# The role of bevacizumab in solid tumours: A literature based meta-analysis of randomised trials

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**KEYWORDS**
Bevacizumab;
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**Abstract** ***Background:*** Bevacizumab is a humanised monoclonal antibody which blocks the binding of circulating vascular endothelial growth factor to its receptors. To date, the Food and Drug Administration has approved bevacizumab for the treatment of several solid tumours. To assess the impact of bevacizumab-based regimens on outcome in these advanced solid tumour types, we performed a meta-analysis. We included all of the randomised trials (phase II or III) where bevacizumab was tested in the first line setting compared with a control arm, including chemotherapy, placebo or other anti-neoplastic agents.
***Methods:*** A literature-based meta-analysis of randomised controlled trials (RCTs) in accordance with the preferences for reported items in systematic reviews and meta-analyses guidelines were undertaken. The primary end-point considered was overall survival (OS). The secondary end-points were progression-free survival (PFS) time, response rate and safety. A subgroup analysis was performed to highlight any differences between studies in different tumour types for all end-points.
***Results:*** The pooled analysis from RCTs on bevacizumab-based regimens revealed significantly increased OS (hazard ratio [HR] for death 0.92, 95% confidence interval [CI]: 0.88

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−0.95; P < 0.0001), PFS (HR: 0.72, 95% CI: 0.67−0.78; P < 0.00001) and response rate (risk ratio: 1.38, 95% CI: 1.27−1.50; P < 0.00001) compared to control arm in solid tumours overall and in colorectal, lung, ovarian and renal cancer as single indications. However, notably, no effect on survival was seen in breast cancer.

***Conclusion:*** This study confirmed that bevacizumab-based regimens result in a significant effect on survival and response in advanced colorectal, lung, ovarian and kidney cancer. In cancers where bevacizumab failed overall as in breast cancer, a dedicated biomarkers analysis is warranted to select the proper subgroup of patient that might have the adequate clinical benefit.

## 1. Introduction

The formation of new blood vessels in tumours (tumour angiogensis) has been linked with enhanced tumour growth and increased metastatic potential. Vascular endothelial growth factor (VEGF) is one of the most potent pro-angiogenic factors and is expressed in most solid cancers [1−5]. Investigators have sought novel therapeutic approaches to target VEGF-dependent tumour angiogenesis, including: agents that bind and inhibit VEGF ligands, agents that bind and inhibit VEGF receptors and small molecular inhibitors of VEGF receptor tyrosine kinase activity. Bevacizumab is a humanised monoclonal antibody that blocks the binding of all known VEGF-A isoforms to VEGF receptors. Preclinical studies have shown that anti-VEGF antibodies, alone or in combination with chemotherapy, can suppress tumour angiogenesis and tumour growth in animal models [6]. These preclinical data provided a strong rationale for the clinical development of bevacizumab for the treatment of solid tumours.

However, the results reported for bevacizumab for the treatment of patients with advanced solid tumours have been variable, with some studies reporting a strong effect on outcome, whilst others have reported minimal or no effect. In order to evaluate the impact of bevacizumab on patient outcomes, in the current meta-analysis the efficacy and safety of bevacizumab was evaluated in randomised controlled trials (RCTs) across multiple malignancies.

## 2. Materials and methods

### 2.1. Data retrieval strategies

We conducted a meta-analysis of RCTs in accordance with the preferences for reported items in systematic reviews and meta-analyses guidelines [7]. Relevant publications from PubMed and the Central Registry of Controlled Trials of the Cochrane Library were identified. The initial search was focussed on terms describing cancer, bevacizumab and clinical trials; the following medical subject heading terms therefore were used: 'Solid tumours OR Neoplasm OR Cancer' AND 'Bevacizumab OR Avastin OR Genentech brand of Bevacizumab' AND 'prospective' OR 'clinical' OR 'human' OR 'random'. After the first search, article types were chosen as follows: 'clinical trial' and 'humans' was chosen in PubMed and no restrictions were imposed in the Cochrane library. In addition, we manually searched through abstracts submitted to the 2010 and 2016 American Society of Clinical Oncologists general meeting for applicable trials. Publications available in these databases up to December 01, 2016, were analysed. To minimise the risk of selection or information bias, the search criteria were limited to articles reporting the results of phase II or phase III Randomized controlled trials (RCTs). The computer search was supplemented with a manual search of the primary studies referenced in all of the retrieved review articles. When the results of a study were reported in subsequent analysis, only the most recent and complete version was included in this meta-analysis.

### 2.2. Inclusion criteria

Two authors (GR and DG) screened the studies according to specific selection and exclusion criteria. The inclusion/exclusion decisions regarding contentious studies were made in consultation with a third author (GR). The studies were identified according to the following inclusion criteria: (1) participants with solid tumours; (2) a bevacizumab-based therapy; (3) the presence of a control arm for comparison without bevacizumab (chemotherapy, placebo or other anti-neoplastic agents) and (4) a primary outcome of overall survival (OS) expressed as the hazard ratio (HR) and secondary outcomes of progression-free survival (PFS) expressed as the HR, response rate expressed as relative risk (RR) and major side-effects of special interest (grade III−IV adverse events) expressed as RR. The following exclusion criteria were used: (1) insufficient data were available to estimate the outcomes; (2) the size of each arm was <10 participants; (3) non-randomised studies and (4) studies involving haematological patients.

### 2.3. Data extraction

Two authors independently extracted the relevant data including the name of the first author, publication year,

patient demographics (i.e. age, number, drug administered and type of tumours), median follow-up, median treatment duration, study design (i.e. the type of blinding, the type of control and the methods for randomisation), survival outcomes expressed as HRs for OS and PFS, number of patients who experienced a response rate and grade III–IV adverse events (hypertension, proteinuria and thromboembolic events). For each trial, the arm with bevacizumab was considered to be the experimental arm and chemotherapy, placebo or other anti-neoplastic agent the control.

### 2.4. Quality assessment

Study quality was assessed using the Jadad five-item scale, taking into account randomisation, double blinding and withdrawals. The final score ranged from 0 to 5 [8]. In the event of disagreements, consensus was achieved in discussion with the corresponding author (GR).

### 2.5. Statistical analysis

The statistical analyses were performed with Revman 5.3. The summary estimates were generated using a fixed-effect model (Mantel–Haenszel method) or a random-effect model (DerSimonian–Laird method) [9,10] depending on the absence or presence of heterogeneity. Statistical heterogeneity was assessed with the Q-test and the $I^2$ statistic. $I^2$ values of 25%, 50% and 75% were considered to indicate low, moderate and high heterogeneity, respectively [11]. When $P > 0.1$ and $I^2<50\%$, the fixed-effects model was used; otherwise, the random-effects model was used. For the time-to-event variables, including OS, PFS and HRs with 95% confidence intervals (CI) were calculated for each study. For the dichotomous variables, including response rate and the rate of adverse events, RRs with 95% CIs were calculated for each study. A subgroup analysis was performed to highlight any differences between studies in the different type of tumours and different administration of bevacizumab for all end-points. A funnel plot was generated to evaluate the publication bias, and Egger's regression method was used to test the symmetry of funnel plot. For all the statistical analyses, a value of $P < 0.05$ was regarded as statistically significant, and all tests were two-sided.

## 3. Results

### 3.1. Literature review and characteristics of the included studies

The search yielded 935 potentially relevant articles. A total of 164 studies were excluded as duplicates. After viewing the titles and abstracts of the 771 remaining studies, the full texts of 130 studies were retrieved and 47 studies [12–58] were included in the analysis (Fig. 1). There were 12 studies on metastatic colorectal, 10 breast cancer, 6 ovarian cancer, 5 non-small cell lung cancer, 2 renal cancer, 2 cervical/uterine, 3 glioblastoma and 7 which included several kind of tumours (2 small cell lung cancer, 2 gastric cancer, 2 pancreatic cancer, 1 prostate cancer). The characteristics of the studies have been summarised in Table 1. A total of 27,996 cases were included; among these, 15,083 cases in the experimental and 12,913 cases in the control group. There were 42 phase III studies, 1 phase II study and 1 phase II/III study (Table 1). The median Jadad score was 5, showing a good quality of the included studies (Table 1). The funnel plot (Fig. 2) of the included studies showed symmetric funnel plot and no significant publication bias was identified.

### 3.2. Efficacy and safety

Data on efficacy and characteristics of the patients in the included studies are summarised in Table 1. OS analysis included 38 trials, a total of 9 studies did not report data on OS The pooled analysis revealed bevacizumab-based therapy definitely improved the OS in solid tumours compared with control arm (HR = 0.92, 95% CI: 0.88–0.95; $P < 0.0001$, Fig. 3). The analysis was performed using a fixed-effects model ($I^2 = 20\%$). Subgroup analysis according to the primary tumour location revealed that OS favoured the bevacizumab arm compared to the control arm, in all kinds of tumours examined, except for breast cancer. However, the improvement in OS only reached statistical significance in four diseases: colorectal cancer, renal cancer, cervical/uterine and non-small cell lung cancer (Fig. 3). With regards to PFS, the analysis included 39 trials, a total of 8 studies did not report data on PFS. No study reported data on PFS in renal cancer. The pooled analysis revealed an improvement in PFS related to the use of bevacizumab-based therapy (HR = 0.72, 95% CI: 0.67–0.78; $P < 0.00001$ Fig. 4). The random-effects model was used for the analysis of the PFS data due to the presence of high heterogeneity ($I^2 = 85\%$) between the trials. A subgroup analysis according to the tumour location revealed that bevacizumab-based therapy significantly improved PFS in all tumour types with the exception of cervical/uterine cancer (Fig. 4). A response rate has been observed in a total of 4244/10,144 (41.8%) patients for experimental arm and a total of 3027/9555 (31.6%) patients in the control arm. Using the Mantel–Haenszel method for combining trials, the pooled response rate was 1.38 (95% CI: 1.27–1.50; $P < 0.00001$; $I^2 = 81\%$; Fig. 5) in favour of a regimen containing bevacizumab. The analysis was performed using a random-effects model.

With regards to adverse events, the analysis revealed that grade III–IV hypertension, proteinuria and thromboembolic events were the most frequently

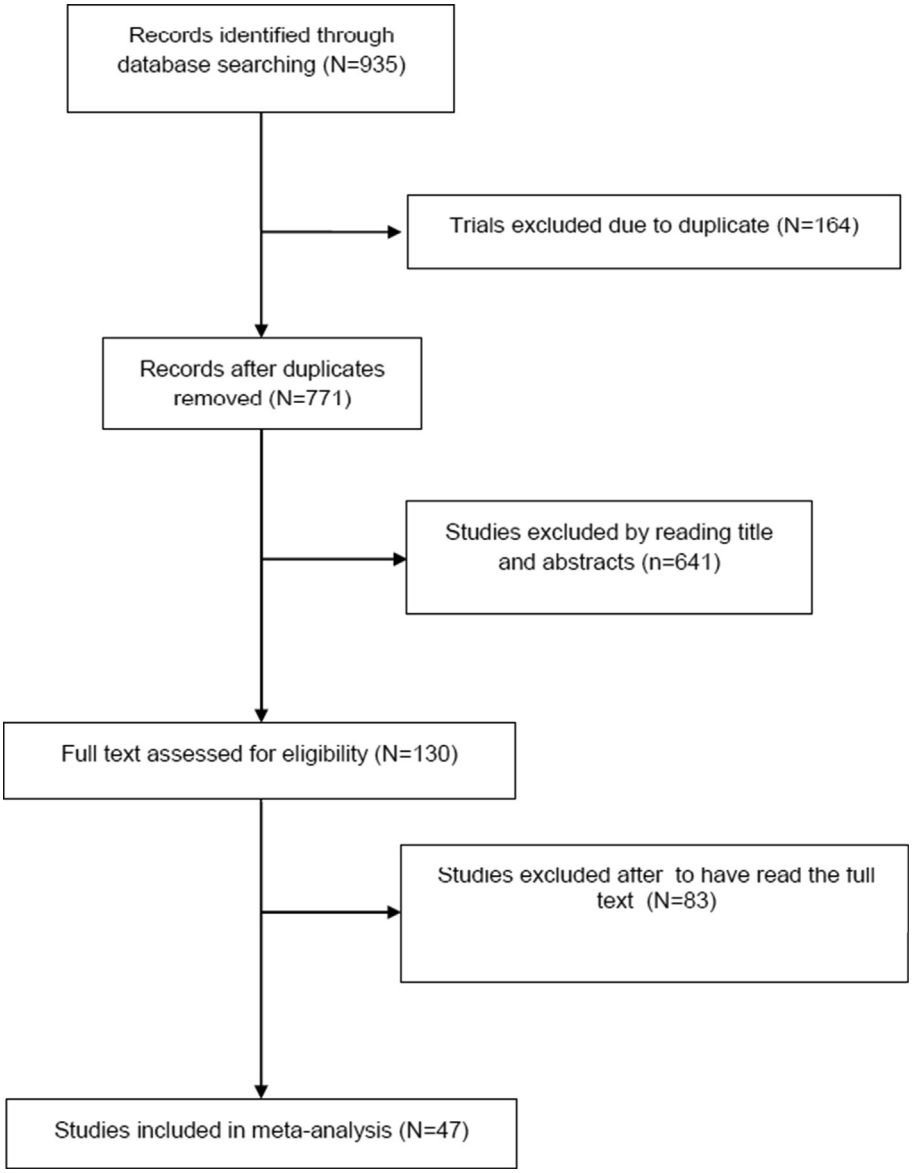


Fig. 1. Trial selection flow chart.

observed toxicities among the studies (Figs. 1,2,3 supplementary data). Hypertension was reported in a total of 1002/10,675 (9.3%) patients for the experimental arm and 271/9491 (2.8%) for the control arm (Fig. 1 supplementary data). Proteinuria was reported in a total of 317/9234 (3.4%) patients for the experimental arm and 19/7361 (0.2%) for the control arm (Fig. 2 supplementary data). Thromboembolic events were reported in a total of 606/9995 (6%) patients for the experimental arm and 402/8482 (4.7%) for the control arm (Fig. 3 supplementary data).

## 4. Discussion

Bevacizumab is one of the most active biological agents, and it significantly improves efficacy and survival in many types of cancer. However, the role of bevacizumab is controversial, and its efficacy is not similar in all solid tumours. The present systematic review and meta-analysis indicates overall that the addition of bevacizumab in patients with advanced solid tumours resulted in a statistically significant improvement in OS and/or PFS and/or response rate depending on the tumour type. To best of our knowledge, this is the largest meta-analysis of this kind reported to date, which involved 47 trials for a total of 27,996 patients and 100 arms for the evaluation of bevacizumab in solid tumours. The OS benefit was significant with a HR 0.92 (95% CI: 0.88−0.95; $P < 0.0001$, $I^2 = 20\%$) showing a survival benefit. In the subgroup analysis by tumour type, the anti-tumour effect of bevacizumab resulted in an improvement in OS that was significant in colorectal cervical/uterine, non-small cell lung cancer and renal cancer. Notably, it was not significant in breast cancer

Table 1
Characteristics of the included studies.

| Study | Phase | Tx line | Patients experimental arm | Patients control arm | Protocol | Bevacizumab duration | Primary end-point | PFS (month) | | | OS (month) | | | Jaded Score |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Experimental arm | Control arm | P value | Experimental arm | Control arm | P value | |
| **Colorectal cancer** | | | | | | | | | | | | | | |
| Bennouna 2013 | III | 2nd | 409 | 411 | Fluorouracile/capecitabine + irinotecan/oxaliplatin + bevacizumab 10 mg/kg | Till PD | OS | 5.7 (5.2−6.2) | 4.1 (3.7 −4.4) | <0.0001 | 11.2 (10.4−12.2) | 9.8 (8.9 −10.7) | 0.0062 | 5 |
| Benson 2016 | II | 1st | 88 | 177 | mFOLFOX6 +bevacizumab 5 mg/kg | Till PD | PFS | 10.7 (7.5 −12.8) | 9.4 (8.5 −10.1) | 0.706 | NR | NR | 0.754 | 4 |
| Cunningham 2013 | III | 1st | 140 | 140 | Capecitabine + bevacizumab 7.5 mg/kg | Till PD | PFS | 9.1 (7.3−11.4) | 5.1 (4.2 −6.3) | <0.0001 | 20.7 (17−26) | 16.8 (12.6 −20.1) | 0.18 | 5 |
| Guan 2011 | III | 1st | 139 | 64 | Irinotecan + leucovorin + bevacizumab 5 mg/kg | Till PD | PFS | 8.3 (7.4−8.9) | 4.2 (3.7 −4.9) | <0.001 | 18.7 (15.8−19.6) | 13.4 (9.7 −17.2) | 0.014 | 4 |
| Hegewisch-Becker 2015 | III | 1st | 156 | 158 | Bevacizumab 7.5 mg/kg or 5 mg/kg | Till PD | TTF | 4.6 (4−5.3) | 3.5 (2.9 −4.1) | <0.0001 | 21.9 (18.7−26.9) | 23.1 (19.2 −27.3) | 0.77 | 5 |
| Hurwitz 2005 | III | 1st | 110 | 100 | Fluorouracil + leucovorin + bevacizumab 5 mg/kg | Till PD | PFS | 8.8 | 6.8 | 0.4192 | 18.3 | 15.1 | 0.2521 | 4 |
| Passardi 2015 | III | 1st | 176 | 194 | FOLFIRI or FOLFOX4 + bevacizumab 5 mg/kg | Till PD | PFS | 9.6 (8.2−10.3) | 8.4 (7.2 −9.0) | 0.182 | 20.8 (15.9−23.2) | 21.3 (19.9 −24.1) | 0.317 | 4 |
| Saltz 2008 | III | 1st | 699 | 701 | FOLFOX4/XELOX + bevacizumab 5 mg/kg or 7.5 mg/kg | Till PD | PFS | 9.4 | 8 | 0.0023 | 21.3 | 19.9 | 0.0769 | 4 |
| Simkens 2015 | III | 1st | 278 | 279 | Capecitabine + Bevacizumab 7.5 mg/kg | Till PD | PFS | 13.5 (12.3 −15.6) | 11.1 (10.3 −12.6) | <0.0001 | 21.6 (19.3−23.8) | 18.1 (16.3 −20.2) | 0.06 | 5 |
| Stathopoulos 2010 | III | 1st | 114 | 108 | Leucovorin + fluorouracil + irinotecan + bevacizumab 7.5 mg/kg | 8 cycles | OS | NR | NR | NR | 22 (18.1−25.9) | 25 (18.1 −31.9) | 0.1391 | 5 |
| Tebbutt 2010 | III | 1st | 157/158 | 156 | Capecitabine + mytomycin C + bevacizumab 7.5 mg/kg | | PFS | 8.5 (7.3−9.2)/ 8.4 (7.5−9) | 5.7 (5.4 −6.2) | 0.03/0.01 | NR/16.4 | 18.9 | 0.314/0.642 | 5 |
| Xie 2014 | III | 2nd | 137 | 155 | FOLFIRI + panitumumab + bevacizumab 3 mg/kg | Till PD | RR | 5.5 | 4.2 | NR | 13.9 | 10.7 | NR | 5 |
| **Breast cancer** | | | | | | | | | | | | | | |
| Brufsky 2011 (RIBBON2) | III | 2nd | 459 | 225 | Chemotherapy + bevacizumab 10 or 15 mg/ kg | Till PD | PFS | 7.2 (6.5−7.6) | 5.1 (4.1 −6.0) | 0.0072 | 69.5 (65−74) | 66.2 (59.7 −72.8) | 0.3741 | 5 |
| Gianni 2013 | III | 1st | 216 | 208 | Docetaxel + trastuzumab + bevacizumab 15 mg/kg | 42 cycles | PFS | 16.5 (14.1 −19.5) | 13.7 (11.4 −16.3) | 0.0775 | NR | NR | 0.9543 | 5 |
| Gray 2009 | III | 1st | 368 | 354 | Paclitaxel + bevacizumab 10 mg/kg | Till PD | PFS | 11.4 | 5.8 | <0.00001 | NR | NR | NR | 5 |
| Martin 2015 | III | 1st | 190 | 184 | Endocrine therapy + bevacizumab 15 mg/kg | Till PD | PFS | 19.3 (16.5 −22.1) | 14.4 (11.4 −17.5) | 0.125 | 52.1 | 51.8 | 0.518 | 5 |
| Miles 2010 | III | 1st | 248/247 | 241 | Docetaxel + bevacizumab 7.5 or 15 mg/kg | 9 cycles | PFS | 9/10.1 | 8.2 | 0.12/0.006 | 30.8/30.2 | 31.9 | 0.72/0.85 | 5 |
| Miller 2005 | III | 2nd | 232 | 230 | Capecitabine + bevacizumab 15 mg/kg | 35 cycles | PFS | 4.8 | 4.1 | NR | 15.1 | 14.5 | NR | 5 |

(*continued on next page*)

Table 1 (*continued*)

| Study | Phase | Tx line | Patients experimental arm | Patients control arm | Protocol | Bevacizumab duration | Primary end-point | PFS (month) | | | OS (month) | | | Jaded Score |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Experimental arm | Control arm | P value | Experimental arm | Control arm | P value | |
| Miller 2007 | III | 1st | 347 | 326 | Paclitaxel + bevacizumab 15 mg/kg | Till PD | PFS | 11.8 | 5.9 | <0.001 | 26.7 | 25.2 | 0.16 | 4 |
| Robert [1] 2011 (RIBBON1) | III | 1st | 409/415 | 206/207 | Capecitabine or anthracycline/taxane + bevacizumab 15 mg/kg | Till PD | PFS | 8.6/9.2 | 5.7/8 | <0.001/ <0.001 | NR | NR | NR | 5 |
| Robert [2] 2011 | III | 1st | 243 | 242 | Paclitaxel + bevacizumab 10 mg/kg | NR | PFS | 9.2 (7.7−13) | 7.4 (6.9 −8.5) | 0.999 | NR | 17.6 (16.4 −NR) | 0.996 | 5 |
| Von Minckwitz 2014 | III | 2nd | 247 | 247 | Chemotherapy + bevacizumab 10 mg/kg or 15 mg/kg | Till PD | PFS | 6.3 (5.4−7.2) | 4.2 (3.9 −4.7) | 0.0068 | NR | NR | NR | 5 |
| **Lung cancer** | | | | | | | | | | | | | | |
| Herbst 2011 | III | 2nd | 319 | 317 | Erlotinib + bevacizumab 15 mg/kg | Till PD | OS | 3.4 (1.4−8.4) | 1.7 (1.3 −4.1) | NR | 9.2 | 9.3 | 0.7583 | 5 |
| Reck 2010 | III | 1st | 345/351 | 347 | Cisplatin + gemcitabine + bevacizumab 7.5 or 15 mg/ kg | 5/6 cycles | PFS | NR | NR | NR | 13.6 (11.8−15.8) /13.4 (11.1−15.1) | 13.1 (11.8 −15.2) | 0.420/0.761 | 5 |
| Sandler 2006 | III | 1st | 417 | 433 | Paclitaxel + carboplatin + bevacizumab 15 mg/kg | 7 cycles | OS | 6.2 | 4.5 | <0.001 | 12.3 | 10.3 | 0.003 | 4 |
| Zhou 2015 | III | 1st | 138 | 138 | Carboplatin + paclitaxel + bevacizumab 15 mg/kg | Till PD | PFS | 9.2 (8.4−10.7) | 6.5 (5.8 −7.1) | <0.001 | 24.3 | 17.7 | 0.0154 | 5 |
| Zinner 2015 | III | 1st | 179 | 182 | Pemetrexed + carboplatin + bevacizumab 15 mg/kg | 6 cycles | PFS | 5.49 | 4.4 | 0.610 | 11.7 | 10.5 | 0.615 | 5 |
| **Ovarian cancer** | | | | | | | | | | | | | | |
| Aghajanian 2012 | III | 2nd | 242 | 242 | Gemcitabine + carboplatin + bevacizumab 15 mg/kg | Till PD | PFS | 12.4 (11.4 −12.7) | 8.4 (8.3 −9.7) | <0.0001 | 33.3 | 35.2 | NR | 5 |
| Burger 2011 | III | 1st | 625/623 | 625 | Paclitaxel + carboplatin + bevacizumab 15 mg/kg | Till PD | PFS | 11.2/14.1 | 10.3 | 0.16/ <0.001 | 38.7/39.7 | 39.3 | 0.76/0.45 | 5 |
| Oza 2015 | III | 1st | 764 | 764 | Paclitaxel + carboplatin + bevacizumab 7.5 mg/kg | Till PD | PFS | 19.9 (19.1 −22) | 17.5 (15.7 −18.7) | 0.25 | 58 (52.4−66.9) | 58.6 (53.5 −67.5) | 0.85 | 5 |
| Perren 2011 | III | 1st | 745 | 753 | Paclitaxel + carboplatin + bevacizumab 7.5 mg/kg | Till PD | PFS | 19 | 17.3 | 0.004 | NR | NR | NR | 5 |
| Pujade-Lauraine 2014 | III | 2nd | 179 | 182 | Chemotherapy + bevacizumab 7.5 mg/kg or 10 mg/kg | Till PD | PFS | 6.7 (5.7−7.9) | 3.4 (2.2 −3.7) | <0.001 | 16.6 (13.7−19) | 13.3 (11.9 −16.4) | 0.174 | 5 |
| Zhao 2015 | III | 1st | 31 | 27 | Cisplatin + bevacizumab 3 mg/kg | NR | ORR | NR | NR | NR | NR | NR | NR | 5 |
| **Renal cancer** | | | | | | | | | | | | | | |
| Escudier 2010 | III | 1st | 327 | 322 | IFNα + bevacizumab 10 mg/kg | Till PD | OS | NR | NR | NR | 23.3 | 21.3 | 0.3660 | 5 |
| Rini 2010 | III | 1st | 369 | 363 | IFNα + bevacizumab 10 mg/kg versus IFNα | Till PD | OS | NR | NR | NR | 18.3 (16.5−22.5) | 17.4 (14.4 −20) | 0.097 | 5 |
| **Glioblastoma** | | | | | | | | | | | | | | |
| Chinot 2014 | III | 1st | 458 | 463 | Temozolomide + | NR | PFS/OS | 10.6 | 6.2 | <0.001 | 16.8 | 16.7 | 0.10 | 5 |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | radiotherapy + bevacizumab 10 mg/kg | | | | | | | | |
| Gilbert 2014 | III | 1st | 320 | 317 | Temozolomide + radiotherapy + bevacizumab 10 mg/kg | 12 cycles | PFS/OS | 10.7 (10−12.2) | 7.3 (5.9−7.9) | 0.007 | 15.7 (14.2−16.8) | 16.1 (14.8−18.7) | 0.21 | 5 |
| Wick 2016 | III | 2nd | 288 | 149 | Lomustine + bevacizumab 10 mg/kg | Till PD | OS | 4.2 (3.7−4.3) | 1.5 (1.5−2.5) | NR | 9.1 (8.1−10.1) | 8.6 (7.6−10.4) | 0.650 | 4 |
| **Small cell lung cancer** | | | | | | | | | | | | | | |
| Pujol 2015 | II−III | 1st | 37 | 37 | Chemotherapy + bevacizumab 7.5 mg/kg | Till PD | OS | 5.3 (4.8−5.8) | 5.5 (4.9−6) | 0.82 | 13.3 (9.8−16.6) | 11.1 (8.7−14) | 0.35 | 4 |
| Spigel 2011 | II | 1st | 52 | 50 | Cisplatin/carboplatin + bevacizumab 15 mg/kg | Till PD | PFS | 5.5 (4.5−6.7) | 4.4 (4.2−4.9) | NR | 9.4 (8.7−11.3) | 10.9 (8.1−14.7) | NR | 4 |
| **Cervical-uterine cancer** | | | | | | | | | | | | | | |
| Hensley 2015 | III | 1st | 53 | 54 | Gemcitabine + docetaxel + bevacizumab 15 mg/kg | 9 cycles | PFS | 4.2 (3.1−8.4) | 6.2 (2.9−9.9) | 0.58 | 23.3 (16.6−27.3) | 26.9 (15.9−32.1) | 0.81 | 5 |
| Tewari 2014 | III | 2nd | 220 | 219 | Cisplatin/topotecan + paclitaxel l + bevacizumab 15 mg/kg | Till PD | OS | 8.2 | 5.9 | 0.002 | 17 | 13.3 | 0.004 | 5 |
| **Miscellany** | | | | | | | | | | | | | | |
| Kelly 2012 | III | 1st | 524 | 526 | Docetaxel + prednisone + bevacizumab 15 mg/kg | Till PD | OS | 9.9 (9−10.6) | 7.5 (6.8−8) | <0.001 | 22.6 (21.1−24.5) | 21.5 (20−23) | 0.181 | 5 |
| Kindler 2010 | III | 1st | 302 | 300 | Gemcitabine + bevacizumab 10 mg/kg | Till PD | OS | 3.8 (3.4−4) | 2.9 (2.4−3.7) | 0.075 | 5.8 (4.9−6.6) | 5.9 (5.1−6.9) | 0.95 | 5 |
| Ohtsu 2011 | III | 1st | 387 | 387 | Cisplatin + capecitabine + bevacizumab 7.5 mg/kg | Till PD | OS | 6.7 (5.9−7.1) | 5.3 (4.4−5.6) | 0.0037 | 12.1 (11.1−13.8) | 10.1 (9−11.3) | 0.1002 | 5 |
| Shen 2015 | III | 1st | 100 | 102 | Capecitabine + cisplatin + bevacizumab 7.5 mg/kg | Till PD | OS | 10.5 (8.9−14.1) | 11.4 (8.6−16) | 0.5567 | 6.3 (5.7−7.4) | 6 (4.9−7.4) | 0.4709 | 5 |
| Van Cutsem 2009 | III | 1st | 306 | 301 | Gemcitabine + erlotinib + bevacizumab 5 mg/kg | Till PD | OS | 4.6 (0−18.3) | 3.6 (0−13.6) | 0.0002 | 7.1 (0−19.8) | 6 (0.1−19.5) | 0.2087 | 5 |

NR, not reported; PFS, progression-free survival; PD, progression disease; OS, overall survival; RR, relative risk; IFN, interferon; ORR, Overall response rate; TTF, Time to treatment failure.

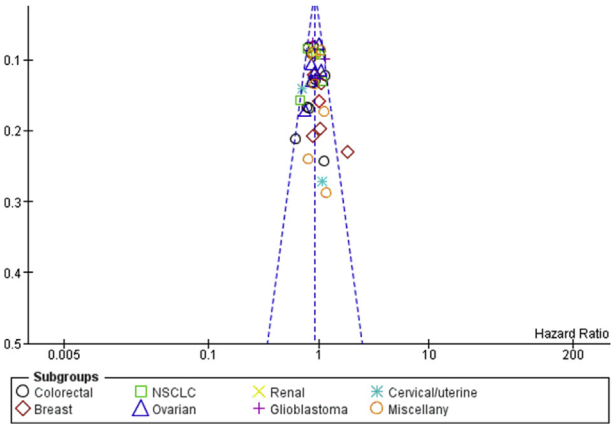


Fig. 2. The funnel plot of included studies.

(HR = 1.04) and these data support the decision of the Food and Drug Administration (FDA) to revoke the approval of bevacizumab in breast cancer. However, we reported a slightly bigger variance for breast cancer than for the others. This lasts maybe due to the different subtypes of where the triple negative has a major impact compared to the ER+. Recently, the UNICANCER initiative (a large-scale real-life setting database composed of 18 French Comprehensive Cancer Centers) recorded the data of 14,014 patients with metastatic breast cancer. Of these, 2127 and 1299 received paclitaxel and bevacizumab and paclitaxel, respectively as first-line of treatment. OS was significantly higher in the bevacizumab group (HR = 0.672). Results were consistent across all supportive and sensitivity analyses, including in triple-negative and oestrogen receptor-positive tumour subgroups. Nonetheless, real-world data should be interpreted with caution [59]. Additionally, further studies are required to allow definitive conclusions in the treatment of other tumours, such as ovarian and glioblastoma, in which, although we found an advantage in OS, the absence of a statistical significance does not allow definitive conclusions. The reasons for these results are maybe related to the fact that the PFS or RR were designated as the primary end-point in several of the analysed studies (Table 1), therefore, these studies are not adequately powered to detect differences in OS. In addition, it is well known that OS may be influenced by several factors such as: additional lines of therapies, the heterogeneity of different subtypes of cancers and the presence of a brief follow-up that may impact on the results of the survival data. Finally, an important consideration is also related to the chemotherapy backbone for anti-angiogenic treatment; at present, no studies have definitively reported the best chemotherapeutical companion for bevacizumab.

The PFS-related benefit in the bevacizumab arm was significant with a HR 0.72, (95% CI: 0.67–0.78; $P < 0.00001$; $I^2 = 85\%$) and with the exception of cervical/uterine cancer, the PFS and RR-related benefits were observed in all of the malignancies. These data are not surprising, as the angiogenesis process is a hallmark of cancer and is required for the disease progression. Thus, the anti-angiogenic therapies have a strong rational in the cancer treatment; however in the near future, to improve the OS with bevacizumab-based therapy, the real main challenge would be the proper selection of the candidate to be treated with bevacizumab maybe through the discovery of molecular surrogate markers able to select those patients most likely to respond to bevacizumab.

Our analysis dedicated to toxicities showed an increase in bevacizumab-related adverse events (hypertension, proteinuria and thromboembolic events) in the bevacizumab arms compared to the control arms. The higher incidence of adverse events related to bevacizumab was observed mainly for proteinuria and hypertension (RR: 9.96 and 4.89, respectively). However, clinical experience shows that these last two adverse events are generally found to be easily manageable during bevacizumab-based treatment. Interestingly, and in accordance with other recent meta-analyses, the risk of thromboembolic events was moderate [60]. Moreover, it is notable that the risk of thromboembolic events was higher in non-small cell lung and cervical/uterine cancer compared to the other solid tumour types.

There are several limitations to our meta-analysis: (1) the difference in chemotherapeutic regimens, dosing and schedules reported in the various analysed trials and (2) the different locations of metastatic tumours. With regards to the subgroup analysis, we recognise that it is arbitrary with patients collected from different cancers. Finally, even though the analysis has been performed on a large sample size, our analysis was based on the present literature rather than on individual patients' data with consequent limitations on the analysis itself.

## 5. Conclusions

Our results suggest that adding bevacizumab to first-line standard therapy results in a significant effect on OS, PFS and response rate in advanced solid tumours. However, in reality, the ability of bevacizumab to prolong OS in unselected patient populations is limited. Unfortunately, up to now, little data are available on predictive biomarkers to guide which patients benefit from bevacizumab-based therapy. In the near future, the proper identification of predictive biomarkers, based on sound tumour biology studies, could help to identify those patient that may be particularly sensitive to anti-angiogenic agents, even in those malignancies for which the FDA does not approve the use of bevacizumab, including breast cancer.

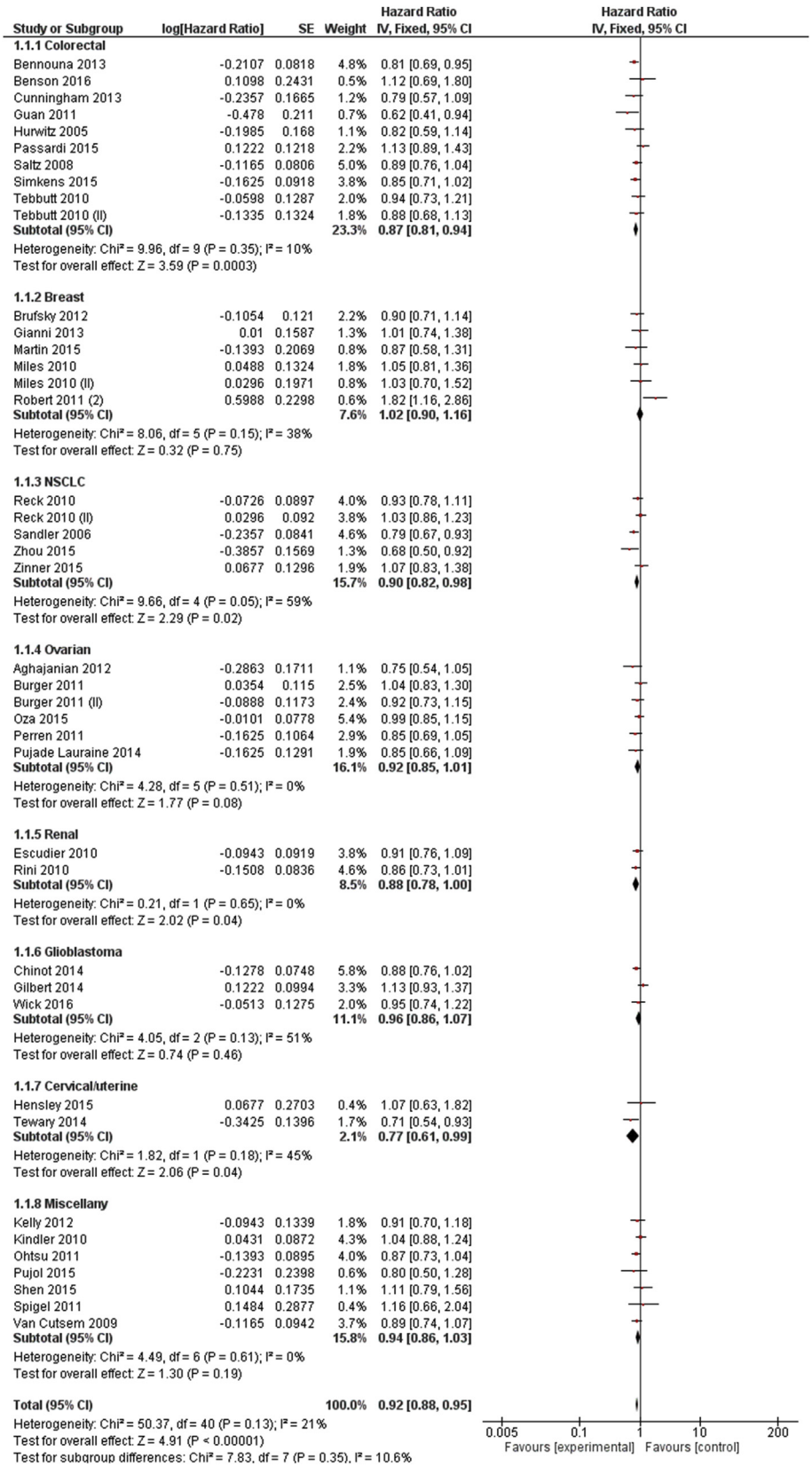


Fig. 3. Forest plots of hazard ratios (HRs) for overall survival (OS) comparing bevacizumab-based regimens to the control arm. The fixed-effects model was used.

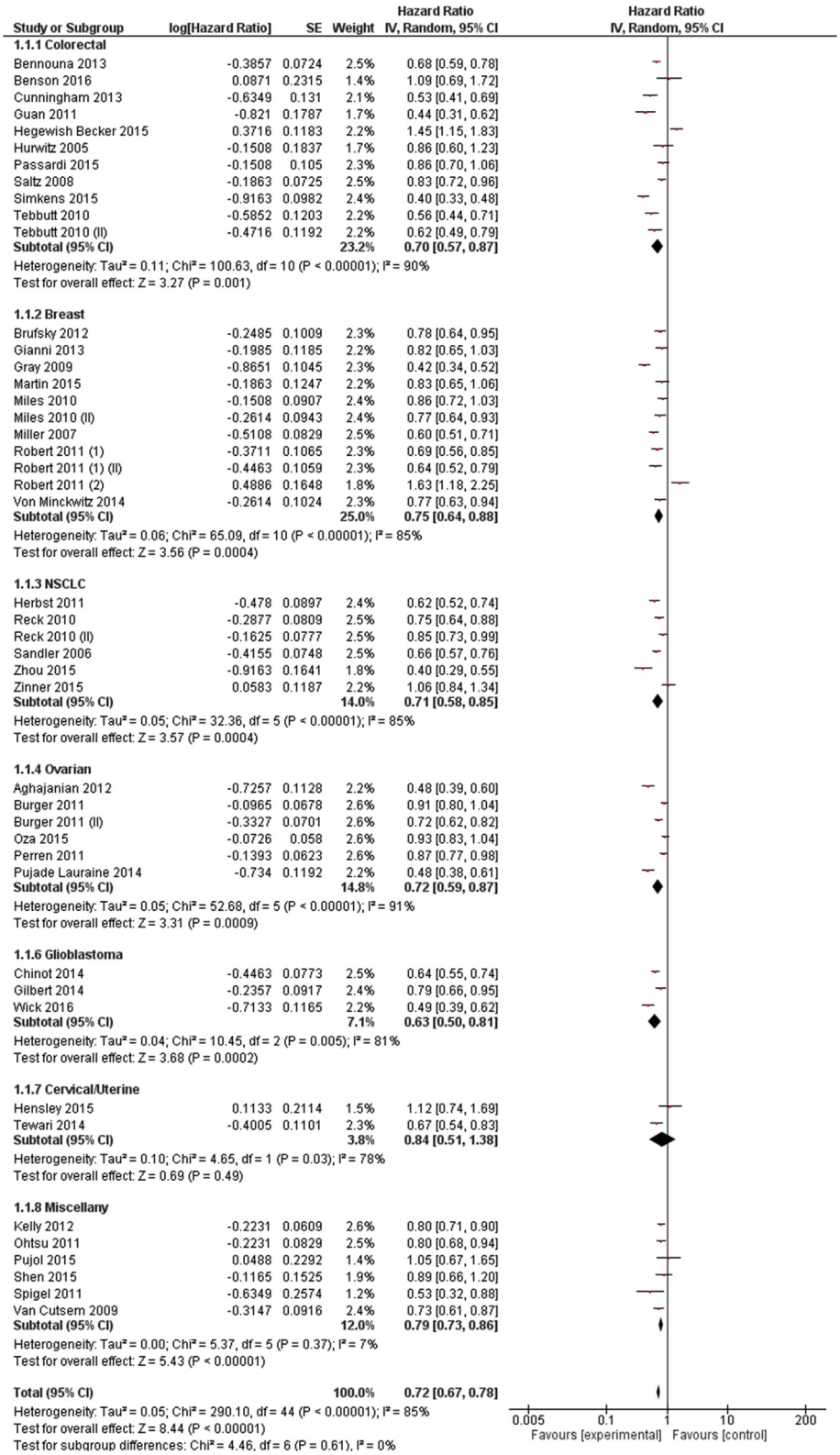


Fig. 4. Forest plots of hazard ratios (HRs) for progression-free survival (PFS) comparing bevacizumab-based regimens to the control arm. The random-effects model was used.

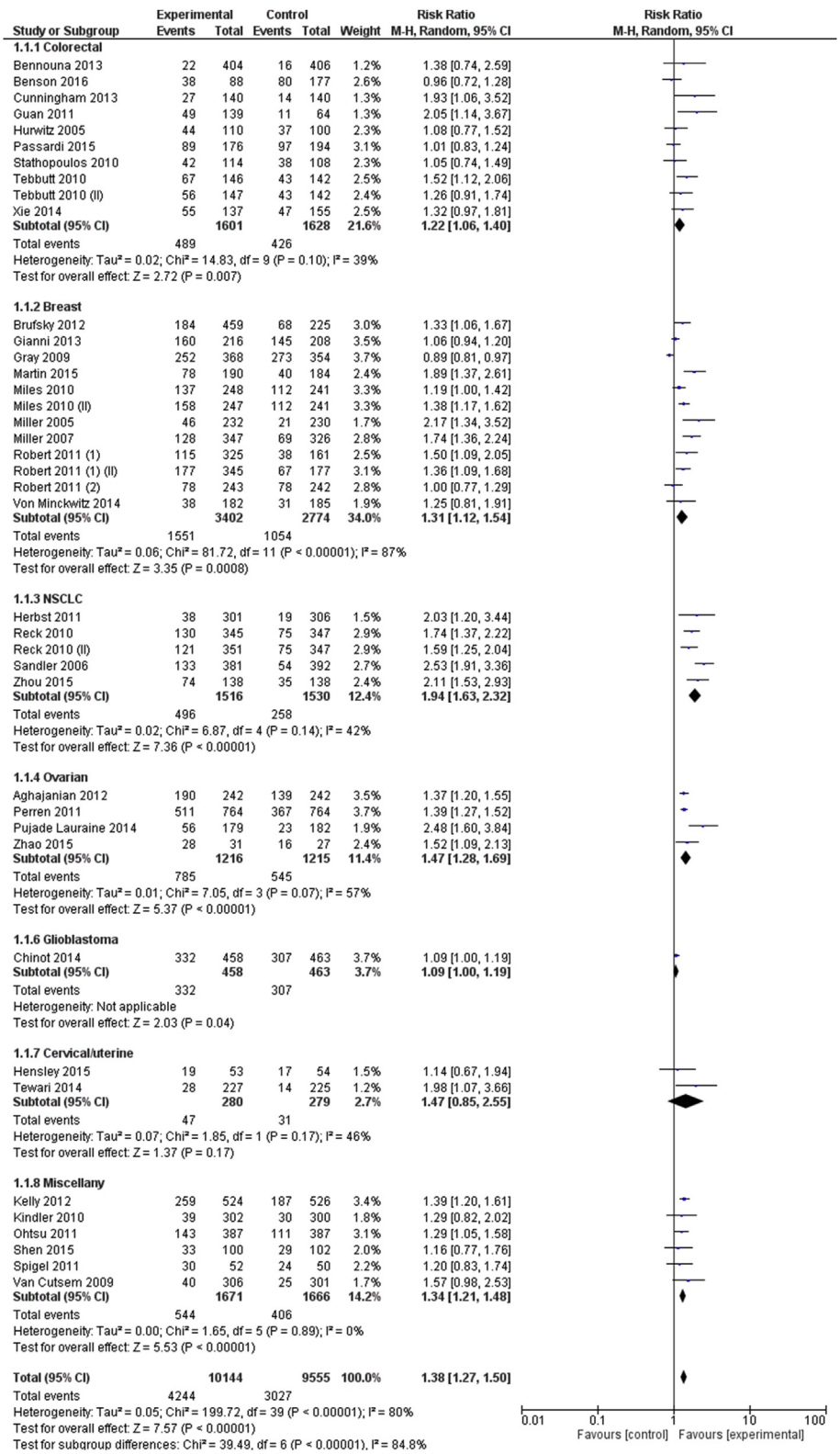


Fig. 5. Forest plots of relative risk (RR) for overall response rate comparing bevacizumab-based regimens to the control arm. The random-effects model was used.

## Conflict of interest statement

None declared.


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