| Test for overall effect: Z = 9.61 (P < 0.00001) | | | | | | | |
| 2 more than 10% of participants per study arm excluded | | | | | | | |
| Dammacco 2001 | 66 | 1.49 (2.73) | 66 | 2.18 (2.95) | | 4.2 % | -0.69 [ -1.66, 0.28 ] |
| **Subtotal (95% CI)** | **66** | | **66** | | | **4.2 %** | **-0.69 [ -1.66, 0.28 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 1.39 (P = 0.16) | | | | | | | |
| **Total (95% CI)** | **2574** | | **2141** | | | **100.0 %** | **-0.98 [ -1.17, -0.78 ]** |
| Heterogeneity: $Chi^2$ = 34.52, df = 24 (P = 0.08); $I^2$ =30% | | | | | | | |
| Test for overall effect: Z = 9.69 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 0.35, df = 1 (P = 0.55), $I^2$ =0.0% | | | | | | | |

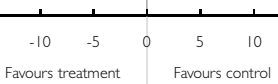
## Analysis 4.14. Comparison 4 Number of red blood cell units transfused per patient, Outcome 14 Number of RBC units transfused - publication.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 4 Number of red blood cell units transfused per patient

Outcome: 14 Number of RBC units transfused - publication

| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 full text publication | | | | | | | |
| Grote 2005 | 109 | 0.5 (3.6) | 115 | 0.4 (0.7) | | 8.2 % | 0.10 [ -0.59, 0.79 ] |
| Hernandez 2009 | 181 | 1 (2) | 185 | 1.5 (2.5) | | 18.2 % | -0.50 [ -0.96, -0.04 ] |
| Savonije 2005 | 211 | 1.5 (2.6) | 102 | 3.1 (3.1) | | 8.0 % | -1.60 [ -2.30, -0.90 ] |
| Vansteenkiste 2002 | 148 | 0.67 (1.7) | 149 | 1.92 (3.27) | | 11.1 % | -1.25 [ -1.84, -0.66 ] |
| **Subtotal (95% CI)** | **649** | | **551** | | | **45.6 %** | **-0.77 [ -1.06, -0.48 ]** |
| Heterogeneity: $Chi^2$ = 15.43, df = 3 (P = 0.001); $I^2$ =81% | | | | | | | |
| Test for overall effect: Z = 5.15 (P < 0.00001) | | | | | | | |
| 2 abstract publication | | | | | | | |
| Engert 2009 | 637 | 3.7 (4.8) | 632 | 5.3 (5.7) | | 11.6 % | -1.60 [ -2.18, -1.02 ] |
| **Subtotal (95% CI)** | **637** | | **632** | | | **11.6 %** | **-1.60 [ -2.18, -1.02 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 5.41 (P < 0.00001) | | | | | | | |
| 3 unpublished data | | | | | | | |
| Abels 1993 | 63 | 1.52 (2.61) | 55 | 2.19 (3.57) | | 3.0 % | -0.67 [ -1.81, 0.47 ] |
| Boogaerts 2003 | 133 | 2.11 (4.97) | 129 | 3.78 (6.53) | | 2.0 % | -1.67 [ -3.08, -0.26 ] |
| Cascinu 1994 | 50 | 0.3 (0.07) | 50 | 1.8 (2.12) | | 11.3 % | -1.50 [ -2.09, -0.91 ] |
| Case 1993 | 79 | 2.03 (3.88) | 74 | 2.75 (4.15) | | 2.4 % | -0.72 [ -2.00, 0.56 ] |
| Cazzola 1995a | 31 | 1.19 (2.69) | 7 | 1.55 (4.31) | | 0.4 % | -0.36 [ -3.69, 2.97 ] |
| Cazzola 1995b | 29 | 1.45 (4.57) | 8 | 1.55 (4.31) | | 0.3 % | -0.10 [ -3.52, 3.32 ] |
| Cazzola 1995c | 31 | 0.97 (2.64) | 7 | 1.55 (4.31) | | 0.4 % | -0.58 [ -3.91, 2.75 ] |
| Cazzola 1995d | 26 | 0.81 (2.3) | 7 | 1.55 (4.31) | | 0.4 % | -0.74 [ -4.05, 2.57 ] |
| Dammacco 2001 | 66 | 1.49 (2.73) | 66 | 2.18 (2.95) | | 4.2 % | -0.69 [ -1.66, 0.28 ] |
| Henry 1995 | 64 | 3.56 (7.01) | 61 | 4.01 (4.87) | | 0.9 % | -0.45 [ -2.56, 1.66 ] |
| Kurz 1997 | 23 | 1.43 (3.8) | 12 | 3.7 (3.09) | | 0.7 % | -2.27 [ -4.61, 0.07 ] |
| Oberhoff 1998 | 114 | 1.32 (3.04) | 104 | 1.91 (3.28) | | 5.5 % | -0.59 [ -1.43, 0.25 ] |
| Osterborg 1996a | 47 | 6.8 (10.1) | 24 | 9.3 (9.2) | | 0.2 % | -2.50 [ -7.18, 2.18 ] |

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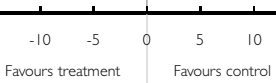
| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Osterborg 1996b | 48 | 8.7 (9.6) | 25 | 9.3 (9.2) | | 0.2 % | -0.60 [ -5.11, 3.91 ] |
| Osterborg 2002 | 169 | 2.66 (5.56) | 173 | 3.22 (5.17) | | 3.0 % | -0.56 [ -1.70, 0.58 ] |
| Rose 1994 | 142 | 5.8 (10.7) | 79 | 8 (17.5) | | 0.2 % | -2.20 [ -6.44, 2.04 ] |
| Ten Bokkel 1998a | 45 | 0.33 (1.6) | 17 | 1.27 (1.97) | | 3.6 % | -0.94 [ -1.99, 0.11 ] |
| Ten Bokkel 1998b | 42 | 0.43 (1.23) | 16 | 1.27 (1.97) | | 3.6 % | -0.84 [ -1.87, 0.19 ] |
| Thatcher 1999a | 42 | 3.8 (5.58) | 22 | 6.13 (7.13) | | 0.3 % | -2.33 [ -5.75, 1.09 ] |
| Thatcher 1999b | 44 | 2.1 (4.6) | 22 | 6.13 (7.13) | | 0.4 % | -4.03 [ -7.30, -0.76 ] |
| **Subtotal (95% CI)** | **1288** | | **958** | | | **42.8 %** | **-1.03 [ -1.33, -0.73 ]** |
| Heterogeneity: $Chi^2$ = 12.59, df = 19 (P = 0.86); $I^2$ =0.0% | | | | | | | |
| Test for overall effect: Z = 6.69 (P < 0.00001) | | | | | | | |
| 4 FDA presented data | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| **Total (95% CI)** | **2574** | | **2141** | | | **100.0 %** | **-0.98 [ -1.17, -0.78 ]** |
| Heterogeneity: $Chi^2$ = 34.52, df = 24 (P = 0.08); $I^2$ =30% | | | | | | | |
| Test for overall effect: Z = 9.69 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 6.50, df = 2 (P = 0.04), $I^2$ =69% | | | | | | | |



## Analysis 4.15. Comparison 4 Number of red blood cell units transfused per patient, Outcome 15 Number of RBC units transfused - first 4 weeks are....

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 4 Number of red blood cell units transfused per patient

Outcome: 15 Number of RBC units transfused - first 4 weeks are...

| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 included in the analysis | | | | | | | |
| Abels 1993 | 63 | 1.52 (2.61) | 55 | 2.19 (3.57) | | 3.0 % | -0.67 [ -1.81, 0.47 ] |
| Boogaerts 2003 | 133 | 2.11 (4.97) | 129 | 3.78 (6.53) | | 2.0 % | -1.67 [ -3.08, -0.26 ] |
| Cascinu 1994 | 50 | 0.3 (0.07) | 50 | 1.8 (2.12) | | 11.3 % | -1.50 [ -2.09, -0.91 ] |
| Case 1993 | 79 | 2.03 (3.88) | 74 | 2.75 (4.15) | | 2.4 % | -0.72 [ -2.00, 0.56 ] |
| Cazzola 1995a | 31 | 1.19 (2.69) | 7 | 1.55 (4.31) | | 0.4 % | -0.36 [ -3.69, 2.97 ] |
| Cazzola 1995b | 29 | 1.45 (4.57) | 8 | 1.55 (4.31) | | 0.3 % | -0.10 [ -3.52, 3.32 ] |
| Cazzola 1995c | 31 | 0.97 (2.64) | 7 | 1.55 (4.31) | | 0.4 % | -0.58 [ -3.91, 2.75 ] |
| Cazzola 1995d | 26 | 0.81 (2.3) | 7 | 1.55 (4.31) | | 0.4 % | -0.74 [ -4.05, 2.57 ] |
| Grote 2005 | 109 | 0.5 (3.6) | 115 | 0.4 (0.7) | | 8.2 % | 0.10 [ -0.59, 0.79 ] |
| Oberhoff 1998 | 114 | 1.32 (3.04) | 104 | 1.91 (3.28) | | 5.5 % | -0.59 [ -1.43, 0.25 ] |
| Osterborg 1996a | 47 | 6.8 (10.1) | 24 | 9.3 (9.2) | | 0.2 % | -2.50 [ -7.18, 2.18 ] |
| Osterborg 1996b | 48 | 8.7 (9.6) | 25 | 9.3 (9.2) | | 0.2 % | -0.60 [ -5.11, 3.91 ] |
| Osterborg 2002 | 169 | 2.66 (5.56) | 173 | 3.22 (5.17) | | 3.0 % | -0.56 [ -1.70, 0.58 ] |
| Rose 1994 | 142 | 5.8 (10.7) | 79 | 8 (17.5) | | 0.2 % | -2.20 [ -6.44, 2.04 ] |
| Savonije 2005 | 211 | 1.5 (2.6) | 102 | 3.1 (3.1) | | 8.0 % | -1.60 [ -2.30, -0.90 ] |
| Ten Bokkel 1998a | 45 | 0.33 (1.6) | 17 | 1.27 (1.97) | | 3.6 % | -0.94 [ -1.99, 0.11 ] |
| Ten Bokkel 1998b | 42 | 0.43 (1.23) | 16 | 1.27 (1.97) | | 3.6 % | -0.84 [ -1.87, 0.19 ] |
| Vansteenkiste 2002 | 148 | 0.67 (1.7) | 149 | 1.92 (3.27) | | 11.1 % | -1.25 [ -1.84, -0.66 ] |
| **Subtotal (95% CI)** | **1517** | | **1141** | | | **63.8 %** | **-0.99 [ -1.23, -0.74 ]** |
| Heterogeneity: Chi² = 20.32, df = 17 (P = 0.26); I² =16% | | | | | | | |
| Test for overall effect: Z = 7.82 (P < 0.00001) | | | | | | | |
| 2 excluded from the analysis | | | | | | | |
| Dammacco 2001 | 66 | 1.49 (2.73) | 66 | 2.18 (2.95) | | 4.2 % | -0.69 [ -1.66, 0.28 ] |
| Henry 1995 | 64 | 3.56 (7.01) | 61 | 4.01 (4.87) | | 0.9 % | -0.45 [ -2.56, 1.66 ] |
| Hernandez 2009 | 181 | 1 (2) | 185 | 1.5 (2.5) | | 18.2 % | -0.50 [ -0.96, -0.04 ] |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(. . . *Continued*)

| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| **Subtotal (95% CI)** | **311** | | **312** | | | **23.2 %** | **-0.53 [ -0.94, -0.12 ]** |
| Heterogeneity: $Chi^2$ = 0.13, df = 2 (P = 0.94); $I^2$ =0.0% | | | | | | | |
| Test for overall effect: Z = 2.54 (P = 0.011) | | | | | | | |
| 3 unclear | | | | | | | |
| Engert 2009 | 637 | 3.7 (4.8) | 632 | 5.3 (5.7) | | 11.6 % | -1.60 [ -2.18, -1.02 ] |
| Kurz 1997 | 23 | 1.43 (3.8) | 12 | 3.7 (3.09) | | 0.7 % | -2.27 [ -4.61, 0.07 ] |
| Thatcher 1999a | 42 | 3.8 (5.58) | 22 | 6.13 (7.13) | | 0.3 % | -2.33 [ -5.75, 1.09 ] |
| Thatcher 1999b | 44 | 2.1 (4.6) | 22 | 6.13 (7.13) | | 0.4 % | -4.03 [ -7.30, -0.76 ] |
| **Subtotal (95% CI)** | **746** | | **688** | | | **13.0 %** | **-1.72 [ -2.27, -1.18 ]** |
| Heterogeneity: $Chi^2$ = 2.41, df = 3 (P = 0.49); $I^2$ =0.0% | | | | | | | |
| Test for overall effect: Z = 6.17 (P < 0.00001) | | | | | | | |
| **Total (95% CI)** | **2574** | | **2141** | | | **100.0 %** | **-0.98 [ -1.17, -0.78 ]** |
| Heterogeneity: $Chi^2$ = 34.52, df = 24 (P = 0.08); $I^2$ =30% | | | | | | | |
| Test for overall effect: Z = 9.69 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 11.66, df = 2 (P = 0.00), $I^2$ =83% | | | | | | | |

## Analysis 4.16. Comparison 4 Number of red blood cell units transfused per patient, Outcome 16 Number of RBC units transfused - experimental arms merged.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 4 Number of red blood cell units transfused per patient

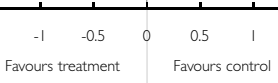
Outcome: 16 Number of RBC units transfused - experimental arms merged

| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Abels 1993 | 63 | 1.52 (2.61) | 55 | 2.19 (3.57) | | 3.0 % | -0.67 [ -1.81, 0.47 ] |
| Boogaerts 2003 | 133 | 2.11 (4.97) | 129 | 3.78 (6.53) | | 2.0 % | -1.67 [ -3.08, -0.26 ] |
| Cascinu 1994 | 50 | 0.3 (0.07) | 50 | 1.8 (2.12) | | 11.3 % | -1.50 [ -2.09, -0.91 ] |
| Case 1993 | 79 | 2.03 (3.88) | 74 | 2.75 (4.15) | | 2.4 % | -0.72 [ -2.00, 0.56 ] |
| Cazzola 1995 | 117 | 1.105 (3.05) | 29 | 1.55 (4.31) | | 1.4 % | -0.45 [ -2.11, 1.22 ] |
| Dammacco 2001 | 66 | 1.49 (2.73) | 66 | 2.18 (2.95) | | 4.2 % | -0.69 [ -1.66, 0.28 ] |
| Engert 2009 | 637 | 3.7 (4.8) | 632 | 5.3 (5.7) | | 11.6 % | -1.60 [ -2.18, -1.02 ] |
| Grote 2005 | 109 | 0.5 (3.6) | 115 | 0.4 (0.7) | | 8.2 % | 0.10 [ -0.59, 0.79 ] |
| Henry 1995 | 64 | 3.56 (7.01) | 61 | 4.01 (4.87) | | 0.9 % | -0.45 [ -2.56, 1.66 ] |
| Hernandez 2009 | 181 | 1 (2) | 185 | 1.5 (2.5) | | 18.2 % | -0.50 [ -0.96, -0.04 ] |
| Kurz 1997 | 23 | 1.43 (3.8) | 12 | 3.7 (3.09) | | 0.7 % | -2.27 [ -4.61, 0.07 ] |
| Oberhoff 1998 | 114 | 1.32 (3.04) | 104 | 1.91 (3.28) | | 5.5 % | -0.59 [ -1.43, 0.25 ] |
| Osterborg 1996 | 95 | 7.76 (9.85) | 49 | 9.3 (9.2) | | 0.4 % | -1.54 [ -4.79, 1.71 ] |
| Osterborg 2002 | 169 | 2.66 (5.56) | 173 | 3.22 (5.17) | | 3.0 % | -0.56 [ -1.70, 0.58 ] |
| Rose 1994 | 142 | 5.8 (10.7) | 79 | 8 (17.5) | | 0.2 % | -2.20 [ -6.44, 2.04 ] |
| Savonije 2005 | 211 | 1.5 (2.6) | 102 | 3.1 (3.1) | | 8.0 % | -1.60 [ -2.30, -0.90 ] |
| Ten Bokkel 1998 | 87 | 0.38 (1.43) | 33 | 1.27 (1.97) | | 7.2 % | -0.89 [ -1.63, -0.15 ] |
| Thatcher 1999 | 86 | 2.93 (5.1) | 44 | 6.13 (7.13) | | 0.7 % | -3.20 [ -5.57, -0.83 ] |
| Vansteenkiste 2002 | 148 | 0.67 (1.7) | 149 | 1.92 (3.27) | | 11.1 % | -1.25 [ -1.84, -0.66 ] |
| **Total (95% CI)** | **2574** | | **2141** | | | **100.0 %** | **-0.98 [ -1.17, -0.78 ]** |

Heterogeneity: $Chi^2$ = 33.56, df = 18 (P = 0.01); $I^2$ =46%

Test for overall effect: Z = 9.69 (P < 0.00001)

Test for subgroup differences: Not applicable



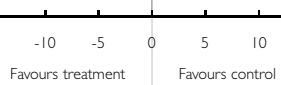
## Analysis 4.17. Comparison 4 Number of red blood cell units transfused per patient, Outcome 17 Number of RBC units transfused - age differentiated sensitivity analysis.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 4 Number of red blood cell units transfused per patient

Outcome: 17 Number of RBC units transfused - age differentiated sensitivity analysis

| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 only children <18 years | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| 2 adults ≥18 years | | | | | | | |
| Abels 1993 | 63 | 1.52 (2.61) | 55 | 2.19 (3.57) | | 3.0 % | -0.67 [ -1.81, 0.47 ] |
| Boogaerts 2003 | 133 | 2.11 (4.97) | 129 | 3.78 (6.53) | | 2.0 % | -1.67 [ -3.08, -0.26 ] |
| Case 1993 | 79 | 2.03 (3.88) | 74 | 2.75 (4.15) | | 2.4 % | -0.72 [ -2.00, 0.56 ] |
| Cazzola 1995a | 31 | 1.19 (2.69) | 7 | 1.55 (4.31) | | 0.4 % | -0.36 [ -3.69, 2.97 ] |
| Cazzola 1995b | 29 | 1.45 (4.57) | 8 | 1.55 (4.31) | | 0.3 % | -0.10 [ -3.52, 3.32 ] |
| Cazzola 1995c | 31 | 0.97 (2.64) | 7 | 1.55 (4.31) | | 0.4 % | -0.58 [ -3.91, 2.75 ] |
| Cazzola 1995d | 26 | 0.81 (2.3) | 7 | 1.55 (4.31) | | 0.4 % | -0.74 [ -4.05, 2.57 ] |
| Dammacco 2001 | 66 | 1.49 (2.73) | 66 | 2.18 (2.95) | | 4.2 % | -0.69 [ -1.66, 0.28 ] |
| Grote 2005 | 109 | 0.5 (3.6) | 115 | 0.4 (0.7) | | 8.2 % | 0.10 [ -0.59, 0.79 ] |
| Henry 1995 | 64 | 3.56 (7.01) | 61 | 4.01 (4.87) | | 0.9 % | -0.45 [ -2.56, 1.66 ] |
| Hernandez 2009 | 181 | 1 (2) | 185 | 1.5 (2.5) | | 18.2 % | -0.50 [ -0.96, -0.04 ] |
| Osterborg 1996a | 47 | 6.8 (10.1) | 24 | 9.3 (9.2) | | 0.2 % | -2.50 [ -7.18, 2.18 ] |
| Osterborg 1996b | 48 | 8.7 (9.6) | 25 | 9.3 (9.2) | | 0.2 % | -0.60 [ -5.11, 3.91 ] |
| Osterborg 2002 | 169 | 2.66 (5.56) | 173 | 3.22 (5.17) | | 3.0 % | -0.56 [ -1.70, 0.58 ] |
| Rose 1994 | 142 | 5.8 (10.7) | 79 | 8 (17.5) | | 0.2 % | -2.20 [ -6.44, 2.04 ] |
| Savonije 2005 | 211 | 1.5 (2.6) | 102 | 3.1 (3.1) | | 8.0 % | -1.60 [ -2.30, -0.90 ] |
| Ten Bokkel 1998a | 45 | 0.33 (1.6) | 17 | 1.27 (1.97) | | 3.6 % | -0.94 [ -1.99, 0.11 ] |
| Ten Bokkel 1998b | 42 | 0.43 (1.23) | 16 | 1.27 (1.97) | | 3.6 % | -0.84 [ -1.87, 0.19 ] |
| Thatcher 1999a | 42 | 3.8 (5.58) | 22 | 6.13 (7.13) | | 0.3 % | -2.33 [ -5.75, 1.09 ] |
| Thatcher 1999b | 44 | 2.1 (4.6) | 22 | 6.13 (7.13) | | 0.4 % | -4.03 [ -7.30, -0.76 ] |
| Vansteenkiste 2002 | 148 | 0.67 (1.7) | 149 | 1.92 (3.27) | | 11.1 % | -1.25 [ -1.84, -0.66 ] |

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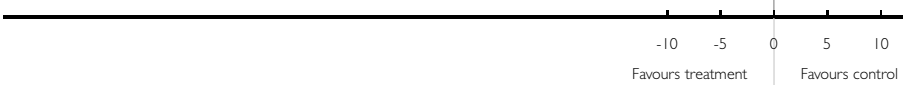
| Study or subgroup | Treatment N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| **Subtotal (95% CI)** | **1750** | | **1343** | | | **70.9 %** | **-0.81 [ -1.04, -0.57 ]** |
| Heterogeneity: $Chi^2$ = 23.08, df = 20 (P = 0.28); $I^2$ =13% | | | | | | | |
| Test for overall effect: Z = 6.76 (P < 0.00001) | | | | | | | |
| 3 >68% non-elderly 18-65 years | | | | | | | |
| Cascinu 1994 | 50 | 0.3 (0.07) | 50 | 1.8 (2.12) | | 11.3 % | -1.50 [ -2.09, -0.91 ] |
| Engert 2009 | 637 | 3.7 (4.8) | 632 | 5.3 (5.7) | | 11.6 % | -1.60 [ -2.18, -1.02 ] |
| Kurz 1997 | 23 | 1.43 (3.8) | 12 | 3.7 (3.09) | | 0.7 % | -2.27 [ -4.61, 0.07 ] |
| Oberhoff 1998 | 114 | 1.32 (3.04) | 104 | 1.91 (3.28) | | 5.5 % | -0.59 [ -1.43, 0.25 ] |
| **Subtotal (95% CI)** | **824** | | **798** | | | **29.1 %** | **-1.39 [ -1.75, -1.02 ]** |
| Heterogeneity: $Chi^2$ = 4.65, df = 3 (P = 0.20); $I^2$ =35% | | | | | | | |
| Test for overall effect: Z = 7.42 (P < 0.00001) | | | | | | | |
| 4 only non-elderly adults | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| 5 >68% elderly >65 years | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| 6 only elderly > 65 J | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| **Total (95% CI)** | **2574** | | **2141** | | | **100.0 %** | **-0.98 [ -1.17, -0.78 ]** |
| Heterogeneity: $Chi^2$ = 34.52, df = 24 (P = 0.08); $I^2$ =30% | | | | | | | |
| Test for overall effect: Z = 9.69 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 6.78, df = 1 (P = 0.01), $I^2$ =85% | | | | | | | |



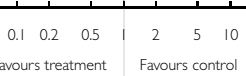
## Analysis 5.1. Comparison 5 Overall survival, Outcome 1 Overall survival - overall.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 5 Overall survival

Outcome: 1 Overall survival - overall

| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Aapro 2008 IPD | 169/231 | 169/232 | | 1.07 [ 0.87, 1.32 ] |
| Abels 1993 IPD | 13/65 | 12/59 | | 0.96 [ 0.44, 2.10 ] |
| Antonadou 2001 | 10/190 | 30/195 | | 0.35 [ 0.19, 0.66 ] |
| Bamias 2003 | 7/72 | 4/72 | | 1.80 [ 0.53, 6.12 ] |
| Blohmer 2011 | 25/127 | 29/129 | | 0.88 [ 0.51, 1.51 ] |
| Boogaerts 2003 IPD | 16/132 | 12/127 | | 1.53 [ 0.72, 3.26 ] |
| Cascinu 1994 | 0/50 | 0/50 | | 0.0 [ 0.0, 0.0 ] |
| Case 1993 IPD | 10/81 | 9/76 | | 1.11 [ 0.45, 2.73 ] |
| Cazzola 1995 IPD | 5/114 | 3/29 | | 0.69 [ 0.13, 3.57 ] |
| Chang 2005 IPD | 27/176 | 28/178 | | 0.94 [ 0.55, 1.60 ] |
| Charu 2007 IPD | 8/228 | 2/59 | | 0.89 [ 0.19, 4.18 ] |
| Christodoulou 2009 | 71/167 | 87/170 | | 1.25 [ 0.92, 1.71 ] |
| Dammacco 2001 IPD | 1/69 | 7/76 | | 0.23 [ 0.06, 0.90 ] |
| Debus 2006 IPD | 146/195 | 159/190 | | 0.81 [ 0.64, 1.02 ] |
| Del Mastro 1997 | 1/31 | 3/31 | | 0.36 [ 0.05, 2.53 ] |
| Dunphy 1999 | 0/15 | 1/15 | | 0.14 [ 0.00, 6.82 ] |
| Engert 2010 | 27/648 | 36/655 | | 0.74 [ 0.45, 1.22 ] |
| EPO-GER-20 IPD | 7/48 | 8/45 | | 0.71 [ 0.26, 1.95 ] |
| EPO-INT-1 IPD | 11/165 | 3/81 | | 1.88 [ 0.63, 5.64 ] |
| EPO-INT-3 IPD | 9/135 | 3/65 | | 1.55 [ 0.47, 5.10 ] |
| Fujisaka 2011 | 37/89 | 34/92 | | 1.15 [ 0.72, 1.85 ] |
| Gordon 2008 IPD | 11/164 | 5/56 | | 0.74 [ 0.26, 2.14 ] |
| Goss 2005 IPD | 28/52 | 29/52 | | 1.13 [ 0.67, 1.91 ] |
| Grote 2005 IPD | 100/109 | 101/115 | | 1.17 [ 0.89, 1.54 ] |
| Gupta 2009 | 17/58 | 14/57 | | 0.90 [ 0.51, 1.59 ] |

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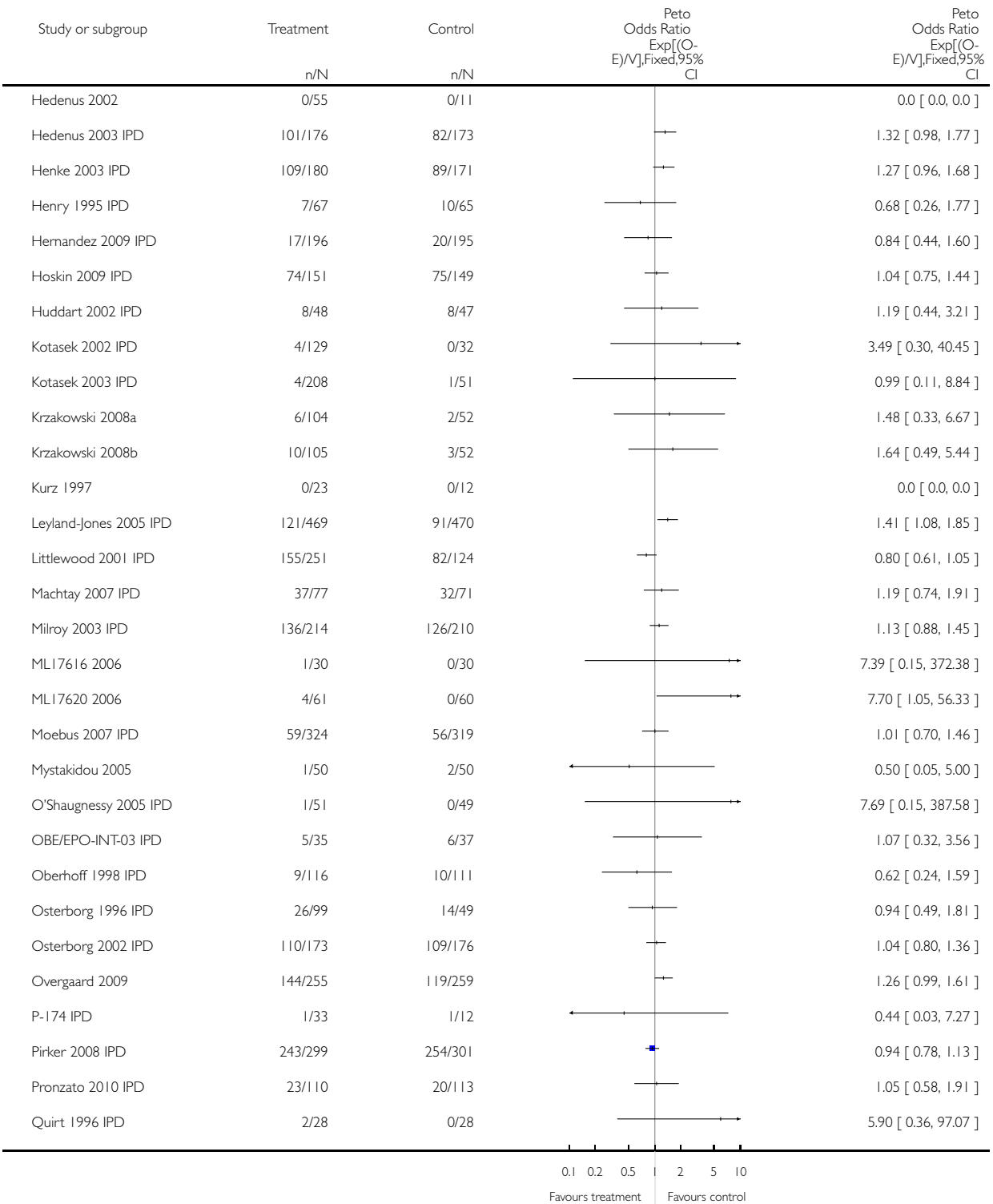


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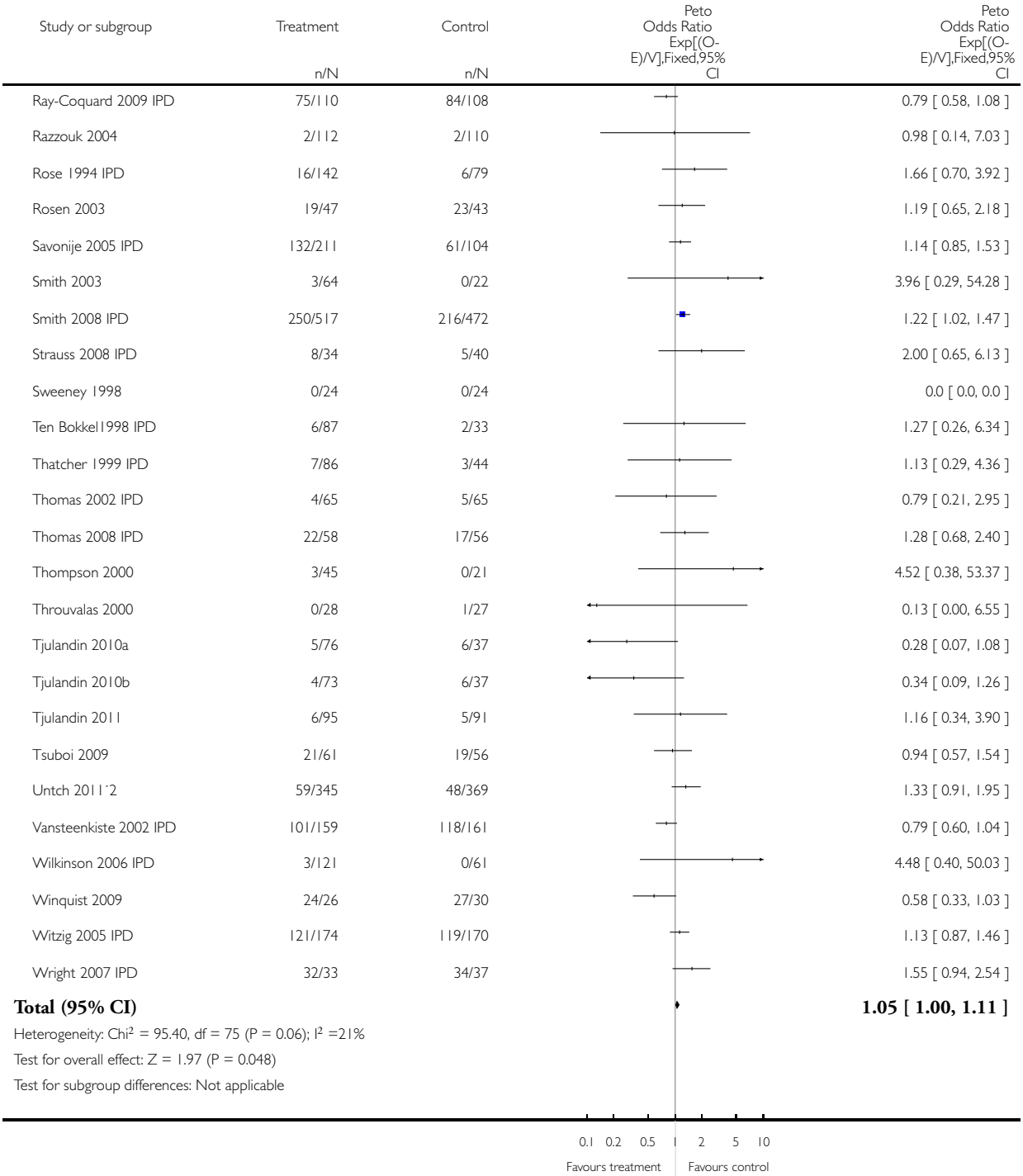


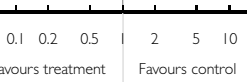
## Analysis 5.2. Comparison 5 Overall survival, Outcome 2 Overall survival updated review (adjusted results).

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 5 Overall survival

Outcome: 2 Overall survival updated review (adjusted results)

| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Aapro 2008 IPD | 169/231 | 169/232 | | 1.07 [ 0.87, 1.32 ] |
| Abels 1993 IPD | 13/65 | 12/59 | | 0.96 [ 0.44, 2.10 ] |
| Antonadou 2001 | 10/190 | 30/195 | | 0.35 [ 0.19, 0.66 ] |
| Bamias 2003 | 7/72 | 4/72 | | 1.80 [ 0.53, 6.12 ] |
| Blohmer 2011 | 25/127 | 29/129 | | 0.88 [ 0.51, 1.51 ] |
| Boogaerts 2003 IPD | 16/132 | 12/127 | | 1.53 [ 0.72, 3.26 ] |
| Cascinu 1994 | 0/50 | 0/50 | | 0.0 [ 0.0, 0.0 ] |
| Case 1993 IPD | 10/81 | 9/76 | | 1.11 [ 0.45, 2.73 ] |
| Cazzola 1995 IPD | 5/114 | 3/29 | | 0.69 [ 0.13, 3.57 ] |
| Chang 2005 IPD | 27/176 | 28/178 | | 0.94 [ 0.55, 1.60 ] |
| Charu 2007 IPD | 8/228 | 2/59 | | 0.89 [ 0.19, 4.18 ] |
| Christodoulou 2009 | 71/167 | 87/170 | | 1.25 [ 0.92, 1.71 ] |
| Dammacco 2001 IPD | 1/69 | 7/76 | | 0.23 [ 0.06, 0.90 ] |
| Debus 2006 IPD | 146/195 | 159/190 | | 0.81 [ 0.64, 1.02 ] |
| Del Mastro 1997 | 1/31 | 3/31 | | 0.36 [ 0.05, 2.53 ] |
| Dunphy 1999 | 0/15 | 1/15 | | 0.14 [ 0.00, 6.82 ] |
| Engert 2010 | 27/648 | 36/655 | | 0.74 [ 0.45, 1.22 ] |
| EPO-GER-20 IPD | 7/48 | 8/45 | | 0.71 [ 0.26, 1.95 ] |
| EPO-INT-1 IPD | 11/165 | 3/81 | | 1.88 [ 0.63, 5.64 ] |
| EPO-INT-3 IPD | 9/135 | 3/65 | | 1.55 [ 0.47, 5.10 ] |
| Fujisaka 2011 | 37/89 | 34/92 | | 1.15 [ 0.72, 1.85 ] |
| Gordon 2008 IPD | 11/164 | 5/56 | | 0.74 [ 0.26, 2.14 ] |
| Goss 2005 IPD | 28/52 | 29/52 | | 1.13 [ 0.67, 1.91 ] |
| Grote 2005 IPD | 100/109 | 101/115 | | 1.17 [ 0.89, 1.54 ] |
| Gupta 2009 | 17/58 | 14/57 | | 0.90 [ 0.51, 1.59 ] |

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| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Hedenus 2002 | 0/55 | 0/11 | | 0.0 [ 0.0, 0.0 ] |
| Hedenus 2003 IPD | 101/176 | 82/173 | | 1.32 [ 0.98, 1.77 ] |
| Henke 2003 | 109/180 | 89/171 | | 1.39 [ 1.05, 1.84 ] |
| Henry 1995 IPD | 7/67 | 10/65 | | 0.68 [ 0.26, 1.77 ] |
| Hernandez 2009 IPD | 17/196 | 20/195 | | 0.84 [ 0.44, 1.60 ] |
| Hoskin 2009 IPD | 74/151 | 75/149 | | 1.04 [ 0.75, 1.44 ] |
| Huddart 2002 IPD | 8/48 | 8/47 | | 1.19 [ 0.44, 3.21 ] |
| Kotasek 2002 IPD | 4/129 | 0/32 | | 3.49 [ 0.30, 40.45 ] |
| Kotasek 2003 IPD | 4/208 | 1/51 | | 0.99 [ 0.11, 8.84 ] |
| Krzakowski 2008a | 6/104 | 2/52 | | 1.48 [ 0.33, 6.67 ] |
| Krzakowski 2008b | 10/105 | 3/52 | | 1.64 [ 0.49, 5.44 ] |
| Kurz 1997 | 0/23 | 0/12 | | 0.0 [ 0.0, 0.0 ] |
| Leyland-Jones 2005 IPD | 121/469 | 91/470 | | 1.41 [ 1.08, 1.85 ] |
| Littlewood 2001 | 155/251 | 82/124 | | 0.76 [ 0.58, 1.00 ] |
| Machtay 2007 IPD | 37/77 | 32/71 | | 1.19 [ 0.74, 1.91 ] |
| Milroy 2003 IPD | 136/214 | 126/210 | | 1.13 [ 0.88, 1.45 ] |
| ML17616 2006 | 1/30 | 0/30 | | 7.39 [ 0.15, 372.38 ] |
| ML17620 2006 | 4/61 | 0/60 | | 7.70 [ 1.05, 56.33 ] |
| Moebus 2007 IPD | 59/324 | 56/319 | | 1.01 [ 0.70, 1.46 ] |
| Mystakidou 2005 | 1/50 | 2/50 | | 0.50 [ 0.05, 5.00 ] |
| O'Shaugnessy 2005 IPD | 1/51 | 0/49 | | 7.69 [ 0.15, 387.58 ] |
| OBE/EPO-INT-03 IPD | 5/35 | 6/37 | | 1.07 [ 0.32, 3.56 ] |
| Oberhoff 1998 IPD | 9/116 | 10/111 | | 0.62 [ 0.24, 1.59 ] |
| Osterborg 1996 IPD | 26/99 | 14/49 | | 0.94 [ 0.49, 1.81 ] |
| Osterborg 2002 IPD | 110/173 | 109/176 | | 1.04 [ 0.80, 1.36 ] |
| Overgaard 2009 | 144/255 | 119/259 | | 1.26 [ 0.99, 1.61 ] |
| P-174 IPD | 1/33 | 1/12 | | 0.44 [ 0.03, 7.27 ] |
| Pirker 2008 IPD | 243/299 | 254/301 | | 0.94 [ 0.78, 1.13 ] |
| Pronzato 2010 IPD | 23/110 | 20/113 | | 1.05 [ 0.58, 1.91 ] |
| Quirt 1996 IPD | 2/28 | 0/28 | | 5.90 [ 0.36, 97.07 ] |


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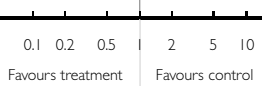
| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Ray-Coquard 2009 IPD | 75/110 | 84/108 | | 0.79 [ 0.58, 1.08 ] |
| Razzouk 2004 | 2/112 | 2/110 | | 0.98 [ 0.14, 7.03 ] |
| Rose 1994 IPD | 16/142 | 6/79 | | 1.66 [ 0.70, 3.92 ] |
| Rosen 2003 | 19/47 | 23/43 | | 1.19 [ 0.65, 2.18 ] |
| Savonije 2005 IPD | 132/211 | 61/104 | | 1.14 [ 0.85, 1.53 ] |
| Smith 2003 | 3/64 | 0/22 | | 3.96 [ 0.29, 54.28 ] |
| Smith 2008 IPD | 250/517 | 216/472 | | 1.22 [ 1.02, 1.47 ] |
| Strauss 2008 IPD | 8/34 | 5/40 | | 2.00 [ 0.65, 6.13 ] |
| Sweeney 1998 | 0/24 | 0/24 | | 0.0 [ 0.0, 0.0 ] |
| Ten Bokkel1998 IPD | 6/87 | 2/33 | | 1.27 [ 0.26, 6.34 ] |
| Thatcher 1999 IPD | 7/86 | 3/44 | | 1.13 [ 0.29, 4.36 ] |
| Thomas 2002 IPD | 4/65 | 5/65 | | 0.79 [ 0.21, 2.95 ] |
| Thomas 2008 IPD | 22/58 | 17/56 | | 1.28 [ 0.68, 2.40 ] |
| Thompson 2000 | 3/45 | 0/21 | | 4.52 [ 0.38, 53.37 ] |
| Throuvalas 2000 | 0/28 | 1/27 | | 0.13 [ 0.00, 6.55 ] |
| Tjulandin 2010a | 5/76 | 6/37 | | 0.28 [ 0.07, 1.08 ] |
| Tjulandin 2010b | 4/73 | 6/37 | | 0.34 [ 0.09, 1.26 ] |
| Tjulandin 2011 | 6/95 | 5/91 | | 1.16 [ 0.34, 3.90 ] |
| Tsuboi 2009 | 21/61 | 19/56 | | 0.94 [ 0.57, 1.54 ] |
| Untch 2011˙2 | 59/345 | 48/369 | | 1.33 [ 0.91, 1.95 ] |
| Vansteenkiste 2002 IPD | 101/159 | 118/161 | | 0.79 [ 0.60, 1.04 ] |
| Wilkinson 2006 IPD | 3/121 | 0/61 | | 4.48 [ 0.40, 50.03 ] |
| Winquist 2009 | 24/26 | 27/30 | | 0.58 [ 0.33, 1.03 ] |
| Witzig 2005 IPD | 121/174 | 119/170 | | 1.13 [ 0.87, 1.46 ] |
| Wright 2007 IPD | 32/33 | 34/37 | | 1.55 [ 0.94, 2.54 ] |
| **Total (95% CI)** | | | | **1.05 [ 1.00, 1.11 ]** |

Heterogeneity: Chi² = 99.00, df = 75 (P = 0.03); I² =24%

Test for overall effect: Z = 2.01 (P = 0.044)

Test for subgroup differences: Not applicable

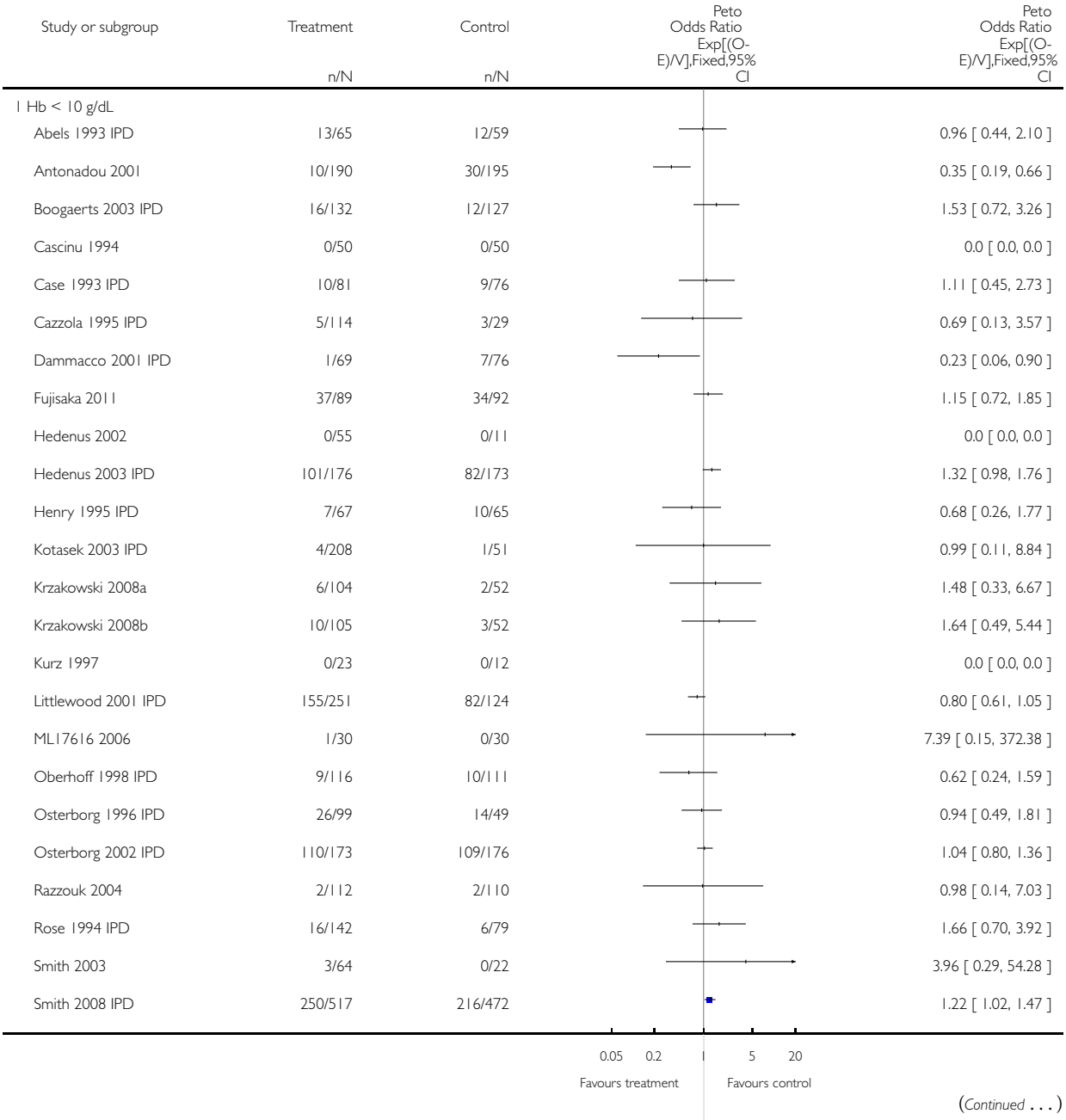


## Analysis 5.3. Comparison 5 Overall survival, Outcome 3 Overall survival - baseline Hb.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 5 Overall survival

Outcome: 3 Overall survival - baseline Hb

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| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Thompson 2000 | 3/45 | 0/21 | | 4.52 [ 0.38, 53.37 ] |
| Tjulandin 2010a | 5/76 | 6/37 | | 0.28 [ 0.07, 1.08 ] |
| Tjulandin 2010b | 4/73 | 6/37 | | 0.34 [ 0.09, 1.26 ] |
| Tjulandin 2011 | 6/95 | 5/91 | | 1.16 [ 0.34, 3.90 ] |
| Witzig 2005 IPD | 121/174 | 119/170 | | 1.13 [ 0.87, 1.46 ] |
| **Subtotal (95% CI)** | **3495** | **2649** | | **1.06 [ 0.96, 1.17 ]** |
| Heterogeneity: $Chi^2$ = 40.70, df = 25 (P = 0.02); $I^2$ =39% | | | | |
| Test for overall effect: Z = 1.13 (P = 0.26) | | | | |
| 2 Hb 10 to 12 g/dL | | | | |
| Aapro 2008 IPD | 169/231 | 169/232 | | 1.07 [ 0.87, 1.32 ] |
| Bamias 2003 | 7/72 | 4/72 | | 1.80 [ 0.53, 6.12 ] |
| Blohmer 2011 | 25/127 | 29/129 | | 0.88 [ 0.51, 1.51 ] |
| Chang 2005 IPD | 27/176 | 28/178 | | 0.94 [ 0.55, 1.60 ] |
| Charu 2007 IPD | 8/228 | 2/59 | | 0.89 [ 0.19, 4.18 ] |
| Christodoulou 2009 | 71/167 | 87/170 | | 1.25 [ 0.92, 1.71 ] |
| EPO-INT-1 IPD | 11/165 | 3/81 | | 1.88 [ 0.63, 5.64 ] |
| EPO-INT-3 IPD | 9/135 | 3/65 | | 1.55 [ 0.47, 5.10 ] |
| Gordon 2008 IPD | 11/164 | 5/56 | | 0.74 [ 0.26, 2.14 ] |
| Gupta 2009 | 17/58 | 14/57 | | 0.90 [ 0.51, 1.59 ] |
| Henke 2003 IPD | 109/180 | 89/171 | | 1.27 [ 0.96, 1.68 ] |
| Hernandez 2009 IPD | 17/196 | 20/195 | | 0.84 [ 0.44, 1.60 ] |
| Huddart 2002 IPD | 8/48 | 8/47 | | 1.19 [ 0.44, 3.21 ] |
| Kotasek 2002 IPD | 4/129 | 0/32 | | 3.49 [ 0.30, 40.45 ] |
| Mystakidou 2005 | 1/50 | 2/50 | | 0.50 [ 0.05, 5.00 ] |
| Pirker 2008 IPD | 243/299 | 254/301 | | 0.94 [ 0.78, 1.13 ] |
| Pronzato 2010 IPD | 23/110 | 20/113 | | 1.05 [ 0.58, 1.91 ] |
| Quirt 1996 IPD | 2/28 | 0/28 | | 5.90 [ 0.36, 97.07 ] |
| Ray-Coquard 2009 IPD | 75/110 | 84/108 | | 0.79 [ 0.58, 1.08 ] |
| Savonije 2005 IPD | 132/211 | 61/104 | | 1.14 [ 0.85, 1.53 ] |
| Strauss 2008 IPD | 8/34 | 5/40 | | 2.00 [ 0.65, 6.13 ] |
| Sweeney 1998 | 0/24 | 0/24 | | 0.0 [ 0.0, 0.0 ] |
| Ten Bokkel1998 IPD | 6/87 | 2/33 | | 1.27 [ 0.26, 6.34 ] |


(*Continued* . . . )

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| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Thomas 2002 IPD | 4/65 | 5/65 | | 0.79 [ 0.21, 2.95 ] |
| Thomas 2008 IPD | 22/58 | 17/56 | | 1.28 [ 0.68, 2.40 ] |
| Throuvalas 2000 | 0/28 | 1/27 | | 0.13 [ 0.00, 6.55 ] |
| Tsuboi 2009 | 21/61 | 19/56 | | 0.94 [ 0.57, 1.54 ] |
| Vansteenkiste 2002 IPD | 101/159 | 118/161 | | 0.79 [ 0.60, 1.04 ] |
| Wilkinson 2006 IPD | 3/121 | 0/61 | | 4.48 [ 0.40, 50.03 ] |
| Winquist 2009 | 24/26 | 27/30 | | 0.58 [ 0.33, 1.03 ] |
| Wright 2007 IPD | 32/33 | 34/37 | | 1.55 [ 0.94, 2.54 ] |
| **Subtotal (95% CI)** | **3580** | **2838** | | **1.01 [ 0.93, 1.10 ]** |
| Heterogeneity: Chi² = 29.34, df = 29 (P = 0.45); I² =1% | | | | |
| Test for overall effect: Z = 0.33 (P = 0.74) | | | | |
| 3 Hb > 12 g/dL | | | | |
| Del Mastro 1997 | 1/31 | 3/31 | | 0.36 [ 0.05, 2.53 ] |
| Dunphy 1999 | 0/15 | 1/15 | | 0.14 [ 0.00, 6.82 ] |
| Engert 2010 | 27/648 | 36/655 | | 0.74 [ 0.45, 1.22 ] |
| Goss 2005 IPD | 28/52 | 29/52 | | 1.13 [ 0.67, 1.91 ] |
| Grote 2005 IPD | 100/109 | 101/115 | | 1.17 [ 0.89, 1.54 ] |
| Hoskin 2009 IPD | 74/151 | 75/149 | | 1.04 [ 0.75, 1.44 ] |
| Leyland-Jones 2005 IPD | 121/469 | 91/470 | | 1.41 [ 1.08, 1.85 ] |
| Machtay 2007 IPD | 37/77 | 32/71 | | 1.19 [ 0.74, 1.91 ] |
| Milroy 2003 IPD | 136/214 | 126/210 | | 1.13 [ 0.88, 1.45 ] |
| Moebus 2007 IPD | 59/324 | 56/319 | | 1.01 [ 0.70, 1.46 ] |
| O'Shaugnessy 2005 IPD | 1/51 | 0/49 | | 7.69 [ 0.15, 387.58 ] |
| Overgaard 2009 | 144/255 | 119/259 | | 1.26 [ 0.99, 1.61 ] |
| Rosen 2003 | 19/47 | 23/43 | | 1.19 [ 0.65, 2.18 ] |
| Thatcher 1999 IPD | 7/86 | 3/44 | | 1.13 [ 0.29, 4.36 ] |
| Untch 2011˙2 | 59/345 | 48/369 | | 1.33 [ 0.91, 1.95 ] |
| **Subtotal (95% CI)** | **2874** | **2851** | | **1.17 [ 1.06, 1.29 ]** |
| Heterogeneity: Chi² = 10.57, df = 14 (P = 0.72); I² =0.0% | | | | |
| Test for overall effect: Z = 3.02 (P = 0.0025) | | | | |
| 4 unclear | | | | |
| Debus 2006 IPD | 146/195 | 159/190 | | 0.81 [ 0.64, 1.02 ] |
| EPO-GER-20 IPD | 7/48 | 8/45 | | 0.71 [ 0.26, 1.95 ] |


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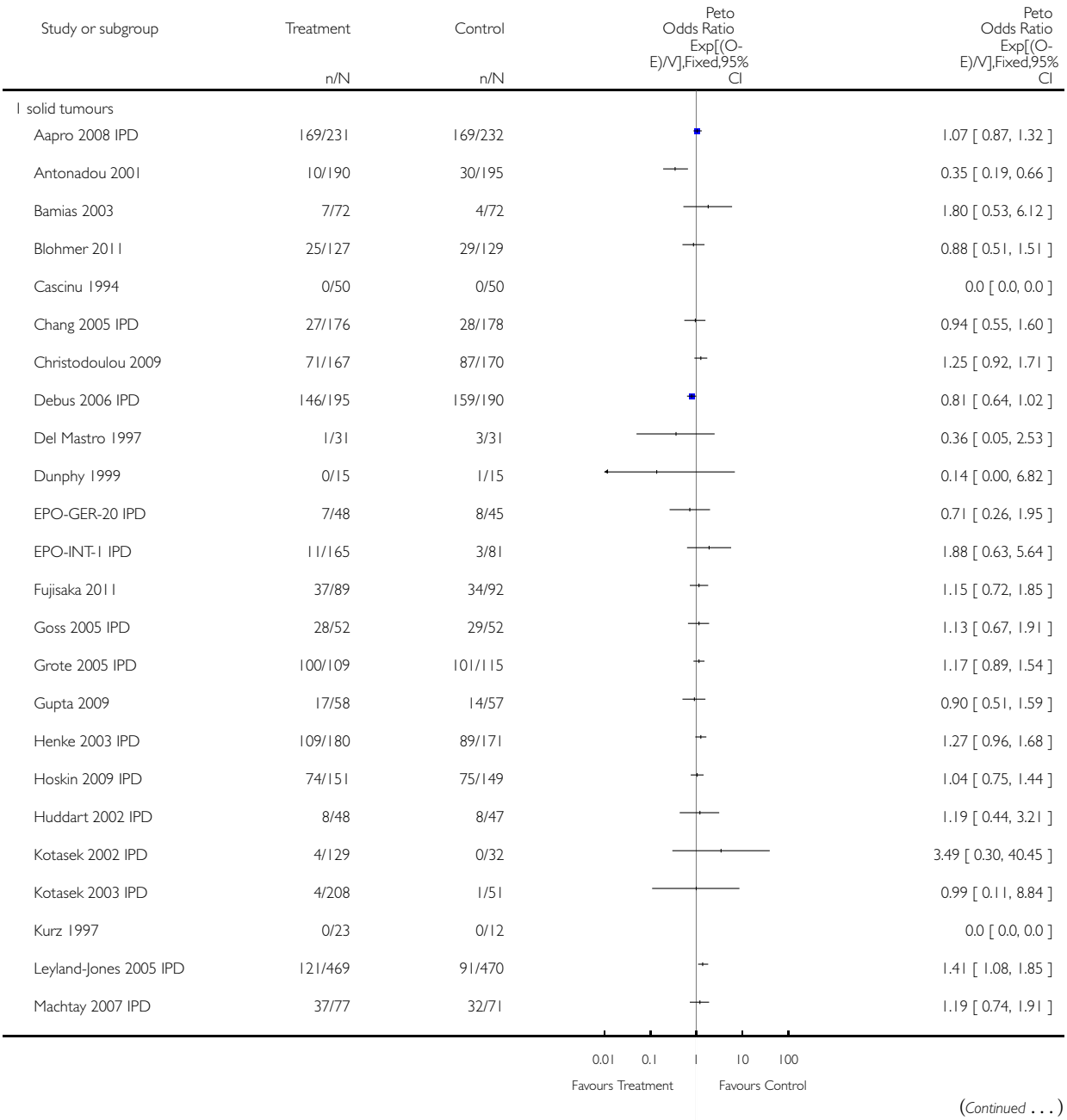
| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| ML17620 2006 | 4/61 | 0/60 | | 7.70 [ 1.05, 56.33 ] |
| OBE/EPO-INT-03 IPD | 5/35 | 6/37 | | 1.07 [ 0.32, 3.56 ] |
| P-174 IPD | 1/33 | 1/12 | | 0.44 [ 0.03, 7.27 ] |
| **Subtotal (95% CI)** | **372** | **344** | | **0.83 [ 0.67, 1.03 ]** |
| Heterogeneity: $Chi^2$ = 5.32, df = 4 (P = 0.26); $I^2$ =25% | | | | |
| Test for overall effect: Z = 1.67 (P = 0.095) | | | | |
| **Total (95% CI)** | | | | **1.05 [ 1.00, 1.11 ]** |
| Heterogeneity: $Chi^2$ = 95.36, df = 75 (P = 0.06); $I^2$ =21% | | | | |
| Test for overall effect: Z = 1.97 (P = 0.048) | | | | |
| Test for subgroup differences: $Chi^2$ = 9.43, df = 3 (P = 0.02), $I^2$ =68% | | | | |

## Analysis 5.4. Comparison 5 Overall survival, Outcome 4 Overall survival - different malignancies.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 5 Overall survival

Outcome: 4 Overall survival - different malignancies



| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| 1 solid tumours | | | | |
| Aapro 2008 IPD | 169/231 | 169/232 | | 1.07 [ 0.87, 1.32 ] |
| Antonadou 2001 | 10/190 | 30/195 | | 0.35 [ 0.19, 0.66 ] |
| Bamias 2003 | 7/72 | 4/72 | | 1.80 [ 0.53, 6.12 ] |
| Blohmer 2011 | 25/127 | 29/129 | | 0.88 [ 0.51, 1.51 ] |
| Cascinu 1994 | 0/50 | 0/50 | | 0.0 [ 0.0, 0.0 ] |
| Chang 2005 IPD | 27/176 | 28/178 | | 0.94 [ 0.55, 1.60 ] |
| Christodoulou 2009 | 71/167 | 87/170 | | 1.25 [ 0.92, 1.71 ] |
| Debus 2006 IPD | 146/195 | 159/190 | | 0.81 [ 0.64, 1.02 ] |
| Del Mastro 1997 | 1/31 | 3/31 | | 0.36 [ 0.05, 2.53 ] |
| Dunphy 1999 | 0/15 | 1/15 | | 0.14 [ 0.00, 6.82 ] |
| EPO-GER-20 IPD | 7/48 | 8/45 | | 0.71 [ 0.26, 1.95 ] |
| EPO-INT-1 IPD | 11/165 | 3/81 | | 1.88 [ 0.63, 5.64 ] |
| Fujisaka 2011 | 37/89 | 34/92 | | 1.15 [ 0.72, 1.85 ] |
| Goss 2005 IPD | 28/52 | 29/52 | | 1.13 [ 0.67, 1.91 ] |
| Grote 2005 IPD | 100/109 | 101/115 | | 1.17 [ 0.89, 1.54 ] |
| Gupta 2009 | 17/58 | 14/57 | | 0.90 [ 0.51, 1.59 ] |
| Henke 2003 IPD | 109/180 | 89/171 | | 1.27 [ 0.96, 1.68 ] |
| Hoskin 2009 IPD | 74/151 | 75/149 | | 1.04 [ 0.75, 1.44 ] |
| Huddart 2002 IPD | 8/48 | 8/47 | | 1.19 [ 0.44, 3.21 ] |
| Kotasek 2002 IPD | 4/129 | 0/32 | | 3.49 [ 0.30, 40.45 ] |
| Kotasek 2003 IPD | 4/208 | 1/51 | | 0.99 [ 0.11, 8.84 ] |
| Kurz 1997 | 0/23 | 0/12 | | 0.0 [ 0.0, 0.0 ] |
| Leyland-Jones 2005 IPD | 121/469 | 91/470 | | 1.41 [ 1.08, 1.85 ] |
| Machtay 2007 IPD | 37/77 | 32/71 | | 1.19 [ 0.74, 1.91 ] |



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| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Milroy 2003 IPD | 136/214 | 126/210 | | 1.13 [ 0.88, 1.45 ] |
| ML17620 2006 | 4/61 | 0/60 | | 7.70 [ 1.05, 56.33 ] |
| Moebus 2007 IPD | 59/324 | 56/319 | | 1.01 [ 0.70, 1.46 ] |
| Mystakidou 2005 | 1/50 | 2/50 | | 0.50 [ 0.05, 5.00 ] |
| O'Shaugnessy 2005 IPD | 1/51 | 0/49 | | 7.69 [ 0.15, 387.58 ] |
| Oberhoff 1998 IPD | 9/116 | 10/111 | | 0.62 [ 0.24, 1.59 ] |
| Overgaard 2009 | 144/255 | 119/259 | | 1.26 [ 0.99, 1.61 ] |
| Pirker 2008 IPD | 243/299 | 254/301 | | 0.94 [ 0.78, 1.13 ] |
| Pronzato 2010 IPD | 23/110 | 20/113 | | 1.05 [ 0.58, 1.91 ] |
| Rosen 2003 | 19/47 | 23/43 | | 1.19 [ 0.65, 2.18 ] |
| Savonije 2005 IPD | 132/211 | 61/104 | | 1.14 [ 0.85, 1.53 ] |
| Strauss 2008 IPD | 8/34 | 5/40 | | 2.00 [ 0.65, 6.13 ] |
| Sweeney 1998 | 0/24 | 0/24 | | 0.0 [ 0.0, 0.0 ] |
| Ten Bokkel1998 IPD | 6/87 | 2/33 | | 1.27 [ 0.26, 6.34 ] |
| Thatcher 1999 IPD | 7/86 | 3/44 | | 1.13 [ 0.29, 4.36 ] |
| Thomas 2002 IPD | 4/65 | 5/65 | | 0.79 [ 0.21, 2.95 ] |
| Thomas 2008 IPD | 22/58 | 17/56 | | 1.28 [ 0.68, 2.40 ] |
| Throuvalas 2000 | 0/28 | 1/27 | | 0.13 [ 0.00, 6.55 ] |
| Tjulandin 2010a | 5/76 | 6/37 | | 0.28 [ 0.07, 1.08 ] |
| Tjulandin 2010b | 4/73 | 6/37 | | 0.34 [ 0.09, 1.26 ] |
| Untch 2011˙2 | 59/345 | 48/369 | | 1.33 [ 0.91, 1.95 ] |
| Vansteenkiste 2002 IPD | 101/159 | 118/161 | | 0.79 [ 0.60, 1.04 ] |
| Wilkinson 2006 IPD | 3/121 | 0/61 | | 4.48 [ 0.40, 50.03 ] |
| Winquist 2009 | 24/26 | 27/30 | | 0.58 [ 0.33, 1.03 ] |
| Witzig 2005 IPD | 121/174 | 119/170 | | 1.13 [ 0.87, 1.46 ] |
| Wright 2007 IPD | 32/33 | 34/37 | | 1.55 [ 0.94, 2.54 ] |
| **Subtotal (95% CI)** | **6187** | **5517** | | **1.06 [ 1.00, 1.13 ]** |
| Heterogeneity: Chi² = 66.13, df = 46 (P = 0.03); I² =30% | | | | |
| Test for overall effect: Z = 1.86 (P = 0.062) | | | | |
| 2 haematological malignancies | | | | |
| Cazzola 1995 IPD | 5/114 | 3/29 | | 0.69 [ 0.13, 3.57 ] |
| Dammacco 2001 IPD | 1/69 | 7/76 | | 0.23 [ 0.06, 0.90 ] |


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| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Engert 2010 | 27/648 | 36/655 | | 0.74 [ 0.45, 1.22 ] |
| Hedenus 2002 | 0/55 | 0/11 | | 0.0 [ 0.0, 0.0 ] |
| Hedenus 2003 IPD | 101/176 | 82/173 | | 1.32 [ 0.98, 1.77 ] |
| ML17616 2006 | 1/30 | 0/30 | | 7.39 [ 0.15, 372.38 ] |
| OBE/EPO-INT-03 IPD | 5/35 | 6/37 | | 1.07 [ 0.32, 3.56 ] |
| Osterborg 1996 IPD | 26/99 | 14/49 | | 0.94 [ 0.49, 1.81 ] |
| Osterborg 2002 IPD | 110/173 | 109/176 | | 1.04 [ 0.80, 1.36 ] |
| P-174 IPD | 1/33 | 1/12 | | 0.44 [ 0.03, 7.27 ] |
| Rose 1994 IPD | 16/142 | 6/79 | | 1.66 [ 0.70, 3.92 ] |
| **Subtotal (95% CI)** | **1574** | **1327** | | **1.07 [ 0.90, 1.26 ]** |
| Heterogeneity: $Chi^2$ = 11.73, df = 9 (P = 0.23); $I^2$ =23% | | | | |
| Test for overall effect: Z = 0.75 (P = 0.45) | | | | |
| 3 MDS | | | | |
| Thompson 2000 | 3/45 | 0/21 | | 4.52 [ 0.38, 53.37 ] |
| **Subtotal (95% CI)** | **45** | **21** | | **4.52 [ 0.38, 53.37 ]** |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: Z = 1.20 (P = 0.23) | | | | |
| 4 mixed | | | | |
| Abels 1993 IPD | 13/65 | 12/59 | | 0.96 [ 0.44, 2.10 ] |
| Boogaerts 2003 IPD | 16/132 | 12/127 | | 1.53 [ 0.72, 3.26 ] |
| Case 1993 IPD | 10/81 | 9/76 | | 1.11 [ 0.45, 2.73 ] |
| Charu 2007 IPD | 8/228 | 2/59 | | 0.89 [ 0.19, 4.18 ] |
| EPO-INT-3 IPD | 9/135 | 3/65 | | 1.55 [ 0.47, 5.10 ] |
| Gordon 2008 IPD | 11/164 | 5/56 | | 0.74 [ 0.26, 2.14 ] |
| Henry 1995 IPD | 7/67 | 10/65 | | 0.68 [ 0.26, 1.77 ] |
| Hernandez 2009 IPD | 17/196 | 20/195 | | 0.84 [ 0.44, 1.60 ] |
| Krzakowski 2008a | 6/104 | 2/52 | | 1.48 [ 0.33, 6.67 ] |
| Krzakowski 2008b | 10/105 | 3/52 | | 1.64 [ 0.49, 5.44 ] |
| Littlewood 2001 IPD | 155/251 | 82/124 | | 0.80 [ 0.61, 1.05 ] |
| Quirt 1996 IPD | 2/28 | 0/28 | | 5.90 [ 0.36, 97.07 ] |
| Ray-Coquard 2009 IPD | 75/110 | 84/108 | | 0.79 [ 0.58, 1.08 ] |
| Razzouk 2004 | 2/112 | 2/110 | | 0.98 [ 0.14, 7.03 ] |
| Smith 2003 | 3/64 | 0/22 | | 3.96 [ 0.29, 54.28 ] |


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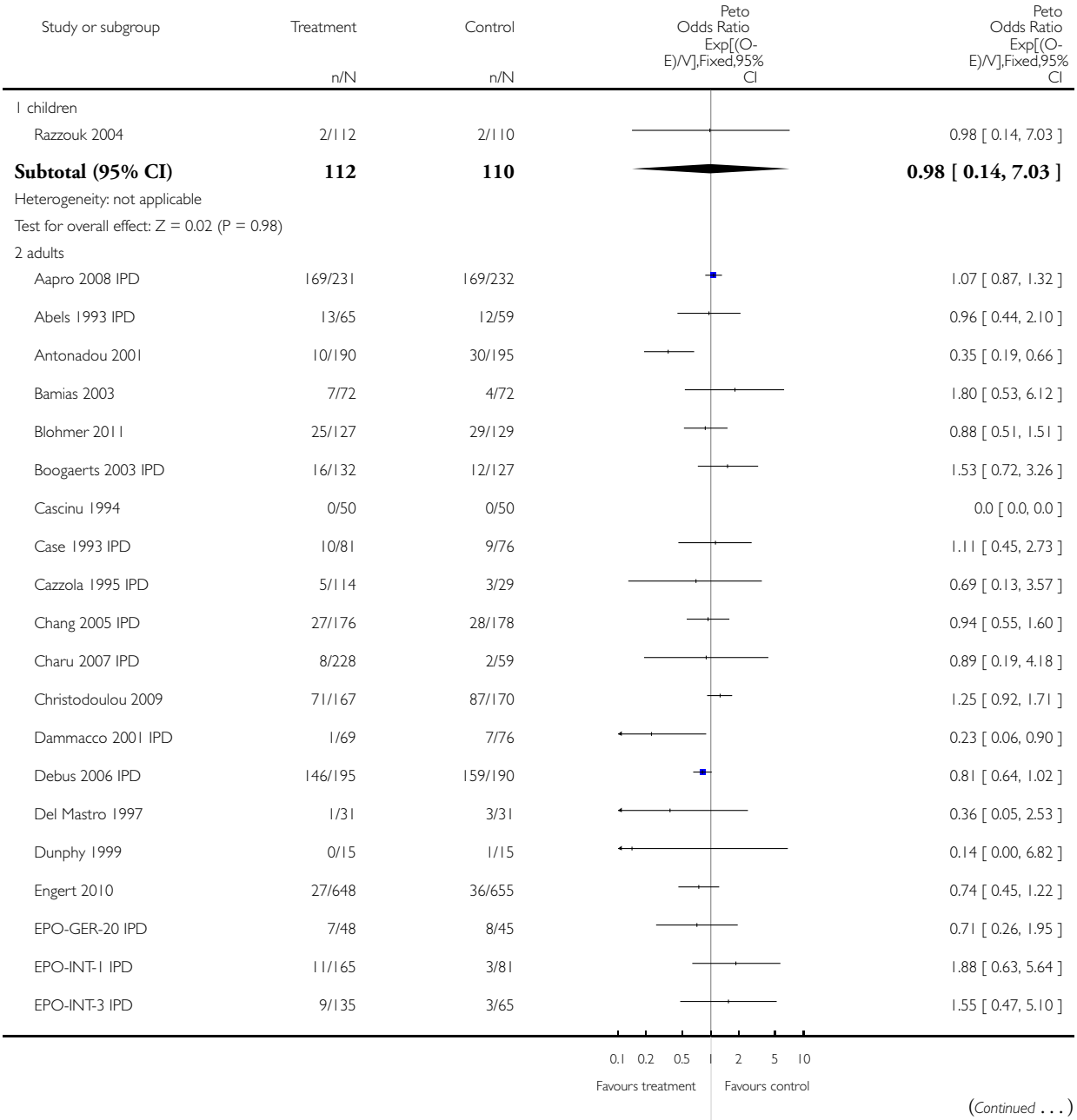
| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Smith 2008 IPD | 250/517 | 216/472 | | 1.22 [ 1.02, 1.47 ] |
| Tjulandin 2011 | 6/95 | 5/91 | | 1.16 [ 0.34, 3.90 ] |
| Tsuboi 2009 | 21/61 | 19/56 | | 0.94 [ 0.57, 1.54 ] |
| **Subtotal (95% CI)** | **2515** | **1817** | | **1.02 [ 0.91, 1.15 ]** |
| Heterogeneity: $Chi^2$ = 15.87, df = 17 (P = 0.53); $I^2$ =0.0% | | | | |
| Test for overall effect: Z = 0.32 (P = 0.75) | | | | |
| 5 not reported | | | | |
| **Subtotal (95% CI)** | **0** | **0** | | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: not applicable | | | | |
| **Total (95% CI)** | | | | **1.05 [ 1.00, 1.11 ]** |
| Heterogeneity: $Chi^2$ = 95.40, df = 75 (P = 0.06); $I^2$ =21% | | | | |
| Test for overall effect: Z = 1.97 (P = 0.048) | | | | |
| Test for subgroup differences: $Chi^2$ = 1.67, df = 3 (P = 0.64), $I^2$ =0.0% | | | | |

## Analysis 5.5. Comparison 5 Overall survival, Outcome 5 Overall survival - age.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 5 Overall survival

Outcome: 5 Overall survival - age

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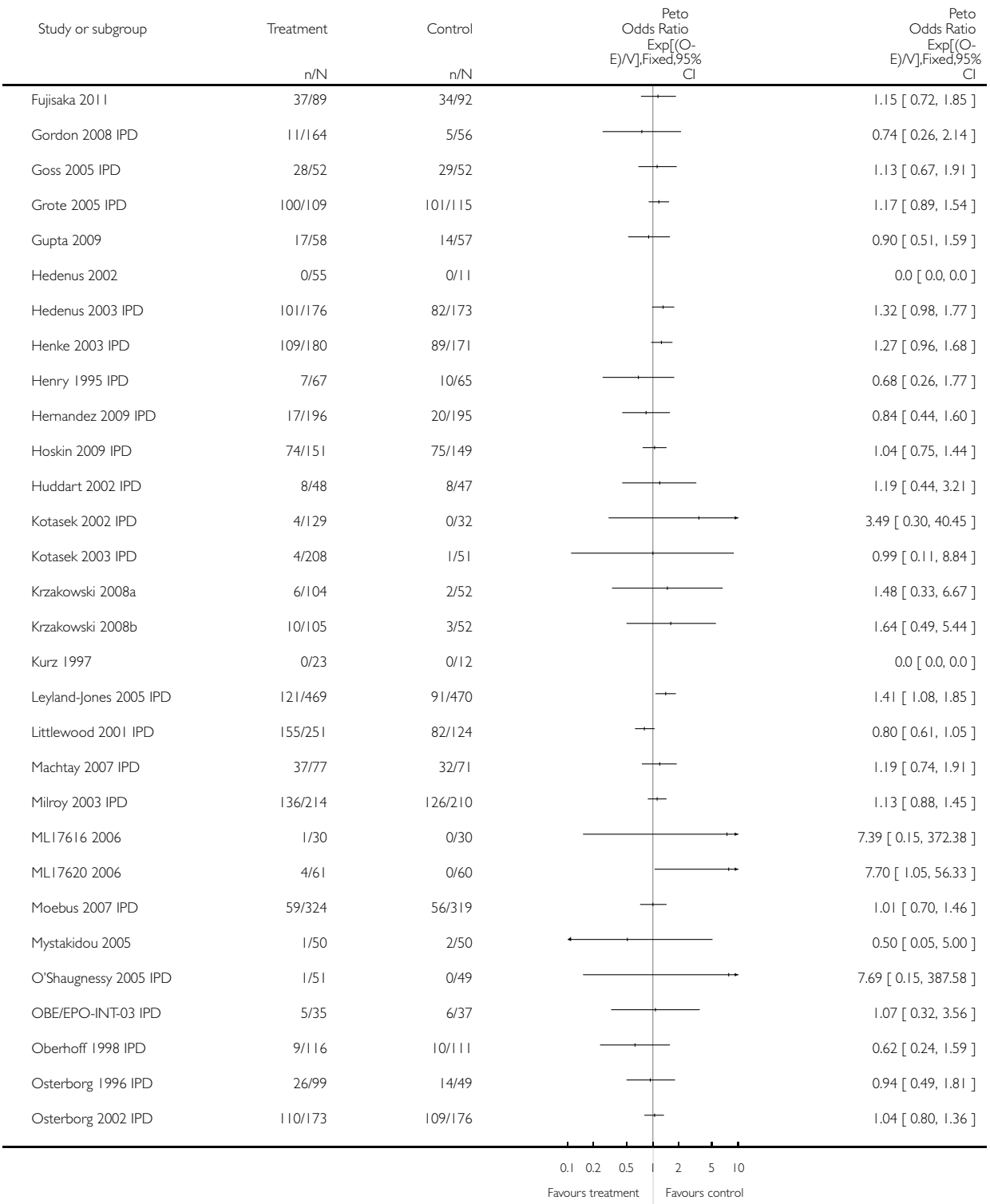


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| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Overgaard 2009 | 144/255 | 119/259 | | 1.26 [ 0.99, 1.61 ] |
| P-174 IPD | 1/33 | 1/12 | | 0.44 [ 0.03, 7.27 ] |
| Pirker 2008 IPD | 243/299 | 254/301 | | 0.94 [ 0.78, 1.13 ] |
| Pronzato 2010 IPD | 23/110 | 20/113 | | 1.05 [ 0.58, 1.91 ] |
| Quirt 1996 IPD | 2/28 | 0/28 | | 5.90 [ 0.36, 97.07 ] |
| Ray-Coquard 2009 IPD | 75/110 | 84/108 | | 0.79 [ 0.58, 1.08 ] |
| Rose 1994 IPD | 16/142 | 6/79 | | 1.66 [ 0.70, 3.92 ] |
| Rosen 2003 | 19/47 | 23/43 | | 1.19 [ 0.65, 2.18 ] |
| Savonije 2005 IPD | 132/211 | 61/104 | | 1.14 [ 0.85, 1.53 ] |
| Smith 2003 | 3/64 | 0/22 | | 3.96 [ 0.29, 54.28 ] |
| Smith 2008 IPD | 250/517 | 216/472 | | 1.22 [ 1.02, 1.47 ] |
| Strauss 2008 IPD | 8/34 | 5/40 | | 2.00 [ 0.65, 6.13 ] |
| Sweeney 1998 | 0/24 | 0/24 | | 0.0 [ 0.0, 0.0 ] |
| Ten Bokkel1998 IPD | 6/87 | 2/33 | | 1.27 [ 0.26, 6.34 ] |
| Thatcher 1999 IPD | 7/86 | 3/44 | | 1.13 [ 0.29, 4.36 ] |
| Thomas 2002 IPD | 4/65 | 5/65 | | 0.79 [ 0.21, 2.95 ] |
| Thomas 2008 IPD | 22/58 | 17/56 | | 1.28 [ 0.68, 2.40 ] |
| Thompson 2000 | 3/45 | 0/21 | | 4.52 [ 0.38, 53.37 ] |
| Throuvalas 2000 | 0/28 | 1/27 | | 0.13 [ 0.00, 6.55 ] |
| Tjulandin 2010a | 5/76 | 6/37 | | 0.28 [ 0.07, 1.08 ] |
| Tjulandin 2010b | 4/73 | 6/37 | | 0.34 [ 0.09, 1.26 ] |
| Tjulandin 2011 | 6/95 | 5/91 | | 1.16 [ 0.34, 3.90 ] |
| Tsuboi 2009 | 21/61 | 19/56 | | 0.94 [ 0.57, 1.54 ] |
| Untch 2011˙2 | 59/345 | 48/369 | | 1.33 [ 0.91, 1.95 ] |
| Vansteenkiste 2002 IPD | 101/159 | 118/161 | | 0.79 [ 0.60, 1.04 ] |
| Wilkinson 2006 IPD | 3/121 | 0/61 | | 4.48 [ 0.40, 50.03 ] |
| Winquist 2009 | 24/26 | 27/30 | | 0.58 [ 0.33, 1.03 ] |
| Witzig 2005 IPD | 121/174 | 119/170 | | 1.13 [ 0.87, 1.46 ] |
| Wright 2007 IPD | 32/33 | 34/37 | | 1.55 [ 0.94, 2.54 ] |
| **Subtotal (95% CI)** | **10209** | **8572** | | **1.05 [ 1.00, 1.11 ]** |
| Heterogeneity: $Chi^2$ = 95.39, df = 74 (P = 0.05); $I^2$ =22% | | | | |


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| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Test for overall effect: Z = 1.98 (P = 0.048) | | | | |
| **Total (95% CI)** | | | | **1.05 [ 1.00, 1.11 ]** |
| Heterogeneity: $Chi^2$ = 95.40, df = 75 (P = 0.06); $I^2$ =21% | | | | |
| Test for overall effect: Z = 1.97 (P = 0.048) | | | | |
| Test for subgroup differences: $Chi^2$ = 0.01, df = 1 (P = 0.94), $I^2$ =0.0% | | | | |


### Analysis 5.6. Comparison 5 Overall survival, Outcome 6 Overall survival - age differentiated.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 5 Overall survival

Outcome: 6 Overall survival - age differentiated

| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| 1 only children < 18 | | | | |
| Razzouk 2004 | 2/112 | 2/110 | | 0.98 [ 0.14, 7.03 ] |
| **Subtotal (95% CI)** | **112** | **110** | | **0.98 [ 0.14, 7.03 ]** |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: Z = 0.02 (P = 0.98) | | | | |
| 2 adults >= 18 | | | | |
| Aapro 2008 IPD | 169/231 | 169/232 | | 1.07 [ 0.87, 1.32 ] |
| Abels 1993 IPD | 13/65 | 12/59 | | 0.96 [ 0.44, 2.10 ] |
| Bamias 2003 | 7/72 | 4/72 | | 1.80 [ 0.53, 6.12 ] |
| Boogaerts 2003 IPD | 16/132 | 12/127 | | 1.53 [ 0.72, 3.26 ] |
| Case 1993 IPD | 10/81 | 9/76 | | 1.11 [ 0.45, 2.73 ] |
| Cazzola 1995 IPD | 5/114 | 3/29 | | 0.69 [ 0.13, 3.57 ] |


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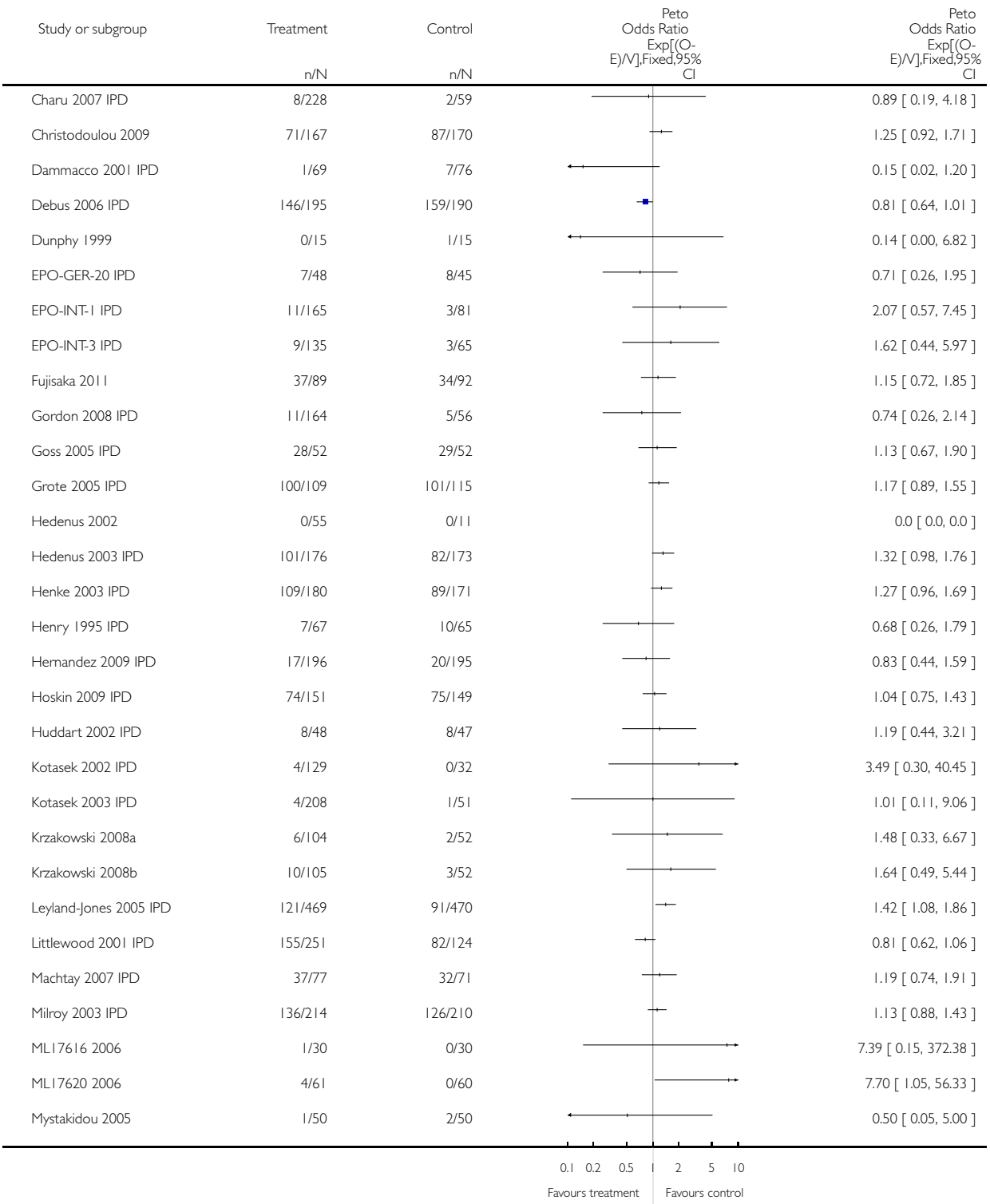


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| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| O'Shaugnessy 2005 IPD | 1/51 | 0/49 | | 7.69 [ 0.15, 387.58 ] |
| OBE/EPO-INT-03 IPD | 5/35 | 6/37 | | 1.07 [ 0.32, 3.56 ] |
| Osterborg 1996 IPD | 26/99 | 14/49 | | 0.94 [ 0.49, 1.81 ] |
| Osterborg 2002 IPD | 110/173 | 109/176 | | 1.04 [ 0.80, 1.36 ] |
| Overgaard 2009 | 144/255 | 119/259 | | 1.26 [ 0.99, 1.61 ] |
| P-174 IPD | 1/33 | 1/12 | | 0.44 [ 0.03, 7.27 ] |
| Pirker 2008 IPD | 243/299 | 254/301 | | 0.94 [ 0.78, 1.12 ] |
| Quirt 1996 IPD | 2/28 | 0/28 | | 5.90 [ 0.36, 97.07 ] |
| Ray-Coquard 2009 IPD | 75/110 | 84/108 | | 0.79 [ 0.58, 1.08 ] |
| Rose 1994 IPD | 16/142 | 6/79 | | 1.73 [ 0.67, 4.42 ] |
| Savonije 2005 IPD | 132/211 | 61/104 | | 1.15 [ 0.85, 1.55 ] |
| Smith 2003 | 3/64 | 0/22 | | 3.96 [ 0.29, 54.28 ] |
| Smith 2008 IPD | 250/517 | 216/472 | | 1.22 [ 1.02, 1.47 ] |
| Sweeney 1998 | 0/24 | 0/24 | | 0.0 [ 0.0, 0.0 ] |
| Ten Bokkel1998 IPD | 6/87 | 2/33 | | 1.27 [ 0.26, 6.34 ] |
| Thatcher 1999 IPD | 7/86 | 3/44 | | 1.13 [ 0.29, 4.36 ] |
| Thomas 2002 IPD | 4/65 | 5/65 | | 0.79 [ 0.21, 2.96 ] |
| Thompson 2000 | 3/45 | 0/21 | | 4.52 [ 0.38, 53.37 ] |
| Tjulandin 2010a | 5/76 | 6/37 | | 0.28 [ 0.07, 1.08 ] |
| Tjulandin 2010b | 4/73 | 6/37 | | 0.34 [ 0.09, 1.26 ] |
| Tjulandin 2011 | 6/95 | 5/91 | | 1.16 [ 0.34, 3.90 ] |
| Tsuboi 2009 | 21/61 | 19/56 | | 0.94 [ 0.57, 1.54 ] |
| Vansteenkiste 2002 IPD | 101/159 | 118/161 | | 0.79 [ 0.60, 1.03 ] |
| Wilkinson 2006 IPD | 3/121 | 0/61 | | 0.0 [ 0.0, 0.0 ] |
| Witzig 2005 IPD | 121/174 | 119/170 | | 1.13 [ 0.87, 1.46 ] |
| Wright 2007 IPD | 32/33 | 34/37 | | 1.55 [ 0.94, 2.54 ] |
| **Subtotal (95% CI)** | **7818** | **6157** | | **1.07 [ 1.01, 1.13 ]** |
| Heterogeneity: Chi² = 67.27, df = 58 (P = 0.19); I² =14% | | | | |
| Test for overall effect: Z = 2.42 (P = 0.015) | | | | |
| 3 > 68% non elderly 18-65 | | | | |
| Antonadou 2001 | 10/190 | 30/195 | | 0.35 [ 0.19, 0.66 ] |
| Cascinu 1994 | 0/50 | 0/50 | | 0.0 [ 0.0, 0.0 ] |


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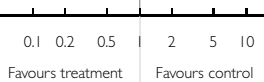
| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Chang 2005 IPD | 27/176 | 28/178 | | 0.94 [ 0.55, 1.60 ] |
| Del Mastro 1997 | 1/31 | 3/31 | | 0.36 [ 0.05, 2.53 ] |
| Gupta 2009 | 17/58 | 14/57 | | 0.90 [ 0.51, 1.59 ] |
| Kurz 1997 | 0/23 | 0/12 | | 0.0 [ 0.0, 0.0 ] |
| Oberhoff 1998 IPD | 9/116 | 10/111 | | 0.62 [ 0.25, 1.58 ] |
| Rosen 2003 | 19/47 | 23/43 | | 1.19 [ 0.65, 2.18 ] |
| Strauss 2008 IPD | 8/34 | 5/40 | | 2.00 [ 0.65, 6.13 ] |
| Thomas 2008 IPD | 22/58 | 17/56 | | 1.28 [ 0.68, 2.42 ] |
| Throuvalas 2000 | 0/28 | 1/27 | | 0.13 [ 0.00, 6.55 ] |
| **Subtotal (95% CI)** | **811** | **800** | | **0.86 [ 0.67, 1.10 ]** |
| Heterogeneity: Chi² = 15.01, df = 8 (P = 0.06); I² =47% | | | | |
| Test for overall effect: Z = 1.22 (P = 0.22) | | | | |
| 4 only non-elderly adults | | | | |
| Blohmer 2011 | 25/127 | 29/129 | | 0.88 [ 0.51, 1.51 ] |
| Engert 2010 | 27/648 | 36/655 | | 0.74 [ 0.45, 1.22 ] |
| Moebus 2007 IPD | 59/324 | 56/319 | | 1.01 [ 0.70, 1.46 ] |
| Untch 2011˙2 | 59/345 | 48/369 | | 1.33 [ 0.91, 1.95 ] |
| **Subtotal (95% CI)** | **1444** | **1472** | | **1.02 [ 0.82, 1.26 ]** |
| Heterogeneity: Chi² = 3.74, df = 3 (P = 0.29); I² =20% | | | | |
| Test for overall effect: Z = 0.18 (P = 0.86) | | | | |
| 5 > 68% elderly > 65 | | | | |
| Pronzato 2010 IPD | 23/110 | 20/113 | | 1.05 [ 0.58, 1.92 ] |
| Winquist 2009 | 24/26 | 27/30 | | 0.58 [ 0.33, 1.03 ] |
| **Subtotal (95% CI)** | **136** | **143** | | **0.77 [ 0.51, 1.17 ]** |
| Heterogeneity: Chi² = 1.97, df = 1 (P = 0.16); I² =49% | | | | |
| Test for overall effect: Z = 1.21 (P = 0.23) | | | | |
| 6 only elderly > 65 | | | | |
| **Subtotal (95% CI)** | **0** | **0** | | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: not applicable | | | | |
| **Total (95% CI)** | | | | **1.05 [ 1.00, 1.11 ]** |
| Heterogeneity: Chi² = 93.19, df = 74 (P = 0.07); I² =21% | | | | |
| Test for overall effect: Z = 1.91 (P = 0.056) | | | | |
| Test for subgroup differences: Chi² = 5.20, df = 4 (P = 0.27), I² =23% | | | | |

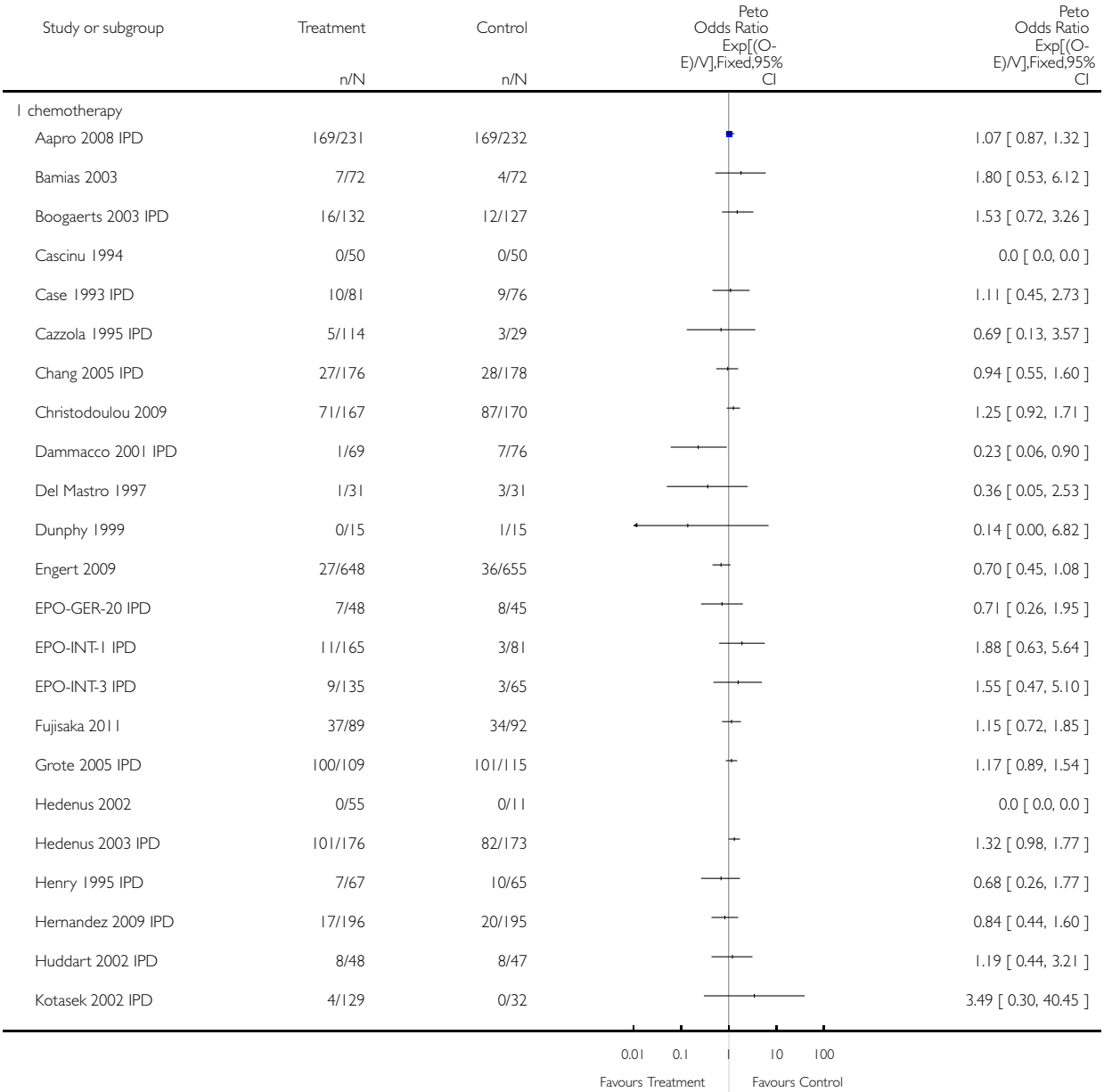


## Analysis 5.7. Comparison 5 Overall survival, Outcome 7 Overall survival - different therapies.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 5 Overall survival

Outcome: 7 Overall survival - different therapies

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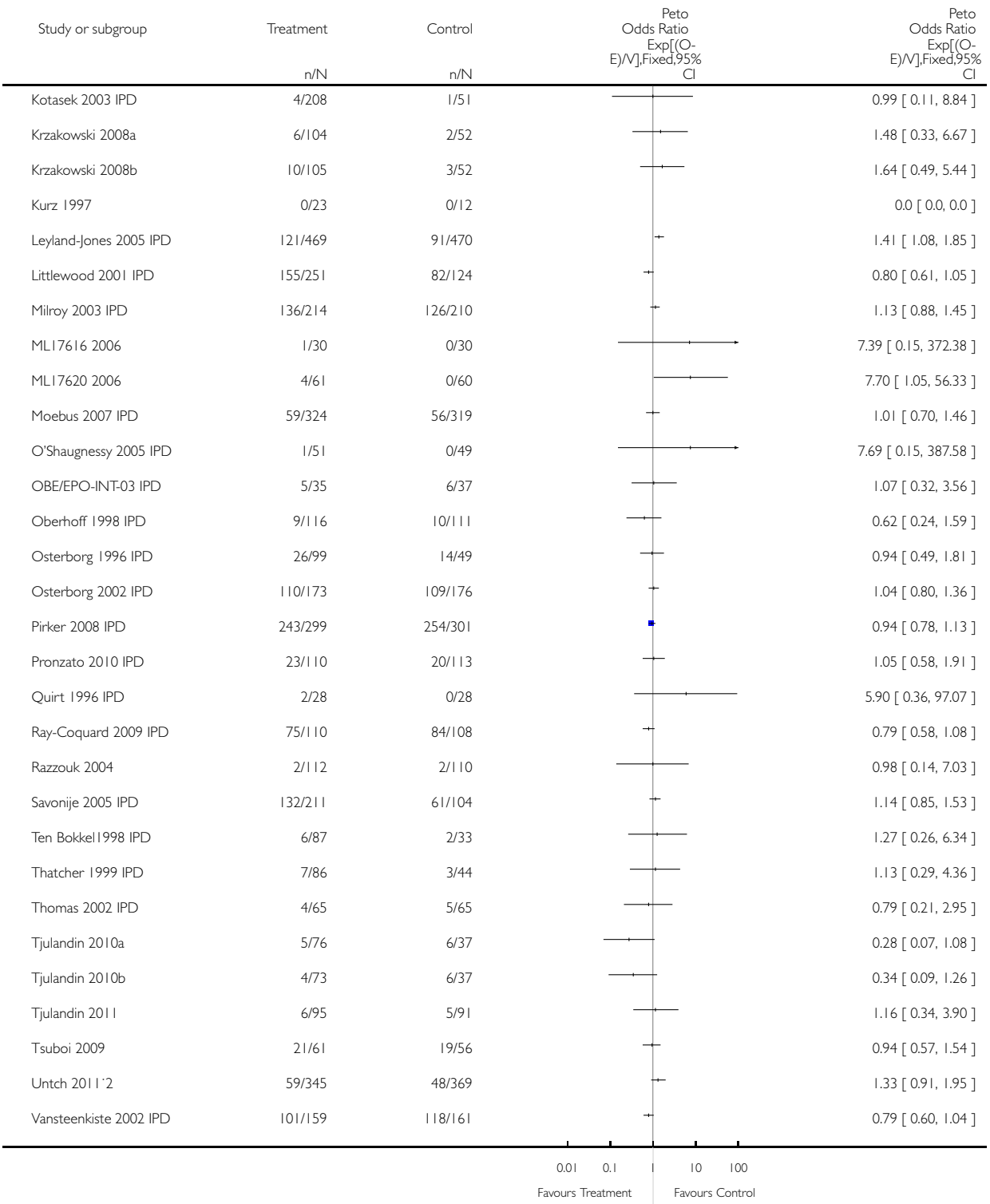


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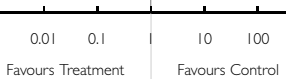
| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Wilkinson 2006 IPD | 3/121 | 0/61 | | 4.48 [ 0.40, 50.03 ] |
| Witzig 2005 IPD | 121/174 | 119/170 | | 1.13 [ 0.87, 1.46 ] |
| **Subtotal (95% CI)** | **7478** | **6322** | | **1.04 [ 0.98, 1.11 ]** |
| Heterogeneity: Chi² = 58.28, df = 51 (P = 0.23); I² =12% | | | | |
| Test for overall effect: Z = 1.19 (P = 0.24) | | | | |
| 2 radiotherapy/radiochemotherapy | | | | |
| Antonadou 2001 | 10/190 | 30/195 | | 0.35 [ 0.19, 0.66 ] |
| Blohmer 2011 | 25/127 | 29/129 | | 0.88 [ 0.51, 1.51 ] |
| Debus 2006 IPD | 146/195 | 159/190 | | 0.81 [ 0.64, 1.02 ] |
| Goss 2005 IPD | 28/52 | 29/52 | | 1.13 [ 0.67, 1.91 ] |
| Gupta 2009 | 17/58 | 14/57 | | 0.90 [ 0.51, 1.59 ] |
| Henke 2003 IPD | 109/180 | 89/171 | | 1.27 [ 0.96, 1.68 ] |
| Hoskin 2009 IPD | 74/151 | 75/149 | | 1.04 [ 0.75, 1.44 ] |
| Machtay 2007 IPD | 37/77 | 32/71 | | 1.19 [ 0.74, 1.91 ] |
| Overgaard 2009 | 144/255 | 119/259 | | 1.26 [ 0.99, 1.61 ] |
| Rosen 2003 | 19/47 | 23/43 | | 1.19 [ 0.65, 2.18 ] |
| Strauss 2008 IPD | 8/34 | 5/40 | | 2.00 [ 0.65, 6.13 ] |
| Sweeney 1998 | 0/24 | 0/24 | | 0.0 [ 0.0, 0.0 ] |
| Thomas 2008 IPD | 22/58 | 17/56 | | 1.28 [ 0.68, 2.40 ] |
| Throuvalas 2000 | 0/28 | 1/27 | | 0.13 [ 0.00, 6.55 ] |
| **Subtotal (95% CI)** | **1476** | **1463** | | **1.03 [ 0.92, 1.15 ]** |
| Heterogeneity: Chi² = 24.60, df = 12 (P = 0.02); I² =51% | | | | |
| Test for overall effect: Z = 0.55 (P = 0.58) | | | | |
| 3 no therapy | | | | |
| Abels 1993 IPD | 13/65 | 12/59 | | 0.96 [ 0.44, 2.10 ] |
| Charu 2007 IPD | 8/228 | 2/59 | | 0.89 [ 0.19, 4.18 ] |
| Gordon 2008 IPD | 11/164 | 5/56 | | 0.74 [ 0.26, 2.14 ] |
| Mystakidou 2005 | 1/50 | 2/50 | | 0.50 [ 0.05, 5.00 ] |
| Smith 2003 | 3/64 | 0/22 | | 3.96 [ 0.29, 54.28 ] |
| Smith 2008 IPD | 250/517 | 216/472 | | 1.22 [ 1.02, 1.47 ] |
| Thompson 2000 | 3/45 | 0/21 | | 4.52 [ 0.38, 53.37 ] |
| Wright 2007 IPD | 32/33 | 34/37 | | 1.55 [ 0.94, 2.54 ] |
| **Subtotal (95% CI)** | **1166** | **776** | | **1.23 [ 1.04, 1.45 ]** |

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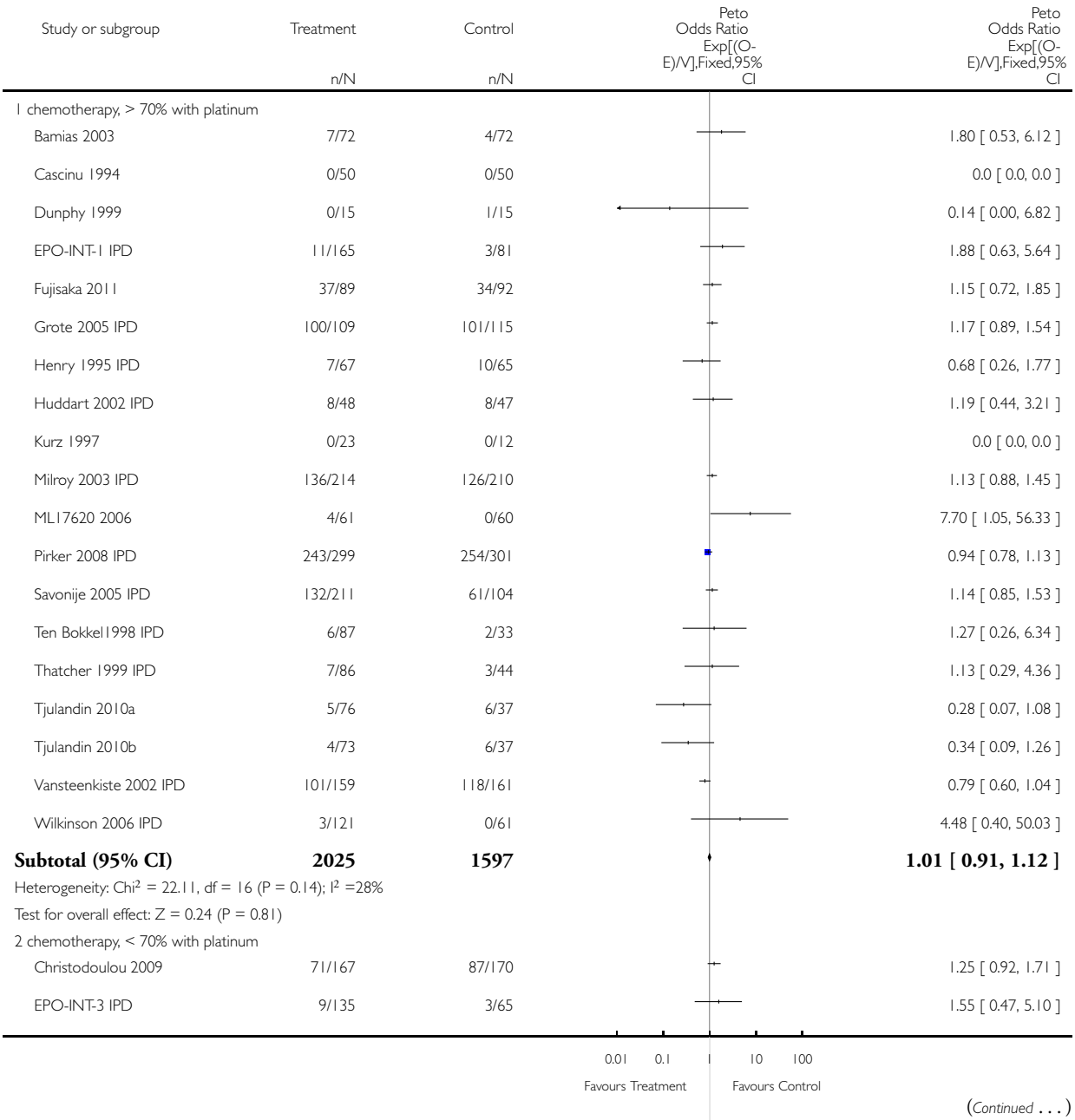
| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Heterogeneity: Chi² = 4.67, df = 7 (P = 0.70); I² =0.0% | | | | |
| Test for overall effect: Z = 2.47 (P = 0.014) | | | | |
| 4 unclear/other | | | | |
| P-174 IPD | 1/33 | 1/12 | | 0.44 [ 0.03, 7.27 ] |
| Rose 1994 IPD | 16/142 | 6/79 | | 1.66 [ 0.70, 3.92 ] |
| Winquist 2009 | 24/26 | 27/30 | | 0.58 [ 0.33, 1.03 ] |
| **Subtotal (95% CI)** | **201** | **121** | | **0.79 [ 0.49, 1.27 ]** |
| Heterogeneity: Chi² = 4.12, df = 2 (P = 0.13); I² =51% | | | | |
| Test for overall effect: Z = 0.97 (P = 0.33) | | | | |
| **Total (95% CI)** | | | | **1.05 [ 1.00, 1.11 ]** |
| Heterogeneity: Chi² = 96.80, df = 75 (P = 0.05); I² =23% | | | | |
| Test for overall effect: Z = 1.90 (P = 0.057) | | | | |
| Test for subgroup differences: Chi² = 5.12, df = 3 (P = 0.16), I² =41% | | | | |

## Analysis 5.8. Comparison 5 Overall survival, Outcome 8 Overall survival - different therapies differentiated.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 5 Overall survival

Outcome: 8 Overall survival - different therapies differentiated

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| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Hernandez 2009 IPD | 17/196 | 20/195 | | 0.84 [ 0.44, 1.60 ] |
| Krzakowski 2008a | 6/104 | 2/52 | | 1.48 [ 0.33, 6.67 ] |
| Krzakowski 2008b | 10/105 | 3/52 | | 1.64 [ 0.49, 5.44 ] |
| Oberhoff 1998 IPD | 9/116 | 10/111 | | 0.62 [ 0.24, 1.59 ] |
| Witzig 2005 IPD | 121/174 | 119/170 | | 1.13 [ 0.87, 1.46 ] |
| **Subtotal (95% CI)** | **997** | **815** | | **1.14 [ 0.95, 1.36 ]** |
| Heterogeneity: Chi² = 3.54, df = 6 (P = 0.74); I² =0.0% | | | | |
| Test for overall effect: Z = 1.41 (P = 0.16) | | | | |
| 3 chemotherapy without platinum (all patients) | | | | |
| Aapro 2008 IPD | 169/231 | 169/232 | | 1.07 [ 0.87, 1.32 ] |
| Case 1993 IPD | 10/81 | 9/76 | | 1.11 [ 0.45, 2.73 ] |
| Cazzola 1995 IPD | 5/114 | 3/29 | | 0.69 [ 0.13, 3.57 ] |
| Chang 2005 IPD | 27/176 | 28/178 | | 0.94 [ 0.55, 1.60 ] |
| Del Mastro 1997 | 1/31 | 3/31 | | 0.36 [ 0.05, 2.53 ] |
| Engert 2010 | 27/648 | 36/655 | | 0.74 [ 0.45, 1.22 ] |
| Hedenus 2002 | 0/55 | 0/11 | | 0.0 [ 0.0, 0.0 ] |
| Hedenus 2003 IPD | 101/176 | 82/173 | | 1.32 [ 0.98, 1.77 ] |
| Leyland-Jones 2005 IPD | 121/469 | 91/470 | | 1.41 [ 1.08, 1.85 ] |
| Littlewood 2001 IPD | 155/251 | 82/124 | | 0.80 [ 0.61, 1.05 ] |
| ML17616 2006 | 1/30 | 0/30 | | 7.39 [ 0.15, 372.38 ] |
| Moebus 2007 IPD | 59/324 | 56/319 | | 1.01 [ 0.70, 1.46 ] |
| O'Shaugnessy 2005 IPD | 1/51 | 0/49 | | 7.69 [ 0.15, 387.58 ] |
| OBE/EPO-INT-03 IPD | 5/35 | 6/37 | | 1.07 [ 0.32, 3.56 ] |
| Osterborg 1996 IPD | 26/99 | 14/49 | | 0.94 [ 0.49, 1.81 ] |
| Osterborg 2002 IPD | 110/173 | 109/176 | | 1.04 [ 0.80, 1.36 ] |
| Pronzato 2010 IPD | 23/110 | 20/113 | | 1.05 [ 0.58, 1.91 ] |
| Tjulandin 2011 | 6/95 | 5/91 | | 1.16 [ 0.34, 3.90 ] |
| Untch 2011˙2 | 59/345 | 48/369 | | 1.33 [ 0.91, 1.95 ] |
| **Subtotal (95% CI)** | **3494** | **3212** | | **1.08 [ 0.98, 1.19 ]** |
| Heterogeneity: Chi² = 17.52, df = 17 (P = 0.42); I² =3% | | | | |
| Test for overall effect: Z = 1.50 (P = 0.13) | | | | |
| 4 chemotherapy, platinum and non platinum containing, no numbers given | | | | |
| Boogaerts 2003 IPD | 16/132 | 12/127 | | 1.53 [ 0.72, 3.26 ] |


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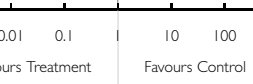
| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Dammacco 2001 IPD | 1/69 | 7/76 | | 0.23 [ 0.06, 0.90 ] |
| Kotasek 2003 IPD | 4/208 | 1/51 | | 0.99 [ 0.11, 8.84 ] |
| Thomas 2002 IPD | 4/65 | 5/65 | | 0.79 [ 0.21, 2.95 ] |
| Tsuboi 2009 | 21/61 | 19/56 | | 0.94 [ 0.57, 1.54 ] |
| **Subtotal (95% CI)** | **535** | **375** | | **0.94 [ 0.65, 1.37 ]** |
| Heterogeneity: Chi² = 5.75, df = 4 (P = 0.22); I² =30% | | | | |
| Test for overall effect: Z = 0.32 (P = 0.75) | | | | |
| 5 chemotherapy no details given | | | | |
| EPO-GER-20 IPD | 7/48 | 8/45 | | 0.71 [ 0.26, 1.95 ] |
| Kotasek 2002 IPD | 4/129 | 0/32 | | 3.49 [ 0.30, 40.45 ] |
| Quirt 1996 IPD | 2/28 | 0/28 | | 5.90 [ 0.36, 97.07 ] |
| Ray-Coquard 2009 IPD | 75/110 | 84/108 | | 0.79 [ 0.58, 1.08 ] |
| Razzouk 2004 | 2/112 | 2/110 | | 0.98 [ 0.14, 7.03 ] |
| **Subtotal (95% CI)** | **427** | **323** | | **0.82 [ 0.61, 1.10 ]** |
| Heterogeneity: Chi² = 3.42, df = 4 (P = 0.49); I² =0.0% | | | | |
| Test for overall effect: Z = 1.34 (P = 0.18) | | | | |
| 6 radiochemotherapy | | | | |
| Blohmer 2011 | 25/127 | 29/129 | | 0.88 [ 0.51, 1.51 ] |
| Debus 2006 IPD | 146/195 | 159/190 | | 0.81 [ 0.64, 1.02 ] |
| Goss 2005 IPD | 28/52 | 29/52 | | 1.13 [ 0.67, 1.91 ] |
| Gupta 2009 | 17/58 | 14/57 | | 0.90 [ 0.51, 1.59 ] |
| Rosen 2003 | 19/47 | 23/43 | | 1.19 [ 0.65, 2.18 ] |
| Strauss 2008 IPD | 8/34 | 5/40 | | 2.00 [ 0.65, 6.13 ] |
| Thomas 2008 IPD | 22/58 | 17/56 | | 1.28 [ 0.68, 2.40 ] |
| Throuvalas 2000 | 0/28 | 1/27 | | 0.13 [ 0.00, 6.55 ] |
| **Subtotal (95% CI)** | **599** | **594** | | **0.92 [ 0.78, 1.09 ]** |
| Heterogeneity: Chi² = 6.37, df = 7 (P = 0.50); I² =0.0% | | | | |
| Test for overall effect: Z = 0.94 (P = 0.35) | | | | |
| 7 radiotherapy | | | | |
| Antonadou 2001 | 10/190 | 30/195 | | 0.35 [ 0.19, 0.66 ] |
| Henke 2003 IPD | 109/180 | 89/171 | | 1.27 [ 0.96, 1.68 ] |
| Hoskin 2009 IPD | 74/151 | 75/149 | | 1.04 [ 0.75, 1.44 ] |
| Machtay 2007 IPD | 37/77 | 32/71 | | 1.19 [ 0.74, 1.91 ] |
| Overgaard 2009 | 144/255 | 119/259 | | 1.26 [ 0.99, 1.61 ] |

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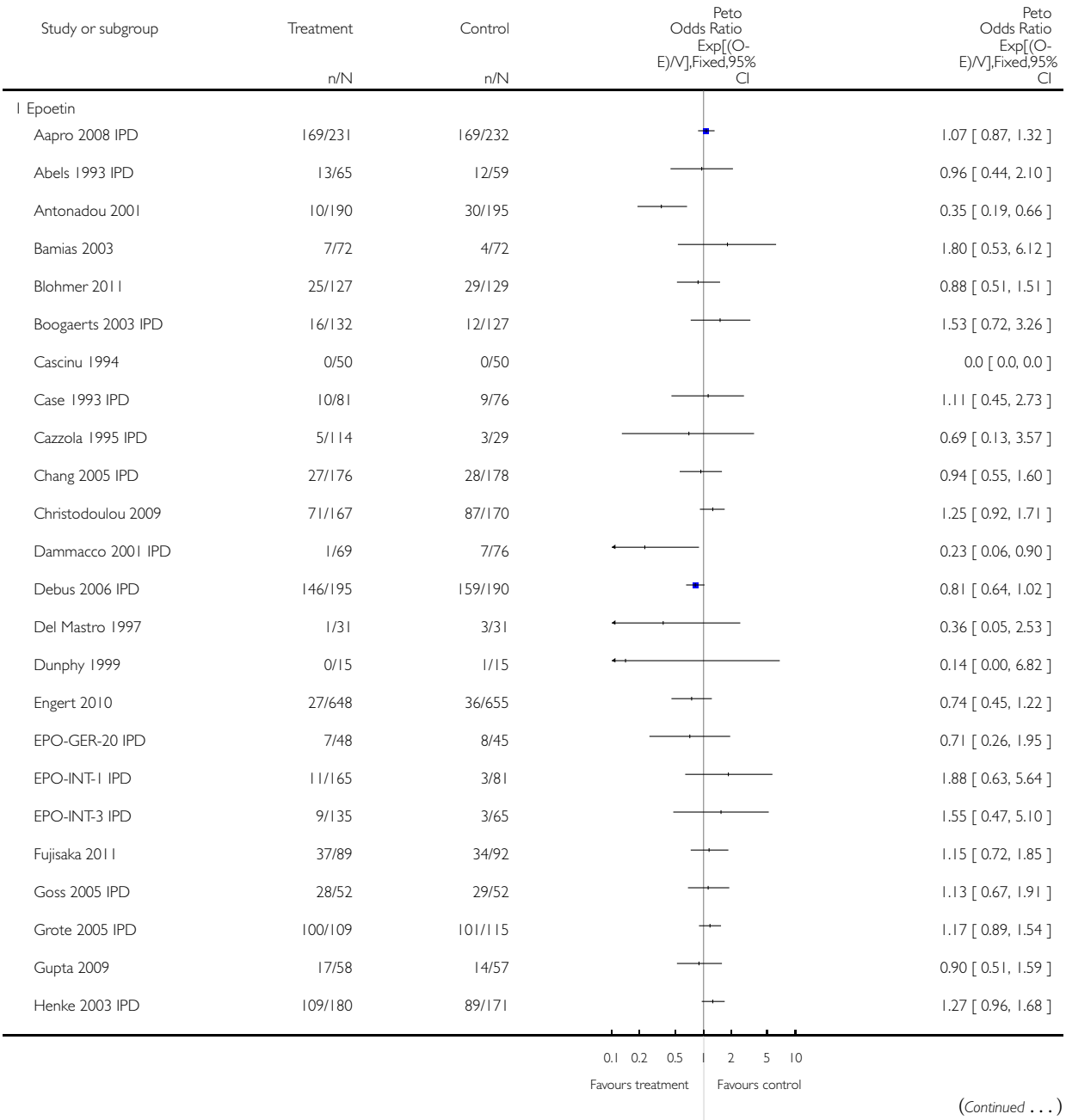
| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Sweeney 1998 | 0/24 | 0/24 | | 0.0 [ 0.0, 0.0 ] |
| **Subtotal (95% CI)** | **877** | **869** | | **1.12 [ 0.97, 1.30 ]** |
| Heterogeneity: Chi² = 15.24, df = 4 (P = 0.004); I² =74% | | | | |
| Test for overall effect: Z = 1.56 (P = 0.12) | | | | |
| 8 no therapy | | | | |
| Abels 1993 IPD | 13/65 | 12/59 | | 0.96 [ 0.44, 2.10 ] |
| Charu 2007 IPD | 8/228 | 2/59 | | 0.89 [ 0.19, 4.18 ] |
| Gordon 2008 IPD | 11/164 | 5/56 | | 0.74 [ 0.26, 2.14 ] |
| Mystakidou 2005 | 1/50 | 2/50 | | 0.50 [ 0.05, 5.00 ] |
| Smith 2003 | 3/64 | 0/22 | | 3.96 [ 0.29, 54.28 ] |
| Smith 2008 IPD | 250/517 | 216/472 | | 1.22 [ 1.02, 1.47 ] |
| Thompson 2000 | 3/45 | 0/21 | | 4.52 [ 0.38, 53.37 ] |
| Wright 2007 IPD | 32/33 | 34/37 | | 1.55 [ 0.94, 2.54 ] |
| **Subtotal (95% CI)** | **1166** | **776** | | **1.23 [ 1.04, 1.45 ]** |
| Heterogeneity: Chi² = 4.67, df = 7 (P = 0.70); I² =0.0% | | | | |
| Test for overall effect: Z = 2.47 (P = 0.014) | | | | |
| 9 unclear/other | | | | |
| P-174 IPD | 1/33 | 1/12 | | 0.44 [ 0.03, 7.27 ] |
| Rose 1994 IPD | 16/142 | 6/79 | | 1.66 [ 0.70, 3.92 ] |
| Winquist 2009 | 24/26 | 27/30 | | 0.58 [ 0.33, 1.03 ] |
| **Subtotal (95% CI)** | **201** | **121** | | **0.79 [ 0.49, 1.27 ]** |
| Heterogeneity: Chi² = 4.12, df = 2 (P = 0.13); I² =51% | | | | |
| Test for overall effect: Z = 0.97 (P = 0.33) | | | | |
| **Total (95% CI)** | | | | **1.05 [ 1.00, 1.11 ]** |
| Heterogeneity: Chi² = 95.40, df = 75 (P = 0.06); I² =21% | | | | |
| Test for overall effect: Z = 1.97 (P = 0.048) | | | | |
| Test for subgroup differences: Chi² = 12.64, df = 8 (P = 0.12), I² =37% | | | | |

## Analysis 5.9. Comparison 5 Overall survival, Outcome 9 Overall survival - epoetin vs darbepoetin.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 5 Overall survival

Outcome: 9 Overall survival - epoetin vs darbepoetin

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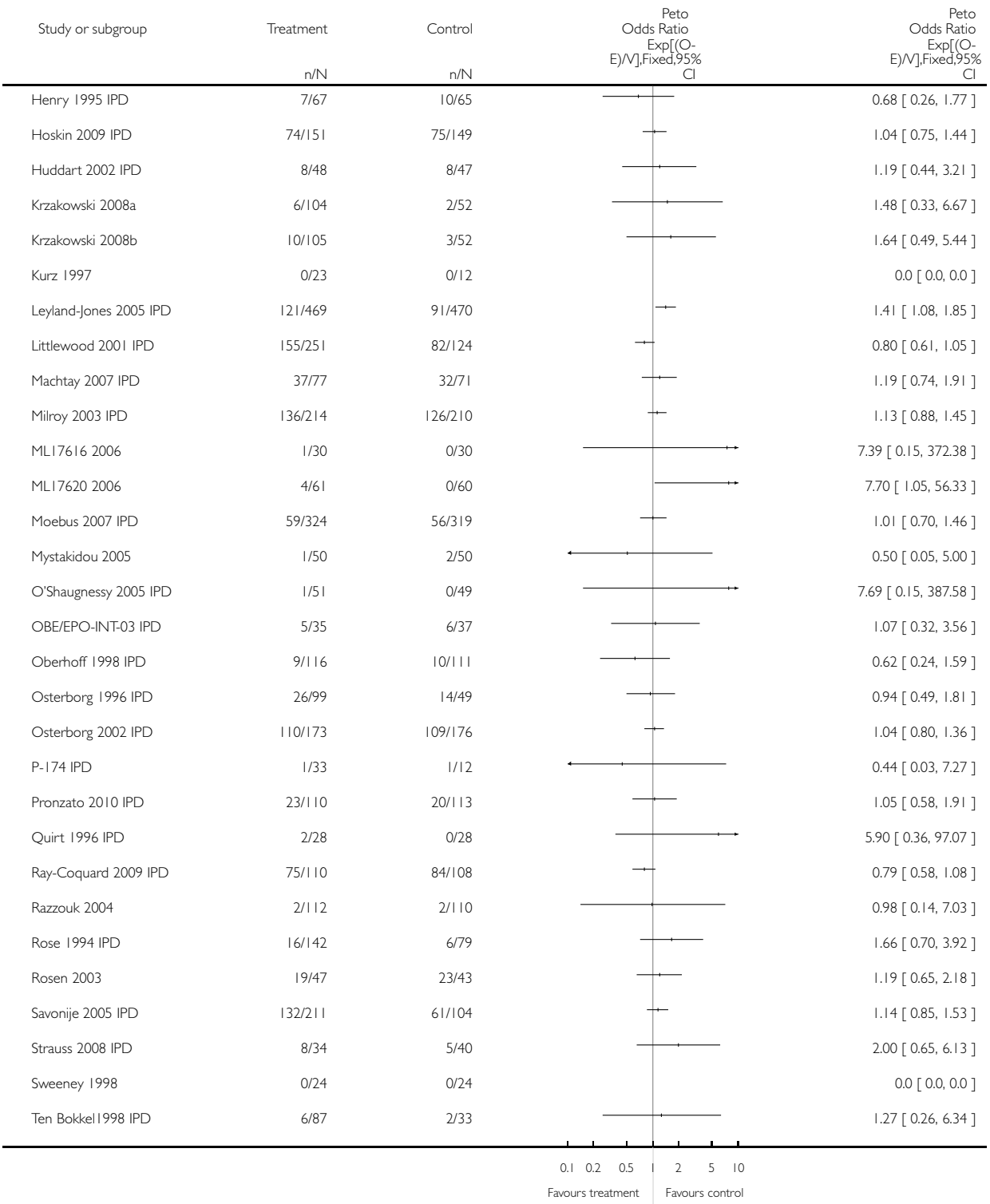


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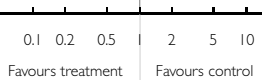
| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Thatcher 1999 IPD | 7/86 | 3/44 | | 1.13 [ 0.29, 4.36 ] |
| Thomas 2002 IPD | 4/65 | 5/65 | | 0.79 [ 0.21, 2.95 ] |
| Thomas 2008 IPD | 22/58 | 17/56 | | 1.28 [ 0.68, 2.40 ] |
| Thompson 2000 | 3/45 | 0/21 | | 4.52 [ 0.38, 53.37 ] |
| Throuvalas 2000 | 0/28 | 1/27 | | 0.13 [ 0.00, 6.55 ] |
| Tjulandin 2010a | 5/76 | 6/37 | | 0.28 [ 0.07, 1.08 ] |
| Tjulandin 2010b | 4/73 | 6/37 | | 0.34 [ 0.09, 1.26 ] |
| Tjulandin 2011 | 6/95 | 5/91 | | 1.16 [ 0.34, 3.90 ] |
| Tsuboi 2009 | 21/61 | 19/56 | | 0.94 [ 0.57, 1.54 ] |
| Wilkinson 2006 IPD | 3/121 | 0/61 | | 4.48 [ 0.40, 50.03 ] |
| Winquist 2009 | 24/26 | 27/30 | | 0.58 [ 0.33, 1.03 ] |
| Witzig 2005 IPD | 121/174 | 119/170 | | 1.13 [ 0.87, 1.46 ] |
| Wright 2007 IPD | 32/33 | 34/37 | | 1.55 [ 0.94, 2.54 ] |
| **Subtotal (95% CI)** | **7526** | **6521** | | **1.04 [ 0.98, 1.10 ]** |
| Heterogeneity: Chi² = 78.15, df = 63 (P = 0.09); I² =19% | | | | |
| Test for overall effect: Z = 1.19 (P = 0.23) | | | | |
| 2 Darbepoetin | | | | |
| Charu 2007 IPD | 8/228 | 2/59 | | 0.89 [ 0.19, 4.18 ] |
| Gordon 2008 IPD | 11/164 | 5/56 | | 0.74 [ 0.26, 2.14 ] |
| Hedenus 2002 | 0/55 | 0/11 | | 0.0 [ 0.0, 0.0 ] |
| Hedenus 2003 IPD | 101/176 | 82/173 | | 1.32 [ 0.98, 1.77 ] |
| Hernandez 2009 IPD | 17/196 | 20/195 | | 0.84 [ 0.44, 1.60 ] |
| Kotasek 2002 IPD | 4/129 | 0/32 | | 3.49 [ 0.30, 40.45 ] |
| Kotasek 2003 IPD | 4/208 | 1/51 | | 0.99 [ 0.11, 8.84 ] |
| Overgaard 2009 | 144/255 | 119/259 | | 1.26 [ 0.99, 1.61 ] |
| Pirker 2008 IPD | 243/299 | 254/301 | | 0.94 [ 0.78, 1.13 ] |
| Smith 2003 | 3/64 | 0/22 | | 3.96 [ 0.29, 54.28 ] |
| Smith 2008 IPD | 250/517 | 216/472 | | 1.22 [ 1.02, 1.47 ] |
| Untch 2011˙2 | 59/345 | 48/369 | | 1.33 [ 0.91, 1.95 ] |
| Vansteenkiste 2002 IPD | 101/159 | 118/161 | | 0.79 [ 0.60, 1.04 ] |
| **Subtotal (95% CI)** | **2795** | **2161** | | **1.09 [ 0.99, 1.20 ]** |
| Heterogeneity: Chi² = 16.57, df = 11 (P = 0.12); I² =34% | | | | |

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| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Test for overall effect: Z = 1.77 (P = 0.076) | | | | |
| **Total (95% CI)** | | | ◆ | **1.05 [ 1.00, 1.11 ]** |
| Heterogeneity: $Chi^2$ = 95.40, df = 75 (P = 0.06); $I^2$ =21% | | | | |
| Test for overall effect: Z = 1.97 (P = 0.048) | | | | |
| Test for subgroup differences: $Chi^2$ = 0.67, df = 1 (P = 0.41), $I^2$ =0.0% | | | | |

0.1 0.2 0.5 1 2 5 10

Favours treatment Favours control

### Analysis 5.10. Comparison 5 Overall survival, Outcome 10 Overall survival - duration of ESA medication.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 5 Overall survival

Outcome: 10 Overall survival - duration of ESA medication

| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| 1 6 to 9 weeks | | | | |
| Abels 1993 IPD | 13/65 | 12/59 | | 0.96 [ 0.44, 2.10 ] |
| Antonadou 2001 | 10/190 | 30/195 | | 0.35 [ 0.19, 0.66 ] |
| Cascinu 1994 | 0/50 | 0/50 | | 0.0 [ 0.0, 0.0 ] |
| Cazzola 1995 IPD | 5/114 | 3/29 | | 0.69 [ 0.13, 3.57 ] |
| Dunphy 1999 | 0/15 | 1/15 | | 0.14 [ 0.00, 6.82 ] |
| Gupta 2009 | 17/58 | 14/57 | | 0.90 [ 0.51, 1.59 ] |
| Henke 2003 IPD | 109/180 | 89/171 | | 1.27 [ 0.96, 1.68 ] |
| Machtay 2007 IPD | 37/77 | 32/71 | | 1.19 [ 0.74, 1.91 ] |
| Overgaard 2009 | 144/255 | 119/259 | | 1.26 [ 0.99, 1.61 ] |
| Sweeney 1998 | 0/24 | 0/24 | | 0.0 [ 0.0, 0.0 ] |

0.1 0.2 0.5 1 2 5 10

Favours treatment Favours control

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| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Thomas 2008 IPD | 22/58 | 17/56 | | 1.28 [ 0.68, 2.40 ] |
| Throuvalas 2000 | 0/28 | 1/27 | | 0.13 [ 0.00, 6.55 ] |
| Tsuboi 2009 | 21/61 | 19/56 | | 0.94 [ 0.57, 1.54 ] |
| **Subtotal (95% CI)** | **1175** | **1069** | | **1.10 [ 0.95, 1.27 ]** |
| Heterogeneity: Chi² = 18.96, df = 10 (P = 0.04); I² =47% | | | | |
| Test for overall effect: Z = 1.30 (P = 0.20) | | | | |
| 2 12 to 16 weeks | | | | |
| Boogaerts 2003 IPD | 16/132 | 12/127 | | 1.53 [ 0.72, 3.26 ] |
| Case 1993 IPD | 10/81 | 9/76 | | 1.11 [ 0.45, 2.73 ] |
| Chang 2005 IPD | 27/176 | 28/178 | | 0.94 [ 0.55, 1.60 ] |
| Charu 2007 IPD | 8/228 | 2/59 | | 0.89 [ 0.19, 4.18 ] |
| Christodoulou 2009 | 71/167 | 87/170 | | 1.25 [ 0.92, 1.71 ] |
| Dammacco 2001 IPD | 1/69 | 7/76 | | 0.23 [ 0.06, 0.90 ] |
| Debus 2006 IPD | 146/195 | 159/190 | | 0.81 [ 0.64, 1.02 ] |
| Del Mastro 1997 | 1/31 | 3/31 | | 0.36 [ 0.05, 2.53 ] |
| EPO-INT-3 IPD | 9/135 | 3/65 | | 1.55 [ 0.47, 5.10 ] |
| Fujisaka 2011 | 37/89 | 34/92 | | 1.15 [ 0.72, 1.85 ] |
| Gordon 2008 IPD | 11/164 | 5/56 | | 0.74 [ 0.26, 2.14 ] |
| Grote 2005 IPD | 100/109 | 101/115 | | 1.17 [ 0.89, 1.54 ] |
| Hedenus 2002 | 0/55 | 0/11 | | 0.0 [ 0.0, 0.0 ] |
| Hedenus 2003 IPD | 101/176 | 82/173 | | 1.32 [ 0.98, 1.77 ] |
| Henry 1995 IPD | 7/67 | 10/65 | | 0.68 [ 0.26, 1.77 ] |
| Hernandez 2009 IPD | 17/196 | 20/195 | | 0.84 [ 0.44, 1.60 ] |
| Hoskin 2009 IPD | 74/151 | 75/149 | | 1.04 [ 0.75, 1.44 ] |
| Kotasek 2002 IPD | 4/129 | 0/32 | | 3.49 [ 0.30, 40.45 ] |
| Kotasek 2003 IPD | 4/208 | 1/51 | | 0.99 [ 0.11, 8.84 ] |
| Krzakowski 2008a | 6/104 | 2/52 | | 1.48 [ 0.33, 6.67 ] |
| Krzakowski 2008b | 10/105 | 3/52 | | 1.64 [ 0.49, 5.44 ] |
| Kurz 1997 | 0/23 | 0/12 | | 0.0 [ 0.0, 0.0 ] |
| ML17616 2006 | 1/30 | 0/30 | | 7.39 [ 0.15, 372.38 ] |
| ML17620 2006 | 4/61 | 0/60 | | 7.70 [ 1.05, 56.33 ] |
| O'Shaugnessy 2005 IPD | 1/51 | 0/49 | | 7.69 [ 0.15, 387.58 ] |


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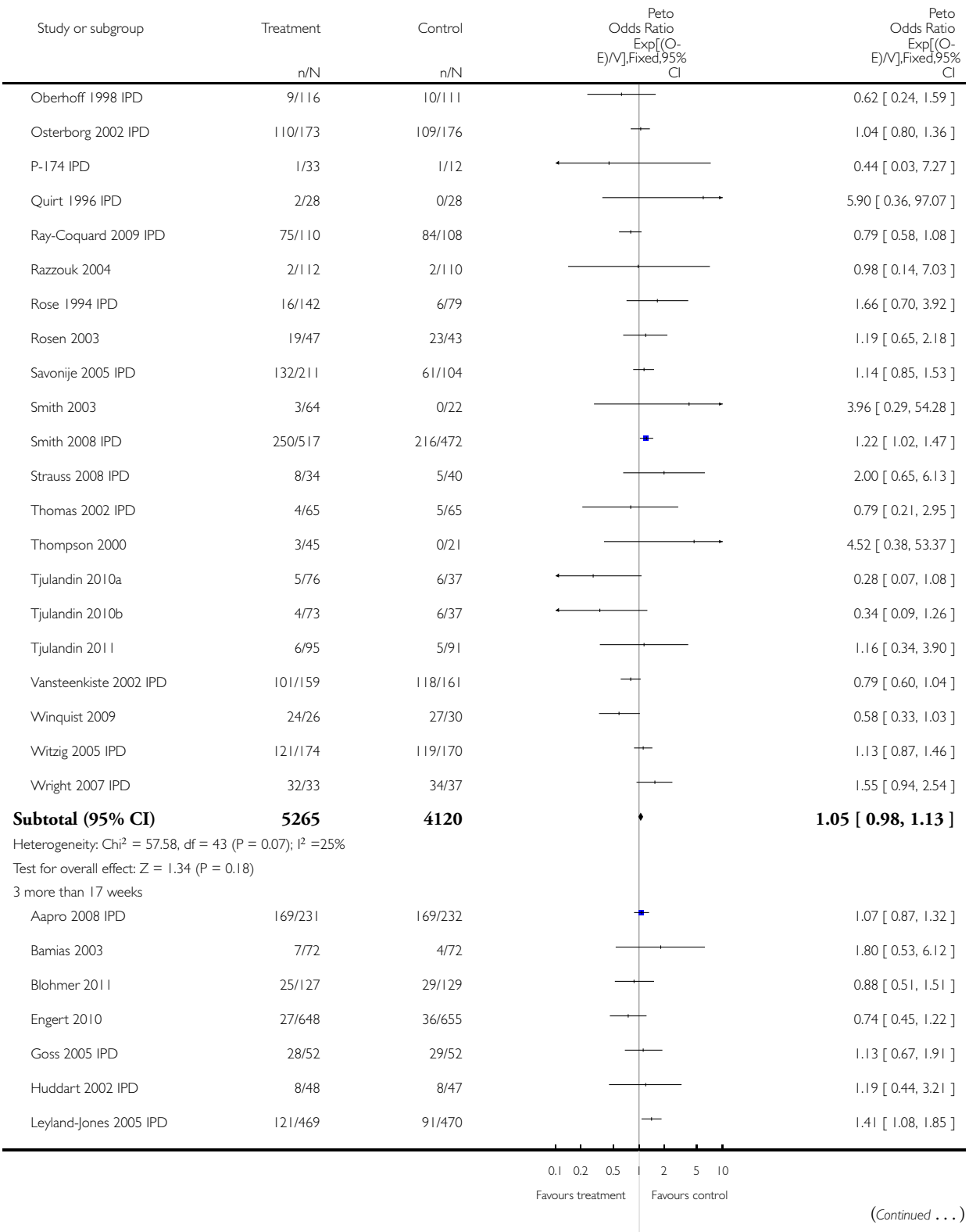


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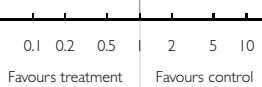
| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Littlewood 2001 IPD | 155/251 | 82/124 | | 0.80 [ 0.61, 1.05 ] |
| Milroy 2003 IPD | 136/214 | 126/210 | | 1.13 [ 0.88, 1.45 ] |
| Moebus 2007 IPD | 59/324 | 56/319 | | 1.01 [ 0.70, 1.46 ] |
| Mystakidou 2005 | 1/50 | 2/50 | | 0.50 [ 0.05, 5.00 ] |
| Osterborg 1996 IPD | 26/99 | 14/49 | | 0.94 [ 0.49, 1.81 ] |
| Pirker 2008 IPD | 243/299 | 254/301 | | 0.94 [ 0.78, 1.13 ] |
| Pronzato 2010 IPD | 23/110 | 20/113 | | 1.05 [ 0.58, 1.91 ] |
| Ten Bokkel1998 IPD | 6/87 | 2/33 | | 1.27 [ 0.26, 6.34 ] |
| Thatcher 1999 IPD | 7/86 | 3/44 | | 1.13 [ 0.29, 4.36 ] |
| Untch 2011˙2 | 59/345 | 48/369 | | 1.33 [ 0.91, 1.95 ] |
| Wilkinson 2006 IPD | 3/121 | 0/61 | | 4.48 [ 0.40, 50.03 ] |
| **Subtotal (95% CI)** | **3633** | **3330** | | **1.04 [ 0.95, 1.14 ]** |
| Heterogeneity: $Chi^2$ = 16.75, df = 17 (P = 0.47); $I^2$ =0.0% | | | | |
| Test for overall effect: Z = 0.88 (P = 0.38) | | | | |
| 4 not reported | | | | |
| EPO-GER-20 IPD | 7/48 | 8/45 | | 0.71 [ 0.26, 1.95 ] |
| EPO-INT-1 IPD | 11/165 | 3/81 | | 1.88 [ 0.63, 5.64 ] |
| OBE/EPO-INT-03 IPD | 5/35 | 6/37 | | 1.07 [ 0.32, 3.56 ] |
| **Subtotal (95% CI)** | **248** | **163** | | **1.10 [ 0.58, 2.07 ]** |
| Heterogeneity: $Chi^2$ = 1.66, df = 2 (P = 0.44); $I^2$ =0.0% | | | | |
| Test for overall effect: Z = 0.29 (P = 0.77) | | | | |
| **Total (95% CI)** | | | | **1.05 [ 1.00, 1.11 ]** |
| Heterogeneity: $Chi^2$ = 95.40, df = 75 (P = 0.06); $I^2$ =21% | | | | |
| Test for overall effect: Z = 1.97 (P = 0.048) | | | | |
| Test for subgroup differences: $Chi^2$ = 0.44, df = 3 (P = 0.93), $I^2$ =0.0% | | | | |

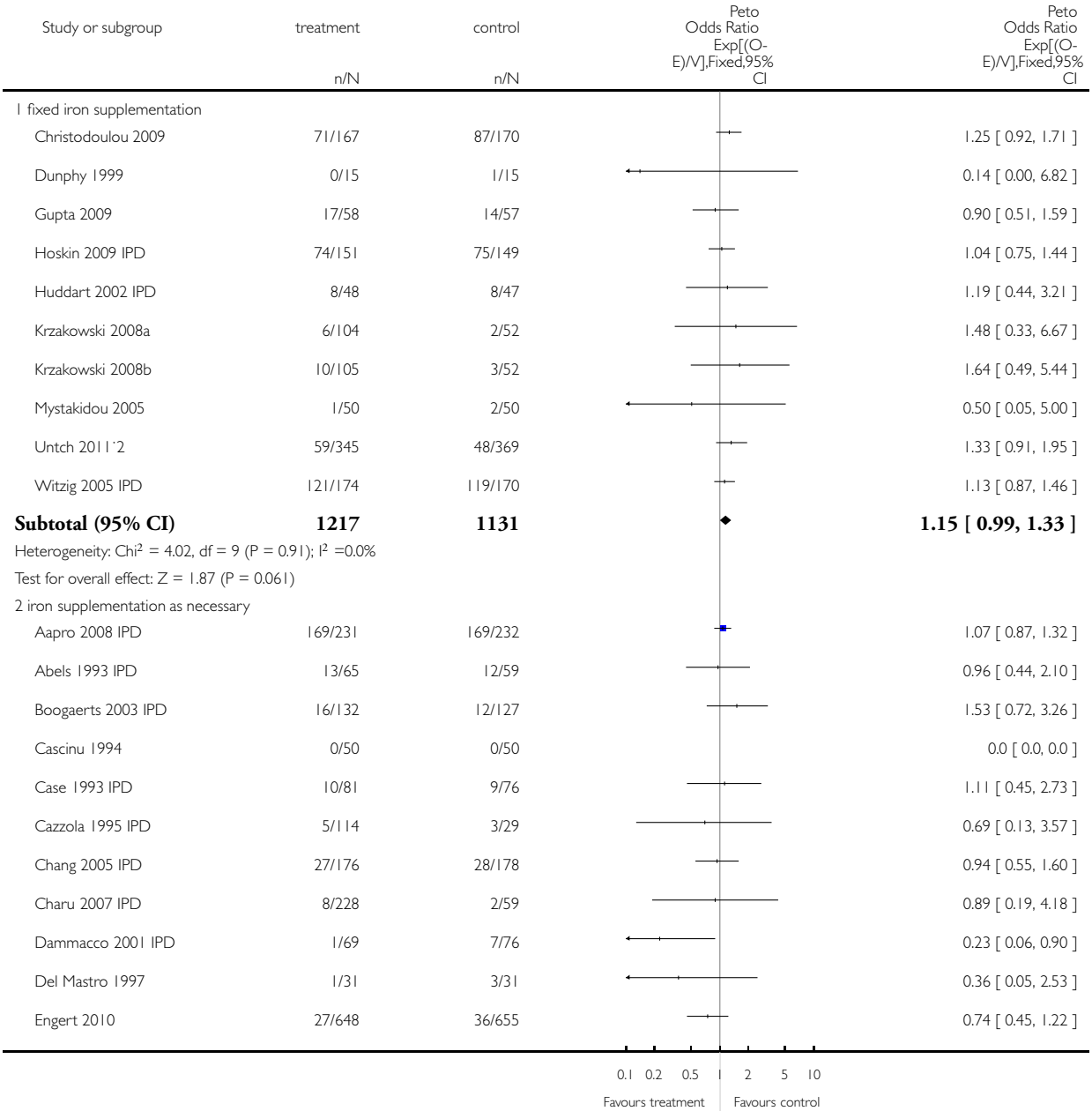


## Analysis 5.11. Comparison 5 Overall survival, Outcome 11 Overall survival - iron supplementation.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 5 Overall survival

Outcome: 11 Overall survival - iron supplementation

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| Study or subgroup | treatment n/N | control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| EPO-INT-1 IPD | 11/165 | 3/81 | | 1.88 [ 0.63, 5.64 ] |
| EPO-INT-3 IPD | 9/135 | 3/65 | | 1.55 [ 0.47, 5.10 ] |
| Fujisaka 2011 | 37/89 | 34/92 | | 1.15 [ 0.72, 1.85 ] |
| Gordon 2008 IPD | 11/164 | 5/56 | | 0.74 [ 0.26, 2.14 ] |
| Goss 2005 IPD | 28/52 | 29/52 | | 1.13 [ 0.67, 1.91 ] |
| Grote 2005 IPD | 100/109 | 101/115 | | 1.17 [ 0.89, 1.54 ] |
| Hedenus 2003 IPD | 101/176 | 82/173 | | 1.32 [ 0.98, 1.77 ] |
| Henke 2003 IPD | 109/180 | 89/171 | | 1.27 [ 0.96, 1.68 ] |
| Henry 1995 IPD | 7/67 | 10/65 | | 0.68 [ 0.26, 1.77 ] |
| Hernandez 2009 IPD | 17/196 | 20/195 | | 0.84 [ 0.44, 1.60 ] |
| Kotasek 2002 IPD | 4/129 | 0/32 | | 3.49 [ 0.30, 40.45 ] |
| Kotasek 2003 IPD | 4/208 | 1/51 | | 0.99 [ 0.11, 8.84 ] |
| Kurz 1997 | 0/23 | 0/12 | | 0.0 [ 0.0, 0.0 ] |
| Leyland-Jones 2005 IPD | 121/469 | 91/470 | | 1.41 [ 1.08, 1.85 ] |
| Littlewood 2001 IPD | 155/251 | 82/124 | | 0.80 [ 0.61, 1.05 ] |
| Milroy 2003 IPD | 136/214 | 126/210 | | 1.13 [ 0.88, 1.45 ] |
| ML17616 2006 | 1/30 | 0/30 | | 7.39 [ 0.15, 372.38 ] |
| ML17620 2006 | 4/61 | 0/60 | | 7.70 [ 1.05, 56.33 ] |
| O'Shaugnessy 2005 IPD | 1/51 | 0/49 | | 7.69 [ 0.15, 387.58 ] |
| Oberhoff 1998 IPD | 9/116 | 10/111 | | 0.62 [ 0.24, 1.59 ] |
| Osterborg 1996 IPD | 26/99 | 14/49 | | 0.94 [ 0.49, 1.81 ] |
| Osterborg 2002 IPD | 110/173 | 109/176 | | 1.04 [ 0.80, 1.36 ] |
| Overgaard 2009 | 144/255 | 119/259 | | 1.26 [ 0.99, 1.61 ] |
| P-174 IPD | 1/33 | 1/12 | | 0.44 [ 0.03, 7.27 ] |
| Pirker 2008 IPD | 243/299 | 254/301 | | 0.94 [ 0.78, 1.13 ] |
| Pronzato 2010 IPD | 23/110 | 20/113 | | 1.05 [ 0.58, 1.91 ] |
| Quirt 1996 IPD | 2/28 | 0/28 | | 5.90 [ 0.36, 97.07 ] |
| Ray-Coquard 2009 IPD | 75/110 | 84/108 | | 0.79 [ 0.58, 1.08 ] |
| Razzouk 2004 | 2/112 | 2/110 | | 0.98 [ 0.14, 7.03 ] |
| Rose 1994 IPD | 16/142 | 6/79 | | 1.66 [ 0.70, 3.92 ] |


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| Study or subgroup | treatment n/N | control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Smith 2003 | 3/64 | 0/22 | | 3.96 [ 0.29, 54.28 ] |
| Smith 2008 IPD | 250/517 | 216/472 | | 1.22 [ 1.02, 1.47 ] |
| Strauss 2008 IPD | 8/34 | 5/40 | | 2.00 [ 0.65, 6.13 ] |
| Ten Bokkel1998 IPD | 6/87 | 2/33 | | 1.27 [ 0.26, 6.34 ] |
| Thatcher 1999 IPD | 7/86 | 3/44 | | 1.13 [ 0.29, 4.36 ] |
| Thomas 2002 IPD | 4/65 | 5/65 | | 0.79 [ 0.21, 2.95 ] |
| Thomas 2008 IPD | 22/58 | 17/56 | | 1.28 [ 0.68, 2.40 ] |
| Throuvalas 2000 | 0/28 | 1/27 | | 0.13 [ 0.00, 6.55 ] |
| Tjulandin 2010a | 5/76 | 6/37 | | 0.28 [ 0.07, 1.08 ] |
| Tjulandin 2010b | 4/73 | 6/37 | | 0.34 [ 0.09, 1.26 ] |
| Tjulandin 2011 | 6/95 | 5/91 | | 1.16 [ 0.34, 3.90 ] |
| Tsuboi 2009 | 21/61 | 19/56 | | 0.94 [ 0.57, 1.54 ] |
| Vansteenkiste 2002 IPD | 101/159 | 118/161 | | 0.79 [ 0.60, 1.04 ] |
| Wilkinson 2006 IPD | 3/121 | 0/61 | | 4.48 [ 0.40, 50.03 ] |
| Wright 2007 IPD | 32/33 | 34/37 | | 1.55 [ 0.94, 2.54 ] |
| **Subtotal (95% CI)** | **7628** | **6260** | | **1.07 [ 1.01, 1.14 ]** |
| Heterogeneity: Chi² = 64.77, df = 53 (P = 0.13); I² =18% | | | | |
| Test for overall effect: Z = 2.21 (P = 0.027) | | | | |
| 3 iron handled differently in the study arms | | | | |
| Blohmer 2011 | 25/127 | 29/129 | | 0.88 [ 0.51, 1.51 ] |
| Debus 2006 IPD | 146/195 | 159/190 | | 0.81 [ 0.64, 1.02 ] |
| EPO-GER-20 IPD | 7/48 | 8/45 | | 0.71 [ 0.26, 1.95 ] |
| Machtay 2007 IPD | 37/77 | 32/71 | | 1.19 [ 0.74, 1.91 ] |
| Moebus 2007 IPD | 59/324 | 56/319 | | 1.01 [ 0.70, 1.46 ] |
| OBE/EPO-INT-03 IPD | 5/35 | 6/37 | | 1.07 [ 0.32, 3.56 ] |
| Rosen 2003 | 19/47 | 23/43 | | 1.19 [ 0.65, 2.18 ] |
| Savonije 2005 IPD | 132/211 | 61/104 | | 1.14 [ 0.85, 1.53 ] |
| Sweeney 1998 | 0/24 | 0/24 | | 0.0 [ 0.0, 0.0 ] |
| **Subtotal (95% CI)** | **1088** | **962** | | **0.96 [ 0.84, 1.11 ]** |
| Heterogeneity: Chi² = 5.27, df = 7 (P = 0.63); I² =0.0% | | | | |
| Test for overall effect: Z = 0.54 (P = 0.59) | | | | |
| 4 no explicit statement on iron supplementation or no iron given | | | | |
| Antonadou 2001 | 10/190 | 30/195 | | 0.35 [ 0.19, 0.66 ] |


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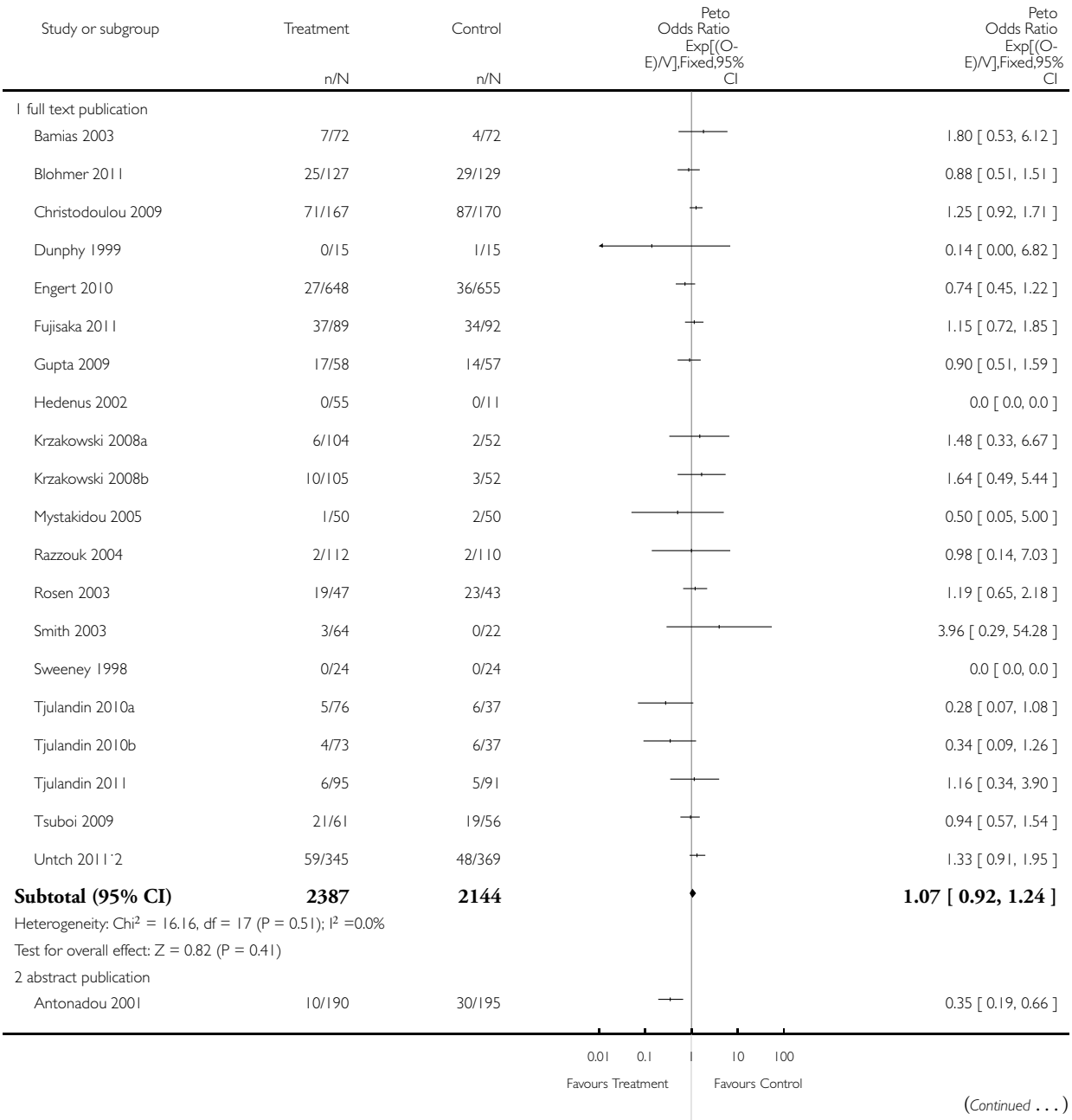
| Study or subgroup | treatment n/N | control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Bamias 2003 | 7/72 | 4/72 | | 1.80 [ 0.53, 6.12 ] |
| Hedenus 2002 | 0/55 | 0/11 | | 0.0 [ 0.0, 0.0 ] |
| Thompson 2000 | 3/45 | 0/21 | | 4.52 [ 0.38, 53.37 ] |
| Winquist 2009 | 24/26 | 27/30 | | 0.58 [ 0.33, 1.03 ] |
| **Subtotal (95% CI)** | **388** | **329** | | **0.56 [ 0.38, 0.83 ]** |
| Heterogeneity: Chi² = 8.36, df = 3 (P = 0.04); I² =64% | | | | |
| Test for overall effect: Z = 2.86 (P = 0.0042) | | | | |
| 5 explicitly stated NO IRON | | | | |
| **Subtotal (95% CI)** | **0** | **0** | | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: not applicable | | | | |
| **Total (95% CI)** | | | | **1.05 [ 1.00, 1.11 ]** |
| Heterogeneity: Chi² = 95.40, df = 75 (P = 0.06); I² =21% | | | | |
| Test for overall effect: Z = 1.97 (P = 0.048) | | | | |
| Test for subgroup differences: Chi² = 12.99, df = 3 (P = 0.00), I² =77% | | | | |

### Analysis 5.12. Comparison 5 Overall survival, Outcome 12 Overall survival - publication.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 5 Overall survival

Outcome: 12 Overall survival - publication

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| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| ML17620 2006 | 4/61 | 0/60 | | 7.70 [ 1.05, 56.33 ] |
| Overgaard 2009 | 144/255 | 119/259 | | 1.26 [ 0.99, 1.61 ] |
| **Subtotal (95% CI)** | **506** | **514** | | **1.09 [ 0.87, 1.37 ]** |
| Heterogeneity: Chi² = 17.76, df = 2 (P = 0.00014); I² =89% | | | | |
| Test for overall effect: Z = 0.76 (P = 0.45) | | | | |
| 3 unpublished data | | | | |
| Cascinu 1994 | 0/50 | 0/50 | | 0.0 [ 0.0, 0.0 ] |
| Del Mastro 1997 | 1/31 | 3/31 | | 0.36 [ 0.05, 2.53 ] |
| Kurz 1997 | 0/23 | 0/12 | | 0.0 [ 0.0, 0.0 ] |
| Thompson 2000 | 3/45 | 0/21 | | 4.52 [ 0.38, 53.37 ] |
| Throuvalas 2000 | 0/28 | 1/27 | | 0.13 [ 0.00, 6.55 ] |
| **Subtotal (95% CI)** | **177** | **141** | | **0.73 [ 0.17, 3.05 ]** |
| Heterogeneity: Chi² = 3.35, df = 2 (P = 0.19); I² =40% | | | | |
| Test for overall effect: Z = 0.43 (P = 0.67) | | | | |
| 4 Data presented at FDA hearing | | | | |
| **Subtotal (95% CI)** | **0** | **0** | | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: not applicable | | | | |
| 5 Data taken from IPD review (Bohlius 2009) | | | | |
| Aapro 2008 IPD | 169/231 | 169/232 | | 1.07 [ 0.87, 1.32 ] |
| Abels 1993 IPD | 13/65 | 12/59 | | 0.96 [ 0.44, 2.10 ] |
| Boogaerts 2003 IPD | 16/132 | 12/127 | | 1.53 [ 0.72, 3.26 ] |
| Case 1993 IPD | 10/81 | 9/76 | | 1.11 [ 0.45, 2.73 ] |
| Cazzola 1995 IPD | 5/114 | 3/29 | | 0.69 [ 0.13, 3.57 ] |
| Chang 2005 IPD | 27/176 | 28/178 | | 0.94 [ 0.55, 1.60 ] |
| Charu 2007 IPD | 8/228 | 2/59 | | 0.89 [ 0.19, 4.18 ] |
| Dammacco 2001 IPD | 1/69 | 7/76 | | 0.23 [ 0.06, 0.90 ] |
| Debus 2006 IPD | 146/195 | 159/190 | | 0.81 [ 0.64, 1.02 ] |
| EPO-GER-20 IPD | 7/48 | 8/45 | | 0.71 [ 0.26, 1.95 ] |
| EPO-INT-1 IPD | 11/165 | 3/81 | | 1.88 [ 0.63, 5.64 ] |
| EPO-INT-3 IPD | 9/135 | 3/65 | | 1.55 [ 0.47, 5.10 ] |
| Gordon 2008 IPD | 11/164 | 5/56 | | 0.74 [ 0.26, 2.14 ] |
| Goss 2005 IPD | 28/52 | 29/52 | | 1.13 [ 0.67, 1.91 ] |
| Grote 2005 IPD | 100/109 | 101/115 | | 1.17 [ 0.89, 1.54 ] |


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| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Hedenus 2003 IPD | 101/176 | 82/173 | | 1.32 [ 0.98, 1.77 ] |
| Henke 2003 IPD | 109/180 | 89/171 | | 1.27 [ 0.96, 1.68 ] |
| Henry 1995 IPD | 7/67 | 10/65 | | 0.68 [ 0.26, 1.77 ] |
| Hernandez 2009 IPD | 17/196 | 20/195 | | 0.84 [ 0.44, 1.60 ] |
| Hoskin 2009 IPD | 74/151 | 75/149 | | 1.04 [ 0.75, 1.44 ] |
| Huddart 2002 IPD | 8/48 | 8/47 | | 1.19 [ 0.44, 3.21 ] |
| Kotasek 2002 IPD | 4/129 | 0/32 | | 3.49 [ 0.30, 40.45 ] |
| Kotasek 2003 IPD | 4/208 | 1/51 | | 0.99 [ 0.11, 8.84 ] |
| Leyland-Jones 2005 IPD | 121/469 | 91/470 | | 1.41 [ 1.08, 1.85 ] |
| Littlewood 2001 IPD | 155/251 | 82/124 | | 0.80 [ 0.61, 1.05 ] |
| Machtay 2007 IPD | 37/77 | 32/71 | | 1.19 [ 0.74, 1.91 ] |
| Milroy 2003 IPD | 136/214 | 126/210 | | 1.13 [ 0.88, 1.45 ] |
| Moebus 2007 IPD | 59/324 | 56/319 | | 1.01 [ 0.70, 1.46 ] |
| O'Shaugnessy 2005 IPD | 1/51 | 0/49 | | 7.69 [ 0.15, 387.58 ] |
| OBE/EPO-INT-03 IPD | 5/35 | 6/37 | | 1.07 [ 0.32, 3.56 ] |
| Oberhoff 1998 IPD | 9/116 | 10/111 | | 0.62 [ 0.24, 1.59 ] |
| Osterborg 1996 IPD | 26/99 | 14/49 | | 0.94 [ 0.49, 1.81 ] |
| Osterborg 2002 IPD | 110/173 | 109/176 | | 1.04 [ 0.80, 1.36 ] |
| P-174 IPD | 1/33 | 1/12 | | 0.44 [ 0.03, 7.27 ] |
| Pirker 2008 IPD | 243/299 | 254/301 | | 0.94 [ 0.78, 1.13 ] |
| Pronzato 2010 IPD | 23/110 | 20/113 | | 1.05 [ 0.58, 1.91 ] |
| Quirt 1996 IPD | 2/28 | 0/28 | | 5.90 [ 0.36, 97.07 ] |
| Ray-Coquard 2009 IPD | 75/110 | 84/108 | | 0.79 [ 0.58, 1.08 ] |
| Rose 1994 IPD | 16/142 | 6/79 | | 1.66 [ 0.70, 3.92 ] |
| Savonije 2005 IPD | 132/211 | 61/104 | | 1.14 [ 0.85, 1.53 ] |
| Smith 2008 IPD | 250/517 | 216/472 | | 1.22 [ 1.02, 1.47 ] |
| Strauss 2008 IPD | 8/34 | 5/40 | | 2.00 [ 0.65, 6.13 ] |
| Ten Bokkel1998 IPD | 6/87 | 2/33 | | 1.27 [ 0.26, 6.34 ] |
| Thatcher 1999 IPD | 7/86 | 3/44 | | 1.13 [ 0.29, 4.36 ] |
| Thomas 2002 IPD | 4/65 | 5/65 | | 0.79 [ 0.21, 2.95 ] |


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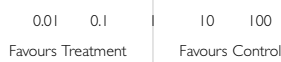
| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Thomas 2008 IPD | 22/58 | 17/56 | | 1.28 [ 0.68, 2.40 ] |
| Vansteenkiste 2002 IPD | 101/159 | 118/161 | | 0.79 [ 0.60, 1.04 ] |
| Wilkinson 2006 IPD | 3/121 | 0/61 | | 4.48 [ 0.40, 50.03 ] |
| Witzig 2005 IPD | 121/174 | 119/170 | | 1.13 [ 0.87, 1.46 ] |
| Wright 2007 IPD | 32/33 | 34/37 | | 1.55 [ 0.94, 2.54 ] |
| **Subtotal (95% CI)** | **7195** | **5823** | | **1.06 [ 1.00, 1.12 ]** |
| Heterogeneity: Chi² = 52.72, df = 49 (P = 0.33); I² =7% | | | | |
| Test for overall effect: Z = 1.86 (P = 0.063) | | | | |
| 6 clinical trial result information | | | | |
| ML17616 2006 | 1/30 | 0/30 | | 7.39 [ 0.15, 372.38 ] |
| **Subtotal (95% CI)** | **30** | **30** | | **7.39 [ 0.15, 372.38 ]** |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: Z = 1.00 (P = 0.32) | | | | |
| 7 other | | | | |
| Winquist 2009 | 24/26 | 27/30 | | 0.58 [ 0.33, 1.03 ] |
| **Subtotal (95% CI)** | **26** | **30** | | **0.58 [ 0.33, 1.03 ]** |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: Z = 1.85 (P = 0.065) | | | | |
| **Total (95% CI)** | | | | **1.05 [ 1.00, 1.11 ]** |
| Heterogeneity: Chi² = 95.40, df = 75 (P = 0.06); I² =21% | | | | |
| Test for overall effect: Z = 1.97 (P = 0.048) | | | | |
| Test for subgroup differences: Chi² = 5.41, df = 5 (P = 0.37), I² =8% | | | | |

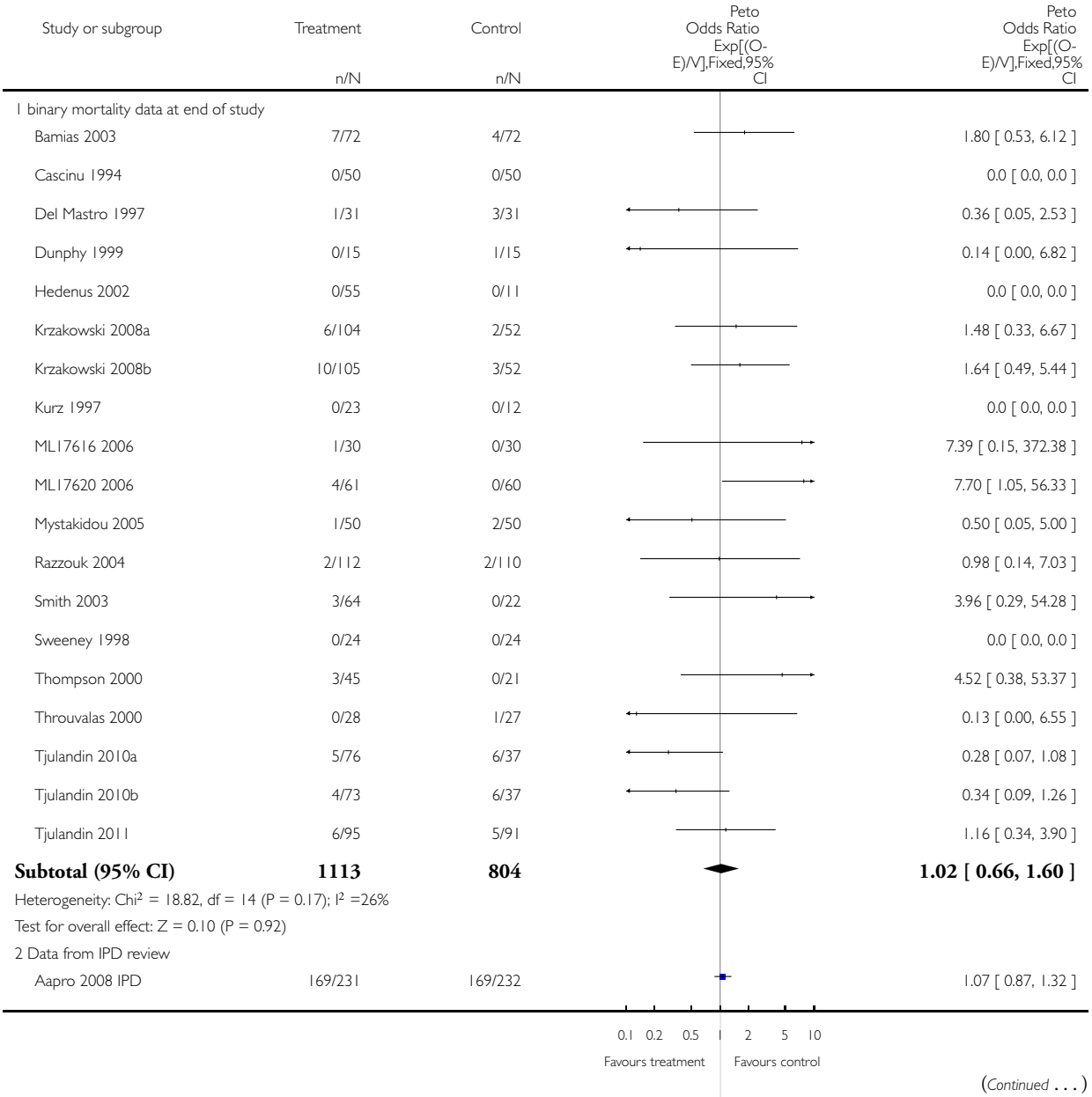


## Analysis 5.13. Comparison 5 Overall survival, Outcome 13 Overall survival - time-to-event or binary mortality data.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 5 Overall survival

Outcome: 13 Overall survival - time-to-event or binary mortality data

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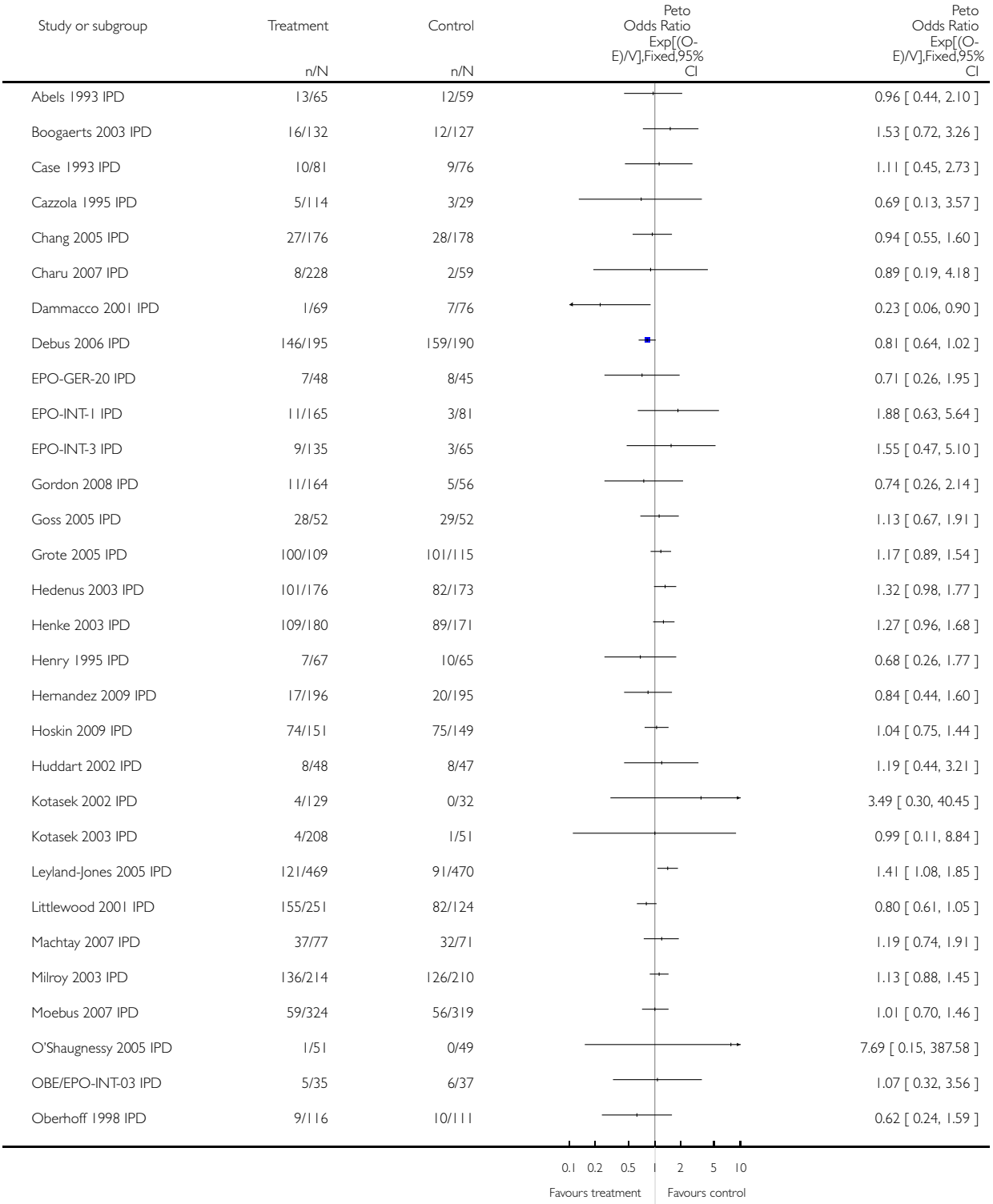


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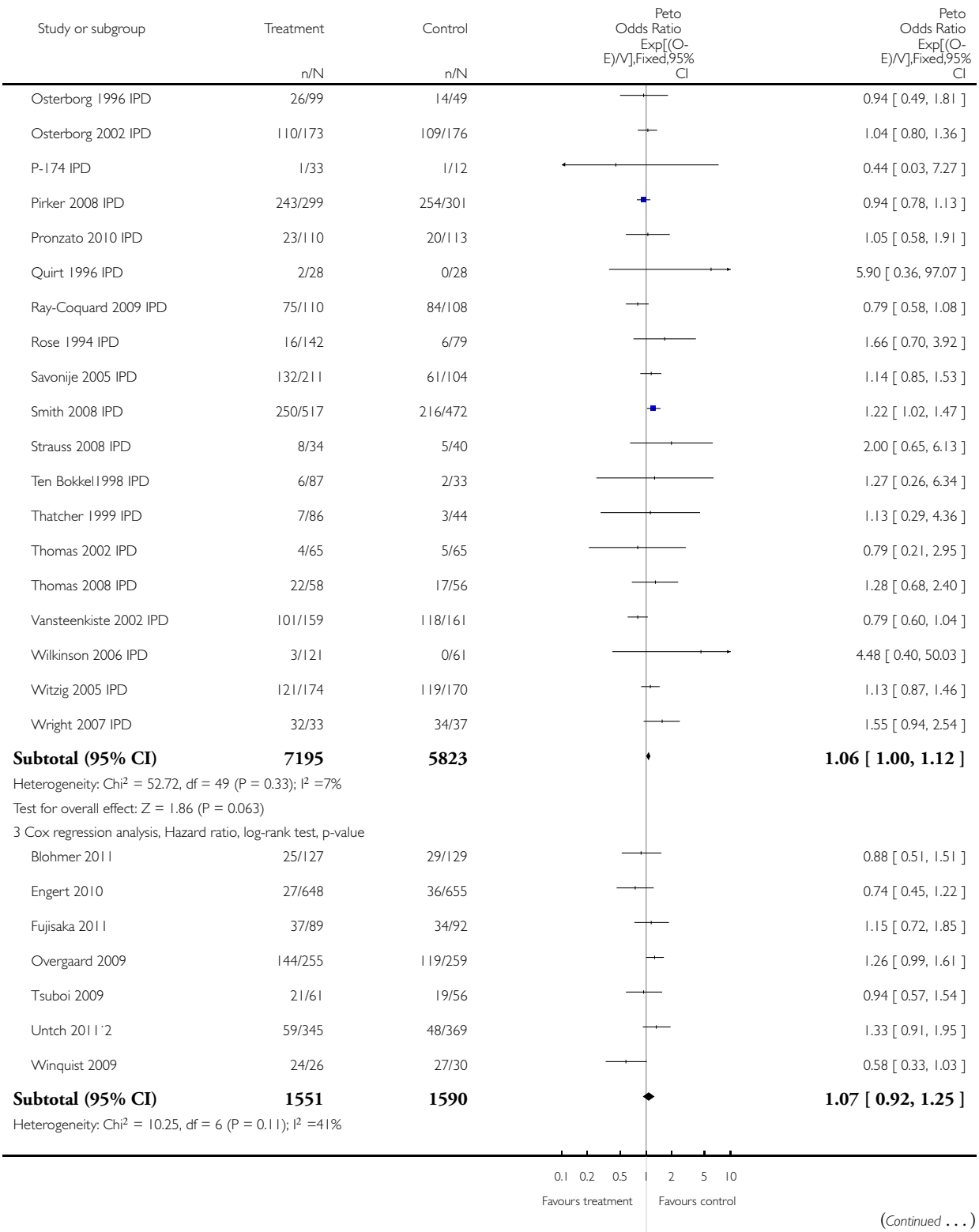


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| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Test for overall effect: Z = 0.89 (P = 0.38) | | | | |
| 4 Survival curve and p-value | | | | |
| Antonadou 2001 | 10/190 | 30/195 | | 0.35 [ 0.19, 0.66 ] |
| Christodoulou 2009 | 71/167 | 87/170 | | 1.25 [ 0.92, 1.71 ] |
| Gupta 2009 | 17/58 | 14/57 | | 0.90 [ 0.51, 1.59 ] |
| Rosen 2003 | 19/47 | 23/43 | | 1.19 [ 0.65, 2.18 ] |
| **Subtotal (95% CI)** | **462** | **465** | | **0.99 [ 0.78, 1.24 ]** |
| Heterogeneity: Chi² = 13.23, df = 3 (P = 0.004); I² =77% | | | | |
| Test for overall effect: Z = 0.12 (P = 0.91) | | | | |
| **Total (95% CI)** | | | | **1.05 [ 1.00, 1.11 ]** |
| Heterogeneity: Chi² = 95.40, df = 75 (P = 0.06); I² =21% | | | | |
| Test for overall effect: Z = 1.97 (P = 0.048) | | | | |
| Test for subgroup differences: Chi² = 0.38, df = 3 (P = 0.94), I² =0.0% | | | | |

### Analysis 5.14. Comparison 5 Overall survival, Outcome 14 Overall survival - allocation concealment.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 5 Overall survival

Outcome: 14 Overall survival - allocation concealment

| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| 1 adequate | | | | |
| Aapro 2008 IPD | 169/231 | 169/232 | | 1.07 [ 0.87, 1.32 ] |
| Blohmer 2011 | 25/127 | 29/129 | | 0.88 [ 0.51, 1.51 ] |
| Boogaerts 2003 IPD | 16/132 | 12/127 | | 1.53 [ 0.72, 3.26 ] |
| Cazzola 1995 IPD | 5/114 | 3/29 | | 0.69 [ 0.13, 3.57 ] |
| Chang 2005 IPD | 27/176 | 28/178 | | 0.94 [ 0.55, 1.60 ] |
| Charu 2007 IPD | 8/228 | 2/59 | | 0.89 [ 0.19, 4.18 ] |
| Christodoulou 2009 | 71/167 | 87/170 | | 1.25 [ 0.92, 1.71 ] |
| Del Mastro 1997 | 1/31 | 3/31 | | 0.36 [ 0.05, 2.53 ] |
| EPO-INT-3 IPD | 9/135 | 3/65 | | 1.55 [ 0.47, 5.10 ] |
| Fujisaka 2011 | 37/89 | 34/92 | | 1.15 [ 0.72, 1.85 ] |
| Gordon 2008 IPD | 11/164 | 5/56 | | 0.74 [ 0.26, 2.14 ] |
| Goss 2005 IPD | 28/52 | 29/52 | | 1.13 [ 0.67, 1.91 ] |
| Hedenus 2002 | 0/55 | 0/11 | | 0.0 [ 0.0, 0.0 ] |
| Hedenus 2003 IPD | 101/176 | 82/173 | | 1.32 [ 0.98, 1.77 ] |
| Henke 2003 IPD | 109/180 | 89/171 | | 1.27 [ 0.96, 1.68 ] |
| Hernandez 2009 IPD | 17/196 | 20/195 | | 0.84 [ 0.44, 1.60 ] |
| Kotasek 2002 IPD | 4/129 | 0/32 | | 3.49 [ 0.30, 40.45 ] |
| Kotasek 2003 IPD | 4/208 | 1/51 | | 0.99 [ 0.11, 8.84 ] |
| Kurz 1997 | 0/23 | 0/12 | | 0.0 [ 0.0, 0.0 ] |
| Leyland-Jones 2005 IPD | 121/469 | 91/470 | | 1.41 [ 1.08, 1.85 ] |
| Littlewood 2001 IPD | 155/251 | 82/124 | | 0.80 [ 0.61, 1.05 ] |
| Machtay 2007 IPD | 37/77 | 32/71 | | 1.19 [ 0.74, 1.91 ] |
| Milroy 2003 IPD | 136/214 | 126/210 | | 1.13 [ 0.88, 1.45 ] |
| Moebus 2007 IPD | 59/324 | 56/319 | | 1.01 [ 0.70, 1.46 ] |


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| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| O'Shaugnessy 2005 IPD | 1/51 | 0/49 | | 7.69 [ 0.15, 387.58 ] |
| OBE/EPO-INT-03 IPD | 5/35 | 6/37 | | 1.07 [ 0.32, 3.56 ] |
| Oberhoff 1998 IPD | 9/116 | 10/111 | | 0.62 [ 0.24, 1.59 ] |
| Osterborg 1996 IPD | 26/99 | 14/49 | | 0.94 [ 0.49, 1.81 ] |
| Osterborg 2002 IPD | 110/173 | 109/176 | | 1.04 [ 0.80, 1.36 ] |
| Overgaard 2009 | 144/255 | 119/259 | | 1.26 [ 0.99, 1.61 ] |
| Pirker 2008 IPD | 243/299 | 254/301 | | 0.94 [ 0.78, 1.13 ] |
| Pronzato 2010 IPD | 23/110 | 20/113 | | 1.05 [ 0.58, 1.91 ] |
| Ray-Coquard 2009 IPD | 75/110 | 84/108 | | 0.79 [ 0.58, 1.08 ] |
| Razzouk 2004 | 2/112 | 2/110 | | 0.98 [ 0.14, 7.03 ] |
| Savonije 2005 IPD | 132/211 | 61/104 | | 1.14 [ 0.85, 1.53 ] |
| Smith 2008 IPD | 250/517 | 216/472 | | 1.22 [ 1.02, 1.47 ] |
| Sweeney 1998 | 0/24 | 0/24 | | 0.0 [ 0.0, 0.0 ] |
| Ten Bokkel1998 IPD | 6/87 | 2/33 | | 1.27 [ 0.26, 6.34 ] |
| Thomas 2002 IPD | 4/65 | 5/65 | | 0.79 [ 0.21, 2.95 ] |
| Thomas 2008 IPD | 22/58 | 17/56 | | 1.28 [ 0.68, 2.40 ] |
| Thompson 2000 | 3/45 | 0/21 | | 4.52 [ 0.38, 53.37 ] |
| Throuvalas 2000 | 0/28 | 1/27 | | 0.13 [ 0.00, 6.55 ] |
| Tsuboi 2009 | 21/61 | 19/56 | | 0.94 [ 0.57, 1.54 ] |
| Vansteenkiste 2002 IPD | 101/159 | 118/161 | | 0.79 [ 0.60, 1.04 ] |
| Winquist 2009 | 24/26 | 27/30 | | 0.58 [ 0.33, 1.03 ] |
| Witzig 2005 IPD | 121/174 | 119/170 | | 1.13 [ 0.87, 1.46 ] |
| Wright 2007 IPD | 32/33 | 34/37 | | 1.55 [ 0.94, 2.54 ] |
| **Subtotal (95% CI)** | **6796** | **5628** | | **1.08 [ 1.02, 1.14 ]** |
| Heterogeneity: Chi² = 45.36, df = 43 (P = 0.37); I² =5% | | | | |
| Test for overall effect: Z = 2.47 (P = 0.014) | | | | |
| 2 unclear | | | | |
| Abels 1993 IPD | 13/65 | 12/59 | | 0.96 [ 0.44, 2.10 ] |
| Antonadou 2001 | 10/190 | 30/195 | | 0.35 [ 0.19, 0.66 ] |
| Bamias 2003 | 7/72 | 4/72 | | 1.80 [ 0.53, 6.12 ] |
| Cascinu 1994 | 0/50 | 0/50 | | 0.0 [ 0.0, 0.0 ] |
| Case 1993 IPD | 10/81 | 9/76 | | 1.11 [ 0.45, 2.73 ] |


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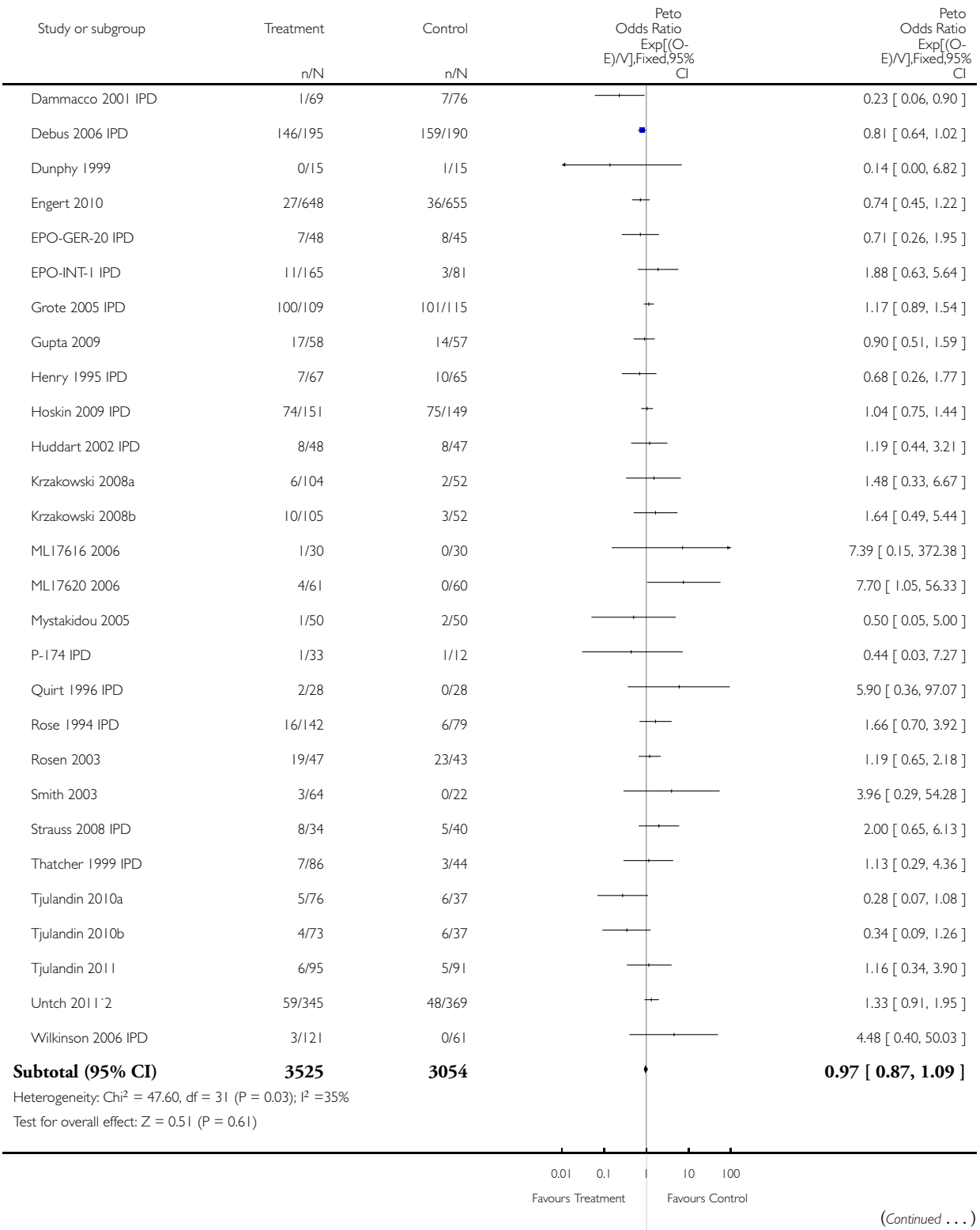

| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Dammacco 2001 IPD | 1/69 | 7/76 | | 0.23 [ 0.06, 0.90 ] |
| Debus 2006 IPD | 146/195 | 159/190 | | 0.81 [ 0.64, 1.02 ] |
| Dunphy 1999 | 0/15 | 1/15 | | 0.14 [ 0.00, 6.82 ] |
| Engert 2010 | 27/648 | 36/655 | | 0.74 [ 0.45, 1.22 ] |
| EPO-GER-20 IPD | 7/48 | 8/45 | | 0.71 [ 0.26, 1.95 ] |
| EPO-INT-1 IPD | 11/165 | 3/81 | | 1.88 [ 0.63, 5.64 ] |
| Grote 2005 IPD | 100/109 | 101/115 | | 1.17 [ 0.89, 1.54 ] |
| Gupta 2009 | 17/58 | 14/57 | | 0.90 [ 0.51, 1.59 ] |
| Henry 1995 IPD | 7/67 | 10/65 | | 0.68 [ 0.26, 1.77 ] |
| Hoskin 2009 IPD | 74/151 | 75/149 | | 1.04 [ 0.75, 1.44 ] |
| Huddart 2002 IPD | 8/48 | 8/47 | | 1.19 [ 0.44, 3.21 ] |
| Krzakowski 2008a | 6/104 | 2/52 | | 1.48 [ 0.33, 6.67 ] |
| Krzakowski 2008b | 10/105 | 3/52 | | 1.64 [ 0.49, 5.44 ] |
| ML17616 2006 | 1/30 | 0/30 | | 7.39 [ 0.15, 372.38 ] |
| ML17620 2006 | 4/61 | 0/60 | | 7.70 [ 1.05, 56.33 ] |
| Mystakidou 2005 | 1/50 | 2/50 | | 0.50 [ 0.05, 5.00 ] |
| P-174 IPD | 1/33 | 1/12 | | 0.44 [ 0.03, 7.27 ] |
| Quirt 1996 IPD | 2/28 | 0/28 | | 5.90 [ 0.36, 97.07 ] |
| Rose 1994 IPD | 16/142 | 6/79 | | 1.66 [ 0.70, 3.92 ] |
| Rosen 2003 | 19/47 | 23/43 | | 1.19 [ 0.65, 2.18 ] |
| Smith 2003 | 3/64 | 0/22 | | 3.96 [ 0.29, 54.28 ] |
| Strauss 2008 IPD | 8/34 | 5/40 | | 2.00 [ 0.65, 6.13 ] |
| Thatcher 1999 IPD | 7/86 | 3/44 | | 1.13 [ 0.29, 4.36 ] |
| Tjulandin 2010a | 5/76 | 6/37 | | 0.28 [ 0.07, 1.08 ] |
| Tjulandin 2010b | 4/73 | 6/37 | | 0.34 [ 0.09, 1.26 ] |
| Tjulandin 2011 | 6/95 | 5/91 | | 1.16 [ 0.34, 3.90 ] |
| Untch 2011˙2 | 59/345 | 48/369 | | 1.33 [ 0.91, 1.95 ] |
| Wilkinson 2006 IPD | 3/121 | 0/61 | | 4.48 [ 0.40, 50.03 ] |
| **Subtotal (95% CI)** | **3525** | **3054** | | **0.97 [ 0.87, 1.09 ]** |
| Heterogeneity: Chi² = 47.60, df = 31 (P = 0.03); I² =35% | | | | |
| Test for overall effect: Z = 0.51 (P = 0.61) | | | | |



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| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| **Total (95% CI)** | | | | **1.05 [ 1.00, 1.11 ]** |
| Heterogeneity: Chi² = 95.40, df = 75 (P = 0.06); I² =21% | | | | |
| Test for overall effect: Z = 1.97 (P = 0.048) | | | | |
| Test for subgroup differences: Chi² = 2.45, df = 1 (P = 0.12), I² =59% | | | | |


## Analysis 5.15. Comparison 5 Overall survival, Outcome 15 Overall survival - masking.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 5 Overall survival

Outcome: 15 Overall survival - masking

| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| 1 double-blind | | | | |
| Abels 1993 IPD | 13/65 | 12/59 | | 0.96 [ 0.44, 2.10 ] |
| Cascinu 1994 | 0/50 | 0/50 | | 0.0 [ 0.0, 0.0 ] |
| Case 1993 IPD | 10/81 | 9/76 | | 1.11 [ 0.45, 2.73 ] |
| Dammacco 2001 IPD | 1/69 | 7/76 | | 0.23 [ 0.06, 0.90 ] |
| Engert 2010 | 27/648 | 36/655 | | 0.74 [ 0.45, 1.22 ] |
| EPO-INT-1 IPD | 11/165 | 3/81 | | 1.88 [ 0.63, 5.64 ] |
| EPO-INT-3 IPD | 9/135 | 3/65 | | 1.55 [ 0.47, 5.10 ] |
| Fujisaka 2011 | 37/89 | 34/92 | | 1.15 [ 0.72, 1.85 ] |
| Gordon 2008 IPD | 11/164 | 5/56 | | 0.74 [ 0.26, 2.14 ] |
| Goss 2005 IPD | 28/52 | 29/52 | | 1.13 [ 0.67, 1.91 ] |
| Grote 2005 IPD | 100/109 | 101/115 | | 1.17 [ 0.89, 1.54 ] |


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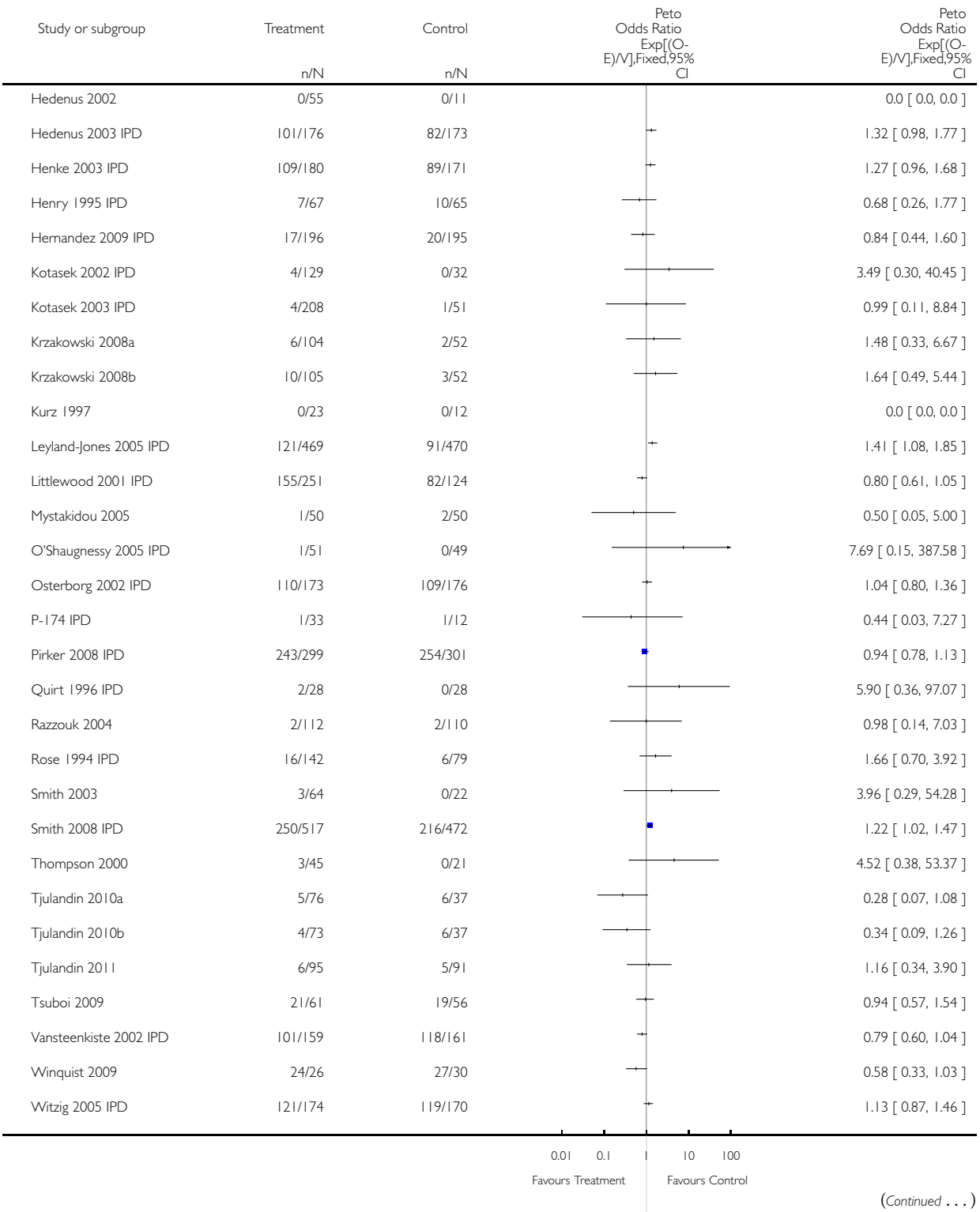

| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Hedenus 2002 | 0/55 | 0/11 | | 0.0 [ 0.0, 0.0 ] |
| Hedenus 2003 IPD | 101/176 | 82/173 | | 1.32 [ 0.98, 1.77 ] |
| Henke 2003 IPD | 109/180 | 89/171 | | 1.27 [ 0.96, 1.68 ] |
| Henry 1995 IPD | 7/67 | 10/65 | | 0.68 [ 0.26, 1.77 ] |
| Hernandez 2009 IPD | 17/196 | 20/195 | | 0.84 [ 0.44, 1.60 ] |
| Kotasek 2002 IPD | 4/129 | 0/32 | | 3.49 [ 0.30, 40.45 ] |
| Kotasek 2003 IPD | 4/208 | 1/51 | | 0.99 [ 0.11, 8.84 ] |
| Krzakowski 2008a | 6/104 | 2/52 | | 1.48 [ 0.33, 6.67 ] |
| Krzakowski 2008b | 10/105 | 3/52 | | 1.64 [ 0.49, 5.44 ] |
| Kurz 1997 | 0/23 | 0/12 | | 0.0 [ 0.0, 0.0 ] |
| Leyland-Jones 2005 IPD | 121/469 | 91/470 | | 1.41 [ 1.08, 1.85 ] |
| Littlewood 2001 IPD | 155/251 | 82/124 | | 0.80 [ 0.61, 1.05 ] |
| Mystakidou 2005 | 1/50 | 2/50 | | 0.50 [ 0.05, 5.00 ] |
| O'Shaugnessy 2005 IPD | 1/51 | 0/49 | | 7.69 [ 0.15, 387.58 ] |
| Osterborg 2002 IPD | 110/173 | 109/176 | | 1.04 [ 0.80, 1.36 ] |
| P-174 IPD | 1/33 | 1/12 | | 0.44 [ 0.03, 7.27 ] |
| Pirker 2008 IPD | 243/299 | 254/301 | | 0.94 [ 0.78, 1.13 ] |
| Quirt 1996 IPD | 2/28 | 0/28 | | 5.90 [ 0.36, 97.07 ] |
| Razzouk 2004 | 2/112 | 2/110 | | 0.98 [ 0.14, 7.03 ] |
| Rose 1994 IPD | 16/142 | 6/79 | | 1.66 [ 0.70, 3.92 ] |
| Smith 2003 | 3/64 | 0/22 | | 3.96 [ 0.29, 54.28 ] |
| Smith 2008 IPD | 250/517 | 216/472 | | 1.22 [ 1.02, 1.47 ] |
| Thompson 2000 | 3/45 | 0/21 | | 4.52 [ 0.38, 53.37 ] |
| Tjulandin 2010a | 5/76 | 6/37 | | 0.28 [ 0.07, 1.08 ] |
| Tjulandin 2010b | 4/73 | 6/37 | | 0.34 [ 0.09, 1.26 ] |
| Tjulandin 2011 | 6/95 | 5/91 | | 1.16 [ 0.34, 3.90 ] |
| Tsuboi 2009 | 21/61 | 19/56 | | 0.94 [ 0.57, 1.54 ] |
| Vansteenkiste 2002 IPD | 101/159 | 118/161 | | 0.79 [ 0.60, 1.04 ] |
| Winquist 2009 | 24/26 | 27/30 | | 0.58 [ 0.33, 1.03 ] |
| Witzig 2005 IPD | 121/174 | 119/170 | | 1.13 [ 0.87, 1.46 ] |



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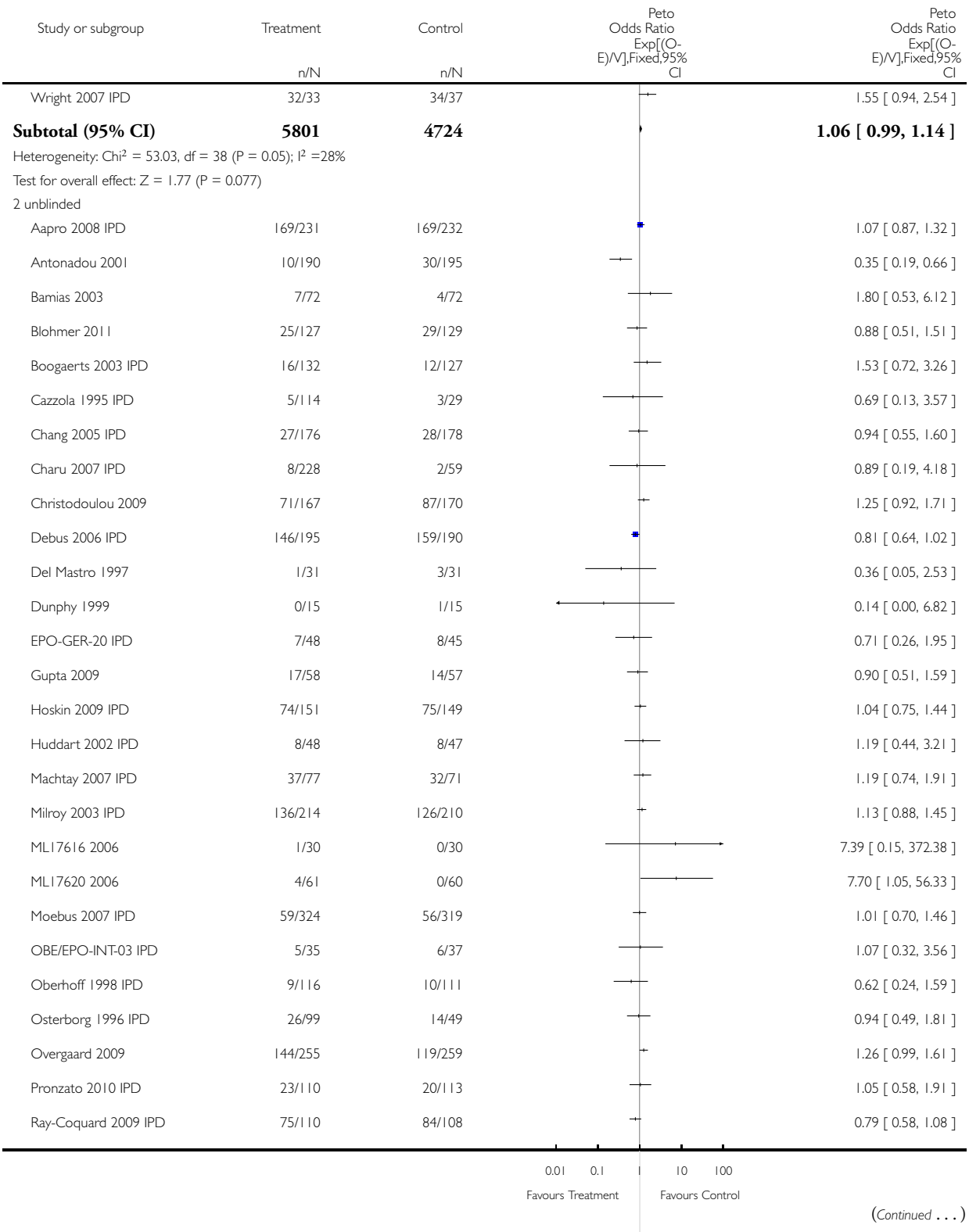


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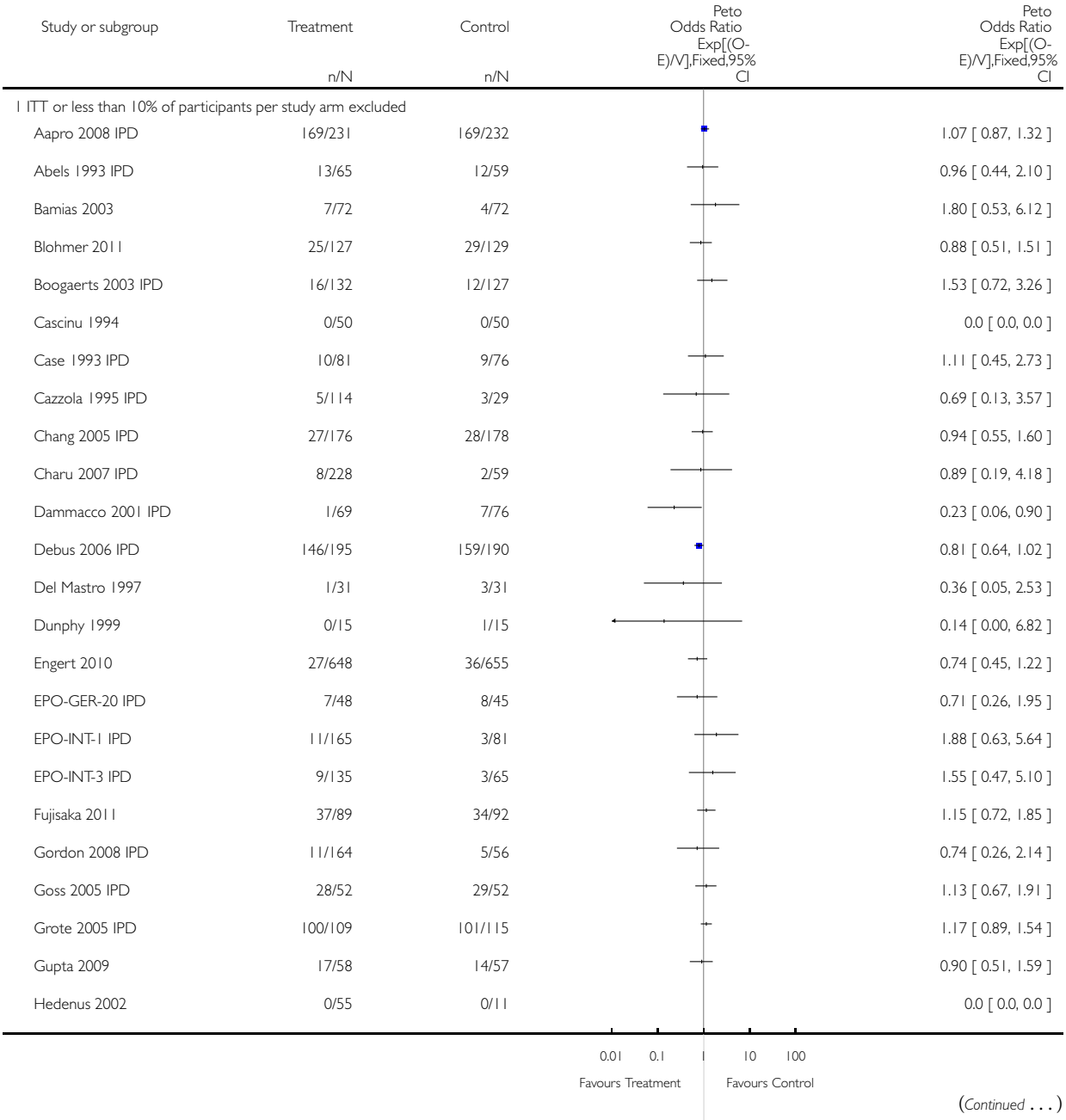
| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Rosen 2003 | 19/47 | 23/43 | | 1.19 [ 0.65, 2.18 ] |
| Savonije 2005 IPD | 132/211 | 61/104 | | 1.14 [ 0.85, 1.53 ] |
| Strauss 2008 IPD | 8/34 | 5/40 | | 2.00 [ 0.65, 6.13 ] |
| Sweeney 1998 | 0/24 | 0/24 | | 0.0 [ 0.0, 0.0 ] |
| Ten Bokkel1998 IPD | 6/87 | 2/33 | | 1.27 [ 0.26, 6.34 ] |
| Thatcher 1999 IPD | 7/86 | 3/44 | | 1.13 [ 0.29, 4.36 ] |
| Thomas 2002 IPD | 4/65 | 5/65 | | 0.79 [ 0.21, 2.95 ] |
| Thomas 2008 IPD | 22/58 | 17/56 | | 1.28 [ 0.68, 2.40 ] |
| Throuvalas 2000 | 0/28 | 1/27 | | 0.13 [ 0.00, 6.55 ] |
| Untch 2011˙2 | 59/345 | 48/369 | | 1.33 [ 0.91, 1.95 ] |
| Wilkinson 2006 IPD | 3/121 | 0/61 | | 4.48 [ 0.40, 50.03 ] |
| **Subtotal (95% CI)** | **4520** | **3958** | | **1.04 [ 0.96, 1.12 ]** |
| Heterogeneity: Chi² = 42.17, df = 36 (P = 0.22); I² =15% | | | | |
| Test for overall effect: Z = 0.99 (P = 0.32) | | | | |
| **Total (95% CI)** | | | | **1.05 [ 1.00, 1.11 ]** |
| Heterogeneity: Chi² = 95.40, df = 75 (P = 0.06); I² =21% | | | | |
| Test for overall effect: Z = 1.97 (P = 0.048) | | | | |
| Test for subgroup differences: Chi² = 0.20, df = 1 (P = 0.65), I² =0.0% | | | | |

## Analysis 5.16. Comparison 5 Overall survival, Outcome 16 Overall survival - intention-to-treat.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 5 Overall survival

Outcome: 16 Overall survival - intention-to-treat

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| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Hedenus 2003 IPD | 101/176 | 82/173 | | 1.32 [ 0.98, 1.77 ] |
| Henke 2003 IPD | 109/180 | 89/171 | | 1.27 [ 0.96, 1.68 ] |
| Henry 1995 IPD | 7/67 | 10/65 | | 0.68 [ 0.26, 1.77 ] |
| Hernandez 2009 IPD | 17/196 | 20/195 | | 0.84 [ 0.44, 1.60 ] |
| Hoskin 2009 IPD | 74/151 | 75/149 | | 1.04 [ 0.75, 1.44 ] |
| Huddart 2002 IPD | 8/48 | 8/47 | | 1.19 [ 0.44, 3.21 ] |
| Kotasek 2002 IPD | 4/129 | 0/32 | | 3.49 [ 0.30, 40.45 ] |
| Kotasek 2003 IPD | 4/208 | 1/51 | | 0.99 [ 0.11, 8.84 ] |
| Krzakowski 2008a | 6/104 | 2/52 | | 1.48 [ 0.33, 6.67 ] |
| Krzakowski 2008b | 10/105 | 3/52 | | 1.64 [ 0.49, 5.44 ] |
| Kurz 1997 | 0/23 | 0/12 | | 0.0 [ 0.0, 0.0 ] |
| Leyland-Jones 2005 IPD | 121/469 | 91/470 | | 1.41 [ 1.08, 1.85 ] |
| Littlewood 2001 IPD | 155/251 | 82/124 | | 0.80 [ 0.61, 1.05 ] |
| Machtay 2007 IPD | 37/77 | 32/71 | | 1.19 [ 0.74, 1.91 ] |
| Milroy 2003 IPD | 136/214 | 126/210 | | 1.13 [ 0.88, 1.45 ] |
| Moebus 2007 IPD | 59/324 | 56/319 | | 1.01 [ 0.70, 1.46 ] |
| Mystakidou 2005 | 1/50 | 2/50 | | 0.50 [ 0.05, 5.00 ] |
| O'Shaugnessy 2005 IPD | 1/51 | 0/49 | | 7.69 [ 0.15, 387.58 ] |
| OBE/EPO-INT-03 IPD | 5/35 | 6/37 | | 1.07 [ 0.32, 3.56 ] |
| Oberhoff 1998 IPD | 9/116 | 10/111 | | 0.62 [ 0.24, 1.59 ] |
| Osterborg 1996 IPD | 26/99 | 14/49 | | 0.94 [ 0.49, 1.81 ] |
| Osterborg 2002 IPD | 110/173 | 109/176 | | 1.04 [ 0.80, 1.36 ] |
| Overgaard 2009 | 144/255 | 119/259 | | 1.26 [ 0.99, 1.61 ] |
| P-174 IPD | 1/33 | 1/12 | | 0.44 [ 0.03, 7.27 ] |
| Pirker 2008 IPD | 243/299 | 254/301 | | 0.94 [ 0.78, 1.13 ] |
| Pronzato 2010 IPD | 23/110 | 20/113 | | 1.05 [ 0.58, 1.91 ] |
| Quirt 1996 IPD | 2/28 | 0/28 | | 5.90 [ 0.36, 97.07 ] |
| Ray-Coquard 2009 IPD | 75/110 | 84/108 | | 0.79 [ 0.58, 1.08 ] |
| Razzouk 2004 | 2/112 | 2/110 | | 0.98 [ 0.14, 7.03 ] |
| Rose 1994 IPD | 16/142 | 6/79 | | 1.66 [ 0.70, 3.92 ] |


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| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Rosen 2003 | 19/47 | 23/43 | | 1.19 [ 0.65, 2.18 ] |
| Savonije 2005 IPD | 132/211 | 61/104 | | 1.14 [ 0.85, 1.53 ] |
| Smith 2003 | 3/64 | 0/22 | | 3.96 [ 0.29, 54.28 ] |
| Smith 2008 IPD | 250/517 | 216/472 | | 1.22 [ 1.02, 1.47 ] |
| Strauss 2008 IPD | 8/34 | 5/40 | | 2.00 [ 0.65, 6.13 ] |
| Ten Bokkel1998 IPD | 6/87 | 2/33 | | 1.27 [ 0.26, 6.34 ] |
| Thatcher 1999 IPD | 7/86 | 3/44 | | 1.13 [ 0.29, 4.36 ] |
| Thomas 2002 IPD | 4/65 | 5/65 | | 0.79 [ 0.21, 2.95 ] |
| Thomas 2008 IPD | 22/58 | 17/56 | | 1.28 [ 0.68, 2.40 ] |
| Thompson 2000 | 3/45 | 0/21 | | 4.52 [ 0.38, 53.37 ] |
| Throuvalas 2000 | 0/28 | 1/27 | | 0.13 [ 0.00, 6.55 ] |
| Tjulandin 2010a | 5/76 | 6/37 | | 0.28 [ 0.07, 1.08 ] |
| Tjulandin 2010b | 4/73 | 6/37 | | 0.34 [ 0.09, 1.26 ] |
| Tjulandin 2011 | 6/95 | 5/91 | | 1.16 [ 0.34, 3.90 ] |
| Tsuboi 2009 | 21/61 | 19/56 | | 0.94 [ 0.57, 1.54 ] |
| Untch 2011˙2 | 59/345 | 48/369 | | 1.33 [ 0.91, 1.95 ] |
| Vansteenkiste 2002 IPD | 101/159 | 118/161 | | 0.79 [ 0.60, 1.04 ] |
| Wilkinson 2006 IPD | 3/121 | 0/61 | | 4.48 [ 0.40, 50.03 ] |
| Winquist 2009 | 24/26 | 27/30 | | 0.58 [ 0.33, 1.03 ] |
| Witzig 2005 IPD | 121/174 | 119/170 | | 1.13 [ 0.87, 1.46 ] |
| Wright 2007 IPD | 32/33 | 34/37 | | 1.55 [ 0.94, 2.54 ] |
| **Subtotal (95% CI)** | **9849** | **8203** | | **1.05 [ 1.00, 1.11 ]** |
| Heterogeneity: Chi² = 77.52, df = 71 (P = 0.28); I² =8% | | | | |
| Test for overall effect: Z = 1.99 (P = 0.047) | | | | |
| 2 more than 10% of participants per study arm excluded | | | | |
| Christodoulou 2009 | 71/167 | 87/170 | | 1.25 [ 0.92, 1.71 ] |
| Sweeney 1998 | 0/24 | 0/24 | | 0.0 [ 0.0, 0.0 ] |
| **Subtotal (95% CI)** | **191** | **194** | | **1.25 [ 0.92, 1.71 ]** |
| Heterogeneity: Chi² = 0.0, df = 0 (P = 1.00); I² =0.0% | | | | |
| Test for overall effect: Z = 1.40 (P = 0.16) | | | | |
| 3 Unclear | | | | |
| Antonadou 2001 | 10/190 | 30/195 | | 0.35 [ 0.19, 0.66 ] |
| ML17616 2006 | 1/30 | 0/30 | | 7.39 [ 0.15, 372.38 ] |


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| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| ML17620 2006 | 4/61 | 0/60 | | 7.70 [ 1.05, 56.33 ] |
| **Subtotal (95% CI)** | **281** | **285** | | **0.49 [ 0.27, 0.89 ]** |
| Heterogeneity: Chi² = 10.27, df = 2 (P = 0.01); I² =81% | | | | |
| Test for overall effect: Z = 2.36 (P = 0.018) | | | | |
| **Total (95% CI)** | | | | **1.05 [ 1.00, 1.11 ]** |
| Heterogeneity: Chi² = 95.40, df = 75 (P = 0.06); I² =21% | | | | |
| Test for overall effect: Z = 1.97 (P = 0.048) | | | | |
| Test for subgroup differences: Chi² = 7.61, df = 2 (P = 0.02), I² =74% | | | | |


## Analysis 5.17. Comparison 5 Overall survival, Outcome 17 Overall survival - follow up.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 5 Overall survival

Outcome: 17 Overall survival - follow up

| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| 1 follow up longer than on-study mortality | | | | |
| Aapro 2008 IPD | 169/231 | 169/232 | | 1.07 [ 0.87, 1.32 ] |
| Antonadou 2001 | 10/190 | 30/195 | | 0.35 [ 0.19, 0.66 ] |
| Blohmer 2011 | 25/127 | 29/129 | | 0.88 [ 0.51, 1.51 ] |
| Boogaerts 2003 IPD | 16/132 | 12/127 | | 1.53 [ 0.72, 3.26 ] |
| Cazzola 1995 IPD | 5/114 | 3/29 | | 0.69 [ 0.13, 3.57 ] |
| Chang 2005 IPD | 27/176 | 28/178 | | 0.94 [ 0.55, 1.60 ] |
| Christodoulou 2009 | 71/167 | 87/170 | | 1.25 [ 0.92, 1.71 ] |
| Debus 2006 IPD | 146/195 | 159/190 | | 0.81 [ 0.64, 1.02 ] |


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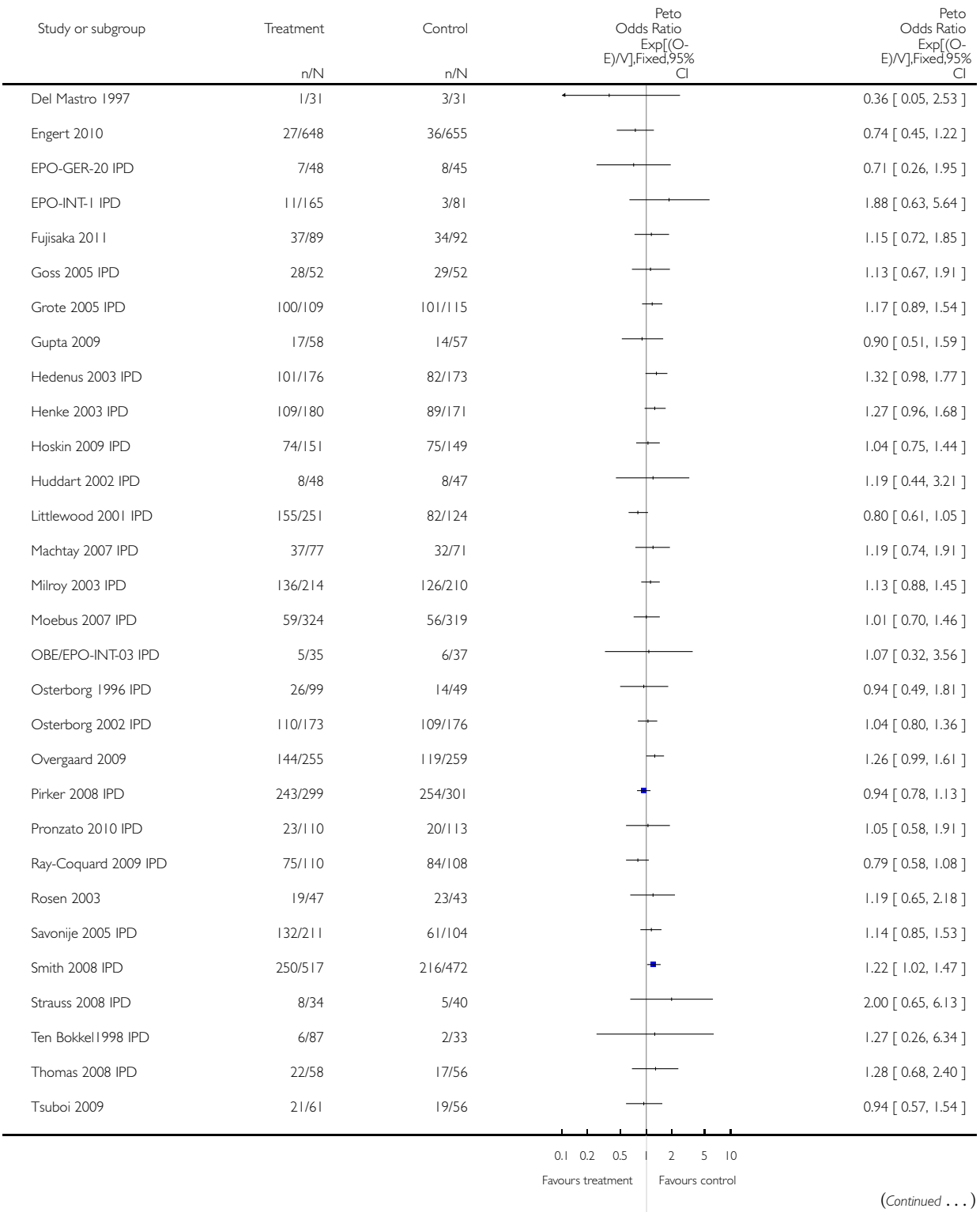


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(. . . *Continued*)

| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Untch 2011˙2 | 59/345 | 48/369 | | 1.33 [ 0.91, 1.95 ] |
| Vansteenkiste 2002 IPD | 101/159 | 118/161 | | 0.79 [ 0.60, 1.04 ] |
| Wilkinson 2006 IPD | 3/121 | 0/61 | | 4.48 [ 0.40, 50.03 ] |
| Winquist 2009 | 24/26 | 27/30 | | 0.58 [ 0.33, 1.03 ] |
| Witzig 2005 IPD | 121/174 | 119/170 | | 1.13 [ 0.87, 1.46 ] |
| Wright 2007 IPD | 32/33 | 34/37 | | 1.55 [ 0.94, 2.54 ] |
| **Subtotal (95% CI)** | **6907** | **6317** | | **1.05 [ 0.99, 1.10 ]** |
| Heterogeneity: Chi² = 59.95, df = 43 (P = 0.04); I² =28% | | | | |
| Test for overall effect: Z = 1.63 (P = 0.10) | | | | |
| 2 Short term follow up | | | | |
| Abels 1993 IPD | 13/65 | 12/59 | | 0.96 [ 0.44, 2.10 ] |
| Bamias 2003 | 7/72 | 4/72 | | 1.80 [ 0.53, 6.12 ] |
| Cascinu 1994 | 0/50 | 0/50 | | 0.0 [ 0.0, 0.0 ] |
| Case 1993 IPD | 10/81 | 9/76 | | 1.11 [ 0.45, 2.73 ] |
| Charu 2007 IPD | 8/228 | 2/59 | | 0.89 [ 0.19, 4.18 ] |
| Dammacco 2001 IPD | 1/69 | 7/76 | | 0.23 [ 0.06, 0.90 ] |
| Dunphy 1999 | 0/15 | 1/15 | | 0.14 [ 0.00, 6.82 ] |
| EPO-INT-3 IPD | 9/135 | 3/65 | | 1.55 [ 0.47, 5.10 ] |
| Gordon 2008 IPD | 11/164 | 5/56 | | 0.74 [ 0.26, 2.14 ] |
| Hedenus 2002 | 0/55 | 0/11 | | 0.0 [ 0.0, 0.0 ] |
| Henry 1995 IPD | 7/67 | 10/65 | | 0.68 [ 0.26, 1.77 ] |
| Hernandez 2009 IPD | 17/196 | 20/195 | | 0.84 [ 0.44, 1.60 ] |
| Kotasek 2002 IPD | 4/129 | 0/32 | | 3.49 [ 0.30, 40.45 ] |
| Kotasek 2003 IPD | 4/208 | 1/51 | | 0.99 [ 0.11, 8.84 ] |
| Krzakowski 2008a | 6/104 | 2/52 | | 1.48 [ 0.33, 6.67 ] |
| Krzakowski 2008b | 10/105 | 3/52 | | 1.64 [ 0.49, 5.44 ] |
| Kurz 1997 | 0/23 | 0/12 | | 0.0 [ 0.0, 0.0 ] |
| Leyland-Jones 2005 IPD | 121/469 | 91/470 | | 1.41 [ 1.08, 1.85 ] |
| ML17616 2006 | 1/30 | 0/30 | | 7.39 [ 0.15, 372.38 ] |
| ML17620 2006 | 4/61 | 0/60 | | 7.70 [ 1.05, 56.33 ] |
| Mystakidou 2005 | 1/50 | 2/50 | | 0.50 [ 0.05, 5.00 ] |
| O'Shaugnessy 2005 IPD | 1/51 | 0/49 | | 7.69 [ 0.15, 387.58 ] |


(*Continued* . . . )

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| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Oberhoff 1998 IPD | 9/116 | 10/111 | | 0.62 [ 0.24, 1.59 ] |
| P-174 IPD | 1/33 | 1/12 | | 0.44 [ 0.03, 7.27 ] |
| Quirt 1996 IPD | 2/28 | 0/28 | | 5.90 [ 0.36, 97.07 ] |
| Razzouk 2004 | 2/112 | 2/110 | | 0.98 [ 0.14, 7.03 ] |
| Rose 1994 IPD | 16/142 | 6/79 | | 1.66 [ 0.70, 3.92 ] |
| Smith 2003 | 3/64 | 0/22 | | 3.96 [ 0.29, 54.28 ] |
| Sweeney 1998 | 0/24 | 0/24 | | 0.0 [ 0.0, 0.0 ] |
| Thatcher 1999 IPD | 7/86 | 3/44 | | 1.13 [ 0.29, 4.36 ] |
| Thomas 2002 IPD | 4/65 | 5/65 | | 0.79 [ 0.21, 2.95 ] |
| Thompson 2000 | 3/45 | 0/21 | | 4.52 [ 0.38, 53.37 ] |
| Throuvalas 2000 | 0/28 | 1/27 | | 0.13 [ 0.00, 6.55 ] |
| Tjulandin 2010a | 5/76 | 6/37 | | 0.28 [ 0.07, 1.08 ] |
| Tjulandin 2010b | 4/73 | 6/37 | | 0.34 [ 0.09, 1.26 ] |
| Tjulandin 2011 | 6/95 | 5/91 | | 1.16 [ 0.34, 3.90 ] |
| **Subtotal (95% CI)** | **3414** | **2365** | | **1.14 [ 0.95, 1.36 ]** |
| Heterogeneity: $Chi^2$ = 34.67, df = 31 (P = 0.30); $I^2$ =11% | | | | |
| Test for overall effect: Z = 1.42 (P = 0.16) | | | | |
| **Total (95% CI)** | | | | **1.05 [ 1.00, 1.11 ]** |
| Heterogeneity: $Chi^2$ = 95.40, df = 75 (P = 0.06); $I^2$ =21% | | | | |
| Test for overall effect: Z = 1.97 (P = 0.048) | | | | |
| Test for subgroup differences: $Chi^2$ = 0.78, df = 1 (P = 0.38), $I^2$ =0.0% | | | | |

## Analysis 5.18. Comparison 5 Overall survival, Outcome 18 Overall survival - follow up and design.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 5 Overall survival

Outcome: 18 Overall survival - follow up and design

| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| 1 Long term follow up and designed for long term follow up | | | | |
| Aapro 2008 IPD | 169/231 | 169/232 | | 1.07 [ 0.87, 1.32 ] |
| Blohmer 2011 | 25/127 | 29/129 | | 0.88 [ 0.51, 1.51 ] |
| Chang 2005 IPD | 27/176 | 28/178 | | 0.94 [ 0.55, 1.60 ] |
| Debus 2006 IPD | 146/195 | 159/190 | | 0.81 [ 0.64, 1.02 ] |
| Engert 2010 | 27/648 | 36/655 | | 0.74 [ 0.45, 1.22 ] |
| Goss 2005 IPD | 28/52 | 29/52 | | 1.13 [ 0.67, 1.91 ] |
| Grote 2005 IPD | 100/109 | 101/115 | | 1.17 [ 0.89, 1.54 ] |
| Hedenus 2003 IPD | 101/176 | 82/173 | | 1.32 [ 0.98, 1.77 ] |
| Henke 2003 IPD | 109/180 | 89/171 | | 1.27 [ 0.96, 1.68 ] |
| Hoskin 2009 IPD | 74/151 | 75/149 | | 1.04 [ 0.75, 1.44 ] |
| Littlewood 2001 IPD | 155/251 | 82/124 | | 0.80 [ 0.61, 1.05 ] |
| Machtay 2007 IPD | 37/77 | 32/71 | | 1.19 [ 0.74, 1.91 ] |
| Milroy 2003 IPD | 136/214 | 126/210 | | 1.13 [ 0.88, 1.45 ] |
| Moebus 2007 IPD | 59/324 | 56/319 | | 1.01 [ 0.70, 1.46 ] |
| OBE/EPO-INT-03 IPD | 5/35 | 6/37 | | 1.07 [ 0.32, 3.56 ] |
| Overgaard 2009 | 144/255 | 119/259 | | 1.26 [ 0.99, 1.61 ] |
| Pirker 2008 IPD | 243/299 | 254/301 | | 0.94 [ 0.78, 1.13 ] |
| Pronzato 2010 IPD | 23/110 | 20/113 | | 1.05 [ 0.58, 1.91 ] |
| Rosen 2003 | 19/47 | 23/43 | | 1.19 [ 0.65, 2.18 ] |
| Savonije 2005 IPD | 132/211 | 61/104 | | 1.14 [ 0.85, 1.53 ] |
| Smith 2008 IPD | 250/517 | 216/472 | | 1.22 [ 1.02, 1.47 ] |
| Strauss 2008 IPD | 8/34 | 5/40 | | 2.00 [ 0.65, 6.13 ] |
| Thomas 2008 IPD | 22/58 | 17/56 | | 1.28 [ 0.68, 2.40 ] |
| Untch 2011`2 | 59/345 | 48/369 | | 1.33 [ 0.91, 1.95 ] |


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| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Vansteenkiste 2002 IPD | 101/159 | 118/161 | | 0.79 [ 0.60, 1.04 ] |
| **Subtotal (95% CI)** | **4981** | **4723** | | **1.06 [ 0.99, 1.12 ]** |
| Heterogeneity: Chi² = 30.66, df = 24 (P = 0.16); I² =22% | | | | |
| Test for overall effect: Z = 1.78 (P = 0.075) | | | | |
| 2 Long term follow up but not designed for long term follow up | | | | |
| Boogaerts 2003 IPD | 16/132 | 12/127 | | 1.53 [ 0.72, 3.26 ] |
| Cazzola 1995 IPD | 5/114 | 3/29 | | 0.69 [ 0.13, 3.57 ] |
| EPO-GER-20 IPD | 7/48 | 8/45 | | 0.71 [ 0.26, 1.95 ] |
| EPO-INT-1 IPD | 11/165 | 3/81 | | 1.88 [ 0.63, 5.64 ] |
| Huddart 2002 IPD | 8/48 | 8/47 | | 1.19 [ 0.44, 3.21 ] |
| Osterborg 1996 IPD | 26/99 | 14/49 | | 0.94 [ 0.49, 1.81 ] |
| Osterborg 2002 IPD | 110/173 | 109/176 | | 1.04 [ 0.80, 1.36 ] |
| Ray-Coquard 2009 IPD | 75/110 | 84/108 | | 0.79 [ 0.58, 1.08 ] |
| Ten Bokkel1998 IPD | 6/87 | 2/33 | | 1.27 [ 0.26, 6.34 ] |
| Wilkinson 2006 IPD | 3/121 | 0/61 | | 4.48 [ 0.40, 50.03 ] |
| Witzig 2005 IPD | 121/174 | 119/170 | | 1.13 [ 0.87, 1.46 ] |
| **Subtotal (95% CI)** | **1271** | **926** | | **1.02 [ 0.89, 1.18 ]** |
| Heterogeneity: Chi² = 7.91, df = 10 (P = 0.64); I² =0.0% | | | | |
| Test for overall effect: Z = 0.32 (P = 0.75) | | | | |
| 3 Long term follow up and design unclear | | | | |
| Antonadou 2001 | 10/190 | 30/195 | | 0.35 [ 0.19, 0.66 ] |
| Christodoulou 2009 | 71/167 | 87/170 | | 1.25 [ 0.92, 1.71 ] |
| Del Mastro 1997 | 1/31 | 3/31 | | 0.36 [ 0.05, 2.53 ] |
| Gupta 2009 | 17/58 | 14/57 | | 0.90 [ 0.51, 1.59 ] |
| Tsuboi 2009 | 21/61 | 19/56 | | 0.94 [ 0.57, 1.54 ] |
| Winquist 2009 | 24/26 | 27/30 | | 0.58 [ 0.33, 1.03 ] |
| Wright 2007 IPD | 32/33 | 34/37 | | 1.55 [ 0.94, 2.54 ] |
| **Subtotal (95% CI)** | **566** | **576** | | **0.96 [ 0.79, 1.16 ]** |
| Heterogeneity: Chi² = 20.26, df = 6 (P = 0.002); I² =70% | | | | |
| Test for overall effect: Z = 0.41 (P = 0.68) | | | | |
| 4 Short term follow up but designed for long term follow up | | | | |
| Fujisaka 2011 | 37/89 | 34/92 | | 1.15 [ 0.72, 1.85 ] |
| Leyland-Jones 2005 IPD | 121/469 | 91/470 | | 1.41 [ 1.08, 1.85 ] |
| Thomas 2002 IPD | 4/65 | 5/65 | | 0.79 [ 0.21, 2.95 ] |


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| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| **Subtotal (95% CI)** | **623** | **627** | ◆ | **1.32 [ 1.05, 1.66 ]** |
| Heterogeneity: $Chi^2$ = 1.14, df = 2 (P = 0.57); $I^2$ =0.0% | | | | |
| Test for overall effect: Z = 2.36 (P = 0.018) | | | | |
| 5 Short term follow up and not designed for long term follow up | | | | |
| Abels 1993 IPD | 13/65 | 12/59 | | 0.96 [ 0.44, 2.10 ] |
| Bamias 2003 | 7/72 | 4/72 | | 1.80 [ 0.53, 6.12 ] |
| Cascinu 1994 | 0/50 | 0/50 | | 0.0 [ 0.0, 0.0 ] |
| Case 1993 IPD | 10/81 | 9/76 | | 1.11 [ 0.45, 2.73 ] |
| Charu 2007 IPD | 8/228 | 2/59 | | 0.89 [ 0.19, 4.18 ] |
| Dammacco 2001 IPD | 1/69 | 7/76 | | 0.23 [ 0.06, 0.90 ] |
| Dunphy 1999 | 0/15 | 1/15 | | 0.14 [ 0.00, 6.82 ] |
| EPO-INT-3 IPD | 9/135 | 3/65 | | 1.55 [ 0.47, 5.10 ] |
| Gordon 2008 IPD | 11/164 | 5/56 | | 0.74 [ 0.26, 2.14 ] |
| Hedenus 2002 | 0/55 | 0/11 | | 0.0 [ 0.0, 0.0 ] |
| Henry 1995 IPD | 7/67 | 10/65 | | 0.68 [ 0.26, 1.77 ] |
| Hernandez 2009 IPD | 17/196 | 20/195 | | 0.84 [ 0.44, 1.60 ] |
| Kotasek 2002 IPD | 4/129 | 0/32 | | 3.49 [ 0.30, 40.45 ] |
| Kotasek 2003 IPD | 4/208 | 1/51 | | 0.99 [ 0.11, 8.84 ] |
| Krzakowski 2008a | 6/104 | 2/52 | | 1.48 [ 0.33, 6.67 ] |
| Krzakowski 2008b | 10/105 | 3/52 | | 1.64 [ 0.49, 5.44 ] |
| Kurz 1997 | 0/23 | 0/12 | | 0.0 [ 0.0, 0.0 ] |
| ML17616 2006 | 1/30 | 0/30 | | 7.39 [ 0.15, 372.38 ] |
| ML17620 2006 | 4/61 | 0/60 | | 7.70 [ 1.05, 56.33 ] |
| Mystakidou 2005 | 1/50 | 2/50 | | 0.50 [ 0.05, 5.00 ] |
| O'Shaugnessy 2005 IPD | 1/51 | 0/49 | | 7.69 [ 0.15, 387.58 ] |
| Oberhoff 1998 IPD | 9/116 | 10/111 | | 0.62 [ 0.24, 1.59 ] |
| P-174 IPD | 1/33 | 1/12 | | 0.44 [ 0.03, 7.27 ] |
| Quirt 1996 IPD | 2/28 | 0/28 | | 5.90 [ 0.36, 97.07 ] |
| Razzouk 2004 | 2/112 | 2/110 | | 0.98 [ 0.14, 7.03 ] |
| Rose 1994 IPD | 16/142 | 6/79 | | 1.66 [ 0.70, 3.92 ] |
| Smith 2003 | 3/64 | 0/22 | | 3.96 [ 0.29, 54.28 ] |
| Sweeney 1998 | 0/24 | 0/24 | | 0.0 [ 0.0, 0.0 ] |

0.01 0.1 1 10 100

Favours treatment Favours control

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| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Thatcher 1999 IPD | 7/86 | 3/44 | | 1.13 [ 0.29, 4.36 ] |
| Thompson 2000 | 3/45 | 0/21 | | 4.52 [ 0.38, 53.37 ] |
| Throuvalas 2000 | 0/28 | 1/27 | | 0.13 [ 0.00, 6.55 ] |
| Tjulandin 2010a | 5/76 | 6/37 | | 0.28 [ 0.07, 1.08 ] |
| Tjulandin 2010b | 4/73 | 6/37 | | 0.34 [ 0.09, 1.26 ] |
| Tjulandin 2011 | 6/95 | 5/91 | | 1.16 [ 0.34, 3.90 ] |
| **Subtotal (95% CI)** | **2880** | **1830** | | **0.97 [ 0.76, 1.23 ]** |
| Heterogeneity: $Chi^2$ = 30.24, df = 29 (P = 0.40); $I^2$ =4% | | | | |
| Test for overall effect: Z = 0.24 (P = 0.81) | | | | |
| 6 short term follow up and design unclear | | | | |
| **Subtotal (95% CI)** | **0** | **0** | | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: not applicable | | | | |
| **Total (95% CI)** | | | | **1.05 [ 1.00, 1.11 ]** |
| Heterogeneity: $Chi^2$ = 95.40, df = 75 (P = 0.06); $I^2$ =21% | | | | |
| Test for overall effect: Z = 1.97 (P = 0.048) | | | | |
| Test for subgroup differences: $Chi^2$ = 5.19, df = 4 (P = 0.27), $I^2$ =23% | | | | |

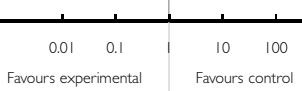
## Analysis 5.19. Comparison 5 Overall survival, Outcome 19 Overall survival- experimental arms merged.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 5 Overall survival

Outcome: 19 Overall survival- experimental arms merged

| Study or subgroup | Experimental n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Aapro 2008 IPD | 169/231 | 169/232 | | 1.07 [ 0.87, 1.32 ] |
| Abels 1993 IPD | 13/65 | 12/59 | | 0.96 [ 0.44, 2.10 ] |
| Antonadou 2001 | 10/190 | 30/195 | | 0.35 [ 0.19, 0.66 ] |
| Bamias 2003 | 7/72 | 4/72 | | 1.80 [ 0.53, 6.12 ] |
| Blohmer 2011 | 25/127 | 29/129 | | 0.88 [ 0.51, 1.51 ] |
| Boogaerts 2003 IPD | 16/132 | 12/127 | | 1.53 [ 0.72, 3.26 ] |
| Cascinu 1994 | 0/50 | 0/50 | | 0.0 [ 0.0, 0.0 ] |
| Case 1993 IPD | 10/81 | 9/76 | | 1.11 [ 0.45, 2.73 ] |
| Cazzola 1995 IPD | 5/114 | 3/29 | | 0.69 [ 0.13, 3.57 ] |
| Chang 2005 IPD | 27/176 | 28/178 | | 0.94 [ 0.55, 1.60 ] |
| Charu 2007 IPD | 8/228 | 2/59 | | 0.89 [ 0.19, 4.18 ] |
| Christodoulou 2009 | 71/167 | 87/170 | | 1.25 [ 0.92, 1.71 ] |
| Dammacco 2001 IPD | 1/69 | 7/76 | | 0.23 [ 0.06, 0.90 ] |
| Debus 2006 IPD | 146/195 | 159/190 | | 0.81 [ 0.64, 1.02 ] |
| Del Mastro 1997 | 1/31 | 3/31 | | 0.36 [ 0.05, 2.53 ] |
| Dunphy 1999 | 0/15 | 1/15 | | 0.14 [ 0.00, 6.82 ] |
| Engert 2010 | 27/648 | 36/655 | | 0.74 [ 0.45, 1.22 ] |
| EPO-GER-20 IPD | 7/48 | 8/45 | | 0.71 [ 0.26, 1.95 ] |
| EPO-INT-1 IPD | 11/165 | 3/81 | | 1.88 [ 0.63, 5.64 ] |
| EPO-INT-3 IPD | 9/135 | 3/65 | | 1.55 [ 0.47, 5.10 ] |
| Fujisaka 2011 | 37/89 | 34/92 | | 1.15 [ 0.72, 1.85 ] |
| Gordon 2008 IPD | 11/164 | 5/56 | | 0.74 [ 0.26, 2.14 ] |
| Goss 2005 IPD | 28/52 | 29/52 | | 1.13 [ 0.67, 1.91 ] |
| Grote 2005 IPD | 100/109 | 101/115 | | 1.17 [ 0.89, 1.54 ] |
| Gupta 2009 | 17/58 | 14/57 | | 0.90 [ 0.51, 1.59 ] |

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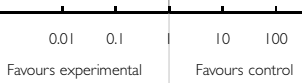
| Study or subgroup | Experimental n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Hedenus 2002 | 0/55 | 0/11 | | 0.0 [ 0.0, 0.0 ] |
| Hedenus 2003 IPD | 101/176 | 82/173 | | 1.32 [ 0.98, 1.77 ] |
| Henke 2003 IPD | 109/180 | 89/171 | | 1.27 [ 0.96, 1.68 ] |
| Henry 1995 IPD | 7/67 | 10/65 | | 0.68 [ 0.26, 1.77 ] |
| Hernandez 2009 IPD | 17/196 | 20/195 | | 0.84 [ 0.44, 1.60 ] |
| Hoskin 2009 IPD | 74/151 | 75/149 | | 1.04 [ 0.75, 1.44 ] |
| Huddart 2002 IPD | 8/48 | 8/47 | | 1.19 [ 0.44, 3.21 ] |
| Kotasek 2002 IPD | 4/129 | 0/32 | | 3.49 [ 0.30, 40.45 ] |
| Kotasek 2003 IPD | 4/208 | 1/51 | | 0.99 [ 0.11, 8.84 ] |
| Krzakowski 2008 | 16/209 | 5/104 | | 1.57 [ 0.62, 4.03 ] |
| Kurz 1997 | 0/23 | 0/12 | | 0.0 [ 0.0, 0.0 ] |
| Leyland-Jones 2005 IPD | 121/469 | 91/470 | | 1.41 [ 1.08, 1.85 ] |
| Littlewood 2001 IPD | 155/251 | 82/124 | | 0.80 [ 0.61, 1.05 ] |
| Machtay 2007 IPD | 37/77 | 32/71 | | 1.19 [ 0.74, 1.91 ] |
| Milroy 2003 IPD | 136/214 | 126/210 | | 1.13 [ 0.88, 1.45 ] |
| ML17616 2006 | 1/30 | 0/30 | | 7.39 [ 0.15, 372.38 ] |
| ML17620 2006 | 4/61 | 0/60 | | 7.70 [ 1.05, 56.33 ] |
| Moebus 2007 IPD | 59/324 | 56/319 | | 1.01 [ 0.70, 1.46 ] |
| Mystakidou 2005 | 1/50 | 2/50 | | 0.50 [ 0.05, 5.00 ] |
| O'Shaugnessy 2005 IPD | 1/51 | 0/49 | | 7.69 [ 0.15, 387.58 ] |
| OBE/EPO-INT-03 IPD | 5/35 | 6/37 | | 1.07 [ 0.32, 3.56 ] |
| Oberhoff 1998 IPD | 9/116 | 10/111 | | 0.62 [ 0.24, 1.59 ] |
| Osterborg 1996 IPD | 26/99 | 14/49 | | 0.94 [ 0.49, 1.81 ] |
| Osterborg 2002 IPD | 110/173 | 109/176 | | 1.04 [ 0.80, 1.36 ] |
| Overgaard 2009 | 144/255 | 119/259 | | 1.26 [ 0.99, 1.61 ] |
| P-174 IPD | 1/33 | 1/12 | | 0.44 [ 0.03, 7.27 ] |
| Pirker 2008 IPD | 243/299 | 254/301 | | 0.94 [ 0.78, 1.13 ] |
| Pronzato 2010 IPD | 23/110 | 20/113 | | 1.05 [ 0.58, 1.91 ] |
| Quirt 1996 IPD | 2/28 | 0/28 | | 5.90 [ 0.36, 97.07 ] |
| Ray-Coquard 2009 IPD | 75/110 | 84/108 | | 0.79 [ 0.58, 1.08 ] |

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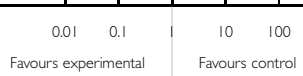
| Study or subgroup | Experimental n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Razzouk 2004 | 2/112 | 2/110 | | 0.98 [ 0.14, 7.03 ] |
| Rose 1994 IPD | 16/142 | 6/79 | | 1.66 [ 0.70, 3.92 ] |
| Rosen 2003 | 19/47 | 23/43 | | 1.19 [ 0.65, 2.18 ] |
| Savonije 2005 IPD | 132/211 | 61/104 | | 1.14 [ 0.85, 1.53 ] |
| Smith 2003 | 3/64 | 0/22 | | 3.96 [ 0.29, 54.28 ] |
| Smith 2008 IPD | 250/517 | 216/472 | | 1.22 [ 1.02, 1.47 ] |
| Strauss 2008 IPD | 8/34 | 5/40 | | 2.00 [ 0.65, 6.13 ] |
| Sweeney 1998 | 0/24 | 0/24 | | 0.0 [ 0.0, 0.0 ] |
| Ten Bokkel1998 IPD | 6/87 | 2/33 | | 1.27 [ 0.26, 6.34 ] |
| Thatcher 1999 IPD | 7/86 | 3/44 | | 1.13 [ 0.29, 4.36 ] |
| Thomas 2002 IPD | 4/65 | 5/65 | | 0.79 [ 0.21, 2.95 ] |
| Thomas 2008 IPD | 22/58 | 17/56 | | 1.28 [ 0.68, 2.40 ] |
| Thompson 2000 | 3/45 | 0/21 | | 4.52 [ 0.38, 53.37 ] |
| Throuvalas 2000 | 0/28 | 1/27 | | 0.13 [ 0.00, 6.55 ] |
| Tjulandin 2010 | 9/149 | 12/74 | | 0.31 [ 0.12, 0.79 ] |
| Tjulandin 2011 | 6/95 | 5/91 | | 1.16 [ 0.34, 3.90 ] |
| Tsuboi 2009 | 21/61 | 19/56 | | 0.94 [ 0.57, 1.54 ] |
| Untch 2011˙2 | 59/345 | 48/369 | | 1.33 [ 0.91, 1.95 ] |
| Vansteenkiste 2002 IPD | 101/159 | 118/161 | | 0.79 [ 0.60, 1.04 ] |
| Wilkinson 2006 IPD | 3/121 | 0/61 | | 4.48 [ 0.40, 50.03 ] |
| Winquist 2009 | 24/26 | 27/30 | | 0.58 [ 0.33, 1.03 ] |
| Witzig 2005 IPD | 121/174 | 119/170 | | 1.13 [ 0.87, 1.46 ] |
| Wright 2007 IPD | 32/33 | 34/37 | | 1.55 [ 0.94, 2.54 ] |
| **Total (95% CI)** | | | | **1.05 [ 1.00, 1.11 ]** |

Heterogeneity: $Chi^2$ = 95.35, df = 73 (P = 0.04); $I^2$ =23%

Test for overall effect: Z = 1.97 (P = 0.048)

Test for subgroup differences: Not applicable



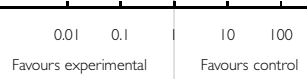
## Analysis 5.20. Comparison 5 Overall survival, Outcome 20 Overall survival- experimental arms merged sens pos.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 5 Overall survival

Outcome: 20 Overall survival- experimental arms merged sens pos

| Study or subgroup | Experimental n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Abels 1993 IPD | 13/65 | 12/59 | | 0.96 [ 0.44, 2.10 ] |
| Antonadou 2001 | 10/190 | 30/195 | | 0.35 [ 0.19, 0.66 ] |
| Bamias 2003 | 7/72 | 4/72 | | 1.80 [ 0.53, 6.12 ] |
| Blohmer 2011 | 25/127 | 29/129 | | 0.88 [ 0.51, 1.51 ] |
| Boogaerts 2003 IPD | 16/132 | 12/127 | | 1.53 [ 0.72, 3.26 ] |
| Cascinu 1994 | 0/50 | 0/50 | | 0.0 [ 0.0, 0.0 ] |
| Case 1993 IPD | 10/81 | 9/76 | | 1.11 [ 0.45, 2.73 ] |
| Cazzola 1995 IPD | 5/114 | 3/29 | | 0.69 [ 0.13, 3.57 ] |
| Chang 2005 IPD | 27/176 | 28/178 | | 0.94 [ 0.55, 1.60 ] |
| Charu 2007 IPD | 8/228 | 2/59 | | 0.89 [ 0.19, 4.18 ] |
| Christodoulou 2009 | 71/167 | 87/170 | | 1.25 [ 0.92, 1.71 ] |
| Dammacco 2001 IPD | 1/69 | 7/76 | | 0.23 [ 0.06, 0.90 ] |
| Debus 2006 IPD | 146/195 | 159/190 | | 0.81 [ 0.64, 1.02 ] |
| Del Mastro 1997 | 1/31 | 3/31 | | 0.36 [ 0.05, 2.53 ] |
| Dunphy 1999 | 0/15 | 1/15 | | 0.14 [ 0.00, 6.82 ] |
| Engert 2010 | 27/648 | 36/655 | | 0.74 [ 0.45, 1.22 ] |
| EPO-GER-20 IPD | 7/48 | 8/45 | | 0.71 [ 0.26, 1.95 ] |
| EPO-INT-1 IPD | 11/165 | 3/81 | | 1.88 [ 0.63, 5.64 ] |
| EPO-INT-3 IPD | 9/135 | 3/65 | | 1.55 [ 0.47, 5.10 ] |
| Fujisaka 2011 | 37/89 | 34/92 | | 1.15 [ 0.72, 1.85 ] |
| Gordon 2008 IPD | 11/164 | 5/56 | | 0.74 [ 0.26, 2.14 ] |
| Goss 2005 IPD | 28/52 | 29/52 | | 1.13 [ 0.67, 1.91 ] |
| Grote 2005 IPD | 100/109 | 101/115 | | 1.17 [ 0.89, 1.54 ] |
| Gupta 2009 | 17/58 | 14/57 | | 0.90 [ 0.51, 1.59 ] |

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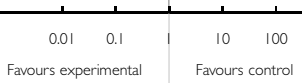
| Study or subgroup | Experimental n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Hedenus 2002 | 0/55 | 0/11 | | 0.0 [ 0.0, 0.0 ] |
| Hedenus 2003 IPD | 101/176 | 82/173 | | 1.32 [ 0.98, 1.77 ] |
| Henke 2003 IPD | 109/180 | 89/171 | | 1.27 [ 0.96, 1.68 ] |
| Henry 1995 IPD | 7/67 | 10/65 | | 0.68 [ 0.26, 1.77 ] |
| Hernandez 2009 IPD | 17/196 | 20/195 | | 0.84 [ 0.44, 1.60 ] |
| Hoskin 2009 IPD | 74/151 | 75/149 | | 1.04 [ 0.75, 1.44 ] |
| Huddart 2002 IPD | 8/48 | 8/47 | | 1.19 [ 0.44, 3.21 ] |
| Kotasek 2002 IPD | 4/129 | 0/32 | | 3.49 [ 0.30, 40.45 ] |
| Kotasek 2003 IPD | 4/208 | 1/51 | | 0.99 [ 0.11, 8.84 ] |
| Krzakowski 2008 | 16/209 | 5/104 | | 1.57 [ 0.62, 4.03 ] |
| Kurz 1997 | 0/23 | 0/12 | | 0.0 [ 0.0, 0.0 ] |
| Leyland-Jones 2005 IPD | 121/469 | 91/470 | | 1.41 [ 1.08, 1.85 ] |
| Littlewood 2001 IPD | 155/251 | 82/124 | | 0.80 [ 0.61, 1.05 ] |
| Machtay 2007 IPD | 37/77 | 32/71 | | 1.19 [ 0.74, 1.91 ] |
| Milroy 2003 IPD | 136/214 | 126/210 | | 1.13 [ 0.88, 1.45 ] |
| ML17616 2006 | 1/30 | 0/30 | | 7.39 [ 0.15, 372.38 ] |
| ML17620 2006 | 4/61 | 0/60 | | 7.70 [ 1.05, 56.33 ] |
| Moebus 2007 IPD | 59/324 | 56/319 | | 1.01 [ 0.70, 1.46 ] |
| Mystakidou 2005 | 1/50 | 2/50 | | 0.50 [ 0.05, 5.00 ] |
| O'Shaugnessy 2005 IPD | 1/51 | 0/49 | | 7.69 [ 0.15, 387.58 ] |
| OBE/EPO-INT-03 IPD | 5/35 | 6/37 | | 1.07 [ 0.32, 3.56 ] |
| Oberhoff 1998 IPD | 9/116 | 10/111 | | 0.62 [ 0.24, 1.59 ] |
| Osterborg 1996 IPD | 26/99 | 14/49 | | 0.94 [ 0.49, 1.81 ] |
| Osterborg 2002 IPD | 110/173 | 109/176 | | 1.04 [ 0.80, 1.36 ] |
| Overgaard 2009 | 144/255 | 119/259 | | 1.26 [ 0.99, 1.61 ] |
| P-174 IPD | 1/33 | 1/12 | | 0.44 [ 0.03, 7.27 ] |
| Pirker 2008 IPD | 243/299 | 254/301 | | 0.94 [ 0.78, 1.13 ] |
| Pronzato 2010 IPD | 23/110 | 20/113 | | 1.05 [ 0.58, 1.91 ] |
| Quirt 1996 IPD | 2/28 | 0/28 | | 5.90 [ 0.36, 97.07 ] |
| Ray-Coquard 2009 IPD | 75/110 | 84/108 | | 0.79 [ 0.58, 1.08 ] |

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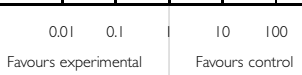
| Study or subgroup | Experimental n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Razzouk 2004 | 2/112 | 2/110 | | 0.98 [ 0.14, 7.03 ] |
| Rose 1994 IPD | 16/142 | 6/79 | | 1.66 [ 0.70, 3.92 ] |
| Rosen 2003 | 19/47 | 23/43 | | 1.19 [ 0.65, 2.18 ] |
| Savonije 2005 IPD | 132/211 | 61/104 | | 1.14 [ 0.85, 1.53 ] |
| Smith 2003 | 3/64 | 0/22 | | 3.96 [ 0.29, 54.28 ] |
| Strauss 2008 IPD | 8/34 | 5/40 | | 2.00 [ 0.65, 6.13 ] |
| Sweeney 1998 | 0/24 | 0/24 | | 0.0 [ 0.0, 0.0 ] |
| Ten Bokkel1998 IPD | 6/87 | 2/33 | | 1.27 [ 0.26, 6.34 ] |
| Thatcher 1999 IPD | 7/86 | 3/44 | | 1.13 [ 0.29, 4.36 ] |
| Thomas 2002 IPD | 4/65 | 5/65 | | 0.79 [ 0.21, 2.95 ] |
| Thomas 2008 IPD | 22/58 | 17/56 | | 1.28 [ 0.68, 2.40 ] |
| Thompson 2000 | 3/45 | 0/21 | | 4.52 [ 0.38, 53.37 ] |
| Throuvalas 2000 | 0/28 | 1/27 | | 0.13 [ 0.00, 6.55 ] |
| Tjulandin 2010 | 9/149 | 12/74 | | 0.31 [ 0.12, 0.79 ] |
| Tjulandin 2011 | 6/95 | 5/91 | | 1.16 [ 0.34, 3.90 ] |
| Tsuboi 2009 | 21/61 | 19/56 | | 0.94 [ 0.57, 1.54 ] |
| Untch 2011˙2 | 59/345 | 48/369 | | 1.33 [ 0.91, 1.95 ] |
| Vansteenkiste 2002 IPD | 101/159 | 118/161 | | 0.79 [ 0.60, 1.04 ] |
| Wilkinson 2006 IPD | 3/121 | 0/61 | | 4.48 [ 0.40, 50.03 ] |
| Winquist 2009 | 24/26 | 27/30 | | 0.58 [ 0.33, 1.03 ] |
| Witzig 2005 IPD | 121/174 | 119/170 | | 1.13 [ 0.87, 1.46 ] |
| Wright 2007 IPD | 32/33 | 34/37 | | 1.55 [ 0.94, 2.54 ] |
| **Total (95% CI)** | | | | **1.04 [ 0.98, 1.10 ]** |

Heterogeneity: Chi² = 92.54, df = 71 (P = 0.04); I² =23%

Test for overall effect: Z = 1.31 (P = 0.19)

Test for subgroup differences: Not applicable



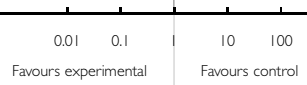
## Analysis 5.21. Comparison 5 Overall survival, Outcome 21 Overall survival- experimental arms merged sens neg.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 5 Overall survival

Outcome: 21 Overall survival- experimental arms merged sens neg

| Study or subgroup | Experimental n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Aapro 2008 IPD | 169/231 | 169/232 | | 1.07 [ 0.87, 1.32 ] |
| Abels 1993 IPD | 13/65 | 12/59 | | 0.96 [ 0.44, 2.10 ] |
| Antonadou 2001 | 10/190 | 30/195 | | 0.35 [ 0.19, 0.66 ] |
| Bamias 2003 | 7/72 | 4/72 | | 1.80 [ 0.53, 6.12 ] |
| Blohmer 2011 | 25/127 | 29/129 | | 0.88 [ 0.51, 1.51 ] |
| Boogaerts 2003 IPD | 16/132 | 12/127 | | 1.53 [ 0.72, 3.26 ] |
| Cascinu 1994 | 0/50 | 0/50 | | 0.0 [ 0.0, 0.0 ] |
| Case 1993 IPD | 10/81 | 9/76 | | 1.11 [ 0.45, 2.73 ] |
| Cazzola 1995 IPD | 5/114 | 3/29 | | 0.69 [ 0.13, 3.57 ] |
| Chang 2005 IPD | 27/176 | 28/178 | | 0.94 [ 0.55, 1.60 ] |
| Charu 2007 IPD | 8/228 | 2/59 | | 0.89 [ 0.19, 4.18 ] |
| Christodoulou 2009 | 71/167 | 87/170 | | 1.25 [ 0.92, 1.71 ] |
| Dammacco 2001 IPD | 1/69 | 7/76 | | 0.23 [ 0.06, 0.90 ] |
| Del Mastro 1997 | 1/31 | 3/31 | | 0.36 [ 0.05, 2.53 ] |
| Dunphy 1999 | 0/15 | 1/15 | | 0.14 [ 0.00, 6.82 ] |
| Engert 2010 | 27/648 | 36/655 | | 0.74 [ 0.45, 1.22 ] |
| EPO-GER-20 IPD | 7/48 | 8/45 | | 0.71 [ 0.26, 1.95 ] |
| EPO-INT-1 IPD | 11/165 | 3/81 | | 1.88 [ 0.63, 5.64 ] |
| EPO-INT-3 IPD | 9/135 | 3/65 | | 1.55 [ 0.47, 5.10 ] |
| Fujisaka 2011 | 37/89 | 34/92 | | 1.15 [ 0.72, 1.85 ] |
| Gordon 2008 IPD | 11/164 | 5/56 | | 0.74 [ 0.26, 2.14 ] |
| Goss 2005 IPD | 28/52 | 29/52 | | 1.13 [ 0.67, 1.91 ] |
| Grote 2005 IPD | 100/109 | 101/115 | | 1.17 [ 0.89, 1.54 ] |
| Gupta 2009 | 17/58 | 14/57 | | 0.90 [ 0.51, 1.59 ] |

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| Study or subgroup | Experimental n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Hedenus 2002 | 0/55 | 0/11 | | 0.0 [ 0.0, 0.0 ] |
| Hedenus 2003 IPD | 101/176 | 82/173 | | 1.32 [ 0.98, 1.77 ] |
| Henke 2003 IPD | 109/180 | 89/171 | | 1.27 [ 0.96, 1.68 ] |
| Henry 1995 IPD | 7/67 | 10/65 | | 0.68 [ 0.26, 1.77 ] |
| Hernandez 2009 IPD | 17/196 | 20/195 | | 0.84 [ 0.44, 1.60 ] |
| Hoskin 2009 IPD | 74/151 | 75/149 | | 1.04 [ 0.75, 1.44 ] |
| Huddart 2002 IPD | 8/48 | 8/47 | | 1.19 [ 0.44, 3.21 ] |
| Kotasek 2002 IPD | 4/129 | 0/32 | | 3.49 [ 0.30, 40.45 ] |
| Kotasek 2003 IPD | 4/208 | 1/51 | | 0.99 [ 0.11, 8.84 ] |
| Krzakowski 2008 | 16/209 | 5/104 | | 1.57 [ 0.62, 4.03 ] |
| Kurz 1997 | 0/23 | 0/12 | | 0.0 [ 0.0, 0.0 ] |
| Leyland-Jones 2005 IPD | 121/469 | 91/470 | | 1.41 [ 1.08, 1.85 ] |
| Littlewood 2001 IPD | 155/251 | 82/124 | | 0.80 [ 0.61, 1.05 ] |
| Machtay 2007 IPD | 37/77 | 32/71 | | 1.19 [ 0.74, 1.91 ] |
| Milroy 2003 IPD | 136/214 | 126/210 | | 1.13 [ 0.88, 1.45 ] |
| ML17616 2006 | 1/30 | 0/30 | | 7.39 [ 0.15, 372.38 ] |
| ML17620 2006 | 4/61 | 0/60 | | 7.70 [ 1.05, 56.33 ] |
| Moebus 2007 IPD | 59/324 | 56/319 | | 1.01 [ 0.70, 1.46 ] |
| Mystakidou 2005 | 1/50 | 2/50 | | 0.50 [ 0.05, 5.00 ] |
| O'Shaugnessy 2005 IPD | 1/51 | 0/49 | | 7.69 [ 0.15, 387.58 ] |
| OBE/EPO-INT-03 IPD | 5/35 | 6/37 | | 1.07 [ 0.32, 3.56 ] |
| Oberhoff 1998 IPD | 9/116 | 10/111 | | 0.62 [ 0.24, 1.59 ] |
| Osterborg 1996 IPD | 26/99 | 14/49 | | 0.94 [ 0.49, 1.81 ] |
| Osterborg 2002 IPD | 110/173 | 109/176 | | 1.04 [ 0.80, 1.36 ] |
| Overgaard 2009 | 144/255 | 119/259 | | 1.26 [ 0.99, 1.61 ] |
| P-174 IPD | 1/33 | 1/12 | | 0.44 [ 0.03, 7.27 ] |
| Pronzato 2010 IPD | 23/110 | 20/113 | | 1.05 [ 0.58, 1.91 ] |
| Quirt 1996 IPD | 2/28 | 0/28 | | 5.90 [ 0.36, 97.07 ] |
| Ray-Coquard 2009 IPD | 75/110 | 84/108 | | 0.79 [ 0.58, 1.08 ] |
| Razzouk 2004 | 2/112 | 2/110 | | 0.98 [ 0.14, 7.03 ] |


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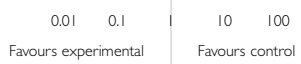
| Study or subgroup | Experimental n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|
| Rose 1994 IPD | 16/142 | 6/79 | 1.66 [ 0.70, 3.92 ] |
| Rosen 2003 | 19/47 | 23/43 | 1.19 [ 0.65, 2.18 ] |
| Savonije 2005 IPD | 132/211 | 61/104 | 1.14 [ 0.85, 1.53 ] |
| Smith 2003 | 3/64 | 0/22 | 3.96 [ 0.29, 54.28 ] |
| Smith 2008 IPD | 250/517 | 216/472 | 1.22 [ 1.02, 1.47 ] |
| Strauss 2008 IPD | 8/34 | 5/40 | 2.00 [ 0.65, 6.13 ] |
| Sweeney 1998 | 0/24 | 0/24 | 0.0 [ 0.0, 0.0 ] |
| Ten Bokkel1998 IPD | 6/87 | 2/33 | 1.27 [ 0.26, 6.34 ] |
| Thatcher 1999 IPD | 7/86 | 3/44 | 1.13 [ 0.29, 4.36 ] |
| Thomas 2002 IPD | 4/65 | 5/65 | 0.79 [ 0.21, 2.95 ] |
| Thomas 2008 IPD | 22/58 | 17/56 | 1.28 [ 0.68, 2.40 ] |
| Thompson 2000 | 3/45 | 0/21 | 4.52 [ 0.38, 53.37 ] |
| Throuvalas 2000 | 0/28 | 1/27 | 0.13 [ 0.00, 6.55 ] |
| Tjulandin 2010 | 9/149 | 12/74 | 0.31 [ 0.12, 0.79 ] |
| Tjulandin 2011 | 6/95 | 5/91 | 1.16 [ 0.34, 3.90 ] |
| Tsuboi 2009 | 21/61 | 19/56 | 0.94 [ 0.57, 1.54 ] |
| Untch 2011˙2 | 59/345 | 48/369 | 1.33 [ 0.91, 1.95 ] |
| Vansteenkiste 2002 IPD | 101/159 | 118/161 | 0.79 [ 0.60, 1.04 ] |
| Wilkinson 2006 IPD | 3/121 | 0/61 | 4.48 [ 0.40, 50.03 ] |
| Winquist 2009 | 24/26 | 27/30 | 0.58 [ 0.33, 1.03 ] |
| Witzig 2005 IPD | 121/174 | 119/170 | 1.13 [ 0.87, 1.46 ] |
| Wright 2007 IPD | 32/33 | 34/37 | 1.55 [ 0.94, 2.54 ] |
| **Total (95% CI)** | | | **1.08 [ 1.02, 1.14 ]** |

Heterogeneity: $Chi^2$ = 87.87, df = 71 (P = 0.09); $I^2$ =19%

Test for overall effect: Z = 2.77 (P = 0.0057)

Test for subgroup differences: Not applicable



## Analysis 5.22. Comparison 5 Overall survival, Outcome 22 Overall survival - sensitivity analysis baseline Hb.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 5 Overall survival

Outcome: 22 Overall survival - sensitivity analysis baseline Hb

| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| 1 Hb < 10 g/dL | | | | |
| Abels 1993 IPD | 13/65 | 12/59 | | 0.96 [ 0.44, 2.10 ] |
| Antonadou 2001 | 10/190 | 30/195 | | 0.35 [ 0.19, 0.66 ] |
| Boogaerts 2003 IPD | 16/132 | 12/127 | | 1.53 [ 0.72, 3.26 ] |
| Cascinu 1994 | 0/50 | 0/50 | | 0.0 [ 0.0, 0.0 ] |
| Case 1993 IPD | 10/81 | 9/76 | | 1.11 [ 0.45, 2.73 ] |
| Cazzola 1995 IPD | 5/114 | 3/29 | | 0.69 [ 0.13, 3.57 ] |
| Dammacco 2001 IPD | 1/69 | 7/76 | | 0.23 [ 0.06, 0.90 ] |
| Fujisaka 2011 | 37/89 | 34/92 | | 1.15 [ 0.72, 1.85 ] |
| Hedenus 2002 | 0/55 | 0/11 | | 0.0 [ 0.0, 0.0 ] |
| Hedenus 2003 IPD | 101/176 | 82/173 | | 1.32 [ 0.98, 1.76 ] |
| Henry 1995 IPD | 7/67 | 10/65 | | 0.68 [ 0.26, 1.77 ] |
| Kotasek 2003 IPD | 4/208 | 1/51 | | 0.99 [ 0.11, 8.84 ] |
| Krzakowski 2008a | 6/104 | 2/52 | | 1.48 [ 0.33, 6.67 ] |
| Krzakowski 2008b | 10/105 | 3/52 | | 1.64 [ 0.49, 5.44 ] |
| Kurz 1997 | 0/23 | 0/12 | | 0.0 [ 0.0, 0.0 ] |
| Littlewood 2001 IPD | 155/251 | 82/124 | | 0.80 [ 0.61, 1.05 ] |
| ML17616 2006 | 1/30 | 0/30 | | 7.39 [ 0.15, 372.38 ] |
| Oberhoff 1998 IPD | 9/116 | 10/111 | | 0.62 [ 0.24, 1.59 ] |
| Osterborg 1996 IPD | 26/99 | 14/49 | | 0.94 [ 0.49, 1.81 ] |
| Osterborg 2002 IPD | 110/173 | 109/176 | | 1.04 [ 0.80, 1.36 ] |
| Razzouk 2004 | 2/112 | 2/110 | | 0.98 [ 0.14, 7.03 ] |
| Rose 1994 IPD | 16/142 | 6/79 | | 1.66 [ 0.70, 3.92 ] |
| Smith 2003 | 3/64 | 0/22 | | 3.96 [ 0.29, 54.28 ] |
| Smith 2008 IPD | 250/517 | 216/472 | | 1.22 [ 1.02, 1.47 ] |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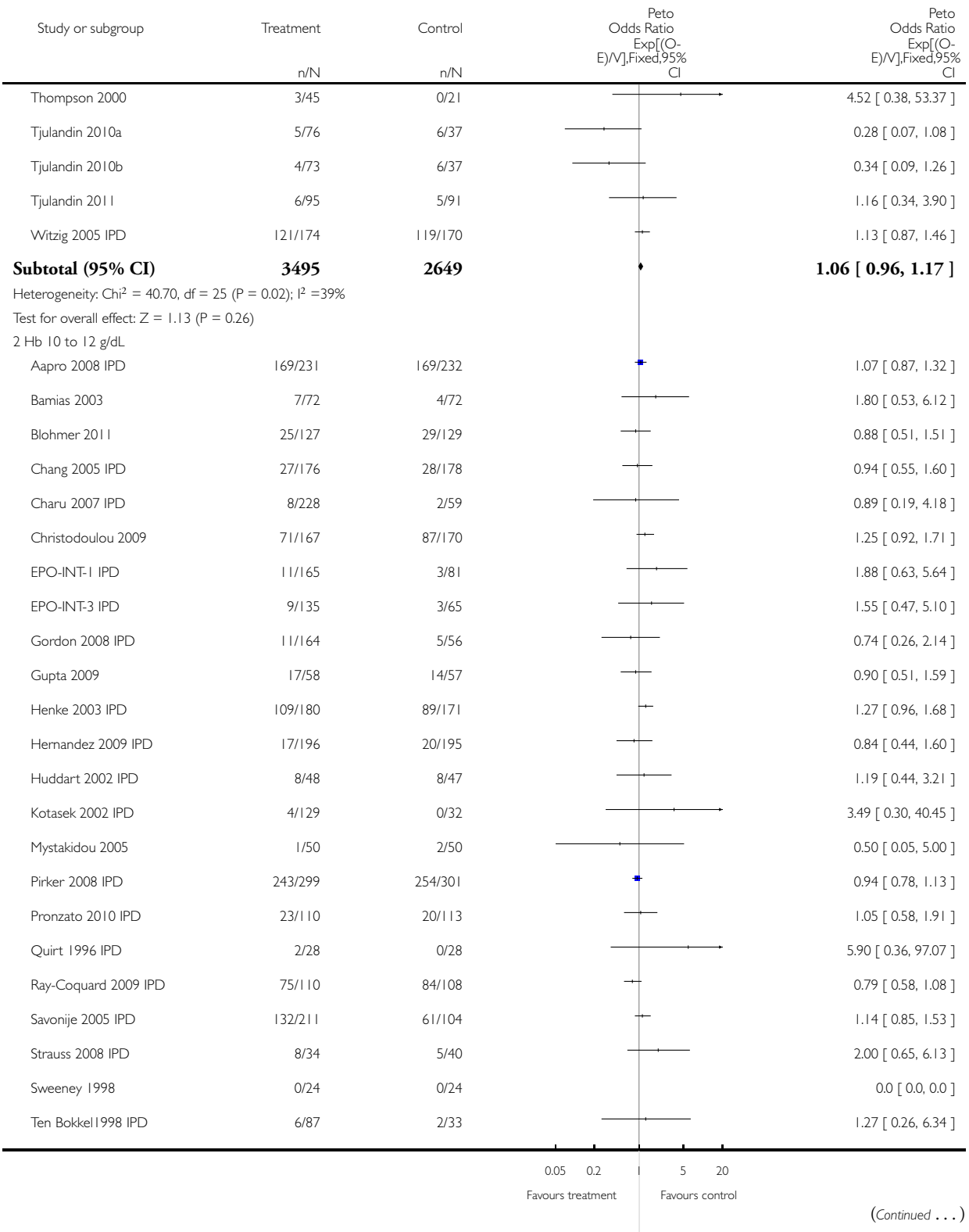


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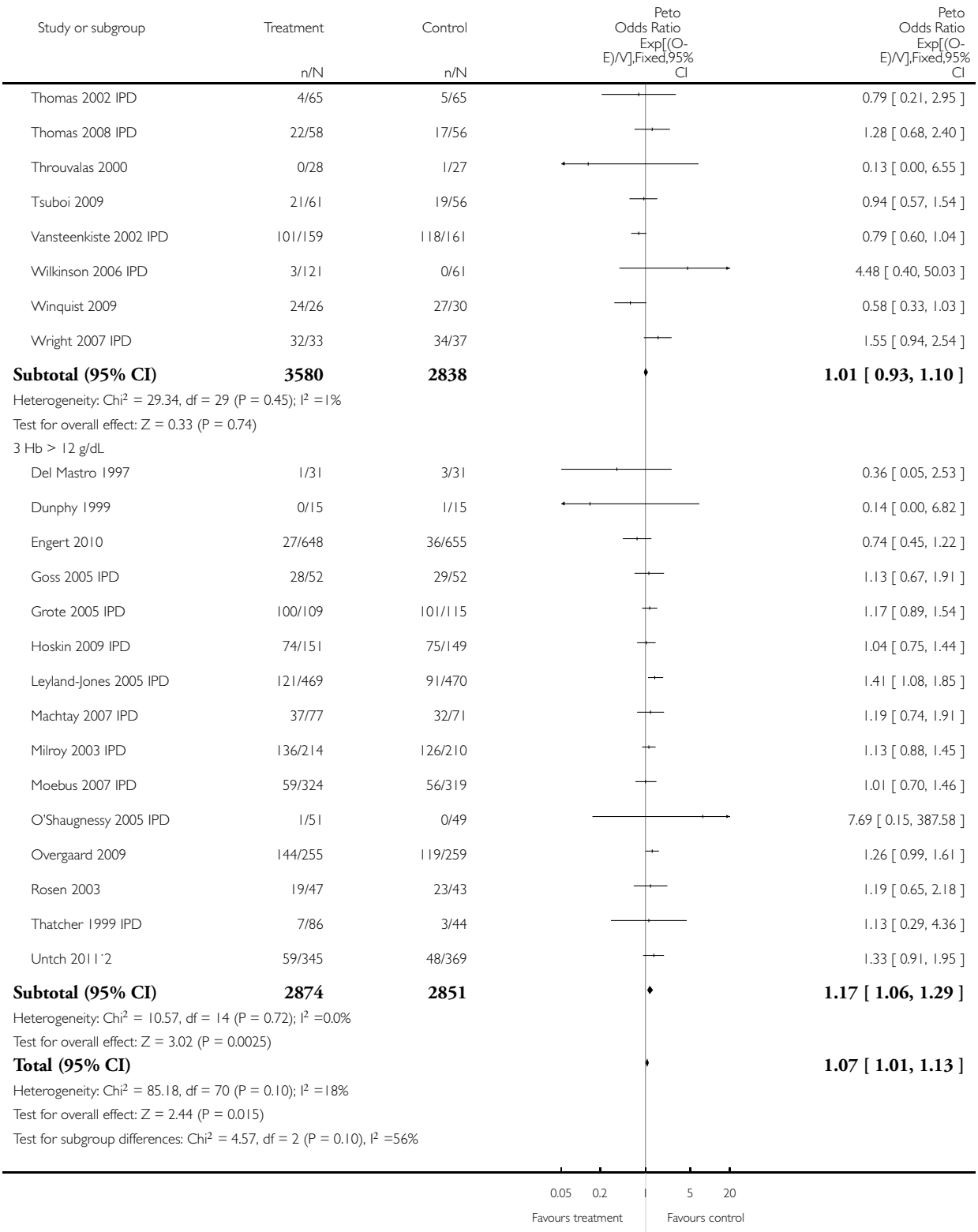


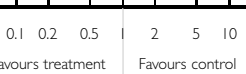
### Analysis 5.23. Comparison 5 Overall survival, Outcome 23 Overall survival - sensitivity analysis iron supplementation.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 5 Overall survival

Outcome: 23 Overall survival - sensitivity analysis iron supplementation

| Study or subgroup | treatment n/N | control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| 1 fixed iron supplementation | | | | |
| Christodoulou 2009 | 71/167 | 87/170 | | 1.25 [ 0.92, 1.71 ] |
| Dunphy 1999 | 0/15 | 1/15 | | 0.14 [ 0.00, 6.82 ] |
| Gupta 2009 | 17/58 | 14/57 | | 0.90 [ 0.51, 1.59 ] |
| Hoskin 2009 IPD | 74/151 | 75/149 | | 1.04 [ 0.75, 1.44 ] |
| Huddart 2002 IPD | 8/48 | 8/47 | | 1.19 [ 0.44, 3.21 ] |
| Krzakowski 2008a | 6/104 | 2/52 | | 1.48 [ 0.33, 6.67 ] |
| Krzakowski 2008b | 10/105 | 3/52 | | 1.64 [ 0.49, 5.44 ] |
| Mystakidou 2005 | 1/50 | 2/50 | | 0.50 [ 0.05, 5.00 ] |
| Untch 2011˙2 | 59/345 | 48/369 | | 1.33 [ 0.91, 1.95 ] |
| Witzig 2005 IPD | 121/174 | 119/170 | | 1.13 [ 0.87, 1.46 ] |
| **Subtotal (95% CI)** | **1217** | **1131** | | **1.15 [ 0.99, 1.33 ]** |
| Heterogeneity: $Chi^2$ = 4.02, df = 9 (P = 0.91); $I^2$ =0.0% | | | | |
| Test for overall effect: Z = 1.87 (P = 0.061) | | | | |
| 2 iron supplementation as necessary | | | | |
| Aapro 2008 IPD | 169/231 | 169/232 | | 1.07 [ 0.87, 1.32 ] |
| Abels 1993 IPD | 13/65 | 12/59 | | 0.96 [ 0.44, 2.10 ] |
| Boogaerts 2003 IPD | 16/132 | 12/127 | | 1.53 [ 0.72, 3.26 ] |
| Cascinu 1994 | 0/50 | 0/50 | | 0.0 [ 0.0, 0.0 ] |
| Case 1993 IPD | 10/81 | 9/76 | | 1.11 [ 0.45, 2.73 ] |
| Cazzola 1995 IPD | 5/114 | 3/29 | | 0.69 [ 0.13, 3.57 ] |

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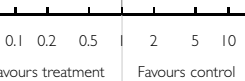
| Study or subgroup | treatment n/N | control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Chang 2005 IPD | 27/176 | 28/178 | | 0.94 [ 0.55, 1.60 ] |
| Charu 2007 IPD | 8/228 | 2/59 | | 0.89 [ 0.19, 4.18 ] |
| Dammacco 2001 IPD | 1/69 | 7/76 | | 0.23 [ 0.06, 0.90 ] |
| Del Mastro 1997 | 1/31 | 3/31 | | 0.36 [ 0.05, 2.53 ] |
| Engert 2010 | 27/648 | 36/655 | | 0.74 [ 0.45, 1.22 ] |
| EPO-INT-1 IPD | 11/165 | 3/81 | | 1.88 [ 0.63, 5.64 ] |
| EPO-INT-3 IPD | 9/135 | 3/65 | | 1.55 [ 0.47, 5.10 ] |
| Fujisaka 2011 | 37/89 | 34/92 | | 1.15 [ 0.72, 1.85 ] |
| Gordon 2008 IPD | 11/164 | 5/56 | | 0.74 [ 0.26, 2.14 ] |
| Goss 2005 IPD | 28/52 | 29/52 | | 1.13 [ 0.67, 1.91 ] |
| Grote 2005 IPD | 100/109 | 101/115 | | 1.17 [ 0.89, 1.54 ] |
| Hedenus 2003 IPD | 101/176 | 82/173 | | 1.32 [ 0.98, 1.77 ] |
| Henke 2003 IPD | 109/180 | 89/171 | | 1.27 [ 0.96, 1.68 ] |
| Henry 1995 IPD | 7/67 | 10/65 | | 0.68 [ 0.26, 1.77 ] |
| Hernandez 2009 IPD | 17/196 | 20/195 | | 0.84 [ 0.44, 1.60 ] |
| Kotasek 2002 IPD | 4/129 | 0/32 | | 3.49 [ 0.30, 40.45 ] |
| Kotasek 2003 IPD | 4/208 | 1/51 | | 0.99 [ 0.11, 8.84 ] |
| Kurz 1997 | 0/23 | 0/12 | | 0.0 [ 0.0, 0.0 ] |
| Leyland-Jones 2005 IPD | 121/469 | 91/470 | | 1.41 [ 1.08, 1.85 ] |
| Littlewood 2001 IPD | 155/251 | 82/124 | | 0.80 [ 0.61, 1.05 ] |
| Milroy 2003 IPD | 136/214 | 126/210 | | 1.13 [ 0.88, 1.45 ] |
| ML17616 2006 | 1/30 | 0/30 | | 7.39 [ 0.15, 372.38 ] |
| ML17620 2006 | 4/61 | 0/60 | | 7.70 [ 1.05, 56.33 ] |
| O'Shaugnessy 2005 IPD | 1/51 | 0/49 | | 7.69 [ 0.15, 387.58 ] |
| Oberhoff 1998 IPD | 9/116 | 10/111 | | 0.62 [ 0.24, 1.59 ] |
| Osterborg 1996 IPD | 26/99 | 14/49 | | 0.94 [ 0.49, 1.81 ] |
| Osterborg 2002 IPD | 110/173 | 109/176 | | 1.04 [ 0.80, 1.36 ] |
| Overgaard 2009 | 144/255 | 119/259 | | 1.26 [ 0.99, 1.61 ] |
| P-174 IPD | 1/33 | 1/12 | | 0.44 [ 0.03, 7.27 ] |
| Pirker 2008 IPD | 243/299 | 254/301 | | 0.94 [ 0.78, 1.13 ] |

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| Study or subgroup | treatment n/N | control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Pronzato 2010 IPD | 23/110 | 20/113 | | 1.05 [ 0.58, 1.91 ] |
| Quirt 1996 IPD | 2/28 | 0/28 | | 5.90 [ 0.36, 97.07 ] |
| Ray-Coquard 2009 IPD | 75/110 | 84/108 | | 0.79 [ 0.58, 1.08 ] |
| Razzouk 2004 | 2/112 | 2/110 | | 0.98 [ 0.14, 7.03 ] |
| Rose 1994 IPD | 16/142 | 6/79 | | 1.66 [ 0.70, 3.92 ] |
| Smith 2003 | 3/64 | 0/22 | | 3.96 [ 0.29, 54.28 ] |
| Smith 2008 IPD | 250/517 | 216/472 | | 1.22 [ 1.02, 1.47 ] |
| Strauss 2008 IPD | 8/34 | 5/40 | | 2.00 [ 0.65, 6.13 ] |
| Ten Bokkel1998 IPD | 6/87 | 2/33 | | 1.27 [ 0.26, 6.34 ] |
| Thatcher 1999 IPD | 7/86 | 3/44 | | 1.13 [ 0.29, 4.36 ] |
| Thomas 2002 IPD | 4/65 | 5/65 | | 0.79 [ 0.21, 2.95 ] |
| Thomas 2008 IPD | 22/58 | 17/56 | | 1.28 [ 0.68, 2.40 ] |
| Throuvalas 2000 | 0/28 | 1/27 | | 0.13 [ 0.00, 6.55 ] |
| Tjulandin 2010a | 5/76 | 6/37 | | 0.28 [ 0.07, 1.08 ] |
| Tjulandin 2010b | 4/73 | 6/37 | | 0.34 [ 0.09, 1.26 ] |
| Tjulandin 2011 | 6/95 | 5/91 | | 1.16 [ 0.34, 3.90 ] |
| Tsuboi 2009 | 21/61 | 19/56 | | 0.94 [ 0.57, 1.54 ] |
| Vansteenkiste 2002 IPD | 101/159 | 118/161 | | 0.79 [ 0.60, 1.04 ] |
| Wilkinson 2006 IPD | 3/121 | 0/61 | | 4.48 [ 0.40, 50.03 ] |
| Wright 2007 IPD | 32/33 | 34/37 | | 1.55 [ 0.94, 2.54 ] |
| **Subtotal (95% CI)** | **7628** | **6260** | | **1.07 [ 1.01, 1.14 ]** |
| Heterogeneity: Chi² = 64.77, df = 53 (P = 0.13); I² =18% | | | | |
| Test for overall effect: Z = 2.21 (P = 0.027) | | | | |
| 3 iron handled differently in the study arms | | | | |
| Blohmer 2011 | 25/127 | 29/129 | | 0.88 [ 0.51, 1.51 ] |
| Debus 2006 IPD | 146/195 | 159/190 | | 0.81 [ 0.64, 1.02 ] |
| EPO-GER-20 IPD | 7/48 | 8/45 | | 0.71 [ 0.26, 1.95 ] |
| Machtay 2007 IPD | 37/77 | 32/71 | | 1.19 [ 0.74, 1.91 ] |
| Moebus 2007 IPD | 59/324 | 56/319 | | 1.01 [ 0.70, 1.46 ] |
| OBE/EPO-INT-03 IPD | 5/35 | 6/37 | | 1.07 [ 0.32, 3.56 ] |
| Rosen 2003 | 19/47 | 23/43 | | 1.19 [ 0.65, 2.18 ] |
| Savonije 2005 IPD | 132/211 | 61/104 | | 1.14 [ 0.85, 1.53 ] |

0.1 0.2 0.5 1 2 5 10

Favours treatment Favours control

(*Continued* . . . )

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| Study or subgroup | treatment n/N | control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Sweeney 1998 | 0/24 | 0/24 | | 0.0 [ 0.0, 0.0 ] |
| **Subtotal (95% CI)** | **1088** | **962** | ◆ | **0.96 [ 0.84, 1.11 ]** |
| Heterogeneity: Chi² = 5.27, df = 7 (P = 0.63); I² =0.0% | | | | |
| Test for overall effect: Z = 0.54 (P = 0.59) | | | | |
| 4 explicitly stated NO IRON | | | | |
| **Subtotal (95% CI)** | **0** | **0** | | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: not applicable | | | | |
| **Total (95% CI)** | | | ◆ | **1.07 [ 1.01, 1.12 ]** |
| Heterogeneity: Chi² = 77.15, df = 71 (P = 0.29); I² =8% | | | | |
| Test for overall effect: Z = 2.37 (P = 0.018) | | | | |
| Test for subgroup differences: Chi² = 3.10, df = 2 (P = 0.21), I² =35% | | | | |

0.1 0.2 0.5 1 2 5 10

Favours treatment Favours control

## Analysis 5.24. Comparison 5 Overall survival, Outcome 24 Overall survival - sensitivity analysis intention-to-treat.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 5 Overall survival

Outcome: 24 Overall survival - sensitivity analysis intention-to-treat

| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| 1 ITT or less than 10% of participants per study arm excluded | | | | |
| Aapro 2008 IPD | 169/231 | 169/232 | | 1.07 [ 0.87, 1.32 ] |
| Abels 1993 IPD | 13/65 | 12/59 | | 0.96 [ 0.44, 2.10 ] |
| Bamias 2003 | 7/72 | 4/72 | | 1.80 [ 0.53, 6.12 ] |
| Blohmer 2011 | 25/127 | 29/129 | | 0.88 [ 0.51, 1.51 ] |
| Boogaerts 2003 IPD | 16/132 | 12/127 | | 1.53 [ 0.72, 3.26 ] |
| Cascinu 1994 | 0/50 | 0/50 | | 0.0 [ 0.0, 0.0 ] |
| Case 1993 IPD | 10/81 | 9/76 | | 1.11 [ 0.45, 2.73 ] |
| Cazzola 1995 IPD | 5/114 | 3/29 | | 0.69 [ 0.13, 3.57 ] |
| Chang 2005 IPD | 27/176 | 28/178 | | 0.94 [ 0.55, 1.60 ] |
| Charu 2007 IPD | 8/228 | 2/59 | | 0.89 [ 0.19, 4.18 ] |
| Dammacco 2001 IPD | 1/69 | 7/76 | | 0.23 [ 0.06, 0.90 ] |
| Debus 2006 IPD | 146/195 | 159/190 | | 0.81 [ 0.64, 1.02 ] |
| Del Mastro 1997 | 1/31 | 3/31 | | 0.36 [ 0.05, 2.53 ] |
| Dunphy 1999 | 0/15 | 1/15 | | 0.14 [ 0.00, 6.82 ] |
| Engert 2010 | 27/648 | 36/655 | | 0.74 [ 0.45, 1.22 ] |
| EPO-GER-20 IPD | 7/48 | 8/45 | | 0.71 [ 0.26, 1.95 ] |
| EPO-INT-1 IPD | 11/165 | 3/81 | | 1.88 [ 0.63, 5.64 ] |
| EPO-INT-3 IPD | 9/135 | 3/65 | | 1.55 [ 0.47, 5.10 ] |
| Fujisaka 2011 | 37/89 | 34/92 | | 1.15 [ 0.72, 1.85 ] |
| Gordon 2008 IPD | 11/164 | 5/56 | | 0.74 [ 0.26, 2.14 ] |
| Goss 2005 IPD | 28/52 | 29/52 | | 1.13 [ 0.67, 1.91 ] |
| Grote 2005 IPD | 100/109 | 101/115 | | 1.17 [ 0.89, 1.54 ] |
| Gupta 2009 | 17/58 | 14/57 | | 0.90 [ 0.51, 1.59 ] |


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| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Hedenus 2002 | 0/55 | 0/11 | | 0.0 [ 0.0, 0.0 ] |
| Hedenus 2003 IPD | 101/176 | 82/173 | | 1.32 [ 0.98, 1.77 ] |
| Henke 2003 IPD | 109/180 | 89/171 | | 1.27 [ 0.96, 1.68 ] |
| Henry 1995 IPD | 7/67 | 10/65 | | 0.68 [ 0.26, 1.77 ] |
| Hernandez 2009 IPD | 17/196 | 20/195 | | 0.84 [ 0.44, 1.60 ] |
| Hoskin 2009 IPD | 74/151 | 75/149 | | 1.04 [ 0.75, 1.44 ] |
| Huddart 2002 IPD | 8/48 | 8/47 | | 1.19 [ 0.44, 3.21 ] |
| Kotasek 2002 IPD | 4/129 | 0/32 | | 3.49 [ 0.30, 40.45 ] |
| Kotasek 2003 IPD | 4/208 | 1/51 | | 0.99 [ 0.11, 8.84 ] |
| Krzakowski 2008a | 6/104 | 2/52 | | 1.48 [ 0.33, 6.67 ] |
| Krzakowski 2008b | 10/105 | 3/52 | | 1.64 [ 0.49, 5.44 ] |
| Kurz 1997 | 0/23 | 0/12 | | 0.0 [ 0.0, 0.0 ] |
| Leyland-Jones 2005 IPD | 121/469 | 91/470 | | 1.41 [ 1.08, 1.85 ] |
| Littlewood 2001 IPD | 155/251 | 82/124 | | 0.80 [ 0.61, 1.05 ] |
| Machtay 2007 IPD | 37/77 | 32/71 | | 1.19 [ 0.74, 1.91 ] |
| Milroy 2003 IPD | 136/214 | 126/210 | | 1.13 [ 0.88, 1.45 ] |
| Moebus 2007 IPD | 59/324 | 56/319 | | 1.01 [ 0.70, 1.46 ] |
| Mystakidou 2005 | 1/50 | 2/50 | | 0.50 [ 0.05, 5.00 ] |
| O'Shaugnessy 2005 IPD | 1/51 | 0/49 | | 7.69 [ 0.15, 387.58 ] |
| OBE/EPO-INT-03 IPD | 5/35 | 6/37 | | 1.07 [ 0.32, 3.56 ] |
| Oberhoff 1998 IPD | 9/116 | 10/111 | | 0.62 [ 0.24, 1.59 ] |
| Osterborg 1996 IPD | 26/99 | 14/49 | | 0.94 [ 0.49, 1.81 ] |
| Osterborg 2002 IPD | 110/173 | 109/176 | | 1.04 [ 0.80, 1.36 ] |
| Overgaard 2009 | 144/255 | 119/259 | | 1.26 [ 0.99, 1.61 ] |
| P-174 IPD | 1/33 | 1/12 | | 0.44 [ 0.03, 7.27 ] |
| Pirker 2008 IPD | 243/299 | 254/301 | | 0.94 [ 0.78, 1.13 ] |
| Pronzato 2010 IPD | 23/110 | 20/113 | | 1.05 [ 0.58, 1.91 ] |
| Quirt 1996 IPD | 2/28 | 0/28 | | 5.90 [ 0.36, 97.07 ] |
| Ray-Coquard 2009 IPD | 75/110 | 84/108 | | 0.79 [ 0.58, 1.08 ] |
| Razzouk 2004 | 2/112 | 2/110 | | 0.98 [ 0.14, 7.03 ] |


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| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Rose 1994 IPD | 16/142 | 6/79 | | 1.66 [ 0.70, 3.92 ] |
| Rosen 2003 | 19/47 | 23/43 | | 1.19 [ 0.65, 2.18 ] |
| Savonije 2005 IPD | 132/211 | 61/104 | | 1.14 [ 0.85, 1.53 ] |
| Smith 2003 | 3/64 | 0/22 | | 3.96 [ 0.29, 54.28 ] |
| Smith 2008 IPD | 250/517 | 216/472 | | 1.22 [ 1.02, 1.47 ] |
| Strauss 2008 IPD | 8/34 | 5/40 | | 2.00 [ 0.65, 6.13 ] |
| Ten Bokkel1998 IPD | 6/87 | 2/33 | | 1.27 [ 0.26, 6.34 ] |
| Thatcher 1999 IPD | 7/86 | 3/44 | | 1.13 [ 0.29, 4.36 ] |
| Thomas 2002 IPD | 4/65 | 5/65 | | 0.79 [ 0.21, 2.95 ] |
| Thomas 2008 IPD | 22/58 | 17/56 | | 1.28 [ 0.68, 2.40 ] |
| Thompson 2000 | 3/45 | 0/21 | | 4.52 [ 0.38, 53.37 ] |
| Throuvalas 2000 | 0/28 | 1/27 | | 0.13 [ 0.00, 6.55 ] |
| Tjulandin 2010a | 5/76 | 6/37 | | 0.28 [ 0.07, 1.08 ] |
| Tjulandin 2010b | 4/73 | 6/37 | | 0.34 [ 0.09, 1.26 ] |
| Tjulandin 2011 | 6/95 | 5/91 | | 1.16 [ 0.34, 3.90 ] |
| Tsuboi 2009 | 21/61 | 19/56 | | 0.94 [ 0.57, 1.54 ] |
| Untch 2011˙2 | 59/345 | 48/369 | | 1.33 [ 0.91, 1.95 ] |
| Vansteenkiste 2002 IPD | 101/159 | 118/161 | | 0.79 [ 0.60, 1.04 ] |
| Wilkinson 2006 IPD | 3/121 | 0/61 | | 4.48 [ 0.40, 50.03 ] |
| Winquist 2009 | 24/26 | 27/30 | | 0.58 [ 0.33, 1.03 ] |
| Witzig 2005 IPD | 121/174 | 119/170 | | 1.13 [ 0.87, 1.46 ] |
| Wright 2007 IPD | 32/33 | 34/37 | | 1.55 [ 0.94, 2.54 ] |
| **Subtotal (95% CI)** | **9849** | **8203** | | **1.05 [ 1.00, 1.11 ]** |
| Heterogeneity: Chi² = 77.52, df = 71 (P = 0.28); I² =8% | | | | |
| Test for overall effect: Z = 1.99 (P = 0.047) | | | | |
| 2 more than 10% of participants per study arm excluded | | | | |
| Christodoulou 2009 | 71/167 | 87/170 | | 1.25 [ 0.92, 1.71 ] |
| Sweeney 1998 | 0/24 | 0/24 | | 0.0 [ 0.0, 0.0 ] |
| **Subtotal (95% CI)** | **191** | **194** | | **1.25 [ 0.92, 1.71 ]** |
| Heterogeneity: Chi² = 0.0, df = 0 (P = 1.00); I² =0.0% | | | | |
| Test for overall effect: Z = 1.40 (P = 0.16) | | | | |
| **Total (95% CI)** | | | | **1.06 [ 1.01, 1.12 ]** |
| Heterogeneity: Chi² = 78.64, df = 72 (P = 0.28); I² =8% | | | | |


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| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Test for overall effect: Z = 2.19 (P = 0.028) | | | | |
| Test for subgroup differences: Chi² = 1.11, df = 1 (P = 0.29), I² =10% | | | | |


### Analysis 6.1. Comparison 6 On-study mortality, Outcome 1 On-study mortality - overall.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 6 On-study mortality

Outcome: 1 On-study mortality - overall

| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Aapro 2008 IPD | 47/231 | 35/232 | | 1.38 [ 0.89, 2.13 ] |
| Abels 1993 IPD | 13/65 | 12/59 | | 0.96 [ 0.44, 2.10 ] |
| Bamias 2003 | 7/72 | 4/72 | | 1.80 [ 0.53, 6.12 ] |
| Boogaerts 2003 IPD | 10/132 | 10/127 | | 1.02 [ 0.42, 2.46 ] |
| Cascinu 1994 | 0/50 | 0/50 | | 0.0 [ 0.0, 0.0 ] |
| Case 1993 IPD | 10/81 | 9/76 | | 1.11 [ 0.45, 2.73 ] |
| Cazzola 1995 IPD | 3/114 | 2/29 | | 0.38 [ 0.06, 2.30 ] |
| Chang 2005 IPD | 7/176 | 5/178 | | 1.36 [ 0.44, 4.22 ] |
| Charu 2007 IPD | 8/228 | 2/59 | | 0.89 [ 0.19, 4.18 ] |
| Dammacco 2001 IPD | 1/69 | 7/76 | | 0.23 [ 0.06, 0.90 ] |
| Debus 2006 IPD | 26/195 | 18/190 | | 1.38 [ 0.76, 2.50 ] |
| Del Mastro 1997 | 0/31 | 0/31 | | 0.0 [ 0.0, 0.0 ] |
| Dunphy 1999 | 0/15 | 1/15 | | 0.14 [ 0.00, 6.82 ] |


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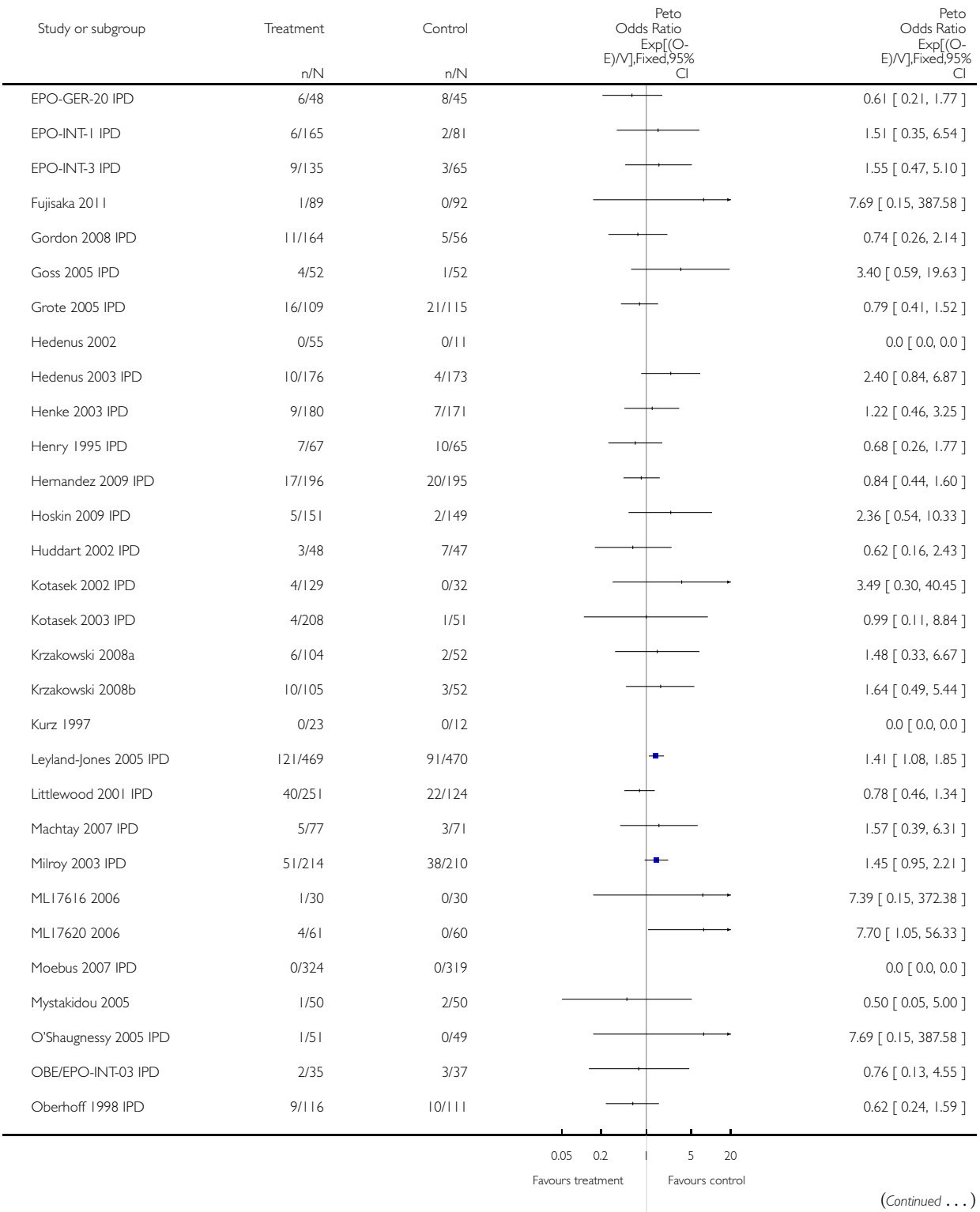


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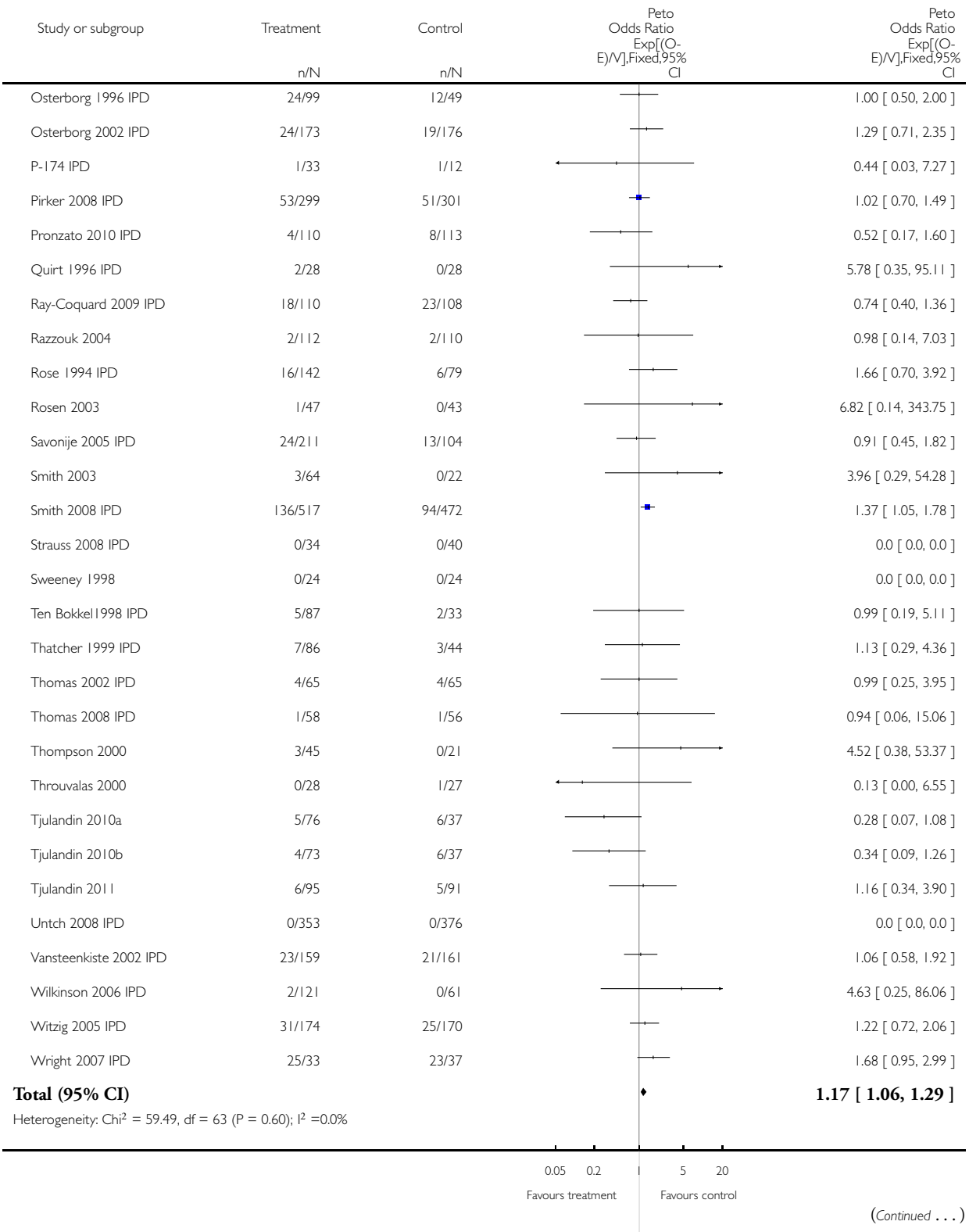


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| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Test for overall effect: Z = 3.06 (P = 0.0022) | | | | |
| Test for subgroup differences: Not applicable | | | | |


### Analysis 6.2. Comparison 6 On-study mortality, Outcome 2 On-study mortality - baseline Hb.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 6 On-study mortality

Outcome: 2 On-study mortality - baseline Hb

| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| 1 Hb < 10 g/dL | | | | |
| Abels 1993 IPD | 13/65 | 12/59 | | 0.96 [ 0.44, 2.10 ] |
| Boogaerts 2003 IPD | 10/132 | 10/127 | | 1.02 [ 0.42, 2.46 ] |
| Cascinu 1994 | 0/50 | 0/50 | | 0.0 [ 0.0, 0.0 ] |
| Case 1993 IPD | 10/81 | 9/76 | | 1.11 [ 0.45, 2.73 ] |
| Cazzola 1995 IPD | 3/114 | 2/29 | | 0.38 [ 0.06, 2.30 ] |
| Dammacco 2001 IPD | 1/69 | 7/76 | | 0.23 [ 0.06, 0.90 ] |
| Fujisaka 2011 | 1/89 | 0/92 | | 7.69 [ 0.15, 387.58 ] |
| Hedenus 2002 | 0/55 | 0/11 | | 0.0 [ 0.0, 0.0 ] |
| Hedenus 2003 IPD | 10/176 | 4/173 | | 2.40 [ 0.84, 6.87 ] |
| Henry 1995 IPD | 7/67 | 10/65 | | 0.68 [ 0.26, 1.77 ] |
| Kotasek 2003 IPD | 4/208 | 1/51 | | 0.99 [ 0.11, 8.84 ] |
| Krzakowski 2008a | 6/104 | 2/52 | | 1.48 [ 0.33, 6.67 ] |


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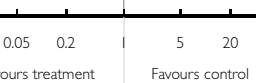
| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Krzakowski 2008b | 10/105 | 3/52 | | 1.64 [ 0.49, 5.44 ] |
| Kurz 1997 | 0/23 | 0/12 | | 0.0 [ 0.0, 0.0 ] |
| Littlewood 2001 IPD | 40/251 | 22/124 | | 0.78 [ 0.46, 1.34 ] |
| ML17616 2006 | 1/30 | 0/30 | | 7.39 [ 0.15, 372.38 ] |
| Oberhoff 1998 IPD | 9/116 | 10/111 | | 0.62 [ 0.24, 1.59 ] |
| Osterborg 1996 IPD | 24/99 | 12/49 | | 1.00 [ 0.50, 2.00 ] |
| Osterborg 2002 IPD | 24/173 | 19/176 | | 1.29 [ 0.71, 2.35 ] |
| Razzouk 2004 | 2/112 | 2/110 | | 0.98 [ 0.14, 7.03 ] |
| Rose 1994 IPD | 16/142 | 6/79 | | 1.66 [ 0.70, 3.92 ] |
| Smith 2003 | 3/64 | 0/22 | | 3.96 [ 0.29, 54.28 ] |
| Smith 2008 IPD | 136/517 | 94/472 | | 1.37 [ 1.05, 1.78 ] |
| Thompson 2000 | 3/45 | 0/21 | | 4.52 [ 0.38, 53.37 ] |
| Tjulandin 2010a | 5/76 | 6/37 | | 0.28 [ 0.07, 1.08 ] |
| Tjulandin 2010b | 4/73 | 6/37 | | 0.34 [ 0.09, 1.26 ] |
| Tjulandin 2011 | 6/95 | 5/91 | | 1.16 [ 0.34, 3.90 ] |
| Witzig 2005 IPD | 31/174 | 25/170 | | 1.22 [ 0.72, 2.06 ] |
| **Subtotal (95% CI)** | **3305** | **2454** | | **1.12 [ 0.96, 1.32 ]** |
| Heterogeneity: Chi² = 28.22, df = 24 (P = 0.25); I² =15% | | | | |
| Test for overall effect: Z = 1.44 (P = 0.15) | | | | |
| 2 Hb 10 to 12 g/dL | | | | |
| Aapro 2008 IPD | 47/231 | 35/232 | | 1.38 [ 0.89, 2.13 ] |
| Bamias 2003 | 7/72 | 4/72 | | 1.80 [ 0.53, 6.12 ] |
| Chang 2005 IPD | 7/176 | 5/178 | | 1.36 [ 0.44, 4.22 ] |
| Charu 2007 IPD | 8/228 | 2/59 | | 0.89 [ 0.19, 4.18 ] |
| EPO-INT-1 IPD | 6/165 | 2/81 | | 1.51 [ 0.35, 6.54 ] |
| EPO-INT-3 IPD | 9/135 | 3/65 | | 1.55 [ 0.47, 5.10 ] |
| Gordon 2008 IPD | 11/164 | 5/56 | | 0.74 [ 0.26, 2.14 ] |
| Henke 2003 IPD | 9/180 | 7/171 | | 1.22 [ 0.46, 3.25 ] |
| Hernandez 2009 IPD | 17/196 | 20/195 | | 0.84 [ 0.44, 1.60 ] |
| Huddart 2002 IPD | 3/48 | 7/47 | | 0.62 [ 0.16, 2.43 ] |
| Kotasek 2002 IPD | 4/129 | 0/32 | | 3.49 [ 0.30, 40.45 ] |
| Mystakidou 2005 | 1/50 | 2/50 | | 0.50 [ 0.05, 5.00 ] |

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| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Pirker 2008 IPD | 53/299 | 51/301 | | 1.02 [ 0.70, 1.49 ] |
| Pronzato 2010 IPD | 4/110 | 8/113 | | 0.52 [ 0.17, 1.60 ] |
| Quirt 1996 IPD | 2/28 | 0/28 | | 5.78 [ 0.35, 95.11 ] |
| Ray-Coquard 2009 IPD | 18/110 | 23/108 | | 0.74 [ 0.40, 1.36 ] |
| Savonije 2005 IPD | 24/211 | 13/104 | | 0.91 [ 0.45, 1.82 ] |
| Strauss 2008 IPD | 0/34 | 0/40 | | 0.0 [ 0.0, 0.0 ] |
| Sweeney 1998 | 0/24 | 0/24 | | 0.0 [ 0.0, 0.0 ] |
| Ten Bokkel1998 IPD | 5/87 | 2/33 | | 0.99 [ 0.19, 5.11 ] |
| Thomas 2002 IPD | 4/65 | 4/65 | | 0.99 [ 0.25, 3.95 ] |
| Thomas 2008 IPD | 1/58 | 1/56 | | 0.94 [ 0.06, 15.06 ] |
| Throuvalas 2000 | 0/28 | 1/27 | | 0.13 [ 0.00, 6.55 ] |
| Vansteenkiste 2002 IPD | 23/159 | 21/161 | | 1.06 [ 0.58, 1.92 ] |
| Wilkinson 2006 IPD | 2/121 | 0/61 | | 4.63 [ 0.25, 86.06 ] |
| Wright 2007 IPD | 25/33 | 23/37 | | 1.68 [ 0.95, 2.99 ] |
| **Subtotal (95% CI)** | **3141** | **2396** | | **1.09 [ 0.91, 1.29 ]** |
| Heterogeneity: Chi² = 14.91, df = 23 (P = 0.90); I² =0.0% | | | | |
| Test for overall effect: Z = 0.93 (P = 0.35) | | | | |
| 3 Hb > 12 g/dL | | | | |
| Del Mastro 1997 | 0/31 | 0/31 | | 0.0 [ 0.0, 0.0 ] |
| Dunphy 1999 | 0/15 | 1/15 | | 0.14 [ 0.00, 6.82 ] |
| Goss 2005 IPD | 4/52 | 1/52 | | 3.40 [ 0.59, 19.63 ] |
| Grote 2005 IPD | 16/109 | 21/115 | | 0.79 [ 0.41, 1.52 ] |
| Hoskin 2009 IPD | 5/151 | 2/149 | | 2.36 [ 0.54, 10.33 ] |
| Leyland-Jones 2005 IPD | 121/469 | 91/470 | | 1.41 [ 1.08, 1.85 ] |
| Machtay 2007 IPD | 5/77 | 3/71 | | 1.57 [ 0.39, 6.31 ] |
| Milroy 2003 IPD | 51/214 | 38/210 | | 1.45 [ 0.95, 2.21 ] |
| Moebus 2007 IPD | 0/324 | 0/319 | | 0.0 [ 0.0, 0.0 ] |
| O'Shaugnessy 2005 IPD | 1/51 | 0/49 | | 7.69 [ 0.15, 387.58 ] |
| Rosen 2003 | 1/47 | 0/43 | | 6.82 [ 0.14, 343.75 ] |
| Thatcher 1999 IPD | 7/86 | 3/44 | | 1.13 [ 0.29, 4.36 ] |
| Untch 2008 IPD | 0/353 | 0/376 | | 0.0 [ 0.0, 0.0 ] |
| **Subtotal (95% CI)** | **1979** | **1944** | | **1.37 [ 1.12, 1.68 ]** |


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| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Heterogeneity: Chi² = 7.25, df = 9 (P = 0.61); I² =0.0% | | | | |
| Test for overall effect: Z = 3.02 (P = 0.0026) | | | | |
| 4 unclear | | | | |
| Debus 2006 IPD | 26/195 | 18/190 | | 1.38 [ 0.76, 2.50 ] |
| EPO-GER-20 IPD | 6/48 | 8/45 | | 0.61 [ 0.21, 1.77 ] |
| ML17620 2006 | 4/61 | 0/60 | | 7.70 [ 1.05, 56.33 ] |
| OBE/EPO-INT-03 IPD | 2/35 | 3/37 | | 0.76 [ 0.13, 4.55 ] |
| P-174 IPD | 1/33 | 1/12 | | 0.44 [ 0.03, 7.27 ] |
| **Subtotal (95% CI)** | **372** | **344** | | **1.20 [ 0.75, 1.93 ]** |
| Heterogeneity: Chi² = 5.86, df = 4 (P = 0.21); I² =32% | | | | |
| Test for overall effect: Z = 0.75 (P = 0.45) | | | | |
| **Total (95% CI)** | | | | **1.17 [ 1.06, 1.29 ]** |
| Heterogeneity: Chi² = 59.49, df = 63 (P = 0.60); I² =0.0% | | | | |
| Test for overall effect: Z = 3.06 (P = 0.0022) | | | | |
| Test for subgroup differences: Chi² = 3.24, df = 3 (P = 0.36), I² =7% | | | | |

## Analysis 6.3. Comparison 6 On-study mortality, Outcome 3 On-study mortality - different malignancies.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 6 On-study mortality

Outcome: 3 On-study mortality - different malignancies

| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| 1 solid tumours | | | | |
| Aapro 2008 IPD | 47/231 | 35/232 | | 1.38 [ 0.89, 2.13 ] |
| Bamias 2003 | 7/72 | 4/72 | | 1.80 [ 0.53, 6.12 ] |
| Cascinu 1994 | 0/50 | 0/50 | | 0.0 [ 0.0, 0.0 ] |
| Chang 2005 IPD | 7/176 | 5/178 | | 1.36 [ 0.44, 4.22 ] |
| Debus 2006 IPD | 26/195 | 18/190 | | 1.38 [ 0.76, 2.50 ] |
| Del Mastro 1997 | 0/31 | 0/31 | | 0.0 [ 0.0, 0.0 ] |
| Dunphy 1999 | 0/15 | 1/15 | | 0.14 [ 0.00, 6.82 ] |
| EPO-GER-20 IPD | 6/48 | 8/45 | | 0.61 [ 0.21, 1.77 ] |
| EPO-INT-1 IPD | 6/165 | 2/81 | | 1.51 [ 0.35, 6.54 ] |
| Fujisaka 2011 | 1/89 | 0/92 | | 7.69 [ 0.15, 387.58 ] |
| Goss 2005 IPD | 4/52 | 1/52 | | 3.40 [ 0.59, 19.63 ] |
| Grote 2005 IPD | 16/109 | 21/115 | | 0.79 [ 0.41, 1.52 ] |
| Henke 2003 IPD | 9/180 | 7/171 | | 1.22 [ 0.46, 3.25 ] |
| Hoskin 2009 IPD | 5/151 | 2/149 | | 2.36 [ 0.54, 10.33 ] |
| Huddart 2002 IPD | 3/48 | 7/47 | | 0.62 [ 0.16, 2.43 ] |
| Kotasek 2002 IPD | 4/129 | 0/32 | | 3.49 [ 0.30, 40.45 ] |
| Kotasek 2003 IPD | 4/208 | 1/51 | | 0.99 [ 0.11, 8.84 ] |
| Kurz 1997 | 0/23 | 0/12 | | 0.0 [ 0.0, 0.0 ] |
| Leyland-Jones 2005 IPD | 121/469 | 91/470 | | 1.41 [ 1.08, 1.85 ] |
| Machtay 2007 IPD | 5/77 | 3/71 | | 1.57 [ 0.39, 6.31 ] |
| Milroy 2003 IPD | 51/214 | 38/210 | | 1.45 [ 0.95, 2.21 ] |
| ML17620 2006 | 4/61 | 0/60 | | 7.70 [ 1.05, 56.33 ] |
| Moebus 2007 IPD | 0/324 | 0/319 | | 0.0 [ 0.0, 0.0 ] |
| Mystakidou 2005 | 1/50 | 2/50 | | 0.50 [ 0.05, 5.00 ] |


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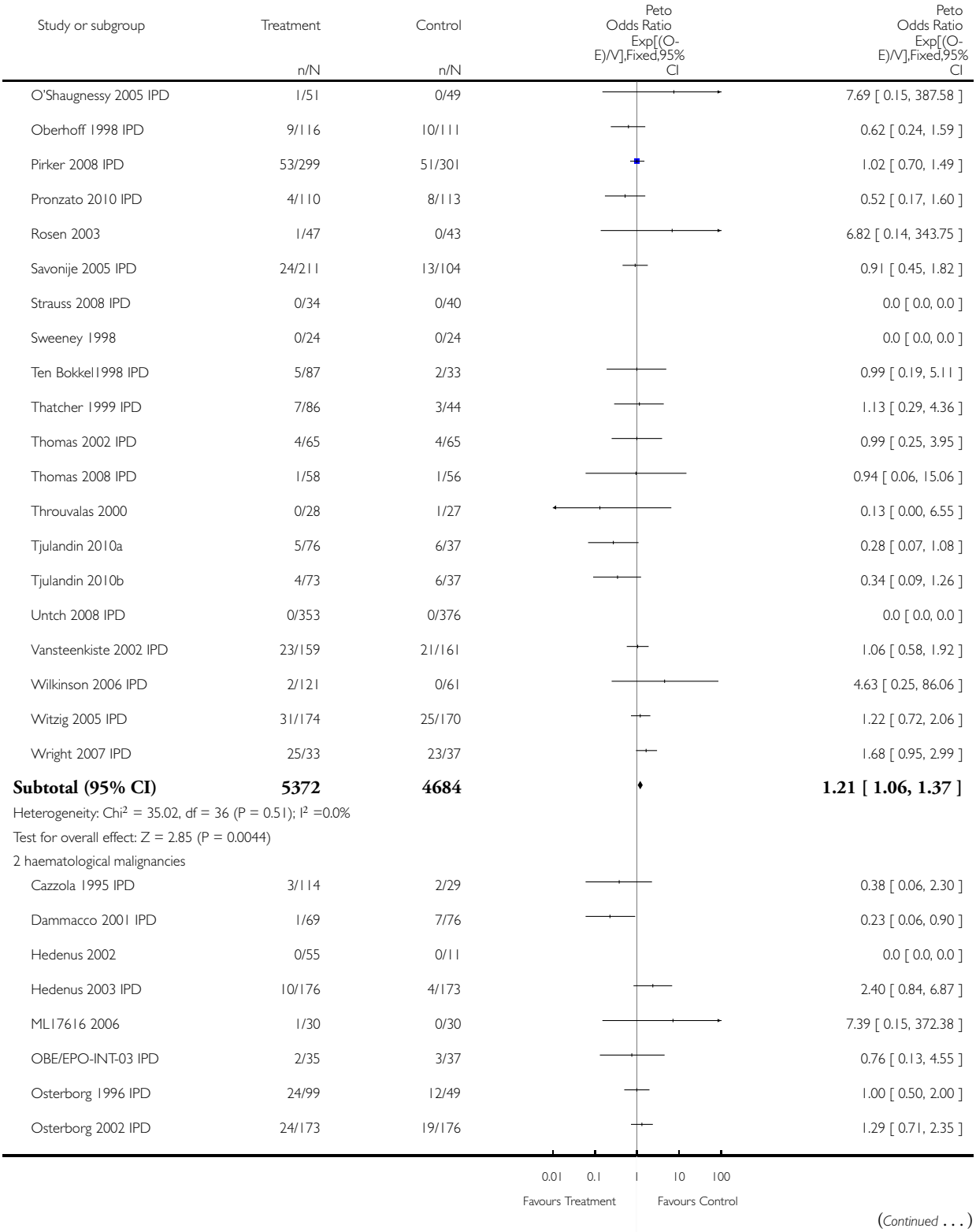

| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| O'Shaugnessy 2005 IPD | 1/51 | 0/49 | | 7.69 [ 0.15, 387.58 ] |
| Oberhoff 1998 IPD | 9/116 | 10/111 | | 0.62 [ 0.24, 1.59 ] |
| Pirker 2008 IPD | 53/299 | 51/301 | | 1.02 [ 0.70, 1.49 ] |
| Pronzato 2010 IPD | 4/110 | 8/113 | | 0.52 [ 0.17, 1.60 ] |
| Rosen 2003 | 1/47 | 0/43 | | 6.82 [ 0.14, 343.75 ] |
| Savonije 2005 IPD | 24/211 | 13/104 | | 0.91 [ 0.45, 1.82 ] |
| Strauss 2008 IPD | 0/34 | 0/40 | | 0.0 [ 0.0, 0.0 ] |
| Sweeney 1998 | 0/24 | 0/24 | | 0.0 [ 0.0, 0.0 ] |
| Ten Bokkel1998 IPD | 5/87 | 2/33 | | 0.99 [ 0.19, 5.11 ] |
| Thatcher 1999 IPD | 7/86 | 3/44 | | 1.13 [ 0.29, 4.36 ] |
| Thomas 2002 IPD | 4/65 | 4/65 | | 0.99 [ 0.25, 3.95 ] |
| Thomas 2008 IPD | 1/58 | 1/56 | | 0.94 [ 0.06, 15.06 ] |
| Throuvalas 2000 | 0/28 | 1/27 | | 0.13 [ 0.00, 6.55 ] |
| Tjulandin 2010a | 5/76 | 6/37 | | 0.28 [ 0.07, 1.08 ] |
| Tjulandin 2010b | 4/73 | 6/37 | | 0.34 [ 0.09, 1.26 ] |
| Untch 2008 IPD | 0/353 | 0/376 | | 0.0 [ 0.0, 0.0 ] |
| Vansteenkiste 2002 IPD | 23/159 | 21/161 | | 1.06 [ 0.58, 1.92 ] |
| Wilkinson 2006 IPD | 2/121 | 0/61 | | 4.63 [ 0.25, 86.06 ] |
| Witzig 2005 IPD | 31/174 | 25/170 | | 1.22 [ 0.72, 2.06 ] |
| Wright 2007 IPD | 25/33 | 23/37 | | 1.68 [ 0.95, 2.99 ] |
| **Subtotal (95% CI)** | **5372** | **4684** | | **1.21 [ 1.06, 1.37 ]** |
| Heterogeneity: Chi² = 35.02, df = 36 (P = 0.51); I² =0.0% | | | | |
| Test for overall effect: Z = 2.85 (P = 0.0044) | | | | |
| 2 haematological malignancies | | | | |
| Cazzola 1995 IPD | 3/114 | 2/29 | | 0.38 [ 0.06, 2.30 ] |
| Dammacco 2001 IPD | 1/69 | 7/76 | | 0.23 [ 0.06, 0.90 ] |
| Hedenus 2002 | 0/55 | 0/11 | | 0.0 [ 0.0, 0.0 ] |
| Hedenus 2003 IPD | 10/176 | 4/173 | | 2.40 [ 0.84, 6.87 ] |
| ML17616 2006 | 1/30 | 0/30 | | 7.39 [ 0.15, 372.38 ] |
| OBE/EPO-INT-03 IPD | 2/35 | 3/37 | | 0.76 [ 0.13, 4.55 ] |
| Osterborg 1996 IPD | 24/99 | 12/49 | | 1.00 [ 0.50, 2.00 ] |
| Osterborg 2002 IPD | 24/173 | 19/176 | | 1.29 [ 0.71, 2.35 ] |



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| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| P-174 IPD | 1/33 | 1/12 | | 0.44 [ 0.03, 7.27 ] |
| Rose 1994 IPD | 16/142 | 6/79 | | 1.66 [ 0.70, 3.92 ] |
| **Subtotal (95% CI)** | **926** | **672** | | **1.13 [ 0.80, 1.59 ]** |
| Heterogeneity: Chi² = 11.19, df = 8 (P = 0.19); I² =29% | | | | |
| Test for overall effect: Z = 0.70 (P = 0.49) | | | | |
| 3 MDS | | | | |
| Thompson 2000 | 3/45 | 0/21 | | 4.52 [ 0.38, 53.37 ] |
| **Subtotal (95% CI)** | **45** | **21** | | **4.52 [ 0.38, 53.37 ]** |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: Z = 1.20 (P = 0.23) | | | | |
| 4 mixed | | | | |
| Abels 1993 IPD | 13/65 | 12/59 | | 0.96 [ 0.44, 2.10 ] |
| Boogaerts 2003 IPD | 10/132 | 10/127 | | 1.02 [ 0.42, 2.46 ] |
| Case 1993 IPD | 10/81 | 9/76 | | 1.11 [ 0.45, 2.73 ] |
| Charu 2007 IPD | 8/228 | 2/59 | | 0.89 [ 0.19, 4.18 ] |
| EPO-INT-3 IPD | 9/135 | 3/65 | | 1.55 [ 0.47, 5.10 ] |
| Gordon 2008 IPD | 11/164 | 5/56 | | 0.74 [ 0.26, 2.14 ] |
| Henry 1995 IPD | 7/67 | 10/65 | | 0.68 [ 0.26, 1.77 ] |
| Hernandez 2009 IPD | 17/196 | 20/195 | | 0.84 [ 0.44, 1.60 ] |
| Krzakowski 2008a | 6/104 | 2/52 | | 1.48 [ 0.33, 6.67 ] |
| Krzakowski 2008b | 10/105 | 3/52 | | 1.64 [ 0.49, 5.44 ] |
| Littlewood 2001 IPD | 40/251 | 22/124 | | 0.78 [ 0.46, 1.34 ] |
| Quirt 1996 IPD | 2/28 | 0/28 | | 5.78 [ 0.35, 95.11 ] |
| Ray-Coquard 2009 IPD | 18/110 | 23/108 | | 0.74 [ 0.40, 1.36 ] |
| Razzouk 2004 | 2/112 | 2/110 | | 0.98 [ 0.14, 7.03 ] |
| Smith 2003 | 3/64 | 0/22 | | 3.96 [ 0.29, 54.28 ] |
| Smith 2008 IPD | 136/517 | 94/472 | | 1.37 [ 1.05, 1.78 ] |
| Tjulandin 2011 | 6/95 | 5/91 | | 1.16 [ 0.34, 3.90 ] |
| **Subtotal (95% CI)** | **2454** | **1761** | | **1.10 [ 0.92, 1.31 ]** |
| Heterogeneity: Chi² = 11.42, df = 16 (P = 0.78); I² =0.0% | | | | |
| Test for overall effect: Z = 1.09 (P = 0.28) | | | | |
| 5 not reported | | | | |
| **Subtotal (95% CI)** | **0** | **0** | | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: not applicable | | | | |


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| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| **Total (95% CI)** | | | | **1.17 [ 1.06, 1.29 ]** |
| Heterogeneity: Chi² = 59.49, df = 63 (P = 0.60); I² =0.0% | | | | |
| Test for overall effect: Z = 3.06 (P = 0.0022) | | | | |
| Test for subgroup differences: Chi² = 1.86, df = 3 (P = 0.60), I² =0.0% | | | | |


### Analysis 6.4. Comparison 6 On-study mortality, Outcome 4 On-study mortality - age.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 6 On-study mortality

Outcome: 4 On-study mortality - age

| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| 1 children | | | | |
| Razzouk 2004 | 2/112 | 2/110 | | 0.98 [ 0.14, 7.03 ] |
| **Subtotal (95% CI)** | **112** | **110** | | **0.98 [ 0.14, 7.03 ]** |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: Z = 0.02 (P = 0.98) | | | | |
| 2 adults | | | | |
| Aapro 2008 IPD | 47/231 | 35/232 | | 1.38 [ 0.89, 2.13 ] |
| Abels 1993 IPD | 13/65 | 12/59 | | 0.96 [ 0.44, 2.10 ] |
| Bamias 2003 | 7/72 | 4/72 | | 1.80 [ 0.53, 6.12 ] |
| Boogaerts 2003 IPD | 10/132 | 10/127 | | 1.02 [ 0.42, 2.46 ] |
| Cascinu 1994 | 0/50 | 0/50 | | 0.0 [ 0.0, 0.0 ] |
| Case 1993 IPD | 10/81 | 9/76 | | 1.11 [ 0.45, 2.73 ] |
| Cazzola 1995 IPD | 3/114 | 2/29 | | 0.38 [ 0.06, 2.30 ] |


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| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Chang 2005 IPD | 7/176 | 5/178 | | 1.36 [ 0.44, 4.22 ] |
| Charu 2007 IPD | 8/228 | 2/59 | | 0.89 [ 0.19, 4.18 ] |
| Dammacco 2001 IPD | 1/69 | 7/76 | | 0.23 [ 0.06, 0.90 ] |
| Debus 2006 IPD | 26/195 | 18/190 | | 1.38 [ 0.76, 2.50 ] |
| Del Mastro 1997 | 0/31 | 0/31 | | 0.0 [ 0.0, 0.0 ] |
| Dunphy 1999 | 0/15 | 1/15 | | 0.14 [ 0.00, 6.82 ] |
| EPO-GER-20 IPD | 6/48 | 8/45 | | 0.61 [ 0.21, 1.77 ] |
| EPO-INT-1 IPD | 6/165 | 2/81 | | 1.51 [ 0.35, 6.54 ] |
| EPO-INT-3 IPD | 9/135 | 3/65 | | 1.55 [ 0.47, 5.10 ] |
| Fujisaka 2011 | 1/89 | 0/92 | | 7.69 [ 0.15, 387.58 ] |
| Gordon 2008 IPD | 11/164 | 5/56 | | 0.74 [ 0.26, 2.14 ] |
| Goss 2005 IPD | 4/52 | 1/52 | | 3.40 [ 0.59, 19.63 ] |
| Grote 2005 IPD | 16/109 | 21/115 | | 0.79 [ 0.41, 1.52 ] |
| Hedenus 2002 | 0/55 | 0/11 | | 0.0 [ 0.0, 0.0 ] |
| Hedenus 2003 IPD | 10/176 | 4/173 | | 2.40 [ 0.84, 6.87 ] |
| Henke 2003 IPD | 9/180 | 7/171 | | 1.22 [ 0.46, 3.25 ] |
| Henry 1995 IPD | 7/67 | 10/65 | | 0.68 [ 0.26, 1.77 ] |
| Hernandez 2009 IPD | 17/196 | 20/195 | | 0.84 [ 0.44, 1.60 ] |
| Hoskin 2009 IPD | 5/151 | 2/149 | | 2.36 [ 0.54, 10.33 ] |
| Huddart 2002 IPD | 3/48 | 7/47 | | 0.62 [ 0.16, 2.43 ] |
| Kotasek 2002 IPD | 4/129 | 0/32 | | 3.49 [ 0.30, 40.45 ] |
| Kotasek 2003 IPD | 4/208 | 1/51 | | 0.99 [ 0.11, 8.84 ] |
| Krzakowski 2008a | 6/104 | 2/52 | | 1.48 [ 0.33, 6.67 ] |
| Krzakowski 2008b | 10/105 | 3/52 | | 1.64 [ 0.49, 5.44 ] |
| Kurz 1997 | 0/23 | 0/12 | | 0.0 [ 0.0, 0.0 ] |
| Leyland-Jones 2005 IPD | 121/469 | 91/470 | | 1.41 [ 1.08, 1.85 ] |
| Littlewood 2001 IPD | 40/251 | 22/124 | | 0.78 [ 0.46, 1.34 ] |
| Machtay 2007 IPD | 5/77 | 3/71 | | 1.57 [ 0.39, 6.31 ] |
| Milroy 2003 IPD | 51/214 | 38/210 | | 1.45 [ 0.95, 2.21 ] |
| ML17616 2006 | 1/30 | 0/30 | | 7.39 [ 0.15, 372.38 ] |


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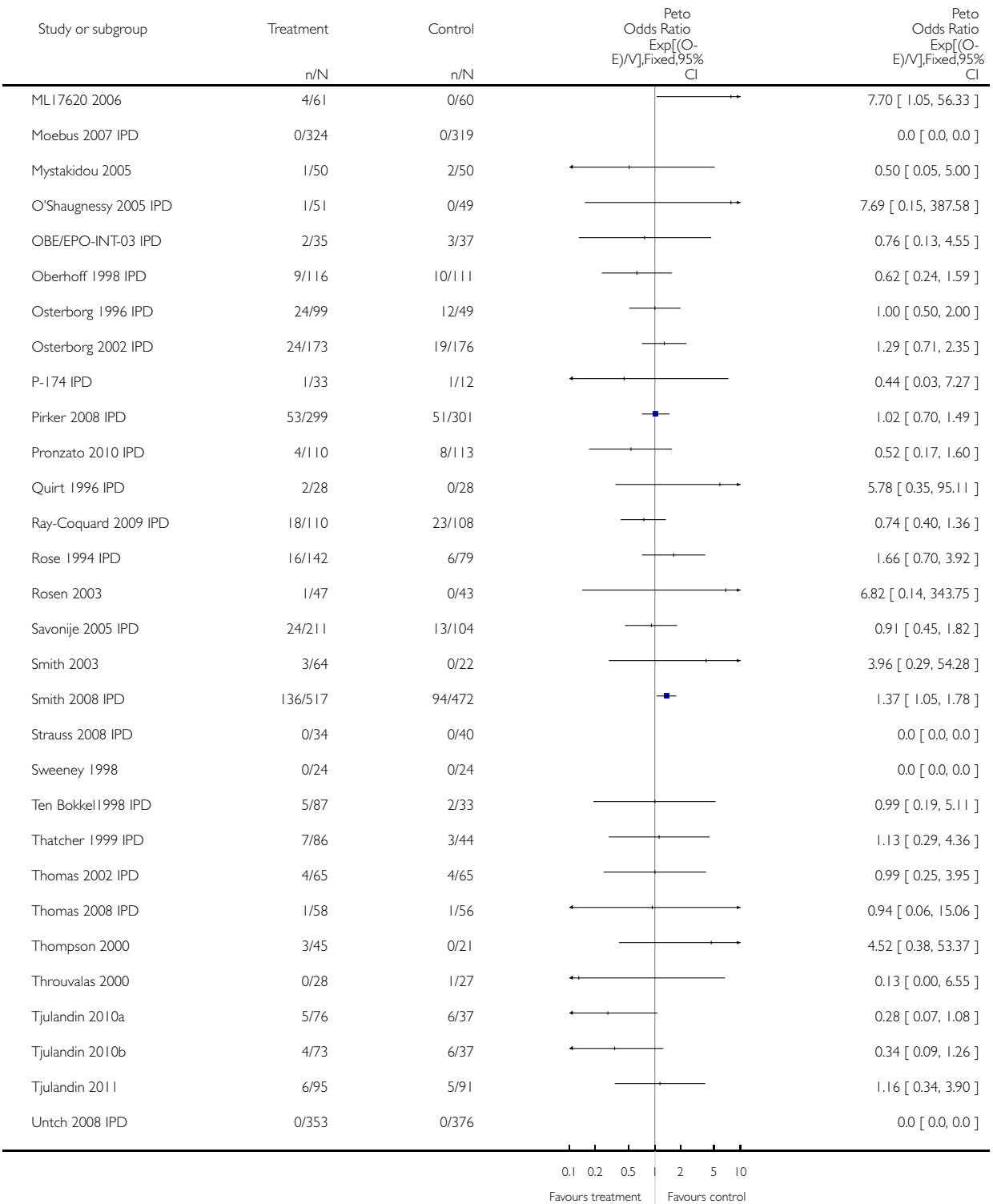


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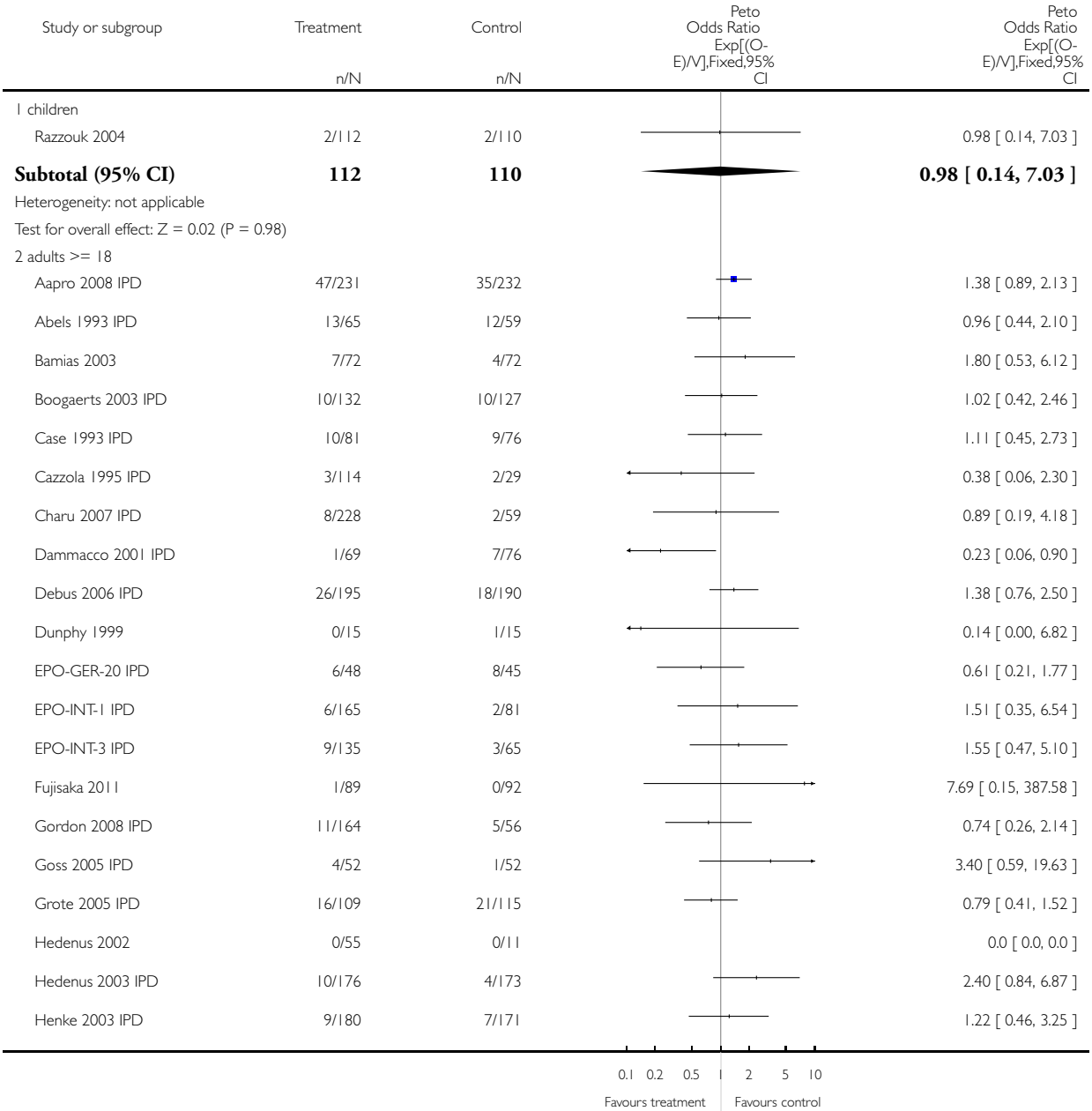
| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Vansteenkiste 2002 IPD | 23/159 | 21/161 | | 1.06 [ 0.58, 1.92 ] |
| Wilkinson 2006 IPD | 2/121 | 0/61 | | 4.63 [ 0.25, 86.06 ] |
| Witzig 2005 IPD | 31/174 | 25/170 | | 1.22 [ 0.72, 2.06 ] |
| Wright 2007 IPD | 25/33 | 23/37 | | 1.68 [ 0.95, 2.99 ] |
| **Subtotal (95% CI)** | **8685** | **7028** | ♦ | **1.17 [ 1.06, 1.29 ]** |
| Heterogeneity: $Chi^2$ = 59.46, df = 62 (P = 0.57); $I^2$ =0.0% | | | | |
| Test for overall effect: Z = 3.07 (P = 0.0022) | | | | |
| **Total (95% CI)** | | | ♦ | **1.17 [ 1.06, 1.29 ]** |
| Heterogeneity: $Chi^2$ = 59.49, df = 63 (P = 0.60); $I^2$ =0.0% | | | | |
| Test for overall effect: Z = 3.06 (P = 0.0022) | | | | |
| Test for subgroup differences: $Chi^2$ = 0.03, df = 1 (P = 0.86), $I^2$ =0.0% | | | | |

### Analysis 6.5. Comparison 6 On-study mortality, Outcome 5 On-study mortality - age differentiated.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 6 On-study mortality

Outcome: 5 On-study mortality - age differentiated

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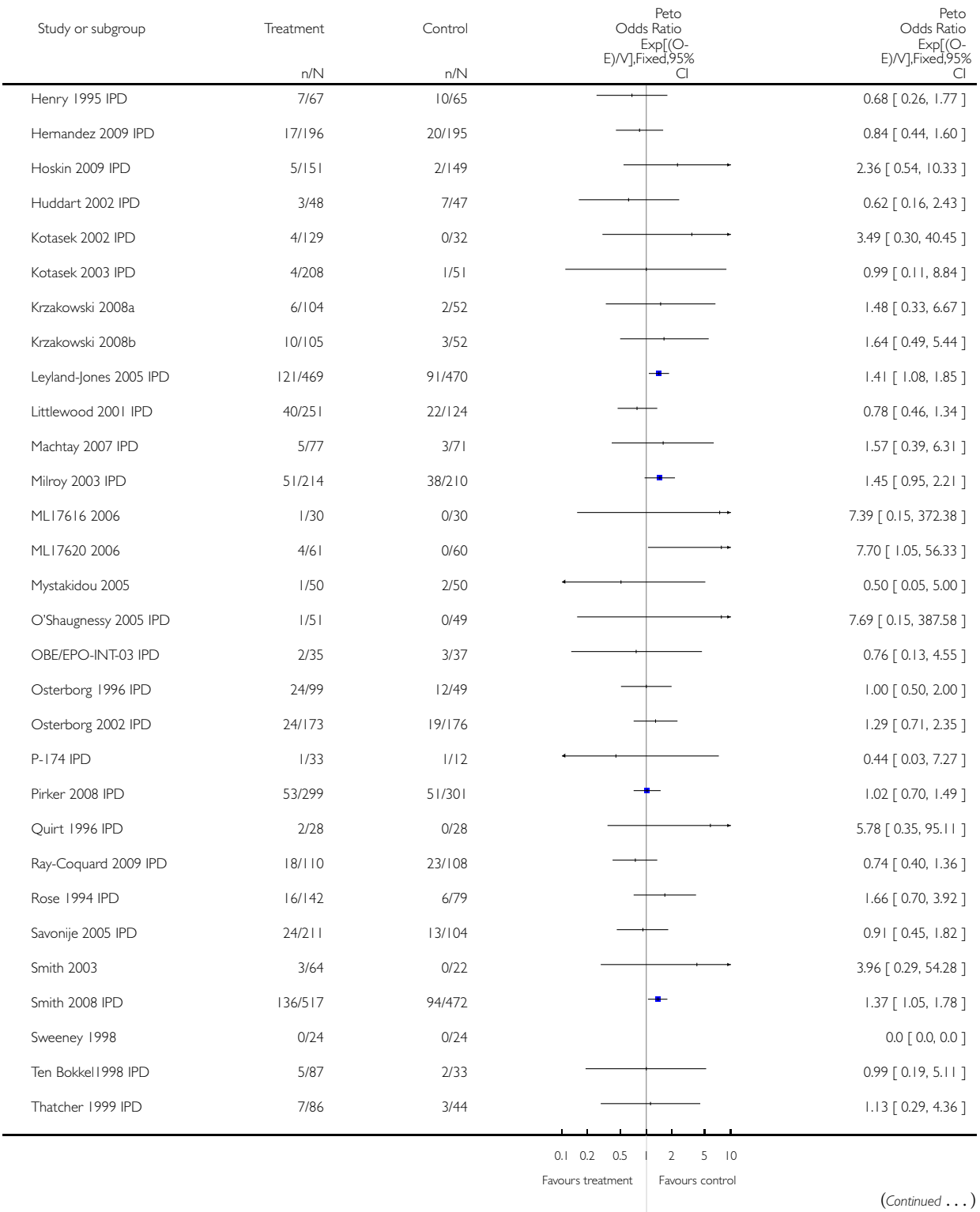


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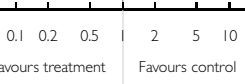
| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Thomas 2002 IPD | 4/65 | 4/65 | | 0.99 [ 0.25, 3.95 ] |
| Thompson 2000 | 3/45 | 0/21 | | 4.52 [ 0.38, 53.37 ] |
| Tjulandin 2010a | 5/76 | 6/37 | | 0.28 [ 0.07, 1.08 ] |
| Tjulandin 2010b | 4/73 | 6/37 | | 0.34 [ 0.09, 1.26 ] |
| Tjulandin 2011 | 6/95 | 5/91 | | 1.16 [ 0.34, 3.90 ] |
| Vansteenkiste 2002 IPD | 23/159 | 21/161 | | 1.06 [ 0.58, 1.92 ] |
| Wilkinson 2006 IPD | 2/121 | 0/61 | | 4.63 [ 0.25, 86.06 ] |
| Witzig 2005 IPD | 31/174 | 25/170 | | 1.22 [ 0.72, 2.06 ] |
| Wright 2007 IPD | 25/33 | 23/37 | | 1.68 [ 0.95, 2.99 ] |
| **Subtotal (95% CI)** | **7335** | **5672** | | **1.18 [ 1.07, 1.31 ]** |
| Heterogeneity: Chi² = 53.58, df = 56 (P = 0.57); I² =0.0% | | | | |
| Test for overall effect: Z = 3.28 (P = 0.0011) | | | | |
| 3 > 68% non elderly, 18-65 | | | | |
| Cascinu 1994 | 0/50 | 0/50 | | 0.0 [ 0.0, 0.0 ] |
| Chang 2005 IPD | 7/176 | 5/178 | | 1.36 [ 0.44, 4.22 ] |
| Del Mastro 1997 | 0/31 | 0/31 | | 0.0 [ 0.0, 0.0 ] |
| Kurz 1997 | 0/23 | 0/12 | | 0.0 [ 0.0, 0.0 ] |
| Oberhoff 1998 IPD | 9/116 | 10/111 | | 0.62 [ 0.24, 1.59 ] |
| Pronzato 2010 IPD | 4/110 | 8/113 | | 0.52 [ 0.17, 1.60 ] |
| Rosen 2003 | 1/47 | 0/43 | | 6.82 [ 0.14, 343.75 ] |
| Strauss 2008 IPD | 0/34 | 0/40 | | 0.0 [ 0.0, 0.0 ] |
| Thomas 2008 IPD | 1/58 | 1/56 | | 0.94 [ 0.06, 15.06 ] |
| Throuvalas 2000 | 0/28 | 1/27 | | 0.13 [ 0.00, 6.55 ] |
| **Subtotal (95% CI)** | **673** | **661** | | **0.76 [ 0.42, 1.35 ]** |
| Heterogeneity: Chi² = 3.65, df = 5 (P = 0.60); I² =0.0% | | | | |
| Test for overall effect: Z = 0.95 (P = 0.34) | | | | |
| 4 only non elderly adults | | | | |
| Moebus 2007 IPD | 0/324 | 0/319 | | 0.0 [ 0.0, 0.0 ] |
| Untch 2008 IPD | 0/353 | 0/376 | | 0.0 [ 0.0, 0.0 ] |
| **Subtotal (95% CI)** | **677** | **695** | | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: Chi² = 0.0, df = 0 (P<0.00001); I² =0.0% | | | | |
| Test for overall effect: Z = 0.0 (P < 0.00001) | | | | |
| 5 > 68% elderly > 65 years | | | | |
| **Subtotal (95% CI)** | **0** | **0** | | **0.0 [ 0.0, 0.0 ]** |

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| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Heterogeneity: not applicable | | | | |
| Test for overall effect: not applicable | | | | |
| 6 only elderly | | | | |
| **Subtotal (95% CI)** | **0** | **0** | | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: not applicable | | | | |
| **Total (95% CI)** | | | ◆ | **1.17 [ 1.06, 1.29 ]** |
| Heterogeneity: $Chi^2$ = 59.49, df = 63 (P = 0.60); $I^2$ =0.0% | | | | |
| Test for overall effect: Z = 3.06 (P = 0.0022) | | | | |
| Test for subgroup differences: $Chi^2$ = 2.26, df = 2 (P = 0.32), $I^2$ =11% | | | | |

## Analysis 6.6. Comparison 6 On-study mortality, Outcome 6 On-study mortality - different therapies.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 6 On-study mortality

Outcome: 6 On-study mortality - different therapies

| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| 1 chemotherapy | | | | |
| Aapro 2008 IPD | 47/231 | 35/232 | | 1.38 [ 0.89, 2.13 ] |
| Bamias 2003 | 7/72 | 4/72 | | 1.80 [ 0.53, 6.12 ] |
| Boogaerts 2003 IPD | 10/132 | 10/127 | | 1.02 [ 0.42, 2.46 ] |
| Cascinu 1994 | 0/50 | 0/50 | | 0.0 [ 0.0, 0.0 ] |
| Case 1993 IPD | 10/81 | 9/76 | | 1.11 [ 0.45, 2.73 ] |
| Cazzola 1995 IPD | 3/114 | 2/29 | | 0.38 [ 0.06, 2.30 ] |
| Chang 2005 IPD | 7/176 | 5/178 | | 1.36 [ 0.44, 4.22 ] |
| Dammacco 2001 IPD | 1/69 | 7/76 | | 0.23 [ 0.06, 0.90 ] |
| Del Mastro 1997 | 0/31 | 0/31 | | 0.0 [ 0.0, 0.0 ] |
| Dunphy 1999 | 0/15 | 1/15 | | 0.14 [ 0.00, 6.82 ] |
| EPO-GER-20 IPD | 6/48 | 8/45 | | 0.61 [ 0.21, 1.77 ] |
| EPO-INT-1 IPD | 6/165 | 2/81 | | 1.51 [ 0.35, 6.54 ] |
| EPO-INT-3 IPD | 9/135 | 3/65 | | 1.55 [ 0.47, 5.10 ] |
| Fujisaka 2011 | 1/89 | 0/92 | | 7.69 [ 0.15, 387.58 ] |
| Grote 2005 IPD | 16/109 | 21/115 | | 0.79 [ 0.41, 1.52 ] |
| Hedenus 2002 | 0/55 | 0/11 | | 0.0 [ 0.0, 0.0 ] |
| Hedenus 2003 IPD | 10/176 | 4/173 | | 2.40 [ 0.84, 6.87 ] |
| Henry 1995 IPD | 7/67 | 10/65 | | 0.68 [ 0.26, 1.77 ] |
| Hernandez 2009 IPD | 17/196 | 20/195 | | 0.84 [ 0.44, 1.60 ] |
| Huddart 2002 IPD | 3/48 | 7/47 | | 0.62 [ 0.16, 2.43 ] |
| Kotasek 2002 IPD | 4/129 | 0/32 | | 3.49 [ 0.30, 40.45 ] |
| Kotasek 2003 IPD | 4/208 | 1/51 | | 0.99 [ 0.11, 8.84 ] |
| Krzakowski 2008a | 6/104 | 2/52 | | 1.48 [ 0.33, 6.67 ] |
| Krzakowski 2008b | 10/105 | 3/52 | | 1.64 [ 0.49, 5.44 ] |


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| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Kurz 1997 | 0/23 | 0/12 | | 0.0 [ 0.0, 0.0 ] |
| Leyland-Jones 2005 IPD | 121/469 | 91/470 | | 1.41 [ 1.08, 1.85 ] |
| Littlewood 2001 IPD | 40/251 | 22/124 | | 0.78 [ 0.46, 1.34 ] |
| Milroy 2003 IPD | 51/214 | 38/210 | | 1.45 [ 0.95, 2.21 ] |
| ML17616 2006 | 1/30 | 0/30 | | 7.39 [ 0.15, 372.38 ] |
| ML17620 2006 | 4/61 | 0/60 | | 7.70 [ 1.05, 56.33 ] |
| Moebus 2007 IPD | 0/324 | 0/319 | | 0.0 [ 0.0, 0.0 ] |
| O'Shaugnessy 2005 IPD | 1/51 | 0/49 | | 7.69 [ 0.15, 387.58 ] |
| OBE/EPO-INT-03 IPD | 2/35 | 3/37 | | 0.76 [ 0.13, 4.55 ] |
| Oberhoff 1998 IPD | 9/116 | 10/111 | | 0.62 [ 0.24, 1.59 ] |
| Osterborg 1996 IPD | 24/99 | 12/49 | | 1.00 [ 0.50, 2.00 ] |
| Osterborg 2002 IPD | 24/173 | 19/176 | | 1.29 [ 0.71, 2.35 ] |
| Pirker 2008 IPD | 53/299 | 51/301 | | 1.02 [ 0.70, 1.49 ] |
| Pronzato 2010 IPD | 4/110 | 8/113 | | 0.52 [ 0.17, 1.60 ] |
| Quirt 1996 IPD | 2/28 | 0/28 | | 5.78 [ 0.35, 95.11 ] |
| Ray-Coquard 2009 IPD | 18/110 | 23/108 | | 0.74 [ 0.40, 1.36 ] |
| Razzouk 2004 | 2/112 | 2/110 | | 0.98 [ 0.14, 7.03 ] |
| Savonije 2005 IPD | 24/211 | 13/104 | | 0.91 [ 0.45, 1.82 ] |
| Ten Bokkel1998 IPD | 5/87 | 2/33 | | 0.99 [ 0.19, 5.11 ] |
| Thatcher 1999 IPD | 7/86 | 3/44 | | 1.13 [ 0.29, 4.36 ] |
| Thomas 2002 IPD | 4/65 | 4/65 | | 0.99 [ 0.25, 3.95 ] |
| Tjulandin 2010a | 5/76 | 6/37 | | 0.28 [ 0.07, 1.08 ] |
| Tjulandin 2010b | 4/73 | 6/37 | | 0.34 [ 0.09, 1.26 ] |
| Tjulandin 2011 | 6/95 | 5/91 | | 1.16 [ 0.34, 3.90 ] |
| Untch 2008 IPD | 0/353 | 0/376 | | 0.0 [ 0.0, 0.0 ] |
| Vansteenkiste 2002 IPD | 23/159 | 21/161 | | 1.06 [ 0.58, 1.92 ] |
| Wilkinson 2006 IPD | 2/121 | 0/61 | | 4.63 [ 0.25, 86.06 ] |
| Witzig 2005 IPD | 31/174 | 25/170 | | 1.22 [ 0.72, 2.06 ] |
| **Subtotal (95% CI)** | **6610** | **5448** | | **1.10 [ 0.98, 1.24 ]** |

Heterogeneity: $Chi^2$ = 46.04, df = 45 (P = 0.43); $I^2$ =2%

Test for overall effect: Z = 1.59 (P = 0.11)

0.01 0.1 1 10 100

Favours Treatment Favours Control

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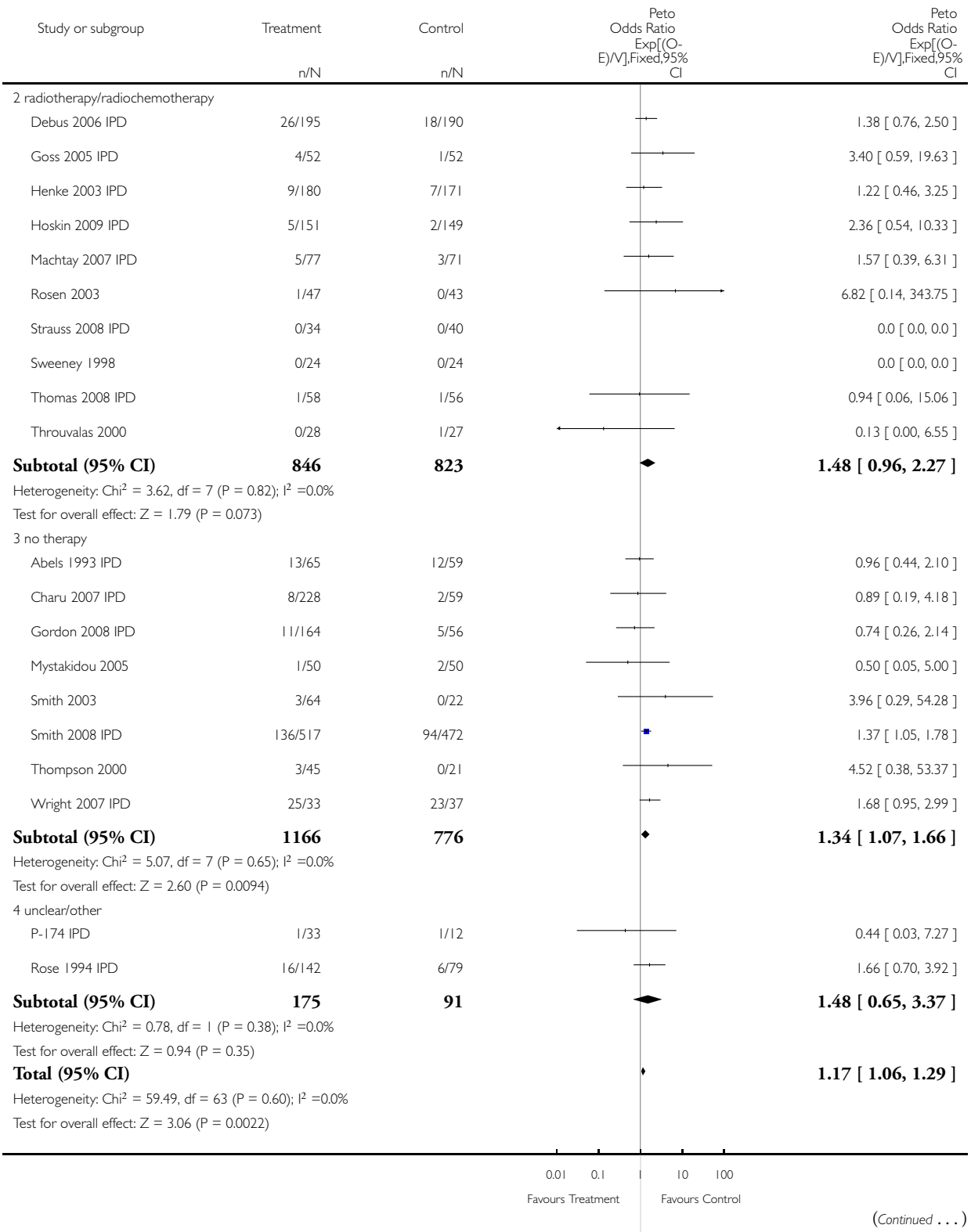


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| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Test for subgroup differences: $Chi^2$ = 3.97, df = 3 (P = 0.26), $I^2$ =24% | | | | |


## Analysis 6.7. Comparison 6 On-study mortality, Outcome 7 On-study mortality - different therapies differentiated.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 6 On-study mortality

Outcome: 7 On-study mortality - different therapies differentiated

| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| 1 chemotherapy, > 70% with platinum | | | | |
| Bamias 2003 | 7/72 | 4/72 | | 1.80 [ 0.53, 6.12 ] |
| Cascinu 1994 | 0/50 | 0/50 | | 0.0 [ 0.0, 0.0 ] |
| Dunphy 1999 | 0/15 | 1/15 | | 0.14 [ 0.00, 6.82 ] |
| EPO-INT-1 IPD | 6/165 | 2/81 | | 1.51 [ 0.35, 6.54 ] |
| Fujisaka 2011 | 1/89 | 0/92 | | 7.69 [ 0.15, 387.58 ] |
| Grote 2005 IPD | 16/109 | 21/115 | | 0.79 [ 0.41, 1.52 ] |
| Henry 1995 IPD | 7/67 | 10/65 | | 0.68 [ 0.26, 1.77 ] |
| Huddart 2002 IPD | 3/48 | 7/47 | | 0.62 [ 0.16, 2.43 ] |
| Kurz 1997 | 0/23 | 0/12 | | 0.0 [ 0.0, 0.0 ] |
| Milroy 2003 IPD | 51/214 | 38/210 | | 1.45 [ 0.95, 2.21 ] |
| ML17620 2006 | 4/61 | 0/60 | | 7.70 [ 1.05, 56.33 ] |
| Pirker 2008 IPD | 53/299 | 51/301 | | 1.02 [ 0.70, 1.49 ] |


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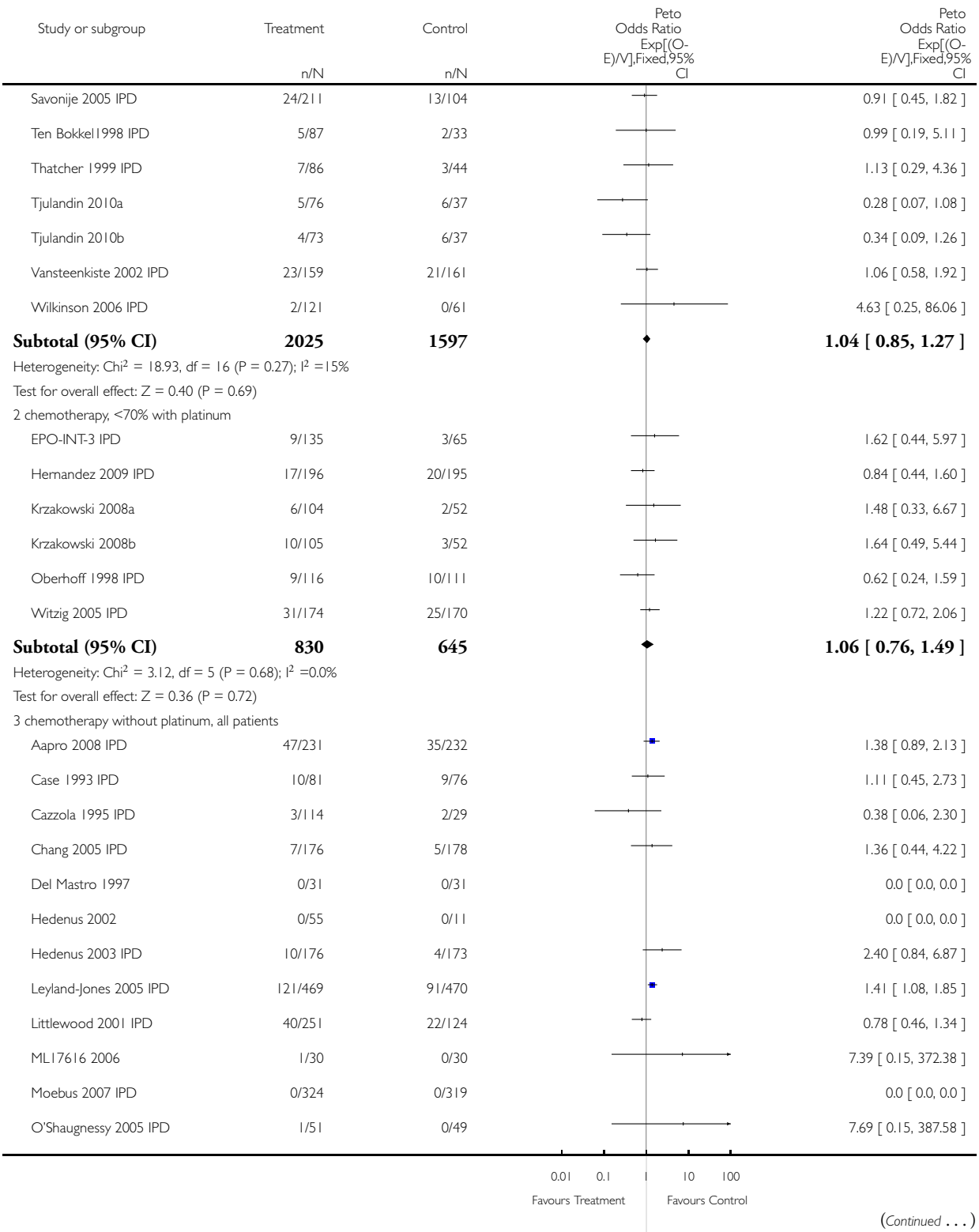


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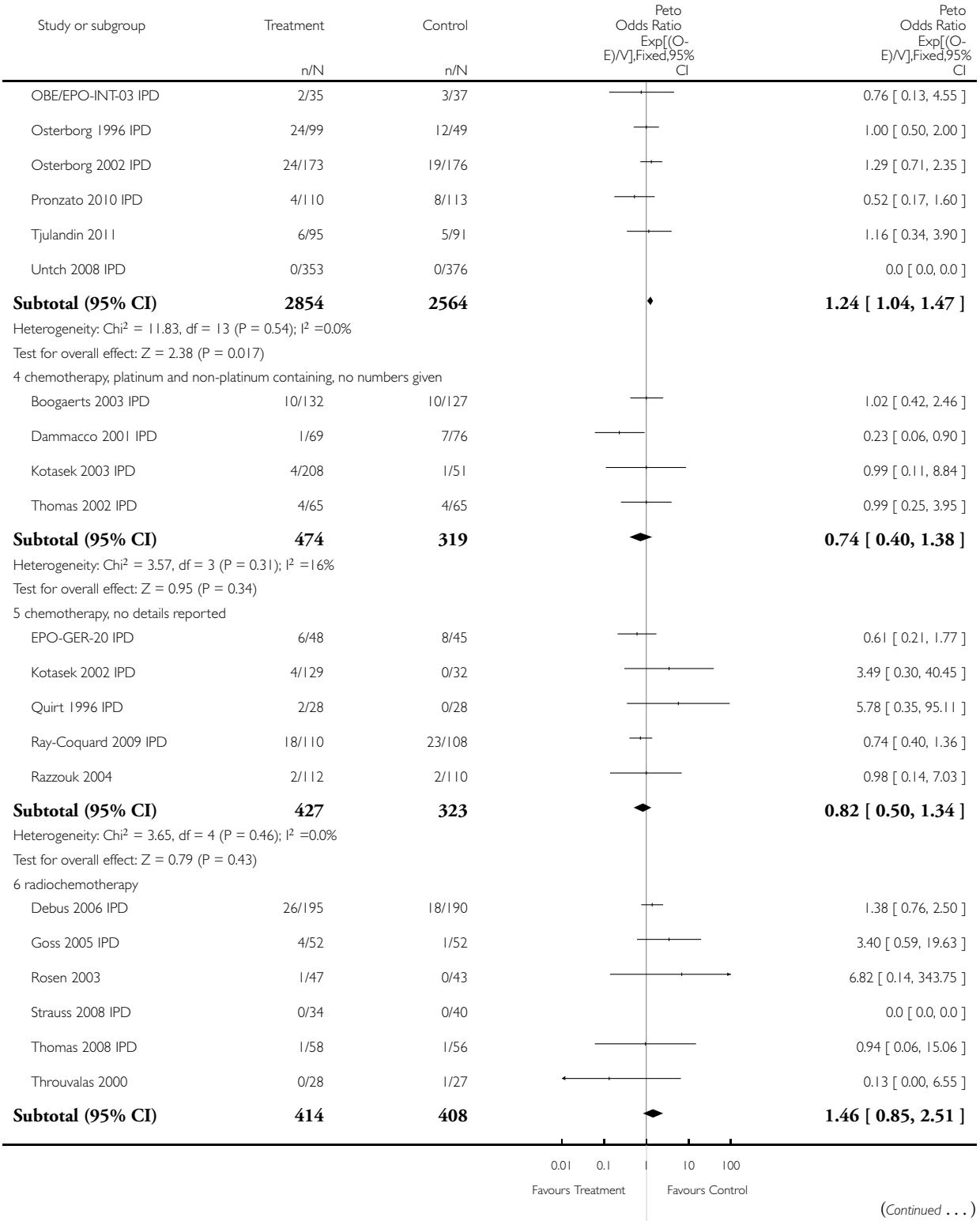


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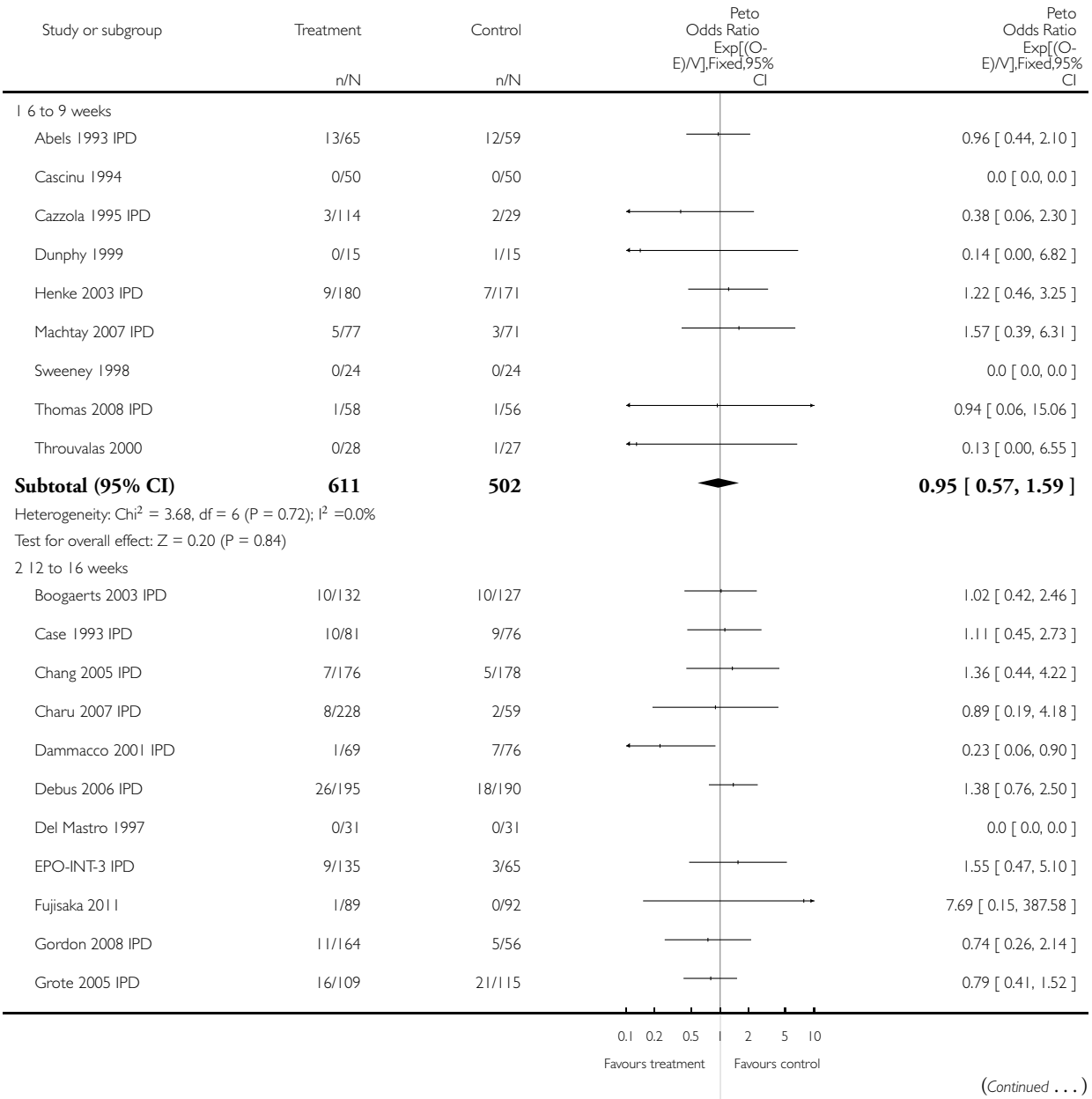
| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Heterogeneity: Chi² = 3.08, df = 4 (P = 0.54); I² =0.0% | | | | |
| Test for overall effect: Z = 1.37 (P = 0.17) | | | | |
| 7 radiotherapy | | | | |
| Henke 2003 IPD | 9/180 | 7/171 | | 1.22 [ 0.46, 3.25 ] |
| Hoskin 2009 IPD | 5/151 | 2/149 | | 2.36 [ 0.54, 10.33 ] |
| Machtay 2007 IPD | 5/77 | 3/71 | | 1.57 [ 0.39, 6.31 ] |
| Sweeney 1998 | 0/24 | 0/24 | | 0.0 [ 0.0, 0.0 ] |
| **Subtotal (95% CI)** | **432** | **415** | | **1.51 [ 0.75, 3.06 ]** |
| Heterogeneity: Chi² = 0.53, df = 2 (P = 0.77); I² =0.0% | | | | |
| Test for overall effect: Z = 1.15 (P = 0.25) | | | | |
| 8 no therapy | | | | |
| Abels 1993 IPD | 13/65 | 12/59 | | 0.96 [ 0.44, 2.10 ] |
| Charu 2007 IPD | 8/228 | 2/59 | | 0.89 [ 0.19, 4.18 ] |
| Gordon 2008 IPD | 11/164 | 5/56 | | 0.74 [ 0.26, 2.14 ] |
| Mystakidou 2005 | 1/50 | 2/50 | | 0.50 [ 0.05, 5.00 ] |
| Smith 2003 | 3/64 | 0/22 | | 3.96 [ 0.29, 54.28 ] |
| Smith 2008 IPD | 136/517 | 94/472 | | 1.37 [ 1.05, 1.78 ] |
| Thompson 2000 | 3/45 | 0/21 | | 4.52 [ 0.38, 53.37 ] |
| Wright 2007 IPD | 25/33 | 23/37 | | 1.68 [ 0.95, 2.99 ] |
| **Subtotal (95% CI)** | **1166** | **776** | | **1.34 [ 1.07, 1.66 ]** |
| Heterogeneity: Chi² = 5.07, df = 7 (P = 0.65); I² =0.0% | | | | |
| Test for overall effect: Z = 2.60 (P = 0.0094) | | | | |
| 9 unclear/other | | | | |
| P-174 IPD | 1/33 | 1/12 | | 0.44 [ 0.03, 7.27 ] |
| Rose 1994 IPD | 16/142 | 6/79 | | 1.66 [ 0.70, 3.92 ] |
| **Subtotal (95% CI)** | **175** | **91** | | **1.48 [ 0.65, 3.37 ]** |
| Heterogeneity: Chi² = 0.78, df = 1 (P = 0.38); I² =0.0% | | | | |
| Test for overall effect: Z = 0.94 (P = 0.35) | | | | |
| **Total (95% CI)** | | | | **1.17 [ 1.06, 1.29 ]** |
| Heterogeneity: Chi² = 59.51, df = 63 (P = 0.60); I² =0.0% | | | | |
| Test for overall effect: Z = 3.06 (P = 0.0022) | | | | |
| Test for subgroup differences: Chi² = 8.94, df = 8 (P = 0.35), I² =11% | | | | |

### Analysis 6.8. Comparison 6 On-study mortality, Outcome 8 On-study mortality - duration of ESA medication.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 6 On-study mortality

Outcome: 8 On-study mortality - duration of ESA medication

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| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Hedenus 2002 | 0/55 | 0/11 | | 0.0 [ 0.0, 0.0 ] |
| Hedenus 2003 IPD | 10/176 | 4/173 | | 2.40 [ 0.84, 6.87 ] |
| Henry 1995 IPD | 7/67 | 10/65 | | 0.68 [ 0.26, 1.77 ] |
| Hernandez 2009 IPD | 17/196 | 20/195 | | 0.84 [ 0.44, 1.60 ] |
| Hoskin 2009 IPD | 5/151 | 2/149 | | 2.36 [ 0.54, 10.33 ] |
| Kotasek 2002 IPD | 4/129 | 0/32 | | 3.49 [ 0.30, 40.45 ] |
| Kotasek 2003 IPD | 4/208 | 1/51 | | 0.99 [ 0.11, 8.84 ] |
| Krzakowski 2008a | 6/104 | 2/52 | | 1.48 [ 0.33, 6.67 ] |
| Krzakowski 2008b | 10/105 | 3/52 | | 1.64 [ 0.49, 5.44 ] |
| Kurz 1997 | 0/23 | 0/12 | | 0.0 [ 0.0, 0.0 ] |
| ML17616 2006 | 1/30 | 0/30 | | 7.39 [ 0.15, 372.38 ] |
| ML17620 2006 | 4/61 | 0/60 | | 7.70 [ 1.05, 56.33 ] |
| O'Shaugnessy 2005 IPD | 1/51 | 0/49 | | 7.69 [ 0.15, 387.58 ] |
| Oberhoff 1998 IPD | 9/116 | 10/111 | | 0.62 [ 0.24, 1.59 ] |
| Osterborg 2002 IPD | 24/173 | 19/176 | | 1.29 [ 0.71, 2.35 ] |
| P-174 IPD | 1/33 | 1/12 | | 0.44 [ 0.03, 7.27 ] |
| Quirt 1996 IPD | 2/28 | 0/28 | | 5.78 [ 0.35, 95.11 ] |
| Ray-Coquard 2009 IPD | 18/110 | 23/108 | | 0.74 [ 0.40, 1.36 ] |
| Razzouk 2004 | 2/112 | 2/110 | | 0.98 [ 0.14, 7.03 ] |
| Rose 1994 IPD | 16/142 | 6/79 | | 1.66 [ 0.70, 3.92 ] |
| Rosen 2003 | 1/47 | 0/43 | | 6.82 [ 0.14, 343.75 ] |
| Savonije 2005 IPD | 24/211 | 13/104 | | 0.91 [ 0.45, 1.82 ] |
| Smith 2003 | 3/64 | 0/22 | | 3.96 [ 0.29, 54.28 ] |
| Smith 2008 IPD | 136/517 | 94/472 | | 1.37 [ 1.05, 1.78 ] |
| Strauss 2008 IPD | 0/34 | 0/40 | | 0.0 [ 0.0, 0.0 ] |
| Thomas 2002 IPD | 4/65 | 4/65 | | 0.99 [ 0.25, 3.95 ] |
| Thompson 2000 | 3/45 | 0/21 | | 4.52 [ 0.38, 53.37 ] |
| Tjulandin 2010a | 5/76 | 6/37 | | 0.28 [ 0.07, 1.08 ] |
| Tjulandin 2010b | 4/73 | 6/37 | | 0.34 [ 0.09, 1.26 ] |
| Tjulandin 2011 | 6/95 | 5/91 | | 1.16 [ 0.34, 3.90 ] |


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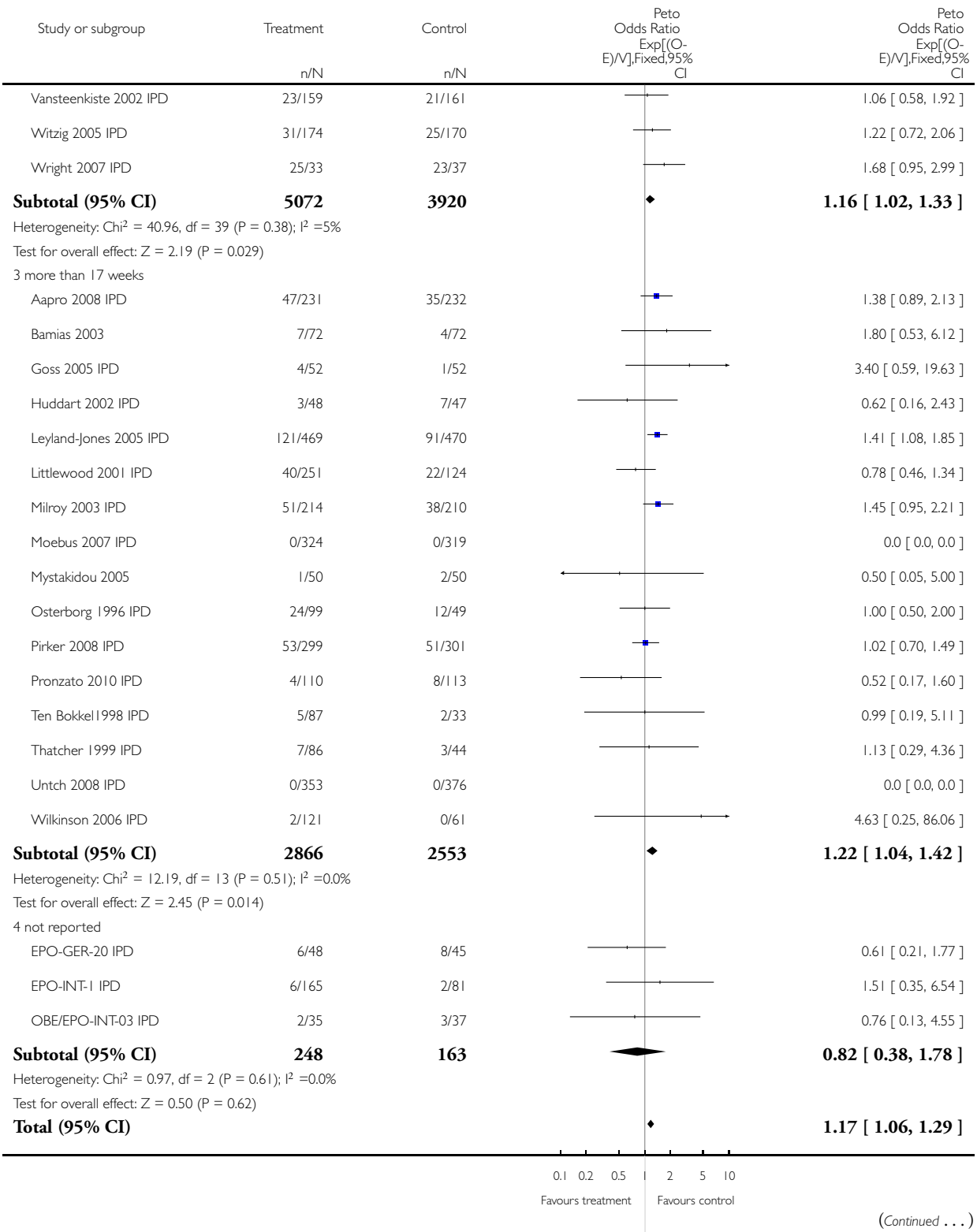


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| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Heterogeneity: $Chi^2$ = 59.49, df = 63 (P = 0.60); $I^2$ =0.0% | | | | |
| Test for overall effect: Z = 3.06 (P = 0.0022) | | | | |
| Test for subgroup differences: $Chi^2$ = 1.68, df = 3 (P = 0.64), $I^2$ =0.0% | | | | |

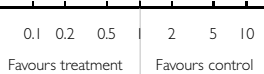

### Analysis 6.9. Comparison 6 On-study mortality, Outcome 9 On-study mortality - epoetin vs darbepoetin.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 6 On-study mortality

Outcome: 9 On-study mortality - epoetin vs darbepoetin

| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| 1 Epoetin | | | | |
| Aapro 2008 IPD | 47/231 | 35/232 | | 1.38 [ 0.89, 2.13 ] |
| Abels 1993 IPD | 13/65 | 12/59 | | 0.96 [ 0.44, 2.10 ] |
| Bamias 2003 | 7/72 | 4/72 | | 1.80 [ 0.53, 6.12 ] |
| Boogaerts 2003 IPD | 10/132 | 10/127 | | 1.02 [ 0.42, 2.46 ] |
| Cascinu 1994 | 0/50 | 0/50 | | 0.0 [ 0.0, 0.0 ] |
| Case 1993 IPD | 10/81 | 9/76 | | 1.11 [ 0.45, 2.73 ] |
| Cazzola 1995 IPD | 3/114 | 2/29 | | 0.38 [ 0.06, 2.30 ] |
| Chang 2005 IPD | 7/176 | 5/178 | | 1.36 [ 0.44, 4.22 ] |
| Dammacco 2001 IPD | 1/69 | 7/76 | | 0.23 [ 0.06, 0.90 ] |
| Debus 2006 IPD | 26/195 | 18/190 | | 1.38 [ 0.76, 2.50 ] |
| Del Mastro 1997 | 0/31 | 0/31 | | 0.0 [ 0.0, 0.0 ] |

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| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Dunphy 1999 | 0/15 | 1/15 | | 0.14 [ 0.00, 6.82 ] |
| EPO-GER-20 IPD | 6/48 | 8/45 | | 0.61 [ 0.21, 1.77 ] |
| EPO-INT-1 IPD | 6/165 | 2/81 | | 1.51 [ 0.35, 6.54 ] |
| EPO-INT-3 IPD | 9/135 | 3/65 | | 1.55 [ 0.47, 5.10 ] |
| Fujisaka 2011 | 1/89 | 0/92 | | 7.69 [ 0.15, 387.58 ] |
| Goss 2005 IPD | 4/52 | 1/52 | | 3.40 [ 0.59, 19.63 ] |
| Grote 2005 IPD | 16/109 | 21/115 | | 0.79 [ 0.41, 1.52 ] |
| Henke 2003 IPD | 9/180 | 7/171 | | 1.22 [ 0.46, 3.25 ] |
| Henry 1995 IPD | 7/67 | 10/65 | | 0.68 [ 0.26, 1.77 ] |
| Hoskin 2009 IPD | 5/151 | 2/149 | | 2.36 [ 0.54, 10.33 ] |
| Huddart 2002 IPD | 3/48 | 7/47 | | 0.62 [ 0.16, 2.43 ] |
| Krzakowski 2008a | 6/104 | 2/52 | | 1.48 [ 0.33, 6.67 ] |
| Krzakowski 2008b | 10/105 | 3/52 | | 1.64 [ 0.49, 5.44 ] |
| Kurz 1997 | 0/23 | 0/12 | | 0.0 [ 0.0, 0.0 ] |
| Leyland-Jones 2005 IPD | 121/469 | 91/470 | | 1.41 [ 1.08, 1.85 ] |
| Littlewood 2001 IPD | 40/251 | 22/124 | | 0.78 [ 0.46, 1.34 ] |
| Machtay 2007 IPD | 5/77 | 3/71 | | 1.57 [ 0.39, 6.31 ] |
| Milroy 2003 IPD | 51/214 | 38/210 | | 1.45 [ 0.95, 2.21 ] |
| ML17616 2006 | 1/30 | 0/30 | | 7.39 [ 0.15, 372.38 ] |
| ML17620 2006 | 4/61 | 0/60 | | 7.70 [ 1.05, 56.33 ] |
| Moebus 2007 IPD | 0/324 | 0/319 | | 0.0 [ 0.0, 0.0 ] |
| Mystakidou 2005 | 1/50 | 2/50 | | 0.50 [ 0.05, 5.00 ] |
| O'Shaugnessy 2005 IPD | 1/51 | 0/49 | | 7.69 [ 0.15, 387.58 ] |
| OBE/EPO-INT-03 IPD | 2/35 | 3/37 | | 0.76 [ 0.13, 4.55 ] |
| Oberhoff 1998 IPD | 9/116 | 10/111 | | 0.62 [ 0.24, 1.59 ] |
| Osterborg 1996 IPD | 24/99 | 12/49 | | 1.00 [ 0.50, 2.00 ] |
| Osterborg 2002 IPD | 24/173 | 19/176 | | 1.29 [ 0.71, 2.35 ] |
| P-174 IPD | 1/33 | 1/12 | | 0.44 [ 0.03, 7.27 ] |
| Pronzato 2010 IPD | 4/110 | 8/113 | | 0.52 [ 0.17, 1.60 ] |
| Quirt 1996 IPD | 2/28 | 0/28 | | 5.78 [ 0.35, 95.11 ] |


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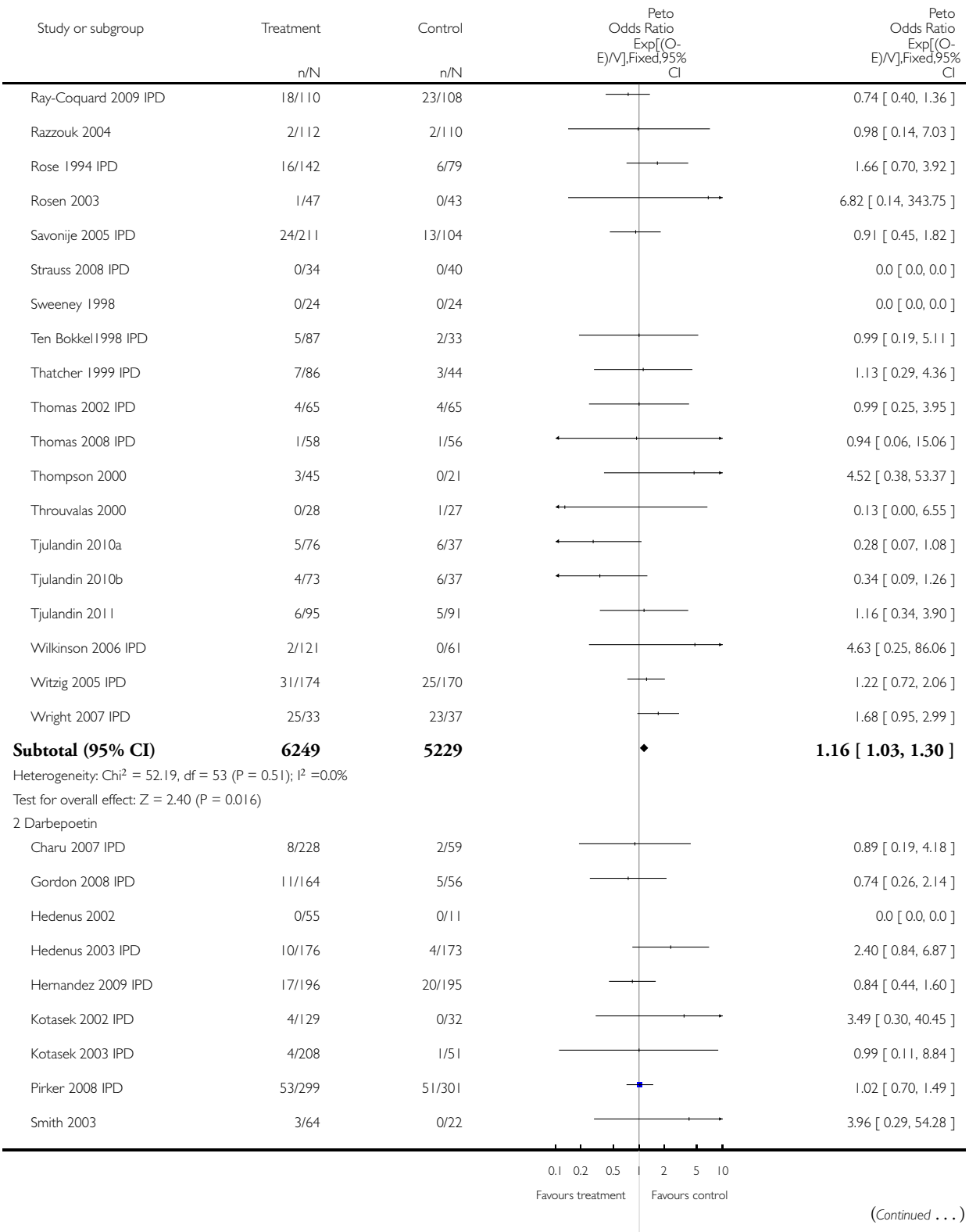


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| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Smith 2008 IPD | 136/517 | 94/472 | | 1.37 [ 1.05, 1.78 ] |
| Untch 2008 IPD | 0/353 | 0/376 | | 0.0 [ 0.0, 0.0 ] |
| Vansteenkiste 2002 IPD | 23/159 | 21/161 | | 1.06 [ 0.58, 1.92 ] |
| **Subtotal (95% CI)** | **2548** | **1909** | | **1.20 [ 1.00, 1.44 ]** |
| Heterogeneity: $Chi^2$ = 7.19, df = 9 (P = 0.62); $I^2$ =0.0% | | | | |
| Test for overall effect: Z = 1.92 (P = 0.054) | | | | |
| **Total (95% CI)** | | | | **1.17 [ 1.06, 1.29 ]** |
| Heterogeneity: $Chi^2$ = 59.49, df = 63 (P = 0.60); $I^2$ =0.0% | | | | |
| Test for overall effect: Z = 3.06 (P = 0.0022) | | | | |
| Test for subgroup differences: $Chi^2$ = 0.11, df = 1 (P = 0.74), $I^2$ =0.0% | | | | |

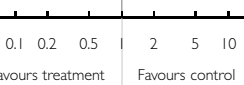
## Analysis 6.10. Comparison 6 On-study mortality, Outcome 10 On-study mortality - iron supplementation.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 6 On-study mortality

Outcome: 10 On-study mortality - iron supplementation

| Study or subgroup | treatment n/N | control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| 1 fixed iron supplementation | | | | |
| Dunphy 1999 | 0/15 | 1/15 | | 0.14 [ 0.00, 6.82 ] |
| Hoskin 2009 IPD | 5/151 | 2/149 | | 2.36 [ 0.54, 10.33 ] |
| Huddart 2002 IPD | 3/48 | 7/47 | | 0.62 [ 0.16, 2.43 ] |
| Krzakowski 2008a | 6/104 | 2/52 | | 1.48 [ 0.33, 6.67 ] |
| Krzakowski 2008b | 10/105 | 3/52 | | 1.64 [ 0.49, 5.44 ] |
| Mystakidou 2005 | 1/50 | 2/50 | | 0.50 [ 0.05, 5.00 ] |
| Untch 2008 IPD | 0/353 | 0/376 | | 0.0 [ 0.0, 0.0 ] |
| Witzig 2005 IPD | 31/174 | 25/170 | | 1.22 [ 0.72, 2.06 ] |
| **Subtotal (95% CI)** | **1000** | **911** | | **1.20 [ 0.80, 1.81 ]** |
| Heterogeneity: Chi² = 3.79, df = 6 (P = 0.71); I² =0.0% | | | | |
| Test for overall effect: Z = 0.89 (P = 0.37) | | | | |
| 2 iron supplementation as necessary | | | | |
| Aapro 2008 IPD | 47/231 | 35/232 | | 1.38 [ 0.89, 2.13 ] |
| Abels 1993 IPD | 13/65 | 12/59 | | 0.96 [ 0.44, 2.10 ] |
| Boogaerts 2003 IPD | 10/132 | 10/127 | | 1.02 [ 0.42, 2.46 ] |
| Cascinu 1994 | 0/50 | 0/50 | | 0.0 [ 0.0, 0.0 ] |
| Case 1993 IPD | 10/81 | 9/76 | | 1.11 [ 0.45, 2.73 ] |
| Cazzola 1995 IPD | 3/114 | 2/29 | | 0.38 [ 0.06, 2.30 ] |
| Chang 2005 IPD | 7/176 | 5/178 | | 1.36 [ 0.44, 4.22 ] |
| Charu 2007 IPD | 8/228 | 2/59 | | 0.89 [ 0.19, 4.18 ] |
| Dammacco 2001 IPD | 1/69 | 7/76 | | 0.23 [ 0.06, 0.90 ] |
| Del Mastro 1997 | 0/31 | 0/31 | | 0.0 [ 0.0, 0.0 ] |
| EPO-INT-1 IPD | 6/165 | 2/81 | | 1.51 [ 0.35, 6.54 ] |
| EPO-INT-3 IPD | 9/135 | 3/65 | | 1.55 [ 0.47, 5.10 ] |
| Fujisaka 2011 | 1/89 | 0/92 | | 7.69 [ 0.15, 387.58 ] |

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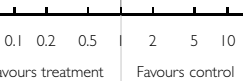
| Study or subgroup | treatment n/N | control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Gordon 2008 IPD | 11/164 | 5/56 | | 0.74 [ 0.26, 2.14 ] |
| Goss 2005 IPD | 4/52 | 1/52 | | 3.40 [ 0.59, 19.63 ] |
| Grote 2005 IPD | 16/109 | 21/115 | | 0.79 [ 0.41, 1.52 ] |
| Hedenus 2003 IPD | 10/176 | 4/173 | | 2.40 [ 0.84, 6.87 ] |
| Henke 2003 IPD | 9/180 | 7/171 | | 1.22 [ 0.46, 3.25 ] |
| Henry 1995 IPD | 7/67 | 10/65 | | 0.68 [ 0.26, 1.77 ] |
| Hernandez 2009 IPD | 17/196 | 20/195 | | 0.84 [ 0.44, 1.60 ] |
| Kotasek 2002 IPD | 4/129 | 0/32 | | 3.49 [ 0.30, 40.45 ] |
| Kotasek 2003 IPD | 4/208 | 1/51 | | 0.99 [ 0.11, 8.84 ] |
| Kurz 1997 | 0/23 | 0/12 | | 0.0 [ 0.0, 0.0 ] |
| Leyland-Jones 2005 IPD | 121/469 | 91/470 | | 1.41 [ 1.08, 1.85 ] |
| Littlewood 2001 IPD | 40/251 | 22/124 | | 0.78 [ 0.46, 1.34 ] |
| Milroy 2003 IPD | 51/214 | 38/210 | | 1.45 [ 0.95, 2.21 ] |
| ML17616 2006 | 1/30 | 0/30 | | 7.39 [ 0.15, 372.38 ] |
| ML17620 2006 | 4/61 | 0/60 | | 7.70 [ 1.05, 56.33 ] |
| O'Shaugnessy 2005 IPD | 1/51 | 0/49 | | 7.69 [ 0.15, 387.58 ] |
| Oberhoff 1998 IPD | 9/116 | 10/111 | | 0.62 [ 0.24, 1.59 ] |
| Osterborg 1996 IPD | 24/99 | 12/49 | | 1.00 [ 0.50, 2.00 ] |
| Osterborg 2002 IPD | 24/173 | 19/176 | | 1.29 [ 0.71, 2.35 ] |
| P-174 IPD | 1/33 | 1/12 | | 0.44 [ 0.03, 7.27 ] |
| Pirker 2008 IPD | 53/299 | 51/301 | | 1.02 [ 0.70, 1.49 ] |
| Pronzato 2010 IPD | 4/110 | 8/113 | | 0.52 [ 0.17, 1.60 ] |
| Quirt 1996 IPD | 2/28 | 0/28 | | 5.78 [ 0.35, 95.11 ] |
| Ray-Coquard 2009 IPD | 18/110 | 23/108 | | 0.74 [ 0.40, 1.36 ] |
| Razzouk 2004 | 2/112 | 2/110 | | 0.98 [ 0.14, 7.03 ] |
| Rose 1994 IPD | 16/142 | 6/79 | | 1.66 [ 0.70, 3.92 ] |
| Smith 2003 | 3/64 | 0/22 | | 3.96 [ 0.29, 54.28 ] |
| Smith 2008 IPD | 136/517 | 94/472 | | 1.37 [ 1.05, 1.78 ] |
| Strauss 2008 IPD | 0/34 | 0/40 | | 0.0 [ 0.0, 0.0 ] |
| Ten Bokkel1998 IPD | 5/87 | 2/33 | | 0.99 [ 0.19, 5.11 ] |

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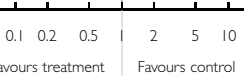
| Study or subgroup | treatment n/N | control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Thatcher 1999 IPD | 7/86 | 3/44 | | 1.13 [ 0.29, 4.36 ] |
| Thomas 2002 IPD | 4/65 | 4/65 | | 0.99 [ 0.25, 3.95 ] |
| Thomas 2008 IPD | 1/58 | 1/56 | | 0.94 [ 0.06, 15.06 ] |
| Throuvalas 2000 | 0/28 | 1/27 | | 0.13 [ 0.00, 6.55 ] |
| Tjulandin 2010a | 5/76 | 6/37 | | 0.28 [ 0.07, 1.08 ] |
| Tjulandin 2010b | 4/73 | 6/37 | | 0.34 [ 0.09, 1.26 ] |
| Tjulandin 2011 | 6/95 | 5/91 | | 1.16 [ 0.34, 3.90 ] |
| Vansteenkiste 2002 IPD | 23/159 | 21/161 | | 1.06 [ 0.58, 1.92 ] |
| Wilkinson 2006 IPD | 2/121 | 0/61 | | 4.63 [ 0.25, 86.06 ] |
| Wright 2007 IPD | 25/33 | 23/37 | | 1.68 [ 0.95, 2.99 ] |
| **Subtotal (95% CI)** | **6664** | **5290** | | **1.17 [ 1.05, 1.30 ]** |
| Heterogeneity: $Chi^2$ = 50.64, df = 48 (P = 0.37); $I^2$ =5% | | | | |
| Test for overall effect: Z = 2.81 (P = 0.0050) | | | | |
| 3 no explicit statement on iron supplementation or no iron given | | | | |
| Bamias 2003 | 7/72 | 4/72 | | 1.80 [ 0.53, 6.12 ] |
| Hedenus 2002 | 0/55 | 0/11 | | 0.0 [ 0.0, 0.0 ] |
| Thompson 2000 | 3/45 | 0/21 | | 4.52 [ 0.38, 53.37 ] |
| **Subtotal (95% CI)** | **172** | **104** | | **2.16 [ 0.72, 6.46 ]** |
| Heterogeneity: $Chi^2$ = 0.43, df = 1 (P = 0.51); $I^2$ =0.0% | | | | |
| Test for overall effect: Z = 1.37 (P = 0.17) | | | | |
| 4 explicitly stated no iron | | | | |
| **Subtotal (95% CI)** | **0** | **0** | | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: not applicable | | | | |
| 5 iron handled differently in the study arms | | | | |
| Debus 2006 IPD | 26/195 | 18/190 | | 1.38 [ 0.76, 2.50 ] |
| EPO-GER-20 IPD | 6/48 | 8/45 | | 0.61 [ 0.21, 1.77 ] |
| Machtay 2007 IPD | 5/77 | 3/71 | | 1.57 [ 0.39, 6.31 ] |
| Moebus 2007 IPD | 0/324 | 0/319 | | 0.0 [ 0.0, 0.0 ] |
| OBE/EPO-INT-03 IPD | 2/35 | 3/37 | | 0.76 [ 0.13, 4.55 ] |
| Rosen 2003 | 1/47 | 0/43 | | 6.82 [ 0.14, 343.75 ] |
| Savonije 2005 IPD | 24/211 | 13/104 | | 0.91 [ 0.45, 1.82 ] |
| Sweeney 1998 | 0/24 | 0/24 | | 0.0 [ 0.0, 0.0 ] |
| **Subtotal (95% CI)** | **961** | **833** | | **1.09 [ 0.74, 1.60 ]** |

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| Study or subgroup | treatment n/N | control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Heterogeneity: Chi² = 3.27, df = 5 (P = 0.66); I² =0.0% | | | | |
| Test for overall effect: Z = 0.42 (P = 0.67) | | | | |
| **Total (95% CI)** | | | ♦ | **1.17 [ 1.06, 1.29 ]** |
| Heterogeneity: Chi² = 59.49, df = 63 (P = 0.60); I² =0.0% | | | | |
| Test for overall effect: Z = 3.06 (P = 0.0022) | | | | |
| Test for subgroup differences: Chi² = 1.35, df = 3 (P = 0.72), I² =0.0% | | | | |


### Analysis 6.11. Comparison 6 On-study mortality, Outcome 11 On-study mortality - publication.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 6 On-study mortality

Outcome: 11 On-study mortality - publication

| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| 1 full text publication | | | | |
| Bamias 2003 | 7/72 | 4/72 | | 1.80 [ 0.53, 6.12 ] |
| Dunphy 1999 | 0/15 | 1/15 | | 0.14 [ 0.00, 6.82 ] |
| Fujisaka 2011 | 1/89 | 0/92 | | 7.69 [ 0.15, 387.58 ] |
| Hedenus 2002 | 0/55 | 0/11 | | 0.0 [ 0.0, 0.0 ] |
| Krzakowski 2008a | 6/104 | 2/52 | | 1.48 [ 0.33, 6.67 ] |
| Krzakowski 2008b | 10/105 | 3/52 | | 1.64 [ 0.49, 5.44 ] |
| Mystakidou 2005 | 1/50 | 2/50 | | 0.50 [ 0.05, 5.00 ] |
| Razzouk 2004 | 2/112 | 2/110 | | 0.98 [ 0.14, 7.03 ] |
| Rosen 2003 | 1/47 | 0/43 | | 6.82 [ 0.14, 343.75 ] |


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| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Smith 2003 | 3/64 | 0/22 | | 3.96 [ 0.29, 54.28 ] |
| Sweeney 1998 | 0/24 | 0/24 | | 0.0 [ 0.0, 0.0 ] |
| Tjulandin 2010a | 5/76 | 6/37 | | 0.28 [ 0.07, 1.08 ] |
| Tjulandin 2010b | 4/73 | 6/37 | | 0.34 [ 0.09, 1.26 ] |
| Tjulandin 2011 | 6/95 | 5/91 | | 1.16 [ 0.34, 3.90 ] |
| **Subtotal (95% CI)** | **981** | **708** | | **0.97 [ 0.60, 1.57 ]** |
| Heterogeneity: Chi² = 12.20, df = 11 (P = 0.35); I² =10% | | | | |
| Test for overall effect: Z = 0.11 (P = 0.91) | | | | |
| 2 abstract publication | | | | |
| ML17616 2006 | 1/30 | 0/30 | | 7.39 [ 0.15, 372.38 ] |
| ML17620 2006 | 4/61 | 0/60 | | 7.70 [ 1.05, 56.33 ] |
| **Subtotal (95% CI)** | **91** | **90** | | **7.64 [ 1.29, 45.03 ]** |
| Heterogeneity: Chi² = 0.00, df = 1 (P = 0.99); I² =0.0% | | | | |
| Test for overall effect: Z = 2.25 (P = 0.025) | | | | |
| 3 unpublished data | | | | |
| Cascinu 1994 | 0/50 | 0/50 | | 0.0 [ 0.0, 0.0 ] |
| Del Mastro 1997 | 0/31 | 0/31 | | 0.0 [ 0.0, 0.0 ] |
| Kurz 1997 | 0/23 | 0/12 | | 0.0 [ 0.0, 0.0 ] |
| Thompson 2000 | 3/45 | 0/21 | | 4.52 [ 0.38, 53.37 ] |
| Throuvalas 2000 | 0/28 | 1/27 | | 0.13 [ 0.00, 6.55 ] |
| **Subtotal (95% CI)** | **177** | **141** | | **1.65 [ 0.20, 13.32 ]** |
| Heterogeneity: Chi² = 2.25, df = 1 (P = 0.13); I² =56% | | | | |
| Test for overall effect: Z = 0.47 (P = 0.64) | | | | |
| 4 Data presented at FDA hearing | | | | |
| **Subtotal (95% CI)** | **0** | **0** | | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: not applicable | | | | |
| 5 IPD Bohlius 2009 | | | | |
| Aapro 2008 IPD | 47/231 | 35/232 | | 1.38 [ 0.89, 2.13 ] |
| Abels 1993 IPD | 13/65 | 12/59 | | 0.96 [ 0.44, 2.10 ] |
| Boogaerts 2003 IPD | 10/132 | 10/127 | | 1.02 [ 0.42, 2.46 ] |
| Case 1993 IPD | 10/81 | 9/76 | | 1.11 [ 0.45, 2.73 ] |
| Cazzola 1995 IPD | 3/114 | 2/29 | | 0.38 [ 0.06, 2.30 ] |
| Chang 2005 IPD | 7/176 | 5/178 | | 1.36 [ 0.44, 4.22 ] |
| Charu 2007 IPD | 8/228 | 2/59 | | 0.89 [ 0.19, 4.18 ] |


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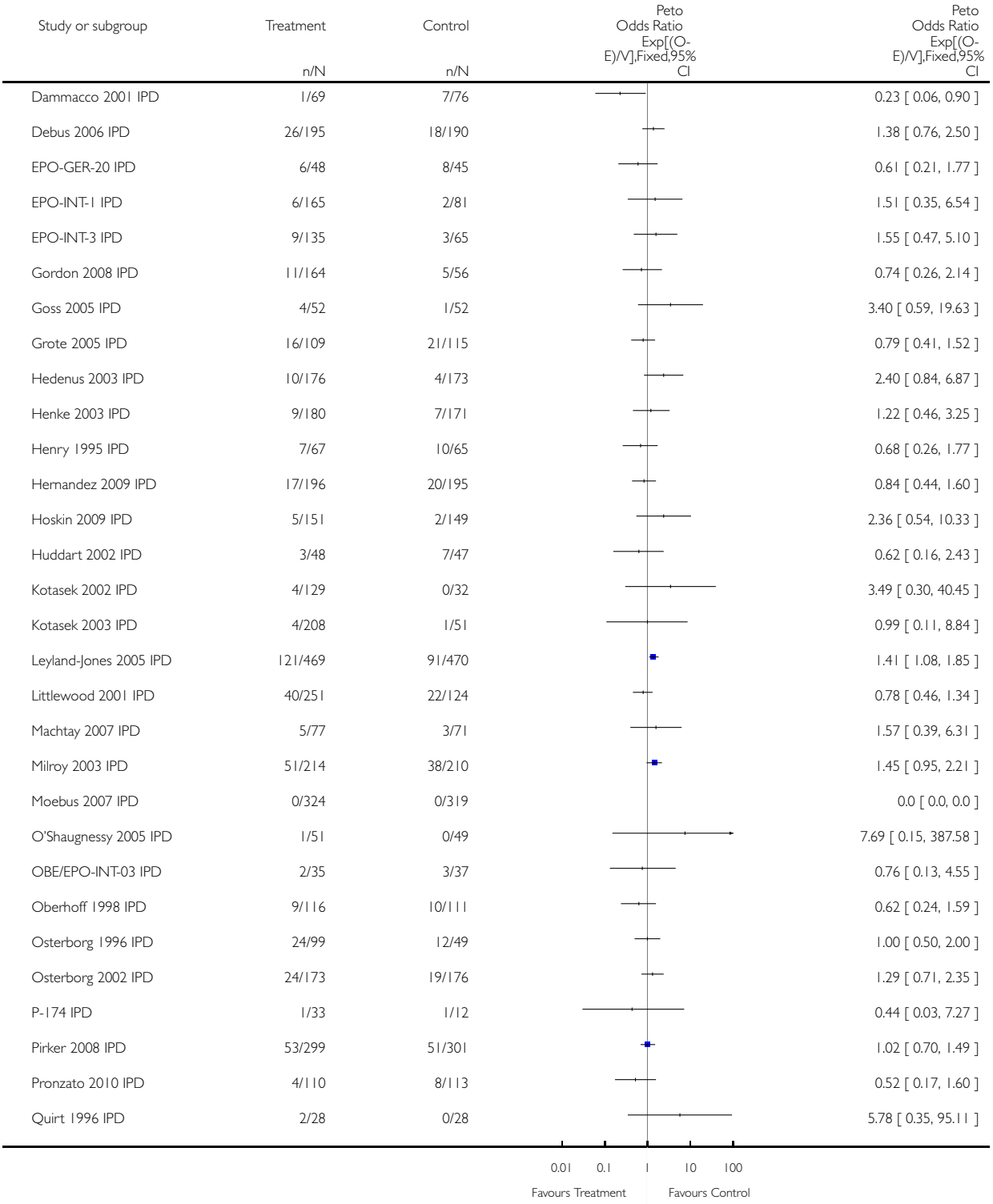


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| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Ray-Coquard 2009 IPD | 18/110 | 23/108 | | 0.74 [ 0.40, 1.36 ] |
| Rose 1994 IPD | 16/142 | 6/79 | | 1.66 [ 0.70, 3.92 ] |
| Savonije 2005 IPD | 24/211 | 13/104 | | 0.91 [ 0.45, 1.82 ] |
| Smith 2008 IPD | 136/517 | 94/472 | | 1.37 [ 1.05, 1.78 ] |
| Strauss 2008 IPD | 0/34 | 0/40 | | 0.0 [ 0.0, 0.0 ] |
| Ten Bokkel1998 IPD | 5/87 | 2/33 | | 0.99 [ 0.19, 5.11 ] |
| Thatcher 1999 IPD | 7/86 | 3/44 | | 1.13 [ 0.29, 4.36 ] |
| Thomas 2002 IPD | 4/65 | 4/65 | | 0.99 [ 0.25, 3.95 ] |
| Thomas 2008 IPD | 1/58 | 1/56 | | 0.94 [ 0.06, 15.06 ] |
| Untch 2008 IPD | 0/353 | 0/376 | | 0.0 [ 0.0, 0.0 ] |
| Vansteenkiste 2002 IPD | 23/159 | 21/161 | | 1.06 [ 0.58, 1.92 ] |
| Wilkinson 2006 IPD | 2/121 | 0/61 | | 4.63 [ 0.25, 86.06 ] |
| Witzig 2005 IPD | 31/174 | 25/170 | | 1.22 [ 0.72, 2.06 ] |
| Wright 2007 IPD | 25/33 | 23/37 | | 1.68 [ 0.95, 2.99 ] |
| **Subtotal (95% CI)** | **7548** | **6199** | | **1.17 [ 1.06, 1.29 ]** |
| Heterogeneity: $Chi^2$ = 40.07, df = 47 (P = 0.75); $I^2$ =0.0% | | | | |
| Test for overall effect: Z = 3.01 (P = 0.0026) | | | | |
| **Total (95% CI)** | | | | **1.17 [ 1.06, 1.29 ]** |
| Heterogeneity: $Chi^2$ = 59.49, df = 63 (P = 0.60); $I^2$ =0.0% | | | | |
| Test for overall effect: Z = 3.06 (P = 0.0022) | | | | |
| Test for subgroup differences: $Chi^2$ = 4.96, df = 3 (P = 0.17), $I^2$ =40% | | | | |

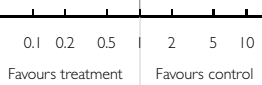
## Analysis 6.12. Comparison 6 On-study mortality, Outcome 12 On-study mortality - time-to-event or binary mortality data.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 6 On-study mortality

Outcome: 12 On-study mortality - time-to-event or binary mortality data

| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| 1 binary mortality data at end of study | | | | |
| Bamias 2003 | 7/72 | 4/72 | | 1.80 [ 0.53, 6.12 ] |
| Cascinu 1994 | 0/50 | 0/50 | | 0.0 [ 0.0, 0.0 ] |
| Del Mastro 1997 | 0/31 | 0/31 | | 0.0 [ 0.0, 0.0 ] |
| Dunphy 1999 | 0/15 | 1/15 | | 0.14 [ 0.00, 6.82 ] |
| Fujisaka 2011 | 1/89 | 0/92 | | 7.69 [ 0.15, 387.58 ] |
| Hedenus 2002 | 0/55 | 0/11 | | 0.0 [ 0.0, 0.0 ] |
| Krzakowski 2008a | 6/104 | 2/52 | | 1.48 [ 0.33, 6.67 ] |
| Krzakowski 2008b | 10/105 | 3/52 | | 1.64 [ 0.49, 5.44 ] |
| Kurz 1997 | 0/23 | 0/12 | | 0.0 [ 0.0, 0.0 ] |
| ML17616 2006 | 1/30 | 0/30 | | 7.39 [ 0.15, 372.38 ] |
| ML17620 2006 | 4/61 | 0/60 | | 7.70 [ 1.05, 56.33 ] |
| Mystakidou 2005 | 1/50 | 2/50 | | 0.50 [ 0.05, 5.00 ] |
| Razzouk 2004 | 2/112 | 2/110 | | 0.98 [ 0.14, 7.03 ] |
| Rosen 2003 | 1/47 | 0/43 | | 6.82 [ 0.14, 343.75 ] |
| Smith 2003 | 3/64 | 0/22 | | 3.96 [ 0.29, 54.28 ] |
| Sweeney 1998 | 0/24 | 0/24 | | 0.0 [ 0.0, 0.0 ] |
| Thompson 2000 | 3/45 | 0/21 | | 4.52 [ 0.38, 53.37 ] |
| Throuvalas 2000 | 0/28 | 1/27 | | 0.13 [ 0.00, 6.55 ] |
| Tjulandin 2010a | 5/76 | 6/37 | | 0.28 [ 0.07, 1.08 ] |
| Tjulandin 2010b | 4/73 | 6/37 | | 0.34 [ 0.09, 1.26 ] |
| Tjulandin 2011 | 6/95 | 5/91 | | 1.16 [ 0.34, 3.90 ] |
| **Subtotal (95% CI)** | **1249** | **939** | | **1.14 [ 0.73, 1.79 ]** |
| Heterogeneity: $Chi^2$ = 19.40, df = 15 (P = 0.20); $I^2$ =23% | | | | |
| Test for overall effect: Z = 0.57 (P = 0.57) | | | | |

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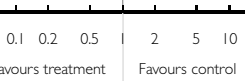
| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| 2 Results from IPD review | | | | |
| Aapro 2008 IPD | 47/231 | 35/232 | | 1.38 [ 0.89, 2.13 ] |
| Abels 1993 IPD | 13/65 | 12/59 | | 0.96 [ 0.44, 2.10 ] |
| Boogaerts 2003 IPD | 10/132 | 10/127 | | 1.02 [ 0.42, 2.46 ] |
| Case 1993 IPD | 10/81 | 9/76 | | 1.11 [ 0.45, 2.73 ] |
| Cazzola 1995 IPD | 3/114 | 2/29 | | 0.38 [ 0.06, 2.30 ] |
| Chang 2005 IPD | 7/176 | 5/178 | | 1.36 [ 0.44, 4.22 ] |
| Charu 2007 IPD | 8/228 | 2/59 | | 0.89 [ 0.19, 4.18 ] |
| Dammacco 2001 IPD | 1/69 | 7/76 | | 0.23 [ 0.06, 0.90 ] |
| Debus 2006 IPD | 26/195 | 18/190 | | 1.38 [ 0.76, 2.50 ] |
| EPO-GER-20 IPD | 6/48 | 8/45 | | 0.61 [ 0.21, 1.77 ] |
| EPO-INT-1 IPD | 6/165 | 2/81 | | 1.51 [ 0.35, 6.54 ] |
| EPO-INT-3 IPD | 9/135 | 3/65 | | 1.55 [ 0.47, 5.10 ] |
| Gordon 2008 IPD | 11/164 | 5/56 | | 0.74 [ 0.26, 2.14 ] |
| Goss 2005 IPD | 4/52 | 1/52 | | 3.40 [ 0.59, 19.63 ] |
| Grote 2005 IPD | 16/109 | 21/115 | | 0.79 [ 0.41, 1.52 ] |
| Hedenus 2003 IPD | 10/176 | 4/173 | | 2.40 [ 0.84, 6.87 ] |
| Henke 2003 IPD | 9/180 | 7/171 | | 1.22 [ 0.46, 3.25 ] |
| Henry 1995 IPD | 7/67 | 10/65 | | 0.68 [ 0.26, 1.77 ] |
| Hernandez 2009 IPD | 17/196 | 20/195 | | 0.84 [ 0.44, 1.60 ] |
| Hoskin 2009 IPD | 5/151 | 2/149 | | 2.36 [ 0.54, 10.33 ] |
| Huddart 2002 IPD | 3/48 | 7/47 | | 0.62 [ 0.16, 2.43 ] |
| Kotasek 2002 IPD | 4/129 | 0/32 | | 3.49 [ 0.30, 40.45 ] |
| Kotasek 2003 IPD | 4/208 | 1/51 | | 0.99 [ 0.11, 8.84 ] |
| Leyland-Jones 2005 IPD | 121/469 | 91/470 | | 1.41 [ 1.08, 1.85 ] |
| Littlewood 2001 IPD | 40/251 | 22/124 | | 0.78 [ 0.46, 1.34 ] |
| Machtay 2007 IPD | 5/77 | 3/71 | | 1.57 [ 0.39, 6.31 ] |
| Milroy 2003 IPD | 51/214 | 38/210 | | 1.45 [ 0.95, 2.21 ] |
| Moebus 2007 IPD | 0/324 | 0/319 | | 0.0 [ 0.0, 0.0 ] |
| O'Shaugnessy 2005 IPD | 1/51 | 0/49 | | 7.69 [ 0.15, 387.58 ] |
| OBE/EPO-INT-03 IPD | 2/35 | 3/37 | | 0.76 [ 0.13, 4.55 ] |

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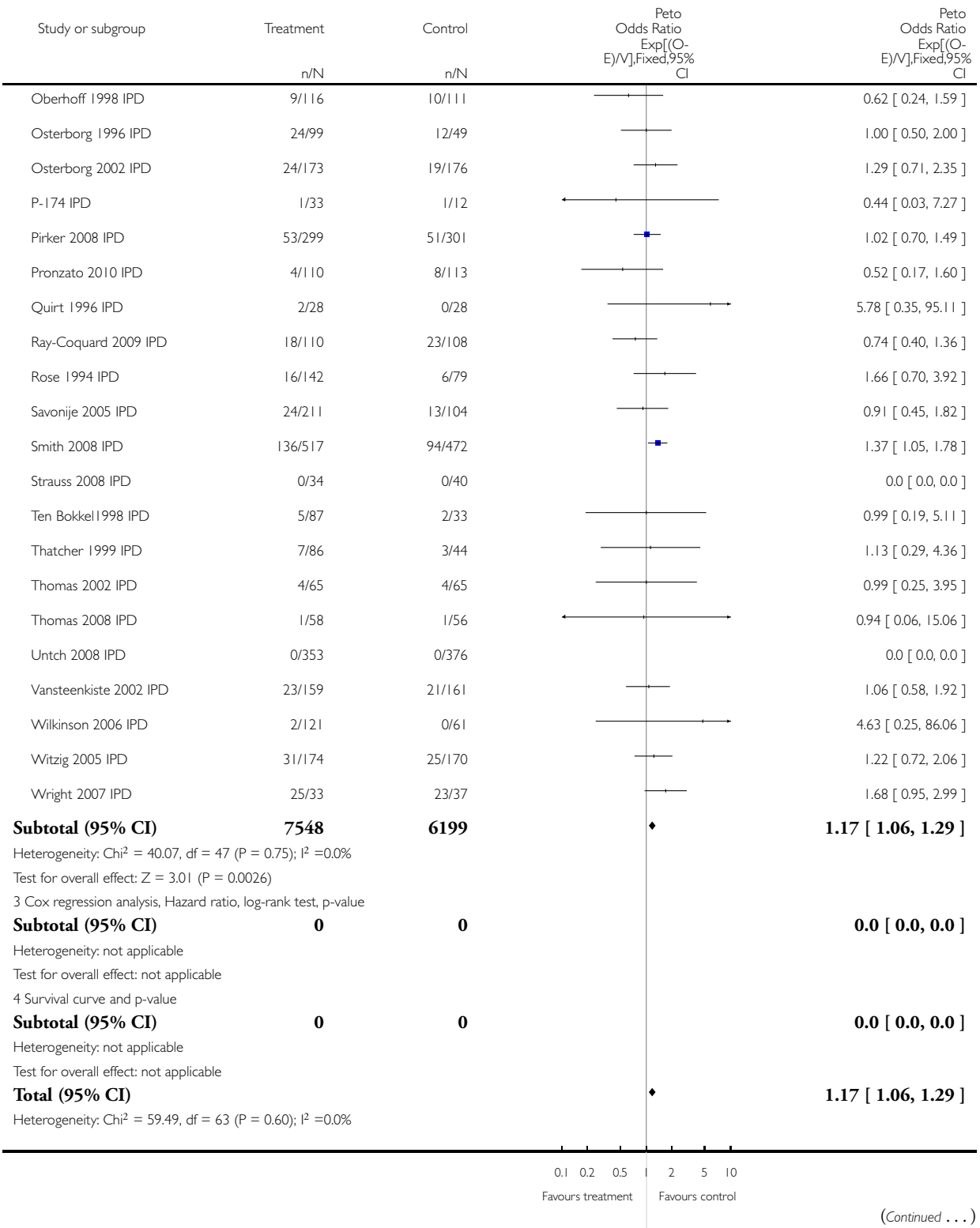


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| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Test for overall effect: Z = 3.06 (P = 0.0022) | | | | |
| Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.91), I² =0.0% | | | | |


### Analysis 6.13. Comparison 6 On-study mortality, Outcome 13 On-study mortality - allocation concealment.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 6 On-study mortality

Outcome: 13 On-study mortality - allocation concealment

| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| 1 adequate | | | | |
| Aapro 2008 IPD | 47/231 | 35/232 | | 1.38 [ 0.89, 2.13 ] |
| Boogaerts 2003 IPD | 10/132 | 10/127 | | 1.02 [ 0.42, 2.46 ] |
| Cazzola 1995 IPD | 3/114 | 2/29 | | 0.38 [ 0.06, 2.30 ] |
| Chang 2005 IPD | 7/176 | 5/178 | | 1.36 [ 0.44, 4.22 ] |
| Charu 2007 IPD | 8/228 | 2/59 | | 0.89 [ 0.19, 4.18 ] |
| Del Mastro 1997 | 0/31 | 0/31 | | 0.0 [ 0.0, 0.0 ] |
| EPO-INT-3 IPD | 9/135 | 3/65 | | 1.55 [ 0.47, 5.10 ] |
| Fujisaka 2011 | 1/89 | 0/92 | | 7.69 [ 0.15, 387.58 ] |
| Gordon 2008 IPD | 11/164 | 5/56 | | 0.74 [ 0.26, 2.14 ] |
| Goss 2005 IPD | 4/52 | 1/52 | | 3.40 [ 0.59, 19.63 ] |
| Hedenus 2002 | 0/55 | 0/11 | | 0.0 [ 0.0, 0.0 ] |
| Hedenus 2003 IPD | 10/176 | 4/173 | | 2.40 [ 0.84, 6.87 ] |


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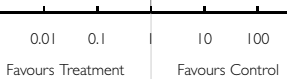
| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Henke 2003 IPD | 9/180 | 7/171 | | 1.22 [ 0.46, 3.25 ] |
| Hernandez 2009 IPD | 17/196 | 20/195 | | 0.84 [ 0.44, 1.60 ] |
| Kotasek 2002 IPD | 4/129 | 0/32 | | 3.49 [ 0.30, 40.45 ] |
| Kotasek 2003 IPD | 4/208 | 1/51 | | 0.99 [ 0.11, 8.84 ] |
| Kurz 1997 | 0/23 | 0/12 | | 0.0 [ 0.0, 0.0 ] |
| Leyland-Jones 2005 IPD | 121/469 | 91/470 | | 1.41 [ 1.08, 1.85 ] |
| Littlewood 2001 IPD | 40/251 | 22/124 | | 0.78 [ 0.46, 1.34 ] |
| Machtay 2007 IPD | 5/77 | 3/71 | | 1.57 [ 0.39, 6.31 ] |
| Milroy 2003 IPD | 51/214 | 38/210 | | 1.45 [ 0.95, 2.21 ] |
| Moebus 2007 IPD | 0/324 | 0/319 | | 0.0 [ 0.0, 0.0 ] |
| O'Shaugnessy 2005 IPD | 1/51 | 0/49 | | 7.69 [ 0.15, 387.58 ] |
| OBE/EPO-INT-03 IPD | 2/35 | 3/37 | | 0.76 [ 0.13, 4.55 ] |
| Oberhoff 1998 IPD | 9/116 | 10/111 | | 0.62 [ 0.24, 1.59 ] |
| Osterborg 1996 IPD | 24/99 | 12/49 | | 1.00 [ 0.50, 2.00 ] |
| Osterborg 2002 IPD | 24/173 | 19/176 | | 1.29 [ 0.71, 2.35 ] |
| Pirker 2008 IPD | 53/299 | 51/301 | | 1.02 [ 0.70, 1.49 ] |
| Pronzato 2010 IPD | 4/110 | 8/113 | | 0.52 [ 0.17, 1.60 ] |
| Ray-Coquard 2009 IPD | 18/110 | 23/108 | | 0.74 [ 0.40, 1.36 ] |
| Razzouk 2004 | 2/112 | 2/110 | | 0.98 [ 0.14, 7.03 ] |
| Savonije 2005 IPD | 24/211 | 13/104 | | 0.91 [ 0.45, 1.82 ] |
| Smith 2008 IPD | 136/517 | 94/472 | | 1.37 [ 1.05, 1.78 ] |
| Sweeney 1998 | 0/24 | 0/24 | | 0.0 [ 0.0, 0.0 ] |
| Ten Bokkel1998 IPD | 5/87 | 2/33 | | 0.99 [ 0.19, 5.11 ] |
| Thomas 2002 IPD | 4/65 | 4/65 | | 0.99 [ 0.25, 3.95 ] |
| Thomas 2008 IPD | 1/58 | 1/56 | | 0.94 [ 0.06, 15.06 ] |
| Thompson 2000 | 3/45 | 0/21 | | 4.52 [ 0.38, 53.37 ] |
| Throuvalas 2000 | 0/28 | 1/27 | | 0.13 [ 0.00, 6.55 ] |
| Vansteenkiste 2002 IPD | 23/159 | 21/161 | | 1.06 [ 0.58, 1.92 ] |
| Witzig 2005 IPD | 31/174 | 25/170 | | 1.22 [ 0.72, 2.06 ] |
| Wright 2007 IPD | 25/33 | 23/37 | | 1.68 [ 0.95, 2.99 ] |

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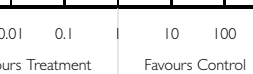
| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| **Subtotal (95% CI)** | **6160** | **4984** | | **1.20 [ 1.08, 1.34 ]** |
| Heterogeneity: Chi² = 28.02, df = 36 (P = 0.83); I² =0.0% | | | | |
| Test for overall effect: Z = 3.27 (P = 0.0011) | | | | |
| 2 unclear | | | | |
| Abels 1993 IPD | 13/65 | 12/59 | | 0.96 [ 0.44, 2.10 ] |
| Bamias 2003 | 7/72 | 4/72 | | 1.80 [ 0.53, 6.12 ] |
| Cascinu 1994 | 0/50 | 0/50 | | 0.0 [ 0.0, 0.0 ] |
| Case 1993 IPD | 10/81 | 9/76 | | 1.11 [ 0.45, 2.73 ] |
| Dammacco 2001 IPD | 1/69 | 7/76 | | 0.23 [ 0.06, 0.90 ] |
| Debus 2006 IPD | 26/195 | 18/190 | | 1.38 [ 0.76, 2.50 ] |
| Dunphy 1999 | 0/15 | 1/15 | | 0.14 [ 0.00, 6.82 ] |
| EPO-GER-20 IPD | 6/48 | 8/45 | | 0.61 [ 0.21, 1.77 ] |
| EPO-INT-1 IPD | 6/165 | 2/81 | | 1.51 [ 0.35, 6.54 ] |
| Grote 2005 IPD | 16/109 | 21/115 | | 0.79 [ 0.41, 1.52 ] |
| Henry 1995 IPD | 7/67 | 10/65 | | 0.68 [ 0.26, 1.77 ] |
| Hoskin 2009 IPD | 5/151 | 2/149 | | 2.36 [ 0.54, 10.33 ] |
| Huddart 2002 IPD | 3/48 | 7/47 | | 0.62 [ 0.16, 2.43 ] |
| Krzakowski 2008a | 6/104 | 2/52 | | 1.48 [ 0.33, 6.67 ] |
| Krzakowski 2008b | 10/105 | 3/52 | | 1.64 [ 0.49, 5.44 ] |
| ML17616 2006 | 1/30 | 0/30 | | 7.39 [ 0.15, 372.38 ] |
| ML17620 2006 | 4/61 | 0/60 | | 7.70 [ 1.05, 56.33 ] |
| Mystakidou 2005 | 1/50 | 2/50 | | 0.50 [ 0.05, 5.00 ] |
| P-174 IPD | 1/33 | 1/12 | | 0.44 [ 0.03, 7.27 ] |
| Quirt 1996 IPD | 2/28 | 0/28 | | 5.78 [ 0.35, 95.11 ] |
| Rose 1994 IPD | 16/142 | 6/79 | | 1.66 [ 0.70, 3.92 ] |
| Rosen 2003 | 1/47 | 0/43 | | 6.82 [ 0.14, 343.75 ] |
| Smith 2003 | 3/64 | 0/22 | | 3.96 [ 0.29, 54.28 ] |
| Strauss 2008 IPD | 0/34 | 0/40 | | 0.0 [ 0.0, 0.0 ] |
| Thatcher 1999 IPD | 7/86 | 3/44 | | 1.13 [ 0.29, 4.36 ] |
| Tjulandin 2010a | 5/76 | 6/37 | | 0.28 [ 0.07, 1.08 ] |
| Tjulandin 2010b | 4/73 | 6/37 | | 0.34 [ 0.09, 1.26 ] |
| Tjulandin 2011 | 6/95 | 5/91 | | 1.16 [ 0.34, 3.90 ] |

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| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Untch 2008 IPD | 0/353 | 0/376 | | 0.0 [ 0.0, 0.0 ] |
| Wilkinson 2006 IPD | 2/121 | 0/61 | | 4.63 [ 0.25, 86.06 ] |
| **Subtotal (95% CI)** | **2637** | **2154** | | **1.03 [ 0.82, 1.30 ]** |
| Heterogeneity: Chi² = 30.08, df = 26 (P = 0.26); I² =14% | | | | |
| Test for overall effect: Z = 0.25 (P = 0.80) | | | | |
| **Total (95% CI)** | | | | **1.17 [ 1.06, 1.29 ]** |
| Heterogeneity: Chi² = 59.49, df = 63 (P = 0.60); I² =0.0% | | | | |
| Test for overall effect: Z = 3.06 (P = 0.0022) | | | | |
| Test for subgroup differences: Chi² = 1.39, df = 1 (P = 0.24), I² =28% | | | | |

### Analysis 6.14. Comparison 6 On-study mortality, Outcome 14 On-study mortality - masking.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 6 On-study mortality

Outcome: 14 On-study mortality - masking

| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| 1 double-blind | | | | |
| Abels 1993 IPD | 13/65 | 12/59 | | 0.96 [ 0.44, 2.10 ] |
| Cascinu 1994 | 0/50 | 0/50 | | 0.0 [ 0.0, 0.0 ] |
| Case 1993 IPD | 10/81 | 9/76 | | 1.11 [ 0.45, 2.73 ] |
| Dammacco 2001 IPD | 1/69 | 7/76 | | 0.23 [ 0.06, 0.90 ] |
| EPO-INT-1 IPD | 6/165 | 2/81 | | 1.51 [ 0.35, 6.54 ] |
| EPO-INT-3 IPD | 9/135 | 3/65 | | 1.55 [ 0.47, 5.10 ] |
| Fujisaka 2011 | 1/89 | 0/92 | | 7.69 [ 0.15, 387.58 ] |
| Gordon 2008 IPD | 11/164 | 5/56 | | 0.74 [ 0.26, 2.14 ] |
| Goss 2005 IPD | 4/52 | 1/52 | | 3.40 [ 0.59, 19.63 ] |
| Grote 2005 IPD | 16/109 | 21/115 | | 0.79 [ 0.41, 1.52 ] |
| Hedenus 2002 | 0/55 | 0/11 | | 0.0 [ 0.0, 0.0 ] |
| Hedenus 2003 IPD | 10/176 | 4/173 | | 2.40 [ 0.84, 6.87 ] |
| Henke 2003 IPD | 9/180 | 7/171 | | 1.22 [ 0.46, 3.25 ] |
| Henry 1995 IPD | 7/67 | 10/65 | | 0.68 [ 0.26, 1.77 ] |
| Hernandez 2009 IPD | 17/196 | 20/195 | | 0.84 [ 0.44, 1.60 ] |
| Kotasek 2002 IPD | 4/129 | 0/32 | | 3.49 [ 0.30, 40.45 ] |
| Kotasek 2003 IPD | 4/208 | 1/51 | | 0.99 [ 0.11, 8.84 ] |
| Krzakowski 2008a | 6/104 | 2/52 | | 1.48 [ 0.33, 6.67 ] |
| Krzakowski 2008b | 10/105 | 3/52 | | 1.64 [ 0.49, 5.44 ] |
| Kurz 1997 | 0/23 | 0/12 | | 0.0 [ 0.0, 0.0 ] |
| Leyland-Jones 2005 IPD | 121/469 | 91/470 | | 1.41 [ 1.08, 1.85 ] |
| Littlewood 2001 IPD | 40/251 | 22/124 | | 0.78 [ 0.46, 1.34 ] |
| Mystakidou 2005 | 1/50 | 2/50 | | 0.50 [ 0.05, 5.00 ] |
| O'Shaugnessy 2005 IPD | 1/51 | 0/49 | | 7.69 [ 0.15, 387.58 ] |


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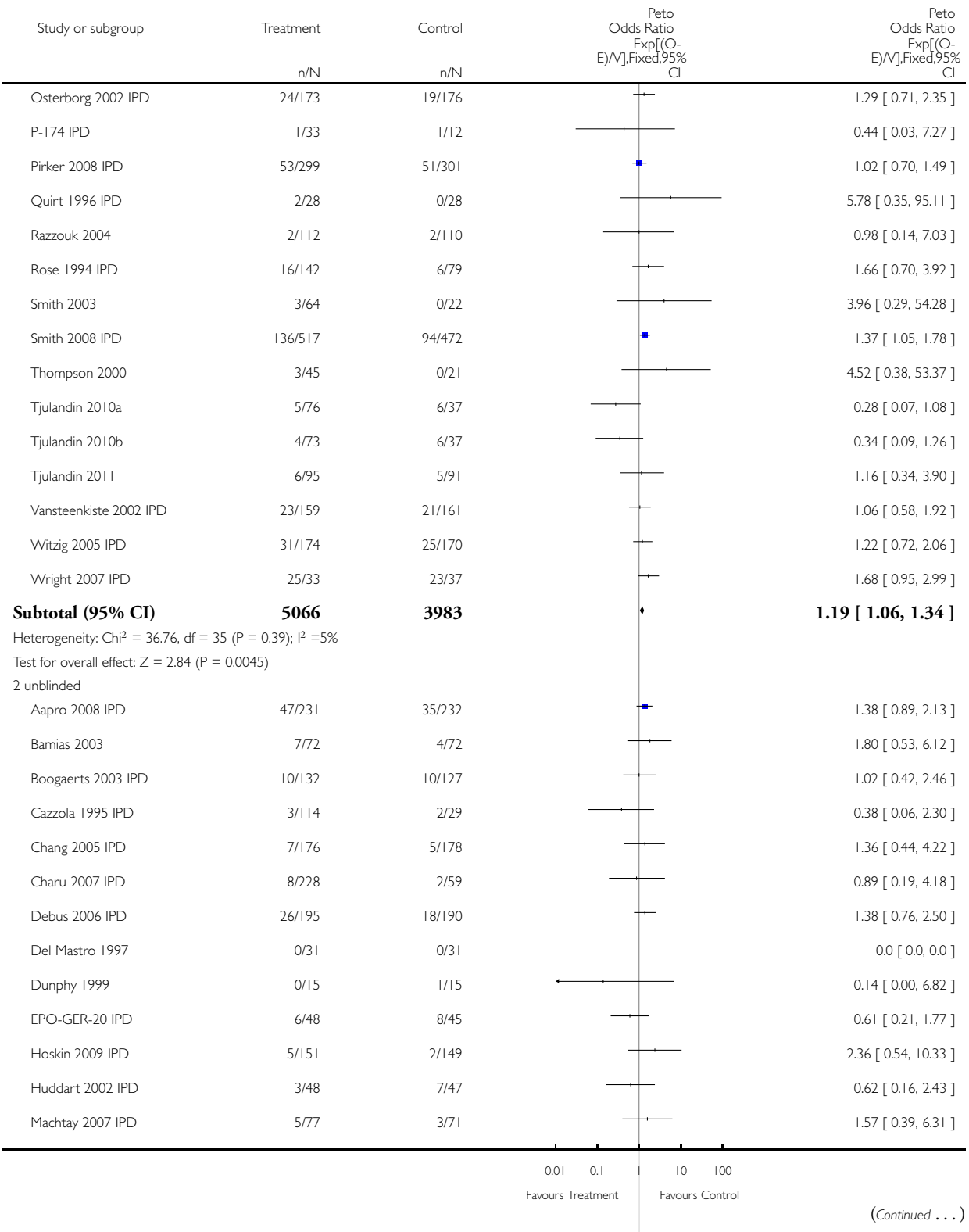


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| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Milroy 2003 IPD | 51/214 | 38/210 | | 1.45 [ 0.95, 2.21 ] |
| ML17616 2006 | 1/30 | 0/30 | | 7.39 [ 0.15, 372.38 ] |
| ML17620 2006 | 4/61 | 0/60 | | 7.70 [ 1.05, 56.33 ] |
| Moebus 2007 IPD | 0/324 | 0/319 | | 0.0 [ 0.0, 0.0 ] |
| OBE/EPO-INT-03 IPD | 2/35 | 3/37 | | 0.76 [ 0.13, 4.55 ] |
| Oberhoff 1998 IPD | 9/116 | 10/111 | | 0.62 [ 0.24, 1.59 ] |
| Osterborg 1996 IPD | 24/99 | 12/49 | | 1.00 [ 0.50, 2.00 ] |
| Pronzato 2010 IPD | 4/110 | 8/113 | | 0.52 [ 0.17, 1.60 ] |
| Ray-Coquard 2009 IPD | 18/110 | 23/108 | | 0.74 [ 0.40, 1.36 ] |
| Rosen 2003 | 1/47 | 0/43 | | 6.82 [ 0.14, 343.75 ] |
| Savonije 2005 IPD | 24/211 | 13/104 | | 0.91 [ 0.45, 1.82 ] |
| Strauss 2008 IPD | 0/34 | 0/40 | | 0.0 [ 0.0, 0.0 ] |
| Sweeney 1998 | 0/24 | 0/24 | | 0.0 [ 0.0, 0.0 ] |
| Ten Bokkel1998 IPD | 5/87 | 2/33 | | 0.99 [ 0.19, 5.11 ] |
| Thatcher 1999 IPD | 7/86 | 3/44 | | 1.13 [ 0.29, 4.36 ] |
| Thomas 2002 IPD | 4/65 | 4/65 | | 0.99 [ 0.25, 3.95 ] |
| Thomas 2008 IPD | 1/58 | 1/56 | | 0.94 [ 0.06, 15.06 ] |
| Throuvalas 2000 | 0/28 | 1/27 | | 0.13 [ 0.00, 6.55 ] |
| Untch 2008 IPD | 0/353 | 0/376 | | 0.0 [ 0.0, 0.0 ] |
| Wilkinson 2006 IPD | 2/121 | 0/61 | | 4.63 [ 0.25, 86.06 ] |
| **Subtotal (95% CI)** | **3731** | **3155** | | **1.12 [ 0.94, 1.34 ]** |
| Heterogeneity: Chi² = 22.46, df = 27 (P = 0.71); I² =0.0% | | | | |
| Test for overall effect: Z = 1.26 (P = 0.21) | | | | |
| **Total (95% CI)** | | | | **1.17 [ 1.06, 1.29 ]** |
| Heterogeneity: Chi² = 59.49, df = 63 (P = 0.60); I² =0.0% | | | | |
| Test for overall effect: Z = 3.06 (P = 0.0022) | | | | |
| Test for subgroup differences: Chi² = 0.27, df = 1 (P = 0.60), I² =0.0% | | | | |

### Analysis 6.15. Comparison 6 On-study mortality, Outcome 15 On-study mortality - intention-to-treat.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 6 On-study mortality

Outcome: 15 On-study mortality - intention-to-treat

| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| 1 ITT or less than 10% of participants per study arm excluded | | | | |
| Aapro 2008 IPD | 47/231 | 35/232 | | 1.38 [ 0.89, 2.13 ] |
| Abels 1993 IPD | 13/65 | 12/59 | | 0.96 [ 0.44, 2.10 ] |
| Bamias 2003 | 7/72 | 4/72 | | 1.80 [ 0.53, 6.12 ] |
| Boogaerts 2003 IPD | 10/132 | 10/127 | | 1.02 [ 0.42, 2.46 ] |
| Cascinu 1994 | 0/50 | 0/50 | | 0.0 [ 0.0, 0.0 ] |
| Case 1993 IPD | 10/81 | 9/76 | | 1.11 [ 0.45, 2.73 ] |
| Cazzola 1995 IPD | 3/114 | 2/29 | | 0.38 [ 0.06, 2.30 ] |
| Chang 2005 IPD | 7/176 | 5/178 | | 1.36 [ 0.44, 4.22 ] |
| Charu 2007 IPD | 8/228 | 2/59 | | 0.89 [ 0.19, 4.18 ] |
| Dammacco 2001 IPD | 1/69 | 7/76 | | 0.23 [ 0.06, 0.90 ] |
| Debus 2006 IPD | 26/195 | 18/190 | | 1.38 [ 0.76, 2.50 ] |
| Del Mastro 1997 | 0/31 | 0/31 | | 0.0 [ 0.0, 0.0 ] |
| Dunphy 1999 | 0/15 | 1/15 | | 0.14 [ 0.00, 6.82 ] |
| EPO-GER-20 IPD | 6/48 | 8/45 | | 0.61 [ 0.21, 1.77 ] |
| EPO-INT-1 IPD | 6/165 | 2/81 | | 1.51 [ 0.35, 6.54 ] |
| EPO-INT-3 IPD | 9/135 | 3/65 | | 1.55 [ 0.47, 5.10 ] |
| Fujisaka 2011 | 1/89 | 0/92 | | 7.69 [ 0.15, 387.58 ] |
| Gordon 2008 IPD | 11/164 | 5/56 | | 0.74 [ 0.26, 2.14 ] |
| Goss 2005 IPD | 4/52 | 1/52 | | 3.40 [ 0.59, 19.63 ] |
| Grote 2005 IPD | 16/109 | 21/115 | | 0.79 [ 0.41, 1.52 ] |
| Hedenus 2002 | 0/55 | 0/11 | | 0.0 [ 0.0, 0.0 ] |
| Hedenus 2003 IPD | 10/176 | 4/173 | | 2.40 [ 0.84, 6.87 ] |
| Henke 2003 IPD | 9/180 | 7/171 | | 1.22 [ 0.46, 3.25 ] |
| Henry 1995 IPD | 7/67 | 10/65 | | 0.68 [ 0.26, 1.77 ] |


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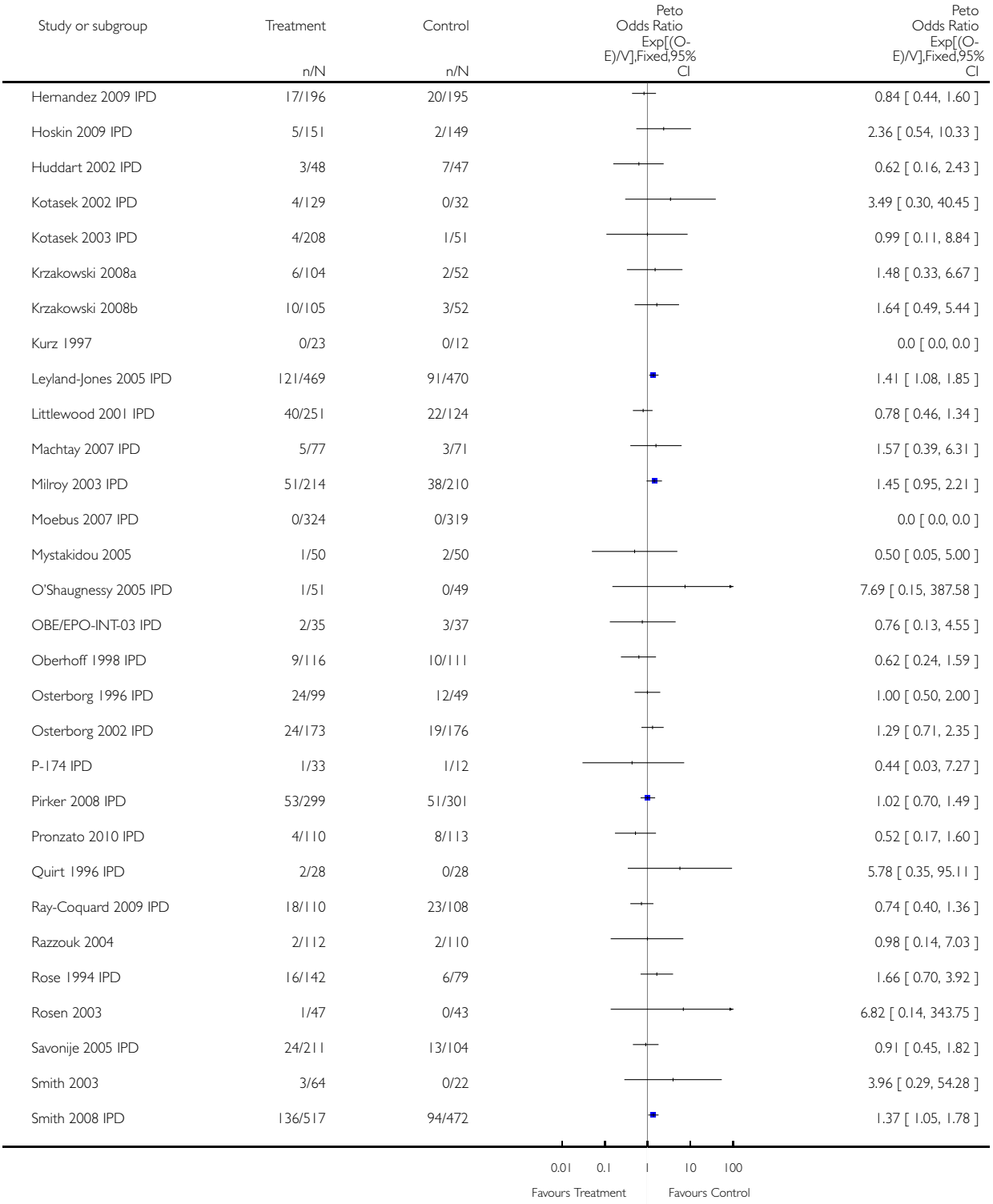


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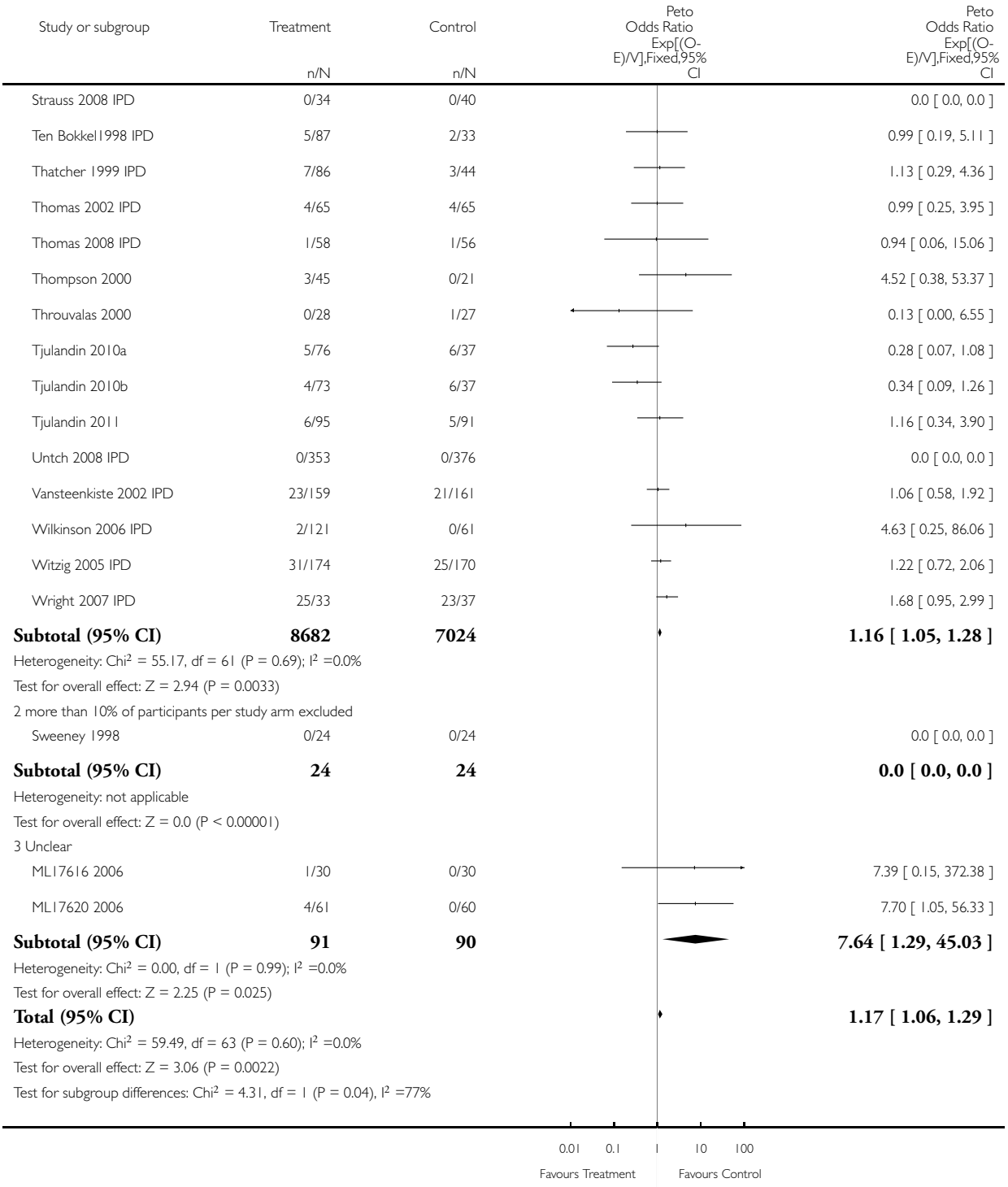

## Analysis 6.16. Comparison 6 On-study mortality, Outcome 16 On-study mortality - sensitivity analysis - follow-up.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 6 On-study mortality

Outcome: 16 On-study mortality - sensitivity analysis - follow-up

| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| 1 Short term follow subgroup | | | | |
| Aapro 2008 IPD | 47/231 | 35/232 | | 1.38 [ 0.89, 2.13 ] |
| Abels 1993 IPD | 13/65 | 12/59 | | 0.96 [ 0.44, 2.10 ] |
| Bamias 2003 | 7/72 | 4/72 | | 1.80 [ 0.53, 6.12 ] |
| Boogaerts 2003 IPD | 10/132 | 10/127 | | 1.02 [ 0.42, 2.46 ] |
| Cascinu 1994 | 0/50 | 0/50 | | 0.0 [ 0.0, 0.0 ] |
| Case 1993 IPD | 10/81 | 9/76 | | 1.11 [ 0.45, 2.73 ] |
| Cazzola 1995 IPD | 3/114 | 2/29 | | 0.38 [ 0.06, 2.30 ] |
| Chang 2005 IPD | 7/176 | 5/178 | | 1.36 [ 0.44, 4.22 ] |
| Charu 2007 IPD | 8/228 | 2/59 | | 0.89 [ 0.19, 4.18 ] |
| Dammacco 2001 IPD | 1/69 | 7/76 | | 0.23 [ 0.06, 0.90 ] |
| Debus 2006 IPD | 26/195 | 18/190 | | 1.38 [ 0.76, 2.50 ] |
| Del Mastro 1997 | 0/31 | 0/31 | | 0.0 [ 0.0, 0.0 ] |
| Dunphy 1999 | 0/15 | 1/15 | | 0.14 [ 0.00, 6.82 ] |
| EPO-GER-20 IPD | 6/48 | 8/45 | | 0.61 [ 0.21, 1.77 ] |
| EPO-INT-1 IPD | 6/165 | 2/81 | | 1.51 [ 0.35, 6.54 ] |
| EPO-INT-3 IPD | 9/135 | 3/65 | | 1.55 [ 0.47, 5.10 ] |
| Fujisaka 2011 | 1/89 | 0/92 | | 7.69 [ 0.15, 387.58 ] |
| Gordon 2008 IPD | 11/164 | 5/56 | | 0.74 [ 0.26, 2.14 ] |
| Goss 2005 IPD | 4/52 | 1/52 | | 3.40 [ 0.59, 19.63 ] |
| Grote 2005 IPD | 16/109 | 21/115 | | 0.79 [ 0.41, 1.52 ] |
| Hedenus 2002 | 0/55 | 0/11 | | 0.0 [ 0.0, 0.0 ] |
| Hedenus 2003 IPD | 10/176 | 4/173 | | 2.40 [ 0.84, 6.87 ] |


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| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Henke 2003 IPD | 9/180 | 7/171 | | 1.22 [ 0.46, 3.25 ] |
| Henry 1995 IPD | 7/67 | 10/65 | | 0.68 [ 0.26, 1.77 ] |
| Hernandez 2009 IPD | 17/196 | 20/195 | | 0.84 [ 0.44, 1.60 ] |
| Hoskin 2009 IPD | 5/151 | 2/149 | | 2.36 [ 0.54, 10.33 ] |
| Huddart 2002 IPD | 3/48 | 7/47 | | 0.62 [ 0.16, 2.43 ] |
| Kotasek 2002 IPD | 4/129 | 0/32 | | 3.49 [ 0.30, 40.45 ] |
| Kotasek 2003 IPD | 4/208 | 1/51 | | 0.99 [ 0.11, 8.84 ] |
| Krzakowski 2008a | 6/104 | 2/52 | | 1.48 [ 0.33, 6.67 ] |
| Krzakowski 2008b | 10/105 | 3/52 | | 1.64 [ 0.49, 5.44 ] |
| Kurz 1997 | 0/23 | 0/12 | | 0.0 [ 0.0, 0.0 ] |
| Leyland-Jones 2005 IPD | 121/469 | 91/470 | | 1.41 [ 1.08, 1.85 ] |
| Littlewood 2001 IPD | 40/251 | 22/124 | | 0.78 [ 0.46, 1.34 ] |
| Machtay 2007 IPD | 5/77 | 3/71 | | 1.57 [ 0.39, 6.31 ] |
| Milroy 2003 IPD | 51/214 | 38/210 | | 1.45 [ 0.95, 2.21 ] |
| ML17616 2006 | 1/30 | 0/30 | | 7.39 [ 0.15, 372.38 ] |
| ML17620 2006 | 4/61 | 0/60 | | 7.70 [ 1.05, 56.33 ] |
| Moebus 2007 IPD | 0/324 | 0/319 | | 0.0 [ 0.0, 0.0 ] |
| Mystakidou 2005 | 1/50 | 2/50 | | 0.50 [ 0.05, 5.00 ] |
| O'Shaugnessy 2005 IPD | 1/51 | 0/49 | | 7.69 [ 0.15, 387.58 ] |
| OBE/EPO-INT-03 IPD | 2/35 | 3/37 | | 0.76 [ 0.13, 4.55 ] |
| Oberhoff 1998 IPD | 9/116 | 10/111 | | 0.62 [ 0.24, 1.59 ] |
| Osterborg 1996 IPD | 24/99 | 12/49 | | 1.00 [ 0.50, 2.00 ] |
| Osterborg 2002 IPD | 24/173 | 19/176 | | 1.29 [ 0.71, 2.35 ] |
| P-174 IPD | 1/33 | 1/12 | | 0.44 [ 0.03, 7.27 ] |
| Pirker 2008 IPD | 53/299 | 51/301 | | 1.02 [ 0.70, 1.49 ] |
| Pronzato 2010 IPD | 4/110 | 8/113 | | 0.52 [ 0.17, 1.60 ] |
| Quirt 1996 IPD | 2/28 | 0/28 | | 5.78 [ 0.35, 95.11 ] |
| Ray-Coquard 2009 IPD | 18/110 | 23/108 | | 0.74 [ 0.40, 1.36 ] |
| Razzouk 2004 | 2/112 | 2/110 | | 0.98 [ 0.14, 7.03 ] |
| Rose 1994 IPD | 16/142 | 6/79 | | 1.66 [ 0.70, 3.92 ] |


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| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Rosen 2003 | 1/47 | 0/43 | | 6.82 [ 0.14, 343.75 ] |
| Savonije 2005 IPD | 24/211 | 13/104 | | 0.91 [ 0.45, 1.82 ] |
| Smith 2003 | 3/64 | 0/22 | | 3.96 [ 0.29, 54.28 ] |
| Smith 2008 IPD | 136/517 | 94/472 | | 1.37 [ 1.05, 1.78 ] |
| Strauss 2008 IPD | 0/34 | 0/40 | | 0.0 [ 0.0, 0.0 ] |
| Sweeney 1998 | 0/24 | 0/24 | | 0.0 [ 0.0, 0.0 ] |
| Ten Bokkel1998 IPD | 5/87 | 2/33 | | 0.99 [ 0.19, 5.11 ] |
| Thatcher 1999 IPD | 7/86 | 3/44 | | 1.13 [ 0.29, 4.36 ] |
| Thomas 2002 IPD | 4/65 | 4/65 | | 0.99 [ 0.25, 3.95 ] |
| Thomas 2008 IPD | 1/58 | 1/56 | | 0.94 [ 0.06, 15.06 ] |
| Thompson 2000 | 3/45 | 0/21 | | 4.52 [ 0.38, 53.37 ] |
| Throuvalas 2000 | 0/28 | 1/27 | | 0.13 [ 0.00, 6.55 ] |
| Tjulandin 2010a | 5/76 | 6/37 | | 0.28 [ 0.07, 1.08 ] |
| Tjulandin 2010b | 4/73 | 6/37 | | 0.34 [ 0.09, 1.26 ] |
| Tjulandin 2011 | 6/95 | 5/91 | | 1.16 [ 0.34, 3.90 ] |
| Untch 2008 IPD | 0/353 | 0/376 | | 0.0 [ 0.0, 0.0 ] |
| Vansteenkiste 2002 IPD | 23/159 | 21/161 | | 1.06 [ 0.58, 1.92 ] |
| Wilkinson 2006 IPD | 2/121 | 0/61 | | 4.63 [ 0.25, 86.06 ] |
| Witzig 2005 IPD | 31/174 | 25/170 | | 1.22 [ 0.72, 2.06 ] |
| Wright 2007 IPD | 25/33 | 23/37 | | 1.68 [ 0.95, 2.99 ] |
| **Subtotal (95% CI)** | **8797** | **7138** | | **1.17 [ 1.06, 1.29 ]** |
| Heterogeneity: Chi² = 59.49, df = 63 (P = 0.60); I² =0.0% | | | | |
| Test for overall effect: Z = 3.06 (P = 0.0022) | | | | |
| 2 Short term from Kaplan Meier curve | | | | |
| Antonadou 2001 | 0/190 | 0/195 | | 0.0 [ 0.0, 0.0 ] |
| Blohmer 2011 | 2/127 | 1/129 | | 1.99 [ 0.20, 19.45 ] |
| Christodoulou 2009 | 17/167 | 14/170 | | 1.26 [ 0.60, 2.64 ] |
| Engert 2010 | 3/648 | 6/655 | | 0.52 [ 0.14, 1.91 ] |
| Gupta 2009 | 1/58 | 2/57 | | 0.50 [ 0.05, 4.90 ] |
| Overgaard 2009 | 3/255 | 2/259 | | 1.52 [ 0.26, 8.84 ] |
| Winquist 2009 | 8/26 | 10/30 | | 0.0 [ 0.0, 0.0 ] |
| **Subtotal (95% CI)** | **1471** | **1495** | | **1.06 [ 0.60, 1.86 ]** |


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| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Heterogeneity: Chi² = 2.24, df = 4 (P = 0.69); I² =0.0% | | | | |
| Test for overall effect: Z = 0.20 (P = 0.84) | | | | |
| 3 Long term follow up | | | | |
| Tsuboi 2009 | 21/61 | 19/56 | | 0.94 [ 0.57, 1.54 ] |
| **Subtotal (95% CI)** | **61** | **56** | | **0.94 [ 0.57, 1.54 ]** |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: Z = 0.25 (P = 0.81) | | | | |
| **Total (95% CI)** | | | | **1.16 [ 1.05, 1.27 ]** |
| Heterogeneity: Chi² = 62.54, df = 69 (P = 0.70); I² =0.0% | | | | |
| Test for overall effect: Z = 2.94 (P = 0.0033) | | | | |
| Test for subgroup differences: Chi² = 0.81, df = 2 (P = 0.67), I² =0.0% | | | | |

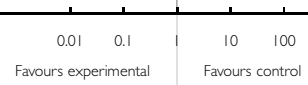
## Analysis 6.17. Comparison 6 On-study mortality, Outcome 17 On-study mortality - sensitivity analysis experimental arms merged.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 6 On-study mortality

Outcome: 17 On-study mortality - sensitivity analysis experimental arms merged

| Study or subgroup | Experimental n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Aapro 2008 IPD | 47/231 | 35/232 | | 1.38 [ 0.89, 2.13 ] |
| Abels 1993 IPD | 13/65 | 12/59 | | 0.96 [ 0.44, 2.10 ] |
| Bamias 2003 | 7/72 | 4/72 | | 1.80 [ 0.53, 6.12 ] |
| Boogaerts 2003 IPD | 10/132 | 10/127 | | 1.02 [ 0.42, 2.46 ] |
| Cascinu 1994 | 0/50 | 0/50 | | 0.0 [ 0.0, 0.0 ] |
| Case 1993 IPD | 10/81 | 9/76 | | 1.11 [ 0.45, 2.73 ] |
| Cazzola 1995 IPD | 3/114 | 2/29 | | 0.38 [ 0.06, 2.30 ] |
| Chang 2005 IPD | 7/176 | 5/178 | | 1.36 [ 0.44, 4.22 ] |
| Charu 2007 IPD | 8/228 | 2/59 | | 0.89 [ 0.19, 4.18 ] |
| Dammacco 2001 IPD | 1/69 | 7/76 | | 0.23 [ 0.06, 0.90 ] |
| Debus 2006 IPD | 26/195 | 18/190 | | 1.38 [ 0.76, 2.50 ] |
| Del Mastro 1997 | 0/31 | 0/31 | | 0.0 [ 0.0, 0.0 ] |
| Dunphy 1999 | 0/15 | 1/15 | | 0.14 [ 0.00, 6.82 ] |
| EPO-GER-20 IPD | 6/48 | 8/45 | | 0.61 [ 0.21, 1.77 ] |
| EPO-INT-1 IPD | 6/165 | 2/81 | | 1.51 [ 0.35, 6.54 ] |
| EPO-INT-3 IPD | 9/135 | 3/65 | | 1.55 [ 0.47, 5.10 ] |
| Fujisaka 2011 | 1/89 | 0/92 | | 7.69 [ 0.15, 387.58 ] |
| Gordon 2008 IPD | 11/164 | 5/56 | | 0.74 [ 0.26, 2.14 ] |
| Goss 2005 IPD | 4/52 | 1/52 | | 3.40 [ 0.59, 19.63 ] |
| Grote 2005 IPD | 16/109 | 21/115 | | 0.79 [ 0.41, 1.52 ] |
| Hedenus 2002 | 0/55 | 0/11 | | 0.0 [ 0.0, 0.0 ] |
| Hedenus 2003 IPD | 10/176 | 4/173 | | 2.40 [ 0.84, 6.87 ] |
| Henke 2003 IPD | 9/180 | 7/171 | | 1.22 [ 0.46, 3.25 ] |
| Henry 1995 IPD | 7/67 | 10/65 | | 0.68 [ 0.26, 1.77 ] |

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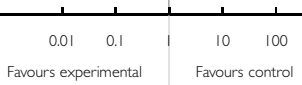
| Study or subgroup | Experimental n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Hernandez 2009 IPD | 17/196 | 20/195 | | 0.84 [ 0.44, 1.60 ] |
| Hoskin 2009 IPD | 5/151 | 2/149 | | 2.36 [ 0.54, 10.33 ] |
| Huddart 2002 IPD | 3/48 | 7/47 | | 0.62 [ 0.16, 2.43 ] |
| Kotasek 2002 IPD | 4/129 | 0/32 | | 3.49 [ 0.30, 40.45 ] |
| Kotasek 2003 IPD | 4/208 | 1/51 | | 0.99 [ 0.11, 8.84 ] |
| Krzakowski 2008 | 16/209 | 5/104 | | 3.20 [ 0.71, 14.41 ] |
| Kurz 1997 | 0/23 | 0/12 | | 0.0 [ 0.0, 0.0 ] |
| Leyland-Jones 2005 IPD | 121/469 | 91/470 | | 1.41 [ 1.08, 1.85 ] |
| Littlewood 2001 IPD | 40/251 | 22/124 | | 0.78 [ 0.46, 1.34 ] |
| Machtay 2007 IPD | 5/77 | 3/71 | | 1.57 [ 0.39, 6.31 ] |
| Milroy 2003 IPD | 51/214 | 38/210 | | 1.45 [ 0.95, 2.21 ] |
| ML17616 2006 | 1/30 | 0/30 | | 7.39 [ 0.15, 372.38 ] |
| ML17620 2006 | 4/61 | 0/60 | | 7.70 [ 1.05, 56.33 ] |
| Moebus 2007 IPD | 0/324 | 0/319 | | 0.0 [ 0.0, 0.0 ] |
| Mystakidou 2005 | 1/50 | 2/50 | | 0.50 [ 0.05, 5.00 ] |
| O'Shaugnessy 2005 IPD | 1/51 | 0/49 | | 7.69 [ 0.15, 387.58 ] |
| OBE/EPO-INT-03 IPD | 2/35 | 3/37 | | 0.76 [ 0.13, 4.55 ] |
| Oberhoff 1998 IPD | 9/116 | 10/111 | | 0.62 [ 0.24, 1.59 ] |
| Osterborg 1996 IPD | 24/99 | 12/49 | | 1.00 [ 0.50, 2.00 ] |
| Osterborg 2002 IPD | 24/173 | 19/176 | | 1.29 [ 0.71, 2.35 ] |
| P-174 IPD | 1/33 | 1/12 | | 0.44 [ 0.03, 7.27 ] |
| Pirker 2008 IPD | 53/299 | 51/301 | | 1.02 [ 0.70, 1.49 ] |
| Pronzato 2010 IPD | 4/110 | 8/113 | | 0.52 [ 0.17, 1.60 ] |
| Quirt 1996 IPD | 2/28 | 0/28 | | 5.78 [ 0.35, 95.11 ] |
| Ray-Coquard 2009 IPD | 18/110 | 23/108 | | 0.74 [ 0.40, 1.36 ] |
| Razzouk 2004 | 2/112 | 2/110 | | 0.98 [ 0.14, 7.03 ] |
| Rose 1994 IPD | 16/142 | 6/79 | | 1.66 [ 0.70, 3.92 ] |
| Rosen 2003 | 1/47 | 0/43 | | 6.82 [ 0.14, 343.75 ] |
| Savonije 2005 IPD | 24/211 | 13/104 | | 0.91 [ 0.45, 1.82 ] |
| Smith 2003 | 3/64 | 0/22 | | 3.96 [ 0.29, 54.28 ] |

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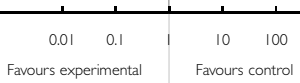
| Study or subgroup | Experimental n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Smith 2008 IPD | 136/517 | 94/472 | | 1.37 [ 1.05, 1.78 ] |
| Strauss 2008 IPD | 0/34 | 0/40 | | 0.0 [ 0.0, 0.0 ] |
| Sweeney 1998 | 0/24 | 0/24 | | 0.0 [ 0.0, 0.0 ] |
| Ten Bokkel1998 IPD | 5/87 | 2/33 | | 0.99 [ 0.19, 5.11 ] |
| Thatcher 1999 IPD | 7/86 | 3/44 | | 1.13 [ 0.29, 4.36 ] |
| Thomas 2002 IPD | 4/65 | 4/65 | | 0.99 [ 0.25, 3.95 ] |
| Thomas 2008 IPD | 1/58 | 1/56 | | 0.94 [ 0.06, 15.06 ] |
| Thompson 2000 | 3/45 | 0/21 | | 4.52 [ 0.38, 53.37 ] |
| Throuvalas 2000 | 0/28 | 1/27 | | 0.13 [ 0.00, 6.55 ] |
| Tjulandin 2010 | 9/149 | 12/74 | | 0.31 [ 0.12, 0.79 ] |
| Tjulandin 2011 | 6/95 | 5/91 | | 1.16 [ 0.34, 3.90 ] |
| Untch 2008 IPD | 0/353 | 0/376 | | 0.0 [ 0.0, 0.0 ] |
| Vansteenkiste 2002 IPD | 23/159 | 21/161 | | 1.06 [ 0.58, 1.92 ] |
| Wilkinson 2006 IPD | 2/121 | 0/61 | | 4.63 [ 0.25, 86.06 ] |
| Witzig 2005 IPD | 31/174 | 25/170 | | 1.22 [ 0.72, 2.06 ] |
| Wright 2007 IPD | 25/33 | 23/37 | | 1.68 [ 0.95, 2.99 ] |
| **Total (95% CI)** | | | | **1.17 [ 1.06, 1.29 ]** |

Heterogeneity: $Chi^2$ = 60.78, df = 61 (P = 0.48); $I^2$ =0.0%

Test for overall effect: Z = 3.07 (P = 0.0021)

Test for subgroup differences: Not applicable



## Analysis 6.18. Comparison 6 On-study mortality, Outcome 18 On-study mortality - sensitivity analysis intention-to-treat.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 6 On-study mortality

Outcome: 18 On-study mortality - sensitivity analysis intention-to-treat

| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| 1 ITT or less than 10% of participants per study arm excluded | | | | |
| Aapro 2008 IPD | 47/231 | 35/232 | | 1.38 [ 0.89, 2.13 ] |
| Abels 1993 IPD | 13/65 | 12/59 | | 0.96 [ 0.44, 2.10 ] |
| Bamias 2003 | 7/72 | 4/72 | | 1.80 [ 0.53, 6.12 ] |
| Boogaerts 2003 IPD | 10/132 | 10/127 | | 1.02 [ 0.42, 2.46 ] |
| Cascinu 1994 | 0/50 | 0/50 | | 0.0 [ 0.0, 0.0 ] |
| Case 1993 IPD | 10/81 | 9/76 | | 1.11 [ 0.45, 2.73 ] |
| Cazzola 1995 IPD | 3/114 | 2/29 | | 0.38 [ 0.06, 2.30 ] |
| Chang 2005 IPD | 7/176 | 5/178 | | 1.36 [ 0.44, 4.22 ] |
| Charu 2007 IPD | 8/228 | 2/59 | | 0.89 [ 0.19, 4.18 ] |
| Dammacco 2001 IPD | 1/69 | 7/76 | | 0.23 [ 0.06, 0.90 ] |
| Debus 2006 IPD | 26/195 | 18/190 | | 1.38 [ 0.76, 2.50 ] |
| Del Mastro 1997 | 0/31 | 0/31 | | 0.0 [ 0.0, 0.0 ] |
| Dunphy 1999 | 0/15 | 1/15 | | 0.14 [ 0.00, 6.82 ] |
| EPO-GER-20 IPD | 6/48 | 8/45 | | 0.61 [ 0.21, 1.77 ] |
| EPO-INT-1 IPD | 6/165 | 2/81 | | 1.51 [ 0.35, 6.54 ] |
| EPO-INT-3 IPD | 9/135 | 3/65 | | 1.55 [ 0.47, 5.10 ] |
| Fujisaka 2011 | 1/89 | 0/92 | | 7.69 [ 0.15, 387.58 ] |
| Gordon 2008 IPD | 11/164 | 5/56 | | 0.74 [ 0.26, 2.14 ] |
| Goss 2005 IPD | 4/52 | 1/52 | | 3.40 [ 0.59, 19.63 ] |
| Grote 2005 IPD | 16/109 | 21/115 | | 0.79 [ 0.41, 1.52 ] |
| Hedenus 2002 | 0/55 | 0/11 | | 0.0 [ 0.0, 0.0 ] |
| Hedenus 2003 IPD | 10/176 | 4/173 | | 2.40 [ 0.84, 6.87 ] |
| Henke 2003 IPD | 9/180 | 7/171 | | 1.22 [ 0.46, 3.25 ] |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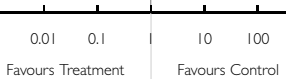
| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Henry 1995 IPD | 7/67 | 10/65 | | 0.68 [ 0.26, 1.77 ] |
| Hernandez 2009 IPD | 17/196 | 20/195 | | 0.84 [ 0.44, 1.60 ] |
| Hoskin 2009 IPD | 5/151 | 2/149 | | 2.36 [ 0.54, 10.33 ] |
| Huddart 2002 IPD | 3/48 | 7/47 | | 0.62 [ 0.16, 2.43 ] |
| Kotasek 2002 IPD | 4/129 | 0/32 | | 3.49 [ 0.30, 40.45 ] |
| Kotasek 2003 IPD | 4/208 | 1/51 | | 0.99 [ 0.11, 8.84 ] |
| Krzakowski 2008a | 6/104 | 2/52 | | 1.48 [ 0.33, 6.67 ] |
| Krzakowski 2008b | 10/105 | 3/52 | | 1.64 [ 0.49, 5.44 ] |
| Kurz 1997 | 0/23 | 0/12 | | 0.0 [ 0.0, 0.0 ] |
| Leyland-Jones 2005 IPD | 121/469 | 91/470 | | 1.41 [ 1.08, 1.85 ] |
| Littlewood 2001 IPD | 40/251 | 22/124 | | 0.78 [ 0.46, 1.34 ] |
| Machtay 2007 IPD | 5/77 | 3/71 | | 1.57 [ 0.39, 6.31 ] |
| Milroy 2003 IPD | 51/214 | 38/210 | | 1.45 [ 0.95, 2.21 ] |
| Moebus 2007 IPD | 0/324 | 0/319 | | 0.0 [ 0.0, 0.0 ] |
| Mystakidou 2005 | 1/50 | 2/50 | | 0.50 [ 0.05, 5.00 ] |
| O'Shaugnessy 2005 IPD | 1/51 | 0/49 | | 7.69 [ 0.15, 387.58 ] |
| OBE/EPO-INT-03 IPD | 2/35 | 3/37 | | 0.76 [ 0.13, 4.55 ] |
| Oberhoff 1998 IPD | 9/116 | 10/111 | | 0.62 [ 0.24, 1.59 ] |
| Osterborg 1996 IPD | 24/99 | 12/49 | | 1.00 [ 0.50, 2.00 ] |
| Osterborg 2002 IPD | 24/173 | 19/176 | | 1.29 [ 0.71, 2.35 ] |
| P-174 IPD | 1/33 | 1/12 | | 0.44 [ 0.03, 7.27 ] |
| Pirker 2008 IPD | 53/299 | 51/301 | | 1.02 [ 0.70, 1.49 ] |
| Pronzato 2010 IPD | 4/110 | 8/113 | | 0.52 [ 0.17, 1.60 ] |
| Quirt 1996 IPD | 2/28 | 0/28 | | 5.78 [ 0.35, 95.11 ] |
| Ray-Coquard 2009 IPD | 18/110 | 23/108 | | 0.74 [ 0.40, 1.36 ] |
| Razzouk 2004 | 2/112 | 2/110 | | 0.98 [ 0.14, 7.03 ] |
| Rose 1994 IPD | 16/142 | 6/79 | | 1.66 [ 0.70, 3.92 ] |
| Rosen 2003 | 1/47 | 0/43 | | 6.82 [ 0.14, 343.75 ] |
| Savonije 2005 IPD | 24/211 | 13/104 | | 0.91 [ 0.45, 1.82 ] |
| Smith 2003 | 3/64 | 0/22 | | 3.96 [ 0.29, 54.28 ] |

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| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Smith 2008 IPD | 136/517 | 94/472 | | 1.37 [ 1.05, 1.78 ] |
| Strauss 2008 IPD | 0/34 | 0/40 | | 0.0 [ 0.0, 0.0 ] |
| Ten Bokkel1998 IPD | 5/87 | 2/33 | | 0.99 [ 0.19, 5.11 ] |
| Thatcher 1999 IPD | 7/86 | 3/44 | | 1.13 [ 0.29, 4.36 ] |
| Thomas 2002 IPD | 4/65 | 4/65 | | 0.99 [ 0.25, 3.95 ] |
| Thomas 2008 IPD | 1/58 | 1/56 | | 0.94 [ 0.06, 15.06 ] |
| Thompson 2000 | 3/45 | 0/21 | | 4.52 [ 0.38, 53.37 ] |
| Throuvalas 2000 | 0/28 | 1/27 | | 0.13 [ 0.00, 6.55 ] |
| Tjulandin 2010a | 5/76 | 6/37 | | 0.28 [ 0.07, 1.08 ] |
| Tjulandin 2010b | 4/73 | 6/37 | | 0.34 [ 0.09, 1.26 ] |
| Tjulandin 2011 | 6/95 | 5/91 | | 1.16 [ 0.34, 3.90 ] |
| Untch 2008 IPD | 0/353 | 0/376 | | 0.0 [ 0.0, 0.0 ] |
| Vansteenkiste 2002 IPD | 23/159 | 21/161 | | 1.06 [ 0.58, 1.92 ] |
| Wilkinson 2006 IPD | 2/121 | 0/61 | | 4.63 [ 0.25, 86.06 ] |
| Witzig 2005 IPD | 31/174 | 25/170 | | 1.22 [ 0.72, 2.06 ] |
| Wright 2007 IPD | 25/33 | 23/37 | | 1.68 [ 0.95, 2.99 ] |
| **Subtotal (95% CI)** | **8682** | **7024** | | **1.16 [ 1.05, 1.28 ]** |
| Heterogeneity: Chi² = 55.17, df = 61 (P = 0.69); I² =0.0% | | | | |
| Test for overall effect: Z = 2.94 (P = 0.0033) | | | | |
| 2 more than 10% of participants per study arm excluded | | | | |
| Sweeney 1998 | 0/24 | 0/24 | | 0.0 [ 0.0, 0.0 ] |
| **Subtotal (95% CI)** | **24** | **24** | | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: Z = 0.0 (P < 0.00001) | | | | |
| **Total (95% CI)** | | | | **1.16 [ 1.05, 1.28 ]** |
| Heterogeneity: Chi² = 55.17, df = 61 (P = 0.69); I² =0.0% | | | | |
| Test for overall effect: Z = 2.94 (P = 0.0033) | | | | |
| Test for subgroup differences: Not applicable | | | | |

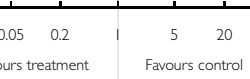
## Analysis 6.19. Comparison 6 On-study mortality, Outcome 19 On-study mortality - sensitivity analysis excluding Leyland and Smith.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 6 On-study mortality

Outcome: 19 On-study mortality - sensitivity analysis excluding Leyland and Smith

| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Aapro 2008 IPD | 47/231 | 35/232 | | 1.38 [ 0.89, 2.13 ] |
| Abels 1993 IPD | 13/65 | 12/59 | | 0.96 [ 0.44, 2.10 ] |
| Bamias 2003 | 7/72 | 4/72 | | 1.80 [ 0.53, 6.12 ] |
| Boogaerts 2003 IPD | 10/132 | 10/127 | | 1.02 [ 0.42, 2.46 ] |
| Cascinu 1994 | 0/50 | 0/50 | | 0.0 [ 0.0, 0.0 ] |
| Case 1993 IPD | 10/81 | 9/76 | | 1.11 [ 0.45, 2.73 ] |
| Cazzola 1995 IPD | 3/114 | 2/29 | | 0.38 [ 0.06, 2.30 ] |
| Chang 2005 IPD | 7/176 | 5/178 | | 1.36 [ 0.44, 4.22 ] |
| Charu 2007 IPD | 8/228 | 2/59 | | 0.89 [ 0.19, 4.18 ] |
| Dammacco 2001 IPD | 1/69 | 7/76 | | 0.23 [ 0.06, 0.90 ] |
| Debus 2006 IPD | 26/195 | 18/190 | | 1.38 [ 0.76, 2.50 ] |
| Del Mastro 1997 | 0/31 | 0/31 | | 0.0 [ 0.0, 0.0 ] |
| Dunphy 1999 | 0/15 | 1/15 | | 0.14 [ 0.00, 6.82 ] |
| EPO-GER-20 IPD | 6/48 | 8/45 | | 0.61 [ 0.21, 1.77 ] |
| EPO-INT-1 IPD | 6/165 | 2/81 | | 1.51 [ 0.35, 6.54 ] |
| EPO-INT-3 IPD | 9/135 | 3/65 | | 1.55 [ 0.47, 5.10 ] |
| Fujisaka 2011 | 1/89 | 0/92 | | 7.69 [ 0.15, 387.58 ] |
| Gordon 2008 IPD | 11/164 | 5/56 | | 0.74 [ 0.26, 2.14 ] |
| Goss 2005 IPD | 4/52 | 1/52 | | 3.40 [ 0.59, 19.63 ] |
| Grote 2005 IPD | 16/109 | 21/115 | | 0.79 [ 0.41, 1.52 ] |
| Hedenus 2002 | 0/55 | 0/11 | | 0.0 [ 0.0, 0.0 ] |
| Hedenus 2003 IPD | 10/176 | 4/173 | | 2.40 [ 0.84, 6.87 ] |
| Henke 2003 IPD | 9/180 | 7/171 | | 1.22 [ 0.46, 3.25 ] |
| Henry 1995 IPD | 7/67 | 10/65 | | 0.68 [ 0.26, 1.77 ] |

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| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Hernandez 2009 IPD | 17/196 | 20/195 | | 0.84 [ 0.44, 1.60 ] |
| Hoskin 2009 IPD | 5/151 | 2/149 | | 2.36 [ 0.54, 10.33 ] |
| Huddart 2002 IPD | 3/48 | 7/47 | | 0.62 [ 0.16, 2.43 ] |
| Kotasek 2002 IPD | 4/129 | 0/32 | | 3.49 [ 0.30, 40.45 ] |
| Kotasek 2003 IPD | 4/208 | 1/51 | | 0.99 [ 0.11, 8.84 ] |
| Krzakowski 2008a | 6/104 | 2/52 | | 1.48 [ 0.33, 6.67 ] |
| Krzakowski 2008b | 10/105 | 3/52 | | 1.64 [ 0.49, 5.44 ] |
| Kurz 1997 | 0/23 | 0/12 | | 0.0 [ 0.0, 0.0 ] |
| Littlewood 2001 IPD | 40/251 | 22/124 | | 0.78 [ 0.46, 1.34 ] |
| Machtay 2007 IPD | 5/77 | 3/71 | | 1.57 [ 0.39, 6.31 ] |
| Milroy 2003 IPD | 51/214 | 38/210 | | 1.45 [ 0.95, 2.21 ] |
| ML17616 2006 | 1/30 | 0/30 | | 7.39 [ 0.15, 372.38 ] |
| ML17620 2006 | 4/61 | 0/60 | | 7.70 [ 1.05, 56.33 ] |
| Moebus 2007 IPD | 0/324 | 0/319 | | 0.0 [ 0.0, 0.0 ] |
| Mystakidou 2005 | 1/50 | 2/50 | | 0.50 [ 0.05, 5.00 ] |
| O'Shaugnessy 2005 IPD | 1/51 | 0/49 | | 7.69 [ 0.15, 387.58 ] |
| OBE/EPO-INT-03 IPD | 2/35 | 3/37 | | 0.76 [ 0.13, 4.55 ] |
| Oberhoff 1998 IPD | 9/116 | 10/111 | | 0.62 [ 0.24, 1.59 ] |
| Osterborg 1996 IPD | 24/99 | 12/49 | | 1.00 [ 0.50, 2.00 ] |
| Osterborg 2002 IPD | 24/173 | 19/176 | | 1.29 [ 0.71, 2.35 ] |
| P-174 IPD | 1/33 | 1/12 | | 0.44 [ 0.03, 7.27 ] |
| Pirker 2008 IPD | 53/299 | 51/301 | | 1.02 [ 0.70, 1.49 ] |
| Pronzato 2010 IPD | 4/110 | 8/113 | | 0.52 [ 0.17, 1.60 ] |
| Quirt 1996 IPD | 2/28 | 0/28 | | 5.78 [ 0.35, 95.11 ] |
| Ray-Coquard 2009 IPD | 18/110 | 23/108 | | 0.74 [ 0.40, 1.36 ] |
| Razzouk 2004 | 2/112 | 2/110 | | 0.98 [ 0.14, 7.03 ] |
| Rose 1994 IPD | 16/142 | 6/79 | | 1.66 [ 0.70, 3.92 ] |
| Rosen 2003 | 1/47 | 0/43 | | 6.82 [ 0.14, 343.75 ] |
| Savonije 2005 IPD | 24/211 | 13/104 | | 0.91 [ 0.45, 1.82 ] |
| Smith 2003 | 3/64 | 0/22 | | 3.96 [ 0.29, 54.28 ] |


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| Study or subgroup | Treatment n/N | Control n/N | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI | Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI |
|---|---|---|---|---|
| Strauss 2008 IPD | 0/34 | 0/40 | | 0.0 [ 0.0, 0.0 ] |
| Sweeney 1998 | 0/24 | 0/24 | | 0.0 [ 0.0, 0.0 ] |
| Ten Bokkel1998 IPD | 5/87 | 2/33 | | 0.99 [ 0.19, 5.11 ] |
| Thatcher 1999 IPD | 7/86 | 3/44 | | 1.13 [ 0.29, 4.36 ] |
| Thomas 2002 IPD | 4/65 | 4/65 | | 0.99 [ 0.25, 3.95 ] |
| Thomas 2008 IPD | 1/58 | 1/56 | | 0.94 [ 0.06, 15.06 ] |
| Thompson 2000 | 3/45 | 0/21 | | 4.52 [ 0.38, 53.37 ] |
| Throuvalas 2000 | 0/28 | 1/27 | | 0.13 [ 0.00, 6.55 ] |
| Tjulandin 2010a | 5/76 | 6/37 | | 0.28 [ 0.07, 1.08 ] |
| Tjulandin 2010b | 4/73 | 6/37 | | 0.34 [ 0.09, 1.26 ] |
| Tjulandin 2011 | 6/95 | 5/91 | | 1.16 [ 0.34, 3.90 ] |
| Untch 2008 IPD | 0/353 | 0/376 | | 0.0 [ 0.0, 0.0 ] |
| Vansteenkiste 2002 IPD | 23/159 | 21/161 | | 1.06 [ 0.58, 1.92 ] |
| Wilkinson 2006 IPD | 2/121 | 0/61 | | 4.63 [ 0.25, 86.06 ] |
| Witzig 2005 IPD | 31/174 | 25/170 | | 1.22 [ 0.72, 2.06 ] |
| Wright 2007 IPD | 25/33 | 23/37 | | 1.68 [ 0.95, 2.99 ] |
| **Total (95% CI)** | | | | **1.09 [ 0.97, 1.23 ]** |

Heterogeneity: $Chi^2$ = 54.92, df = 61 (P = 0.69); $I^2$ =0.0%

Test for overall effect: Z = 1.47 (P = 0.14)

Test for subgroup differences: Not applicable

## Analysis 7.1. Comparison 7 Complete tumour response, Outcome 1 Complete tumour response.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 7 Complete tumour response

Outcome: 1 Complete tumour response

| Study or subgroup | control n/N | treatment n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Cascinu 1994 | 2/50 | 1/50 | | 0.1 % | 2.00 [ 0.19, 21.36 ] |
| Cazzola 1995a | 2/24 | 0/6 | | 0.1 % | 1.40 [ 0.08, 25.92 ] |
| Cazzola 1995b | 1/26 | 1/7 | | 0.2 % | 0.27 [ 0.02, 3.78 ] |
| Cazzola 1995c | 2/26 | 0/6 | | 0.1 % | 1.30 [ 0.07, 24.04 ] |
| Cazzola 1995d | 2/23 | 0/6 | | 0.1 % | 1.46 [ 0.08, 26.97 ] |
| Dammacco 2001 | 15/64 | 10/63 | | 1.0 % | 1.48 [ 0.72, 3.04 ] |
| Engert 2010 | 606/648 | 614/655 | | 59.4 % | 1.00 [ 0.97, 1.03 ] |
| Grote 2005 | 20/109 | 21/115 | | 2.0 % | 1.00 [ 0.58, 1.75 ] |
| Hoskin 2009 GBR-7 FDA 04 | 109/115 | 105/110 | | 10.4 % | 0.99 [ 0.94, 1.05 ] |
| Leyland-Jones 05 J%J 04 | 49/469 | 41/470 | | 4.0 % | 1.20 [ 0.81, 1.78 ] |
| Littlewood 2001 | 46/251 | 10/124 | | 1.3 % | 2.27 [ 1.19, 4.35 ] |
| Machtay 2007 | 52/71 | 52/70 | | 5.1 % | 0.99 [ 0.81, 1.20 ] |
| Osterborg 2002 | 9/154 | 5/162 | | 0.5 % | 1.89 [ 0.65, 5.52 ] |
| Strauss 2008 | 18/34 | 23/40 | | 2.1 % | 0.92 [ 0.61, 1.39 ] |
| Ten Bokkel 1998a | 23/40 | 10/15 | | 1.4 % | 0.86 [ 0.55, 1.35 ] |
| Ten Bokkel 1998b | 18/34 | 9/15 | | 1.2 % | 0.88 [ 0.52, 1.49 ] |
| Throuvalas 2000 | 22/28 | 18/26 | | 1.8 % | 1.13 [ 0.82, 1.56 ] |
| Untch 2011˙1 | 46/356 | 54/377 | | 5.1 % | 0.90 [ 0.63, 1.30 ] |
| Wilkinson 2006 | 55/114 | 33/59 | | 4.2 % | 0.86 [ 0.64, 1.16 ] |
| **Total (95% CI)** | **2636** | **2376** | | **100.0 %** | **1.02 [ 0.98, 1.06 ]** |

Total events: 1097 (control), 1007 (treatment)

Heterogeneity: $Chi^2$ = 16.10, df = 18 (P = 0.59); $I^2$ =0.0%

Test for overall effect: Z = 0.83 (P = 0.40)

Test for subgroup differences: Not applicable

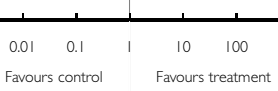
## Analysis 7.2. Comparison 7 Complete tumour response, Outcome 2 Tumour-response specific quality criteria.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 7 Complete tumour response

Outcome: 2 Tumour-response specific quality criteria

| Study or subgroup | control n/N | treatment n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 high quality | | | | | |
| Engert 2010 | 606/648 | 614/655 | | 59.4 % | 1.00 [ 0.97, 1.03 ] |
| Hoskin 2009 GBR-7 FDA 04 | 109/115 | 105/110 | | 10.4 % | 0.99 [ 0.94, 1.05 ] |
| Machtay 2007 | 52/71 | 52/70 | | 5.1 % | 0.99 [ 0.81, 1.20 ] |
| Strauss 2008 | 18/34 | 23/40 | | 2.1 % | 0.92 [ 0.61, 1.39 ] |
| Untch 2011˙1 | 46/356 | 54/377 | | 5.1 % | 0.90 [ 0.63, 1.30 ] |
| **Subtotal (95% CI)** | **1224** | **1252** | | **82.1 %** | **0.99 [ 0.95, 1.02 ]** |
| Total events: 831 (control), 848 (treatment) | | | | | |
| Heterogeneity: $Chi^2$ = 0.79, df = 4 (P = 0.94); $I^2$ =0.0% | | | | | |
| Test for overall effect: Z = 0.66 (P = 0.51) | | | | | |
| 2 low quality | | | | | |
| Cascinu 1994 | 2/50 | 1/50 | | 0.1 % | 2.00 [ 0.19, 21.36 ] |
| Cazzola 1995a | 2/24 | 0/6 | | 0.1 % | 1.40 [ 0.08, 25.92 ] |
| Cazzola 1995b | 1/26 | 1/7 | | 0.2 % | 0.27 [ 0.02, 3.78 ] |
| Cazzola 1995c | 2/26 | 0/6 | | 0.1 % | 1.30 [ 0.07, 24.04 ] |
| Cazzola 1995d | 2/23 | 0/6 | | 0.1 % | 1.46 [ 0.08, 26.97 ] |
| Dammacco 2001 | 15/64 | 10/63 | | 1.0 % | 1.48 [ 0.72, 3.04 ] |
| Grote 2005 | 20/109 | 21/115 | | 2.0 % | 1.00 [ 0.58, 1.75 ] |
| Leyland-Jones 05 J%J 04 | 49/469 | 41/470 | | 4.0 % | 1.20 [ 0.81, 1.78 ] |
| Littlewood 2001 | 46/251 | 10/124 | | 1.3 % | 2.27 [ 1.19, 4.35 ] |
| Osterborg 2002 | 9/154 | 5/162 | | 0.5 % | 1.89 [ 0.65, 5.52 ] |
| Ten Bokkel 1998a | 23/40 | 10/15 | | 1.4 % | 0.86 [ 0.55, 1.35 ] |
| Ten Bokkel 1998b | 18/34 | 9/15 | | 1.2 % | 0.88 [ 0.52, 1.49 ] |
| Throuvalas 2000 | 22/28 | 18/26 | | 1.8 % | 1.13 [ 0.82, 1.56 ] |
| Wilkinson 2006 | 55/114 | 33/59 | | 4.2 % | 0.86 [ 0.64, 1.16 ] |
| **Subtotal (95% CI)** | **1412** | **1124** | | **17.9 %** | **1.15 [ 0.98, 1.36 ]** |
| Total events: 266 (control), 159 (treatment) | | | | | |

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| Study or subgroup | control n/N | treatment n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Heterogeneity: Chi² = 13.53, df = 13 (P = 0.41); I² =4% | | | | | |
| Test for overall effect: Z = 1.72 (P = 0.086) | | | | | |
| **Total (95% CI)** | **2636** | **2376** | | **100.0 %** | **1.02 [ 0.98, 1.06 ]** |
| Total events: 1097 (control), 1007 (treatment) | | | | | |
| Heterogeneity: Chi² = 16.10, df = 18 (P = 0.59); I² =0.0% | | | | | |
| Test for overall effect: Z = 0.83 (P = 0.40) | | | | | |
| Test for subgroup differences: Chi² = 3.29, df = 1 (P = 0.07), I² =70% | | | | | |


## Analysis 7.3. Comparison 7 Complete tumour response, Outcome 3 Complete tumour response - experimental study arms merged.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 7 Complete tumour response

Outcome: 3 Complete tumour response - experimental study arms merged

| Study or subgroup | control n/N | treatment n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Cascinu 1994 | 2/50 | 1/50 | | 0.1 % | 2.00 [ 0.19, 21.36 ] |
| Cazzola 1995 | 7/99 | 1/25 | | 0.2 % | 1.77 [ 0.23, 13.72 ] |
| Dammacco 2001 | 15/64 | 10/63 | | 1.0 % | 1.48 [ 0.72, 3.04 ] |
| Engert 2010 | 606/648 | 614/655 | | 59.6 % | 1.00 [ 0.97, 1.03 ] |
| Grote 2005 | 20/109 | 21/115 | | 2.0 % | 1.00 [ 0.58, 1.75 ] |
| Hoskin 2009 GBR-7 FDA 04 | 109/115 | 105/110 | | 10.5 % | 0.99 [ 0.94, 1.05 ] |
| Leyland-Jones 05 J%J 04 | 49/469 | 41/470 | | 4.0 % | 1.20 [ 0.81, 1.78 ] |
| Littlewood 2001 | 46/251 | 10/124 | | 1.3 % | 2.27 [ 1.19, 4.35 ] |
| Machtay 2007 | 52/71 | 52/70 | | 5.1 % | 0.99 [ 0.81, 1.20 ] |
| Osterborg 2002 | 9/154 | 5/162 | | 0.5 % | 1.89 [ 0.65, 5.52 ] |
| Strauss 2008 | 18/34 | 23/40 | | 2.1 % | 0.92 [ 0.61, 1.39 ] |


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| Study or subgroup | control n/N | treatment n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Ten Bokkel 1998 | 41/74 | 19/30 | | 2.6 % | 0.87 [ 0.62, 1.23 ] |
| Throuvalas 2000 | 22/28 | 18/26 | | 1.8 % | 1.13 [ 0.82, 1.56 ] |
| Untch 2011˙1 | 46/356 | 54/377 | | 5.1 % | 0.90 [ 0.63, 1.30 ] |
| Wilkinson 2006 | 55/114 | 33/59 | | 4.2 % | 0.86 [ 0.64, 1.16 ] |
| **Total (95% CI)** | **2636** | **2376** | | **100.0 %** | **1.02 [ 0.98, 1.06 ]** |

Total events: 1097 (control), 1007 (treatment)

Heterogeneity: $Chi^2$ = 15.61, df = 14 (P = 0.34); $I^2$ =10%

Test for overall effect: Z = 0.91 (P = 0.36)

Test for subgroup differences: Not applicable


**Analysis 8.1. Comparison 8 Change in FACT-Fatigue 13, Outcome 1 Change in FACT-Fatigue (13 items) - overall.**

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 8 Change in FACT-Fatigue 13

Outcome: 1 Change in FACT-Fatigue (13 items) - overall

| Study or subgroup | ESA N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Boogaerts 2003 | 104 | 5.47 (14.47) | 109 | 0.41 (8.47) | | 4.0 % | 5.06 [ 1.86, 8.26 ] |
| Chang 2005 | 168 | 1.55 (10.52) | 170 | -3.55 (11.14) | | 7.7 % | 5.10 [ 2.79, 7.41 ] |
| Charu 2007 | 203 | 6 (12.34) | 42 | 2.2 (7.8) | | 4.9 % | 3.80 [ 0.89, 6.71 ] |
| Christodoulou 2009 | 76 | 3.87 (11.99) | 76 | 0.71 (12.43) | | 2.7 % | 3.16 [ -0.72, 7.04 ] |
| Gordon 2008 | 150 | 4.8 (11.263) | 50 | 5 (11.473) | | 3.1 % | -0.20 [ -3.86, 3.46 ] |
| Hedenus 2003 | 152 | 2.68 (8.88) | 151 | 0.8 (9.71) | | 9.4 % | 1.88 [ -0.22, 3.98 ] |
| Hoskin 2009 | 151 | -2.6 (10.67) | 149 | -2.6 (12.45) | | 6.0 % | 0.0 [ -2.63, 2.63 ] |
| Iconomou 2003 | 57 | 4.6 (12.5) | 55 | -1 (12.8) | | 1.9 % | 5.60 [ 0.91, 10.29 ] |


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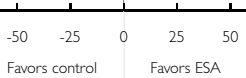
| Study or subgroup | ESA N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Kotasek 2003 | 189 | 3.4 (12.6) | 50 | 2.3 (11.6) | | 3.0 % | 1.10 [ -2.58, 4.78 ] |
| Littlewood 2001 | 200 | 3 (13.5) | 90 | -2.2 (12.5) | | 4.0 % | 5.20 [ 2.01, 8.39 ] |
| Osterborg 2002 | 133 | 5.2 (12.2) | 130 | 3 (12.1) | | 4.8 % | 2.20 [ -0.74, 5.14 ] |
| Pirker 2008 | 245 | 1.5 (13.15) | 239 | 0.7 (13.3) | | 7.4 % | 0.80 [ -1.56, 3.16 ] |
| Savonije 2005 | 156 | 3.48 (12.67) | 65 | -1.67 (11.61) | | 3.5 % | 5.15 [ 1.70, 8.60 ] |
| Smith 2008 | 343 | -0.02 (11.83) | 362 | 0.52 (10.41) | | 15.1 % | -0.54 [ -2.19, 1.11 ] |
| Tjulandin 2011 | 88 | 2.9 (7.9) | 84 | 0.6 (8.8) | | 6.6 % | 2.30 [ -0.20, 4.80 ] |
| Tsuboi 2009 | 61 | -0.5 (9.4) | 54 | -3.6 (9) | | 3.6 % | 3.10 [ -0.27, 6.47 ] |
| Vansteenkiste 2002 | 156 | 0.8 (10) | 158 | -0.6 (10.7) | | 7.8 % | 1.40 [ -0.89, 3.69 ] |
| Witzig 2005 | 151 | 1.56 (12.07) | 148 | 0.31 (14.48) | | 4.5 % | 1.25 [ -1.77, 4.27 ] |
| **Total (95% CI)** | **2783** | | **2182** | | | **100.0 %** | **2.08 [ 1.43, 2.72 ]** |

Heterogeneity: $Chi^2$ = 36.48, df = 17 (P = 0.004); $I^2$ =53%

Test for overall effect: Z = 6.34 (P < 0.00001)

Test for subgroup differences: Not applicable



## Analysis 8.2. Comparison 8 Change in FACT-Fatigue 13, Outcome 2 Change in FACT-Fatigue sensitivity analysis- Tsuboi.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 8 Change in FACT-Fatigue 13

Outcome: 2 Change in FACT-Fatigue sensitivity analysis- Tsuboi

| Study or subgroup | ESA N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Boogaerts 2003 | 104 | 5.47 (14.47) | 109 | 0.41 (8.47) | | 4.0 % | 5.06 [ 1.86, 8.26 ] |
| Chang 2005 | 168 | 1.55 (10.52) | 170 | -3.55 (11.14) | | 7.7 % | 5.10 [ 2.79, 7.41 ] |
| Charu 2007 | 203 | 6 (12.34) | 42 | 2.2 (7.8) | | 4.9 % | 3.80 [ 0.89, 6.71 ] |
| Christodoulou 2009 | 76 | 3.87 (11.99) | 76 | 0.71 (12.43) | | 2.7 % | 3.16 [ -0.72, 7.04 ] |
| Gordon 2008 | 150 | 4.8 (11.263) | 50 | 5 (11.473) | | 3.1 % | -0.20 [ -3.86, 3.46 ] |
| Hedenus 2003 | 152 | 2.68 (8.88) | 151 | 0.8 (9.71) | | 9.4 % | 1.88 [ -0.22, 3.98 ] |
| Hoskin 2009 | 151 | -2.6 (10.67) | 149 | -2.6 (12.45) | | 6.0 % | 0.0 [ -2.63, 2.63 ] |
| Iconomou 2003 | 57 | 4.6 (12.5) | 55 | -1 (12.8) | | 1.9 % | 5.60 [ 0.91, 10.29 ] |
| Kotasek 2003 | 189 | 3.4 (12.6) | 50 | 2.3 (11.6) | | 3.0 % | 1.10 [ -2.58, 4.78 ] |
| Littlewood 2001 | 200 | 3 (13.5) | 90 | -2.2 (12.5) | | 4.1 % | 5.20 [ 2.01, 8.39 ] |
| Osterborg 2002 | 133 | 5.2 (12.2) | 130 | 3 (12.1) | | 4.8 % | 2.20 [ -0.74, 5.14 ] |
| Pirker 2008 | 245 | 1.5 (13.15) | 239 | 0.7 (13.3) | | 7.4 % | 0.80 [ -1.56, 3.16 ] |
| Savonije 2005 | 156 | 3.48 (12.67) | 65 | -1.67 (11.61) | | 3.5 % | 5.15 [ 1.70, 8.60 ] |
| Smith 2008 | 343 | -0.02 (11.83) | 362 | 0.52 (10.41) | | 15.2 % | -0.54 [ -2.19, 1.11 ] |
| Tjulandin 2011 | 88 | 2.9 (7.9) | 84 | 0.6 (8.8) | | 6.6 % | 2.30 [ -0.20, 4.80 ] |
| Tsuboi 2009 | 61 | -0.5 (9.4) | 56 | -4.5 (10) | | 3.3 % | 4.00 [ 0.48, 7.52 ] |
| Vansteenkiste 2002 | 156 | 0.8 (10) | 158 | -0.6 (10.7) | | 7.9 % | 1.40 [ -0.89, 3.69 ] |
| Witzig 2005 | 151 | 1.56 (12.07) | 148 | 0.31 (14.48) | | 4.5 % | 1.25 [ -1.77, 4.27 ] |
| **Total (95% CI)** | **2783** | | **2184** | | | **100.0 %** | **2.10 [ 1.46, 2.75 ]** |

Heterogeneity: Chi² = 37.26, df = 17 (P = 0.003); I² =54%

Test for overall effect: Z = 6.41 (P < 0.00001)

Test for subgroup differences: Not applicable

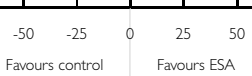
## Analysis 8.3. Comparison 8 Change in FACT-Fatigue 13, Outcome 3 Change in FACT-F 13 - baseline Hb.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 8 Change in FACT-Fatigue 13

Outcome: 3 Change in FACT-F 13 - baseline Hb

| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 Hb <= 10 g/dL | | | | | | | |
| Boogaerts 2003 | 104 | 5.47 (14.47) | 109 | 0.41 (8.47) | | 4.0 % | 5.06 [ 1.86, 8.26 ] |
| Hedenus 2003 | 152 | 2.68 (8.88) | 151 | 0.8 (9.71) | | 9.4 % | 1.88 [ -0.22, 3.98 ] |
| Kotasek 2003 | 189 | 3.4 (12.6) | 50 | 2.3 (11.6) | | 3.0 % | 1.10 [ -2.58, 4.78 ] |
| Littlewood 2001 | 200 | 3 (13.5) | 90 | -2.2 (12.5) | | 4.0 % | 5.20 [ 2.01, 8.39 ] |
| Osterborg 2002 | 133 | 5.2 (12.2) | 130 | 3 (12.1) | | 4.8 % | 2.20 [ -0.74, 5.14 ] |
| Smith 2008 | 343 | -0.02 (11.83) | 362 | 0.52 (10.41) | | 15.1 % | -0.54 [ -2.19, 1.11 ] |
| Tjulandin 2011 | 88 | 2.9 (7.9) | 84 | 0.6 (8.8) | | 6.6 % | 2.30 [ -0.20, 4.80 ] |
| Witzig 2005 | 151 | 1.56 (12.07) | 148 | 0.31 (14.48) | | 4.5 % | 1.25 [ -1.77, 4.27 ] |
| **Subtotal (95% CI)** | **1360** | | **1124** | | | **51.4 %** | **1.66 [ 0.76, 2.55 ]** |
| Heterogeneity: $Chi^2$ = 16.49, df = 7 (P = 0.02); $I^2$ =58% | | | | | | | |
| Test for overall effect: Z = 3.64 (P = 0.00028) | | | | | | | |
| 2 Hb 10 to 12 g/dL | | | | | | | |
| Chang 2005 | 168 | 1.55 (10.52) | 170 | -3.55 (11.14) | | 7.7 % | 5.10 [ 2.79, 7.41 ] |
| Charu 2007 | 203 | 6 (12.34) | 42 | 2.2 (7.8) | | 4.9 % | 3.80 [ 0.89, 6.71 ] |
| Christodoulou 2009 | 76 | 3.87 (11.99) | 76 | 0.71 (12.43) | | 2.7 % | 3.16 [ -0.72, 7.04 ] |
| Gordon 2008 | 150 | 4.8 (11.263) | 50 | 5 (11.473) | | 3.1 % | -0.20 [ -3.86, 3.46 ] |
| Iconomou 2003 | 57 | 4.6 (12.5) | 55 | -1 (12.8) | | 1.9 % | 5.60 [ 0.91, 10.29 ] |
| Pirker 2008 | 245 | 1.5 (13.15) | 239 | 0.7 (13.3) | | 7.4 % | 0.80 [ -1.56, 3.16 ] |
| Savonije 2005 | 156 | 3.48 (12.67) | 65 | -1.67 (11.61) | | 3.5 % | 5.15 [ 1.70, 8.60 ] |
| Tsuboi 2009 | 61 | -0.5 (9.4) | 54 | -3.6 (9) | | 3.6 % | 3.10 [ -0.27, 6.47 ] |
| Vansteenkiste 2002 | 156 | 0.8 (10) | 158 | -0.6 (10.7) | | 7.8 % | 1.40 [ -0.89, 3.69 ] |
| **Subtotal (95% CI)** | **1272** | | **909** | | | **42.6 %** | **2.87 [ 1.89, 3.85 ]** |
| Heterogeneity: $Chi^2$ = 14.25, df = 8 (P = 0.08); $I^2$ =44% | | | | | | | |
| Test for overall effect: Z = 5.72 (P < 0.00001) | | | | | | | |
| 3 Hb > 12 g/dL | | | | | | | |
| Hoskin 2009 | 151 | -2.6 (10.67) | 149 | -2.6 (12.45) | | 6.0 % | 0.0 [ -2.63, 2.63 ] |
| **Subtotal (95% CI)** | **151** | | **149** | | | **6.0 %** | **0.0 [ -2.63, 2.63 ]** |

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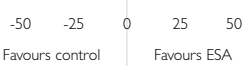
| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 0.0 (P = 1.0) | | | | | | | |
| 4 Hb category unclear | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| **Total (95% CI)** | **2783** | | **2182** | | | **100.0 %** | **2.08 [ 1.43, 2.72 ]** |
| Heterogeneity: $Chi^2$ = 36.48, df = 17 (P = 0.004); $I^2$ =53% | | | | | | | |
| Test for overall effect: Z = 6.34 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 5.75, df = 2 (P = 0.06), $I^2$ =65% | | | | | | | |



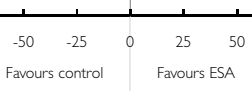
## Analysis 8.4. Comparison 8 Change in FACT-Fatigue 13, Outcome 4 Change in FACT-F 13 - different malignancies.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 8 Change in FACT-Fatigue 13

Outcome: 4 Change in FACT-F 13 - different malignancies

| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 solid tumours | | | | | | | |
| Hoskin 2009 | 151 | -2.6 (10.67) | 149 | -2.6 (12.45) | | 6.0 % | 0.0 [ -2.63, 2.63 ] |
| Pirker 2008 | 245 | 1.5 (13.15) | 239 | 0.7 (13.3) | | 7.4 % | 0.80 [ -1.56, 3.16 ] |
| Kotasek 2003 | 189 | 3.4 (12.6) | 50 | 2.3 (11.6) | | 3.0 % | 1.10 [ -2.58, 4.78 ] |
| Witzig 2005 | 151 | 1.56 (12.07) | 148 | 0.31 (14.48) | | 4.5 % | 1.25 [ -1.77, 4.27 ] |
| Vansteenkiste 2002 | 156 | 0.8 (10) | 158 | -0.6 (10.7) | | 7.8 % | 1.40 [ -0.89, 3.69 ] |
| Christodoulou 2009 | 76 | 3.87 (11.99) | 76 | 0.71 (12.43) | | 2.7 % | 3.16 [ -0.72, 7.04 ] |
| Chang 2005 | 168 | 1.55 (10.52) | 170 | -3.55 (11.14) | | 7.7 % | 5.10 [ 2.79, 7.41 ] |
| Savonije 2005 | 156 | 3.48 (12.67) | 65 | -1.67 (11.61) | | 3.5 % | 5.15 [ 1.70, 8.60 ] |
| Iconomou 2003 | 57 | 4.6 (12.5) | 55 | -1 (12.8) | | 1.9 % | 5.60 [ 0.91, 10.29 ] |
| **Subtotal (95% CI)** | **1349** | | **1110** | | | **44.5 %** | **2.29 [ 1.33, 3.25 ]** |
| Heterogeneity: $Chi^2$ = 16.32, df = 8 (P = 0.04); $I^2$ =51% | | | | | | | |
| Test for overall effect: Z = 4.68 (P < 0.00001) | | | | | | | |
| 2 haematological malignancies | | | | | | | |
| Hedenus 2003 | 152 | 2.68 (8.88) | 151 | 0.8 (9.71) | | 9.4 % | 1.88 [ -0.22, 3.98 ] |
| Osterborg 2002 | 133 | 5.2 (12.2) | 130 | 3 (12.1) | | 4.8 % | 2.20 [ -0.74, 5.14 ] |
| **Subtotal (95% CI)** | **285** | | **281** | | | **14.1 %** | **1.99 [ 0.28, 3.69 ]** |
| Heterogeneity: $Chi^2$ = 0.03, df = 1 (P = 0.86); $I^2$ =0.0% | | | | | | | |
| Test for overall effect: Z = 2.28 (P = 0.022) | | | | | | | |
| 3 mixed | | | | | | | |
| Smith 2008 | 343 | -0.02 (11.83) | 362 | 0.52 (10.41) | | 15.1 % | -0.54 [ -2.19, 1.11 ] |
| Gordon 2008 | 150 | 4.8 (11.263) | 50 | 5 (11.473) | | 3.1 % | -0.20 [ -3.86, 3.46 ] |
| Tjulandin 2011 | 88 | 2.9 (7.9) | 84 | 0.6 (8.8) | | 6.6 % | 2.30 [ -0.20, 4.80 ] |
| Tsuboi 2009 | 61 | -0.5 (9.4) | 54 | -3.6 (9) | | 3.6 % | 3.10 [ -0.27, 6.47 ] |
| Charu 2007 | 203 | 6 (12.34) | 42 | 2.2 (7.8) | | 4.9 % | 3.80 [ 0.89, 6.71 ] |
| Boogaerts 2003 | 104 | 5.47 (14.47) | 109 | 0.41 (8.47) | | 4.0 % | 5.06 [ 1.86, 8.26 ] |
| Littlewood 2001 | 200 | 3 (13.5) | 90 | -2.2 (12.5) | | 4.0 % | 5.20 [ 2.01, 8.39 ] |

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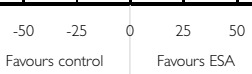
| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| **Subtotal (95% CI)** | **1149** | | **791** | | | **41.3 %** | **1.87 [ 0.87, 2.87 ]** |
| Heterogeneity: $Chi^2$ = 19.76, df = 6 (P = 0.003); $I^2$ =70% | | | | | | | |
| Test for overall effect: Z = 3.68 (P = 0.00023) | | | | | | | |
| 4 unclear | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| **Total (95% CI)** | **2783** | | **2182** | | | **100.0 %** | **2.08 [ 1.43, 2.72 ]** |
| Heterogeneity: $Chi^2$ = 36.48, df = 17 (P = 0.004); $I^2$ =53% | | | | | | | |
| Test for overall effect: Z = 6.34 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 0.37, df = 2 (P = 0.83), $I^2$ =0.0% | | | | | | | |



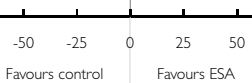
### Analysis 8.5. Comparison 8 Change in FACT-Fatigue 13, Outcome 5 Change in FACT-F 13 - age.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 8 Change in FACT-Fatigue 13

Outcome: 5 Change in FACT-F 13 - age

| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 only children < 18 years | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| 2 adults >= 18 years | | | | | | | |
| Boogaerts 2003 | 104 | 5.47 (14.47) | 109 | 0.41 (8.47) | | 4.0 % | 5.06 [ 1.86, 8.26 ] |
| Charu 2007 | 203 | 6 (12.34) | 42 | 2.2 (7.8) | | 4.9 % | 3.80 [ 0.89, 6.71 ] |
| Christodoulou 2009 | 76 | 3.87 (11.99) | 76 | 0.71 (12.43) | | 2.7 % | 3.16 [ -0.72, 7.04 ] |
| Gordon 2008 | 150 | 4.8 (11.263) | 50 | 5 (11.473) | | 3.1 % | -0.20 [ -3.86, 3.46 ] |
| Hedenus 2003 | 152 | 2.68 (8.88) | 151 | 0.8 (9.71) | | 9.4 % | 1.88 [ -0.22, 3.98 ] |
| Hoskin 2009 | 151 | -2.6 (10.67) | 149 | -2.6 (12.45) | | 6.0 % | 0.0 [ -2.63, 2.63 ] |
| Iconomou 2003 | 57 | 4.6 (12.5) | 55 | -1 (12.8) | | 1.9 % | 5.60 [ 0.91, 10.29 ] |
| Kotasek 2003 | 189 | 3.4 (12.6) | 50 | 2.3 (11.6) | | 3.0 % | 1.10 [ -2.58, 4.78 ] |
| Littlewood 2001 | 200 | 3 (13.5) | 90 | -2.2 (12.5) | | 4.0 % | 5.20 [ 2.01, 8.39 ] |
| Osterborg 2002 | 133 | 5.2 (12.2) | 130 | 3 (12.1) | | 4.8 % | 2.20 [ -0.74, 5.14 ] |
| Pirker 2008 | 245 | 1.5 (13.15) | 239 | 0.7 (13.3) | | 7.4 % | 0.80 [ -1.56, 3.16 ] |
| Savonije 2005 | 156 | 3.48 (12.67) | 65 | -1.67 (11.61) | | 3.5 % | 5.15 [ 1.70, 8.60 ] |
| Smith 2008 | 343 | -0.02 (11.83) | 362 | 0.52 (10.41) | | 15.1 % | -0.54 [ -2.19, 1.11 ] |
| Tjulandin 2011 | 88 | 2.9 (7.9) | 84 | 0.6 (8.8) | | 6.6 % | 2.30 [ -0.20, 4.80 ] |
| Tsuboi 2009 | 61 | -0.5 (9.4) | 54 | -3.6 (9) | | 3.6 % | 3.10 [ -0.27, 6.47 ] |
| Vansteenkiste 2002 | 156 | 0.8 (10) | 158 | -0.6 (10.7) | | 7.8 % | 1.40 [ -0.89, 3.69 ] |
| Witzig 2005 | 151 | 1.56 (12.07) | 148 | 0.31 (14.48) | | 4.5 % | 1.25 [ -1.77, 4.27 ] |
| **Subtotal (95% CI)** | **2615** | | **2012** | | | **92.3 %** | **1.82 [ 1.16, 2.49 ]** |
| Heterogeneity: $Chi^2$ = 29.35, df = 16 (P = 0.02); $I^2$ =45% | | | | | | | |
| Test for overall effect: Z = 5.35 (P < 0.00001) | | | | | | | |
| 3 >70% non elderly 18-65 years | | | | | | | |
| Chang 2005 | 168 | 1.55 (10.52) | 170 | -3.55 (11.14) | | 7.7 % | 5.10 [ 2.79, 7.41 ] |
| **Subtotal (95% CI)** | **168** | | **170** | | | **7.7 %** | **5.10 [ 2.79, 7.41 ]** |

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| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 4.33 (P = 0.000015) | | | | | | | |
| 4 only non-elderly adults | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| 5 >70% elderly >65 years | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| 6 only elderly > 65 years | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| **Total (95% CI)** | **2783** | | **2182** | | | **100.0 %** | **2.08 [ 1.43, 2.72 ]** |
| Heterogeneity: $Chi^2$ = 36.48, df = 17 (P = 0.004); $I^2$ =53% | | | | | | | |
| Test for overall effect: Z = 6.34 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 7.14, df = 1 (P = 0.01), $I^2$ =86% | | | | | | | |

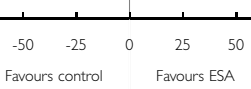
## Analysis 8.6. Comparison 8 Change in FACT-Fatigue 13, Outcome 6 Change in FACT-F 13 - different therapies.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 8 Change in FACT-Fatigue 13

Outcome: 6 Change in FACT-F 13 - different therapies

| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 chemotherapy | | | | | | | |
| Boogaerts 2003 | 104 | 5.47 (14.47) | 109 | 0.41 (8.47) | | 4.0 % | 5.06 [ 1.86, 8.26 ] |
| Chang 2005 | 168 | 1.55 (10.52) | 170 | -3.55 (11.14) | | 7.7 % | 5.10 [ 2.79, 7.41 ] |
| Christodoulou 2009 | 76 | 3.87 (11.99) | 76 | 0.71 (12.43) | | 2.7 % | 3.16 [ -0.72, 7.04 ] |
| Hedenus 2003 | 152 | 2.68 (8.88) | 151 | 0.8 (9.71) | | 9.4 % | 1.88 [ -0.22, 3.98 ] |
| Iconomou 2003 | 57 | 4.6 (12.5) | 55 | -1 (12.8) | | 1.9 % | 5.60 [ 0.91, 10.29 ] |
| Kotasek 2003 | 189 | 3.4 (12.6) | 50 | 2.3 (11.6) | | 3.0 % | 1.10 [ -2.58, 4.78 ] |
| Littlewood 2001 | 200 | 3 (13.5) | 90 | -2.2 (12.5) | | 4.0 % | 5.20 [ 2.01, 8.39 ] |
| Osterborg 2002 | 133 | 5.2 (12.2) | 130 | 3 (12.1) | | 4.8 % | 2.20 [ -0.74, 5.14 ] |
| Pirker 2008 | 245 | 1.5 (13.15) | 239 | 0.7 (13.3) | | 7.4 % | 0.80 [ -1.56, 3.16 ] |
| Savonije 2005 | 156 | 3.48 (12.67) | 65 | -1.67 (11.61) | | 3.5 % | 5.15 [ 1.70, 8.60 ] |
| Tjulandin 2011 | 88 | 2.9 (7.9) | 84 | 0.6 (8.8) | | 6.6 % | 2.30 [ -0.20, 4.80 ] |
| Tsuboi 2009 | 61 | -0.5 (9.4) | 54 | -3.6 (9) | | 3.6 % | 3.10 [ -0.27, 6.47 ] |
| Vansteenkiste 2002 | 156 | 0.8 (10) | 158 | -0.6 (10.7) | | 7.8 % | 1.40 [ -0.89, 3.69 ] |
| Witzig 2005 | 151 | 1.56 (12.07) | 148 | 0.31 (14.48) | | 4.5 % | 1.25 [ -1.77, 4.27 ] |
| **Subtotal (95% CI)** | **1936** | | **1579** | | | **70.9 %** | **2.79 [ 2.03, 3.55 ]** |
| Heterogeneity: Chi² = 18.19, df = 13 (P = 0.15); I² =29% | | | | | | | |
| Test for overall effect: Z = 7.18 (P < 0.00001) | | | | | | | |
| 2 radiotherapy | | | | | | | |
| Hoskin 2009 | 151 | -2.6 (10.67) | 149 | -2.6 (12.45) | | 6.0 % | 0.0 [ -2.63, 2.63 ] |
| **Subtotal (95% CI)** | **151** | | **149** | | | **6.0 %** | **0.0 [ -2.63, 2.63 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 0.0 (P = 1.0) | | | | | | | |
| 3 no therapy | | | | | | | |
| Charu 2007 | 203 | 6 (12.34) | 42 | 2.2 (7.8) | | 4.9 % | 3.80 [ 0.89, 6.71 ] |
| Gordon 2008 | 150 | 4.8 (11.263) | 50 | 5 (11.473) | | 3.1 % | -0.20 [ -3.86, 3.46 ] |
| Smith 2008 | 343 | -0.02 (11.83) | 362 | 0.52 (10.41) | | 15.1 % | -0.54 [ -2.19, 1.11 ] |

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| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| **Subtotal (95% CI)** | **696** | | **454** | | | **23.1 %** | **0.42 [ -0.91, 1.76 ]** |
| Heterogeneity: $Chi^2$ = 6.61, df = 2 (P = 0.04); $I^2$ =70% | | | | | | | |
| Test for overall effect: Z = 0.62 (P = 0.54) | | | | | | | |
| 4 unclear | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| **Total (95% CI)** | **2783** | | **2182** | | | **100.0 %** | **2.08 [ 1.43, 2.72 ]** |
| Heterogeneity: $Chi^2$ = 36.48, df = 17 (P = 0.004); $I^2$ =53% | | | | | | | |
| Test for overall effect: Z = 6.34 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 11.68, df = 2 (P = 0.00), $I^2$ =83% | | | | | | | |

## Analysis 8.7. Comparison 8 Change in FACT-Fatigue 13, Outcome 7 Change in FACT-F 13 - different therapies differentiated.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 8 Change in FACT-Fatigue 13

Outcome: 7 Change in FACT-F 13 - different therapies differentiated

| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 chemotherapy, >70% with platinum | | | | | | | |
| Christodoulou 2009 | 25 | 4.56 (11.95) | 25 | 2.7 (11.65) | | 1.0 % | 1.86 [ -4.68, 8.40 ] |
| Pirker 2008 | 245 | 1.5 (13.15) | 239 | 0.7 (13.3) | | 7.4 % | 0.80 [ -1.56, 3.16 ] |
| Savonije 2005 | 156 | 3.48 (12.67) | 65 | -1.67 (11.61) | | 3.5 % | 5.15 [ 1.70, 8.60 ] |
| Vansteenkiste 2002 | 156 | 0.8 (10) | 158 | -0.6 (10.7) | | 7.8 % | 1.40 [ -0.89, 3.69 ] |
| **Subtotal (95% CI)** | **582** | | **487** | | | **19.7 %** | **1.85 [ 0.41, 3.30 ]** |
| Heterogeneity: Chi² = 4.42, df = 3 (P = 0.22); I² =32% | | | | | | | |
| Test for overall effect: Z = 2.51 (P = 0.012) | | | | | | | |
| 2 chemotherapy, <70% platinum containing | | | | | | | |
| Iconomou 2003 | 57 | 4.6 (12.5) | 55 | -1 (12.8) | | 1.9 % | 5.60 [ 0.91, 10.29 ] |
| Witzig 2005 | 151 | 1.56 (12.07) | 148 | 0.31 (14.48) | | 4.5 % | 1.25 [ -1.77, 4.27 ] |
| **Subtotal (95% CI)** | **208** | | **203** | | | **6.4 %** | **2.53 [ -0.01, 5.07 ]** |
| Heterogeneity: Chi² = 2.34, df = 1 (P = 0.13); I² =57% | | | | | | | |
| Test for overall effect: Z = 1.95 (P = 0.051) | | | | | | | |
| 3 chemotherapy without platinum (all patients) | | | | | | | |
| Chang 2005 | 168 | 1.55 (10.52) | 170 | -3.55 (11.14) | | 7.7 % | 5.10 [ 2.79, 7.41 ] |
| Christodoulou 2009 | 51 | 3.54 (12.04) | 51 | -0.26 (13.16) | | 1.7 % | 3.80 [ -1.10, 8.70 ] |
| Hedenus 2003 | 152 | 2.68 (8.88) | 151 | 0.8 (9.71) | | 9.4 % | 1.88 [ -0.22, 3.98 ] |
| Littlewood 2001 | 200 | 3 (13.5) | 90 | -2.2 (12.5) | | 4.0 % | 5.20 [ 2.01, 8.39 ] |
| Osterborg 2002 | 133 | 5.2 (12.2) | 130 | 3 (12.1) | | 4.8 % | 2.20 [ -0.74, 5.14 ] |
| Tjulandin 2011 | 88 | 2.9 (7.9) | 84 | 0.6 (8.8) | | 6.6 % | 2.30 [ -0.20, 4.80 ] |
| **Subtotal (95% CI)** | **792** | | **676** | | | **34.2 %** | **3.22 [ 2.12, 4.32 ]** |
| Heterogeneity: Chi² = 6.63, df = 5 (P = 0.25); I² =25% | | | | | | | |
| Test for overall effect: Z = 5.75 (P < 0.00001) | | | | | | | |
| 4 chemotherapy, platinum and non-platinum containing, no numbers given | | | | | | | |
| Boogaerts 2003 | 104 | 5.47 (14.47) | 109 | 0.41 (8.47) | | 4.0 % | 5.06 [ 1.86, 8.26 ] |
| Kotasek 2003 | 189 | 3.4 (12.6) | 50 | 2.3 (11.6) | | 3.0 % | 1.10 [ -2.58, 4.78 ] |
| Tsuboi 2009 | 61 | -0.5 (9.4) | 54 | -3.6 (9) | | 3.6 % | 3.10 [ -0.27, 6.47 ] |


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| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| **Subtotal (95% CI)** | **354** | | **213** | | | **10.7 %** | **3.27 [ 1.30, 5.23 ]** |
| Heterogeneity: $Chi^2$ = 2.54, df = 2 (P = 0.28); $I^2$ =21% | | | | | | | |
| Test for overall effect: Z = 3.26 (P = 0.0011) | | | | | | | |
| 5 radiochemotherapy NEW | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| 6 radiotherapy | | | | | | | |
| Hoskin 2009 | 151 | -2.6 (10.67) | 149 | -2.6 (12.45) | | 6.0 % | 0.0 [ -2.63, 2.63 ] |
| **Subtotal (95% CI)** | **151** | | **149** | | | **6.0 %** | **0.0 [ -2.63, 2.63 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 0.0 (P = 1.0) | | | | | | | |
| 7 no therapy | | | | | | | |
| Charu 2007 | 203 | 6 (12.34) | 42 | 2.2 (7.8) | | 4.9 % | 3.80 [ 0.89, 6.71 ] |
| Gordon 2008 | 150 | 4.8 (11.263) | 50 | 5 (11.473) | | 3.1 % | -0.20 [ -3.86, 3.46 ] |
| Smith 2008 | 343 | -0.02 (11.83) | 362 | 0.52 (10.41) | | 15.1 % | -0.54 [ -2.19, 1.11 ] |
| **Subtotal (95% CI)** | **696** | | **454** | | | **23.1 %** | **0.42 [ -0.91, 1.76 ]** |
| Heterogeneity: $Chi^2$ = 6.61, df = 2 (P = 0.04); $I^2$ =70% | | | | | | | |
| Test for overall effect: Z = 0.62 (P = 0.54) | | | | | | | |
| 8 unclear | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| 9 chemotherapy no details given | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| **Total (95% CI)** | **2783** | | **2182** | | | **100.0 %** | **2.07 [ 1.43, 2.72 ]** |
| Heterogeneity: $Chi^2$ = 36.66, df = 18 (P = 0.01); $I^2$ =51% | | | | | | | |
| Test for overall effect: Z = 6.34 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 14.12, df = 5 (P = 0.01), $I^2$ =65% | | | | | | | |

## Analysis 8.8. Comparison 8 Change in FACT-Fatigue 13, Outcome 8 Change in FACT-F 13 - epoetin versus darbepoetin.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 8 Change in FACT-Fatigue 13

Outcome: 8 Change in FACT-F 13 - epoetin versus darbepoetin

| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 Epoetin | | | | | | | |
| Boogaerts 2003 | 104 | 5.47 (14.47) | 109 | 0.41 (8.47) | | 4.0 % | 5.06 [ 1.86, 8.26 ] |
| Chang 2005 | 168 | 1.55 (10.52) | 170 | -3.55 (11.14) | | 7.7 % | 5.10 [ 2.79, 7.41 ] |
| Christodoulou 2009 | 76 | 3.87 (11.99) | 76 | 0.71 (12.43) | | 2.7 % | 3.16 [ -0.72, 7.04 ] |
| Hoskin 2009 | 151 | -2.6 (10.67) | 149 | -2.6 (12.45) | | 6.0 % | 0.0 [ -2.63, 2.63 ] |
| Iconomou 2003 | 57 | 4.6 (12.5) | 55 | -1 (12.8) | | 1.9 % | 5.60 [ 0.91, 10.29 ] |
| Littlewood 2001 | 200 | 3 (13.5) | 90 | -2.2 (12.5) | | 4.0 % | 5.20 [ 2.01, 8.39 ] |
| Osterborg 2002 | 133 | 5.2 (12.2) | 130 | 3 (12.1) | | 4.8 % | 2.20 [ -0.74, 5.14 ] |
| Savonije 2005 | 156 | 3.48 (12.67) | 65 | -1.67 (11.61) | | 3.5 % | 5.15 [ 1.70, 8.60 ] |
| Tjulandin 2011 | 88 | 2.9 (7.9) | 84 | 0.6 (8.8) | | 6.6 % | 2.30 [ -0.20, 4.80 ] |
| Tsuboi 2009 | 61 | -0.5 (9.4) | 54 | -3.6 (9) | | 3.6 % | 3.10 [ -0.27, 6.47 ] |
| Witzig 2005 | 151 | 1.56 (12.07) | 148 | 0.31 (14.48) | | 4.5 % | 1.25 [ -1.77, 4.27 ] |
| **Subtotal (95% CI)** | **1345** | | **1130** | | | **49.3 %** | **3.25 [ 2.33, 4.16 ]** |
| Heterogeneity: $Chi^2$ = 15.88, df = 10 (P = 0.10); $I^2$ =37% | | | | | | | |
| Test for overall effect: Z = 6.97 (P < 0.00001) | | | | | | | |
| 2 Darbepoetin | | | | | | | |
| Charu 2007 | 203 | 6 (12.34) | 42 | 2.2 (7.8) | | 4.9 % | 3.80 [ 0.89, 6.71 ] |
| Gordon 2008 | 150 | 4.8 (11.263) | 50 | 5 (11.473) | | 3.1 % | -0.20 [ -3.86, 3.46 ] |
| Hedenus 2003 | 152 | 2.68 (8.88) | 151 | 0.8 (9.71) | | 9.4 % | 1.88 [ -0.22, 3.98 ] |
| Kotasek 2003 | 189 | 3.4 (12.6) | 50 | 2.3 (11.6) | | 3.0 % | 1.10 [ -2.58, 4.78 ] |
| Pirker 2008 | 245 | 1.5 (13.15) | 239 | 0.7 (13.3) | | 7.4 % | 0.80 [ -1.56, 3.16 ] |
| Smith 2008 | 343 | -0.02 (11.83) | 362 | 0.52 (10.41) | | 15.1 % | -0.54 [ -2.19, 1.11 ] |
| Vansteenkiste 2002 | 156 | 0.8 (10) | 158 | -0.6 (10.7) | | 7.8 % | 1.40 [ -0.89, 3.69 ] |
| **Subtotal (95% CI)** | **1438** | | **1052** | | | **50.7 %** | **0.94 [ 0.04, 1.84 ]** |
| Heterogeneity: $Chi^2$ = 8.14, df = 6 (P = 0.23); $I^2$ =26% | | | | | | | |
| Test for overall effect: Z = 2.04 (P = 0.041) | | | | | | | |
| **Total (95% CI)** | **2783** | | **2182** | | | **100.0 %** | **2.08 [ 1.43, 2.72 ]** |

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| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Heterogeneity: $Chi^2$ = 36.48, df = 17 (P = 0.004); $I^2$ =53% | | | | | | | |
| Test for overall effect: Z = 6.34 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 12.47, df = 1 (P = 0.00), $I^2$ =92% | | | | | | | |


## Analysis 8.9. Comparison 8 Change in FACT-Fatigue 13, Outcome 9 Change in FACT-F 13 - duration of ESA medication.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 8 Change in FACT-Fatigue 13

Outcome: 9 Change in FACT-F 13 - duration of ESA medication

| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 6 to 9 weeks | | | | | | | |
| Tsuboi 2009 | 61 | -0.5 (9.4) | 54 | -3.6 (9) | | 3.6 % | 3.10 [ -0.27, 6.47 ] |
| **Subtotal (95% CI)** | **61** | | **54** | | | **3.6 %** | **3.10 [ -0.27, 6.47 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 1.81 (P = 0.071) | | | | | | | |
| 2 12 to 16 weeks | | | | | | | |
| Boogaerts 2003 | 104 | 5.47 (14.47) | 109 | 0.41 (8.47) | | 4.0 % | 5.06 [ 1.86, 8.26 ] |
| Chang 2005 | 168 | 1.55 (10.52) | 170 | -3.55 (11.14) | | 7.7 % | 5.10 [ 2.79, 7.41 ] |
| Charu 2007 | 203 | 6 (12.34) | 42 | 2.2 (7.8) | | 4.9 % | 3.80 [ 0.89, 6.71 ] |
| Christodoulou 2009 | 76 | 3.87 (11.99) | 76 | 0.71 (12.43) | | 2.7 % | 3.16 [ -0.72, 7.04 ] |
| Gordon 2008 | 150 | 4.8 (11.263) | 50 | 5 (11.473) | | 3.1 % | -0.20 [ -3.86, 3.46 ] |
| Hedenus 2003 | 152 | 2.68 (8.88) | 151 | 0.8 (9.71) | | 9.4 % | 1.88 [ -0.22, 3.98 ] |
| Hoskin 2009 | 151 | -2.6 (10.67) | 149 | -2.6 (12.45) | | 6.0 % | 0.0 [ -2.63, 2.63 ] |
| Iconomou 2003 | 57 | 4.6 (12.5) | 55 | -1 (12.8) | | 1.9 % | 5.60 [ 0.91, 10.29 ] |


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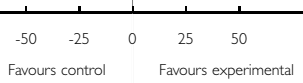
| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Kotasek 2003 | 189 | 3.4 (12.6) | 50 | 2.3 (11.6) | | 3.0 % | 1.10 [ -2.58, 4.78 ] |
| Osterborg 2002 | 133 | 5.2 (12.2) | 130 | 3 (12.1) | | 4.8 % | 2.20 [ -0.74, 5.14 ] |
| Savonije 2005 | 156 | 3.48 (12.67) | 65 | -1.67 (11.61) | | 3.5 % | 5.15 [ 1.70, 8.60 ] |
| Smith 2008 | 343 | -0.02 (11.83) | 362 | 0.52 (10.41) | | 15.1 % | -0.54 [ -2.19, 1.11 ] |
| Tjulandin 2011 | 88 | 2.9 (7.9) | 84 | 0.6 (8.8) | | 6.6 % | 2.30 [ -0.20, 4.80 ] |
| Vansteenkiste 2002 | 156 | 0.8 (10) | 158 | -0.6 (10.7) | | 7.8 % | 1.40 [ -0.89, 3.69 ] |
| Witzig 2005 | 151 | 1.56 (12.07) | 148 | 0.31 (14.48) | | 4.5 % | 1.25 [ -1.77, 4.27 ] |
| **Subtotal (95% CI)** | **2277** | | **1799** | | | **84.9 %** | **1.99 [ 1.30, 2.69 ]** |
| Heterogeneity: $Chi^2$ = 31.26, df = 14 (P = 0.01); $I^2$ =55% | | | | | | | |
| Test for overall effect: Z = 5.62 (P < 0.00001) | | | | | | | |
| 3 more than 17 weeks | | | | | | | |
| Littlewood 2001 | 200 | 3 (13.5) | 90 | -2.2 (12.5) | | 4.0 % | 5.20 [ 2.01, 8.39 ] |
| Pirker 2008 | 245 | 1.5 (13.15) | 239 | 0.7 (13.3) | | 7.4 % | 0.80 [ -1.56, 3.16 ] |
| **Subtotal (95% CI)** | **445** | | **329** | | | **11.5 %** | **2.35 [ 0.46, 4.25 ]** |
| Heterogeneity: $Chi^2$ = 4.73, df = 1 (P = 0.03); $I^2$ =79% | | | | | | | |
| Test for overall effect: Z = 2.43 (P = 0.015) | | | | | | | |
| 4 unclear | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| **Total (95% CI)** | **2783** | | **2182** | | | **100.0 %** | **2.08 [ 1.43, 2.72 ]** |
| Heterogeneity: $Chi^2$ = 36.48, df = 17 (P = 0.004); $I^2$ =53% | | | | | | | |
| Test for overall effect: Z = 6.34 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 0.49, df = 2 (P = 0.78), $I^2$ =0.0% | | | | | | | |



## Analysis 8.10. Comparison 8 Change in FACT-Fatigue 13, Outcome 10 Change in FACT-F 13 - iron supplementation.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 8 Change in FACT-Fatigue 13

Outcome: 10 Change in FACT-F 13 - iron supplementation

| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 fixed iron supplementation | | | | | | | |
| Christodoulou 2009 | 76 | 3.87 (11.99) | 76 | 0.71 (12.43) | | 2.7 % | 3.16 [ -0.72, 7.04 ] |
| Hoskin 2009 | 151 | -2.6 (10.67) | 149 | -2.6 (12.45) | | 6.0 % | 0.0 [ -2.63, 2.63 ] |
| Iconomou 2003 | 57 | 4.6 (12.5) | 55 | -1 (12.8) | | 1.9 % | 5.60 [ 0.91, 10.29 ] |
| Witzig 2005 | 151 | 1.56 (12.07) | 148 | 0.31 (14.48) | | 4.5 % | 1.25 [ -1.77, 4.27 ] |
| **Subtotal (95% CI)** | **435** | | **428** | | | **15.1 %** | **1.64 [ -0.01, 3.29 ]** |
| Heterogeneity: Chi² = 4.89, df = 3 (P = 0.18); I² =39% | | | | | | | |
| Test for overall effect: Z = 1.95 (P = 0.052) | | | | | | | |
| 2 iron supplementation as necessary | | | | | | | |
| Boogaerts 2003 | 104 | 5.47 (14.47) | 109 | 0.41 (8.47) | | 4.0 % | 5.06 [ 1.86, 8.26 ] |
| Chang 2005 | 168 | 1.55 (10.52) | 170 | -3.55 (11.14) | | 7.7 % | 5.10 [ 2.79, 7.41 ] |
| Charu 2007 | 203 | 6 (12.34) | 42 | 2.2 (7.8) | | 4.9 % | 3.80 [ 0.89, 6.71 ] |
| Gordon 2008 | 150 | 4.8 (11.263) | 50 | 5 (11.473) | | 3.1 % | -0.20 [ -3.86, 3.46 ] |
| Hedenus 2003 | 152 | 2.68 (8.88) | 151 | 0.8 (9.71) | | 9.4 % | 1.88 [ -0.22, 3.98 ] |
| Kotasek 2003 | 189 | 3.4 (12.6) | 50 | 2.3 (11.6) | | 3.0 % | 1.10 [ -2.58, 4.78 ] |
| Littlewood 2001 | 200 | 3 (13.5) | 90 | -2.2 (12.5) | | 4.0 % | 5.20 [ 2.01, 8.39 ] |
| Osterborg 2002 | 133 | 5.2 (12.2) | 130 | 3 (12.1) | | 4.8 % | 2.20 [ -0.74, 5.14 ] |
| Pirker 2008 | 245 | 1.5 (13.15) | 239 | 0.7 (13.3) | | 7.4 % | 0.80 [ -1.56, 3.16 ] |
| Smith 2008 | 343 | -0.02 (11.83) | 362 | 0.52 (10.41) | | 15.1 % | -0.54 [ -2.19, 1.11 ] |
| Tjulandin 2011 | 88 | 2.9 (7.9) | 84 | 0.6 (8.8) | | 6.6 % | 2.30 [ -0.20, 4.80 ] |
| Tsuboi 2009 | 61 | -0.5 (9.4) | 54 | -3.6 (9) | | 3.6 % | 3.10 [ -0.27, 6.47 ] |
| Vansteenkiste 2002 | 156 | 0.8 (10) | 158 | -0.6 (10.7) | | 7.8 % | 1.40 [ -0.89, 3.69 ] |
| **Subtotal (95% CI)** | **2192** | | **1689** | | | **81.5 %** | **2.03 [ 1.32, 2.74 ]** |
| Heterogeneity: Chi² = 28.26, df = 12 (P = 0.01); I² =58% | | | | | | | |
| Test for overall effect: Z = 5.59 (P < 0.00001) | | | | | | | |
| 3 no explicit statement on iron supplementation or no iron given | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |

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| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| 4 explicitly stated NO IRON | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| 5 unclear | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| 6 iron given differently in both study arms new | | | | | | | |
| Savonije 2005 | 156 | 3.48 (12.67) | 65 | -1.67 (11.61) | | 3.5 % | 5.15 [ 1.70, 8.60 ] |
| **Subtotal (95% CI)** | **156** | | **65** | | | **3.5 %** | **5.15 [ 1.70, 8.60 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 2.92 (P = 0.0035) | | | | | | | |
| **Total (95% CI)** | **2783** | | **2182** | | | **100.0 %** | **2.08 [ 1.43, 2.72 ]** |
| Heterogeneity: $Chi^2$ = 36.48, df = 17 (P = 0.004); $I^2$ =53% | | | | | | | |
| Test for overall effect: Z = 6.34 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 3.33, df = 2 (P = 0.19), $I^2$ =40% | | | | | | | |

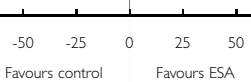
## Analysis 8.11. Comparison 8 Change in FACT-Fatigue 13, Outcome 11 Change in FACT-F 13 - allocation concealment.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 8 Change in FACT-Fatigue 13

Outcome: 11 Change in FACT-F 13 - allocation concealment

| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 adequate | | | | | | | |
| Boogaerts 2003 | 104 | 5.47 (14.47) | 109 | 0.41 (8.47) | | 4.0 % | 5.06 [ 1.86, 8.26 ] |
| Chang 2005 | 168 | 1.55 (10.52) | 170 | -3.55 (11.14) | | 7.7 % | 5.10 [ 2.79, 7.41 ] |
| Charu 2007 | 203 | 6 (12.34) | 42 | 2.2 (7.8) | | 4.9 % | 3.80 [ 0.89, 6.71 ] |
| Christodoulou 2009 | 76 | 3.87 (11.99) | 76 | 0.71 (12.43) | | 2.7 % | 3.16 [ -0.72, 7.04 ] |
| Gordon 2008 | 150 | 4.8 (11.263) | 50 | 5 (11.473) | | 3.1 % | -0.20 [ -3.86, 3.46 ] |
| Hedenus 2003 | 152 | 2.68 (8.88) | 151 | 0.8 (9.71) | | 9.4 % | 1.88 [ -0.22, 3.98 ] |
| Iconomou 2003 | 57 | 4.6 (12.5) | 55 | -1 (12.8) | | 1.9 % | 5.60 [ 0.91, 10.29 ] |
| Kotasek 2003 | 189 | 3.4 (12.6) | 50 | 2.3 (11.6) | | 3.0 % | 1.10 [ -2.58, 4.78 ] |
| Littlewood 2001 | 200 | 3 (13.5) | 90 | -2.2 (12.5) | | 4.0 % | 5.20 [ 2.01, 8.39 ] |
| Osterborg 2002 | 133 | 5.2 (12.2) | 130 | 3 (12.1) | | 4.8 % | 2.20 [ -0.74, 5.14 ] |
| Pirker 2008 | 245 | 1.5 (13.15) | 239 | 0.7 (13.3) | | 7.4 % | 0.80 [ -1.56, 3.16 ] |
| Savonije 2005 | 156 | 3.48 (12.67) | 65 | -1.67 (11.61) | | 3.5 % | 5.15 [ 1.70, 8.60 ] |
| Smith 2008 | 343 | -0.02 (11.83) | 362 | 0.52 (10.41) | | 15.1 % | -0.54 [ -2.19, 1.11 ] |
| Tsuboi 2009 | 61 | -0.5 (9.4) | 54 | -3.6 (9) | | 3.6 % | 3.10 [ -0.27, 6.47 ] |
| Vansteenkiste 2002 | 156 | 0.8 (10) | 158 | -0.6 (10.7) | | 7.8 % | 1.40 [ -0.89, 3.69 ] |
| Witzig 2005 | 151 | 1.56 (12.07) | 148 | 0.31 (14.48) | | 4.5 % | 1.25 [ -1.77, 4.27 ] |
| **Subtotal (95% CI)** | **2544** | | **1949** | | | **87.5 %** | **2.20 [ 1.51, 2.89 ]** |
| Heterogeneity: Chi² = 33.92, df = 15 (P = 0.003); I² =56% | | | | | | | |
| Test for overall effect: Z = 6.29 (P < 0.00001) | | | | | | | |
| 2 unclear | | | | | | | |
| Hoskin 2009 | 151 | -2.6 (10.67) | 149 | -2.6 (12.45) | | 6.0 % | 0.0 [ -2.63, 2.63 ] |
| Tjulandin 2011 | 88 | 2.9 (7.9) | 84 | 0.6 (8.8) | | 6.6 % | 2.30 [ -0.20, 4.80 ] |
| **Subtotal (95% CI)** | **239** | | **233** | | | **12.5 %** | **1.20 [ -0.61, 3.02 ]** |
| Heterogeneity: Chi² = 1.54, df = 1 (P = 0.21); I² =35% | | | | | | | |
| Test for overall effect: Z = 1.30 (P = 0.19) | | | | | | | |
| 3 unclear wether adequate or unclear :) | | | | | | | |

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| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| **Total (95% CI)** | **2783** | | **2182** | | | **100.0 %** | **2.08 [ 1.43, 2.72 ]** |
| Heterogeneity: $Chi^2$ = 36.48, df = 17 (P = 0.004); $I^2$ =53% | | | | | | | |
| Test for overall effect: Z = 6.34 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 1.02, df = 1 (P = 0.31), $I^2$ =2% | | | | | | | |


### Analysis 8.12. Comparison 8 Change in FACT-Fatigue 13, Outcome 12 Change in FACT-F 13 - masking.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 8 Change in FACT-Fatigue 13

Outcome: 12 Change in FACT-F 13 - masking

| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 double-blind | | | | | | | |
| Gordon 2008 | 150 | 4.8 (11.263) | 50 | 5 (11.473) | | 3.1 % | -0.20 [ -3.86, 3.46 ] |
| Hedenus 2003 | 152 | 2.68 (8.88) | 151 | 0.8 (9.71) | | 9.4 % | 1.88 [ -0.22, 3.98 ] |
| Kotasek 2003 | 189 | 3.4 (12.6) | 50 | 2.3 (11.6) | | 3.0 % | 1.10 [ -2.58, 4.78 ] |
| Littlewood 2001 | 200 | 3 (13.5) | 90 | -2.2 (12.5) | | 4.0 % | 5.20 [ 2.01, 8.39 ] |
| Osterborg 2002 | 133 | 5.2 (12.2) | 130 | 3 (12.1) | | 4.8 % | 2.20 [ -0.74, 5.14 ] |
| Pirker 2008 | 245 | 1.5 (13.15) | 239 | 0.7 (13.3) | | 7.4 % | 0.80 [ -1.56, 3.16 ] |
| Smith 2008 | 343 | -0.02 (11.83) | 362 | 0.52 (10.41) | | 15.1 % | -0.54 [ -2.19, 1.11 ] |
| Tjulandin 2011 | 88 | 2.9 (7.9) | 84 | 0.6 (8.8) | | 6.6 % | 2.30 [ -0.20, 4.80 ] |
| Tsuboi 2009 | 61 | -0.5 (9.4) | 54 | -3.6 (9) | | 3.6 % | 3.10 [ -0.27, 6.47 ] |


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| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Vansteenkiste 2002 | 156 | 0.8 (10) | 158 | -0.6 (10.7) | | 7.8 % | 1.40 [ -0.89, 3.69 ] |
| Witzig 2005 | 151 | 1.56 (12.07) | 148 | 0.31 (14.48) | | 4.5 % | 1.25 [ -1.77, 4.27 ] |
| **Subtotal (95% CI)** | **1868** | | **1516** | | | **69.4 %** | **1.33 [ 0.56, 2.10 ]** |
| Heterogeneity: $Chi^2$ = 13.73, df = 10 (P = 0.19); $I^2$ =27% | | | | | | | |
| Test for overall effect: Z = 3.40 (P = 0.00068) | | | | | | | |
| 2 unblinded | | | | | | | |
| Boogaerts 2003 | 104 | 5.47 (14.47) | 109 | 0.41 (8.47) | | 4.0 % | 5.06 [ 1.86, 8.26 ] |
| Chang 2005 | 168 | 1.55 (10.52) | 170 | -3.55 (11.14) | | 7.7 % | 5.10 [ 2.79, 7.41 ] |
| Charu 2007 | 203 | 6 (12.34) | 42 | 2.2 (7.8) | | 4.9 % | 3.80 [ 0.89, 6.71 ] |
| Christodoulou 2009 | 76 | 3.87 (11.99) | 76 | 0.71 (12.43) | | 2.7 % | 3.16 [ -0.72, 7.04 ] |
| Hoskin 2009 | 151 | -2.6 (10.67) | 149 | -2.6 (12.45) | | 6.0 % | 0.0 [ -2.63, 2.63 ] |
| Iconomou 2003 | 57 | 4.6 (12.5) | 55 | -1 (12.8) | | 1.9 % | 5.60 [ 0.91, 10.29 ] |
| Savonije 2005 | 156 | 3.48 (12.67) | 65 | -1.67 (11.61) | | 3.5 % | 5.15 [ 1.70, 8.60 ] |
| **Subtotal (95% CI)** | **915** | | **666** | | | **30.6 %** | **3.76 [ 2.60, 4.92 ]** |
| Heterogeneity: $Chi^2$ = 11.11, df = 6 (P = 0.08); $I^2$ =46% | | | | | | | |
| Test for overall effect: Z = 6.35 (P < 0.00001) | | | | | | | |
| **Total (95% CI)** | **2783** | | **2182** | | | **100.0 %** | **2.08 [ 1.43, 2.72 ]** |
| Heterogeneity: $Chi^2$ = 36.48, df = 17 (P = 0.004); $I^2$ =53% | | | | | | | |
| Test for overall effect: Z = 6.34 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 11.64, df = 1 (P = 0.00), $I^2$ =91% | | | | | | | |

## Analysis 8.13. Comparison 8 Change in FACT-Fatigue 13, Outcome 13 Change in FACT-F 13 - intention-to treat.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 8 Change in FACT-Fatigue 13

Outcome: 13 Change in FACT-F 13 - intention-to treat

| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 ITT or less than 10% of participants per study arm excluded | | | | | | | |
| Chang 2005 | 168 | 1.55 (10.52) | 170 | -3.55 (11.14) | | 7.7 % | 5.10 [ 2.79, 7.41 ] |
| Kotasek 2003 | 189 | 3.4 (12.6) | 50 | 2.3 (11.6) | | 3.0 % | 1.10 [ -2.58, 4.78 ] |
| Tjulandin 2011 | 88 | 2.9 (7.9) | 84 | 0.6 (8.8) | | 6.6 % | 2.30 [ -0.20, 4.80 ] |
| Tsuboi 2009 | 61 | -0.5 (9.4) | 54 | -3.6 (9) | | 3.6 % | 3.10 [ -0.27, 6.47 ] |
| **Subtotal (95% CI)** | **506** | | **358** | | | **20.9 %** | **3.30 [ 1.89, 4.70 ]** |
| Heterogeneity: Chi² = 4.33, df = 3 (P = 0.23); I² =31% | | | | | | | |
| Test for overall effect: Z = 4.61 (P < 0.00001) | | | | | | | |
| 2 more than 10% of participants per study arm excluded | | | | | | | |
| Boogaerts 2003 | 104 | 5.47 (14.47) | 109 | 0.41 (8.47) | | 4.0 % | 5.06 [ 1.86, 8.26 ] |
| Charu 2007 | 203 | 6 (12.34) | 42 | 2.2 (7.8) | | 4.9 % | 3.80 [ 0.89, 6.71 ] |
| Christodoulou 2009 | 76 | 3.87 (11.99) | 76 | 0.71 (12.43) | | 2.7 % | 3.16 [ -0.72, 7.04 ] |
| Gordon 2008 | 150 | 4.8 (11.263) | 50 | 5 (11.473) | | 3.1 % | -0.20 [ -3.86, 3.46 ] |
| Hedenus 2003 | 152 | 2.68 (8.88) | 151 | 0.8 (9.71) | | 9.4 % | 1.88 [ -0.22, 3.98 ] |
| Littlewood 2001 | 200 | 3 (13.5) | 90 | -2.2 (12.5) | | 4.0 % | 5.20 [ 2.01, 8.39 ] |
| Osterborg 2002 | 133 | 5.2 (12.2) | 130 | 3 (12.1) | | 4.8 % | 2.20 [ -0.74, 5.14 ] |
| Pirker 2008 | 245 | 1.5 (13.15) | 239 | 0.7 (13.3) | | 7.4 % | 0.80 [ -1.56, 3.16 ] |
| Savonije 2005 | 156 | 3.48 (12.67) | 65 | -1.67 (11.61) | | 3.5 % | 5.15 [ 1.70, 8.60 ] |
| Smith 2008 | 343 | -0.02 (11.83) | 362 | 0.52 (10.41) | | 15.1 % | -0.54 [ -2.19, 1.11 ] |
| Vansteenkiste 2002 | 156 | 0.8 (10) | 158 | -0.6 (10.7) | | 7.8 % | 1.40 [ -0.89, 3.69 ] |
| Witzig 2005 | 151 | 1.56 (12.07) | 148 | 0.31 (14.48) | | 4.5 % | 1.25 [ -1.77, 4.27 ] |
| **Subtotal (95% CI)** | **2069** | | **1620** | | | **71.2 %** | **1.80 [ 1.04, 2.56 ]** |
| Heterogeneity: Chi² = 24.16, df = 11 (P = 0.01); I² =54% | | | | | | | |
| Test for overall effect: Z = 4.64 (P < 0.00001) | | | | | | | |
| 3 unclear | | | | | | | |
| Hoskin 2009 | 151 | -2.6 (10.67) | 149 | -2.6 (12.45) | | 6.0 % | 0.0 [ -2.63, 2.63 ] |
| Iconomou 2003 | 57 | 4.6 (12.5) | 55 | -1 (12.8) | | 1.9 % | 5.60 [ 0.91, 10.29 ] |

-100 -50 0 50 100

Favours control Favours ESA

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| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| **Subtotal (95% CI)** | **208** | | **204** | | | **7.8 %** | **1.34 [ -0.95, 3.63 ]** |
| Heterogeneity: $Chi^2$ = 4.17, df = 1 (P = 0.04); $I^2$ =76% | | | | | | | |
| Test for overall effect: Z = 1.14 (P = 0.25) | | | | | | | |
| **Total (95% CI)** | **2783** | | **2182** | | | **100.0 %** | **2.08 [ 1.43, 2.72 ]** |
| Heterogeneity: $Chi^2$ = 36.48, df = 17 (P = 0.004); $I^2$ =53% | | | | | | | |
| Test for overall effect: Z = 6.34 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 3.82, df = 2 (P = 0.15), $I^2$ =48% | | | | | | | |

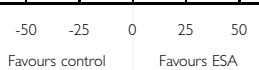

**Analysis 8.14. Comparison 8 Change in FACT-Fatigue 13, Outcome 14 Change in FACT-F 13 - publication.**

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 8 Change in FACT-Fatigue 13

Outcome: 14 Change in FACT-F 13 - publication

| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 full text publication | | | | | | | |
| Boogaerts 2003 | 104 | 5.47 (14.47) | 109 | 0.41 (8.47) | | 4.0 % | 5.06 [ 1.86, 8.26 ] |
| Chang 2005 | 168 | 1.55 (10.52) | 170 | -3.55 (11.14) | | 7.7 % | 5.10 [ 2.79, 7.41 ] |
| Charu 2007 | 203 | 6 (12.34) | 42 | 2.2 (7.8) | | 4.9 % | 3.80 [ 0.89, 6.71 ] |
| Christodoulou 2009 | 76 | 3.87 (11.99) | 76 | 0.71 (12.43) | | 2.7 % | 3.16 [ -0.72, 7.04 ] |
| Gordon 2008 | 150 | 4.8 (11.263) | 50 | 5 (11.473) | | 3.1 % | -0.20 [ -3.86, 3.46 ] |
| Hedenus 2003 | 152 | 2.68 (8.88) | 151 | 0.8 (9.71) | | 9.4 % | 1.88 [ -0.22, 3.98 ] |
| Hoskin 2009 | 151 | -2.6 (10.67) | 149 | -2.6 (12.45) | | 6.0 % | 0.0 [ -2.63, 2.63 ] |
| Iconomou 2003 | 57 | 4.6 (12.5) | 55 | -1 (12.8) | | 1.9 % | 5.60 [ 0.91, 10.29 ] |
| Littlewood 2001 | 200 | 3 (13.5) | 90 | -2.2 (12.5) | | 4.0 % | 5.20 [ 2.01, 8.39 ] |

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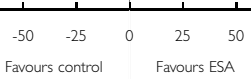
| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Osterborg 2002 | 133 | 5.2 (12.2) | 130 | 3 (12.1) | | 4.8 % | 2.20 [ -0.74, 5.14 ] |
| Pirker 2008 | 245 | 1.5 (13.15) | 239 | 0.7 (13.3) | | 7.4 % | 0.80 [ -1.56, 3.16 ] |
| Savonije 2005 | 156 | 3.48 (12.67) | 65 | -1.67 (11.61) | | 3.5 % | 5.15 [ 1.70, 8.60 ] |
| Smith 2008 | 343 | -0.02 (11.83) | 362 | 0.52 (10.41) | | 15.1 % | -0.54 [ -2.19, 1.11 ] |
| Tjulandin 2011 | 88 | 2.9 (7.9) | 84 | 0.6 (8.8) | | 6.6 % | 2.30 [ -0.20, 4.80 ] |
| Tsuboi 2009 | 61 | -0.5 (9.4) | 54 | -3.6 (9) | | 3.6 % | 3.10 [ -0.27, 6.47 ] |
| Witzig 2005 | 151 | 1.56 (12.07) | 148 | 0.31 (14.48) | | 4.5 % | 1.25 [ -1.77, 4.27 ] |
| **Subtotal (95% CI)** | **2438** | | **1974** | | | **89.1 %** | **2.17 [ 1.49, 2.85 ]** |
| Heterogeneity: $Chi^2$ = 35.81, df = 15 (P = 0.002); $I^2$ =58% | | | | | | | |
| Test for overall effect: Z = 6.26 (P < 0.00001) | | | | | | | |
| 2 abstract publication | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| 3 unpublished data | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| 4 FDA hearing | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| 5 clinical trial result information | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| 6 other source | | | | | | | |
| Kotasek 2003 | 189 | 3.4 (12.6) | 50 | 2.3 (11.6) | | 3.0 % | 1.10 [ -2.58, 4.78 ] |
| Vansteenkiste 2002 | 156 | 0.8 (10) | 158 | -0.6 (10.7) | | 7.8 % | 1.40 [ -0.89, 3.69 ] |
| **Subtotal (95% CI)** | **345** | | **208** | | | **10.9 %** | **1.32 [ -0.63, 3.26 ]** |
| Heterogeneity: $Chi^2$ = 0.02, df = 1 (P = 0.89); $I^2$ =0.0% | | | | | | | |
| Test for overall effect: Z = 1.33 (P = 0.18) | | | | | | | |
| **Total (95% CI)** | **2783** | | **2182** | | | **100.0 %** | **2.08 [ 1.43, 2.72 ]** |
| Heterogeneity: $Chi^2$ = 36.48, df = 17 (P = 0.004); $I^2$ =53% | | | | | | | |
| Test for overall effect: Z = 6.34 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 0.66, df = 1 (P = 0.42), $I^2$ =0.0% | | | | | | | |



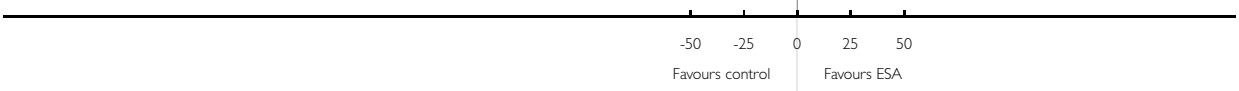
### Analysis 8.15. Comparison 8 Change in FACT-Fatigue 13, Outcome 15 Change in FACT-F 13 - type of data.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 8 Change in FACT-Fatigue 13

Outcome: 15 Change in FACT-F 13 - type of data

| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 Not imputed data | | | | | | | |
| Chang 2005 | 168 | 1.55 (10.52) | 170 | -3.55 (11.14) | | 7.7 % | 5.10 [ 2.79, 7.41 ] |
| Osterborg 2002 | 133 | 5.2 (12.2) | 130 | 3 (12.1) | | 4.8 % | 2.20 [ -0.74, 5.14 ] |
| Pirker 2008 | 245 | 1.5 (13.15) | 239 | 0.7 (13.3) | | 7.4 % | 0.80 [ -1.56, 3.16 ] |
| Savonije 2005 | 156 | 3.48 (12.67) | 65 | -1.67 (11.61) | | 3.5 % | 5.15 [ 1.70, 8.60 ] |
| Smith 2008 | 343 | -0.02 (11.83) | 362 | 0.52 (10.41) | | 15.1 % | -0.54 [ -2.19, 1.11 ] |
| Tjulandin 2011 | 88 | 2.9 (7.9) | 84 | 0.6 (8.8) | | 6.6 % | 2.30 [ -0.20, 4.80 ] |
| Tsuboi 2009 | 61 | -0.5 (9.4) | 54 | -3.6 (9) | | 3.6 % | 3.10 [ -0.27, 6.47 ] |
| **Subtotal (95% CI)** | **1194** | | **1104** | | | **48.7 %** | **1.88 [ 0.96, 2.80 ]** |
| Heterogeneity: Chi² = 20.66, df = 6 (P = 0.002); I² =71% | | | | | | | |
| Test for overall effect: Z = 4.02 (P = 0.000059) | | | | | | | |
| 2 Imputed data | | | | | | | |
| Boogaerts 2003 | 104 | 5.47 (14.47) | 109 | 0.41 (8.47) | | 4.0 % | 5.06 [ 1.86, 8.26 ] |
| Charu 2007 | 203 | 6 (12.34) | 42 | 2.2 (7.8) | | 4.9 % | 3.80 [ 0.89, 6.71 ] |
| Christodoulou 2009 | 76 | 3.87 (11.99) | 76 | 0.71 (12.43) | | 2.7 % | 3.16 [ -0.72, 7.04 ] |
| Gordon 2008 | 150 | 4.8 (11.263) | 50 | 5 (11.473) | | 3.1 % | -0.20 [ -3.86, 3.46 ] |
| Hedenus 2003 | 152 | 2.68 (8.88) | 151 | 0.8 (9.71) | | 9.4 % | 1.88 [ -0.22, 3.98 ] |
| Hoskin 2009 | 151 | -2.6 (10.67) | 149 | -2.6 (12.45) | | 6.0 % | 0.0 [ -2.63, 2.63 ] |
| Iconomou 2003 | 57 | 4.6 (12.5) | 55 | -1 (12.8) | | 1.9 % | 5.60 [ 0.91, 10.29 ] |
| Kotasek 2003 | 189 | 3.4 (12.6) | 50 | 2.3 (11.6) | | 3.0 % | 1.10 [ -2.58, 4.78 ] |
| Littlewood 2001 | 200 | 3 (13.5) | 90 | -2.2 (12.5) | | 4.0 % | 5.20 [ 2.01, 8.39 ] |
| Vansteenkiste 2002 | 156 | 0.8 (10) | 158 | -0.6 (10.7) | | 7.8 % | 1.40 [ -0.89, 3.69 ] |
| Witzig 2005 | 151 | 1.56 (12.07) | 148 | 0.31 (14.48) | | 4.5 % | 1.25 [ -1.77, 4.27 ] |
| **Subtotal (95% CI)** | **1589** | | **1078** | | | **51.3 %** | **2.26 [ 1.36, 3.15 ]** |
| Heterogeneity: Chi² = 15.50, df = 10 (P = 0.11); I² =35% | | | | | | | |
| Test for overall effect: Z = 4.94 (P < 0.00001) | | | | | | | |
| **Total (95% CI)** | **2783** | | **2182** | | | **100.0 %** | **2.08 [ 1.43, 2.72 ]** |
| Heterogeneity: Chi² = 36.48, df = 17 (P = 0.004); I² =53% | | | | | | | |
| Test for overall effect: Z = 6.34 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: Chi² = 0.33, df = 1 (P = 0.57), I² =0.0% | | | | | | | |



### Analysis 9.1. Comparison 9 Change in FACT-An 20, Outcome 1 Change in FACT-An (20 items) - overall.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 9 Change in FACT-An 20

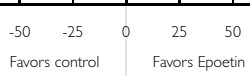
Outcome: 1 Change in FACT-An (20 items) - overall

| Study or subgroup | Epoetin N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Chang 2005 | 168 | 2.16 (12.84) | 170 | -4.43 (13.42) | | 32.2 % | 6.59 [ 3.79, 9.39 ] |
| Christodoulou 2009 | 63 | 4.64 (15.49) | 63 | 1.11 (15.61) | | 8.6 % | 3.53 [ -1.90, 8.96 ] |
| Littlewood 2001 | 200 | 4 (10.5) | 90 | -2.6 (10.9) | | 35.1 % | 6.60 [ 3.92, 9.28 ] |
| O'Shaughnessy 2005 | 40 | -3 (11.9) | 42 | -9.4 (13.8) | | 8.1 % | 6.40 [ 0.83, 11.97 ] |
| Savonije 2005 | 151 | 3.93 (15.63) | 64 | -1.91 (14.66) | | 13.2 % | 5.84 [ 1.47, 10.21 ] |
| Wright 2007 | 14 | 6.5 (14) | 20 | 2.6 (14.3) | | 2.7 % | 3.90 [ -5.75, 13.55 ] |
| **Total (95% CI)** | **636** | | **449** | | | **100.0 %** | **6.14 [ 4.55, 7.73 ]** |

Heterogeneity: $Chi^2 = 1.33$, df = 5 (P = 0.93); $I^2 = 0.0\%$

Test for overall effect: Z = 7.58 (P < 0.00001)

Test for subgroup differences: Not applicable



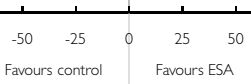
### Analysis 9.2. Comparison 9 Change in FACT-An 20, Outcome 2 Change in FACT-An 20 - baseline Hb.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 9 Change in FACT-An 20

Outcome: 2 Change in FACT-An 20 - baseline Hb

| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 Hb <= 10 g/dL | | | | | | | |
| Littlewood 2001 | 200 | 4 (10.5) | 90 | -2.6 (10.9) | | 35.1 % | 6.60 [ 3.92, 9.28 ] |
| **Subtotal (95% CI)** | **200** | | **90** | | | **35.1 %** | **6.60 [ 3.92, 9.28 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 4.82 (P < 0.00001) | | | | | | | |
| 2 Hb 10 to 12 g/dL | | | | | | | |
| Chang 2005 | 168 | 2.16 (12.84) | 170 | -4.43 (13.42) | | 32.2 % | 6.59 [ 3.79, 9.39 ] |
| Christodoulou 2009 | 63 | 4.64 (15.49) | 63 | 1.11 (15.61) | | 8.6 % | 3.53 [ -1.90, 8.96 ] |
| Savonije 2005 | 151 | 3.93 (15.63) | 64 | -1.91 (14.66) | | 13.2 % | 5.84 [ 1.47, 10.21 ] |
| Wright 2007 | 14 | 6.5 (14) | 20 | 2.6 (14.3) | | 2.7 % | 3.90 [ -5.75, 13.55 ] |
| **Subtotal (95% CI)** | **396** | | **317** | | | **56.7 %** | **5.82 [ 3.71, 7.93 ]** |
| Heterogeneity: $Chi^2$ = 1.13, df = 3 (P = 0.77); $I^2$ =0.0% | | | | | | | |
| Test for overall effect: Z = 5.41 (P < 0.00001) | | | | | | | |
| 3 Hb > 12 g/dL | | | | | | | |
| O'Shaughnessy 2005 | 40 | -3 (11.9) | 42 | -9.4 (13.8) | | 8.1 % | 6.40 [ 0.83, 11.97 ] |
| **Subtotal (95% CI)** | **40** | | **42** | | | **8.1 %** | **6.40 [ 0.83, 11.97 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 2.25 (P = 0.024) | | | | | | | |
| 4 Hb category unclear | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| **Total (95% CI)** | **636** | | **449** | | | **100.0 %** | **6.14 [ 4.55, 7.73 ]** |
| Heterogeneity: $Chi^2$ = 1.33, df = 5 (P = 0.93); $I^2$ =0.0% | | | | | | | |
| Test for overall effect: Z = 7.58 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 0.21, df = 2 (P = 0.90), $I^2$ =0.0% | | | | | | | |



## Analysis 9.3. Comparison 9 Change in FACT-An 20, Outcome 3 Change in FACT-An 20 - different malignancies.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 9 Change in FACT-An 20

Outcome: 3 Change in FACT-An 20 - different malignancies

| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 solid tumours | | | | | | | |
| Chang 2005 | 168 | 2.16 (12.84) | 170 | -4.43 (13.42) | | 32.2 % | 6.59 [ 3.79, 9.39 ] |
| Christodoulou 2009 | 63 | 4.64 (15.49) | 63 | 1.11 (15.61) | | 8.6 % | 3.53 [ -1.90, 8.96 ] |
| O'Shaughnessy 2005 | 40 | -3 (11.9) | 42 | -9.4 (13.8) | | 8.1 % | 6.40 [ 0.83, 11.97 ] |
| Savonije 2005 | 151 | 3.93 (15.63) | 64 | -1.91 (14.66) | | 13.2 % | 5.84 [ 1.47, 10.21 ] |
| Wright 2007 | 14 | 6.5 (14) | 20 | 2.6 (14.3) | | 2.7 % | 3.90 [ -5.75, 13.55 ] |
| **Subtotal (95% CI)** | **436** | | **359** | | | **64.9 %** | **5.90 [ 3.92, 7.87 ]** |
| Heterogeneity: $Chi^2$ = 1.16, df = 4 (P = 0.88); $I^2$ =0.0% | | | | | | | |
| Test for overall effect: Z = 5.86 (P < 0.00001) | | | | | | | |
| 2 haematological malignancies | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| 3 mixed | | | | | | | |
| Littlewood 2001 | 200 | 4 (10.5) | 90 | -2.6 (10.9) | | 35.1 % | 6.60 [ 3.92, 9.28 ] |
| **Subtotal (95% CI)** | **200** | | **90** | | | **35.1 %** | **6.60 [ 3.92, 9.28 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 4.82 (P < 0.00001) | | | | | | | |
| 4 unclear | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| **Total (95% CI)** | **636** | | **449** | | | **100.0 %** | **6.14 [ 4.55, 7.73 ]** |
| Heterogeneity: $Chi^2$ = 1.33, df = 5 (P = 0.93); $I^2$ =0.0% | | | | | | | |
| Test for overall effect: Z = 7.58 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 0.17, df = 1 (P = 0.68), $I^2$ =0.0% | | | | | | | |

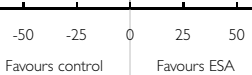
## Analysis 9.4. Comparison 9 Change in FACT-An 20, Outcome 4 Change in FACT-An 20 - age.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 9 Change in FACT-An 20

Outcome: 4 Change in FACT-An 20 - age

| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 only children < 18 years | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| 2 adults >= 18 years | | | | | | | |
| Christodoulou 2009 | 63 | 4.64 (15.49) | 63 | 1.11 (15.61) | | 8.6 % | 3.53 [ -1.90, 8.96 ] |
| Littlewood 2001 | 200 | 4 (10.5) | 90 | -2.6 (10.9) | | 35.1 % | 6.60 [ 3.92, 9.28 ] |
| O'Shaughnessy 2005 | 40 | -3 (11.9) | 42 | -9.4 (13.8) | | 8.1 % | 6.40 [ 0.83, 11.97 ] |
| Savonije 2005 | 151 | 3.93 (15.63) | 64 | -1.91 (14.66) | | 13.2 % | 5.84 [ 1.47, 10.21 ] |
| Wright 2007 | 14 | 6.5 (14) | 20 | 2.6 (14.3) | | 2.7 % | 3.90 [ -5.75, 13.55 ] |
| **Subtotal (95% CI)** | **468** | | **279** | | | **67.8 %** | **5.93 [ 4.00, 7.86 ]** |
| Heterogeneity: $Chi^2$ = 1.19, df = 4 (P = 0.88); $I^2$ =0.0% | | | | | | | |
| Test for overall effect: Z = 6.02 (P < 0.00001) | | | | | | | |
| 3 >70% non elderly 18-65 years | | | | | | | |
| Chang 2005 | 168 | 2.16 (12.84) | 170 | -4.43 (13.42) | | 32.2 % | 6.59 [ 3.79, 9.39 ] |
| **Subtotal (95% CI)** | **168** | | **170** | | | **32.2 %** | **6.59 [ 3.79, 9.39 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 4.61 (P < 0.00001) | | | | | | | |
| 4 only non-elderly adults | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| 5 >70% elderly >65 years | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| 6 only elderly > 65 years | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| **Total (95% CI)** | **636** | | **449** | | | **100.0 %** | **6.14 [ 4.55, 7.73 ]** |
| Heterogeneity: $Chi^2$ = 1.33, df = 5 (P = 0.93); $I^2$ =0.0% | | | | | | | |
| Test for overall effect: Z = 7.58 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 0.14, df = 1 (P = 0.70), $I^2$ =0.0% | | | | | | | |



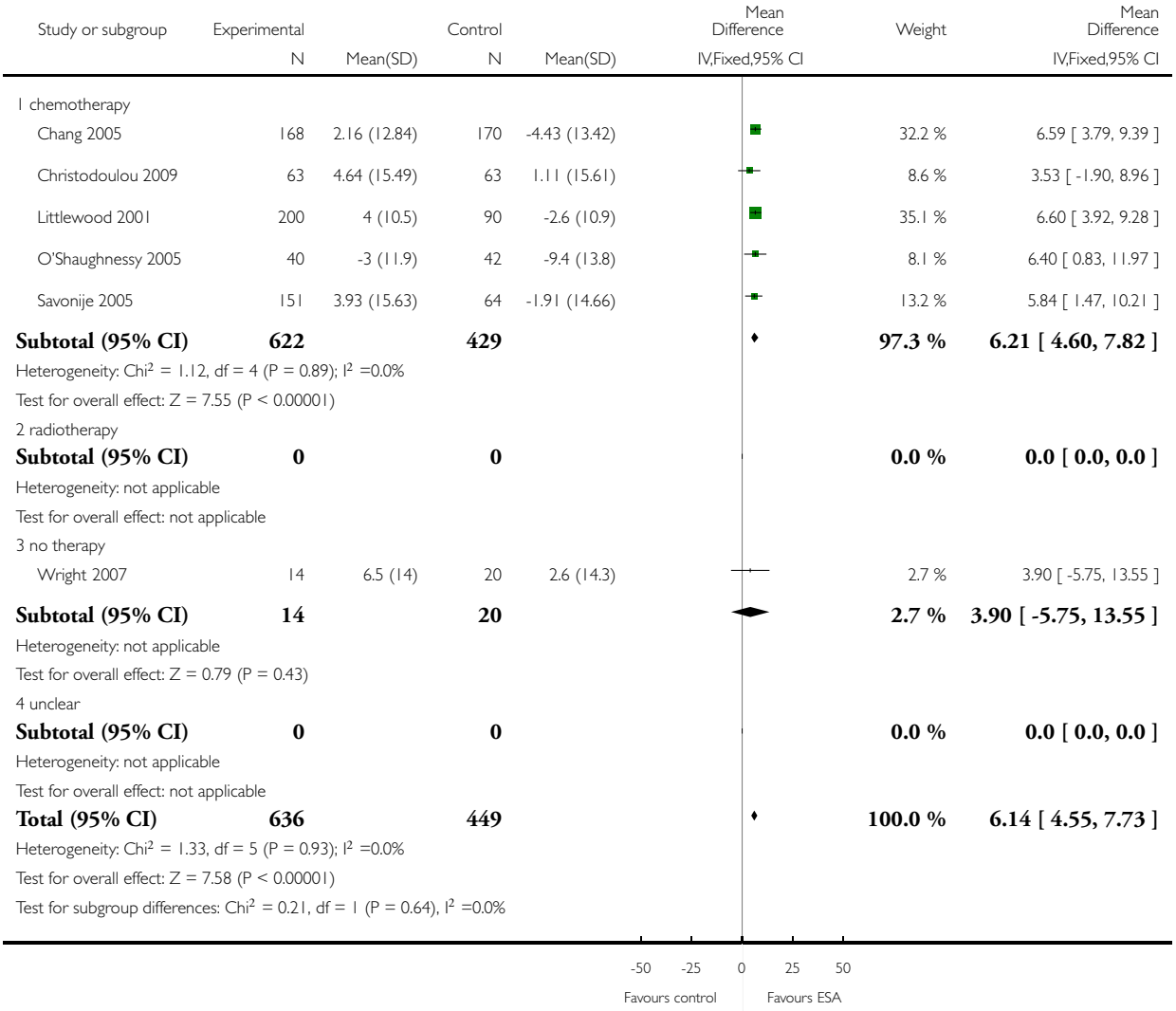
### Analysis 9.5. Comparison 9 Change in FACT-An 20, Outcome 5 Change in FACT-An 20 - different therapies.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 9 Change in FACT-An 20

Outcome: 5 Change in FACT-An 20 - different therapies

| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 chemotherapy | | | | | | | |
| Chang 2005 | 168 | 2.16 (12.84) | 170 | -4.43 (13.42) | | 32.2 % | 6.59 [ 3.79, 9.39 ] |
| Christodoulou 2009 | 63 | 4.64 (15.49) | 63 | 1.11 (15.61) | | 8.6 % | 3.53 [ -1.90, 8.96 ] |
| Littlewood 2001 | 200 | 4 (10.5) | 90 | -2.6 (10.9) | | 35.1 % | 6.60 [ 3.92, 9.28 ] |
| O'Shaughnessy 2005 | 40 | -3 (11.9) | 42 | -9.4 (13.8) | | 8.1 % | 6.40 [ 0.83, 11.97 ] |
| Savonije 2005 | 151 | 3.93 (15.63) | 64 | -1.91 (14.66) | | 13.2 % | 5.84 [ 1.47, 10.21 ] |
| **Subtotal (95% CI)** | **622** | | **429** | | | **97.3 %** | **6.21 [ 4.60, 7.82 ]** |
| Heterogeneity: $Chi^2$ = 1.12, df = 4 (P = 0.89); $I^2$ =0.0% | | | | | | | |
| Test for overall effect: Z = 7.55 (P < 0.00001) | | | | | | | |
| 2 radiotherapy | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| 3 no therapy | | | | | | | |
| Wright 2007 | 14 | 6.5 (14) | 20 | 2.6 (14.3) | | 2.7 % | 3.90 [ -5.75, 13.55 ] |
| **Subtotal (95% CI)** | **14** | | **20** | | | **2.7 %** | **3.90 [ -5.75, 13.55 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 0.79 (P = 0.43) | | | | | | | |
| 4 unclear | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| **Total (95% CI)** | **636** | | **449** | | | **100.0 %** | **6.14 [ 4.55, 7.73 ]** |
| Heterogeneity: $Chi^2$ = 1.33, df = 5 (P = 0.93); $I^2$ =0.0% | | | | | | | |
| Test for overall effect: Z = 7.58 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 0.21, df = 1 (P = 0.64), $I^2$ =0.0% | | | | | | | |



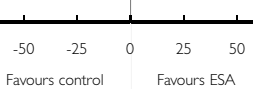
## Analysis 9.6. Comparison 9 Change in FACT-An 20, Outcome 6 Change in FACT-An 20 - different therapies differentiated.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 9 Change in FACT-An 20

Outcome: 6 Change in FACT-An 20 - different therapies differentiated

| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 chemotherapy, >70% with platinum | | | | | | | |
| Christodoulou 2009 | 21 | 4.78 (15.9) | 20 | 3.15 (14.62) | | 2.9 % | 1.63 [ -7.71, 10.97 ] |
| Savonije 2005 | 151 | 3.93 (15.63) | 64 | -1.91 (14.66) | | 13.2 % | 5.84 [ 1.47, 10.21 ] |
| **Subtotal (95% CI)** | **172** | | **84** | | | **16.1 %** | **5.08 [ 1.12, 9.04 ]** |
| Heterogeneity: Chi² = 0.64, df = 1 (P = 0.42); I² =0.0% | | | | | | | |
| Test for overall effect: Z = 2.52 (P = 0.012) | | | | | | | |
| 2 chemotherapy, <70% platinum containing | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| 3 chemotherapy without platinum (all patients) | | | | | | | |
| Chang 2005 | 168 | 2.16 (12.84) | 170 | -4.43 (13.42) | | 32.3 % | 6.59 [ 3.79, 9.39 ] |
| Christodoulou 2009 | 43 | 4.57 (15.07) | 42 | 0.13 (16.54) | | 5.6 % | 4.44 [ -2.29, 11.17 ] |
| Littlewood 2001 | 200 | 4 (10.5) | 90 | -2.6 (10.9) | | 35.2 % | 6.60 [ 3.92, 9.28 ] |
| O'Shaughnessy 2005 | 40 | -3 (11.9) | 42 | -9.4 (13.8) | | 8.2 % | 6.40 [ 0.83, 11.97 ] |
| **Subtotal (95% CI)** | **451** | | **344** | | | **81.2 %** | **6.43 [ 4.66, 8.19 ]** |
| Heterogeneity: Chi² = 0.36, df = 3 (P = 0.95); I² =0.0% | | | | | | | |
| Test for overall effect: Z = 7.14 (P < 0.00001) | | | | | | | |
| 4 chemotherapy, platinum and non-platinum containing, no numbers given | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| 5 radiochemotherapy NEW | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| 6 radiotherapy | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |

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(. . . *Continued*)

| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 7 no therapy | | | | | | | |
| Wright 2007 | 14 | 6.5 (14) | 20 | 2.6 (14.3) | | 2.7 % | 3.90 [ -5.75, 13.55 ] |
| **Subtotal (95% CI)** | **14** | | **20** | | | **2.7 %** | **3.90 [ -5.75, 13.55 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 0.79 (P = 0.43) | | | | | | | |
| 8 unclear | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| 9 chemotherapy no details given | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| **Total (95% CI)** | **637** | | **448** | | | **100.0 %** | **6.14 [ 4.55, 7.73 ]** |
| Heterogeneity: $Chi^2$ = 1.59, df = 6 (P = 0.95); $I^2$ =0.0% | | | | | | | |
| Test for overall effect: Z = 7.57 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 0.58, df = 2 (P = 0.75), $I^2$ =0.0% | | | | | | | |

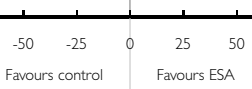
## Analysis 9.7. Comparison 9 Change in FACT-An 20, Outcome 7 Change in FACT-An 20 - epoetin versus darbepoetin.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 9 Change in FACT-An 20

Outcome: 7 Change in FACT-An 20 - epoetin versus darbepoetin

| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 Epoetin | | | | | | | |
| Chang 2005 | 168 | 2.16 (12.84) | 170 | -4.43 (13.42) | | 32.2 % | 6.59 [ 3.79, 9.39 ] |
| Christodoulou 2009 | 63 | 4.64 (15.49) | 63 | 1.11 (15.61) | | 8.6 % | 3.53 [ -1.90, 8.96 ] |
| Littlewood 2001 | 200 | 4 (10.5) | 90 | -2.6 (10.9) | | 35.1 % | 6.60 [ 3.92, 9.28 ] |
| O'Shaughnessy 2005 | 40 | -3 (11.9) | 42 | -9.4 (13.8) | | 8.1 % | 6.40 [ 0.83, 11.97 ] |
| Savonije 2005 | 151 | 3.93 (15.63) | 64 | -1.91 (14.66) | | 13.2 % | 5.84 [ 1.47, 10.21 ] |
| Wright 2007 | 14 | 6.5 (14) | 20 | 2.6 (14.3) | | 2.7 % | 3.90 [ -5.75, 13.55 ] |
| **Subtotal (95% CI)** | **636** | | **449** | | | **100.0 %** | **6.14 [ 4.55, 7.73 ]** |
| Heterogeneity: $Chi^2$ = 1.33, df = 5 (P = 0.93); $I^2$ =0.0% | | | | | | | |
| Test for overall effect: Z = 7.58 (P < 0.00001) | | | | | | | |
| 2 Darbepoetin | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| **Total (95% CI)** | **636** | | **449** | | | **100.0 %** | **6.14 [ 4.55, 7.73 ]** |
| Heterogeneity: $Chi^2$ = 1.33, df = 5 (P = 0.93); $I^2$ =0.0% | | | | | | | |
| Test for overall effect: Z = 7.58 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | |



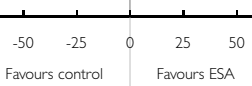
## Analysis 9.8. Comparison 9 Change in FACT-An 20, Outcome 8 Change in FACT-An 20 - duration of ESA medication.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 9 Change in FACT-An 20

Outcome: 8 Change in FACT-An 20 - duration of ESA medication

| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 6 to 9 weeks | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| 2 12 to 16 weeks | | | | | | | |
| Chang 2005 | 168 | 2.16 (12.84) | 170 | -4.43 (13.42) | | 32.2 % | 6.59 [ 3.79, 9.39 ] |
| Christodoulou 2009 | 63 | 4.64 (15.49) | 63 | 1.11 (15.61) | | 8.6 % | 3.53 [ -1.90, 8.96 ] |
| O'Shaughnessy 2005 | 40 | -3 (11.9) | 42 | -9.4 (13.8) | | 8.1 % | 6.40 [ 0.83, 11.97 ] |
| Savonije 2005 | 151 | 3.93 (15.63) | 64 | -1.91 (14.66) | | 13.2 % | 5.84 [ 1.47, 10.21 ] |
| Wright 2007 | 14 | 6.5 (14) | 20 | 2.6 (14.3) | | 2.7 % | 3.90 [ -5.75, 13.55 ] |
| **Subtotal (95% CI)** | **436** | | **359** | | | **64.9 %** | **5.90 [ 3.92, 7.87 ]** |
| Heterogeneity: $Chi^2$ = 1.16, df = 4 (P = 0.88); $I^2$ =0.0% | | | | | | | |
| Test for overall effect: Z = 5.86 (P < 0.00001) | | | | | | | |
| 3 more than 17 weeks | | | | | | | |
| Littlewood 2001 | 200 | 4 (10.5) | 90 | -2.6 (10.9) | | 35.1 % | 6.60 [ 3.92, 9.28 ] |
| **Subtotal (95% CI)** | **200** | | **90** | | | **35.1 %** | **6.60 [ 3.92, 9.28 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 4.82 (P < 0.00001) | | | | | | | |
| 4 unclear | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| **Total (95% CI)** | **636** | | **449** | | | **100.0 %** | **6.14 [ 4.55, 7.73 ]** |
| Heterogeneity: $Chi^2$ = 1.33, df = 5 (P = 0.93); $I^2$ =0.0% | | | | | | | |
| Test for overall effect: Z = 7.58 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 0.17, df = 1 (P = 0.68), $I^2$ =0.0% | | | | | | | |



## Analysis 9.9. Comparison 9 Change in FACT-An 20, Outcome 9 Change in FACT-An 20 - iron supplementation.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 9 Change in FACT-An 20

Outcome: 9 Change in FACT-An 20 - iron supplementation

| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 fixed iron supplementation | | | | | | | |
| Christodoulou 2009 | 63 | 4.64 (15.49) | 63 | 1.11 (15.61) | | 8.6 % | 3.53 [ -1.90, 8.96 ] |
| **Subtotal (95% CI)** | **63** | | **63** | | | **8.6 %** | **3.53 [ -1.90, 8.96 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 1.27 (P = 0.20) | | | | | | | |
| 2 iron supplementation as necessary | | | | | | | |
| Chang 2005 | 168 | 2.16 (12.84) | 170 | -4.43 (13.42) | | 32.2 % | 6.59 [ 3.79, 9.39 ] |
| Littlewood 2001 | 200 | 4 (10.5) | 90 | -2.6 (10.9) | | 35.1 % | 6.60 [ 3.92, 9.28 ] |
| O'Shaughnessy 2005 | 40 | -3 (11.9) | 42 | -9.4 (13.8) | | 8.1 % | 6.40 [ 0.83, 11.97 ] |
| Wright 2007 | 14 | 6.5 (14) | 20 | 2.6 (14.3) | | 2.7 % | 3.90 [ -5.75, 13.55 ] |
| **Subtotal (95% CI)** | **422** | | **322** | | | **78.2 %** | **6.48 [ 4.68, 8.28 ]** |
| Heterogeneity: $Chi^2$ = 0.29, df = 3 (P = 0.96); $I^2$ =0.0% | | | | | | | |
| Test for overall effect: Z = 7.07 (P < 0.00001) | | | | | | | |
| 3 no explicit statement on iron supplementation or no iron given | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| 4 explicitly stated NO IRON | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| 5 unclear | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| 6 iron given differently in both study arms new | | | | | | | |
| Savonije 2005 | 151 | 3.93 (15.63) | 64 | -1.91 (14.66) | | 13.2 % | 5.84 [ 1.47, 10.21 ] |
| **Subtotal (95% CI)** | **151** | | **64** | | | **13.2 %** | **5.84 [ 1.47, 10.21 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 2.62 (P = 0.0088) | | | | | | | |
| **Total (95% CI)** | **636** | | **449** | | | **100.0 %** | **6.14 [ 4.55, 7.73 ]** |
| Heterogeneity: $Chi^2$ = 1.33, df = 5 (P = 0.93); $I^2$ =0.0% | | | | | | | |
| Test for overall effect: Z = 7.58 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 1.04, df = 2 (P = 0.59), $I^2$ =0.0% | | | | | | | |

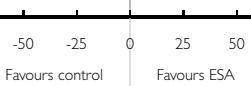
### Analysis 9.10. Comparison 9 Change in FACT-An 20, Outcome 10 Change in FACT-An 20 - allocation concealment.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 9 Change in FACT-An 20

Outcome: 10 Change in FACT-An 20 - allocation concealment

| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 adequate | | | | | | | |
| Chang 2005 | 168 | 2.16 (12.84) | 170 | -4.43 (13.42) | | 32.2 % | 6.59 [ 3.79, 9.39 ] |
| Christodoulou 2009 | 63 | 4.64 (15.49) | 63 | 1.11 (15.61) | | 8.6 % | 3.53 [ -1.90, 8.96 ] |
| Littlewood 2001 | 200 | 4 (10.5) | 90 | -2.6 (10.9) | | 35.1 % | 6.60 [ 3.92, 9.28 ] |
| O'Shaughnessy 2005 | 40 | -3 (11.9) | 42 | -9.4 (13.8) | | 8.1 % | 6.40 [ 0.83, 11.97 ] |
| Savonije 2005 | 151 | 3.93 (15.63) | 64 | -1.91 (14.66) | | 13.2 % | 5.84 [ 1.47, 10.21 ] |
| Wright 2007 | 14 | 6.5 (14) | 20 | 2.6 (14.3) | | 2.7 % | 3.90 [ -5.75, 13.55 ] |
| **Subtotal (95% CI)** | **636** | | **449** | | | **100.0 %** | **6.14 [ 4.55, 7.73 ]** |
| Heterogeneity: $Chi^2$ = 1.33, df = 5 (P = 0.93); $I^2$ =0.0% | | | | | | | |
| Test for overall effect: Z = 7.58 (P < 0.00001) | | | | | | | |
| 2 unclear | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| 3 unclear wether adequate or unclear :) | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| **Total (95% CI)** | **636** | | **449** | | | **100.0 %** | **6.14 [ 4.55, 7.73 ]** |
| Heterogeneity: $Chi^2$ = 1.33, df = 5 (P = 0.93); $I^2$ =0.0% | | | | | | | |
| Test for overall effect: Z = 7.58 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | |



## Analysis 9.11. Comparison 9 Change in FACT-An 20, Outcome 11 Change in FACT-An 20 - masking.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 9 Change in FACT-An 20

Outcome: 11 Change in FACT-An 20 - masking

| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 double-blind | | | | | | | |
| Littlewood 2001 | 200 | 4 (10.5) | 90 | -2.6 (10.9) | | 35.1 % | 6.60 [ 3.92, 9.28 ] |
| O'Shaughnessy 2005 | 40 | -3 (11.9) | 42 | -9.4 (13.8) | | 8.1 % | 6.40 [ 0.83, 11.97 ] |
| Wright 2007 | 14 | 6.5 (14) | 20 | 2.6 (14.3) | | 2.7 % | 3.90 [ -5.75, 13.55 ] |
| **Subtotal (95% CI)** | **254** | | **152** | | | **46.0 %** | **6.41 [ 4.06, 8.75 ]** |
| Heterogeneity: $Chi^2$ = 0.28, df = 2 (P = 0.87); $I^2$ =0.0% | | | | | | | |
| Test for overall effect: Z = 5.36 (P < 0.00001) | | | | | | | |
| 2 unblinded | | | | | | | |
| Chang 2005 | 168 | 2.16 (12.84) | 170 | -4.43 (13.42) | | 32.2 % | 6.59 [ 3.79, 9.39 ] |
| Christodoulou 2009 | 63 | 4.64 (15.49) | 63 | 1.11 (15.61) | | 8.6 % | 3.53 [ -1.90, 8.96 ] |
| Savonije 2005 | 151 | 3.93 (15.63) | 64 | -1.91 (14.66) | | 13.2 % | 5.84 [ 1.47, 10.21 ] |
| **Subtotal (95% CI)** | **382** | | **297** | | | **54.0 %** | **5.92 [ 3.76, 8.08 ]** |
| Heterogeneity: $Chi^2$ = 0.97, df = 2 (P = 0.62); $I^2$ =0.0% | | | | | | | |
| Test for overall effect: Z = 5.37 (P < 0.00001) | | | | | | | |
| **Total (95% CI)** | **636** | | **449** | | | **100.0 %** | **6.14 [ 4.55, 7.73 ]** |
| Heterogeneity: $Chi^2$ = 1.33, df = 5 (P = 0.93); $I^2$ =0.0% | | | | | | | |
| Test for overall effect: Z = 7.58 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 0.09, df = 1 (P = 0.77), $I^2$ =0.0% | | | | | | | |

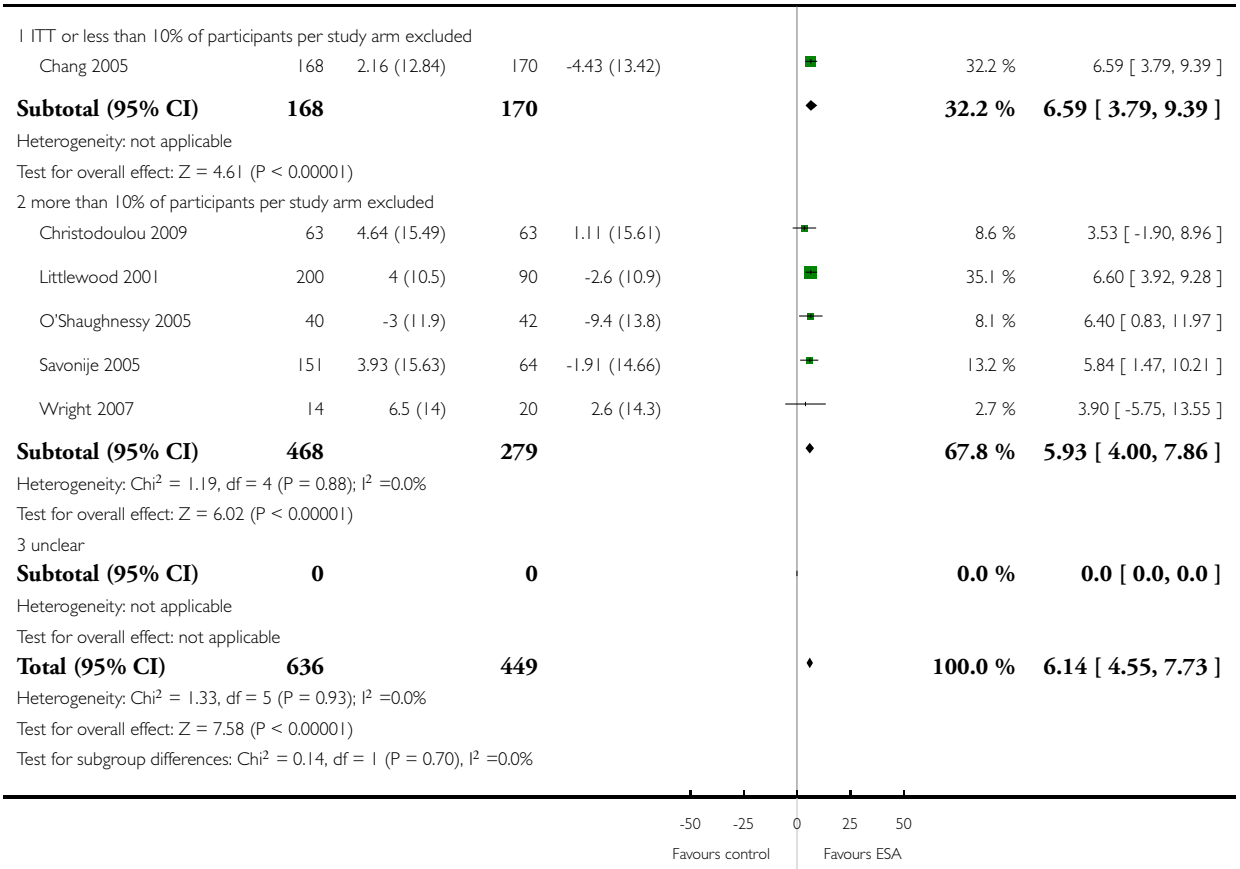
## Analysis 9.12. Comparison 9 Change in FACT-An 20, Outcome 12 Change in FACT-An 20 - intention-to treat.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 9 Change in FACT-An 20

Outcome: 12 Change in FACT-An 20 - intention-to treat

| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 ITT or less than 10% of participants per study arm excluded | | | | | | | |
| Chang 2005 | 168 | 2.16 (12.84) | 170 | -4.43 (13.42) | | 32.2 % | 6.59 [ 3.79, 9.39 ] |
| **Subtotal (95% CI)** | **168** | | **170** | | | **32.2 %** | **6.59 [ 3.79, 9.39 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 4.61 (P < 0.00001) | | | | | | | |
| 2 more than 10% of participants per study arm excluded | | | | | | | |
| Christodoulou 2009 | 63 | 4.64 (15.49) | 63 | 1.11 (15.61) | | 8.6 % | 3.53 [ -1.90, 8.96 ] |
| Littlewood 2001 | 200 | 4 (10.5) | 90 | -2.6 (10.9) | | 35.1 % | 6.60 [ 3.92, 9.28 ] |
| O'Shaughnessy 2005 | 40 | -3 (11.9) | 42 | -9.4 (13.8) | | 8.1 % | 6.40 [ 0.83, 11.97 ] |
| Savonije 2005 | 151 | 3.93 (15.63) | 64 | -1.91 (14.66) | | 13.2 % | 5.84 [ 1.47, 10.21 ] |
| Wright 2007 | 14 | 6.5 (14) | 20 | 2.6 (14.3) | | 2.7 % | 3.90 [ -5.75, 13.55 ] |
| **Subtotal (95% CI)** | **468** | | **279** | | | **67.8 %** | **5.93 [ 4.00, 7.86 ]** |
| Heterogeneity: $Chi^2$ = 1.19, df = 4 (P = 0.88); $I^2$ =0.0% | | | | | | | |
| Test for overall effect: Z = 6.02 (P < 0.00001) | | | | | | | |
| 3 unclear | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| **Total (95% CI)** | **636** | | **449** | | | **100.0 %** | **6.14 [ 4.55, 7.73 ]** |
| Heterogeneity: $Chi^2$ = 1.33, df = 5 (P = 0.93); $I^2$ =0.0% | | | | | | | |
| Test for overall effect: Z = 7.58 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 0.14, df = 1 (P = 0.70), $I^2$ =0.0% | | | | | | | |



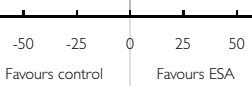
### Analysis 9.13. Comparison 9 Change in FACT-An 20, Outcome 13 Change in FACT-An 20 - publication.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 9 Change in FACT-An 20

Outcome: 13 Change in FACT-An 20 - publication

| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 full text publication | | | | | | | |
| Chang 2005 | 168 | 2.16 (12.84) | 170 | -4.43 (13.42) | | 32.2 % | 6.59 [ 3.79, 9.39 ] |
| Christodoulou 2009 | 63 | 4.64 (15.49) | 63 | 1.11 (15.61) | | 8.6 % | 3.53 [ -1.90, 8.96 ] |
| Littlewood 2001 | 200 | 4 (10.5) | 90 | -2.6 (10.9) | | 35.1 % | 6.60 [ 3.92, 9.28 ] |
| O'Shaughnessy 2005 | 40 | -3 (11.9) | 42 | -9.4 (13.8) | | 8.1 % | 6.40 [ 0.83, 11.97 ] |
| Savonije 2005 | 151 | 3.93 (15.63) | 64 | -1.91 (14.66) | | 13.2 % | 5.84 [ 1.47, 10.21 ] |
| Wright 2007 | 14 | 6.5 (14) | 20 | 2.6 (14.3) | | 2.7 % | 3.90 [ -5.75, 13.55 ] |
| **Subtotal (95% CI)** | **636** | | **449** | | | **100.0 %** | **6.14 [ 4.55, 7.73 ]** |
| Heterogeneity: $Chi^2$ = 1.33, df = 5 (P = 0.93); $I^2$ =0.0% | | | | | | | |
| Test for overall effect: Z = 7.58 (P < 0.00001) | | | | | | | |
| 2 abstract publication | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| 3 unpublished data | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| 4 FDA hearing | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| 5 clinical trial result information | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| **Total (95% CI)** | **636** | | **449** | | | **100.0 %** | **6.14 [ 4.55, 7.73 ]** |
| Heterogeneity: $Chi^2$ = 1.33, df = 5 (P = 0.93); $I^2$ =0.0% | | | | | | | |
| Test for overall effect: Z = 7.58 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | |



### Analysis 9.14. Comparison 9 Change in FACT-An 20, Outcome 14 Change in FACT-An 20 - data type.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 9 Change in FACT-An 20

Outcome: 14 Change in FACT-An 20 - data type

| Study or subgroup | ESA N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 Not imputed data | | | | | | | |
| Chang 2005 | 168 | 2.16 (12.84) | 170 | -4.43 (13.42) | | 32.2 % | 6.59 [ 3.79, 9.39 ] |
| O'Shaughnessy 2005 | 40 | -3 (11.9) | 42 | -9.4 (13.8) | | 8.1 % | 6.40 [ 0.83, 11.97 ] |
| Savonije 2005 | 151 | 3.93 (15.63) | 64 | -1.91 (14.66) | | 13.2 % | 5.84 [ 1.47, 10.21 ] |
| **Subtotal (95% CI)** | **359** | | **276** | | | **53.6 %** | **6.38 [ 4.20, 8.55 ]** |
| Heterogeneity: $Chi^2$ = 0.08, df = 2 (P = 0.96); $I^2$ =0.0% | | | | | | | |
| Test for overall effect: Z = 5.76 (P < 0.00001) | | | | | | | |
| 2 Imputed data | | | | | | | |
| Christodoulou 2009 | 63 | 4.64 (15.49) | 63 | 1.11 (15.61) | | 8.6 % | 3.53 [ -1.90, 8.96 ] |
| Littlewood 2001 | 200 | 4 (10.5) | 90 | -2.6 (10.9) | | 35.1 % | 6.60 [ 3.92, 9.28 ] |
| Wright 2007 | 14 | 6.5 (14) | 20 | 2.6 (14.3) | | 2.7 % | 3.90 [ -5.75, 13.55 ] |
| **Subtotal (95% CI)** | **277** | | **173** | | | **46.4 %** | **5.88 [ 3.54, 8.21 ]** |
| Heterogeneity: $Chi^2$ = 1.16, df = 2 (P = 0.56); $I^2$ =0.0% | | | | | | | |
| Test for overall effect: Z = 4.94 (P < 0.00001) | | | | | | | |
| **Total (95% CI)** | **636** | | **449** | | | **100.0 %** | **6.14 [ 4.55, 7.73 ]** |
| Heterogeneity: $Chi^2$ = 1.33, df = 5 (P = 0.93); $I^2$ =0.0% | | | | | | | |
| Test for overall effect: Z = 7.58 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 0.09, df = 1 (P = 0.76), $I^2$ =0.0% | | | | | | | |

## Analysis 10.1. Comparison 10 Change in FACT-An Total 47, Outcome 1 Change in FACT-An Total (47 items) - overall.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 10 Change in FACT-An Total 47

Outcome: 1 Change in FACT-An Total (47 items) - overall

| Study or subgroup | Epoetin N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Christodoulou 2009 | 64 | 9.93 (31.22) | 63 | 2.18 (29.45) | | 4.9 % | 7.75 [ -2.80, 18.30 ] |
| Hoskin 2009 | 151 | -3.3 (26.41) | 149 | -5.2 (27.43) | | 14.6 % | 1.90 [ -4.19, 7.99 ] |
| Huddart 2002 | 45 | 7.65 (32.87) | 45 | 2.94 (19.72) | | 4.3 % | 4.71 [ -6.49, 15.91 ] |
| Krzakowski 2008a | 104 | 2.7 (25.4) | 52 | 3.12 (23.83) | | 8.3 % | -0.42 [ -8.53, 7.69 ] |
| Krzakowski 2008b | 105 | 3.6 (23.4) | 52 | 3.12 (23.83) | | 8.8 % | 0.48 [ -7.39, 8.35 ] |
| Mystakidou 2005 | 50 | 43.3 (18.4) | 50 | 13.4 (14.2) | | 13.1 % | 29.90 [ 23.46, 36.34 ] |
| Osterborg 2002 | 105 | 14.8 (28) | 101 | 8.7 (28.9) | | 9.0 % | 6.10 [ -1.67, 13.87 ] |
| Savonije 2005 | 155 | 3.98 (26.75) | 65 | -3.69 (24.38) | | 10.3 % | 7.67 [ 0.40, 14.94 ] |
| Tjulandin 2011 | 88 | 6.3 (21.7) | 84 | 0.6 (22) | | 12.7 % | 5.70 [ -0.83, 12.23 ] |
| Witzig 2005 | 148 | 0.56 (28.67) | 139 | 0 (24.87) | | 14.1 % | 0.56 [ -5.64, 6.76 ] |
| **Total (95% CI)** | **1015** | | **800** | | | **100.0 %** | **6.92 [ 4.59, 9.25 ]** |

Heterogeneity: $Chi^2$ = 61.64, df = 9 (P<0.00001); $I^2$ =85%

Test for overall effect: Z = 5.82 (P < 0.00001)

Test for subgroup differences: Not applicable

## Analysis 10.2. Comparison 10 Change in FACT-An Total 47, Outcome 2 Change in FACT-An Total 47- sensitivity analysis.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 10 Change in FACT-An Total 47

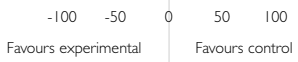
Outcome: 2 Change in FACT-An Total 47- sensitivity analysis

| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Christodoulou 2009 | 64 | 9.93 (31.22) | 63 | 2.18 (29.45) | | 5.6 % | 7.75 [ -2.80, 18.30 ] |
| Hoskin 2009 | 151 | -3.3 (26.41) | 149 | -5.2 (27.43) | | 16.8 % | 1.90 [ -4.19, 7.99 ] |
| Huddart 2002 | 45 | 7.65 (32.87) | 45 | 2.94 (19.72) | | 5.0 % | 4.71 [ -6.49, 15.91 ] |
| Krzakowski 2008a | 104 | 2.7 (25.4) | 52 | 3.12 (23.83) | | 9.5 % | -0.42 [ -8.53, 7.69 ] |
| Krzakowski 2008b | 105 | 3.6 (23.4) | 52 | 3.12 (23.83) | | 10.1 % | 0.48 [ -7.39, 8.35 ] |
| Osterborg 2002 | 105 | 14.8 (28) | 101 | 8.7 (28.9) | | 10.3 % | 6.10 [ -1.67, 13.87 ] |
| Savonije 2005 | 155 | 3.98 (26.75) | 65 | -3.69 (24.38) | | 11.8 % | 7.67 [ 0.40, 14.94 ] |
| Tjulandin 2011 | 88 | 6.3 (21.7) | 84 | 0.6 (22) | | 14.6 % | 5.70 [ -0.83, 12.23 ] |
| Witzig 2005 | 148 | 0.56 (28.67) | 139 | 0 (24.87) | | 16.3 % | 0.56 [ -5.64, 6.76 ] |
| **Total (95% CI)** | **965** | | **750** | | | **100.0 %** | **3.46 [ 0.96, 5.96 ]** |

Heterogeneity: $Chi^2 = 5.39$, df = 8 (P = 0.72); $I^2 = 0.0\%$

Test for overall effect: Z = 2.71 (P = 0.0067)

Test for subgroup differences: Not applicable



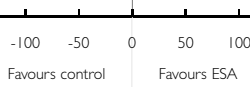
## Analysis 10.3. Comparison 10 Change in FACT-An Total 47, Outcome 3 Change in FACT-An Total 47 - baseline Hb.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 10 Change in FACT-An Total 47

Outcome: 3 Change in FACT-An Total 47 - baseline Hb

| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 Hb <= 10 g/dL | | | | | | | |
| Krzakowski 2008a | 104 | 2.7 (25.4) | 52 | 3.12 (23.83) | | 8.3 % | -0.42 [ -8.53, 7.69 ] |
| Krzakowski 2008b | 105 | 3.6 (23.4) | 52 | 3.12 (23.83) | | 8.8 % | 0.48 [ -7.39, 8.35 ] |
| Osterborg 2002 | 105 | 14.8 (28) | 101 | 8.7 (28.9) | | 9.0 % | 6.10 [ -1.67, 13.87 ] |
| Tjulandin 2011 | 88 | 6.3 (21.7) | 84 | 0.6 (22) | | 12.7 % | 5.70 [ -0.83, 12.23 ] |
| Witzig 2005 | 148 | 0.56 (28.67) | 139 | 0 (24.87) | | 14.1 % | 0.56 [ -5.64, 6.76 ] |
| **Subtotal (95% CI)** | **550** | | **428** | | | **52.8 %** | **2.57 [ -0.63, 5.78 ]** |
| Heterogeneity: $Chi^2$ = 2.87, df = 4 (P = 0.58); $I^2$ =0.0% | | | | | | | |
| Test for overall effect: Z = 1.57 (P = 0.12) | | | | | | | |
| 2 Hb 10 to 12 g/dL | | | | | | | |
| Christodoulou 2009 | 64 | 9.93 (31.22) | 63 | 2.18 (29.45) | | 4.9 % | 7.75 [ -2.80, 18.30 ] |
| Huddart 2002 | 45 | 7.65 (32.87) | 45 | 2.94 (19.72) | | 4.3 % | 4.71 [ -6.49, 15.91 ] |
| Mystakidou 2005 | 50 | 43.3 (18.4) | 50 | 13.4 (14.2) | | 13.1 % | 29.90 [ 23.46, 36.34 ] |
| Savonije 2005 | 155 | 3.98 (26.75) | 65 | -3.69 (24.38) | | 10.3 % | 7.67 [ 0.40, 14.94 ] |
| **Subtotal (95% CI)** | **314** | | **223** | | | **32.6 %** | **16.22 [ 12.14, 20.30 ]** |
| Heterogeneity: $Chi^2$ = 29.17, df = 3 (P<0.00001); $I^2$ =90% | | | | | | | |
| Test for overall effect: Z = 7.79 (P < 0.00001) | | | | | | | |
| 3 Hb > 12 g/dL | | | | | | | |
| Hoskin 2009 | 151 | -3.3 (26.41) | 149 | -5.2 (27.43) | | 14.6 % | 1.90 [ -4.19, 7.99 ] |
| **Subtotal (95% CI)** | **151** | | **149** | | | **14.6 %** | **1.90 [ -4.19, 7.99 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 0.61 (P = 0.54) | | | | | | | |
| 4 Hb category unclear | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| **Total (95% CI)** | **1015** | | **800** | | | **100.0 %** | **6.92 [ 4.59, 9.25 ]** |
| Heterogeneity: $Chi^2$ = 61.64, df = 9 (P<0.00001); $I^2$ =85% | | | | | | | |
| Test for overall effect: Z = 5.82 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 29.60, df = 2 (P = 0.00), $I^2$ =93% | | | | | | | |



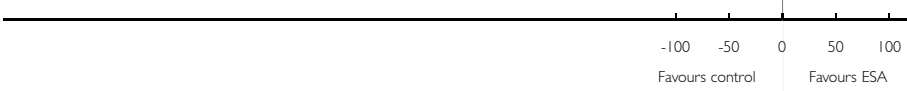
## Analysis 10.4. Comparison 10 Change in FACT-An Total 47, Outcome 4 Change in FACT-An Total 47 - different malignancies.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 10 Change in FACT-An Total 47

Outcome: 4 Change in FACT-An Total 47 - different malignancies

| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 solid tumours | | | | | | | |
| Christodoulou 2009 | 64 | 9.93 (31.22) | 63 | 2.18 (29.45) | | 4.9 % | 7.75 [ -2.80, 18.30 ] |
| Hoskin 2009 | 151 | -3.3 (26.41) | 149 | -5.2 (27.43) | | 14.6 % | 1.90 [ -4.19, 7.99 ] |
| Huddart 2002 | 45 | 7.65 (32.87) | 45 | 2.94 (19.72) | | 4.3 % | 4.71 [ -6.49, 15.91 ] |
| Krzakowski 2008a | 104 | 2.7 (25.4) | 52 | 3.12 (23.83) | | 8.3 % | -0.42 [ -8.53, 7.69 ] |
| Krzakowski 2008b | 105 | 3.6 (23.4) | 52 | 3.12 (23.83) | | 8.8 % | 0.48 [ -7.39, 8.35 ] |
| Mystakidou 2005 | 50 | 43.3 (18.4) | 50 | 13.4 (14.2) | | 13.1 % | 29.90 [ 23.46, 36.34 ] |
| Savonije 2005 | 155 | 3.98 (26.75) | 65 | -3.69 (24.38) | | 10.3 % | 7.67 [ 0.40, 14.94 ] |
| Witzig 2005 | 148 | 0.56 (28.67) | 139 | 0 (24.87) | | 14.1 % | 0.56 [ -5.64, 6.76 ] |
| **Subtotal (95% CI)** | **822** | | **615** | | | **78.3 %** | **7.21 [ 4.58, 9.84 ]** |
| Heterogeneity: $Chi^2$ = 61.41, df = 7 (P<0.00001); $I^2$ =89% | | | | | | | |
| Test for overall effect: Z = 5.37 (P < 0.00001) | | | | | | | |
| 2 haematological malignancies | | | | | | | |
| Osterborg 2002 | 105 | 14.8 (28) | 101 | 8.7 (28.9) | | 9.0 % | 6.10 [ -1.67, 13.87 ] |
| **Subtotal (95% CI)** | **105** | | **101** | | | **9.0 %** | **6.10 [ -1.67, 13.87 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 1.54 (P = 0.12) | | | | | | | |
| 3 mixed | | | | | | | |
| Tjulandin 2011 | 88 | 6.3 (21.7) | 84 | 0.6 (22) | | 12.7 % | 5.70 [ -0.83, 12.23 ] |
| **Subtotal (95% CI)** | **88** | | **84** | | | **12.7 %** | **5.70 [ -0.83, 12.23 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 1.71 (P = 0.087) | | | | | | | |
| 4 unclear | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| **Total (95% CI)** | **1015** | | **800** | | | **100.0 %** | **6.92 [ 4.59, 9.25 ]** |
| Heterogeneity: $Chi^2$ = 61.64, df = 9 (P<0.00001); $I^2$ =85% | | | | | | | |
| Test for overall effect: Z = 5.82 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 0.22, df = 2 (P = 0.89), $I^2$ =0.0% | | | | | | | |



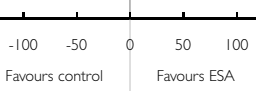
## Analysis 10.5. Comparison 10 Change in FACT-An Total 47, Outcome 5 Change in FACT-An Total 47 - age.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 10 Change in FACT-An Total 47

Outcome: 5 Change in FACT-An Total 47 - age

| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 only children < 18 years | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| 2 adults >= 18 years | | | | | | | |
| Christodoulou 2009 | 64 | 9.93 (31.22) | 63 | 2.18 (29.45) | | 4.9 % | 7.75 [ -2.80, 18.30 ] |
| Hoskin 2009 | 151 | -3.3 (26.41) | 149 | -5.2 (27.43) | | 14.6 % | 1.90 [ -4.19, 7.99 ] |
| Huddart 2002 | 45 | 7.65 (32.87) | 45 | 2.94 (19.72) | | 4.3 % | 4.71 [ -6.49, 15.91 ] |
| Krzakowski 2008a | 104 | 2.7 (25.4) | 52 | 3.12 (23.83) | | 8.3 % | -0.42 [ -8.53, 7.69 ] |
| Krzakowski 2008b | 105 | 3.6 (23.4) | 52 | 3.12 (23.83) | | 8.8 % | 0.48 [ -7.39, 8.35 ] |
| Mystakidou 2005 | 50 | 43.3 (18.4) | 50 | 13.4 (14.2) | | 13.1 % | 29.90 [ 23.46, 36.34 ] |
| Osterborg 2002 | 105 | 14.8 (28) | 101 | 8.7 (28.9) | | 9.0 % | 6.10 [ -1.67, 13.87 ] |
| Savonije 2005 | 155 | 3.98 (26.75) | 65 | -3.69 (24.38) | | 10.3 % | 7.67 [ 0.40, 14.94 ] |
| Tjulandin 2011 | 88 | 6.3 (21.7) | 84 | 0.6 (22) | | 12.7 % | 5.70 [ -0.83, 12.23 ] |
| Witzig 2005 | 148 | 0.56 (28.67) | 139 | 0 (24.87) | | 14.1 % | 0.56 [ -5.64, 6.76 ] |
| **Subtotal (95% CI)** | **1015** | | **800** | | | **100.0 %** | **6.92 [ 4.59, 9.25 ]** |
| Heterogeneity: $Chi^2$ = 61.64, df = 9 (P<0.00001); $I^2$ =85% | | | | | | | |
| Test for overall effect: Z = 5.82 (P < 0.00001) | | | | | | | |
| 3 >70% non elderly 18-65 years | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| 4 only non-elderly adults | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| 5 >70% elderly >65 years | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| 6 only elderly > 65 years | | | | | | | |

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| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| **Total (95% CI)** | **1015** | | **800** | | | **100.0 %** | **6.92 [ 4.59, 9.25 ]** |
| Heterogeneity: $Chi^2$ = 61.64, df = 9 (P<0.00001); $I^2$ =85% | | | | | | | |
| Test for overall effect: Z = 5.82 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | |


## Analysis 10.6. Comparison 10 Change in FACT-An Total 47, Outcome 6 Change in FACT-An Total 47 - different therapies.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 10 Change in FACT-An Total 47

Outcome: 6 Change in FACT-An Total 47 - different therapies

| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 chemotherapy | | | | | | | |
| Christodoulou 2009 | 64 | 9.93 (31.22) | 63 | 2.18 (29.45) | | 4.9 % | 7.75 [ -2.80, 18.30 ] |
| Huddart 2002 | 45 | 7.65 (32.87) | 45 | 2.94 (19.72) | | 4.3 % | 4.71 [ -6.49, 15.91 ] |
| Krzakowski 2008a | 104 | 2.7 (25.4) | 52 | 3.12 (23.83) | | 8.3 % | -0.42 [ -8.53, 7.69 ] |
| Krzakowski 2008b | 105 | 3.6 (23.4) | 52 | 3.12 (23.83) | | 8.8 % | 0.48 [ -7.39, 8.35 ] |
| Osterborg 2002 | 105 | 14.8 (28) | 101 | 8.7 (28.9) | | 9.0 % | 6.10 [ -1.67, 13.87 ] |
| Savonije 2005 | 155 | 3.98 (26.75) | 65 | -3.69 (24.38) | | 10.3 % | 7.67 [ 0.40, 14.94 ] |
| Tjulandin 2011 | 88 | 6.3 (21.7) | 84 | 0.6 (22) | | 12.7 % | 5.70 [ -0.83, 12.23 ] |
| Witzig 2005 | 148 | 0.56 (28.67) | 139 | 0 (24.87) | | 14.1 % | 0.56 [ -5.64, 6.76 ] |
| **Subtotal (95% CI)** | **814** | | **601** | | | **72.3 %** | **3.77 [ 1.03, 6.51 ]** |


(*Continued* . . . )

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| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Heterogeneity: Chi² = 5.08, df = 7 (P = 0.65); I² =0.0% | | | | | | | |
| Test for overall effect: Z = 2.70 (P = 0.0070) | | | | | | | |
| 2 radiotherapy | | | | | | | |
| Hoskin 2009 | 151 | -3.3 (26.41) | 149 | -5.2 (27.43) | | 14.6 % | 1.90 [ -4.19, 7.99 ] |
| **Subtotal (95% CI)** | **151** | | **149** | | | **14.6 %** | **1.90 [ -4.19, 7.99 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 0.61 (P = 0.54) | | | | | | | |
| 3 no therapy | | | | | | | |
| Mystakidou 2005 | 50 | 43.3 (18.4) | 50 | 13.4 (14.2) | | 13.1 % | 29.90 [ 23.46, 36.34 ] |
| **Subtotal (95% CI)** | **50** | | **50** | | | **13.1 %** | **29.90 [ 23.46, 36.34 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 9.10 (P < 0.00001) | | | | | | | |
| 4 unclear | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| **Total (95% CI)** | **1015** | | **800** | | | **100.0 %** | **6.92 [ 4.59, 9.25 ]** |
| Heterogeneity: Chi² = 61.64, df = 9 (P<0.00001); I² =85% | | | | | | | |
| Test for overall effect: Z = 5.82 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: Chi² = 56.55, df = 2 (P = 0.00), I² =96% | | | | | | | |

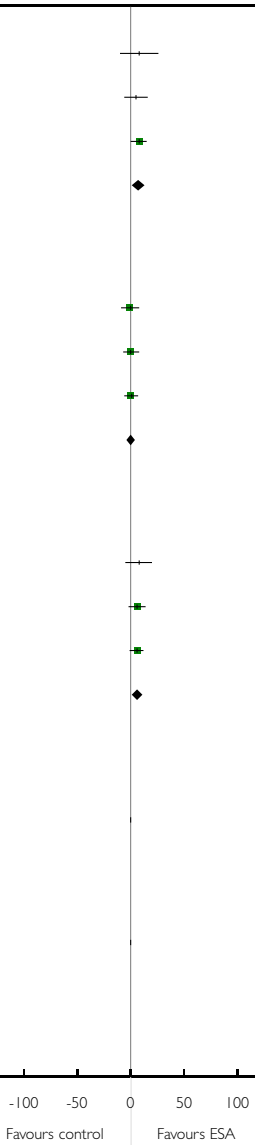
### Analysis 10.7. Comparison 10 Change in FACT-An Total 47, Outcome 7 Change in FACT-An Total 47 - different therapies differentiated.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 10 Change in FACT-An Total 47

Outcome: 7 Change in FACT-An Total 47 - different therapies differentiated

| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 chemotherapy, >70% with platinum | | | | | | | |
| Christodoulou 2009 | 21 | 10.32 (32.28) | 21 | 2.33 (28.61) | | 1.6 % | 7.99 [ -10.46, 26.44 ] |
| Huddart 2002 | 45 | 7.65 (32.87) | 45 | 2.94 (19.72) | | 4.3 % | 4.71 [ -6.49, 15.91 ] |
| Savonije 2005 | 155 | 3.98 (26.75) | 65 | -3.69 (24.38) | | 10.3 % | 7.67 [ 0.40, 14.94 ] |
| **Subtotal (95% CI)** | **221** | | **131** | | | **16.2 %** | **6.91 [ 1.12, 12.70 ]** |
| Heterogeneity: $Chi^2$ = 0.20, df = 2 (P = 0.90); $I^2$ =0.0% | | | | | | | |
| Test for overall effect: Z = 2.34 (P = 0.019) | | | | | | | |
| 2 chemotherapy, <70% platinum containing | | | | | | | |
| Krzakowski 2008a | 104 | 2.7 (25.4) | 52 | 3.12 (23.83) | | 8.3 % | -0.42 [ -8.53, 7.69 ] |
| Krzakowski 2008b | 105 | 3.6 (23.4) | 52 | 3.12 (23.83) | | 8.8 % | 0.48 [ -7.39, 8.35 ] |
| Witzig 2005 | 148 | 0.56 (28.67) | 139 | 0 (24.87) | | 14.1 % | 0.56 [ -5.64, 6.76 ] |
| **Subtotal (95% CI)** | **357** | | **243** | | | **31.1 %** | **0.28 [ -3.90, 4.45 ]** |
| Heterogeneity: $Chi^2$ = 0.04, df = 2 (P = 0.98); $I^2$ =0.0% | | | | | | | |
| Test for overall effect: Z = 0.13 (P = 0.90) | | | | | | | |
| 3 chemotherapy without platinum (all patients) | | | | | | | |
| Christodoulou 2009 | 43 | 9.74 (30.14) | 42 | 2.11 (30.3) | | 3.3 % | 7.63 [ -5.22, 20.48 ] |
| Osterborg 2002 | 105 | 14.8 (28) | 101 | 8.7 (28.9) | | 9.0 % | 6.10 [ -1.67, 13.87 ] |
| Tjulandin 2011 | 88 | 6.3 (21.7) | 84 | 0.6 (22) | | 12.7 % | 5.70 [ -0.83, 12.23 ] |
| **Subtotal (95% CI)** | **236** | | **227** | | | **25.0 %** | **6.10 [ 1.44, 10.76 ]** |
| Heterogeneity: $Chi^2$ = 0.07, df = 2 (P = 0.97); $I^2$ =0.0% | | | | | | | |
| Test for overall effect: Z = 2.56 (P = 0.010) | | | | | | | |
| 4 chemotherapy, platinum and non-platinum containing, no numbers given | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| 5 radiochemotherapy NEW | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| 6 radiotherapy | | | | | | | |

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| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Hoskin 2009 | 151 | -3.3 (26.41) | 149 | -5.2 (27.43) | | 14.6 % | 1.90 [ -4.19, 7.99 ] |
| **Subtotal (95% CI)** | **151** | | **149** | | | **14.6 %** | **1.90 [ -4.19, 7.99 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 0.61 (P = 0.54) | | | | | | | |
| 7 no therapy | | | | | | | |
| Mystakidou 2005 | 50 | 43.3 (18.4) | 50 | 13.4 (14.2) | | 13.1 % | 29.90 [ 23.46, 36.34 ] |
| **Subtotal (95% CI)** | **50** | | **50** | | | **13.1 %** | **29.90 [ 23.46, 36.34 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 9.10 (P < 0.00001) | | | | | | | |
| 8 unclear | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| 9 chemotherapy no details given | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| **Total (95% CI)** | **1015** | | **800** | | | **100.0 %** | **6.92 [ 4.59, 9.25 ]** |
| Heterogeneity: $Chi^2$ = 61.64, df = 10 (P<0.00001); $I^2$ =84% | | | | | | | |
| Test for overall effect: Z = 5.82 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 61.33, df = 4 (P = 0.00), $I^2$ =93% | | | | | | | |

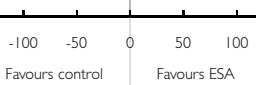
## Analysis 10.8. Comparison 10 Change in FACT-An Total 47, Outcome 8 Change in FACT-An Total 47 - epoetin versus darbepoetin.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 10 Change in FACT-An Total 47

Outcome: 8 Change in FACT-An Total 47 - epoetin versus darbepoetin

| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 Epoetin | | | | | | | |
| Christodoulou 2009 | 64 | 9.93 (31.22) | 63 | 2.18 (29.45) | | 4.9 % | 7.75 [ -2.80, 18.30 ] |
| Hoskin 2009 | 151 | -3.3 (26.41) | 149 | -5.2 (27.43) | | 14.6 % | 1.90 [ -4.19, 7.99 ] |
| Huddart 2002 | 45 | 7.65 (32.87) | 45 | 2.94 (19.72) | | 4.3 % | 4.71 [ -6.49, 15.91 ] |
| Krzakowski 2008a | 104 | 2.7 (25.4) | 52 | 3.12 (23.83) | | 8.3 % | -0.42 [ -8.53, 7.69 ] |
| Krzakowski 2008b | 105 | 3.6 (23.4) | 52 | 3.12 (23.83) | | 8.8 % | 0.48 [ -7.39, 8.35 ] |
| Mystakidou 2005 | 50 | 43.3 (18.4) | 50 | 13.4 (14.2) | | 13.1 % | 29.90 [ 23.46, 36.34 ] |
| Osterborg 2002 | 105 | 14.8 (28) | 101 | 8.7 (28.9) | | 9.0 % | 6.10 [ -1.67, 13.87 ] |
| Savonije 2005 | 155 | 3.98 (26.75) | 65 | -3.69 (24.38) | | 10.3 % | 7.67 [ 0.40, 14.94 ] |
| Tjulandin 2011 | 88 | 6.3 (21.7) | 84 | 0.6 (22) | | 12.7 % | 5.70 [ -0.83, 12.23 ] |
| Witzig 2005 | 148 | 0.56 (28.67) | 139 | 0 (24.87) | | 14.1 % | 0.56 [ -5.64, 6.76 ] |
| **Subtotal (95% CI)** | **1015** | | **800** | | | **100.0 %** | **6.92 [ 4.59, 9.25 ]** |
| Heterogeneity: $Chi^2$ = 61.64, df = 9 (P<0.00001); $I^2$ =85% | | | | | | | |
| Test for overall effect: Z = 5.82 (P < 0.00001) | | | | | | | |
| 2 Darbepoetin | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| **Total (95% CI)** | **1015** | | **800** | | | **100.0 %** | **6.92 [ 4.59, 9.25 ]** |
| Heterogeneity: $Chi^2$ = 61.64, df = 9 (P<0.00001); $I^2$ =85% | | | | | | | |
| Test for overall effect: Z = 5.82 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: Not applicable | | | | | | | |



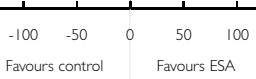
## Analysis 10.9. Comparison 10 Change in FACT-An Total 47, Outcome 9 Change in FACT-An Total 47 - duration of ESA medication.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 10 Change in FACT-An Total 47

Outcome: 9 Change in FACT-An Total 47 - duration of ESA medication

| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 6 to 9 weeks | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| 2 12 to 16 weeks | | | | | | | |
| Christodoulou 2009 | 64 | 9.93 (31.22) | 63 | 2.18 (29.45) | | 4.9 % | 7.75 [ -2.80, 18.30 ] |
| Hoskin 2009 | 151 | -3.3 (26.41) | 149 | -5.2 (27.43) | | 14.6 % | 1.90 [ -4.19, 7.99 ] |
| Krzakowski 2008a | 104 | 2.7 (25.4) | 52 | 3.12 (23.83) | | 8.3 % | -0.42 [ -8.53, 7.69 ] |
| Krzakowski 2008b | 105 | 3.6 (23.4) | 52 | 3.12 (23.83) | | 8.8 % | 0.48 [ -7.39, 8.35 ] |
| Osterborg 2002 | 105 | 14.8 (28) | 101 | 8.7 (28.9) | | 9.0 % | 6.10 [ -1.67, 13.87 ] |
| Savonije 2005 | 155 | 3.98 (26.75) | 65 | -3.69 (24.38) | | 10.3 % | 7.67 [ 0.40, 14.94 ] |
| Tjulandin 2011 | 88 | 6.3 (21.7) | 84 | 0.6 (22) | | 12.7 % | 5.70 [ -0.83, 12.23 ] |
| Witzig 2005 | 148 | 0.56 (28.67) | 139 | 0 (24.87) | | 14.1 % | 0.56 [ -5.64, 6.76 ] |
| **Subtotal (95% CI)** | **920** | | **705** | | | **82.6 %** | **3.39 [ 0.83, 5.96 ]** |
| Heterogeneity: $Chi^2$ = 5.34, df = 7 (P = 0.62); $I^2$ =0.0% | | | | | | | |
| Test for overall effect: Z = 2.59 (P = 0.0095) | | | | | | | |
| 3 more than 17 weeks | | | | | | | |
| Huddart 2002 | 45 | 7.65 (32.87) | 45 | 2.94 (19.72) | | 4.3 % | 4.71 [ -6.49, 15.91 ] |
| Mystakidou 2005 | 50 | 43.3 (18.4) | 50 | 13.4 (14.2) | | 13.1 % | 29.90 [ 23.46, 36.34 ] |
| **Subtotal (95% CI)** | **95** | | **95** | | | **17.4 %** | **23.64 [ 18.05, 29.22 ]** |
| Heterogeneity: $Chi^2$ = 14.60, df = 1 (P = 0.00013); $I^2$ =93% | | | | | | | |
| Test for overall effect: Z = 8.30 (P < 0.00001) | | | | | | | |
| 4 unclear | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| **Total (95% CI)** | **1015** | | **800** | | | **100.0 %** | **6.92 [ 4.59, 9.25 ]** |
| Heterogeneity: $Chi^2$ = 61.64, df = 9 (P<0.00001); $I^2$ =85% | | | | | | | |
| Test for overall effect: Z = 5.82 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 41.70, df = 1 (P = 0.00), $I^2$ =98% | | | | | | | |



## Analysis 10.10. Comparison 10 Change in FACT-An Total 47, Outcome 10 Change in FACT-An Total 47 - iron supplementation.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 10 Change in FACT-An Total 47

Outcome: 10 Change in FACT-An Total 47 - iron supplementation

| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 fixed iron supplementation | | | | | | | |
| Christodoulou 2009 | 64 | 9.93 (31.22) | 63 | 2.18 (29.45) | | 4.9 % | 7.75 [ -2.80, 18.30 ] |
| Hoskin 2009 | 151 | -3.3 (26.41) | 149 | -5.2 (27.43) | | 14.6 % | 1.90 [ -4.19, 7.99 ] |
| Huddart 2002 | 45 | 7.65 (32.87) | 45 | 2.94 (19.72) | | 4.3 % | 4.71 [ -6.49, 15.91 ] |
| Krzakowski 2008a | 104 | 2.7 (25.4) | 52 | 3.12 (23.83) | | 8.3 % | -0.42 [ -8.53, 7.69 ] |
| Krzakowski 2008b | 105 | 3.6 (23.4) | 52 | 3.12 (23.83) | | 8.8 % | 0.48 [ -7.39, 8.35 ] |
| Mystakidou 2005 | 50 | 43.3 (18.4) | 50 | 13.4 (14.2) | | 13.1 % | 29.90 [ 23.46, 36.34 ] |
| Witzig 2005 | 148 | 0.56 (28.67) | 139 | 0 (24.87) | | 14.1 % | 0.56 [ -5.64, 6.76 ] |
| **Subtotal (95% CI)** | **667** | | **550** | | | **68.0 %** | **7.14 [ 4.31, 9.96 ]** |
| Heterogeneity: $Chi^2$ = 61.39, df = 6 (P<0.00001); $I^2$ =90% | | | | | | | |
| Test for overall effect: Z = 4.95 (P < 0.00001) | | | | | | | |
| 2 iron supplementation as necessary | | | | | | | |
| Osterborg 2002 | 105 | 14.8 (28) | 101 | 8.7 (28.9) | | 9.0 % | 6.10 [ -1.67, 13.87 ] |
| Tjulandin 2011 | 88 | 6.3 (21.7) | 84 | 0.6 (22) | | 12.7 % | 5.70 [ -0.83, 12.23 ] |
| **Subtotal (95% CI)** | **193** | | **185** | | | **21.7 %** | **5.87 [ 0.86, 10.87 ]** |
| Heterogeneity: $Chi^2$ = 0.01, df = 1 (P = 0.94); $I^2$ =0.0% | | | | | | | |
| Test for overall effect: Z = 2.30 (P = 0.022) | | | | | | | |
| 3 no explicit statement on iron supplementation or no iron given | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| 4 explicitly stated NO IRON | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| 5 unclear | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |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| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 6 iron given differently in both study arms new | | | | | | | |
| Savonije 2005 | 155 | 3.98 (26.75) | 65 | -3.69 (24.38) | | 10.3 % | 7.67 [ 0.40, 14.94 ] |
| **Subtotal (95% CI)** | **155** | | **65** | | | **10.3 %** | **7.67 [ 0.40, 14.94 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 2.07 (P = 0.039) | | | | | | | |
| **Total (95% CI)** | **1015** | | **800** | | | **100.0 %** | **6.92 [ 4.59, 9.25 ]** |
| Heterogeneity: $Chi^2$ = 61.64, df = 9 (P<0.00001); $I^2$ =85% | | | | | | | |
| Test for overall effect: Z = 5.82 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 0.23, df = 2 (P = 0.89), $I^2$ =0.0% | | | | | | | |

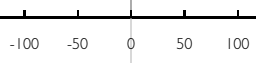

## Analysis 10.11. Comparison 10 Change in FACT-An Total 47, Outcome 11 Change in FACT-An Total 47 - allocation concealment.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 10 Change in FACT-An Total 47

Outcome: 11 Change in FACT-An Total 47 - allocation concealment

| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 adequate | | | | | | | |
| Christodoulou 2009 | 64 | 9.93 (31.22) | 63 | 2.18 (29.45) | | 4.9 % | 7.75 [ -2.80, 18.30 ] |
| Osterborg 2002 | 105 | 14.8 (28) | 101 | 8.7 (28.9) | | 9.0 % | 6.10 [ -1.67, 13.87 ] |
| Savonije 2005 | 155 | 3.98 (26.75) | 65 | -3.69 (24.38) | | 10.3 % | 7.67 [ 0.40, 14.94 ] |
| Witzig 2005 | 148 | 0.56 (28.67) | 139 | 0 (24.87) | | 14.1 % | 0.56 [ -5.64, 6.76 ] |
| **Subtotal (95% CI)** | **472** | | **368** | | | **38.2 %** | **4.69 [ 0.92, 8.45 ]** |
| Heterogeneity: $Chi^2$ = 2.80, df = 3 (P = 0.42); $I^2$ =0.0% | | | | | | | |
| Test for overall effect: Z = 2.44 (P = 0.015) | | | | | | | |
| 2 unclear | | | | | | | |

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| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Hoskin 2009 | 151 | -3.3 (26.41) | 149 | -5.2 (27.43) | | 14.6 % | 1.90 [ -4.19, 7.99 ] |
| Huddart 2002 | 45 | 7.65 (32.87) | 45 | 2.94 (19.72) | | 4.3 % | 4.71 [ -6.49, 15.91 ] |
| Krzakowski 2008a | 104 | 2.7 (25.4) | 52 | 3.12 (23.83) | | 8.3 % | -0.42 [ -8.53, 7.69 ] |
| Krzakowski 2008b | 105 | 3.6 (23.4) | 52 | 3.12 (23.83) | | 8.8 % | 0.48 [ -7.39, 8.35 ] |
| Mystakidou 2005 | 50 | 43.3 (18.4) | 50 | 13.4 (14.2) | | 13.1 % | 29.90 [ 23.46, 36.34 ] |
| Tjulandin 2011 | 88 | 6.3 (21.7) | 84 | 0.6 (22) | | 12.7 % | 5.70 [ -0.83, 12.23 ] |
| **Subtotal (95% CI)** | **543** | | **432** | | | **61.8 %** | **8.30 [ 5.33, 11.26 ]** |
| Heterogeneity: $Chi^2$ = 56.65, df = 5 (P<0.00001); $I^2$ =91% | | | | | | | |
| Test for overall effect: Z = 5.49 (P < 0.00001) | | | | | | | |
| **Total (95% CI)** | **1015** | | **800** | | | **100.0 %** | **6.92 [ 4.59, 9.25 ]** |
| Heterogeneity: $Chi^2$ = 61.64, df = 9 (P<0.00001); $I^2$ =85% | | | | | | | |
| Test for overall effect: Z = 5.82 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 2.18, df = 1 (P = 0.14), $I^2$ =54% | | | | | | | |

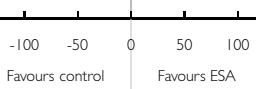
## Analysis 10.12. Comparison 10 Change in FACT-An Total 47, Outcome 12 Change in FACT-An Total 47 - masking.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 10 Change in FACT-An Total 47

Outcome: 12 Change in FACT-An Total 47 - masking

| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 double-blind | | | | | | | |
| Krzakowski 2008a | 104 | 2.7 (25.4) | 52 | 3.12 (23.83) | | 8.3 % | -0.42 [ -8.53, 7.69 ] |
| Krzakowski 2008b | 105 | 3.6 (23.4) | 52 | 3.12 (23.83) | | 8.8 % | 0.48 [ -7.39, 8.35 ] |
| Mystakidou 2005 | 50 | 43.3 (18.4) | 50 | 13.4 (14.2) | | 13.1 % | 29.90 [ 23.46, 36.34 ] |
| Osterborg 2002 | 105 | 14.8 (28) | 101 | 8.7 (28.9) | | 9.0 % | 6.10 [ -1.67, 13.87 ] |
| Tjulandin 2011 | 88 | 6.3 (21.7) | 84 | 0.6 (22) | | 12.7 % | 5.70 [ -0.83, 12.23 ] |
| Witzig 2005 | 148 | 0.56 (28.67) | 139 | 0 (24.87) | | 14.1 % | 0.56 [ -5.64, 6.76 ] |
| **Subtotal (95% CI)** | **600** | | **478** | | | **65.9 %** | **8.00 [ 5.13, 10.87 ]** |
| Heterogeneity: $Chi^2$ = 58.28, df = 5 (P<0.00001); $I^2$ =91% | | | | | | | |
| Test for overall effect: Z = 5.46 (P < 0.00001) | | | | | | | |
| 2 unblinded | | | | | | | |
| Christodoulou 2009 | 64 | 9.93 (31.22) | 63 | 2.18 (29.45) | | 4.9 % | 7.75 [ -2.80, 18.30 ] |
| Hoskin 2009 | 151 | -3.3 (26.41) | 149 | -5.2 (27.43) | | 14.6 % | 1.90 [ -4.19, 7.99 ] |
| Huddart 2002 | 45 | 7.65 (32.87) | 45 | 2.94 (19.72) | | 4.3 % | 4.71 [ -6.49, 15.91 ] |
| Savonije 2005 | 155 | 3.98 (26.75) | 65 | -3.69 (24.38) | | 10.3 % | 7.67 [ 0.40, 14.94 ] |
| **Subtotal (95% CI)** | **415** | | **322** | | | **34.1 %** | **4.83 [ 0.84, 8.82 ]** |
| Heterogeneity: $Chi^2$ = 1.77, df = 3 (P = 0.62); $I^2$ =0.0% | | | | | | | |
| Test for overall effect: Z = 2.37 (P = 0.018) | | | | | | | |
| **Total (95% CI)** | **1015** | | **800** | | | **100.0 %** | **6.92 [ 4.59, 9.25 ]** |
| Heterogeneity: $Chi^2$ = 61.64, df = 9 (P<0.00001); $I^2$ =85% | | | | | | | |
| Test for overall effect: Z = 5.82 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 1.59, df = 1 (P = 0.21), $I^2$ =37% | | | | | | | |



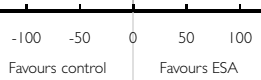
## Analysis 10.13. Comparison 10 Change in FACT-An Total 47, Outcome 13 Change in FACT-An Total 47 - intention-to treat.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 10 Change in FACT-An Total 47

Outcome: 13 Change in FACT-An Total 47 - intention-to treat

| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 ITT or less than 10% of participants per study arm excluded | | | | | | | |
| Krzakowski 2008a | 104 | 2.7 (25.4) | 52 | 3.12 (23.83) | | 8.3 % | -0.42 [ -8.53, 7.69 ] |
| Krzakowski 2008b | 105 | 3.6 (23.4) | 52 | 3.12 (23.83) | | 8.8 % | 0.48 [ -7.39, 8.35 ] |
| Mystakidou 2005 | 50 | 43.3 (18.4) | 50 | 13.4 (14.2) | | 13.1 % | 29.90 [ 23.46, 36.34 ] |
| Tjulandin 2011 | 88 | 6.3 (21.7) | 84 | 0.6 (22) | | 12.7 % | 5.70 [ -0.83, 12.23 ] |
| **Subtotal (95% CI)** | **347** | | **238** | | | **42.8 %** | **10.85 [ 7.29, 14.41 ]** |
| Heterogeneity: $Chi^2$ = 50.06, df = 3 (P<0.00001); $I^2$ =94% | | | | | | | |
| Test for overall effect: Z = 5.97 (P < 0.00001) | | | | | | | |
| 2 more than 10% of participants per study arm excluded | | | | | | | |
| Christodoulou 2009 | 64 | 9.93 (31.22) | 63 | 2.18 (29.45) | | 4.9 % | 7.75 [ -2.80, 18.30 ] |
| Osterborg 2002 | 105 | 14.8 (28) | 101 | 8.7 (28.9) | | 9.0 % | 6.10 [ -1.67, 13.87 ] |
| Savonije 2005 | 155 | 3.98 (26.75) | 65 | -3.69 (24.38) | | 10.3 % | 7.67 [ 0.40, 14.94 ] |
| Witzig 2005 | 148 | 0.56 (28.67) | 139 | 0 (24.87) | | 14.1 % | 0.56 [ -5.64, 6.76 ] |
| **Subtotal (95% CI)** | **472** | | **368** | | | **38.2 %** | **4.69 [ 0.92, 8.45 ]** |
| Heterogeneity: $Chi^2$ = 2.80, df = 3 (P = 0.42); $I^2$ =0.0% | | | | | | | |
| Test for overall effect: Z = 2.44 (P = 0.015) | | | | | | | |
| 3 unclear | | | | | | | |
| Hoskin 2009 | 151 | -3.3 (26.41) | 149 | -5.2 (27.43) | | 14.6 % | 1.90 [ -4.19, 7.99 ] |
| Huddart 2002 | 45 | 7.65 (32.87) | 45 | 2.94 (19.72) | | 4.3 % | 4.71 [ -6.49, 15.91 ] |
| **Subtotal (95% CI)** | **196** | | **194** | | | **18.9 %** | **2.54 [ -2.81, 7.90 ]** |
| Heterogeneity: $Chi^2$ = 0.19, df = 1 (P = 0.67); $I^2$ =0.0% | | | | | | | |
| Test for overall effect: Z = 0.93 (P = 0.35) | | | | | | | |
| **Total (95% CI)** | **1015** | | **800** | | | **100.0 %** | **6.92 [ 4.59, 9.25 ]** |
| Heterogeneity: $Chi^2$ = 61.64, df = 9 (P<0.00001); $I^2$ =85% | | | | | | | |
| Test for overall effect: Z = 5.82 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 8.59, df = 2 (P = 0.01), $I^2$ =77% | | | | | | | |



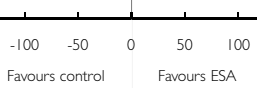
## Analysis 10.14. Comparison 10 Change in FACT-An Total 47, Outcome 14 Change in FACT-An Total 47 - publication.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 10 Change in FACT-An Total 47

Outcome: 14 Change in FACT-An Total 47 - publication

| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 full text publication | | | | | | | |
| Christodoulou 2009 | 64 | 9.93 (31.22) | 63 | 2.18 (29.45) | | 4.9 % | 7.75 [ -2.80, 18.30 ] |
| Hoskin 2009 | 151 | -3.3 (26.41) | 149 | -5.2 (27.43) | | 14.6 % | 1.90 [ -4.19, 7.99 ] |
| Krzakowski 2008a | 104 | 2.7 (25.4) | 52 | 3.12 (23.83) | | 8.3 % | -0.42 [ -8.53, 7.69 ] |
| Krzakowski 2008b | 105 | 3.6 (23.4) | 52 | 3.12 (23.83) | | 8.8 % | 0.48 [ -7.39, 8.35 ] |
| Mystakidou 2005 | 50 | 43.3 (18.4) | 50 | 13.4 (14.2) | | 13.1 % | 29.90 [ 23.46, 36.34 ] |
| Osterborg 2002 | 105 | 14.8 (28) | 101 | 8.7 (28.9) | | 9.0 % | 6.10 [ -1.67, 13.87 ] |
| Savonije 2005 | 155 | 3.98 (26.75) | 65 | -3.69 (24.38) | | 10.3 % | 7.67 [ 0.40, 14.94 ] |
| Tjulandin 2011 | 88 | 6.3 (21.7) | 84 | 0.6 (22) | | 12.7 % | 5.70 [ -0.83, 12.23 ] |
| Witzig 2005 | 148 | 0.56 (28.67) | 139 | 0 (24.87) | | 14.1 % | 0.56 [ -5.64, 6.76 ] |
| **Subtotal (95% CI)** | **970** | | **755** | | | **95.7 %** | **7.02 [ 4.63, 9.40 ]** |
| Heterogeneity: $Chi^2$ = 61.48, df = 8 (P<0.00001); $I^2$ =87% | | | | | | | |
| Test for overall effect: Z = 5.77 (P < 0.00001) | | | | | | | |
| 2 abstract publication | | | | | | | |
| Huddart 2002 | 45 | 7.65 (32.87) | 45 | 2.94 (19.72) | | 4.3 % | 4.71 [ -6.49, 15.91 ] |
| **Subtotal (95% CI)** | **45** | | **45** | | | **4.3 %** | **4.71 [ -6.49, 15.91 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 0.82 (P = 0.41) | | | | | | | |
| 3 unpublished data | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| 4 FDA hearing | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |
| 5 clinical trial result information | | | | | | | |
| **Subtotal (95% CI)** | **0** | | **0** | | | **0.0 %** | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: not applicable | | | | | | | |

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| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| **Total (95% CI)** | **1015** | | **800** | | | **100.0 %** | **6.92 [ 4.59, 9.25 ]** |
| Heterogeneity: $Chi^2$ = 61.64, df = 9 (P<0.00001); $I^2$ =85% | | | | | | | |
| Test for overall effect: Z = 5.82 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 0.16, df = 1 (P = 0.69), $I^2$ =0.0% | | | | | | | |


## Analysis 10.15. Comparison 10 Change in FACT-An Total 47, Outcome 15 Change in Fact-An Total 47 - data type.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 10 Change in FACT-An Total 47

Outcome: 15 Change in Fact-An Total 47 - data type

| Study or subgroup | ESA N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 Not imputed data | | | | | | | |
| Huddart 2002 | 45 | 7.65 (32.87) | 45 | 2.94 (19.72) | | 4.3 % | 4.71 [ -6.49, 15.91 ] |
| Krzakowski 2008a | 104 | 2.7 (25.4) | 52 | 3.12 (23.83) | | 8.3 % | -0.42 [ -8.53, 7.69 ] |
| Krzakowski 2008b | 105 | 3.6 (23.4) | 52 | 3.12 (23.83) | | 8.8 % | 0.48 [ -7.39, 8.35 ] |
| Mystakidou 2005 | 50 | 43.3 (18.4) | 50 | 13.4 (14.2) | | 13.1 % | 29.90 [ 23.46, 36.34 ] |
| Osterborg 2002 | 105 | 14.8 (28) | 101 | 8.7 (28.9) | | 9.0 % | 6.10 [ -1.67, 13.87 ] |
| Savonije 2005 | 155 | 3.98 (26.75) | 65 | -3.69 (24.38) | | 10.3 % | 7.67 [ 0.40, 14.94 ] |
| Tjulandin 2011 | 88 | 6.3 (21.7) | 84 | 0.6 (22) | | 12.7 % | 5.70 [ -0.83, 12.23 ] |
| **Subtotal (95% CI)** | **652** | | **449** | | | **66.4 %** | **9.31 [ 6.45, 12.17 ]** |
| Heterogeneity: $Chi^2$ = 52.27, df = 6 (P<0.00001); $I^2$ =89% | | | | | | | |
| Test for overall effect: Z = 6.38 (P < 0.00001) | | | | | | | |
| 2 Imputed data | | | | | | | |
| Christodoulou 2009 | 64 | 9.93 (31.22) | 63 | 2.18 (29.45) | | 4.9 % | 7.75 [ -2.80, 18.30 ] |


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| Study or subgroup | ESA N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Hoskin 2009 | 151 | -3.3 (26.41) | 149 | -5.2 (27.43) | | 14.6 % | 1.90 [ -4.19, 7.99 ] |
| Witzig 2005 | 148 | 0.56 (28.67) | 139 | 0 (24.87) | | 14.1 % | 0.56 [ -5.64, 6.76 ] |
| **Subtotal (95% CI)** | **363** | | **351** | | | **33.6 %** | **2.19 [ -1.83, 6.20 ]** |
| Heterogeneity: $Chi^2$ = 1.34, df = 2 (P = 0.51); $I^2$ =0.0% | | | | | | | |
| Test for overall effect: Z = 1.07 (P = 0.29) | | | | | | | |
| **Total (95% CI)** | **1015** | | **800** | | | **100.0 %** | **6.92 [ 4.59, 9.25 ]** |
| Heterogeneity: $Chi^2$ = 61.64, df = 9 (P<0.00001); $I^2$ =85% | | | | | | | |
| Test for overall effect: Z = 5.82 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 8.02, df = 1 (P = 0.00), $I^2$ =88% | | | | | | | |

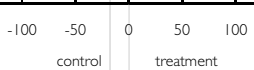

## Analysis 10.16. Comparison 10 Change in FACT-An Total 47, Outcome 16 FACT-An Total 47 - merged experimental study arms.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 10 Change in FACT-An Total 47

Outcome: 16 FACT-An Total 47 - merged experimental study arms

| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Christodoulou 2009 | 64 | 9.93 (31.22) | 63 | 2.18 (29.45) | | 4.9 % | 7.75 [ -2.80, 18.30 ] |
| Hoskin 2009 | 151 | -3.3 (26.41) | 149 | -5.2 (27.43) | | 14.6 % | 1.90 [ -4.19, 7.99 ] |
| Huddart 2002 | 45 | 7.65 (32.87) | 45 | 2.94 (19.72) | | 4.3 % | 4.71 [ -6.49, 15.91 ] |
| Krzakowski 2008 | 209 | 3.15 (24.42) | 104 | 3.12 (23.83) | | 17.0 % | 0.03 [ -5.62, 5.68 ] |
| Mystakidou 2005 | 50 | 43.3 (18.4) | 50 | 13.4 (14.2) | | 13.1 % | 29.90 [ 23.46, 36.34 ] |
| Osterborg 2002 | 105 | 14.8 (28) | 101 | 8.7 (28.9) | | 9.0 % | 6.10 [ -1.67, 13.87 ] |
| Savonije 2005 | 155 | 3.98 (26.75) | 65 | -3.69 (24.38) | | 10.3 % | 7.67 [ 0.40, 14.94 ] |

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| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Tjulandin 2011 | 88 | 6.3 (21.7) | 84 | 0.6 (22) | | 12.7 % | 5.70 [ -0.83, 12.23 ] |
| Witzig 2005 | 148 | 0.56 (28.67) | 139 | 0 (24.87) | | 14.1 % | 0.56 [ -5.64, 6.76 ] |
| **Total (95% CI)** | **1015** | | **800** | | | **100.0 %** | **6.92 [ 4.59, 9.25 ]** |

Heterogeneity: Chi$^2$ = 61.63, df = 8 (P<0.00001); I$^2$ =87%

Test for overall effect: Z = 5.82 (P < 0.00001)

Test for subgroup differences: Not applicable

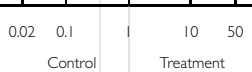

## Analysis 11.1. Comparison 11 Thrombotic events, Outcome 1 Thrombotic events - overall.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 11 Thrombotic events

Outcome: 1 Thrombotic events - overall

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Aapro 2008 | 29/231 | 13/231 | | 2.23 [ 1.19, 4.18 ] |
| Abels 1993 J%J 2004 | 1/65 | 0/59 | | 2.73 [ 0.11, 65.68 ] |
| Bamias 2003 | 0/72 | 1/72 | | 0.33 [ 0.01, 8.05 ] |
| Blohmer 2011 | 2/127 | 3/129 | | 0.68 [ 0.12, 3.98 ] |
| Cascinu 1994 | 0/50 | 0/50 | | 0.0 [ 0.0, 0.0 ] |
| Case 1993 J%J 2004 | 2/81 | 3/76 | | 0.63 [ 0.11, 3.64 ] |
| Chang 2005 | 19/176 | 14/178 | | 1.37 [ 0.71, 2.65 ] |
| Charu 2007 Amgen 2007 | 8/226 | 1/59 | | 2.09 [ 0.27, 16.37 ] |
| Dammacco 2001 J%J 2004 | 5/69 | 1/76 | | 5.51 [ 0.66, 45.98 ] |
| Debus 2006 J%J 2007 | 38/192 | 23/191 | | 1.64 [ 1.02, 2.65 ] |
| Engert 2009 | 45/645 | 44/644 | | 1.02 [ 0.68, 1.52 ] |

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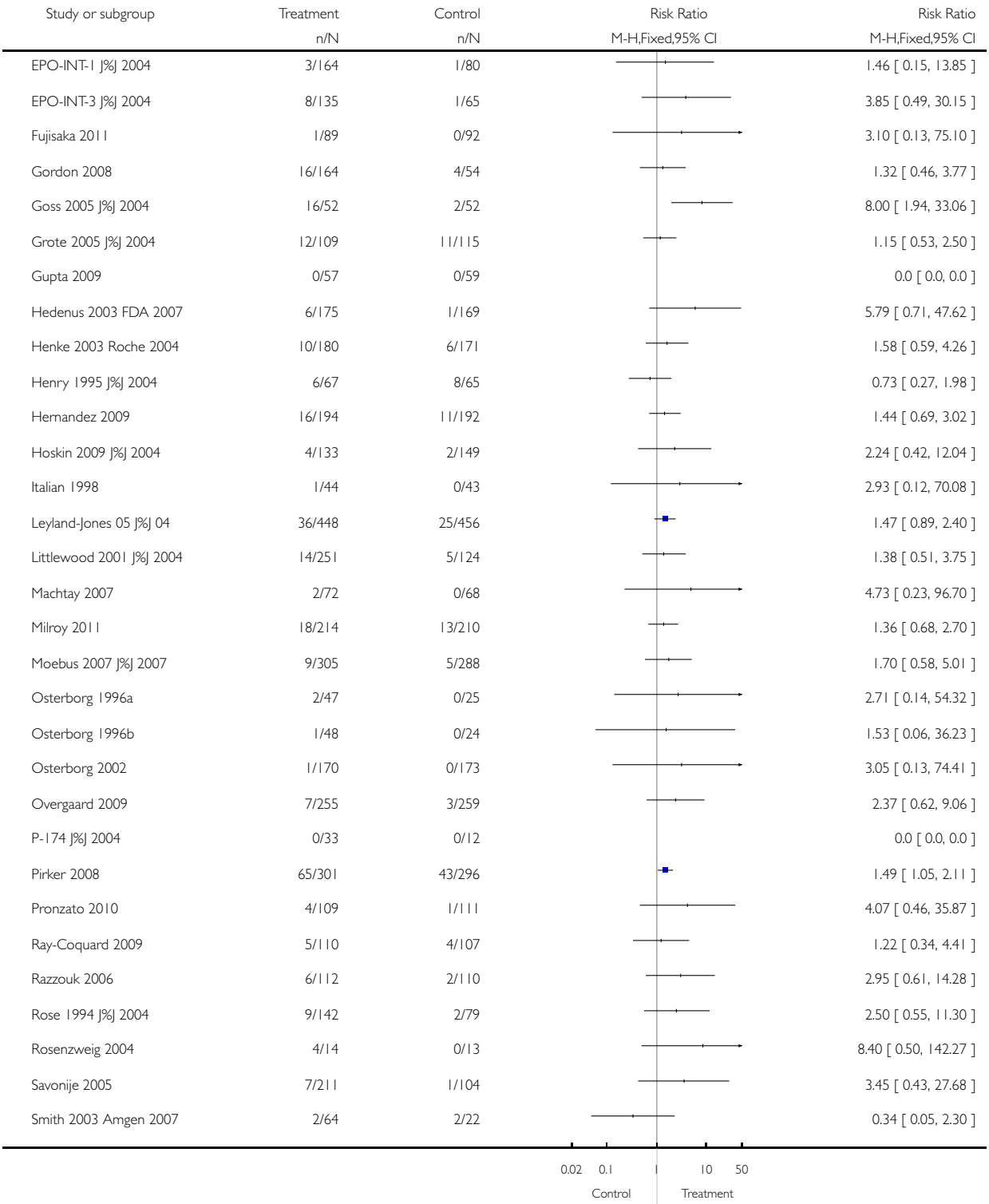


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| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Smith 2008 | 50/515 | 36/470 | | 1.27 [ 0.84, 1.91 ] |
| Strauss 2008 | 1/33 | 0/38 | | 3.44 [ 0.14, 81.71 ] |
| Ten Bokkel 1998a | 2/45 | 0/17 | | 1.96 [ 0.10, 38.79 ] |
| Ten Bokkel 1998b | 4/42 | 0/16 | | 3.56 [ 0.20, 62.58 ] |
| Thatcher 1999a | 0/42 | 0/22 | | 0.0 [ 0.0, 0.0 ] |
| Thatcher 1999b | 2/44 | 0/22 | | 2.56 [ 0.13, 51.05 ] |
| Thomas 2008 J%J 2004 | 10/58 | 5/55 | | 1.90 [ 0.69, 5.20 ] |
| Thompson 2000 | 1/45 | 0/21 | | 1.43 [ 0.06, 33.82 ] |
| Throuvalas 2000 | 1/28 | 0/26 | | 2.79 [ 0.12, 65.66 ] |
| Tjulandin 2011 | 0/95 | 1/91 | | 0.32 [ 0.01, 7.74 ] |
| Tsuboi 2009 | 1/62 | 0/58 | | 2.81 [ 0.12, 67.62 ] |
| Untch 2011˙1 | 20/318 | 17/396 | | 1.47 [ 0.78, 2.75 ] |
| Vansteenkiste 2002 | 7/155 | 5/159 | | 1.44 [ 0.47, 4.43 ] |
| Welch 1995 | 1/15 | 0/15 | | 3.00 [ 0.13, 68.26 ] |
| Wilkinson 2006 | 10/121 | 1/60 | | 4.96 [ 0.65, 37.84 ] |
| Winquist 2009 | 0/26 | 2/30 | | 0.23 [ 0.01, 4.58 ] |
| Witzig 2005 J%J 2004 | 9/168 | 6/165 | | 1.47 [ 0.54, 4.05 ] |
| Wright 2007 | 2/33 | 3/37 | | 0.75 [ 0.13, 4.20 ] |
| **Total (95% CI)** | **8248** | **7250** | | **1.52 [ 1.34, 1.74 ]** |

Total events: 561 (Treatment), 332 (Control)

Heterogeneity: $Chi^2$ = 34.99, df = 55 (P = 0.98); $I^2$ =0.0%

Test for overall effect: Z = 6.36 (P < 0.00001)

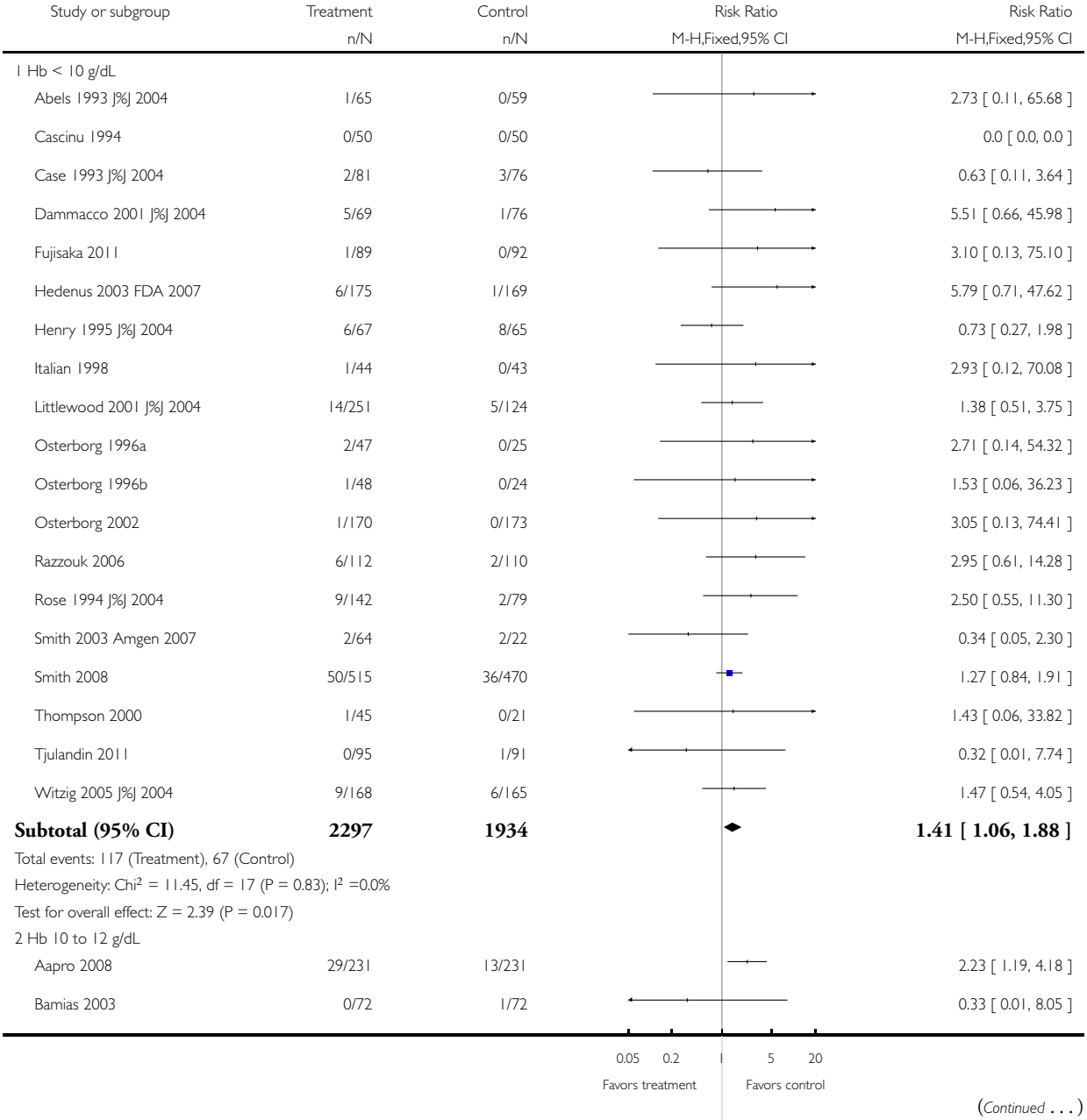
Test for subgroup differences: Not applicable

## Analysis 11.2. Comparison 11 Thrombotic events, Outcome 2 Thrombotic events - baseline Hb.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 11 Thrombotic events

Outcome: 2 Thrombotic events - baseline Hb

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| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Blohmer 2011 | 2/127 | 3/129 | | 0.68 [ 0.12, 3.98 ] |
| Chang 2005 | 19/176 | 14/178 | | 1.37 [ 0.71, 2.65 ] |
| Charu 2007 Amgen 2007 | 8/226 | 1/59 | | 2.09 [ 0.27, 16.37 ] |
| EPO-INT-1 J%J 2004 | 3/164 | 1/80 | | 1.46 [ 0.15, 13.85 ] |
| EPO-INT-3 J%J 2004 | 8/135 | 1/65 | | 3.85 [ 0.49, 30.15 ] |
| Gordon 2008 | 16/164 | 4/54 | | 1.32 [ 0.46, 3.77 ] |
| Gupta 2009 | 0/57 | 0/59 | | 0.0 [ 0.0, 0.0 ] |
| Henke 2003 Roche 2004 | 10/180 | 6/171 | | 1.58 [ 0.59, 4.26 ] |
| Hernandez 2009 | 16/194 | 11/192 | | 1.44 [ 0.69, 3.02 ] |
| Pirker 2008 | 65/301 | 43/296 | | 1.49 [ 1.05, 2.11 ] |
| Pronzato 2010 | 4/109 | 1/111 | | 4.07 [ 0.46, 35.87 ] |
| Ray-Coquard 2009 | 5/110 | 4/107 | | 1.22 [ 0.34, 4.41 ] |
| Rosenzweig 2004 | 4/14 | 0/13 | | 8.40 [ 0.50, 142.27 ] |
| Savonije 2005 | 7/211 | 1/104 | | 3.45 [ 0.43, 27.68 ] |
| Strauss 2008 | 1/33 | 0/38 | | 3.44 [ 0.14, 81.71 ] |
| Ten Bokkel 1998a | 2/45 | 0/17 | | 1.96 [ 0.10, 38.79 ] |
| Ten Bokkel 1998b | 4/42 | 0/16 | | 3.56 [ 0.20, 62.58 ] |
| Thomas 2008 J%J 2004 | 10/58 | 5/55 | | 1.90 [ 0.69, 5.20 ] |
| Throuvalas 2000 | 1/28 | 0/26 | | 2.79 [ 0.12, 65.66 ] |
| Tsuboi 2009 | 1/62 | 0/58 | | 2.81 [ 0.12, 67.62 ] |
| Vansteenkiste 2002 | 7/155 | 5/159 | | 1.44 [ 0.47, 4.43 ] |
| Wilkinson 2006 | 10/121 | 1/60 | | 4.96 [ 0.65, 37.84 ] |
| Winquist 2009 | 0/26 | 2/30 | | 0.23 [ 0.01, 4.58 ] |
| Wright 2007 | 2/33 | 3/37 | | 0.75 [ 0.13, 4.20 ] |
| **Subtotal (95% CI)** | **3074** | **2417** | ◆ | **1.64 [ 1.33, 2.03 ]** |
| Total events: 234 (Treatment), 120 (Control) | | | | |
| Heterogeneity: $Chi^2$ = 11.55, df = 24 (P = 0.98); $I^2$ =0.0% | | | | |
| Test for overall effect: Z = 4.62 (P < 0.00001) | | | | |
| 3 Hb > 12 g/dL | | | | |
| Engert 2009 | 45/645 | 44/644 | | 1.02 [ 0.68, 1.52 ] |
| Goss 2005 J%J 2004 | 16/52 | 2/52 | | 8.00 [ 1.94, 33.06 ] |
| Grote 2005 J%J 2004 | 12/109 | 11/115 | | 1.15 [ 0.53, 2.50 ] |
| Hoskin 2009 J%J 2004 | 4/133 | 2/149 | | 2.24 [ 0.42, 12.04 ] |

0.05 0.2 1 5 20

Favors treatment Favors control

(*Continued* . . . )

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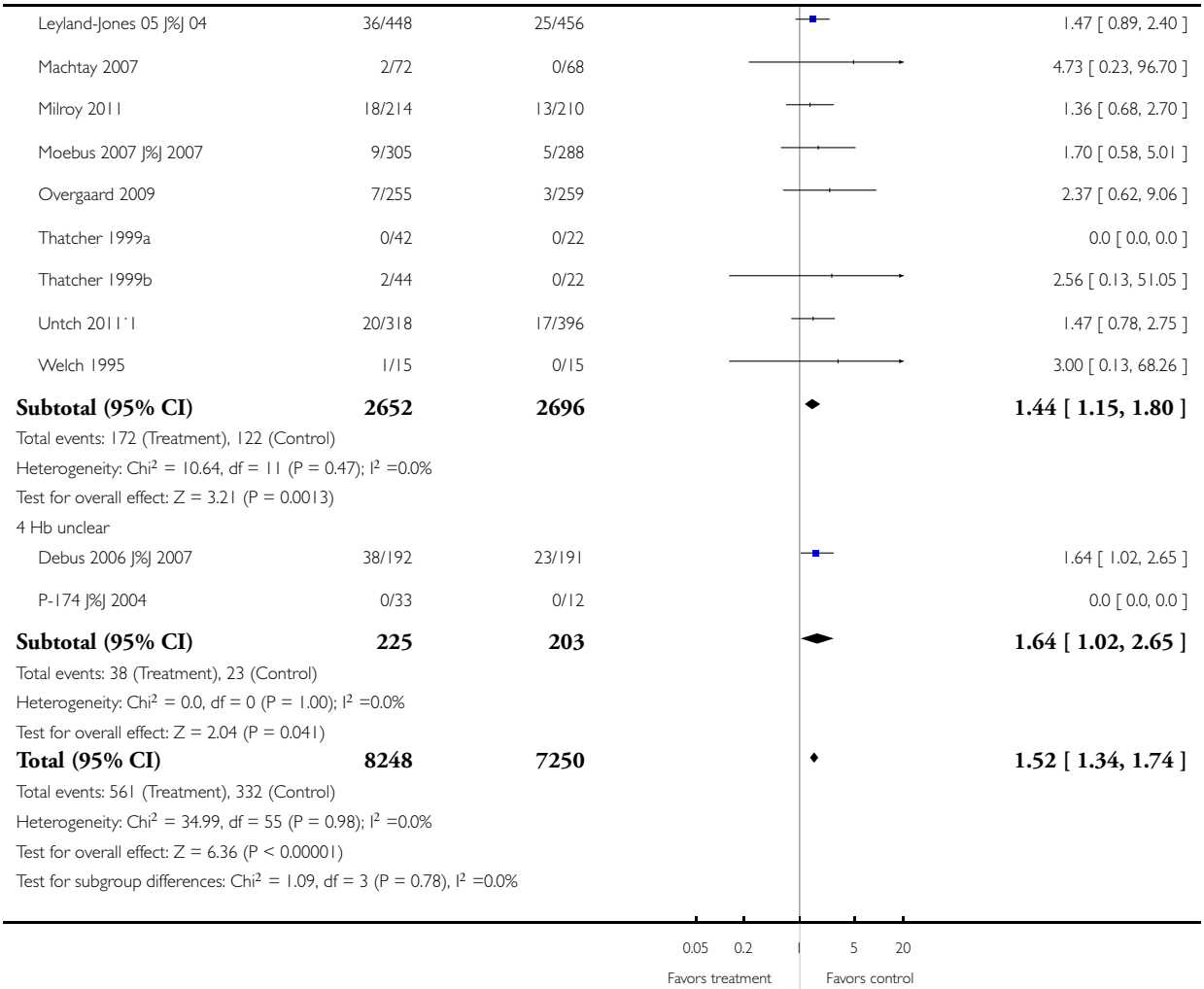
| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Leyland-Jones 05 J%J 04 | 36/448 | 25/456 | | 1.47 [ 0.89, 2.40 ] |
| Machtay 2007 | 2/72 | 0/68 | | 4.73 [ 0.23, 96.70 ] |
| Milroy 2011 | 18/214 | 13/210 | | 1.36 [ 0.68, 2.70 ] |
| Moebus 2007 J%J 2007 | 9/305 | 5/288 | | 1.70 [ 0.58, 5.01 ] |
| Overgaard 2009 | 7/255 | 3/259 | | 2.37 [ 0.62, 9.06 ] |
| Thatcher 1999a | 0/42 | 0/22 | | 0.0 [ 0.0, 0.0 ] |
| Thatcher 1999b | 2/44 | 0/22 | | 2.56 [ 0.13, 51.05 ] |
| Untch 2011˙1 | 20/318 | 17/396 | | 1.47 [ 0.78, 2.75 ] |
| Welch 1995 | 1/15 | 0/15 | | 3.00 [ 0.13, 68.26 ] |
| **Subtotal (95% CI)** | **2652** | **2696** | | **1.44 [ 1.15, 1.80 ]** |
| Total events: 172 (Treatment), 122 (Control) | | | | |
| Heterogeneity: Chi² = 10.64, df = 11 (P = 0.47); I² =0.0% | | | | |
| Test for overall effect: Z = 3.21 (P = 0.0013) | | | | |
| 4 Hb unclear | | | | |
| Debus 2006 J%J 2007 | 38/192 | 23/191 | | 1.64 [ 1.02, 2.65 ] |
| P-174 J%J 2004 | 0/33 | 0/12 | | 0.0 [ 0.0, 0.0 ] |
| **Subtotal (95% CI)** | **225** | **203** | | **1.64 [ 1.02, 2.65 ]** |
| Total events: 38 (Treatment), 23 (Control) | | | | |
| Heterogeneity: Chi² = 0.0, df = 0 (P = 1.00); I² =0.0% | | | | |
| Test for overall effect: Z = 2.04 (P = 0.041) | | | | |
| **Total (95% CI)** | **8248** | **7250** | | **1.52 [ 1.34, 1.74 ]** |
| Total events: 561 (Treatment), 332 (Control) | | | | |
| Heterogeneity: Chi² = 34.99, df = 55 (P = 0.98); I² =0.0% | | | | |
| Test for overall effect: Z = 6.36 (P < 0.00001) | | | | |
| Test for subgroup differences: Chi² = 1.09, df = 3 (P = 0.78), I² =0.0% | | | | |



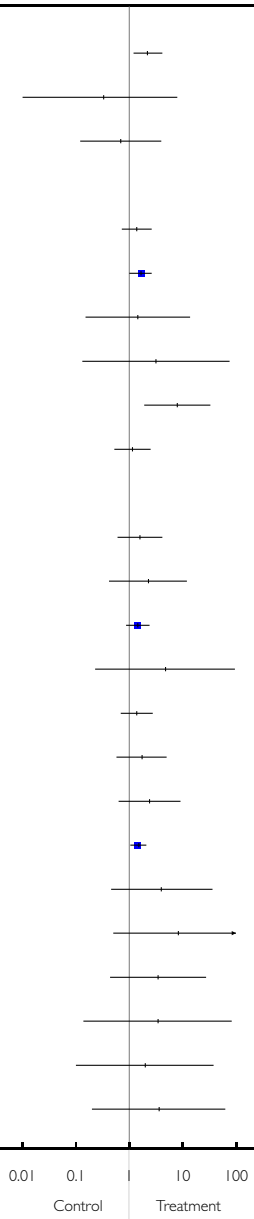
## Analysis 11.3. Comparison 11 Thrombotic events, Outcome 3 Thrombotic events - different malignancies.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 11 Thrombotic events

Outcome: 3 Thrombotic events - different malignancies

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| 1 solid tumours | | | | |
| Aapro 2008 | 29/231 | 13/231 | | 2.23 [ 1.19, 4.18 ] |
| Bamias 2003 | 0/72 | 1/72 | | 0.33 [ 0.01, 8.05 ] |
| Blohmer 2011 | 2/127 | 3/129 | | 0.68 [ 0.12, 3.98 ] |
| Cascinu 1994 | 0/50 | 0/50 | | 0.0 [ 0.0, 0.0 ] |
| Chang 2005 | 19/176 | 14/178 | | 1.37 [ 0.71, 2.65 ] |
| Debus 2006 J%J 2007 | 38/192 | 23/191 | | 1.64 [ 1.02, 2.65 ] |
| EPO-INT-1 J%J 2004 | 3/164 | 1/80 | | 1.46 [ 0.15, 13.85 ] |
| Fujisaka 2011 | 1/89 | 0/92 | | 3.10 [ 0.13, 75.10 ] |
| Goss 2005 J%J 2004 | 16/52 | 2/52 | | 8.00 [ 1.94, 33.06 ] |
| Grote 2005 J%J 2004 | 12/109 | 11/115 | | 1.15 [ 0.53, 2.50 ] |
| Gupta 2009 | 0/57 | 0/59 | | 0.0 [ 0.0, 0.0 ] |
| Henke 2003 Roche 2004 | 10/180 | 6/171 | | 1.58 [ 0.59, 4.26 ] |
| Hoskin 2009 J%J 2004 | 4/133 | 2/149 | | 2.24 [ 0.42, 12.04 ] |
| Leyland-Jones 05 J%J 04 | 36/448 | 25/456 | | 1.47 [ 0.89, 2.40 ] |
| Machtay 2007 | 2/72 | 0/68 | | 4.73 [ 0.23, 96.70 ] |
| Milroy 2011 | 18/214 | 13/210 | | 1.36 [ 0.68, 2.70 ] |
| Moebus 2007 J%J 2007 | 9/305 | 5/288 | | 1.70 [ 0.58, 5.01 ] |
| Overgaard 2009 | 7/255 | 3/259 | | 2.37 [ 0.62, 9.06 ] |
| Pirker 2008 | 65/301 | 43/296 | | 1.49 [ 1.05, 2.11 ] |
| Pronzato 2010 | 4/109 | 1/111 | | 4.07 [ 0.46, 35.87 ] |
| Rosenzweig 2004 | 4/14 | 0/13 | | 8.40 [ 0.50, 142.27 ] |
| Savonije 2005 | 7/211 | 1/104 | | 3.45 [ 0.43, 27.68 ] |
| Strauss 2008 | 1/33 | 0/38 | | 3.44 [ 0.14, 81.71 ] |
| Ten Bokkel 1998a | 2/45 | 0/17 | | 1.96 [ 0.10, 38.79 ] |
| Ten Bokkel 1998b | 4/42 | 0/16 | | 3.56 [ 0.20, 62.58 ] |

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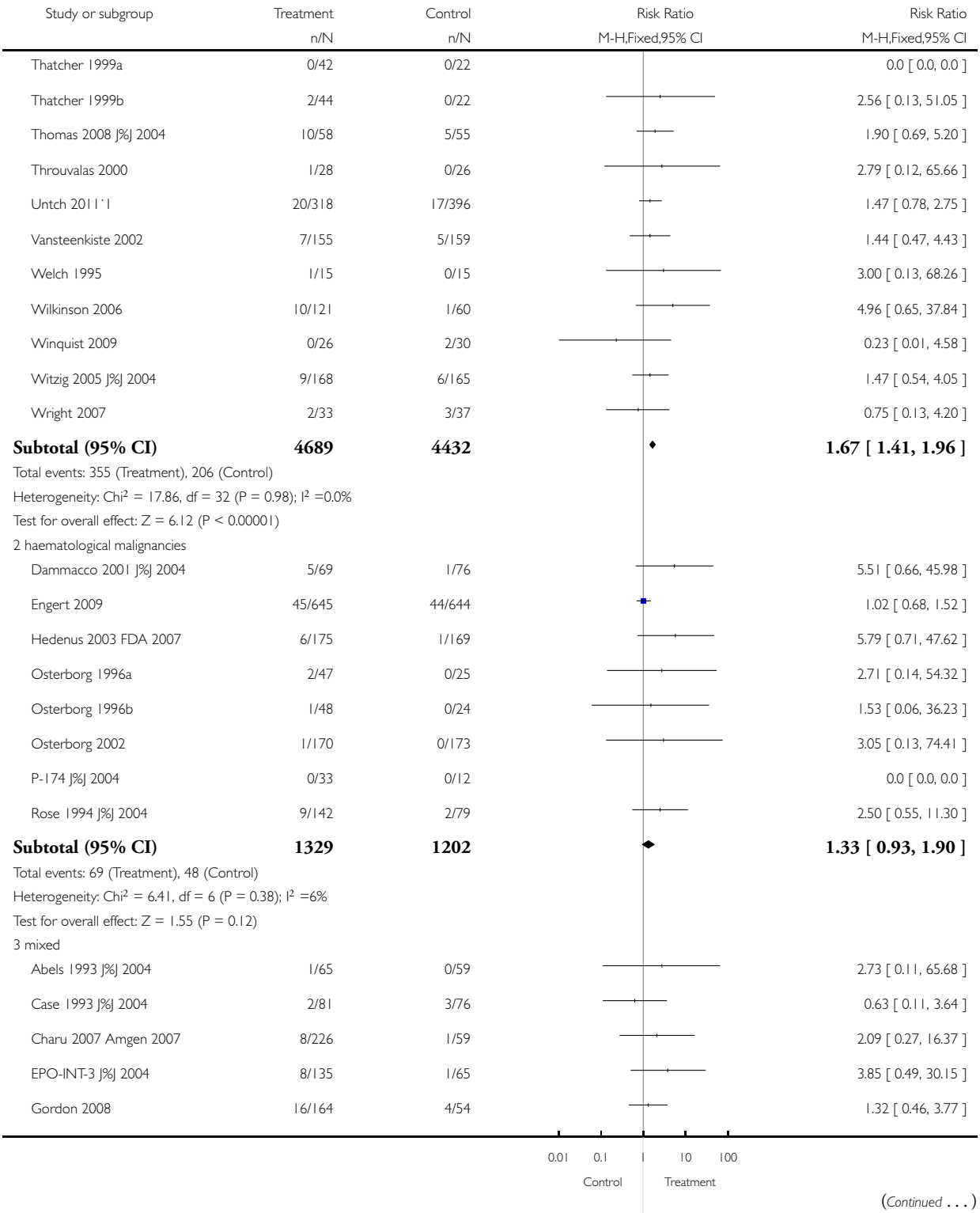


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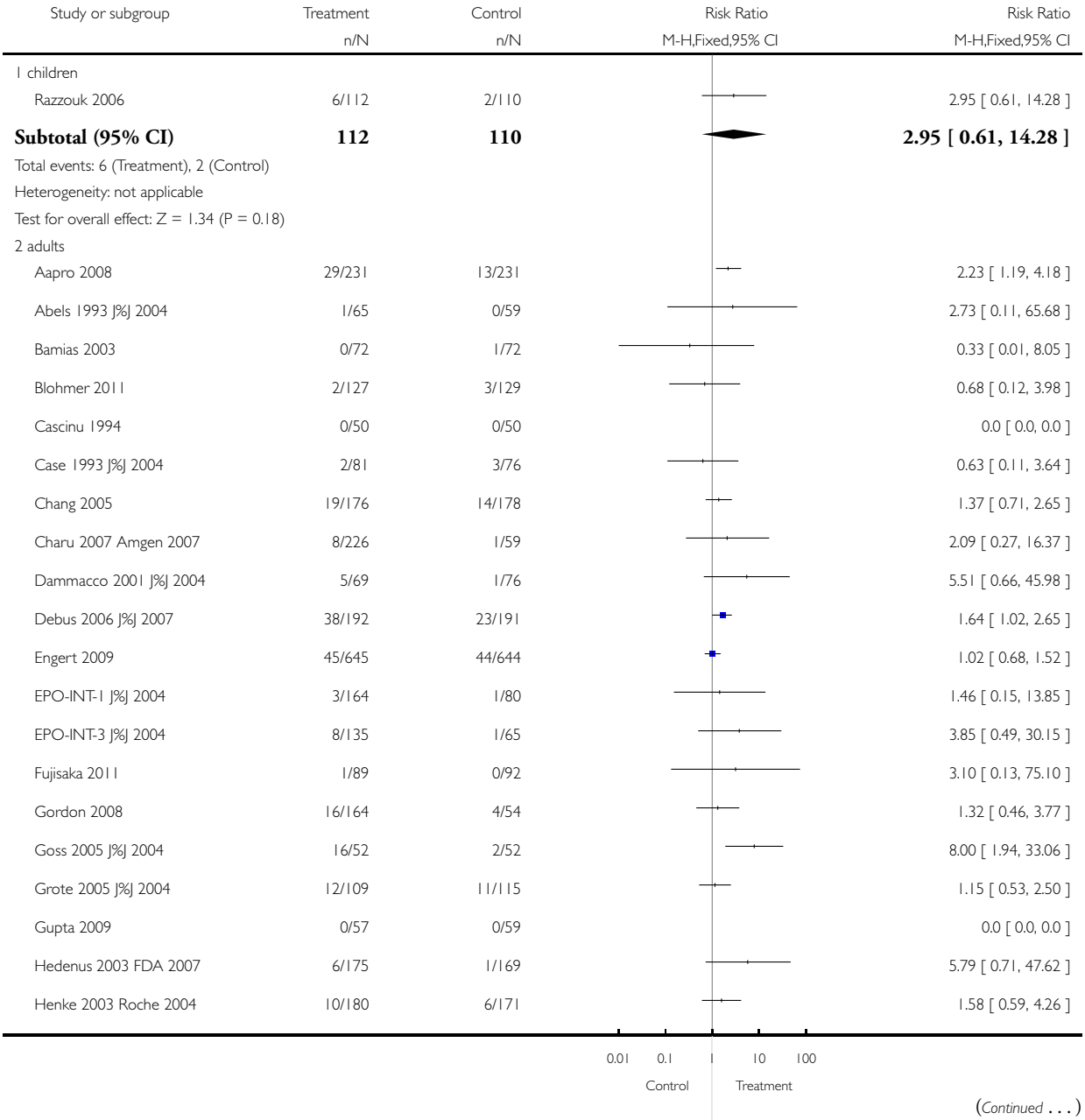
| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Henry 1995 J%J 2004 | 6/67 | 8/65 | | 0.73 [ 0.27, 1.98 ] |
| Hernandez 2009 | 16/194 | 11/192 | | 1.44 [ 0.69, 3.02 ] |
| Littlewood 2001 J%J 2004 | 14/251 | 5/124 | | 1.38 [ 0.51, 3.75 ] |
| Ray-Coquard 2009 | 5/110 | 4/107 | | 1.22 [ 0.34, 4.41 ] |
| Razzouk 2006 | 6/112 | 2/110 | | 2.95 [ 0.61, 14.28 ] |
| Smith 2003 Amgen 2007 | 2/64 | 2/22 | | 0.34 [ 0.05, 2.30 ] |
| Smith 2008 | 50/515 | 36/470 | | 1.27 [ 0.84, 1.91 ] |
| Tjulandin 2011 | 0/95 | 1/91 | | 0.32 [ 0.01, 7.74 ] |
| Tsuboi 2009 | 1/62 | 0/58 | | 2.81 [ 0.12, 67.62 ] |
| **Subtotal (95% CI)** | **2141** | **1552** | | **1.29 [ 0.98, 1.69 ]** |
| Total events: 135 (Treatment), 78 (Control) | | | | |
| Heterogeneity: $Chi^2$ = 7.41, df = 13 (P = 0.88); $I^2$ =0.0% | | | | |
| Test for overall effect: Z = 1.83 (P = 0.067) | | | | |
| 4 MDS | | | | |
| Italian 1998 | 1/44 | 0/43 | | 2.93 [ 0.12, 70.08 ] |
| Thompson 2000 | 1/45 | 0/21 | | 1.43 [ 0.06, 33.82 ] |
| **Subtotal (95% CI)** | **89** | **64** | | **2.08 [ 0.23, 18.84 ]** |
| Total events: 2 (Treatment), 0 (Control) | | | | |
| Heterogeneity: $Chi^2$ = 0.10, df = 1 (P = 0.75); $I^2$ =0.0% | | | | |
| Test for overall effect: Z = 0.65 (P = 0.52) | | | | |
| 5 not reported | | | | |
| **Subtotal (95% CI)** | **0** | **0** | | **0.0 [ 0.0, 0.0 ]** |
| Total events: 0 (Treatment), 0 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: not applicable | | | | |
| **Total (95% CI)** | **8248** | **7250** | | **1.52 [ 1.34, 1.74 ]** |
| Total events: 561 (Treatment), 332 (Control) | | | | |
| Heterogeneity: $Chi^2$ = 34.99, df = 55 (P = 0.98); $I^2$ =0.0% | | | | |
| Test for overall effect: Z = 6.36 (P < 0.00001) | | | | |
| Test for subgroup differences: $Chi^2$ = 3.23, df = 3 (P = 0.36), $I^2$ =7% | | | | |

## Analysis 11.4. Comparison 11 Thrombotic events, Outcome 4 Thrombotic events - age.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 11 Thrombotic events

Outcome: 4 Thrombotic events - age

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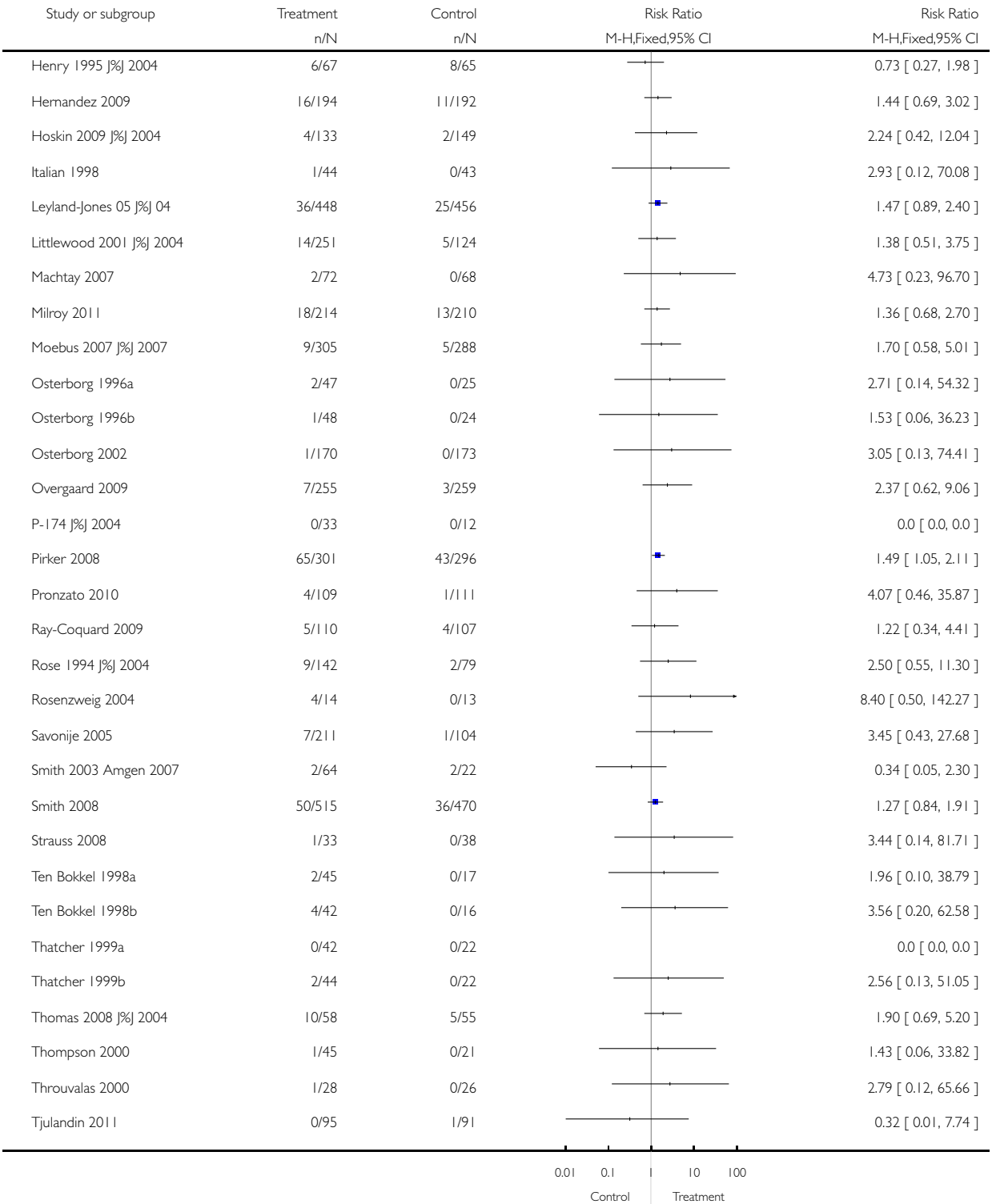


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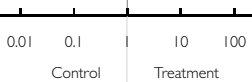
| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Tsuboi 2009 | 1/62 | 0/58 | | 2.81 [ 0.12, 67.62 ] |
| Untch 2011˙1 | 20/318 | 17/396 | | 1.47 [ 0.78, 2.75 ] |
| Vansteenkiste 2002 | 7/155 | 5/159 | | 1.44 [ 0.47, 4.43 ] |
| Welch 1995 | 1/15 | 0/15 | | 3.00 [ 0.13, 68.26 ] |
| Wilkinson 2006 | 10/121 | 1/60 | | 4.96 [ 0.65, 37.84 ] |
| Winquist 2009 | 0/26 | 2/30 | | 0.23 [ 0.01, 4.58 ] |
| Witzig 2005 J%J 2004 | 9/168 | 6/165 | | 1.47 [ 0.54, 4.05 ] |
| Wright 2007 | 2/33 | 3/37 | | 0.75 [ 0.13, 4.20 ] |
| **Subtotal (95% CI)** | **8136** | **7140** | | **1.52 [ 1.33, 1.73 ]** |
| Total events: 555 (Treatment), 330 (Control) | | | | |
| Heterogeneity: $Chi^2$ = 34.23, df = 54 (P = 0.98); $I^2$ =0.0% | | | | |
| Test for overall effect: Z = 6.25 (P < 0.00001) | | | | |
| **Total (95% CI)** | **8248** | **7250** | | **1.52 [ 1.34, 1.74 ]** |
| Total events: 561 (Treatment), 332 (Control) | | | | |
| Heterogeneity: $Chi^2$ = 34.99, df = 55 (P = 0.98); $I^2$ =0.0% | | | | |
| Test for overall effect: Z = 6.36 (P < 0.00001) | | | | |
| Test for subgroup differences: $Chi^2$ = 0.68, df = 1 (P = 0.41), $I^2$ =0.0% | | | | |

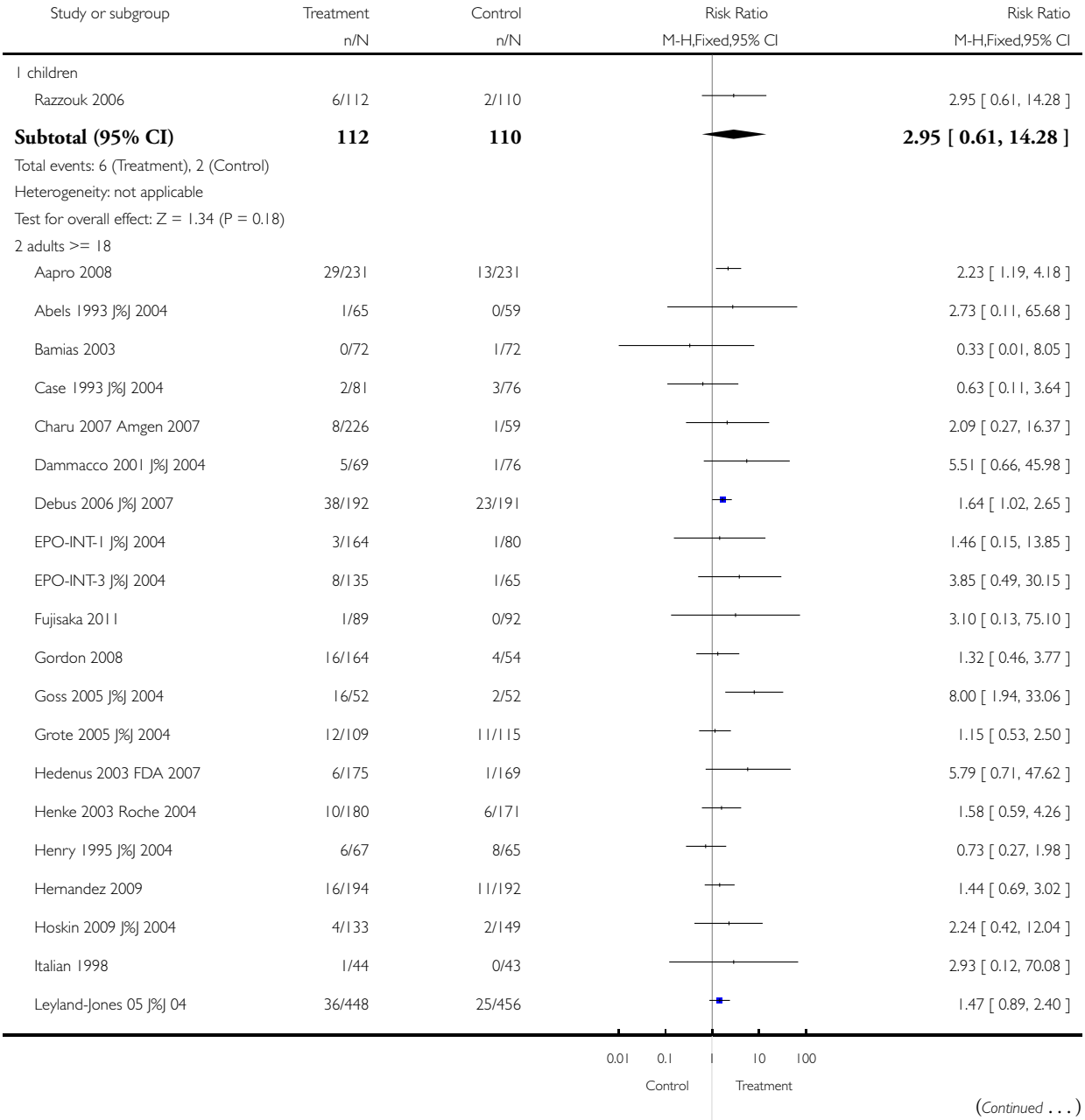


### Analysis 11.5. Comparison 11 Thrombotic events, Outcome 5 Thrombotic events - age differentiated.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 11 Thrombotic events

Outcome: 5 Thrombotic events - age differentiated

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| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Littlewood 2001 J%J 2004 | 14/251 | 5/124 | | 1.38 [ 0.51, 3.75 ] |
| Machtay 2007 | 2/72 | 0/68 | | 4.73 [ 0.23, 96.70 ] |
| Milroy 2011 | 18/214 | 13/210 | | 1.36 [ 0.68, 2.70 ] |
| Osterborg 1996a | 2/47 | 0/25 | | 2.71 [ 0.14, 54.32 ] |
| Osterborg 1996b | 1/48 | 0/24 | | 1.53 [ 0.06, 36.23 ] |
| Osterborg 2002 | 1/170 | 0/173 | | 3.05 [ 0.13, 74.41 ] |
| Overgaard 2009 | 7/255 | 3/259 | | 2.37 [ 0.62, 9.06 ] |
| P-174 J%J 2004 | 0/33 | 0/12 | | 0.0 [ 0.0, 0.0 ] |
| Pirker 2008 | 65/301 | 43/296 | | 1.49 [ 1.05, 2.11 ] |
| Ray-Coquard 2009 | 5/110 | 4/107 | | 1.22 [ 0.34, 4.41 ] |
| Rose 1994 J%J 2004 | 9/142 | 2/79 | | 2.50 [ 0.55, 11.30 ] |
| Rosenzweig 2004 | 4/14 | 0/13 | | 8.40 [ 0.50, 142.27 ] |
| Savonije 2005 | 7/211 | 1/104 | | 3.45 [ 0.43, 27.68 ] |
| Smith 2003 Amgen 2007 | 2/64 | 2/22 | | 0.34 [ 0.05, 2.30 ] |
| Smith 2008 | 50/515 | 36/470 | | 1.27 [ 0.84, 1.91 ] |
| Ten Bokkel 1998a | 2/45 | 0/17 | | 1.96 [ 0.10, 38.79 ] |
| Ten Bokkel 1998b | 4/42 | 0/16 | | 3.56 [ 0.20, 62.58 ] |
| Thatcher 1999a | 0/42 | 0/22 | | 0.0 [ 0.0, 0.0 ] |
| Thatcher 1999b | 2/44 | 0/22 | | 2.56 [ 0.13, 51.05 ] |
| Thompson 2000 | 1/45 | 0/21 | | 1.43 [ 0.06, 33.82 ] |
| Tjulandin 2011 | 0/95 | 1/91 | | 0.32 [ 0.01, 7.74 ] |
| Tsuboi 2009 | 1/62 | 0/58 | | 2.81 [ 0.12, 67.62 ] |
| Vansteenkiste 2002 | 7/155 | 5/159 | | 1.44 [ 0.47, 4.43 ] |
| Wilkinson 2006 | 10/121 | 1/60 | | 4.96 [ 0.65, 37.84 ] |
| Witzig 2005 J%J 2004 | 9/168 | 6/165 | | 1.47 [ 0.54, 4.05 ] |
| Wright 2007 | 2/33 | 3/37 | | 0.75 [ 0.13, 4.20 ] |
| **Subtotal (95% CI)** | **6189** | **5121** | | **1.60 [ 1.38, 1.86 ]** |
| Total events: 443 (Treatment), 239 (Control) | | | | |
| Heterogeneity: $Chi^2$ = 26.75, df = 43 (P = 0.98); $I^2$ =0.0% | | | | |
| Test for overall effect: Z = 6.16 (P < 0.00001) | | | | |
| 3 > 68% non elderly, 18-65 | | | | |
| Cascinu 1994 | 0/50 | 0/50 | | 0.0 [ 0.0, 0.0 ] |
| Chang 2005 | 19/176 | 14/178 | | 1.37 [ 0.71, 2.65 ] |


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| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Gupta 2009 | 0/57 | 0/59 | | 0.0 [ 0.0, 0.0 ] |
| Pronzato 2010 | 4/109 | 1/111 | | 4.07 [ 0.46, 35.87 ] |
| Strauss 2008 | 1/33 | 0/38 | | 3.44 [ 0.14, 81.71 ] |
| Thomas 2008 J%J 2004 | 10/58 | 5/55 | | 1.90 [ 0.69, 5.20 ] |
| Throuvalas 2000 | 1/28 | 0/26 | | 2.79 [ 0.12, 65.66 ] |
| **Subtotal (95% CI)** | **511** | **517** | | **1.71 [ 1.02, 2.86 ]** |
| Total events: 35 (Treatment), 20 (Control) | | | | |
| Heterogeneity: $Chi^2$ = 1.36, df = 4 (P = 0.85); $I^2$ =0.0% | | | | |
| Test for overall effect: Z = 2.04 (P = 0.041) | | | | |
| 4 only non elderly | | | | |
| Blohmer 2011 | 2/127 | 3/129 | | 0.68 [ 0.12, 3.98 ] |
| Engert 2009 | 45/645 | 44/644 | | 1.02 [ 0.68, 1.52 ] |
| Moebus 2007 J%J 2007 | 9/305 | 5/288 | | 1.70 [ 0.58, 5.01 ] |
| Untch 2011˙1 | 20/318 | 17/396 | | 1.47 [ 0.78, 2.75 ] |
| Welch 1995 | 1/15 | 0/15 | | 3.00 [ 0.13, 68.26 ] |
| **Subtotal (95% CI)** | **1410** | **1472** | | **1.17 [ 0.86, 1.60 ]** |
| Total events: 77 (Treatment), 69 (Control) | | | | |
| Heterogeneity: $Chi^2$ = 2.11, df = 4 (P = 0.72); $I^2$ =0.0% | | | | |
| Test for overall effect: Z = 0.99 (P = 0.32) | | | | |
| 5 > 68% elderly > 65 years | | | | |
| Winquist 2009 | 0/26 | 2/30 | | 0.23 [ 0.01, 4.58 ] |
| **Subtotal (95% CI)** | **26** | **30** | | **0.23 [ 0.01, 4.58 ]** |
| Total events: 0 (Treatment), 2 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: Z = 0.96 (P = 0.34) | | | | |
| 6 only elderly | | | | |
| **Subtotal (95% CI)** | **0** | **0** | | **0.0 [ 0.0, 0.0 ]** |
| Total events: 0 (Treatment), 0 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: not applicable | | | | |
| **Total (95% CI)** | **8248** | **7250** | | **1.52 [ 1.34, 1.74 ]** |
| Total events: 561 (Treatment), 332 (Control) | | | | |
| Heterogeneity: $Chi^2$ = 34.99, df = 55 (P = 0.98); $I^2$ =0.0% | | | | |
| Test for overall effect: Z = 6.36 (P < 0.00001) | | | | |
| Test for subgroup differences: $Chi^2$ = 5.53, df = 4 (P = 0.24), $I^2$ =28% | | | | |

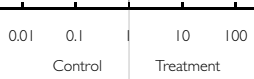
## Analysis 11.6. Comparison 11 Thrombotic events, Outcome 6 Thrombotic events - different therapies.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 11 Thrombotic events

Outcome: 6 Thrombotic events - different therapies

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| 1 chemotherapy | | | | |
| Aapro 2008 | 29/231 | 13/231 | | 2.23 [ 1.19, 4.18 ] |
| Bamias 2003 | 0/72 | 1/72 | | 0.33 [ 0.01, 8.05 ] |
| Cascinu 1994 | 0/50 | 0/50 | | 0.0 [ 0.0, 0.0 ] |
| Case 1993 J%J 2004 | 2/81 | 3/76 | | 0.63 [ 0.11, 3.64 ] |
| Chang 2005 | 19/176 | 14/178 | | 1.37 [ 0.71, 2.65 ] |
| Dammacco 2001 J%J 2004 | 5/69 | 1/76 | | 5.51 [ 0.66, 45.98 ] |
| Engert 2009 | 45/645 | 44/644 | | 1.02 [ 0.68, 1.52 ] |
| EPO-INT-1 J%J 2004 | 3/164 | 1/80 | | 1.46 [ 0.15, 13.85 ] |
| EPO-INT-3 J%J 2004 | 8/135 | 1/65 | | 3.85 [ 0.49, 30.15 ] |
| Fujisaka 2011 | 1/89 | 0/92 | | 3.10 [ 0.13, 75.10 ] |
| Grote 2005 J%J 2004 | 12/109 | 11/115 | | 1.15 [ 0.53, 2.50 ] |
| Hedenus 2003 FDA 2007 | 6/175 | 1/169 | | 5.79 [ 0.71, 47.62 ] |
| Henry 1995 J%J 2004 | 6/67 | 8/65 | | 0.73 [ 0.27, 1.98 ] |
| Hernandez 2009 | 16/194 | 11/192 | | 1.44 [ 0.69, 3.02 ] |
| Leyland-Jones 05 J%J 04 | 36/448 | 25/456 | | 1.47 [ 0.89, 2.40 ] |
| Littlewood 2001 J%J 2004 | 14/251 | 5/124 | | 1.38 [ 0.51, 3.75 ] |
| Milroy 2011 | 18/214 | 13/210 | | 1.36 [ 0.68, 2.70 ] |
| Moebus 2007 J%J 2007 | 9/305 | 5/288 | | 1.70 [ 0.58, 5.01 ] |
| Osterborg 1996a | 2/47 | 0/25 | | 2.71 [ 0.14, 54.32 ] |
| Osterborg 1996b | 1/48 | 0/24 | | 1.53 [ 0.06, 36.23 ] |
| Osterborg 2002 | 1/170 | 0/173 | | 3.05 [ 0.13, 74.41 ] |
| Pirker 2008 | 65/301 | 43/296 | | 1.49 [ 1.05, 2.11 ] |
| Pronzato 2010 | 4/109 | 1/111 | | 4.07 [ 0.46, 35.87 ] |
| Ray-Coquard 2009 | 5/110 | 4/107 | | 1.22 [ 0.34, 4.41 ] |
| Razzouk 2006 | 6/112 | 2/110 | | 2.95 [ 0.61, 14.28 ] |

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| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Savonije 2005 | 7/211 | 1/104 | | 3.45 [ 0.43, 27.68 ] |
| Ten Bokkel 1998a | 2/45 | 0/17 | | 1.96 [ 0.10, 38.79 ] |
| Ten Bokkel 1998b | 4/42 | 0/16 | | 3.56 [ 0.20, 62.58 ] |
| Thatcher 1999a | 0/42 | 0/22 | | 0.0 [ 0.0, 0.0 ] |
| Thatcher 1999b | 2/44 | 0/22 | | 2.56 [ 0.13, 51.05 ] |
| Tjulandin 2011 | 0/95 | 1/91 | | 0.32 [ 0.01, 7.74 ] |
| Tsuboi 2009 | 1/62 | 0/58 | | 2.81 [ 0.12, 67.62 ] |
| Untch 2011˙1 | 20/318 | 17/396 | | 1.47 [ 0.78, 2.75 ] |
| Vansteenkiste 2002 | 7/155 | 5/159 | | 1.44 [ 0.47, 4.43 ] |
| Welch 1995 | 1/15 | 0/15 | | 3.00 [ 0.13, 68.26 ] |
| Wilkinson 2006 | 10/121 | 1/60 | | 4.96 [ 0.65, 37.84 ] |
| Witzig 2005 J%J 2004 | 9/168 | 6/165 | | 1.47 [ 0.54, 4.05 ] |
| **Subtotal (95% CI)** | **5690** | **5154** | | **1.48 [ 1.27, 1.73 ]** |
| Total events: 376 (Treatment), 238 (Control) | | | | |
| Heterogeneity: $Chi^2$ = 19.10, df = 34 (P = 0.98); $I^2$ =0.0% | | | | |
| Test for overall effect: Z = 4.92 (P < 0.00001) | | | | |
| 2 radiotherapy/radiochemotherapy | | | | |
| Blohmer 2011 | 2/127 | 3/129 | | 0.68 [ 0.12, 3.98 ] |
| Debus 2006 J%J 2007 | 38/192 | 23/191 | | 1.64 [ 1.02, 2.65 ] |
| Goss 2005 J%J 2004 | 16/52 | 2/52 | | 8.00 [ 1.94, 33.06 ] |
| Gupta 2009 | 0/57 | 0/59 | | 0.0 [ 0.0, 0.0 ] |
| Henke 2003 Roche 2004 | 10/180 | 6/171 | | 1.58 [ 0.59, 4.26 ] |
| Hoskin 2009 J%J 2004 | 4/133 | 2/149 | | 2.24 [ 0.42, 12.04 ] |
| Machtay 2007 | 2/72 | 0/68 | | 4.73 [ 0.23, 96.70 ] |
| Overgaard 2009 | 7/255 | 3/259 | | 2.37 [ 0.62, 9.06 ] |
| Strauss 2008 | 1/33 | 0/38 | | 3.44 [ 0.14, 81.71 ] |
| Thomas 2008 J%J 2004 | 10/58 | 5/55 | | 1.90 [ 0.69, 5.20 ] |
| Throuvalas 2000 | 1/28 | 0/26 | | 2.79 [ 0.12, 65.66 ] |
| **Subtotal (95% CI)** | **1187** | **1197** | | **2.02 [ 1.44, 2.83 ]** |
| Total events: 91 (Treatment), 44 (Control) | | | | |
| Heterogeneity: $Chi^2$ = 6.56, df = 9 (P = 0.68); $I^2$ =0.0% | | | | |
| Test for overall effect: Z = 4.08 (P = 0.000045) | | | | |
| 3 no therapy | | | | |
| Abels 1993 J%J 2004 | 1/65 | 0/59 | | 2.73 [ 0.11, 65.68 ] |


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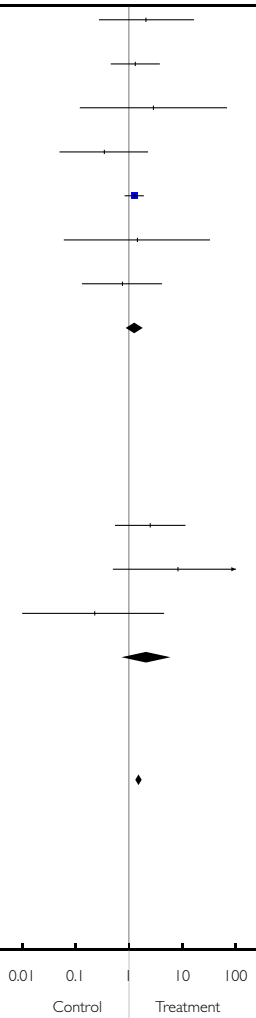
| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Charu 2007 Amgen 2007 | 8/226 | 1/59 | | 2.09 [ 0.27, 16.37 ] |
| Gordon 2008 | 16/164 | 4/54 | | 1.32 [ 0.46, 3.77 ] |
| Italian 1998 | 1/44 | 0/43 | | 2.93 [ 0.12, 70.08 ] |
| Smith 2003 Amgen 2007 | 2/64 | 2/22 | | 0.34 [ 0.05, 2.30 ] |
| Smith 2008 | 50/515 | 36/470 | | 1.27 [ 0.84, 1.91 ] |
| Thompson 2000 | 1/45 | 0/21 | | 1.43 [ 0.06, 33.82 ] |
| Wright 2007 | 2/33 | 3/37 | | 0.75 [ 0.13, 4.20 ] |
| **Subtotal (95% CI)** | **1156** | **765** | | **1.25 [ 0.88, 1.78 ]** |
| Total events: 81 (Treatment), 46 (Control) | | | | |
| Heterogeneity: $Chi^2$ = 2.88, df = 7 (P = 0.90); $I^2$ =0.0% | | | | |
| Test for overall effect: Z = 1.25 (P = 0.21) | | | | |
| 4 unclear/other | | | | |
| P-174 J%J 2004 | 0/33 | 0/12 | | 0.0 [ 0.0, 0.0 ] |
| Rose 1994 J%J 2004 | 9/142 | 2/79 | | 2.50 [ 0.55, 11.30 ] |
| Rosenzweig 2004 | 4/14 | 0/13 | | 8.40 [ 0.50, 142.27 ] |
| Winquist 2009 | 0/26 | 2/30 | | 0.23 [ 0.01, 4.58 ] |
| **Subtotal (95% CI)** | **215** | **134** | | **2.09 [ 0.74, 5.93 ]** |
| Total events: 13 (Treatment), 4 (Control) | | | | |
| Heterogeneity: $Chi^2$ = 3.08, df = 2 (P = 0.21); $I^2$ =35% | | | | |
| Test for overall effect: Z = 1.38 (P = 0.17) | | | | |
| **Total (95% CI)** | **8248** | **7250** | | **1.52 [ 1.34, 1.74 ]** |
| Total events: 561 (Treatment), 332 (Control) | | | | |
| Heterogeneity: $Chi^2$ = 34.99, df = 55 (P = 0.98); $I^2$ =0.0% | | | | |
| Test for overall effect: Z = 6.36 (P < 0.00001) | | | | |
| Test for subgroup differences: $Chi^2$ = 4.37, df = 3 (P = 0.22), $I^2$ =31% | | | | |

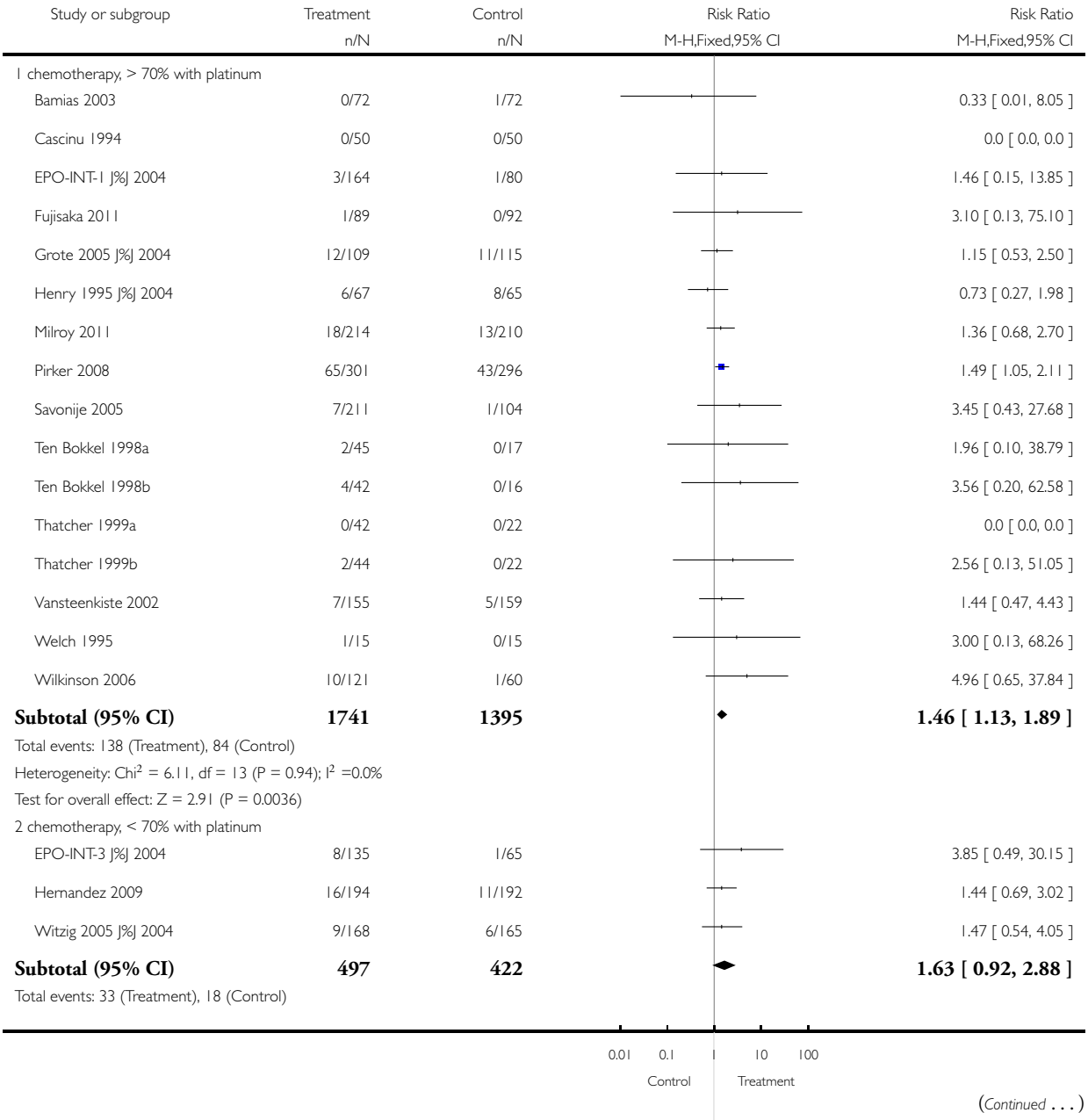


## Analysis 11.7. Comparison 11 Thrombotic events, Outcome 7 Thrombotic events - different therapies differentiated.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 11 Thrombotic events

Outcome: 7 Thrombotic events - different therapies differentiated

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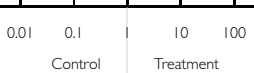
| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Heterogeneity: Chi² = 0.82, df = 2 (P = 0.67); I² =0.0% | | | | |
| Test for overall effect: Z = 1.67 (P = 0.095) | | | | |
| 3 chemotherapy, without platinum, all patients | | | | |
| Aapro 2008 | 29/231 | 13/231 | | 2.23 [ 1.19, 4.18 ] |
| Case 1993 J%J 2004 | 2/81 | 3/76 | | 0.63 [ 0.11, 3.64 ] |
| Chang 2005 | 19/176 | 14/178 | | 1.37 [ 0.71, 2.65 ] |
| Engert 2009 | 45/645 | 44/644 | | 1.02 [ 0.68, 1.52 ] |
| Hedenus 2003 FDA 2007 | 6/175 | 1/169 | | 5.79 [ 0.71, 47.62 ] |
| Leyland-Jones 05 J%J 04 | 36/448 | 25/456 | | 1.47 [ 0.89, 2.40 ] |
| Littlewood 2001 J%J 2004 | 14/251 | 5/124 | | 1.38 [ 0.51, 3.75 ] |
| Moebus 2007 J%J 2007 | 9/305 | 5/288 | | 1.70 [ 0.58, 5.01 ] |
| Osterborg 1996a | 2/47 | 0/25 | | 2.71 [ 0.14, 54.32 ] |
| Osterborg 1996b | 1/48 | 0/24 | | 1.53 [ 0.06, 36.23 ] |
| Osterborg 2002 | 1/170 | 0/173 | | 3.05 [ 0.13, 74.41 ] |
| Pronzato 2010 | 4/109 | 1/111 | | 4.07 [ 0.46, 35.87 ] |
| Tjulandin 2011 | 0/95 | 1/91 | | 0.32 [ 0.01, 7.74 ] |
| Untch 2011˙1 | 20/318 | 17/396 | | 1.47 [ 0.78, 2.75 ] |
| **Subtotal (95% CI)** | **3099** | **2986** | | **1.42 [ 1.14, 1.76 ]** |
| Total events: 188 (Treatment), 129 (Control) | | | | |
| Heterogeneity: Chi² = 9.42, df = 13 (P = 0.74); I² =0.0% | | | | |
| Test for overall effect: Z = 3.17 (P = 0.0015) | | | | |
| 4 chemotherapy, platinum and non platinum containing, no numbers given | | | | |
| Dammacco 2001 J%J 2004 | 5/69 | 1/76 | | 5.51 [ 0.66, 45.98 ] |
| Tsuboi 2009 | 1/62 | 0/58 | | 2.81 [ 0.12, 67.62 ] |
| **Subtotal (95% CI)** | **131** | **134** | | **4.56 [ 0.79, 26.20 ]** |
| Total events: 6 (Treatment), 1 (Control) | | | | |
| Heterogeneity: Chi² = 0.12, df = 1 (P = 0.73); I² =0.0% | | | | |
| Test for overall effect: Z = 1.70 (P = 0.089) | | | | |
| 5 chemotherapy no details given | | | | |
| Ray-Coquard 2009 | 5/110 | 4/107 | | 1.22 [ 0.34, 4.41 ] |
| Razzouk 2006 | 6/112 | 2/110 | | 2.95 [ 0.61, 14.28 ] |
| **Subtotal (95% CI)** | **222** | **217** | | **1.79 [ 0.67, 4.76 ]** |
| Total events: 11 (Treatment), 6 (Control) | | | | |
| Heterogeneity: Chi² = 0.73, df = 1 (P = 0.39); I² =0.0% | | | | |
| Test for overall effect: Z = 1.17 (P = 0.24) | | | | |
| 6 radiochemotherapy | | | | |
| Blohmer 2011 | 2/127 | 3/129 | | 0.68 [ 0.12, 3.98 ] |

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| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Debus 2006 J%J 2007 | 38/192 | 23/191 | | 1.64 [ 1.02, 2.65 ] |
| Goss 2005 J%J 2004 | 16/52 | 2/52 | | 8.00 [ 1.94, 33.06 ] |
| Gupta 2009 | 0/57 | 0/59 | | 0.0 [ 0.0, 0.0 ] |
| Strauss 2008 | 1/33 | 0/38 | | 3.44 [ 0.14, 81.71 ] |
| Thomas 2008 J%J 2004 | 10/58 | 5/55 | | 1.90 [ 0.69, 5.20 ] |
| Throuvalas 2000 | 1/28 | 0/26 | | 2.79 [ 0.12, 65.66 ] |
| **Subtotal (95% CI)** | **547** | **550** | | **2.01 [ 1.37, 2.96 ]** |
| Total events: 68 (Treatment), 33 (Control) | | | | |
| Heterogeneity: $Chi^2$ = 5.94, df = 5 (P = 0.31); $I^2$ =16% | | | | |
| Test for overall effect: Z = 3.56 (P = 0.00038) | | | | |
| 7 radiotherapy | | | | |
| Henke 2003 Roche 2004 | 10/180 | 6/171 | | 1.58 [ 0.59, 4.26 ] |
| Hoskin 2009 J%J 2004 | 4/133 | 2/149 | | 2.24 [ 0.42, 12.04 ] |
| Machtay 2007 | 2/72 | 0/68 | | 4.73 [ 0.23, 96.70 ] |
| Overgaard 2009 | 7/255 | 3/259 | | 2.37 [ 0.62, 9.06 ] |
| **Subtotal (95% CI)** | **640** | **647** | | **2.03 [ 1.02, 4.07 ]** |
| Total events: 23 (Treatment), 11 (Control) | | | | |
| Heterogeneity: $Chi^2$ = 0.61, df = 3 (P = 0.89); $I^2$ =0.0% | | | | |
| Test for overall effect: Z = 2.00 (P = 0.045) | | | | |
| 8 no therapy | | | | |
| Abels 1993 J%J 2004 | 1/65 | 0/59 | | 2.73 [ 0.11, 65.68 ] |
| Charu 2007 Amgen 2007 | 8/226 | 1/59 | | 2.09 [ 0.27, 16.37 ] |
| Gordon 2008 | 16/164 | 4/54 | | 1.32 [ 0.46, 3.77 ] |
| Italian 1998 | 1/44 | 0/43 | | 2.93 [ 0.12, 70.08 ] |
| Smith 2003 Amgen 2007 | 2/64 | 2/22 | | 0.34 [ 0.05, 2.30 ] |
| Smith 2008 | 50/515 | 36/470 | | 1.27 [ 0.84, 1.91 ] |
| Thompson 2000 | 1/45 | 0/21 | | 1.43 [ 0.06, 33.82 ] |
| Wright 2007 | 2/33 | 3/37 | | 0.75 [ 0.13, 4.20 ] |
| **Subtotal (95% CI)** | **1156** | **765** | | **1.25 [ 0.88, 1.78 ]** |
| Total events: 81 (Treatment), 46 (Control) | | | | |
| Heterogeneity: $Chi^2$ = 2.88, df = 7 (P = 0.90); $I^2$ =0.0% | | | | |
| Test for overall effect: Z = 1.25 (P = 0.21) | | | | |
| 9 unclear/other | | | | |
| P-174 J%J 2004 | 0/33 | 0/12 | | 0.0 [ 0.0, 0.0 ] |
| Rose 1994 J%J 2004 | 9/142 | 2/79 | | 2.50 [ 0.55, 11.30 ] |
| Rosenzweig 2004 | 4/14 | 0/13 | | 8.40 [ 0.50, 142.27 ] |


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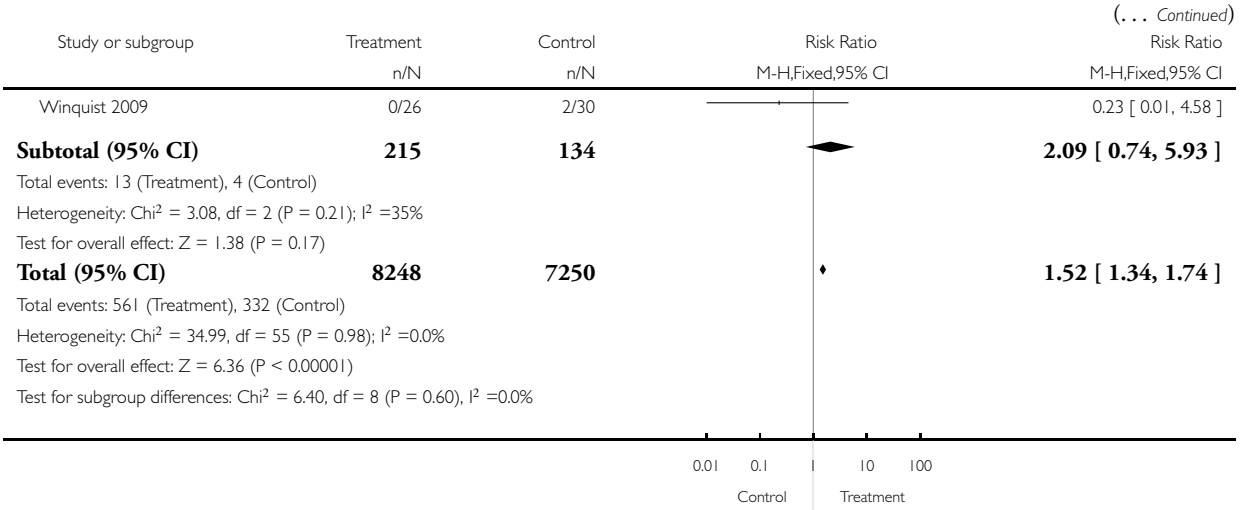
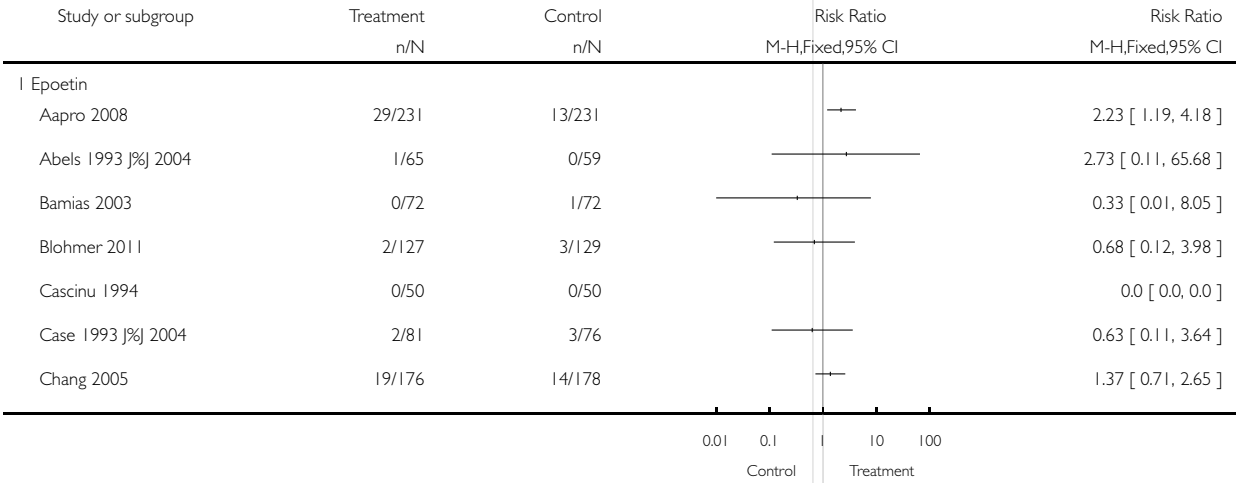



**Analysis 11.8. Comparison 11 Thrombotic events, Outcome 8 Thrombotic events - epoetin versus darbepoetin.**

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 11 Thrombotic events

Outcome: 8 Thrombotic events - epoetin versus darbepoetin

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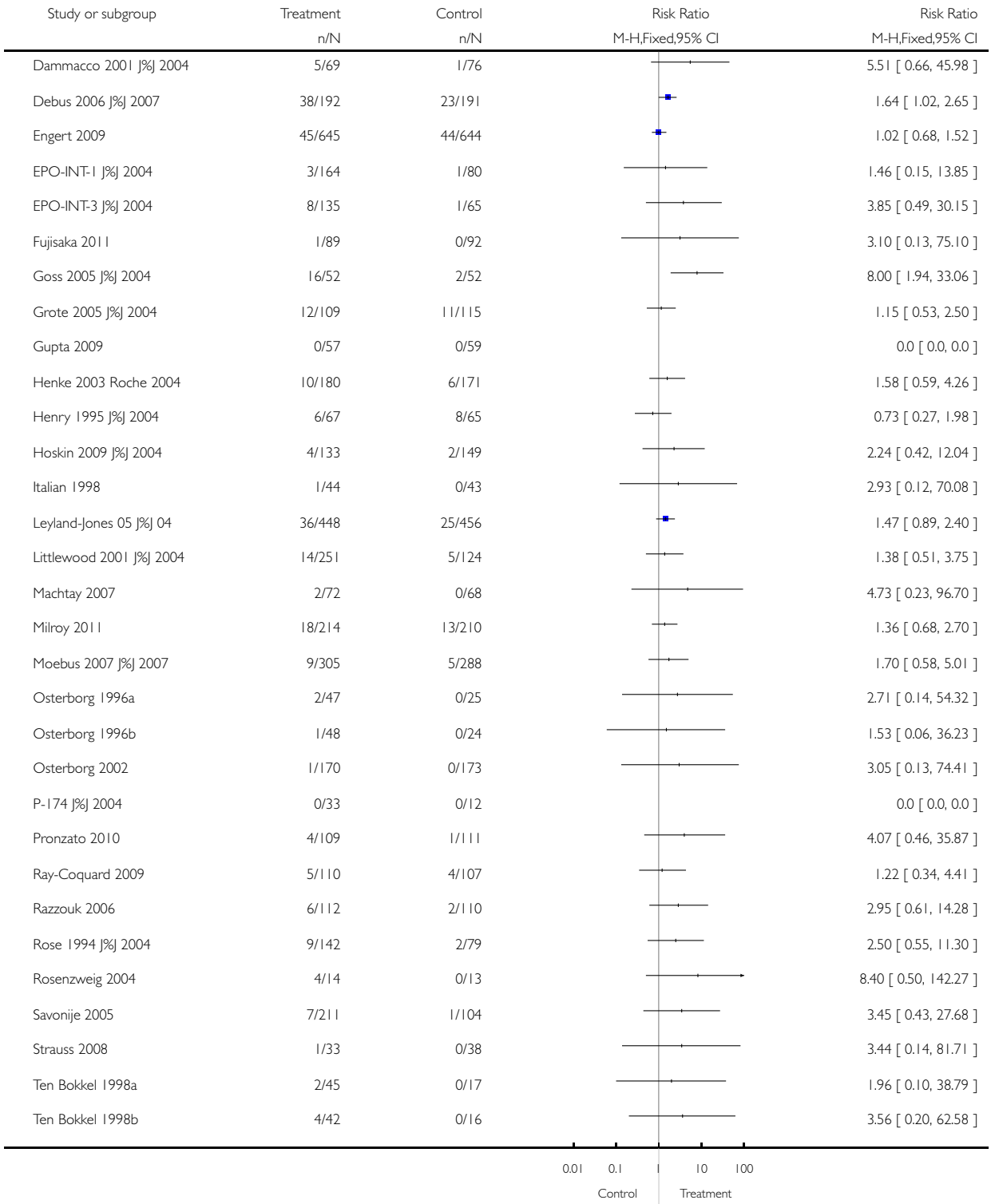


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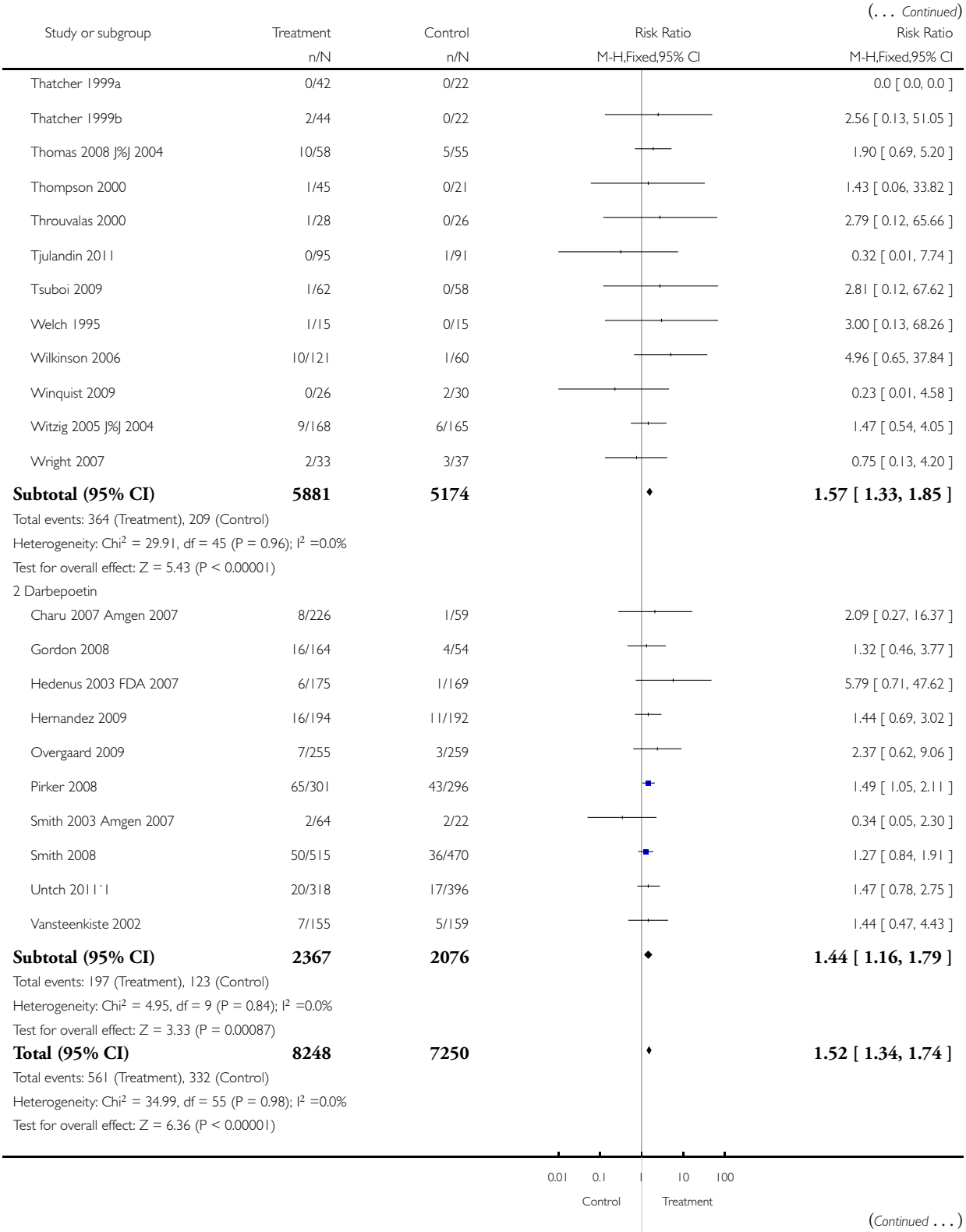


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| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Test for subgroup differences: Chi² = 0.40, df = 1 (P = 0.53), I² =0.0% | | | | |


## Analysis 11.9. Comparison 11 Thrombotic events, Outcome 9 Thrombotic events - duration of ESA treatment.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 11 Thrombotic events

Outcome: 9 Thrombotic events - duration of ESA treatment

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| 1 6 to 9 weeks | | | | |
| Abels 1993 J%J 2004 | 1/65 | 0/59 | | 2.73 [ 0.11, 65.68 ] |
| Cascinu 1994 | 0/50 | 0/50 | | 0.0 [ 0.0, 0.0 ] |
| Gupta 2009 | 0/57 | 0/59 | | 0.0 [ 0.0, 0.0 ] |
| Henke 2003 Roche 2004 | 10/180 | 6/171 | | 1.58 [ 0.59, 4.26 ] |
| Italian 1998 | 1/44 | 0/43 | | 2.93 [ 0.12, 70.08 ] |
| Machtay 2007 | 2/72 | 0/68 | | 4.73 [ 0.23, 96.70 ] |
| Overgaard 2009 | 7/255 | 3/259 | | 2.37 [ 0.62, 9.06 ] |
| Thomas 2008 J%J 2004 | 10/58 | 5/55 | | 1.90 [ 0.69, 5.20 ] |
| Throuvalas 2000 | 1/28 | 0/26 | | 2.79 [ 0.12, 65.66 ] |
| Tsuboi 2009 | 1/62 | 0/58 | | 2.81 [ 0.12, 67.62 ] |
| **Subtotal (95% CI)** | **871** | **848** | | **2.06 [ 1.17, 3.64 ]** |
| Total events: 33 (Treatment), 14 (Control) | | | | |
| Heterogeneity: Chi² = 0.78, df = 7 (P = 1.00); I² =0.0% | | | | |
| Test for overall effect: Z = 2.50 (P = 0.012) | | | | |
| 2 12 to 16 weeks | | | | |
| Case 1993 J%J 2004 | 2/81 | 3/76 | | 0.63 [ 0.11, 3.64 ] |


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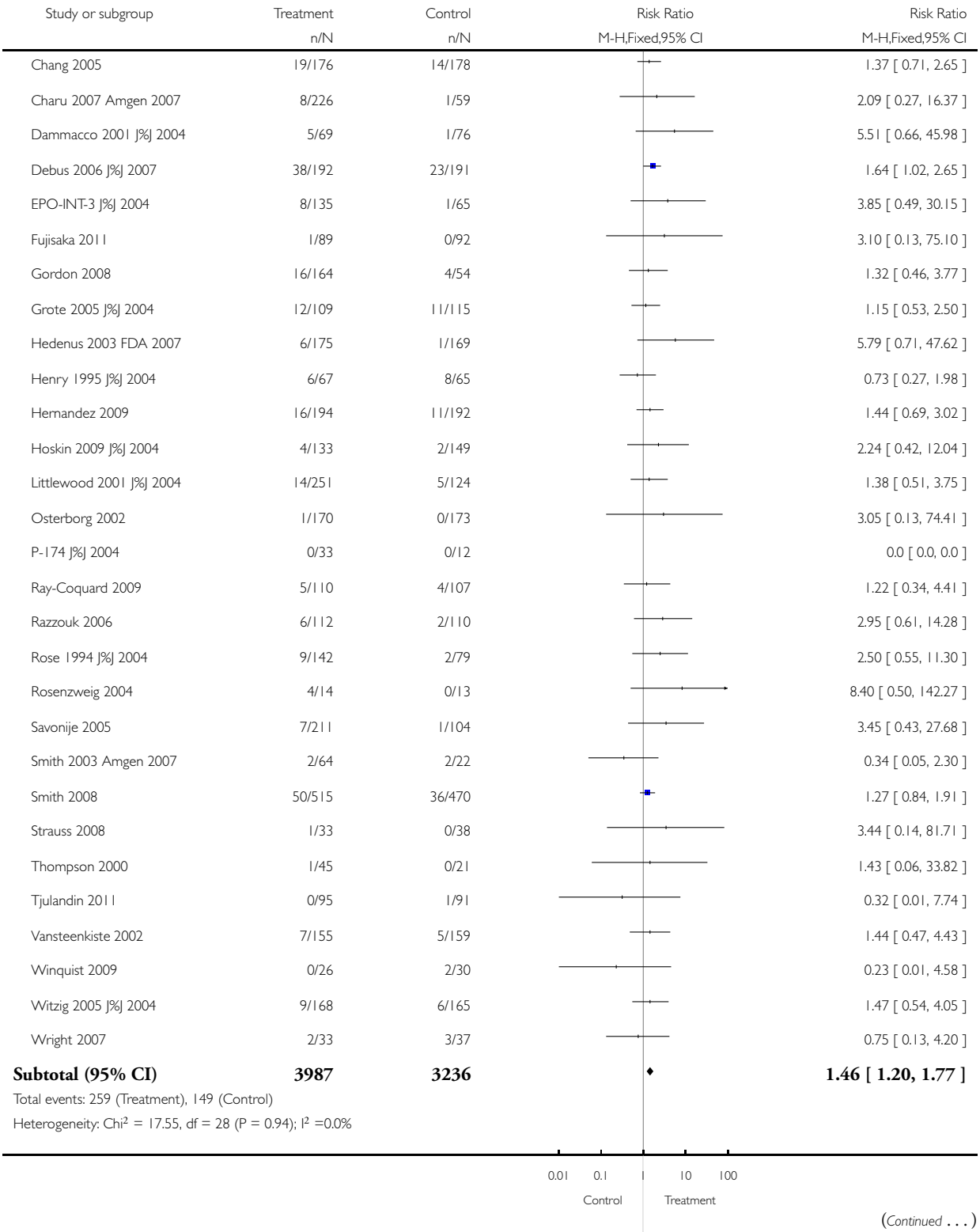


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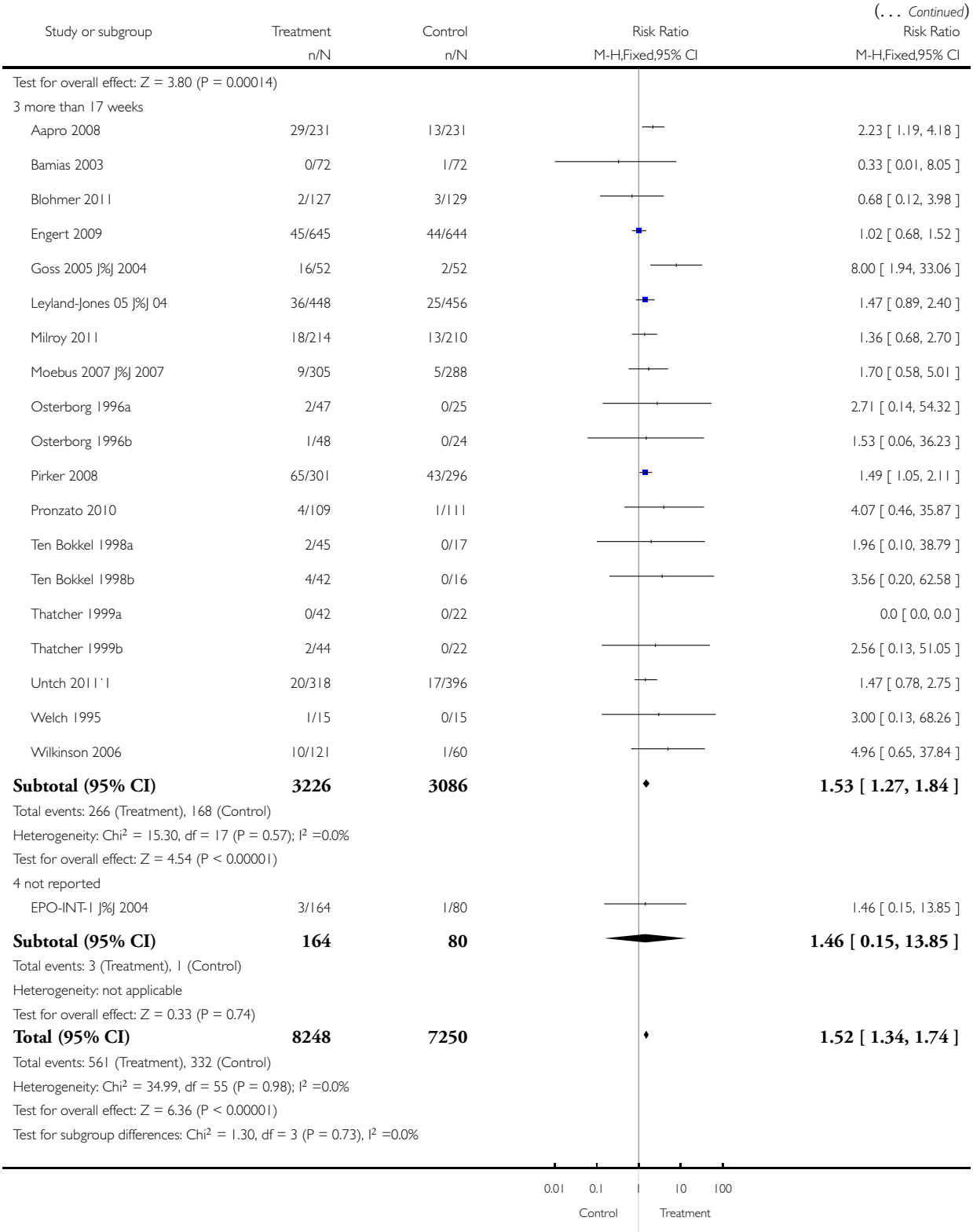

### Analysis 11.10. Comparison 11 Thrombotic events, Outcome 10 Thrombotic events - iron supplementation.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 11 Thrombotic events

Outcome: 10 Thrombotic events - iron supplementation

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| 1 fixed iron supplementation | | | | |
| Gupta 2009 | 0/57 | 0/59 | | 0.0 [ 0.0, 0.0 ] |
| Hoskin 2009 J%J 2004 | 4/133 | 2/149 | | 2.24 [ 0.42, 12.04 ] |
| Untch 2011˙1 | 20/318 | 17/396 | | 1.47 [ 0.78, 2.75 ] |
| Witzig 2005 J%J 2004 | 9/168 | 6/165 | | 1.47 [ 0.54, 4.05 ] |
| **Subtotal (95% CI)** | **676** | **769** | | **1.53 [ 0.92, 2.54 ]** |
| Total events: 33 (Treatment), 25 (Control) | | | | |
| Heterogeneity: $Chi^2$ = 0.22, df = 2 (P = 0.90); $I^2$ =0.0% | | | | |
| Test for overall effect: Z = 1.64 (P = 0.10) | | | | |
| 2 iron supplementation as necessary | | | | |
| Aapro 2008 | 29/231 | 13/231 | | 2.23 [ 1.19, 4.18 ] |
| Abels 1993 J%J 2004 | 1/65 | 0/59 | | 2.73 [ 0.11, 65.68 ] |
| Cascinu 1994 | 0/50 | 0/50 | | 0.0 [ 0.0, 0.0 ] |
| Case 1993 J%J 2004 | 2/81 | 3/76 | | 0.63 [ 0.11, 3.64 ] |
| Chang 2005 | 19/176 | 14/178 | | 1.37 [ 0.71, 2.65 ] |
| Charu 2007 Amgen 2007 | 8/226 | 1/59 | | 2.09 [ 0.27, 16.37 ] |
| Dammacco 2001 J%J 2004 | 5/69 | 1/76 | | 5.51 [ 0.66, 45.98 ] |
| Engert 2009 | 45/645 | 44/644 | | 1.02 [ 0.68, 1.52 ] |
| EPO-INT-1 J%J 2004 | 3/164 | 1/80 | | 1.46 [ 0.15, 13.85 ] |
| EPO-INT-3 J%J 2004 | 8/135 | 1/65 | | 3.85 [ 0.49, 30.15 ] |
| Fujisaka 2011 | 1/89 | 0/92 | | 3.10 [ 0.13, 75.10 ] |
| Gordon 2008 | 16/164 | 4/54 | | 1.32 [ 0.46, 3.77 ] |
| Goss 2005 J%J 2004 | 16/52 | 2/52 | | 8.00 [ 1.94, 33.06 ] |
| Grote 2005 J%J 2004 | 12/109 | 11/115 | | 1.15 [ 0.53, 2.50 ] |
| Hedenus 2003 FDA 2007 | 6/175 | 1/169 | | 5.79 [ 0.71, 47.62 ] |


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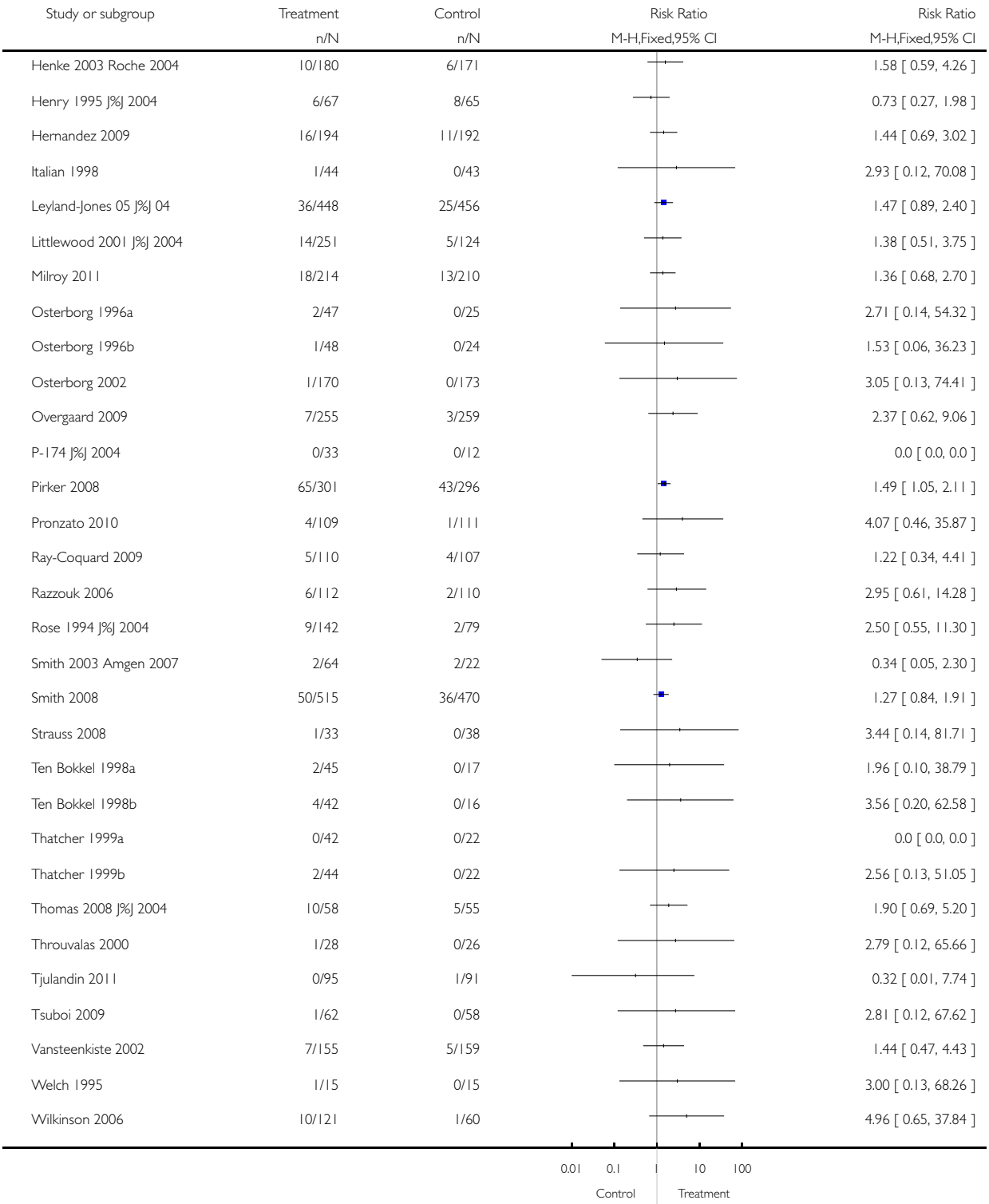


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| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Wright 2007 | 2/33 | 3/37 | | 0.75 [ 0.13, 4.20 ] |
| **Subtotal (95% CI)** | **6508** | **5565** | | **1.51 [ 1.31, 1.74 ]** |
| Total events: 465 (Treatment), 272 (Control) | | | | |
| Heterogeneity: Chi² = 28.73, df = 43 (P = 0.95); I² =0.0% | | | | |
| Test for overall effect: Z = 5.63 (P < 0.00001) | | | | |
| 3 no explicit statement on iron supplementation or no iron given | | | | |
| Bamias 2003 | 0/72 | 1/72 | | 0.33 [ 0.01, 8.05 ] |
| Rosenzweig 2004 | 4/14 | 0/13 | | 8.40 [ 0.50, 142.27 ] |
| Thompson 2000 | 1/45 | 0/21 | | 1.43 [ 0.06, 33.82 ] |
| Winquist 2009 | 0/26 | 2/30 | | 0.23 [ 0.01, 4.58 ] |
| **Subtotal (95% CI)** | **157** | **136** | | **1.26 [ 0.39, 4.06 ]** |
| Total events: 5 (Treatment), 3 (Control) | | | | |
| Heterogeneity: Chi² = 3.65, df = 3 (P = 0.30); I² =18% | | | | |
| Test for overall effect: Z = 0.39 (P = 0.69) | | | | |
| 4 iron handled differently in the study arms | | | | |
| Blohmer 2011 | 2/127 | 3/129 | | 0.68 [ 0.12, 3.98 ] |
| Debus 2006 J%J 2007 | 38/192 | 23/191 | | 1.64 [ 1.02, 2.65 ] |
| Machtay 2007 | 2/72 | 0/68 | | 4.73 [ 0.23, 96.70 ] |
| Moebus 2007 J%J 2007 | 9/305 | 5/288 | | 1.70 [ 0.58, 5.01 ] |
| Savonije 2005 | 7/211 | 1/104 | | 3.45 [ 0.43, 27.68 ] |
| **Subtotal (95% CI)** | **907** | **780** | | **1.69 [ 1.12, 2.54 ]** |
| Total events: 58 (Treatment), 32 (Control) | | | | |
| Heterogeneity: Chi² = 1.93, df = 4 (P = 0.75); I² =0.0% | | | | |
| Test for overall effect: Z = 2.50 (P = 0.012) | | | | |
| 5 explicitly stated NO IRON | | | | |
| **Subtotal (95% CI)** | **0** | **0** | | **0.0 [ 0.0, 0.0 ]** |
| Total events: 0 (Treatment), 0 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: not applicable | | | | |
| **Total (95% CI)** | **8248** | **7250** | | **1.52 [ 1.34, 1.74 ]** |
| Total events: 561 (Treatment), 332 (Control) | | | | |
| Heterogeneity: Chi² = 34.99, df = 55 (P = 0.98); I² =0.0% | | | | |
| Test for overall effect: Z = 6.36 (P < 0.00001) | | | | |
| Test for subgroup differences: Chi² = 0.35, df = 3 (P = 0.95), I² =0.0% | | | | |

## Analysis 11.11. Comparison 11 Thrombotic events, Outcome 11 Thrombotic events - concealment of allocation.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 11 Thrombotic events

Outcome: 11 Thrombotic events - concealment of allocation

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| 1 adequate | | | | |
| Aapro 2008 | 29/231 | 13/231 | | 2.23 [ 1.19, 4.18 ] |
| Blohmer 2011 | 2/127 | 3/129 | | 0.68 [ 0.12, 3.98 ] |
| Chang 2005 | 19/176 | 14/178 | | 1.37 [ 0.71, 2.65 ] |
| Charu 2007 Amgen 2007 | 8/226 | 1/59 | | 2.09 [ 0.27, 16.37 ] |
| EPO-INT-3 J%J 2004 | 8/135 | 1/65 | | 3.85 [ 0.49, 30.15 ] |
| Fujisaka 2011 | 1/89 | 0/92 | | 3.10 [ 0.13, 75.10 ] |
| Gordon 2008 | 16/164 | 4/54 | | 1.32 [ 0.46, 3.77 ] |
| Goss 2005 J%J 2004 | 16/52 | 2/52 | | 8.00 [ 1.94, 33.06 ] |
| Hedenus 2003 FDA 2007 | 6/175 | 1/169 | | 5.79 [ 0.71, 47.62 ] |
| Henke 2003 Roche 2004 | 10/180 | 6/171 | | 1.58 [ 0.59, 4.26 ] |
| Hernandez 2009 | 16/194 | 11/192 | | 1.44 [ 0.69, 3.02 ] |
| Italian 1998 | 1/44 | 0/43 | | 2.93 [ 0.12, 70.08 ] |
| Leyland-Jones 05 J%J 04 | 36/448 | 25/456 | | 1.47 [ 0.89, 2.40 ] |
| Littlewood 2001 J%J 2004 | 14/251 | 5/124 | | 1.38 [ 0.51, 3.75 ] |
| Machtay 2007 | 2/72 | 0/68 | | 4.73 [ 0.23, 96.70 ] |
| Milroy 2011 | 18/214 | 13/210 | | 1.36 [ 0.68, 2.70 ] |
| Moebus 2007 J%J 2007 | 9/305 | 5/288 | | 1.70 [ 0.58, 5.01 ] |
| Osterborg 1996a | 2/47 | 0/25 | | 2.71 [ 0.14, 54.32 ] |
| Osterborg 1996b | 1/48 | 0/24 | | 1.53 [ 0.06, 36.23 ] |
| Osterborg 2002 | 1/170 | 0/173 | | 3.05 [ 0.13, 74.41 ] |
| Overgaard 2009 | 7/255 | 3/259 | | 2.37 [ 0.62, 9.06 ] |
| Pirker 2008 | 65/301 | 43/296 | | 1.49 [ 1.05, 2.11 ] |
| Pronzato 2010 | 4/109 | 1/111 | | 4.07 [ 0.46, 35.87 ] |
| Ray-Coquard 2009 | 5/110 | 4/107 | | 1.22 [ 0.34, 4.41 ] |


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| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Razzouk 2006 | 6/112 | 2/110 | | 2.95 [ 0.61, 14.28 ] |
| Rosenzweig 2004 | 4/14 | 0/13 | | 8.40 [ 0.50, 142.27 ] |
| Savonije 2005 | 7/211 | 1/104 | | 3.45 [ 0.43, 27.68 ] |
| Smith 2008 | 50/515 | 36/470 | | 1.27 [ 0.84, 1.91 ] |
| Ten Bokkel 1998a | 2/45 | 0/17 | | 1.96 [ 0.10, 38.79 ] |
| Ten Bokkel 1998b | 4/42 | 0/16 | | 3.56 [ 0.20, 62.58 ] |
| Thomas 2008 J%J 2004 | 10/58 | 5/55 | | 1.90 [ 0.69, 5.20 ] |
| Thompson 2000 | 1/45 | 0/21 | | 1.43 [ 0.06, 33.82 ] |
| Throuvalas 2000 | 1/28 | 0/26 | | 2.79 [ 0.12, 65.66 ] |
| Tsuboi 2009 | 1/62 | 0/58 | | 2.81 [ 0.12, 67.62 ] |
| Vansteenkiste 2002 | 7/155 | 5/159 | | 1.44 [ 0.47, 4.43 ] |
| Winquist 2009 | 0/26 | 2/30 | | 0.23 [ 0.01, 4.58 ] |
| Witzig 2005 J%J 2004 | 9/168 | 6/165 | | 1.47 [ 0.54, 4.05 ] |
| Wright 2007 | 2/33 | 3/37 | | 0.75 [ 0.13, 4.20 ] |
| **Subtotal (95% CI)** | **5637** | **4857** | ◆ | **1.64 [ 1.40, 1.92 ]** |
| Total events: 400 (Treatment), 215 (Control) | | | | |
| Heterogeneity: $Chi^2$ = 19.36, df = 37 (P = 0.99); $I^2$ =0.0% | | | | |
| Test for overall effect: Z = 6.08 (P < 0.00001) | | | | |
| 2 unclear | | | | |
| Abels 1993 J%J 2004 | 1/65 | 0/59 | | 2.73 [ 0.11, 65.68 ] |
| Bamias 2003 | 0/72 | 1/72 | | 0.33 [ 0.01, 8.05 ] |
| Cascinu 1994 | 0/50 | 0/50 | | 0.0 [ 0.0, 0.0 ] |
| Case 1993 J%J 2004 | 2/81 | 3/76 | | 0.63 [ 0.11, 3.64 ] |
| Dammacco 2001 J%J 2004 | 5/69 | 1/76 | | 5.51 [ 0.66, 45.98 ] |
| Debus 2006 J%J 2007 | 38/192 | 23/191 | | 1.64 [ 1.02, 2.65 ] |
| Engert 2009 | 45/645 | 44/644 | | 1.02 [ 0.68, 1.52 ] |
| EPO-INT-1 J%J 2004 | 3/164 | 1/80 | | 1.46 [ 0.15, 13.85 ] |
| Grote 2005 J%J 2004 | 12/109 | 11/115 | | 1.15 [ 0.53, 2.50 ] |
| Gupta 2009 | 0/57 | 0/59 | | 0.0 [ 0.0, 0.0 ] |
| Henry 1995 J%J 2004 | 6/67 | 8/65 | | 0.73 [ 0.27, 1.98 ] |
| Hoskin 2009 J%J 2004 | 4/133 | 2/149 | | 2.24 [ 0.42, 12.04 ] |
| P-174 J%J 2004 | 0/33 | 0/12 | | 0.0 [ 0.0, 0.0 ] |
| Rose 1994 J%J 2004 | 9/142 | 2/79 | | 2.50 [ 0.55, 11.30 ] |


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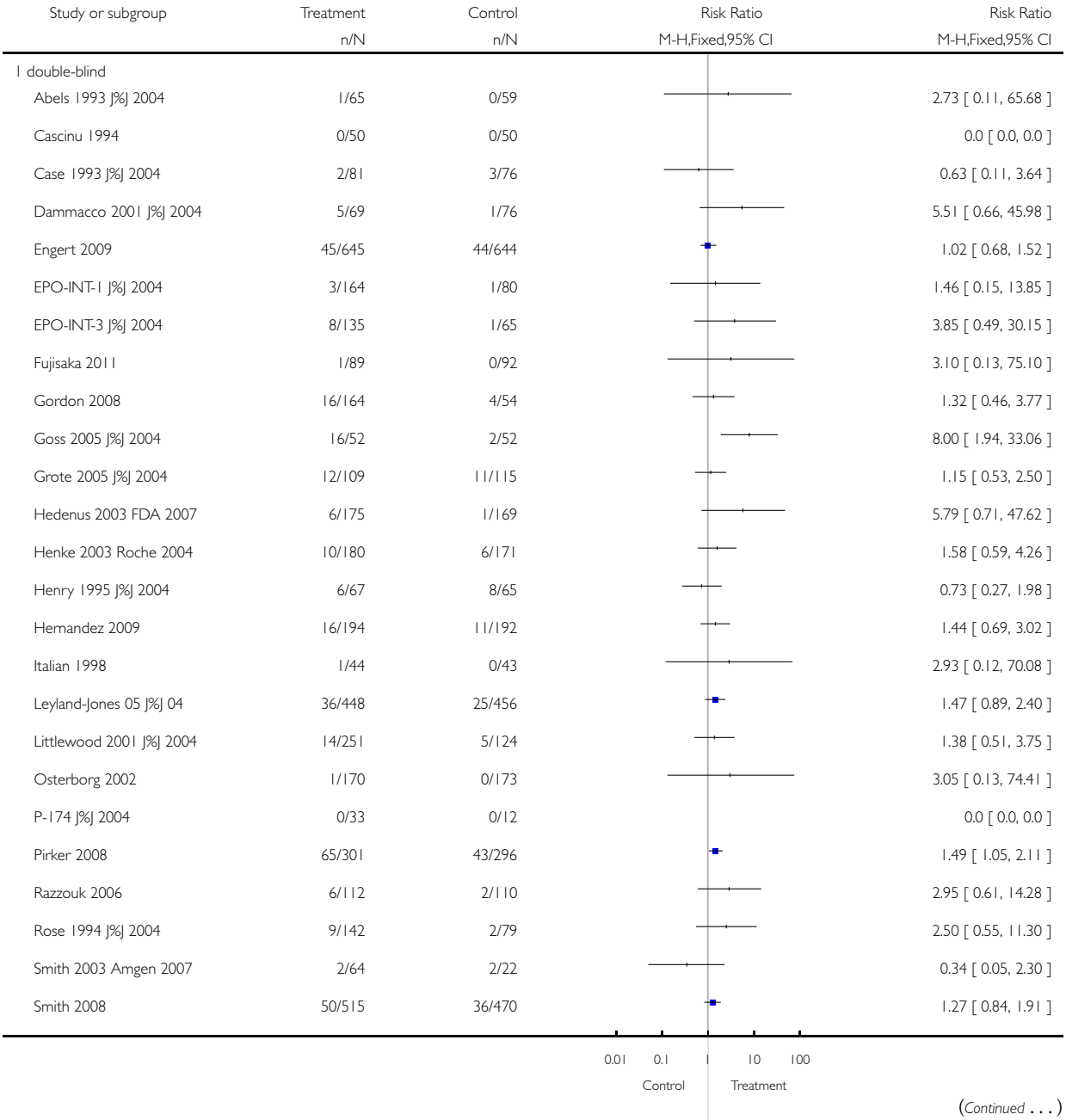
| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Smith 2003 Amgen 2007 | 2/64 | 2/22 | | 0.34 [ 0.05, 2.30 ] |
| Strauss 2008 | 1/33 | 0/38 | | 3.44 [ 0.14, 81.71 ] |
| Thatcher 1999a | 0/42 | 0/22 | | 0.0 [ 0.0, 0.0 ] |
| Thatcher 1999b | 2/44 | 0/22 | | 2.56 [ 0.13, 51.05 ] |
| Tjulandin 2011 | 0/95 | 1/91 | | 0.32 [ 0.01, 7.74 ] |
| Untch 2011˙1 | 20/318 | 17/396 | | 1.47 [ 0.78, 2.75 ] |
| Welch 1995 | 1/15 | 0/15 | | 3.00 [ 0.13, 68.26 ] |
| Wilkinson 2006 | 10/121 | 1/60 | | 4.96 [ 0.65, 37.84 ] |
| **Subtotal (95% CI)** | **2611** | **2393** | | **1.31 [ 1.04, 1.65 ]** |
| Total events: 161 (Treatment), 117 (Control) | | | | |
| Heterogeneity: $Chi^2$ = 13.49, df = 17 (P = 0.70); $I^2$ =0.0% | | | | |
| Test for overall effect: Z = 2.33 (P = 0.020) | | | | |
| **Total (95% CI)** | **8248** | **7250** | | **1.52 [ 1.34, 1.74 ]** |
| Total events: 561 (Treatment), 332 (Control) | | | | |
| Heterogeneity: $Chi^2$ = 34.99, df = 55 (P = 0.98); $I^2$ =0.0% | | | | |
| Test for overall effect: Z = 6.36 (P < 0.00001) | | | | |
| Test for subgroup differences: $Chi^2$ = 2.43, df = 1 (P = 0.12), $I^2$ =59% | | | | |

## Analysis 11.12. Comparison 11 Thrombotic events, Outcome 12 Thrombotic events - masking.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 11 Thrombotic events

Outcome: 12 Thrombotic events - masking

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| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Thompson 2000 | 1/45 | 0/21 | | 1.43 [ 0.06, 33.82 ] |
| Tjulandin 2011 | 0/95 | 1/91 | | 0.32 [ 0.01, 7.74 ] |
| Tsuboi 2009 | 1/62 | 0/58 | | 2.81 [ 0.12, 67.62 ] |
| Vansteenkiste 2002 | 7/155 | 5/159 | | 1.44 [ 0.47, 4.43 ] |
| Winquist 2009 | 0/26 | 2/30 | | 0.23 [ 0.01, 4.58 ] |
| Witzig 2005 J%J 2004 | 9/168 | 6/165 | | 1.47 [ 0.54, 4.05 ] |
| Wright 2007 | 2/33 | 3/37 | | 0.75 [ 0.13, 4.20 ] |
| **Subtotal (95% CI)** | **4903** | **4306** | | **1.40 [ 1.19, 1.64 ]** |
| Total events: 351 (Treatment), 225 (Control) | | | | |
| Heterogeneity: $Chi^2$ = 22.90, df = 29 (P = 0.78); $I^2$ =0.0% | | | | |
| Test for overall effect: Z = 4.13 (P = 0.000037) | | | | |
| 2 unblinded | | | | |
| Aapro 2008 | 29/231 | 13/231 | | 2.23 [ 1.19, 4.18 ] |
| Bamias 2003 | 0/72 | 1/72 | | 0.33 [ 0.01, 8.05 ] |
| Blohmer 2011 | 2/127 | 3/129 | | 0.68 [ 0.12, 3.98 ] |
| Chang 2005 | 19/176 | 14/178 | | 1.37 [ 0.71, 2.65 ] |
| Charu 2007 Amgen 2007 | 8/226 | 1/59 | | 2.09 [ 0.27, 16.37 ] |
| Debus 2006 J%J 2007 | 38/192 | 23/191 | | 1.64 [ 1.02, 2.65 ] |
| Gupta 2009 | 0/57 | 0/59 | | 0.0 [ 0.0, 0.0 ] |
| Hoskin 2009 J%J 2004 | 4/133 | 2/149 | | 2.24 [ 0.42, 12.04 ] |
| Machtay 2007 | 2/72 | 0/68 | | 4.73 [ 0.23, 96.70 ] |
| Milroy 2011 | 18/214 | 13/210 | | 1.36 [ 0.68, 2.70 ] |
| Moebus 2007 J%J 2007 | 9/305 | 5/288 | | 1.70 [ 0.58, 5.01 ] |
| Osterborg 1996a | 2/47 | 0/25 | | 2.71 [ 0.14, 54.32 ] |
| Osterborg 1996b | 1/48 | 0/24 | | 1.53 [ 0.06, 36.23 ] |
| Overgaard 2009 | 7/255 | 3/259 | | 2.37 [ 0.62, 9.06 ] |
| Pronzato 2010 | 4/109 | 1/111 | | 4.07 [ 0.46, 35.87 ] |
| Ray-Coquard 2009 | 5/110 | 4/107 | | 1.22 [ 0.34, 4.41 ] |
| Rosenzweig 2004 | 4/14 | 0/13 | | 8.40 [ 0.50, 142.27 ] |
| Savonije 2005 | 7/211 | 1/104 | | 3.45 [ 0.43, 27.68 ] |
| Strauss 2008 | 1/33 | 0/38 | | 3.44 [ 0.14, 81.71 ] |
| Ten Bokkel 1998a | 2/45 | 0/17 | | 1.96 [ 0.10, 38.79 ] |
| Ten Bokkel 1998b | 4/42 | 0/16 | | 3.56 [ 0.20, 62.58 ] |


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| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Thatcher 1999a | 0/42 | 0/22 | | 0.0 [ 0.0, 0.0 ] |
| Thatcher 1999b | 2/44 | 0/22 | | 2.56 [ 0.13, 51.05 ] |
| Thomas 2008 J%J 2004 | 10/58 | 5/55 | | 1.90 [ 0.69, 5.20 ] |
| Throuvalas 2000 | 1/28 | 0/26 | | 2.79 [ 0.12, 65.66 ] |
| Untch 2011˙1 | 20/318 | 17/396 | | 1.47 [ 0.78, 2.75 ] |
| Welch 1995 | 1/15 | 0/15 | | 3.00 [ 0.13, 68.26 ] |
| Wilkinson 2006 | 10/121 | 1/60 | | 4.96 [ 0.65, 37.84 ] |
| **Subtotal (95% CI)** | **3345** | **2944** | ◆ | **1.78 [ 1.43, 2.23 ]** |
| Total events: 210 (Treatment), 107 (Control) | | | | |
| Heterogeneity: $Chi^2$ = 9.20, df = 25 (P = 1.00); $I^2$ =0.0% | | | | |
| Test for overall effect: Z = 5.07 (P < 0.00001) | | | | |
| **Total (95% CI)** | **8248** | **7250** | ◆ | **1.52 [ 1.34, 1.74 ]** |
| Total events: 561 (Treatment), 332 (Control) | | | | |
| Heterogeneity: $Chi^2$ = 34.99, df = 55 (P = 0.98); $I^2$ =0.0% | | | | |
| Test for overall effect: Z = 6.36 (P < 0.00001) | | | | |
| Test for subgroup differences: $Chi^2$ = 2.95, df = 1 (P = 0.09), $I^2$ =66% | | | | |

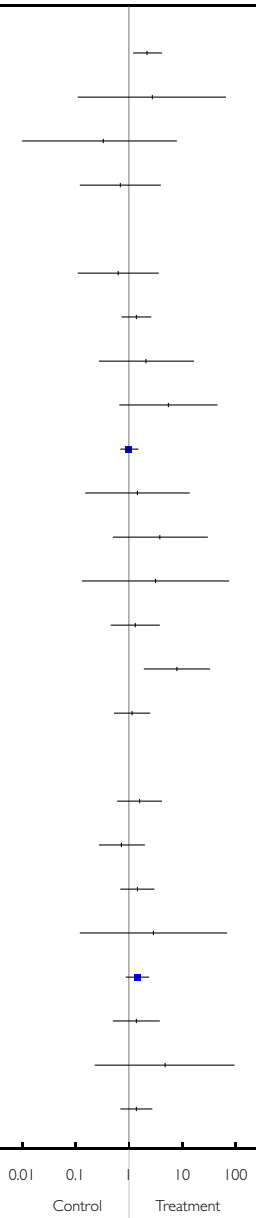
## Analysis 11.13. Comparison 11 Thrombotic events, Outcome 13 Thrombotic events - intention-to-treat.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 11 Thrombotic events

Outcome: 13 Thrombotic events - intention-to-treat

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| 1 ITT or less than 10% of participants per study arm excluded | | | | |
| Aapro 2008 | 29/231 | 13/231 | | 2.23 [ 1.19, 4.18 ] |
| Abels 1993 J%J 2004 | 1/65 | 0/59 | | 2.73 [ 0.11, 65.68 ] |
| Bamias 2003 | 0/72 | 1/72 | | 0.33 [ 0.01, 8.05 ] |
| Blohmer 2011 | 2/127 | 3/129 | | 0.68 [ 0.12, 3.98 ] |
| Cascinu 1994 | 0/50 | 0/50 | | 0.0 [ 0.0, 0.0 ] |
| Case 1993 J%J 2004 | 2/81 | 3/76 | | 0.63 [ 0.11, 3.64 ] |
| Chang 2005 | 19/176 | 14/178 | | 1.37 [ 0.71, 2.65 ] |
| Charu 2007 Amgen 2007 | 8/226 | 1/59 | | 2.09 [ 0.27, 16.37 ] |
| Dammacco 2001 J%J 2004 | 5/69 | 1/76 | | 5.51 [ 0.66, 45.98 ] |
| Engert 2009 | 45/645 | 44/644 | | 1.02 [ 0.68, 1.52 ] |
| EPO-INT-1 J%J 2004 | 3/164 | 1/80 | | 1.46 [ 0.15, 13.85 ] |
| EPO-INT-3 J%J 2004 | 8/135 | 1/65 | | 3.85 [ 0.49, 30.15 ] |
| Fujisaka 2011 | 1/89 | 0/92 | | 3.10 [ 0.13, 75.10 ] |
| Gordon 2008 | 16/164 | 4/54 | | 1.32 [ 0.46, 3.77 ] |
| Goss 2005 J%J 2004 | 16/52 | 2/52 | | 8.00 [ 1.94, 33.06 ] |
| Grote 2005 J%J 2004 | 12/109 | 11/115 | | 1.15 [ 0.53, 2.50 ] |
| Gupta 2009 | 0/57 | 0/59 | | 0.0 [ 0.0, 0.0 ] |
| Henke 2003 Roche 2004 | 10/180 | 6/171 | | 1.58 [ 0.59, 4.26 ] |
| Henry 1995 J%J 2004 | 6/67 | 8/65 | | 0.73 [ 0.27, 1.98 ] |
| Hernandez 2009 | 16/194 | 11/192 | | 1.44 [ 0.69, 3.02 ] |
| Italian 1998 | 1/44 | 0/43 | | 2.93 [ 0.12, 70.08 ] |
| Leyland-Jones 05 J%J 04 | 36/448 | 25/456 | | 1.47 [ 0.89, 2.40 ] |
| Littlewood 2001 J%J 2004 | 14/251 | 5/124 | | 1.38 [ 0.51, 3.75 ] |
| Machtay 2007 | 2/72 | 0/68 | | 4.73 [ 0.23, 96.70 ] |
| Milroy 2011 | 18/214 | 13/210 | | 1.36 [ 0.68, 2.70 ] |

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| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Osterborg 1996a | 2/47 | 0/25 | | 2.71 [ 0.14, 54.32 ] |
| Osterborg 1996b | 1/48 | 0/24 | | 1.53 [ 0.06, 36.23 ] |
| Osterborg 2002 | 1/170 | 0/173 | | 3.05 [ 0.13, 74.41 ] |
| Overgaard 2009 | 7/255 | 3/259 | | 2.37 [ 0.62, 9.06 ] |
| P-174 J%J 2004 | 0/33 | 0/12 | | 0.0 [ 0.0, 0.0 ] |
| Pirker 2008 | 65/301 | 43/296 | | 1.49 [ 1.05, 2.11 ] |
| Pronzato 2010 | 4/109 | 1/111 | | 4.07 [ 0.46, 35.87 ] |
| Ray-Coquard 2009 | 5/110 | 4/107 | | 1.22 [ 0.34, 4.41 ] |
| Razzouk 2006 | 6/112 | 2/110 | | 2.95 [ 0.61, 14.28 ] |
| Rose 1994 J%J 2004 | 9/142 | 2/79 | | 2.50 [ 0.55, 11.30 ] |
| Rosenzweig 2004 | 4/14 | 0/13 | | 8.40 [ 0.50, 142.27 ] |
| Savonije 2005 | 7/211 | 1/104 | | 3.45 [ 0.43, 27.68 ] |
| Smith 2003 Amgen 2007 | 2/64 | 2/22 | | 0.34 [ 0.05, 2.30 ] |
| Smith 2008 | 50/515 | 36/470 | | 1.27 [ 0.84, 1.91 ] |
| Strauss 2008 | 1/33 | 0/38 | | 3.44 [ 0.14, 81.71 ] |
| Ten Bokkel 1998a | 2/45 | 0/17 | | 1.96 [ 0.10, 38.79 ] |
| Ten Bokkel 1998b | 4/42 | 0/16 | | 3.56 [ 0.20, 62.58 ] |
| Thatcher 1999a | 0/42 | 0/22 | | 0.0 [ 0.0, 0.0 ] |
| Thatcher 1999b | 2/44 | 0/22 | | 2.56 [ 0.13, 51.05 ] |
| Thomas 2008 J%J 2004 | 10/58 | 5/55 | | 1.90 [ 0.69, 5.20 ] |
| Thompson 2000 | 1/45 | 0/21 | | 1.43 [ 0.06, 33.82 ] |
| Throuvalas 2000 | 1/28 | 0/26 | | 2.79 [ 0.12, 65.66 ] |
| Tjulandin 2011 | 0/95 | 1/91 | | 0.32 [ 0.01, 7.74 ] |
| Tsuboi 2009 | 1/62 | 0/58 | | 2.81 [ 0.12, 67.62 ] |
| Vansteenkiste 2002 | 7/155 | 5/159 | | 1.44 [ 0.47, 4.43 ] |
| Welch 1995 | 1/15 | 0/15 | | 3.00 [ 0.13, 68.26 ] |
| Wilkinson 2006 | 10/121 | 1/60 | | 4.96 [ 0.65, 37.84 ] |
| Winquist 2009 | 0/26 | 2/30 | | 0.23 [ 0.01, 4.58 ] |
| Witzig 2005 J%J 2004 | 9/168 | 6/165 | | 1.47 [ 0.54, 4.05 ] |
| Wright 2007 | 2/33 | 3/37 | | 0.75 [ 0.13, 4.20 ] |
| **Subtotal (95% CI)** | **7125** | **6057** | | **1.50 [ 1.30, 1.72 ]** |
| Total events: 484 (Treatment), 284 (Control) | | | | |

0.01 0.1 1 10 100

Control Treatment

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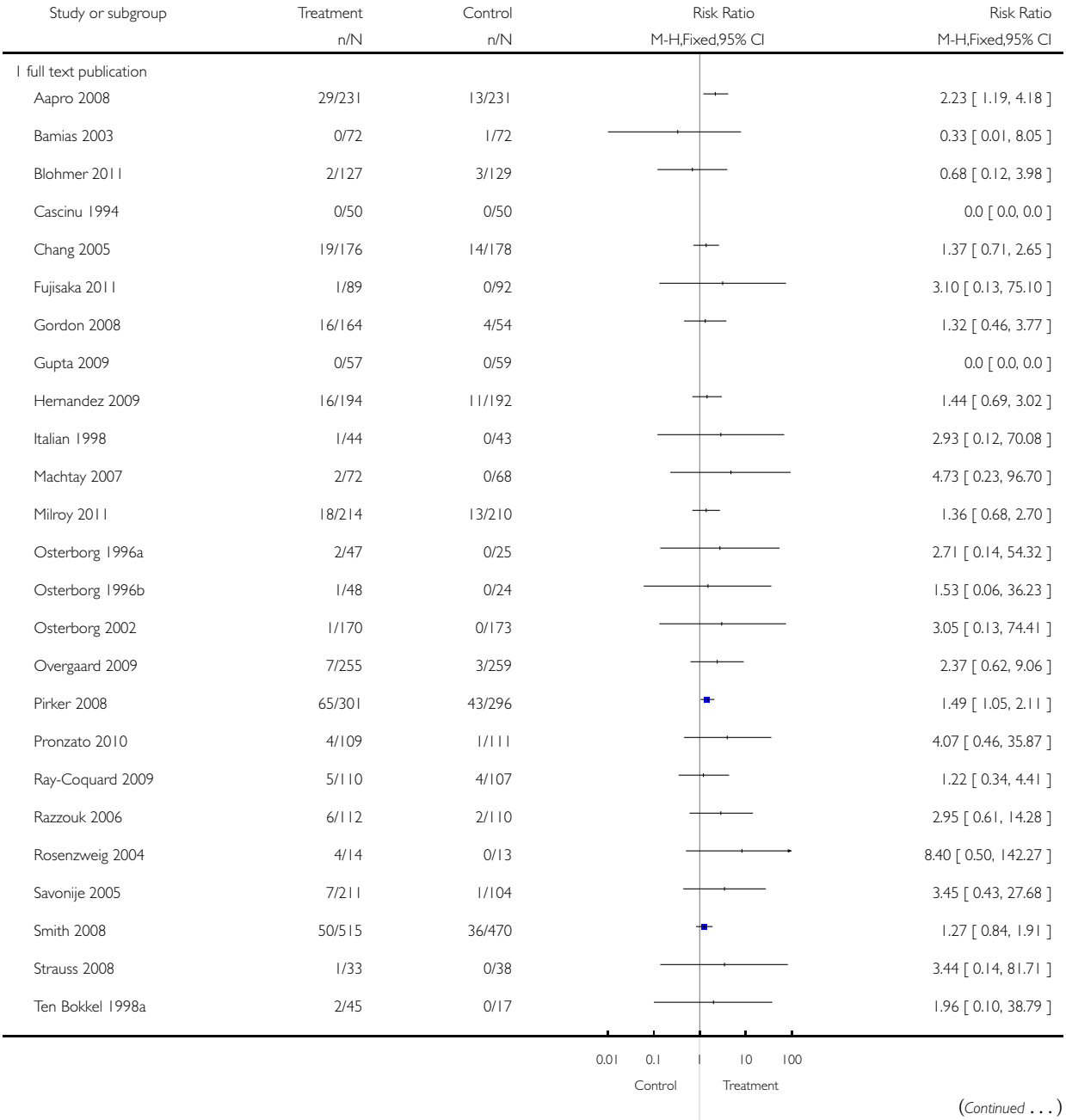
| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Heterogeneity: Chi² = 32.77, df = 50 (P = 0.97); I² =0.0% | | | | |
| Test for overall effect: Z = 5.63 (P < 0.00001) | | | | |
| 2 more than 10% of participants per study arm excluded | | | | |
| Hoskin 2009 J%J 2004 | 4/133 | 2/149 | | 2.24 [ 0.42, 12.04 ] |
| Moebus 2007 J%J 2007 | 9/305 | 5/288 | | 1.70 [ 0.58, 5.01 ] |
| Untch 2011˙1 | 20/318 | 17/396 | | 1.47 [ 0.78, 2.75 ] |
| **Subtotal (95% CI)** | **756** | **833** | | **1.59 [ 0.95, 2.66 ]** |
| Total events: 33 (Treatment), 24 (Control) | | | | |
| Heterogeneity: Chi² = 0.24, df = 2 (P = 0.89); I² =0.0% | | | | |
| Test for overall effect: Z = 1.75 (P = 0.081) | | | | |
| 3 unclear | | | | |
| Debus 2006 J%J 2007 | 38/192 | 23/191 | | 1.64 [ 1.02, 2.65 ] |
| Hedenus 2003 FDA 2007 | 6/175 | 1/169 | | 5.79 [ 0.71, 47.62 ] |
| **Subtotal (95% CI)** | **367** | **360** | | **1.82 [ 1.15, 2.89 ]** |
| Total events: 44 (Treatment), 24 (Control) | | | | |
| Heterogeneity: Chi² = 1.34, df = 1 (P = 0.25); I² =25% | | | | |
| Test for overall effect: Z = 2.53 (P = 0.011) | | | | |
| **Total (95% CI)** | **8248** | **7250** | | **1.52 [ 1.34, 1.74 ]** |
| Total events: 561 (Treatment), 332 (Control) | | | | |
| Heterogeneity: Chi² = 34.99, df = 55 (P = 0.98); I² =0.0% | | | | |
| Test for overall effect: Z = 6.36 (P < 0.00001) | | | | |
| Test for subgroup differences: Chi² = 0.65, df = 2 (P = 0.72), I² =0.0% | | | | |

## Analysis 11.14. Comparison 11 Thrombotic events, Outcome 14 Thrombotic events - publication.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 11 Thrombotic events

Outcome: 14 Thrombotic events - publication

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| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Ten Bokkel 1998b | 4/42 | 0/16 | | 3.56 [ 0.20, 62.58 ] |
| Thatcher 1999a | 0/42 | 0/22 | | 0.0 [ 0.0, 0.0 ] |
| Thatcher 1999b | 2/44 | 0/22 | | 2.56 [ 0.13, 51.05 ] |
| Tjulandin 2011 | 0/95 | 1/91 | | 0.32 [ 0.01, 7.74 ] |
| Tsuboi 2009 | 1/62 | 0/58 | | 2.81 [ 0.12, 67.62 ] |
| Untch 2011˙1 | 20/318 | 17/396 | | 1.47 [ 0.78, 2.75 ] |
| Vansteenkiste 2002 | 7/155 | 5/159 | | 1.44 [ 0.47, 4.43 ] |
| Welch 1995 | 1/15 | 0/15 | | 3.00 [ 0.13, 68.26 ] |
| Wilkinson 2006 | 10/121 | 1/60 | | 4.96 [ 0.65, 37.84 ] |
| Wright 2007 | 2/33 | 3/37 | | 0.75 [ 0.13, 4.20 ] |
| **Subtotal (95% CI)** | **4387** | **4001** | ◆ | **1.57 [ 1.32, 1.87 ]** |
| Total events: 306 (Treatment), 176 (Control) | | | | |
| Heterogeneity: $Chi^2$ = 13.43, df = 31 (P = 1.00); $I^2$ =0.0% | | | | |
| Test for overall effect: Z = 5.02 (P < 0.00001) | | | | |
| 2 abstract publication | | | | |
| Engert 2009 | 45/645 | 44/644 | | 1.02 [ 0.68, 1.52 ] |
| Throuvalas 2000 | 1/28 | 0/26 | | 2.79 [ 0.12, 65.66 ] |
| **Subtotal (95% CI)** | **673** | **670** | ◆ | **1.04 [ 0.70, 1.55 ]** |
| Total events: 46 (Treatment), 44 (Control) | | | | |
| Heterogeneity: $Chi^2$ = 0.38, df = 1 (P = 0.54); $I^2$ =0.0% | | | | |
| Test for overall effect: Z = 0.20 (P = 0.84) | | | | |
| 3 unpublished data | | | | |
| Thompson 2000 | 1/45 | 0/21 | | 1.43 [ 0.06, 33.82 ] |
| **Subtotal (95% CI)** | **45** | **21** | ◆ | **1.43 [ 0.06, 33.82 ]** |
| Total events: 1 (Treatment), 0 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: Z = 0.22 (P = 0.82) | | | | |
| 4 data presented at ODAC hearing | | | | |
| Abels 1993 J%J 2004 | 1/65 | 0/59 | | 2.73 [ 0.11, 65.68 ] |
| Case 1993 J%J 2004 | 2/81 | 3/76 | | 0.63 [ 0.11, 3.64 ] |
| Charu 2007 Amgen 2007 | 8/226 | 1/59 | | 2.09 [ 0.27, 16.37 ] |
| Dammacco 2001 J%J 2004 | 5/69 | 1/76 | | 5.51 [ 0.66, 45.98 ] |
| Debus 2006 J%J 2007 | 38/192 | 23/191 | | 1.64 [ 1.02, 2.65 ] |
| EPO-INT-1 J%J 2004 | 3/164 | 1/80 | | 1.46 [ 0.15, 13.85 ] |
| EPO-INT-3 J%J 2004 | 8/135 | 1/65 | | 3.85 [ 0.49, 30.15 ] |
| Goss 2005 J%J 2004 | 16/52 | 2/52 | | 8.00 [ 1.94, 33.06 ] |


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| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Grote 2005 J%J 2004 | 12/109 | 11/115 | | 1.15 [ 0.53, 2.50 ] |
| Hedenus 2003 FDA 2007 | 6/175 | 1/169 | | 5.79 [ 0.71, 47.62 ] |
| Henke 2003 Roche 2004 | 10/180 | 6/171 | | 1.58 [ 0.59, 4.26 ] |
| Henry 1995 J%J 2004 | 6/67 | 8/65 | | 0.73 [ 0.27, 1.98 ] |
| Hoskin 2009 J%J 2004 | 4/133 | 2/149 | | 2.24 [ 0.42, 12.04 ] |
| Leyland-Jones 05 J%J 04 | 36/448 | 25/456 | | 1.47 [ 0.89, 2.40 ] |
| Littlewood 2001 J%J 2004 | 14/251 | 5/124 | | 1.38 [ 0.51, 3.75 ] |
| Moebus 2007 J%J 2007 | 9/305 | 5/288 | | 1.70 [ 0.58, 5.01 ] |
| P-174 J%J 2004 | 0/33 | 0/12 | | 0.0 [ 0.0, 0.0 ] |
| Rose 1994 J%J 2004 | 9/142 | 2/79 | | 2.50 [ 0.55, 11.30 ] |
| Smith 2003 Amgen 2007 | 2/64 | 2/22 | | 0.34 [ 0.05, 2.30 ] |
| Thomas 2008 J%J 2004 | 10/58 | 5/55 | | 1.90 [ 0.69, 5.20 ] |
| Witzig 2005 J%J 2004 | 9/168 | 6/165 | | 1.47 [ 0.54, 4.05 ] |
| **Subtotal (95% CI)** | **3117** | **2528** | | **1.66 [ 1.33, 2.08 ]** |
| Total events: 208 (Treatment), 110 (Control) | | | | |
| Heterogeneity: $Chi^2$ = 16.31, df = 19 (P = 0.64); $I^2$ =0.0% | | | | |
| Test for overall effect: Z = 4.46 (P < 0.00001) | | | | |
| 5 other | | | | |
| Winquist 2009 | 0/26 | 2/30 | | 0.23 [ 0.01, 4.58 ] |
| **Subtotal (95% CI)** | **26** | **30** | | **0.23 [ 0.01, 4.58 ]** |
| Total events: 0 (Treatment), 2 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: Z = 0.96 (P = 0.34) | | | | |
| **Total (95% CI)** | **8248** | **7250** | | **1.52 [ 1.34, 1.74 ]** |
| Total events: 561 (Treatment), 332 (Control) | | | | |
| Heterogeneity: $Chi^2$ = 34.99, df = 55 (P = 0.98); $I^2$ =0.0% | | | | |
| Test for overall effect: Z = 6.36 (P < 0.00001) | | | | |
| Test for subgroup differences: $Chi^2$ = 5.76, df = 4 (P = 0.22), $I^2$ =31% | | | | |

## Analysis 11.15. Comparison 11 Thrombotic events, Outcome 15 Thrombotic events - experimental arms merged.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 11 Thrombotic events

Outcome: 15 Thrombotic events - experimental arms merged

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Aapro 2008 | 29/231 | 13/231 | | 2.23 [ 1.19, 4.18 ] |
| Abels 1993 J%J 2004 | 1/65 | 0/59 | | 2.73 [ 0.11, 65.68 ] |
| Bamias 2003 | 0/72 | 1/72 | | 0.33 [ 0.01, 8.05 ] |
| Blohmer 2011 | 2/127 | 3/129 | | 0.68 [ 0.12, 3.98 ] |
| Cascinu 1994 | 0/50 | 0/50 | | 0.0 [ 0.0, 0.0 ] |
| Case 1993 J%J 2004 | 2/81 | 3/76 | | 0.63 [ 0.11, 3.64 ] |
| Chang 2005 | 19/176 | 14/178 | | 1.37 [ 0.71, 2.65 ] |
| Charu 2007 Amgen 2007 | 8/226 | 1/59 | | 2.09 [ 0.27, 16.37 ] |
| Dammacco 2001 J%J 2004 | 5/69 | 1/76 | | 5.51 [ 0.66, 45.98 ] |
| Debus 2006 J%J 2007 | 38/192 | 23/191 | | 1.64 [ 1.02, 2.65 ] |
| Engert 2009 | 45/645 | 44/644 | | 1.02 [ 0.68, 1.52 ] |
| EPO-INT-1 J%J 2004 | 3/164 | 1/80 | | 1.46 [ 0.15, 13.85 ] |
| EPO-INT-3 J%J 2004 | 8/135 | 1/65 | | 3.85 [ 0.49, 30.15 ] |
| Fujisaka 2011 | 1/89 | 0/92 | | 3.10 [ 0.13, 75.10 ] |
| Gordon 2008 | 16/164 | 4/54 | | 1.32 [ 0.46, 3.77 ] |
| Goss 2005 J%J 2004 | 16/52 | 2/52 | | 8.00 [ 1.94, 33.06 ] |
| Grote 2005 J%J 2004 | 12/109 | 11/115 | | 1.15 [ 0.53, 2.50 ] |
| Gupta 2009 | 0/57 | 0/59 | | 0.0 [ 0.0, 0.0 ] |
| Hedenus 2003 FDA 2007 | 6/175 | 1/169 | | 5.79 [ 0.71, 47.62 ] |
| Henke 2003 Roche 2004 | 10/180 | 6/171 | | 1.58 [ 0.59, 4.26 ] |
| Henry 1995 J%J 2004 | 6/67 | 8/65 | | 0.73 [ 0.27, 1.98 ] |
| Hernandez 2009 | 16/194 | 11/192 | | 1.44 [ 0.69, 3.02 ] |
| Hoskin 2009 J%J 2004 | 4/133 | 2/149 | | 2.24 [ 0.42, 12.04 ] |
| Italian 1998 | 1/44 | 0/43 | | 2.93 [ 0.12, 70.08 ] |
| Leyland-Jones 05 J%J 04 | 36/448 | 25/456 | | 1.47 [ 0.89, 2.40 ] |


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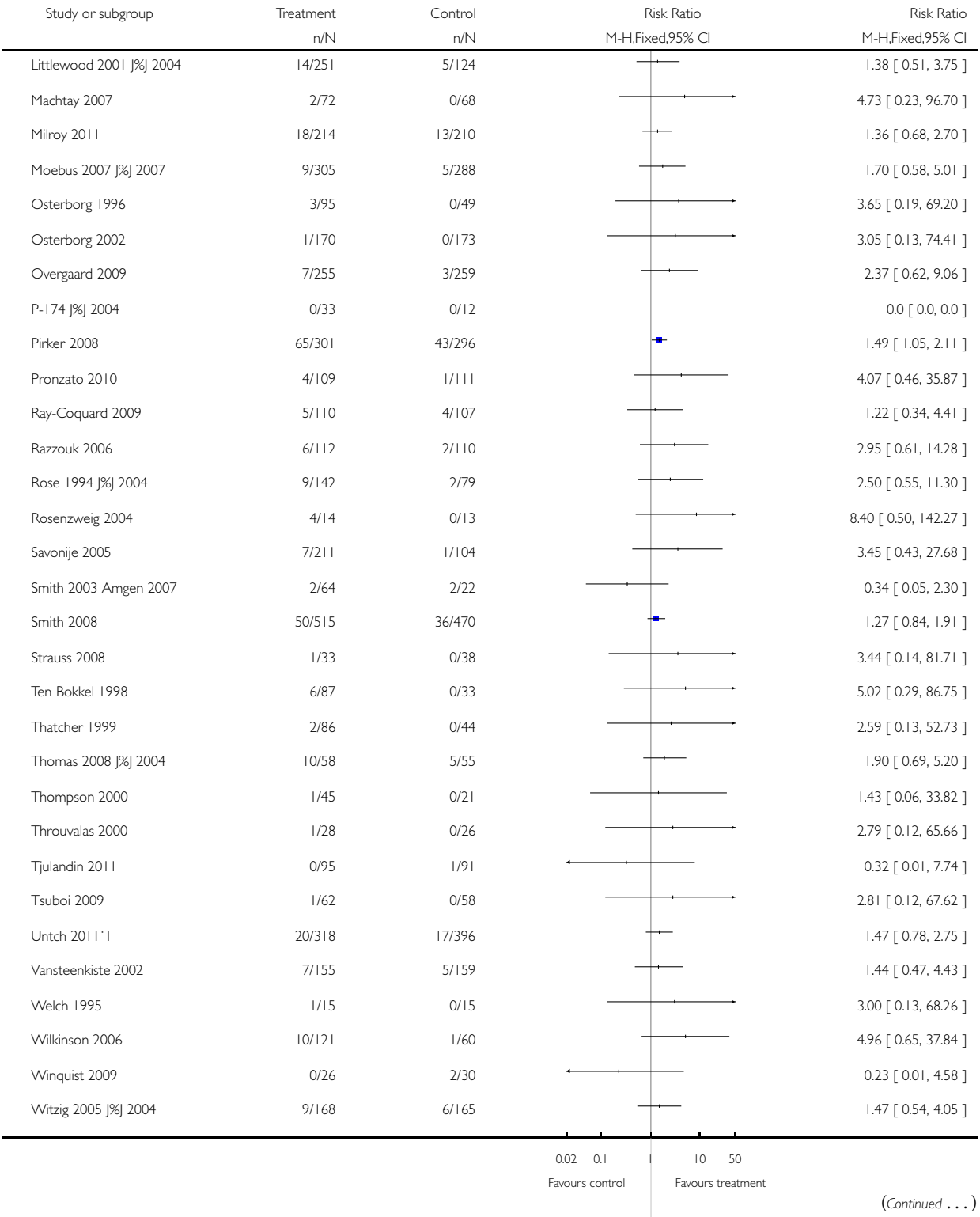


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| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Wright 2007 | 2/33 | 3/37 | | 0.75 [ 0.13, 4.20 ] |
| **Total (95% CI)** | **8248** | **7250** | ♦ | **1.53 [ 1.34, 1.74 ]** |
| Total events: 561 (Treatment), 332 (Control) | | | | |
| Heterogeneity: $Chi^2$ = 35.54, df = 53 (P = 0.97); $I^2$ =0.0% | | | | |
| Test for overall effect: Z = 6.38 (P < 0.00001) | | | | |
| Test for subgroup differences: Not applicable | | | | |

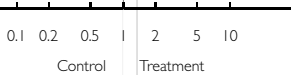

## Analysis 12.1. Comparison 12 Hypertension, Outcome 1 Hypertension - overall.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 12 Hypertension

Outcome: 1 Hypertension - overall

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Bamias 2003 | 2/72 | 0/72 | | 5.00 [ 0.24, 102.35 ] |
| Cascinu 1994 | 0/50 | 0/50 | | 0.0 [ 0.0, 0.0 ] |
| Case 1993 | 4/81 | 2/76 | | 1.88 [ 0.35, 9.95 ] |
| Dammacco 2001 | 3/69 | 1/76 | | 3.30 [ 0.35, 31.03 ] |
| Fujisaka 2011 | 5/89 | 3/92 | | 1.72 [ 0.42, 7.00 ] |
| Gordon 2008 | 1/164 | 0/54 | | 1.00 [ 0.04, 24.19 ] |
| Henry 1995 | 2/67 | 4/65 | | 0.49 [ 0.09, 2.56 ] |
| Hernandez 2009 | 6/194 | 4/192 | | 1.48 [ 0.43, 5.18 ] |
| Hoskin 2009 | 5/133 | 5/149 | | 1.12 [ 0.33, 3.78 ] |
| Iconomou 2003 | 0/61 | 0/61 | | 0.0 [ 0.0, 0.0 ] |
| Krzakowski 2008a | 2/100 | 1/50 | | 1.00 [ 0.09, 10.77 ] |
| Krzakowski 2008b | 1/103 | 0/49 | | 1.44 [ 0.06, 34.78 ] |

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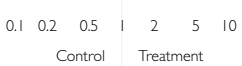
| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Kunikane 2001a | 3/22 | 2/9 | | 0.61 [ 0.12, 3.08 ] |
| Kunikane 2001b | 2/21 | 2/8 | | 0.38 [ 0.06, 2.27 ] |
| Littlewood 2001 | 9/251 | 1/124 | | 4.45 [ 0.57, 34.70 ] |
| Milroy 2011 | 6/214 | 3/210 | | 1.96 [ 0.50, 7.74 ] |
| Osterborg 1996a | 4/47 | 1/25 | | 2.13 [ 0.25, 18.03 ] |
| Osterborg 1996b | 5/48 | 0/24 | | 5.61 [ 0.32, 97.48 ] |
| Osterborg 2002 | 15/170 | 9/173 | | 1.70 [ 0.76, 3.77 ] |
| Pirker 2008 | 18/301 | 15/296 | | 1.18 [ 0.61, 2.30 ] |
| Razzouk 2006 | 2/112 | 1/110 | | 1.96 [ 0.18, 21.35 ] |
| Rose 1994 | 80/142 | 47/79 | | 0.95 [ 0.75, 1.19 ] |
| Rosenzweig 2004 | 1/14 | 0/13 | | 2.80 [ 0.12, 63.20 ] |
| Savonije 2005 | 7/211 | 3/104 | | 1.15 [ 0.30, 4.36 ] |
| Silvestris 1995 | 4/30 | 0/24 | | 7.26 [ 0.41, 128.50 ] |
| Smith 2008 | 8/515 | 12/470 | | 0.61 [ 0.25, 1.48 ] |
| Ten Bokkel 1998a | 4/43 | 1/14 | | 1.30 [ 0.16, 10.71 ] |
| Ten Bokkel 1998b | 7/37 | 0/14 | | 5.92 [ 0.36, 97.33 ] |
| Thatcher 1999a | 2/42 | 0/22 | | 2.67 [ 0.13, 53.39 ] |
| Thatcher 1999b | 1/44 | 0/22 | | 1.53 [ 0.06, 36.18 ] |
| Tjulandin 2010a | 2/76 | 1/37 | | 0.97 [ 0.09, 10.40 ] |
| Tjulandin 2010b | 2/73 | 1/37 | | 1.01 [ 0.09, 10.82 ] |
| Tjulandin 2011 | 8/95 | 1/91 | | 7.66 [ 0.98, 60.06 ] |
| Tsuboi 2009 | 4/62 | 2/58 | | 1.87 [ 0.36, 9.83 ] |
| Vansteenkiste 2002 | 9/155 | 6/159 | | 1.54 [ 0.56, 4.22 ] |
| Welch 1995 | 2/15 | 0/15 | | 5.00 [ 0.26, 96.13 ] |
| Wilkinson 2006 | 3/121 | 0/60 | | 3.50 [ 0.18, 66.68 ] |
| **Total (95% CI)** | **4044** | **3184** | | **1.30 [ 1.08, 1.56 ]** |

Total events: 239 (Treatment), 128 (Control)

Heterogeneity: $Chi^2$ = 26.87, df = 34 (P = 0.80); $I^2$ =0.0%

Test for overall effect: Z = 2.73 (P = 0.0064)

Test for subgroup differences: Not applicable



## Analysis 12.2. Comparison 12 Hypertension, Outcome 2 Hypertension - merged experimental study arms.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 12 Hypertension

Outcome: 2 Hypertension - merged experimental study arms

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Bamias 2003 | 2/72 | 0/72 | | 5.00 [ 0.24, 102.35 ] |
| Cascinu 1994 | 0/50 | 0/50 | | 0.0 [ 0.0, 0.0 ] |
| Case 1993 | 4/81 | 2/76 | | 1.88 [ 0.35, 9.95 ] |
| Dammacco 2001 | 3/69 | 1/76 | | 3.30 [ 0.35, 31.03 ] |
| Fujisaka 2011 | 5/89 | 3/92 | | 1.72 [ 0.42, 7.00 ] |
| Gordon 2008 | 1/164 | 0/54 | | 1.00 [ 0.04, 24.19 ] |
| Henry 1995 | 2/67 | 4/65 | | 0.49 [ 0.09, 2.56 ] |
| Hernandez 2009 | 6/194 | 4/192 | | 1.48 [ 0.43, 5.18 ] |
| Hoskin 2009 | 5/133 | 5/149 | | 1.12 [ 0.33, 3.78 ] |
| Iconomou 2003 | 0/61 | 0/61 | | 0.0 [ 0.0, 0.0 ] |
| Krzakowski 2008 | 3/203 | 1/99 | | 1.46 [ 0.15, 13.89 ] |
| Kunikane 2001 | 5/43 | 4/17 | | 0.49 [ 0.15, 1.62 ] |
| Littlewood 2001 | 9/251 | 1/124 | | 4.45 [ 0.57, 34.70 ] |
| Milroy 2011 | 6/214 | 3/210 | | 1.96 [ 0.50, 7.74 ] |
| Osterborg 1996 | 9/95 | 1/49 | | 4.64 [ 0.61, 35.59 ] |
| Osterborg 2002 | 15/170 | 9/173 | | 1.70 [ 0.76, 3.77 ] |
| Pirker 2008 | 18/301 | 15/296 | | 1.18 [ 0.61, 2.30 ] |
| Razzouk 2006 | 2/112 | 1/110 | | 1.96 [ 0.18, 21.35 ] |
| Rose 1994 | 80/142 | 47/79 | | 0.95 [ 0.75, 1.19 ] |
| Rosenzweig 2004 | 1/14 | 0/13 | | 2.80 [ 0.12, 63.20 ] |
| Savonije 2005 | 7/211 | 3/104 | | 1.15 [ 0.30, 4.36 ] |
| Silvestris 1995 | 4/30 | 0/24 | | 7.26 [ 0.41, 128.50 ] |
| Smith 2008 | 8/515 | 12/470 | | 0.61 [ 0.25, 1.48 ] |
| Ten Bokkel 1998 | 11/80 | 1/28 | | 3.85 [ 0.52, 28.49 ] |
| Thatcher 1999 | 3/86 | 0/44 | | 3.62 [ 0.19, 68.57 ] |
| Tjulandin 2010 | 4/149 | 2/74 | | 0.99 [ 0.19, 5.30 ] |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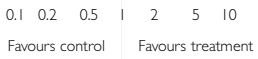
| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Tjulandin 2011 | 8/95 | 1/91 | | 7.66 [ 0.98, 60.06 ] |
| Tsuboi 2009 | 4/62 | 2/58 | | 1.87 [ 0.36, 9.83 ] |
| Vansteenkiste 2002 | 9/155 | 6/159 | | 1.54 [ 0.56, 4.22 ] |
| Welch 1995 | 2/15 | 0/15 | | 5.00 [ 0.26, 96.13 ] |
| Wilkinson 2006 | 3/121 | 0/60 | | 3.50 [ 0.18, 66.68 ] |
| **Total (95% CI)** | **4044** | **3184** | | **1.31 [ 1.09, 1.58 ]** |

Total events: 239 (Treatment), 128 (Control)
Heterogeneity: $Chi^2$ = 27.60, df = 28 (P = 0.49); $I^2$ =0.0%
Test for overall effect: Z = 2.81 (P = 0.0049)
Test for subgroup differences: Not applicable




### Analysis 12.3. Comparison 12 Hypertension, Outcome 3 Hypertension - sensitivity analysis Dammacco.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 12 Hypertension

Outcome: 3 Hypertension - sensitivity analysis Dammacco

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Bamias 2003 | 2/72 | 0/72 | | 5.00 [ 0.24, 102.35 ] |
| Cascinu 1994 | 0/50 | 0/50 | | 0.0 [ 0.0, 0.0 ] |
| Case 1993 | 4/81 | 2/76 | | 1.88 [ 0.35, 9.95 ] |
| Dammacco 2001 | 43/69 | 36/76 | | 1.32 [ 0.97, 1.78 ] |
| Fujisaka 2011 | 5/89 | 3/92 | | 1.72 [ 0.42, 7.00 ] |
| Gordon 2008 | 1/164 | 0/54 | | 1.00 [ 0.04, 24.19 ] |
| Henry 1995 | 2/67 | 4/65 | | 0.49 [ 0.09, 2.56 ] |
| Hernandez 2009 | 6/194 | 4/192 | | 1.48 [ 0.43, 5.18 ] |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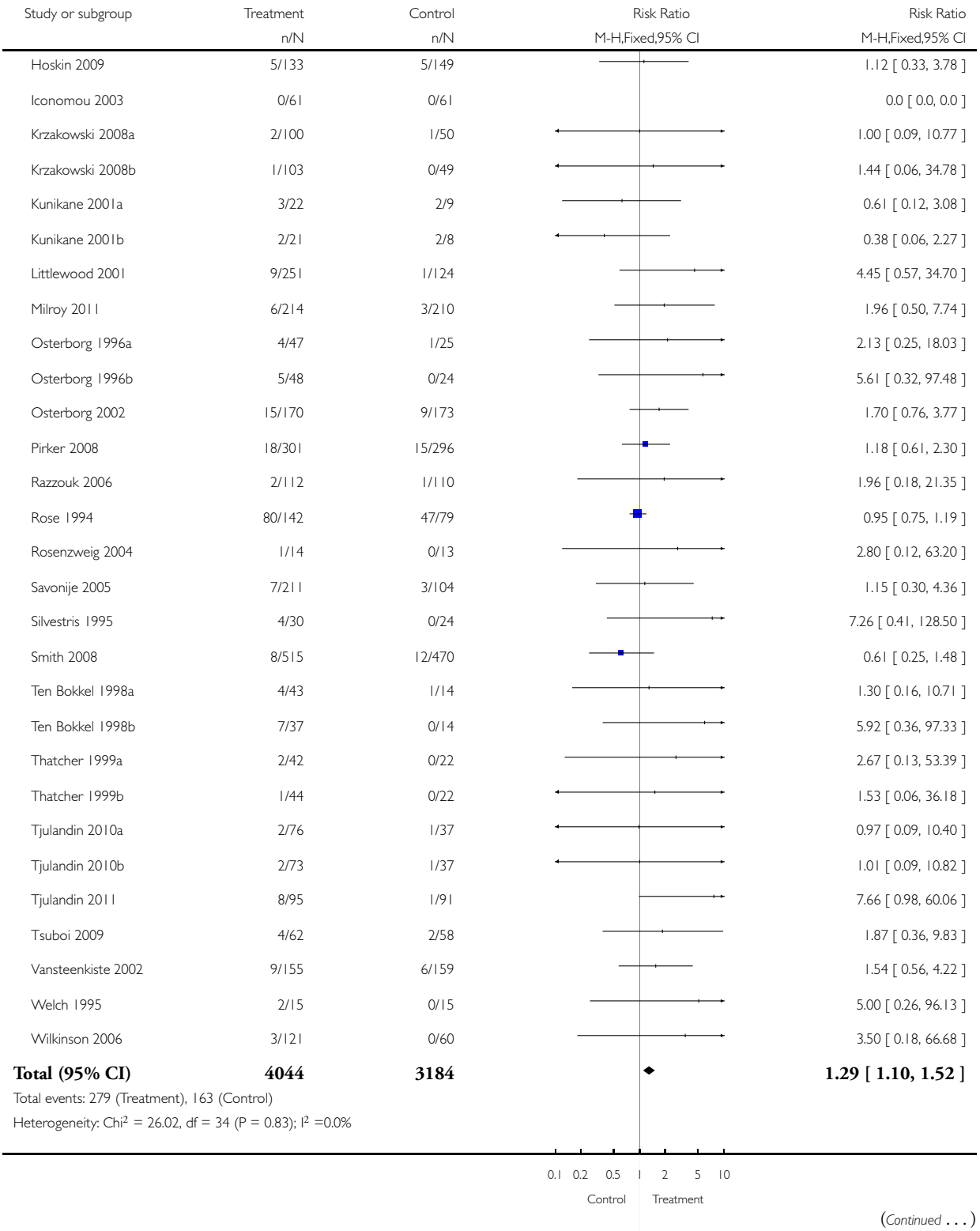


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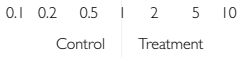
| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Test for overall effect: Z = 3.07 (P = 0.0021) | | | | |
| Test for subgroup differences: Not applicable | | | | |




## Analysis 12.4. Comparison 12 Hypertension, Outcome 4 Hypertension - sensitivity analysis random effects.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 12 Hypertension

Outcome: 4 Hypertension - sensitivity analysis random effects

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Random,95% CI | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|
| Bamias 2003 | 2/72 | 0/72 | | 5.00 [ 0.24, 102.35 ] |
| Cascinu 1994 | 0/50 | 0/50 | | 0.0 [ 0.0, 0.0 ] |
| Case 1993 | 4/81 | 2/76 | | 1.88 [ 0.35, 9.95 ] |
| Dammacco 2001 | 3/69 | 1/76 | | 3.30 [ 0.35, 31.03 ] |
| Fujisaka 2011 | 5/89 | 3/92 | | 1.72 [ 0.42, 7.00 ] |
| Gordon 2008 | 1/164 | 0/54 | | 1.00 [ 0.04, 24.19 ] |
| Henry 1995 | 2/67 | 4/65 | | 0.49 [ 0.09, 2.56 ] |
| Hernandez 2009 | 6/194 | 4/192 | | 1.48 [ 0.43, 5.18 ] |
| Hoskin 2009 | 5/133 | 5/149 | | 1.12 [ 0.33, 3.78 ] |
| Iconomou 2003 | 0/61 | 0/61 | | 0.0 [ 0.0, 0.0 ] |
| Krzakowski 2008a | 2/100 | 1/50 | | 1.00 [ 0.09, 10.77 ] |
| Krzakowski 2008b | 1/103 | 0/49 | | 1.44 [ 0.06, 34.78 ] |
| Kunikane 2001a | 3/22 | 2/9 | | 0.61 [ 0.12, 3.08 ] |
| Kunikane 2001b | 2/21 | 2/8 | | 0.38 [ 0.06, 2.27 ] |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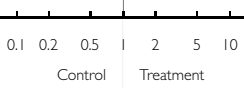
| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Random,95% CI | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|
| Littlewood 2001 | 9/251 | 1/124 | | 4.45 [ 0.57, 34.70 ] |
| Milroy 2011 | 6/214 | 3/210 | | 1.96 [ 0.50, 7.74 ] |
| Osterborg 1996a | 4/47 | 1/25 | | 2.13 [ 0.25, 18.03 ] |
| Osterborg 1996b | 5/48 | 0/24 | | 5.61 [ 0.32, 97.48 ] |
| Osterborg 2002 | 15/170 | 9/173 | | 1.70 [ 0.76, 3.77 ] |
| Pirker 2008 | 18/301 | 15/296 | | 1.18 [ 0.61, 2.30 ] |
| Razzouk 2006 | 2/112 | 1/110 | | 1.96 [ 0.18, 21.35 ] |
| Rose 1994 | 80/142 | 47/79 | | 0.95 [ 0.75, 1.19 ] |
| Rosenzweig 2004 | 1/14 | 0/13 | | 2.80 [ 0.12, 63.20 ] |
| Savonije 2005 | 7/211 | 3/104 | | 1.15 [ 0.30, 4.36 ] |
| Silvestris 1995 | 4/30 | 0/24 | | 7.26 [ 0.41, 128.50 ] |
| Smith 2008 | 8/515 | 12/470 | | 0.61 [ 0.25, 1.48 ] |
| Ten Bokkel 1998a | 4/43 | 1/14 | | 1.30 [ 0.16, 10.71 ] |
| Ten Bokkel 1998b | 7/37 | 0/14 | | 5.92 [ 0.36, 97.33 ] |
| Thatcher 1999a | 2/42 | 0/22 | | 2.67 [ 0.13, 53.39 ] |
| Thatcher 1999b | 1/44 | 0/22 | | 1.53 [ 0.06, 36.18 ] |
| Tjulandin 2010a | 2/76 | 1/37 | | 0.97 [ 0.09, 10.40 ] |
| Tjulandin 2010b | 2/73 | 1/37 | | 1.01 [ 0.09, 10.82 ] |
| Tjulandin 2011 | 8/95 | 1/91 | | 7.66 [ 0.98, 60.06 ] |
| Tsuboi 2009 | 4/62 | 2/58 | | 1.87 [ 0.36, 9.83 ] |
| Vansteenkiste 2002 | 9/155 | 6/159 | | 1.54 [ 0.56, 4.22 ] |
| Welch 1995 | 2/15 | 0/15 | | 5.00 [ 0.26, 96.13 ] |
| Wilkinson 2006 | 3/121 | 0/60 | | 3.50 [ 0.18, 66.68 ] |
| **Total (95% CI)** | **4044** | **3184** | | **1.12 [ 0.94, 1.33 ]** |

Total events: 239 (Treatment), 128 (Control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 26.87$, df = 34 (P = 0.80); $I^2 = 0.0\%$

Test for overall effect: Z = 1.25 (P = 0.21)

Test for subgroup differences: Not applicable



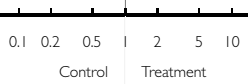
## Analysis 12.5. Comparison 12 Hypertension, Outcome 5 Hypertension - sensitivity analysis without Rose.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 12 Hypertension

Outcome: 5 Hypertension - sensitivity analysis without Rose

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Bamias 2003 | 2/72 | 0/72 | | 5.00 [ 0.24, 102.35 ] |
| Cascinu 1994 | 0/50 | 0/50 | | 0.0 [ 0.0, 0.0 ] |
| Case 1993 | 4/81 | 2/76 | | 1.88 [ 0.35, 9.95 ] |
| Dammacco 2001 | 3/69 | 1/76 | | 3.30 [ 0.35, 31.03 ] |
| Fujisaka 2011 | 5/89 | 3/92 | | 1.72 [ 0.42, 7.00 ] |
| Gordon 2008 | 1/164 | 0/54 | | 1.00 [ 0.04, 24.19 ] |
| Henry 1995 | 2/67 | 4/65 | | 0.49 [ 0.09, 2.56 ] |
| Hernandez 2009 | 6/194 | 4/192 | | 1.48 [ 0.43, 5.18 ] |
| Hoskin 2009 | 5/133 | 5/149 | | 1.12 [ 0.33, 3.78 ] |
| Iconomou 2003 | 0/61 | 0/61 | | 0.0 [ 0.0, 0.0 ] |
| Krzakowski 2008a | 2/100 | 1/50 | | 1.00 [ 0.09, 10.77 ] |
| Krzakowski 2008b | 1/103 | 0/49 | | 1.44 [ 0.06, 34.78 ] |
| Kunikane 2001a | 3/22 | 2/9 | | 0.61 [ 0.12, 3.08 ] |
| Kunikane 2001b | 2/21 | 2/8 | | 0.38 [ 0.06, 2.27 ] |
| Littlewood 2001 | 9/251 | 1/124 | | 4.45 [ 0.57, 34.70 ] |
| Milroy 2011 | 6/214 | 3/210 | | 1.96 [ 0.50, 7.74 ] |
| Osterborg 1996a | 4/47 | 1/25 | | 2.13 [ 0.25, 18.03 ] |
| Osterborg 1996b | 5/48 | 0/24 | | 5.61 [ 0.32, 97.48 ] |
| Osterborg 2002 | 15/170 | 9/173 | | 1.70 [ 0.76, 3.77 ] |
| Pirker 2008 | 18/301 | 15/296 | | 1.18 [ 0.61, 2.30 ] |
| Razzouk 2006 | 2/112 | 1/110 | | 1.96 [ 0.18, 21.35 ] |
| Rosenzweig 2004 | 1/14 | 0/13 | | 2.80 [ 0.12, 63.20 ] |
| Savonije 2005 | 7/211 | 3/104 | | 1.15 [ 0.30, 4.36 ] |
| Silvestris 1995 | 4/30 | 0/24 | | 7.26 [ 0.41, 128.50 ] |
| Smith 2008 | 8/515 | 12/470 | | 0.61 [ 0.25, 1.48 ] |
| Ten Bokkel 1998a | 4/43 | 1/14 | | 1.30 [ 0.16, 10.71 ] |

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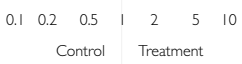
| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Ten Bokkel 1998b | 7/37 | 0/14 | | 5.92 [ 0.36, 97.33 ] |
| Thatcher 1999a | 2/42 | 0/22 | | 2.67 [ 0.13, 53.39 ] |
| Thatcher 1999b | 1/44 | 0/22 | | 1.53 [ 0.06, 36.18 ] |
| Tjulandin 2010a | 2/76 | 1/37 | | 0.97 [ 0.09, 10.40 ] |
| Tjulandin 2010b | 2/73 | 1/37 | | 1.01 [ 0.09, 10.82 ] |
| Tjulandin 2011 | 8/95 | 1/91 | | 7.66 [ 0.98, 60.06 ] |
| Tsuboi 2009 | 4/62 | 2/58 | | 1.87 [ 0.36, 9.83 ] |
| Vansteenkiste 2002 | 9/155 | 6/159 | | 1.54 [ 0.56, 4.22 ] |
| Welch 1995 | 2/15 | 0/15 | | 5.00 [ 0.26, 96.13 ] |
| Wilkinson 2006 | 3/121 | 0/60 | | 3.50 [ 0.18, 66.68 ] |
| **Total (95% CI)** | **3902** | **3105** | | **1.52 [ 1.18, 1.97 ]** |

Total events: 159 (Treatment), 81 (Control)

Heterogeneity: $Chi^2$ = 19.94, df = 33 (P = 0.96); $I^2$ =0.0%

Test for overall effect: Z = 3.20 (P = 0.0014)

Test for subgroup differences: Not applicable



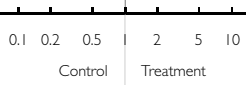
## Analysis 13.1. Comparison 13 Thrombocytopenia or haemorrhage, Outcome 1 Thrombocytopenia - overall.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 13 Thrombocytopenia or haemorrhage

Outcome: 1 Thrombocytopenia - overall

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Bamias 2003 | 2/72 | 0/72 | | 5.00 [ 0.24, 102.35 ] |
| Boogaerts 2003 | 8/133 | 13/129 | | 0.60 [ 0.26, 1.39 ] |
| Cascinu 1994 | 0/50 | 0/50 | | 0.0 [ 0.0, 0.0 ] |
| Dammacco 2001 | 5/69 | 5/76 | | 1.10 [ 0.33, 3.64 ] |
| Del Mastro 1997 | 4/31 | 4/31 | | 1.00 [ 0.27, 3.65 ] |
| Fujisaka 2011 | 61/89 | 55/92 | | 1.15 [ 0.92, 1.43 ] |
| Gebbia 2003 | 3/22 | 3/23 | | 1.05 [ 0.24, 4.64 ] |
| Goss 2005 | 1/52 | 0/52 | | 3.00 [ 0.13, 71.99 ] |
| Gupta 2009 | 0/58 | 0/57 | | 0.0 [ 0.0, 0.0 ] |
| Kunikane 2001a | 12/22 | 2/9 | | 2.45 [ 0.68, 8.83 ] |
| Kunikane 2001b | 7/21 | 1/8 | | 2.67 [ 0.39, 18.38 ] |
| Littlewood 2001 | 18/251 | 9/124 | | 0.99 [ 0.46, 2.14 ] |
| Milroy 2011 | 15/214 | 9/210 | | 1.64 [ 0.73, 3.66 ] |
| Osterborg 1996a | 3/47 | 1/25 | | 1.60 [ 0.17, 14.55 ] |
| Osterborg 1996b | 0/48 | 0/24 | | 0.0 [ 0.0, 0.0 ] |
| Pirker 2008 | 60/301 | 38/296 | | 1.55 [ 1.07, 2.26 ] |
| Savonije 2005 | 22/211 | 6/104 | | 1.81 [ 0.76, 4.32 ] |
| Strauss 2008 | 1/33 | 4/38 | | 0.29 [ 0.03, 2.45 ] |
| Thatcher 1999a | 11/42 | 5/22 | | 1.15 [ 0.46, 2.90 ] |
| Thatcher 1999b | 9/44 | 4/22 | | 1.13 [ 0.39, 3.25 ] |
| Thompson 2000 | 5/45 | 0/21 | | 5.26 [ 0.30, 90.96 ] |
| Tsuboi 2009 | 31/62 | 28/58 | | 1.04 [ 0.72, 1.49 ] |
| Untch 2011˙1 | 8/318 | 10/396 | | 1.00 [ 0.40, 2.49 ] |
| Witzig 2005 | 7/168 | 10/165 | | 0.69 [ 0.27, 1.76 ] |
| **Total (95% CI)** | **2403** | **2104** | | **1.21 [ 1.04, 1.42 ]** |
| Total events: 293 (Treatment), 207 (Control) | | | | |

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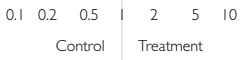
| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Heterogeneity: Chi² = 14.50, df = 20 (P = 0.80); I² =0.0% | | | | |
| Test for overall effect: Z = 2.49 (P = 0.013) | | | | |
| Test for subgroup differences: Not applicable | | | | |




## Analysis 13.2. Comparison 13 Thrombocytopenia or haemorrhage, Outcome 2 Thrombocytopenia - merged experimental arms.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 13 Thrombocytopenia or haemorrhage

Outcome: 2 Thrombocytopenia - merged experimental arms

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Bamias 2003 | 2/72 | 0/72 | | 5.00 [ 0.24, 102.35 ] |
| Boogaerts 2003 | 8/133 | 13/129 | | 0.60 [ 0.26, 1.39 ] |
| Cascinu 1994 | 0/50 | 0/50 | | 0.0 [ 0.0, 0.0 ] |
| Dammacco 2001 | 5/69 | 5/76 | | 1.10 [ 0.33, 3.64 ] |
| Del Mastro 1997 | 4/31 | 4/31 | | 1.00 [ 0.27, 3.65 ] |
| Fujisaka 2011 | 61/89 | 55/92 | | 1.15 [ 0.92, 1.43 ] |
| Gebbia 2003 | 3/22 | 3/23 | | 1.05 [ 0.24, 4.64 ] |
| Goss 2005 | 1/52 | 0/52 | | 3.00 [ 0.13, 71.99 ] |
| Gupta 2009 | 0/58 | 0/57 | | 0.0 [ 0.0, 0.0 ] |
| Kunikane 2001 | 19/43 | 3/17 | | 2.50 [ 0.85, 7.38 ] |
| Littlewood 2001 | 18/251 | 9/124 | | 0.99 [ 0.46, 2.14 ] |
| Milroy 2011 | 15/214 | 9/210 | | 1.64 [ 0.73, 3.66 ] |
| Osterborg 1996 | 3/95 | 1/49 | | 1.55 [ 0.17, 14.49 ] |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| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Pirker 2008 | 60/301 | 38/296 | | 1.55 [ 1.07, 2.26 ] |
| Savonije 2005 | 22/211 | 6/104 | | 1.81 [ 0.76, 4.32 ] |
| Strauss 2008 | 1/33 | 4/38 | | 0.29 [ 0.03, 2.45 ] |
| Thatcher 1999 | 20/86 | 9/44 | | 1.14 [ 0.57, 2.28 ] |
| Thompson 2000 | 5/45 | 0/21 | | 5.26 [ 0.30, 90.96 ] |
| Tsuboi 2009 | 31/62 | 28/58 | | 1.04 [ 0.72, 1.49 ] |
| Untch 2011˙1 | 8/318 | 10/396 | | 1.00 [ 0.40, 2.49 ] |
| Witzig 2005 | 7/168 | 10/165 | | 0.69 [ 0.27, 1.76 ] |
| **Total (95% CI)** | **2403** | **2104** | | **1.21 [ 1.04, 1.41 ]** |

Total events: 293 (Treatment), 207 (Control)

Heterogeneity: $Chi^2$ = 14.40, df = 18 (P = 0.70); $I^2$ =0.0%

Test for overall effect: Z = 2.48 (P = 0.013)

Test for subgroup differences: Not applicable

## Analysis 13.3. Comparison 13 Thrombocytopenia or haemorrhage, Outcome 3 Thrombocytopenia - sensitivity analysis random effects.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 13 Thrombocytopenia or haemorrhage

Outcome: 3 Thrombocytopenia - sensitivity analysis random effects

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Random,95% CI | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|
| Bamias 2003 | 2/72 | 0/72 | | 5.00 [ 0.24, 102.35 ] |
| Boogaerts 2003 | 8/133 | 13/129 | | 0.60 [ 0.26, 1.39 ] |
| Cascinu 1994 | 0/50 | 0/50 | | 0.0 [ 0.0, 0.0 ] |
| Dammacco 2001 | 5/69 | 5/76 | | 1.10 [ 0.33, 3.64 ] |
| Del Mastro 1997 | 4/31 | 4/31 | | 1.00 [ 0.27, 3.65 ] |
| Fujisaka 2011 | 61/89 | 55/92 | | 1.15 [ 0.92, 1.43 ] |
| Gebbia 2003 | 3/22 | 3/23 | | 1.05 [ 0.24, 4.64 ] |
| Goss 2005 | 1/52 | 0/52 | | 3.00 [ 0.13, 71.99 ] |
| Gupta 2009 | 0/58 | 0/57 | | 0.0 [ 0.0, 0.0 ] |
| Kunikane 2001a | 12/22 | 2/9 | | 2.45 [ 0.68, 8.83 ] |
| Kunikane 2001b | 7/21 | 1/8 | | 2.67 [ 0.39, 18.38 ] |
| Littlewood 2001 | 18/251 | 9/124 | | 0.99 [ 0.46, 2.14 ] |
| Milroy 2011 | 15/214 | 9/210 | | 1.64 [ 0.73, 3.66 ] |
| Osterborg 1996a | 3/47 | 1/25 | | 1.60 [ 0.17, 14.55 ] |
| Osterborg 1996b | 0/48 | 0/24 | | 0.0 [ 0.0, 0.0 ] |
| Pirker 2008 | 60/301 | 38/296 | | 1.55 [ 1.07, 2.26 ] |
| Savonije 2005 | 22/211 | 6/104 | | 1.81 [ 0.76, 4.32 ] |
| Strauss 2008 | 1/33 | 4/38 | | 0.29 [ 0.03, 2.45 ] |
| Thatcher 1999a | 11/42 | 5/22 | | 1.15 [ 0.46, 2.90 ] |
| Thatcher 1999b | 9/44 | 4/22 | | 1.13 [ 0.39, 3.25 ] |
| Thompson 2000 | 5/45 | 0/21 | | 5.26 [ 0.30, 90.96 ] |
| Tsuboi 2009 | 31/62 | 28/58 | | 1.04 [ 0.72, 1.49 ] |
| Untch 2011˙1 | 8/318 | 10/396 | | 1.00 [ 0.40, 2.49 ] |
| Witzig 2005 | 7/168 | 10/165 | | 0.69 [ 0.27, 1.76 ] |


(*Continued* . . . )

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| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Random,95% CI | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|
| **Total (95% CI)** | **2403** | **2104** | ◆ | **1.18 [ 1.02, 1.36 ]** |
| Total events: 293 (Treatment), 207 (Control) | | | | |
| Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 14.50$, df = 20 (P = 0.80); $I^2 = 0.0\%$ | | | | |
| Test for overall effect: Z = 2.27 (P = 0.023) | | | | |
| Test for subgroup differences: Not applicable | | | | |


## Analysis 14.1. Comparison 14 Rash, Outcome 1 Rash - overall.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 14 Rash

Outcome: 1 Rash - overall

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Del Mastro 1997 | 2/31 | 0/31 | | 5.00 [ 0.25, 100.08 ] |
| Gordon 2008 | 1/164 | 0/54 | | 1.00 [ 0.04, 24.19 ] |
| Gupta 2009 | 0/58 | 0/57 | | 0.0 [ 0.0, 0.0 ] |
| Henry 1995 | 7/67 | 2/65 | | 3.40 [ 0.73, 15.74 ] |
| Italian 1998 | 0/44 | 1/43 | | 0.33 [ 0.01, 7.79 ] |
| Kurz 1997 | 0/12 | 0/12 | | 0.0 [ 0.0, 0.0 ] |
| Milroy 2011 | 3/214 | 0/210 | | 6.87 [ 0.36, 132.19 ] |
| Osterborg 1996a | 1/47 | 0/25 | | 1.63 [ 0.07, 38.49 ] |
| Osterborg 1996b | 1/48 | 0/24 | | 1.53 [ 0.06, 36.23 ] |
| Osterborg 2002 | 2/170 | 0/173 | | 5.09 [ 0.25, 105.20 ] |
| Strauss 2008 | 1/33 | 0/38 | | 3.44 [ 0.14, 81.71 ] |
| Thatcher 1999a | 5/42 | 2/22 | | 1.31 [ 0.28, 6.21 ] |


(*Continued* . . . )

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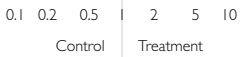
| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Thatcher 1999b | 1/44 | 2/22 | | 0.25 [ 0.02, 2.61 ] |
| Thompson 2000 | 3/45 | 4/21 | | 0.35 [ 0.09, 1.43 ] |
| Tjulandin 2011 | 13/95 | 7/91 | | 1.78 [ 0.74, 4.26 ] |
| Tsuboi 2009 | 0/62 | 2/58 | | 0.19 [ 0.01, 3.82 ] |
| Welch 1995 | 1/15 | 0/15 | | 3.00 [ 0.13, 68.26 ] |
| Witzig 2005 | 12/168 | 7/165 | | 1.68 [ 0.68, 4.17 ] |
| **Total (95% CI)** | **1359** | **1126** | | **1.49 [ 0.99, 2.24 ]** |

Total events: 53 (Treatment), 27 (Control)

Heterogeneity: $Chi^2$ = 13.18, df = 15 (P = 0.59); $I^2$ =0.0%

Test for overall effect: Z = 1.90 (P = 0.058)

Test for subgroup differences: Not applicable



## Analysis 14.2. Comparison 14 Rash, Outcome 2 Rash - merged experimental arms.

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 14 Rash

Outcome: 2 Rash - merged experimental arms

| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Del Mastro 1997 | 2/31 | 0/31 | | 5.00 [ 0.25, 100.08 ] |
| Gordon 2008 | 1/164 | 0/54 | | 1.00 [ 0.04, 24.19 ] |
| Gupta 2009 | 0/58 | 0/57 | | 0.0 [ 0.0, 0.0 ] |
| Henry 1995 | 7/67 | 2/65 | | 3.40 [ 0.73, 15.74 ] |
| Italian 1998 | 0/44 | 1/43 | | 0.33 [ 0.01, 7.79 ] |
| Kurz 1997 | 0/12 | 0/12 | | 0.0 [ 0.0, 0.0 ] |
| Milroy 2011 | 3/214 | 0/210 | | 6.87 [ 0.36, 132.19 ] |
| Osterborg 1996 | 2/95 | 0/49 | | 2.60 [ 0.13, 53.21 ] |
| Osterborg 2002 | 2/170 | 0/173 | | 5.09 [ 0.25, 105.20 ] |
| Strauss 2008 | 1/33 | 0/38 | | 3.44 [ 0.14, 81.71 ] |
| Thatcher 1999 | 6/86 | 4/44 | | 0.77 [ 0.23, 2.58 ] |
| Thompson 2000 | 3/45 | 4/21 | | 0.35 [ 0.09, 1.43 ] |
| Tjulandin 2011 | 13/95 | 7/91 | | 1.78 [ 0.74, 4.26 ] |
| Tsuboi 2009 | 0/62 | 2/58 | | 0.19 [ 0.01, 3.82 ] |
| Welch 1995 | 1/15 | 0/15 | | 3.00 [ 0.13, 68.26 ] |
| Witzig 2005 | 12/168 | 7/165 | | 1.68 [ 0.68, 4.17 ] |
| **Total (95% CI)** | **1359** | **1126** | | **1.50 [ 1.00, 2.27 ]** |

Total events: 53 (Treatment), 27 (Control)

Heterogeneity: $Chi^2$ = 12.22, df = 13 (P = 0.51); $I^2$ =0.0%

Test for overall effect: Z = 1.94 (P = 0.053)

Test for subgroup differences: Not applicable

**Analysis 15.1. Comparison 15 Seizure, Outcome 1 Seizure - overall.**

Review: Erythropoietin or darbepoetin for patients with cancer

Comparison: 15 Seizure

Outcome: 1 Seizure - overall

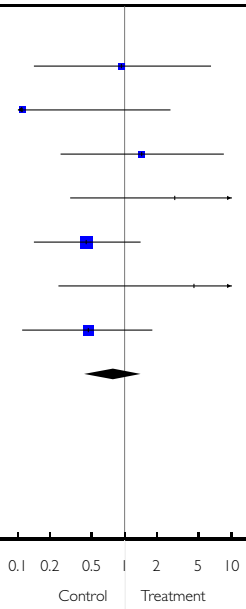
| Study or subgroup | Treatment n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Cascinu 1994 | 0/50 | 0/50 | | 0.0 [ 0.0, 0.0 ] |
| Case 1993 | 2/81 | 2/76 | | 0.94 [ 0.14, 6.50 ] |
| Gordon 2008 | 0/164 | 1/54 | | 0.11 [ 0.00, 2.69 ] |
| Henry 1995 | 3/67 | 2/65 | | 1.46 [ 0.25, 8.43 ] |
| Hernandez 2009 | 3/194 | 1/192 | | 2.97 [ 0.31, 28.29 ] |
| Pirker 2008 | 4/301 | 9/296 | | 0.44 [ 0.14, 1.40 ] |
| Savonije 2005 | 4/211 | 0/104 | | 4.46 [ 0.24, 82.02 ] |
| Smith 2008 | 3/515 | 6/470 | | 0.46 [ 0.11, 1.81 ] |
| **Total (95% CI)** | **1583** | **1307** | | **0.77 [ 0.42, 1.41 ]** |

Total events: 19 (Treatment), 21 (Control)

Heterogeneity: $Chi^2 = 6.19$, df = 6 (P = 0.40); $I^2 = 3\%$

Test for overall effect: Z = 0.85 (P = 0.39)

Test for subgroup differences: Not applicable




## ADDITIONAL TABLES

**Table 1. Haematologic response: results of meta-regression analysis**

| Variable | log (effect size) | standard error | P value |
|---|---|---|---|
| Intercept | 0.81 | 0.1189 | <0.0001 |
| Hb baseline 10-12 g/dL | 0.62 | 0.1430 | <0.0001 |
| Hb baseline > 12 g/dL | 0.85 | 0.4694 | 0.0688 |
| Children | -0.68 | 0.1653 | <0.0001 |
| Iron given differently in both study arms | -0.64 | 0.2348 | 0.0068 |

**Table 1. Haematologic response: results of meta-regression analysis** (*Continued*)

| | | | |
|---|---|---|---|
| Iron supplementation as necessary | 0.35 | 0.1315 | 0.0081 |

Hb: haemoglobin

**Table 2. Hb change: results of meta-regression analysis**

| Variable | mean difference | standard error | P value |
|---|---|---|---|
| Intercept | 1.15 | 0.1792 | <0.0001 |
| Children | -1.41 | 0.6911 | 0.0414 |
| Short acting ESA | 0.56 | 0.2041 | 0.0060 |

ESA: erythropoiesis stimulating agent

**Table 3. Participants receiving RBC transfusions: results of meta-regression analysis**

| **Variable** | **log(effect size)** | **Standard error** | **P value** |
|---|---|---|---|
| Intercept | -0.22 | 0.0506 | <0.0001 |
| Hb 10 - 12 g/dL | -0.15 | 0.0650 | 0.0254 |
| Hb > 12 g/dL | 0.07 | 0.0601 | 0.2774 |
| MDS | 0.01 | 0.1004 | 0.8967 |
| Solid and haematological tumours | -0.03 | 0.0648 | 0.6726 |
| Solid tumours | -0.39 | 0.0637 | <0.0001 |

MDS: myelodysplastic syndrome
RBC: red blood cell

**Table 4. FACT-F 13: results of meta-regression analysis**

| Variable | mean difference | standard error | P value |
|---|---|---|---|
| Intercept | 1.09 | 0.6158 | 0.0779 |
| Short acting ESA | 2.20 | 0.8346 | 0.0083 |

ESA: erythropoiesis stimulating agent

**Table 5. FACT-An 47: results of meta-regression analysis**

| Variable | mean difference | Standard error | P value |
|---|---|---|---|
| Intercept | 6.10 | 2.3783 | 0.0103 |
| Chemotherapy, < 70% of participants receiving platinum-based chemotherapy | -5.82 | 3.1929 | 0.0683 |
| Chemotherapy, > 70% of participants receiving platinum-based chemotherapy | 0.81 | 3.7926 | 0.8303 |
| No anticancer therapy | 23.80 | 4.0571 | <0.0001 |
| Radiotherapy | -4.20 | 3.9147 | 0.2836 |

# APPENDICES

## Appendix 1. EMBASE search strategy

Please note that the same search strategy was used for the other searches conducted on the dates mentioned in the main text.

| No. | Query |
|---|---|
| **#70** | #68 AND [1-8-2009]/sd NOT [11-1-2011]/sd |
| **#68** | #38 AND #67 |
| **#67** | #63 NOT #66 |
| **#66** | #64 NOT #65 |
| **#65** | 'human'/exp OR human |
| **#64** | 'animal'/exp OR animal |
| **#63** | #58 NOT #62 |
| **#62** | #59 OR #60 OR #61 |

(*Continued*)

| | |
|---|---|
| **#61** | 'abstract report' OR letter |
| **#60** | 'case report' |
| **#59** | 'case study' |
| **#58** | #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 |
| **#57** | 'prospective study' |
| **#56** | placebo* |
| **#55** | 'triple' NEAR/5 'blind' |
| **#54** | 'treble' NEAR/5 'blind' |
| **#53** | double AND blind* |
| **#52** | single AND blind* |
| **#51** | 'allocated' NEAR/2 'random' |
| **#50** | 'allocated randomly' |
| **#49** | 'randomly allocated' |
| **#48** | 'random allocation' |
| **#47** | rct |
| **#46** | randomi?ed AND controlled AND trial? |
| **#45** | 'placebo'/exp OR placebo |
| **#44** | 'crossover procedure'/exp OR 'crossover procedure' |
| **#43** | 'double blind procedure'/exp OR 'double blind procedure' |
| **#42** | 'single blind procedure'/exp OR 'single blind procedure' |
| **#41** | 'randomization'/exp OR 'randomization' |
| **#40** | 'randomized controlled trial'/exp OR 'randomized controlled trial' |
| **#39** | 'clinical trial'/exp OR 'clinical trial' |
| **#38** | #36 AND #37 |

(*Continued*)

| | |
|---|---|
| **#37** | #21 AND #27 |
| **#36** | #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 |
| **#35** | carcinoma* |
| **#34** | tumo?r* |
| **#33** | chemotherapy |
| **#32** | myelodysplas* |
| **#31** | oncolog* |
| **#30** | cancer* |
| **#29** | malignan* |
| **#28** | 'neoplasm'/exp OR neoplasm |
| **#27** | #22 OR #23 OR #24 OR #25 OR #26 |
| **#26** | anemi* |
| **#25** | anaemi* |
| **#24** | anemia |
| **#23** | anaemia |
| **#22** | 'anemia'/exp OR anemia |
| **#21** | #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 |
| **#20** | 'erythropoietin receptor'/exp OR 'erythropoietin receptor' |
| **#19** | micer* |
| **#18** | mircer* |
| **#17** | methoxy AND polyethylene AND 'glycol epoetin' AND beta |
| **#16** | continuous AND erythropo?es* AND ('receptor'/exp OR receptor) AND activator |
| **#15** | cera* |
| **#14** | darbepo?eti* |

(*Continued*)

| | |
|---|---|
| **#13** | cepo* |
| **#12** | procit* |
| **#11** | aranesp* |
| **#10** | neorecormon* |
| **#9** | eprex* |
| **#8** | haemopo*etin* |
| **#7** | haematopo*etin* |
| **#6** | hemopo*etin* |
| **#5** | hematopo*etin* |
| **#4** | epo* |
| **#3** | eritropo* |
| **#2** | eryt*ropo* |
| **#1** | 'erythropoietin' OR 'recombinant erythropoietin'/exp |

## Appendix 2. MEDLINE search strategy

Please note that the same search strategy was used for the other searches conducted on the dates mentioned in the main text.
MEDLINE /Ovid (February 2011 to November 2011)

| # | **Searches** |
|---|---|
| 1 | exp ERYTHROPOIETIN/ |
| 2 | exp ERYTHROPOIETIN, RECOMBINANT/ |
| 3 | erythropoietin.mp. |
| 4 | erythropoiesis.mp. |
| 5 | exp EPOETIN ALFA/ |
| 6 | epoetin.mp. |

(*Continued*)

| | |
|---|---|
| 7 | epo.mp. |
| 8 | epoetin alfa.mp. |
| 9 | epoetin beta.mp. |
| 10 | eprex.mp. |
| 11 | neorecormon.mp. |
| 12 | aranesp.mp. |
| 13 | procrit.mp. |
| 14 | recombinant erythropoietin.mp. |
| 15 | darbepoetin alfa.mp. |
| 16 | darbepoetin.mp. |
| 17 | RECEPTORS, ERYTHROPOIETIN/ |
| 18 | CERA.mp. |
| 19 | or/1-18 |
| 20 | exp ANEMIA/dt, th [Drug Therapy, Therapy] |
| 21 | anaemia.mp. |
| 22 | anemia.mp. |
| 23 | (anemi$ adj3 cancer).mp. |
| 24 | (anaemi$ adj3 cancer).mp. |
| 25 | or/20-24 |
| 26 | exp Neoplasms/ |
| 27 | malignan$.mp. |
| 28 | cancer$.mp. |
| 29 | oncolog$.tw. |
| 30 | myelodysplas$.tw. |

(*Continued*)

| | |
|---|---|
| 31 | chemotherapy.mp. |
| 32 | tumo?r$.mp. |
| 33 | carcinom$.mp. |
| 34 | or/26-33 |
| 35 | 19 and 25 |
| 36 | 34 and 35 |
| 37 | randomized controlled trial.pt. |
| 38 | controlled clinical trial.pt. |
| 39 | randomized.ab. |
| 40 | placebo.ab. |
| 41 | drug therapy.fs. |
| 42 | randomly.ab. |
| 43 | trial.ab. |
| 44 | groups.ab. |
| 45 | or/37-44 |
| 46 | humans.sh. |
| 47 | 45 and 46 |
| 48 | 36 and 47 |
| 49 | limit 48 to ed=20080101-20081231 |
| 50 | randomized controlled trial.pt. |
| 51 | controlled clinical trial.pt. |
| 52 | randomized controlled trials as topic/ |
| 53 | random allocation/ |
| 54 | double blind method/ |

(*Continued*)

| | |
|---|---|
| 55 | single blind method/ |
| 56 | or/50-55 |
| 57 | (ANIMALS not HUMANS).sh. |
| 58 | 56 not 57 |
| 59 | clinical trial.pt. |
| 60 | exp clinical trial as topic/ |
| 61 | (clin$ adj25 trial$).ti,ab. |
| 62 | ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab |
| 63 | placebos/ |
| 64 | placebo$.ti,ab. |
| 65 | random$.ti,ab. |
| 66 | research design/ |
| 67 | or/59-66 |
| 68 | 67 not 57 |
| 69 | 68 not 58 |
| 70 | comparative study/ |
| 71 | exp evaluation studies/ |
| 72 | follow up studies/ |
| 73 | prospective studies/ |
| 74 | (control$ or prospectiv$ or volunteer$).ti,ab. |
| 75 | or/70-74 |
| 76 | 75 not 57 |
| 77 | 76 not (58 or 69) |
| 78 | 58 or 69 or 77 |

(*Continued*)

| | |
|---|---|
| 79 | 36 and 78 |
| 80 | 48 or 79 |
| 81 | limit 80 to ed=20090801-20110201 |
| 82 | limit 80 to ed=20110201-20111201 |

## Appendix 3. CENTRAL search strategy

Please note that the same search strategy was used for the other searches conducted on the dates mentioned in the main text.
Cochrane Central Register of Controlled Trials (Cochrane Library 2011, Issue 3)

| ID | Search |
|---|---|
| #1 | (erythropoietin) |
| #2 | MeSH descriptor Erythropoietin explode all trees |
| #3 | epoetin |
| #4 | epo |
| #5 | (epoetin next alfa) |
| #6 | (epoetin next beta) |
| #7 | (darbepoetin next alfa) |
| #8 | eprex |
| #9 | neorecormon |
| #10 | aranesp |
| #11 | procrit |
| #12 | (recombinant near erythropoietin) |
| #13 | “continuous erythropoietin receptor activation” |
| #14 | “continuous erythropoietin receptor activator” |
| #15 | CERA |
| #16 | C.E.R.A. |

(*Continued*)

| | |
|---|---|
| #17 | erythropoiesis |
| #18 | darbepoetin |
| #19 | (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18) |
| #20 | anemia |
| #21 | anaemia |
| #22 | MeSH descriptor Anemia explode all trees |
| #23 | (anemi* near cancer) |
| #24 | (anaemi* near cancer) |
| #25 | (#20 OR #21 OR #22 OR #23 OR #24) |
| #26 | (#19 AND #25) |
| #27 | (#26), from 2007 to 2008 |
| #28 | (#26), from 2008 to 2009 |
| #29 | (#26), from 2009 |
| #30 | (#28 OR #29) |
| #31 | (#26), from 2009 to 2011 |
| #32 | (#26), in 2011 |

## WHAT'S NEW

Last assessed as up-to-date: 2 May 2012.

| Date | Event | Description |
|---|---|---|
| 11 May 2012 | New citation required and conclusions have changed | Authors changed (new authors: Tonia T, Mettler A, Robert N)<br>Substantive update, in the previous review the outcome haematological response was restricted to studies with baseline Hb levels < 12 g/dL; in the current update this restriction was removed. On-study mortality |

(*Continued*)

| | | |
|---|---|---|
| | | was added as a new outcome to the current update of the review. Studies using iron supplements in one study arm only were included, in the previous version these studies were excluded. Studies using any dose of ESAs were included, in the previous review studies using very low dosages had been excluded. Any type of ESA was included in the review |
| 30 November 2011 | New search has been performed | New search |

## HISTORY

Protocol first published: Issue 4, 2002

Review first published: Issue 3, 2004

| Date | Event | Description |
|---|---|---|
| 15 August 2008 | Amended | Converted to new review format. |
| 24 May 2006 | New citation required and conclusions have changed | Substantive amendment |

## CONTRIBUTIONS OF AUTHORS

Thomy Tonia: Quality of Life analysis, searching for trials, eligibility and quality assessment, fact checking, data extraction and analysis, drafting of QoL and discussion, revision of review

Annette Mettler: Searching for trials, eligibility and quality assessment, data extraction and analysis

Nadège Robert: Searching for trials, eligibility and quality assessment, data extraction and analysis

Guido Schwarzer: Statistical and methodological advice, data analysis, content input

Olaf Weingart: eligibility and quality assessment, fact checking, creating summary of findings table

Jerome Seidenfeld: Clinical and scientific advice, content input, revision of draft review

Chris Hyde: Protocol development, searching for trials, eligibility and quality assessment, data extraction and analysis

Andreas Engert: Clinical and scientific advice, content input

Julia Bohlius: Protocol development, searching for trials, eligibility and quality assessment, data extraction and analysis, drafting and revision of review

## DECLARATIONS OF INTEREST

Thomy Tonia, Annette Mettler, Nadège Robert, Olaf Weingart, Guido Schwarzer, Jerome Seidenfeld, Chris Hyde, Andreas Engert, Julia Bohlius: none known.

## SOURCES OF SUPPORT


### Internal sources

- Department of Internal Medicine I, University of Cologne, Germany.
- Cochrane Haematological Malignancies Group (CHMG), Germany.
- Institute of Social and Preventive Medicine, University of Bern, Switzerland.

### External sources

- Department of Health, UK.


## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In previous versions of this review, we required dosages of at least 300 U/kg body weight per week (epoetin-a and beta) given for at least four weeks. For the current update this criterion was removed and we included studies or study arms with low dosages as well. In previous versions of this review, iron supplementation had to be identical in the study arms of a given trial. For the current update, we changed this criterion and included trials using iron supplementation in the experimental but not in the control arm as well.

## INDEX TERMS

### Medical Subject Headings (MeSH)

Anemia [*drug therapy; etiology]; Erythrocyte Transfusion [utilization]; Erythropoietin [*analogs & derivatives; *therapeutic use]; Neoplasms [blood; *complications]; Randomized Controlled Trials as Topic; Recombinant Proteins

### MeSH check words

Humans