View metadata, citation and similar papers at core.ac.uk
brought to you by CORE
provided by Sydney eScholarship

Single-agent irinotecan or FOLFIRI as second-line chemotherapy for advanced colorectal cancer; results of a randomised phase II study (DaVINCI) and meta-analysis

Running title:

Irinotecan or FOLFIRI for 2nd line colorectal

Stephen Clarke PhD
Sonia Yip PhD
Chris Brown BSc
Guy van Hazel FRACP
David T. Ransom FRACP
David Goldstein MBBS
G. Mark Jeffrey FRACP
Niall C.Tebbut FRACP
Martin Buck MBBS
Raymond M Lowenthal MD
Amy Boland B Psych (Hons)
Val Gebski MStat
John Zalcberg FRACP
R John Simes FRACP
on behalf of the Australasian Gastro-Intestinal Trials Group

Corresponding author:

Professor Stephen Clarke, Department of Medicine, Concord Hospital, Concord, NSW, 2139, Australia

Phone – 61297676587 Fax – 61297677603 Email – stephen.clarke@sydney.edu.au

Abstract

Background

Second-line treatment with irinotecan for advanced or metastatic colorectal cancer prolongs survival. It is uncertain whether irinotecan is better administered with 5-fluorouracil or alone in patients previously treated with a fluoropyrimidine. We compared toxicity (particularly diarrhoea), quality of life, and efficacy of combination chemotherapy and irinotecan in these patients.

Methods

In DaVINCI, a randomised phase II trial, patients with advanced colorectal cancer were randomly allocated to: combination therapy (FOLFIRI), irinotecan (180 mg/m^2 IV over 90 min, day 1), 5-fluorouracil (400 mg/m^2 IV bolus and 2400 mg/m^2 by 46-hour infusion from day 1) and folinic acid (20 mg/m^2 IV bolus, day 1), 2-weekly; or single-agent, irinotecan (350 mg/m^2 IV over 90 min), 3-weekly. Toxicity was evaluated every treatment cycle; QOL and response 6 weekly. Analysis was by intention to treat. Results were also combined with those of other trials.

Findings

We randomised 44 patients to combination and 45 to single-agent. The most common toxicity was complete alopecia (single-agent 37%, combination 14%, $P<0.02$). Eight patients in the irinotecan arm and 4 in the combination arm had grade 3–4 diarrhoea ($P=0.24$). The treatment groups did not differ significantly in overall QOL changes, response rate, or progression free or overall survival. In a systematic review of 29 trials of second-line irinotecan-based treatment, single-agent irinotecan was associated with more diarrhoea and alopecia than the combination, but efficacy was similar.

Interpretation

Combination treatment compared with single-agent irinotecan appears to reduce the rate of complete alopecia and diarrhoea without compromising efficacy on clinical outcomes.

Background

Systemic therapy for advanced or metastatic colorectal cancer has advanced in the last 10 years [1]New active drugs include the cytotoxic agents, oxaliplatin and irinotecan, and the molecular targeting agents, bevacizumab, cetuximab, and panitumumab. As first-line treatment, chemotherapy with 5-fluorouracil and folinic acid or capecitabine combined with either oxaliplatin or irinotecan plus bevacizumab results in median survival of 20–24 months. [2-4]

The epidermal growth-factor receptor (EGFR) inhibitors, such as cetuximab, increase survival of patients with colorectal tumours expressing wild-type but not mutant K-ras genotype [5] The use of these agents in combination with chemotherapy is a favoured approach after failure of first-line schedules[6]

Optimum second-line chemotherapy options have not been fully defined. The combination of oxaliplatin and the fluoropyrimidine, 5-fluorouracil, with leucovorin in the FOLFOX regimen is superior to oxaliplatin alone in second-line treatment in terms of response rate and survival, albeit with some increase in toxicity.[7] Second-line irinotecan and the combination of irinotecan, 5-fluorouracil and leucovorin (FOLFIRI) improve survival over best supportive care or 5-fluorouracil infusion alone.[8-11] However it is not clear whether FOLFIRI is preferable to irinotecan as second-line treatment. Most patients receiving second-line therapy have been treated with 5-fluorouracil or capecitabine, and hence it could be argued that the use of 5-fluorouracil combined with irinotecan may add nothing in terms of efficacy but potentially increase toxicity. Alternatively, the combination of 5-fluorouracil and irinotecan was associated with less diarrhoea than irinotecan alone in the pivotal study (Saltz et al), suggesting that altered scheduling of irinotecan in combination with 5-fluorouracil may ameliorate the acute toxicity of weekly or 3-weekly irinotecan.

Our study was designed to compare the toxicity, quality of life and efficacy of chemotherapy for patients with previously treated advanced colorectal cancer randomly assigned to 2-weekly schedules of FOLFIRI or single-agent irinotecan every 3 weeks.

Methods

This trial was an investigator-initiated phase II trial sponsored by the Australasian Gastro-Intestinal Trials Group (AGITG) and was registered on the Australian New Zealand Clinical Trials Registry, ACTR 12605000359639.

Study design

The trial was originally designed as a 2×2 factorial study assessing (1) FOLFIRI compared with single-agent irinotecan and (2) celecoxib compared with placebo to assess impacts on quality of life and tumour response in 300 patients. The celecoxib arms were abandoned before the study began due to safety concerns about COX-2 inhibitors.[12] Patients were recruited from 17 sites in Australia and New Zealand. The protocol conformed to the Declaration of Helsinki and was approved by human research ethics committees at all participating institutions. All patients gave written informed consent.

Recruitment was slower than expected and the protocol was amended in June 2007 to a randomised phase II trial to compare rates of toxicity in 100 patients. The primary outcome was the rate of grade 3 or 4 diarrhoea. Secondary outcomes were rates of other grade 3 or 4 toxicities, patient-reported quality of life, tumour response rates, progression-free survival and overall survival.

To be eligible, patients were required to have histologically confirmed incurable locally advanced or metastatic colorectal cancer and at least one measurable lesion. Patients were 18 years of age or older, and had a life expectancy of at least 12 weeks, ECOG performance status 0–2, and disease which had progressed after at least one chemotherapy regimen for advanced disease or adjuvant therapy within the previous 6 months. Required pre-treatment haematological parameters were: haemoglobin >10 g/dL, white blood count $>4.0\times10^9$/L, neutrophils $>1.5\times10^9$/L, and platelets $>100\times10^9$/L. Pretreatment biochemical tests were required to show: serum creatinine <2.0× institution upper limit of normal (iULN) and bilirubin <1.5× iULN. Patients were required to be geographically accessible for follow-up and treatment.

Patients were excluded if they had: evidence of serious infection or intercurrent illness that would prevent assessment of response and toxicity, previous chemotherapy or extensive radiotherapy within 4 weeks of the start of treatment, cerebral metastases, a

history or biochemical evidence of Gilbert's syndrome, or prior therapy with irinotecan; or if they were pregnant or breast feeding.

Randomisation and stratification

The study was co-ordinated by the National Health and Medical Research Council Clinical Trials Centre, University of Sydney. Patients were randomised centrally by telephone using the method of minimisation and stratified according to the presence or absence of liver metastases, ECOG performance status (0, 1 vs 2), institution and, after the 2007 amendment, time to progression after previous chemotherapy (<6 months or ≥6 months).

Trial therapies

Treatment was to commence within 7 days of randomisation. Irinotecan as a single agent was administered at a dose of 300 or 350 mg/m^2 (the lower dose was permissible for patients with ECOG 2 or if there were concerns about prior pelvic radiotherapy) by intravenous infusion over 90 minutes on day 1 and repeated on a 3-weekly schedule. Patients in the combination-therapy arm received a 2-weekly regimen of: irinotecan, 180 mg/m^2, by intravenous infusion over 90 minutes on day 1; 5-fluorouracil, 400 mg/m^2, by intravenous bolus on day 1 followed by 2400 mg/m^2 in a 46-hour infusion; and folinic acid (leucovorin), 20 mg/m^2, by intravenous bolus. Trial therapies were discontinued on progressive disease or excessive toxicity or if requested by the patient or physician.

Study assessments

Toxicity was evaluated at every treatment cycle and within 30 days of the last treatment cycle. Quality of life was measured at baseline and every 6 weeks with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ) C-30, version 3.0[13], and the Patient Disease and Treatment Assessment (DATA) form.[14].. Response was assessed every 6 weeks and classified according to RECIST 1.0.[15]

Dose modification

Single-agent irinotecan dose was reduced by 25% if grade 3 or 4 toxicity occurred and further reduced by 25% (relative to day 1 dose of the previous cycle) on a second episode. If further severe toxicity occurred, study treatment was discontinued.

In the combination-treatment arm, if grade 3 or 4 toxicity occurred, the irinotecan dose was reduced to 135 mg/m^2 and the 5-fluorouracil bolus dose was reduced to 200 mg/m^2. The infusional 5-fluorouracil and folinic acid doses were not changed. On a second episode, the irinotecan dose was reduced to 90 mg/m^2 and the 5-fluorouracil infusion to 1800 mg/m^2, the bolus dose of 5-fluorouracil was omitted and the folinic acid dose remained unchanged.

A new cycle of treatment could begin when the absolute neutrophil count was $\geq 1.5 \times 0^9$/L, the platelet count $\geq 75 \times 10^9$/L and any treatment-related diarrhoea had returned to grade 0. Otherwise, treatment was delayed for 1 week until these conditions had been met, and if not, the doses were reduced. If toxicities had not settled after a delay of 2 weeks or more, the patient was removed from the study.

Concomitant therapies

Anti-emetic and other supportive drugs, including atropine, were prescribed according to local treatment guidelines. It was recommended that patients experiencing severe diarrhoea receive loperamide, 2 tablets every 4–6 hours, until diarrhoea had not occurred for 12 hours.

Statistical analyses

Response rates, progression-free survival, and overall survival were analysed on the basis of intention to treat. Analysis of response rates used chi-squared tests for comparing proportions, or Leibermeister tests if cell counts were less than 5. Secondary analysis of toxicity from diarrhoea was adjusted for time on treatment using generalised linear models (log-log link function) with an exposure time offset. Survival endpoints were summarised with Kaplan-Meier estimates and compared using log-rank tests.

We compared quality of life by measuring the change in score from baseline until progression and comparing change scores with two sample *t*-tests.

Systematic review method

We systematically searched the following electronic databases and abstract collections for randomised trials of the same or similar second-line treatment as ours: MEDLINE (1950–January 2010), EMBASE (1980–January 2010), and the Cochrane Central

Register of Controlled Trials (CENTRAL), the American Society of Clinical Oncology (1998–2010), and the European Society of Medical Oncology (2002–1010). Citation lists were searched for additional references. No restrictions, such as language, were applied.

Trials assessing second-line irinotecan (alone or in combination with both leucovorin and 5-fluorouracil) in advanced colorectal cancer previously treated with 5-fluorouracil-based regimens were considered for inclusion. Retrospective studies and trials where 5-fluorouracil was administered as bolus only were excluded, since 5-fluorouracil administered as a bolus followed by IV infusion has a sufficiently different toxicity profile.

Three authors (SY, CB and SC) independently screened the results of the literature review. One author extracted the relevant data from the shortlisted trials, and a second author double-checked the results. All outcomes used in our study were investigated: rates of grade 3/4 diarrhoea, rates of other grade 3/4 toxicities, quality of life, response rates, progression-free survival and overall survival

Randomised comparisons were combined using fixed-effects models weighted by inverse variance. Many clinically heterogeneous single-arm studies were expected, and therefore, pooled estimates were calculated for each arm separately.

Results

Between June 2005 and January 2008, 89 patients were randomised (Figure 1). Recruitment was slower than had been expected, which contributed to the trial being stopped before the planned 100 patients had been enrolled. The study arms were well balanced except that more men and fewer patients with chemotherapy-free interval longer than 6 months were allocated to the combination-therapy arm (Table 1). All patients had received previous chemotherapy with a fluoropyrimidine, and some patients had had more than one previous line of treatment.

Four patients withdrew from the study early. Three withdrew before having baseline tumour assessments and did not receive any treatment. The fourth patient opted 3 days after consent to receive off-study irinotecan plus cetuximab. One of the four patients explicitly withdrew consent for their data to be used in the study and was not included in

any analysis. The other three patients were included in the analysis but censored at the time of withdrawal.

All other patients received at least 1 cycle of protocol treatment. Median time on treatment was 3.2 months on single agent compared with 4.4 months on combination (Table 2). Over 95% of planned doses were administered, but 66% of patients on the combination arm and 41% of patients receiving single-agent irinotecan experienced at least one treatment delay.

Toxicity

Eight patients in the single-agent arm and 4 in the combination-therapy arm had grade 3 or 4 diarrhoea. This was not a statistically significantly difference (odds ratio (OR) 0.46; 95% confidence interval (95%CI) 0.13–1.67, *P*=0.24). When adjustment was made for the longer time on treatment for combination therapy, the observed rate of grade 3+ diarrhoea appeared lower than for single-agent treatment, but the difference remained non-significant after this adjustment (OR 0.34; 95%CI 0.10–1.13; *P*=0.08). (Tables 3 and 4). The only statistically significant non-haematological toxicity difference was complete alopecia (OR 0.28; 95%CI 0.10–0.81; *P*=0.02), which was more frequent in the patients receiving irinotecan alone. Some toxicities had a higher incidence in the combination arm. Serious haematological toxicity was uncommon, and incidence similar in both the arms.

Tumour response and survival

No patient completely responded to treatment. Five patients in each treatment arm had a partial response (Table 4). Thirty-one patients in each arm had a best response rate of stable disease.

With median follow-up of 37 months, the median progression-free survival for patients in the single-agent arm was 4.0 months and in the combination arm was 6.2 months (Figure 2). The median survival for single-agent was 11.2 months and in the combination arm was 15.4 months. There was no statistically significant difference between the treatment arms in progression-free survival (p=0.34) or overall survival (p=0.14).

Quality of life

Quality of life questionnaire completion was reasonable at baseline (83%) but diminished during treatment (6 weeks 69%, 12 weeks 52%, 18 weeks 62%, 24 weeks 58%). Baseline scores were similar in both groups except for worse diarrhoea (6.0 vs. 15.7) and financial difficulties (8.6 vs. 20.0) in the combination arm. After treatment, in the single-agent arm, patients rated diarrhoea and nausea and vomiting significantly worse than at baseline. In the combination arm, there was a statistically significant worsening in patients' rating of nausea and vomiting, constipation and overall quality of life (Figure 4). For all other scales there was no evidence of a significant effect of treatment on quality of life. None of the changes in quality of life from baseline were significantly different between the two treatment arms.

Systematic review

Twenty-nine clinical trials with a second-line irinotecan treatment arm, alone or in combination with both leucovorin and 5-fluorouracil were found (; ; [8-10, 16-41] Of these, two were randomised controlled trials comparing single-agent irinotecan with irinotecan in combination.[36, 38] Seymour et al. provided significant evidence of a reduction in diarrhoea for those receiving second-line combination treatment.[38] These patients were randomised before first-line treatment, and so comparisons of second-line treatments represent non-randomised comparisons since results cannot be adjusted for potential bias due to variable experiences with the earlier treatments. The study by Graeven et al. used a weekly regimen of irinotecan in both treatment arms but apart from this difference provides an unbiased comparison.[36] Analysis of other studies using irinotecan-based therapy was hampered by substantial variation in doses and schedules of regimens used.

Results of DaVINCI were consistent with those of the other studies (Table 5). In the trial reported by Seymour et al., the pooled odds ratio for reduction in the incidence of diarrhoea associated with combination therapy compared with single-agent irinotecan was 0.45 (95% CI 0.30–0.75).[38] The response rate for patients receiving the combination was higher (16.2 vs. 10.7%), although this difference was not statistically significant. There was no difference in progression-free survival (4.4 vs. 4.3 months). In the study reported by Graeven et al., there was a non-statistically significant higher, rate of

diarrhoea in the single-agent arm (18.5 vs. 10.7%).[36] Response rates were similar (15.8 vs. 15.0%), progression-free survival was 3.7 months in both arms, and overall survival was 9.5 months (combination) and 10.7 months (single agent). Data from the non-randomised studies were consistent with these findings (Table 5 and Figure 5).

Discussion

In the treatment of patients with metastatic colorectal cancer, these two commonly used and previously not compared, second-line irinotecan-containing treatment options had essentially similar efficacy in the DaVINCI trial. Response rate, progression-free survival, and overall survival were statistically similar, which is consistent with previous studies. The slightly longer progression-free survival and overall survival among patients on combination therapy was possibly because of patient selection. While there was more diarrhoea and nausea and vomiting in patients receiving irinotecan only, the only significant toxicity difference was for alopecia, which was worse in the irinotecan arm. These data are consistent with the findings of a meta-analysis of other randomised and non-randomised trials. There were no significant differences in changes in QOL over time, or from baseline, between the two study treatments. Although some individual quality of life indices, including diarrhoea, favoured the combination arm, patients in the single-agent arm experienced better global quality of life.

Thus, there does not appear to be the same synergy between irinotecan and 5-fluorouracil with leucovorin as there is between oxaliplatin and fluoropyrimidines. In the study reported by Rothenberg et al. comparing the combination of 5-fluorouracil and oxaliplatin with each agent alone as second-line therapy, the response rate and time to progression were higher for the oxaliplatin combination.[7] Nonetheless, the combination treatment in DaVINCI, with its comparatively better toxicity profile to single-agent irinotecan, was not associated with any worsening of clinical outcomes.

The DaVINCI results are consistent with those of other studies that assessed irinotecan with or without 5-fluorouracil plus leucovorin. Findings from our systematic review also suggested equivalence of these 2 therapeutic options, albeit with a greater incidence of severe diarrhoea (approximately double) and alopecia in the single-agent arms. However, lower toxicity in the combination arm did not compromise tumour response, progression-

free survival or overall survival. The DaVINCI results are consistent with those of the Medical Research Council Fluorouracil, Oxaliplatin and Irinotecan: Use and Sequencing (MRC FOCUS) trial, which also found slightly longer survival in the irinotecan combination arms.[38]

In spite of a simple design, DaVINCI accrued patients more slowly than expected, which led to early closure. One possible explanation is that many medical oncologists were keen to treat their patients with molecular targeted agents, even in the absence of evidence at the time.

The observed differences in toxicity between the two arms may be confounded by the differences in irinotecan scheduling and dose. For some patients the toxicity profile of the combination arm may be preferable despite similar efficacy. Those with pre-existing diarrhoea may not wish to risk the modest increase in severe diarrhoea that accompanies single-agent treatment, especially patients receiving concomitant EGFR-inhibiting antibodies, the use of which is frequently complicated by diarrhoea.[42-43] Similarly, many patients might choose to avoid a greater risk of total alopecia. For others, the efficacy of the single-agent arm means that a central venous catheter can be avoided and they can be treated on a more convenient 3-weekly schedule. Furthermore, the limitations in evaluating the combined data — the use of non-randomised trial comparisons, that the DaVINCI trial in isolation was not powered to show significant differences in most outcomes, and that toxicity differences may be confounded by irinotecan scheduling and dose — should not exclude the consideration of use of single-agent irinotecan as a treatment option.

In summary, both single agent irinotecan and irinotecan in combination with infusional 5-fluorouracil are acceptable second-line treatments for patients with advanced or metastatic colorectal cancer. Toxicity was slightly greater in the single-agent irinotecan arm, but it should not be ruled out as a treatment option. Based on our results, we feel comfortable recommending that this choice of treatment be made based on personal preference.

Authors' contributions

SC was the principal investigator. SC, JS, JZ and VG were primarily responsible for the overall trial design. SC, GvH, DR, DG, MJ, NT, MB and RL were involved with accrual of patients, data collection and review of the manuscript. CB conducted the statistical analysis. SY conducted the systematic review. AB was involved in data collection and management and review of the manuscript. SC, SY and CB prepared the manuscript and interpretation. SC and JS approved the manuscript.

Conflicts of interest

Authors recruiting patients received per patient payments from the NHMRC Coordinating Centre. The other authors declared no conflicts of interest.

Acknowledgements

AGITG was the sponsor responsible for undertaking the trial, and CTC was the coordinating centre responsible for performing the trial under the auspices of AGITG. This trial was supported by an educational grant from Pfizer Australia Pty Ltd.

In addition to the authors, the following committee members, site investigators and key trial staff participated in the DaVINCI trial:

Australasian Gastro-Intestinal Trials Group (AGITG) investigators in Australia: Tweed Hospital, New South Wales - Ehtesham Abdi; Riverina Cancer Care Centre, New South Wales - Jane Hill; St Vincent's Hospital, Melbourne , Victoria - Ivon Burns; Frankston Hospital, Victoria - Vinod Ganju; Ballarat, Victoria -Geoffrey Chong; Queen Elizabeth Hospital, South Australia - Tim Price; Nambour General Hospital, Queensland - Michelle Cronk

Australian National Health and Medical Research Council (NHMRC) Clinical Trials Centre (AGITG Coordinating Centre) staff: Reena Gill, Rhana Pike

Figure legends

Figure 1

Enrolment and analysis of patients in the DaVINCI study

Figure 2

Kaplan-Meier graph of progression-free survival in the two study arms.

Figure 3

Kaplan-Meier graph of overall survival in the two study arms.

Figure 4

Change in score from baseline until treatment progression. Positive changes represent improvement in quality of life

Figure 5

Proportions of patients with grade 3 or 4 diarrhoea for single-arm trials of irinotecan (top panel) or combination therapy including irinotecan (bottom panel) in studies identified in systematic review. Irinotecan dosage (mg), length of cycle (days) are shown.

References

1. Aschele C, Bergamo F, Lonardi S. Chemotherapy for operable and advanced colorectal cancer. Cancer Treat Rev. 2009;35(6):509-16.

2. Cassidy J, Clarke S, Diaz-Rubio E, Scheithauer W, Figer A, Wong R, et al. Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. J Clin Oncol. 2008 Apr 20;26(12):2006-12.

3. Saltz LB, Clarke S, Diaz-Rubio E, Scheithauer W, Figer A, Wong R, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. J Clin Oncol. 2008 Apr 20;26(12):2013-9.

4. Sobrero A, Ackland S, Clarke S, Perez-Carrion R, Chiara S, Gapski J, et al. Phase IV study of bevacizumab in combination with infusional fluorouracil, leucovorin and irinotecan (FOLFIRI) in first-line metastatic colorectal cancer. Oncology. 2009;77(2):113-9.

5. Karapetis CS, Khambata-Ford S, Jonker DJ, O'Callaghan CJ, Tu D, Tebbutt NC, et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. N Engl J Med. 2008 Oct 23;359(17):1757-65.

6. Bouche O, Beretta GD, Alfonso PG, Geissler M. The role of anti-epidermal growth factor receptor monoclonal antibody monotherapy in the treatment of metastatic colorectal cancer. Cancer Treat Rev. 2010 Feb;36 Suppl 1:S1-10.

7. Rothenberg ML, Oza AM, Bigelow RH, Berlin JD, Marshall JL, Ramanathan RK, et al. Superiority of oxaliplatin and fluorouracil-leucovorin compared with either therapy alone in patients with progressive colorectal cancer after irinotecan and fluorouracil-leucovorin: interim results of a phase III trial. J Clin Oncol. 2003 Jun 1;21(11):2059-69.

8. Cunningham D, Pyrhonen S, James RD, Punt CJ, Hickish TF, Heikkila R, et al. Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. Lancet. 1998 Oct 31;352(9138):1413-8.

9. Rougier P, Van Cutsem E, Bajetta E, Niederle N, Possinger K, Labianca R, et al. Randomised trial of irinotecan versus fluorouracil by continuous infusion after fluorouracil failure in patients with metastatic colorectal cancer. Lancet. 1998 Oct 31;352(9138):1407-12.

10. Frontini L, Labianca R, Sobrero A, Rosso R, Turci D, Pergola M, et al. Irinotecan (CPT-11) Is Effective as Second-Line Chemotherapy in Advanced Colorectal Cancer (ACC): A Phase II Trial of GISCAD (Italian Group for the Study of Gastrointestinal Cancer). Proc Am Soc Clin Oncol. 1999;18:Abstract 1000.

11. Bittoni A, Pistelli M, Scartozzi M, E G, R B, S C. Second-line chemotherapy with irinotecan, 5-fluorouracil and leucovorin (FOLFIRI) in relapsed or metastatic gastric cancer: lessons from the clinical practice. Annals of Oncology. 2009;20 (Suppl 8):viii62 - D22.

12. Bresalier RS, Sandler RS, Quan H, Bolognese JA, Oxenius B, Horgan K, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. N Engl J Med. 2005 Mar 17;352(11):1092-102.

13. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85(5):365-76.

14. Stockler MR, O'Connell R, Nowak AK, Goldstein D, Turner J, Wilcken NR, et al. Effect of sertraline on symptoms and survival in patients with advanced cancer, but without major depression: a placebo-controlled double-blind randomised trial. Lancet Oncol. 2007 Jul;8(7):603-12.

15. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst. 2000 Feb 2;92(3):205-16.

16. Rothenberg ML, Eckardt JR, Kuhn JG, Burris HA, 3rd, Nelson J, Hilsenbeck SG, et al. Phase II trial of irinotecan in patients with progressive or rapidly recurrent colorectal cancer. J Clin Oncol. 1996 1996;14(4):1128-35.

17. Pitot HC, Wender DB, O'Connell MJ, Schroeder G, Goldberg RM, Rubin J, et al. Phase II trial of irinotecan in patients with metastatic colorectal carcinoma. J Clin Oncol. 1997 1997;15(8):2910-9.

18. Rougier P, Bugat R, Douillard JY, Culine S, Suc E, Brunet P, et al. Phase II study of irinotecan in the treatment of advanced colorectal cancer in chemotherapy-naive patients and patients pretreated with fluorouracil-based chemotherapy. J Clin Oncol. 1997 1997;15(1):251-60.

19. Ang PCS, Koo WH, Au E, Ang PT, Khoo KS. Phase II Study of Irinotecan (CPT-11) in patients with 5-Fluorouracil-refractory metastatic colorectal carcinoma - An Asian experience. Ann Oncol. 1998;9 (suppl 4):45 Abstract 212.

20. Antón AE, Marcuello E, Massutí B, Carrato A, Abad A, Cervantes A, et al. The experience of the TTD Spanish Cooperative Group in advanced colorectal cancer resistant to 5-FU with irinotecan (CPT-11) on a 3 weeks schedule: Final results. 23rd Congress of the European Society for Medical Oncology (ESMO). . Ann Oncol 1998;9(Supp4):184.

21. Lara MA, Feliu J, Salinas P, Fernandez Y, Garcia-Giron C. Irinotecan (CPT-11) in pretreated metastatic colorectal cancer (CRC). Ann Oncol. 1998;9 (Suppl 4):45 Abstract 215.

22. Aravantinos G, Skarlos DV, Kosmidis P, Georgoulias V, Sgouros I, Bafaloukos D, et al. Irinotecan (CPT-11) in patients with advanced colorectal cancer previously treated with 5-fluorouracil-based chemotherapy. Crit Rev Oncol Hematol. 1999 Dec;32(3):209-19.

23. Hoeffken K, Ridwelsky C, Wein A, Mezger J, Stoffregen C, Weber B, et al. Phase II Study of Irinotecan as Second Line Chemotherapy (CT) in Metastatic Colorectal Cancer (CRC). (Meeting abstract). Proc Am Soc Clin Oncol. 1999;18:Abstract 937

24. Rothenberg ML, Cox JV, DeVore RF, Hainsworth JD, Pazdur R, Rivkin SE, et al. A multicenter, phase II trial of weekly irinotecan (CPT-11) in patients with previously treated colorectal carcinoma. Cancer. 1999 1999 Feb;85(4):786-95.

25. Van Cutsem E, Cunningham D, Ten Bokkel Huinink WW, Punt CJA, Alexopoulos CG, Dirix L, et al. Clinical activity and benefit of irinotecan (CPT-11) in patients with colorectal cancer truly resistant to 5-fluorouracil (5-FU). Eur J Cancer. 1999;35(1):54-9.

26. Schöffski P, Vanhoefer U, Kirchner H, Trenn G, Bokemeyer C, Preusser P, et al. Phase II study of irinotecan as second line chemotherapy in metastatic colorectal cancer after prior exposure to infusional 5-FU-based chemotherapy. Proc Am Soc Clin Oncol. 2000;19(Abstract 1155).

27. Gil-Delgado MA, Guinet F, Castaing D, Adam R, Coeffic D, Durrani AK, et al. Prospective phase II trial of iriontecan, 5-fluorouracil, and leucovorin in combination as salvage therapy for advanced colorectal cancer. Am J Clin Oncol. 2001 Feb;24(1):101-5.

28. Leonard P, Seymour MT, James R, Hochhauser D, Ledermann JA. Phase II study of irinotecan with bolus and high dose infusional 5-FU and folinic acid (modified de Gramont) for first or second line treatment of advanced or metastatic colorectal cancer. Br J Cancer. 2002 Nov 18;87(11):1216-20.

29. Tsavaris NB, Polyzos A, Gennatas K, Kosmas C, Vadiaka M, Dimitrakopoulos A, et al. Irinotecan (CPT-11) in patients with advanced colon carcinoma relapsing after 5-fluorouracil-leucovorin combination. Chemotherapy. 2002 May;48(2):94-9.

30. Fuchs CS, Moore MR, Harker G, Villa L, Rinaldi D, Hecht JR. Phase III comparison of two irinotecan dosing regimens in second-line therapy of metastatic colorectal cancer. J Clin Oncol. 2003 Mar 1;21(5):807-14.

31. Mendez M, Salut A, Garcia-Giron C, Navalon M, Diz P, Garcia Lopez MJ, et al. A multicenter phase II study of irinotecan in patients with advanced colorectal cancer previously treated with 5-fluorouracil. Clin Colorectal Cancer. 2003 Nov;3(3):174-9.

32. Tsavaris N, Ziras N, Kosmas C, Giannakakis T, Gouveris P, Vadiaka M, et al. Two different schedules of irinotecan (CPT-11) in patients with advanced colorectal carcinoma relapsing after a 5-fluorouracil and leucovorin combination. A randomized study. Cancer Chemother Pharmacol. 2003 Dec;52(6):514-9.

33. Lal R, Dickson J, Cunningham D, Chau I, Norman AR, Ross PJ, et al. A randomized trial comparing defined-duration with continuous irinotecan until disease progression in fluoropyrimidine and thymidylate synthase inhibitor-resistant advanced colorectal cancer. J Clin Oncol. 2004 Aug 1;22(15):3023-31.

34. Tournigand C, Andre T, Achille E, Lledo G, Flesh M, Mery-Mignard D, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol. 2004 Jan 15;22(2):229-37.

35. Garcia-Giron C, Garcia Palomo A, Alonso Lopez C, Leon Carbonero A, Mendez Urena M, Adrover Cebrian E, et al. Phase II trial of fortnightly irinotecan (CPT-11) in the treatment of colorectal cancer patients resistant to previous fluoropyrimidine-based chemotherapy. Clin Transl Oncol. 2005 Jul;7(6):244-9.

36. Graeven U, Arnold D, Reinacher-Schick A, Heuer T, Nusch A, Porschen R, et al. A randomised phase II study of irinotecan in combination with 5-FU/FA compared with irinotecan alone as second-line treatment of patients with metastatic colorectal carcinoma. Onkologie. 2007 Apr;30(4):169-74.

37. Koopman M, Antonini NF, Douma J, Wals J, Honkoop AH, Erdkamp FL, et al. Sequential versus combination chemotherapy with capecitabine, irinotecan, and oxaliplatin in advanced colorectal cancer (CAIRO): a phase III randomised controlled trial. Lancet. 2007 Jul 14;370(9582):135-42.

38. Seymour MT, Maughan TS, Ledermann JA, Topham C, James R, Gwyther SJ, et al. Different strategies of sequential and combination chemotherapy for patients with poor prognosis advanced colorectal cancer (MRC FOCUS): a randomised controlled trial. Lancet. 2007 Jul 14;370(9582):143-52.

39. Tsavaris N, Kosmas C, Skopelitis H, Papadoniou N, Polyzos A, Zografos G, et al. Sequential administration of 5-fluorouracil (5FU)/leucovorin (LV) followed by irinotecan (CPT-11) at relapse versus CPT-11 followed by 5-FU/LV in advanced colorectal carcinoma. A phase III randomized study. Chemotherapy. 2007;53(4):282-91.

40. Haller DG, Rothenberg ML, Wong AO, Koralewski PM, Miller WH, Jr., Bodoky G, et al. Oxaliplatin plus irinotecan compared with irinotecan alone as second-line treatment after single-agent fluoropyrimidine therapy for metastatic colorectal carcinoma. J Clin Oncol. 2008 Oct 1;26(28):4544-50.

41. Kim GP, Sargent DJ, Mahoney MR, Rowland KM, Jr., Philip PA, Mitchell E, et al. Phase III noninferiority trial comparing irinotecan with oxaliplatin, fluorouracil, and leucovorin in patients with advanced colorectal carcinoma previously treated with fluorouracil: N9841. J Clin Oncol. 2009 Jun 10;27(17):2848-54.

42. Jean G, Shah S. Epidermal growth factor receptor monoclonal antibodies for the treatment of metastatic colorectal cancer. Pharmacotherapy 2008 28(6):742-54.

43. Ouwerkerk J, C. B-D. Best practices in the management of toxicities related to anti-EGFR agents for metastatic colorectal cancer.

. Eur J Oncol Nurs. 2010;14(4):337-49.

Table 1 Baseline characteristics, by treatment group

Characteristics	Irinotecan *% (n=44[#])*	Combination *% (n=44)*
Sex male	59	70
ECOG performance status		
0 or 1	98	93
2	2	7
Chemotherapy-free >6 months	20	15
Baseline diarrhoea *	9.1	6.8
Primary site		
colon	67	61
rectum	33	39
Metastases		
liver	68	66
lung	52	61
lymph	39	43
bone	5	7
other	39	32
Tumour grade		
1	5	11
2	61	52
3	16	27
unknown	18	9
Previous treatment†		
radiotherapy	30	27
oxaliplatin	70	77
5-fluorouracil	63	73
capecitabine	53	48
bevacizumab	23	25
mitomycin C	5	2
panitumumab	2	0
Median age (range) (years)	66 (26–84)	64 (35–78)
Median years since diagnosis of advanced disease (range)	*1.1 (0.1–2.8)*	*1.0 (0.0–5.9)*
Laboratory values (median)		
neutrophils (10^9/L)	4.80	4.95
platelets (10^9/L)	269	219

Characteristics	Irinotecan % (*n*=44[#])	Combination % (*n*=44)
haemoglobin (g/dL)	13.5	12.8
serum creatinine (xULN)	0.70	0.75
bilirubin (xULN)	0.50	0.50

1 patient withdrew consent, not included in analysis

* All grade 1.

† All patients had prior chemotherapy.

ULN - Upper limit of normal.

Table 2 Treatment characteristics, by treatment group

Treatment received	Irinotecan % (*n*=43)	Combination % (*n*=42)
Average proportion of initial dose		
irinotecan	96	96
5-fluorouracil bolus	—	95
5-fluorouracil infusion	—	97
leucovorin	—	99
Anti-diarrhoea medication	47	47
Reason for stopping treatment		
Tumour progression	61	39
Patient preference	18	14
Clinician preference	7	14
Toxicity	5	11
Death	7	5
Other	2	14
Median duration of treatment (mths)	3.2	4.4
Median treatment delay (days)	4.5	7.0
Any treatment delay	41	66

Table 3 Numbers of patients with grade 3 or 4 toxicity, by treatment

Toxicity	Irinotecan *n*=43 (%)	Combination *n*=42 (%)
Diarrhoea	8 (19)	4 (10)
Nausea	3 (7)	1 (2)
Vomiting	2 (5)	2 (5)
Stomatitis	0 (0)	1 (2)
Fatigue	4 (9)	4 (10)
Alopecia*	16 (37)	6 (14)
Neutropenia, no infection	2 (5)	6 (14)
Febrile neutropenia	3 (7)	1 (2)

* Grade 2.

Table 4 Primary and secondary endpoints, by treatment group

Endpoint	Irinotecan	Combination	Comparison (95% CI)	P-Value
Diarrhoea, grade 3 or 4 (%)*	18.6	9.5	OR=0.46 (0.13–1.67)	0.24
Alopecia, grade 2 (%)	37.2	14.2	OR=0.28 (0.10–0.81)	0.02
Any grade 3 or 4 toxicity (%)	48.8	47.6	OR=0.95 (0.41–2.23)	
Partial tumour response (%)	11.4 (3.7–24.6)	11.4 (3.7–24.6)	OR=1.00 (0.27–3.73)	0.99
Median progression-free survival (months)	4.0 (2.7–5.7)	6.2 (5.4–6.7)	HR=0.81 (0.52–1.25)	0.34
Median overall survival (months)	11.2 (8.3–13.3)	15.4 (8.1–19.3)	HR=0.72 (0.46–1.12)	0.14

*Analysis adjusted for time on treatment: OR = 0.34 (0.10 - 1.13), p=0.08

Table 5 Systematic review including DaVinci and two other randomised trials of irinotecan compared with combination therapy, and 27 single-arm trials of irinotecan or combination therapy

	Estimates of effect in randomised trials*		Rates of toxicity (%) in all trials, including single-arm trials	
Endpoint	No. studies	Estimate (95%CI)	Irinotecan	Combination
Diarrhoea, grade 3 or 4	3[a,b,c]	OR=0.45 (0.27–0.75)	23.5 (20– 27)	8.4 (6– 11)
Alopecia, grade 2	2 [a,b]	OR=0.28 (0.13–0.60)	38.9 (25– 53)	11.7 (4– 19)
Tumour response	3 [a,b,c]	OR=0.68 (0.43–1.08)	12.5 (11– 14)	14.2 (7– 21)
Median progression-free survival at 3 months (%)	3 [a,b,c]	HR=0.96 (0.84–1.09)	60.4 (55– 66)	62.2 (51– 73)
Median overall survival at 6 months (%)	3 [a,b,c]	HR=0.92 (0.51–1.67)	71.4 (69– 74)	76.1 (63– 90)

* For irinotecan compared with combination therapy in three trials: [a]DaVINCI, [b]Seymour et al[1] and [c]Graeven et al[2]

Figure 1 – Consort diagram

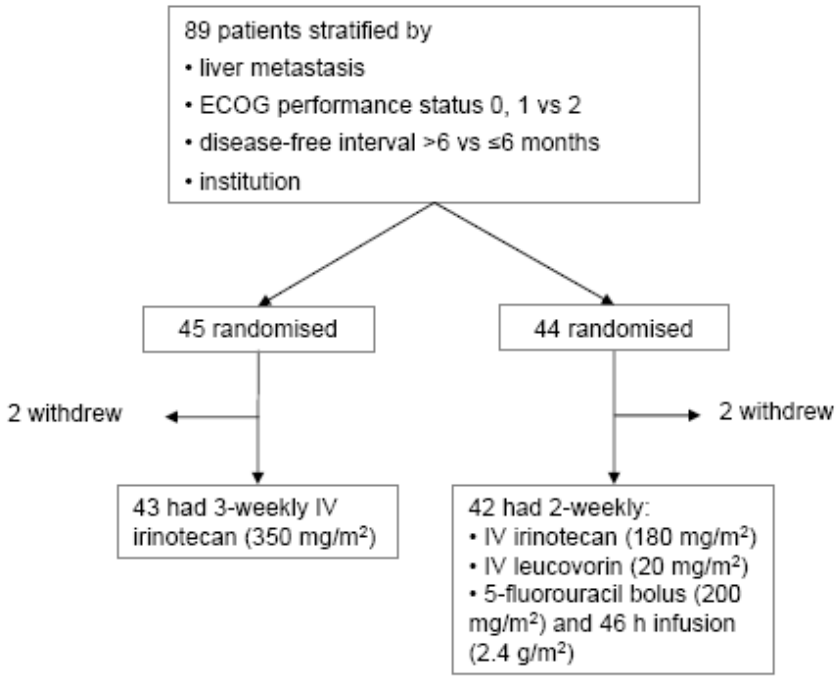
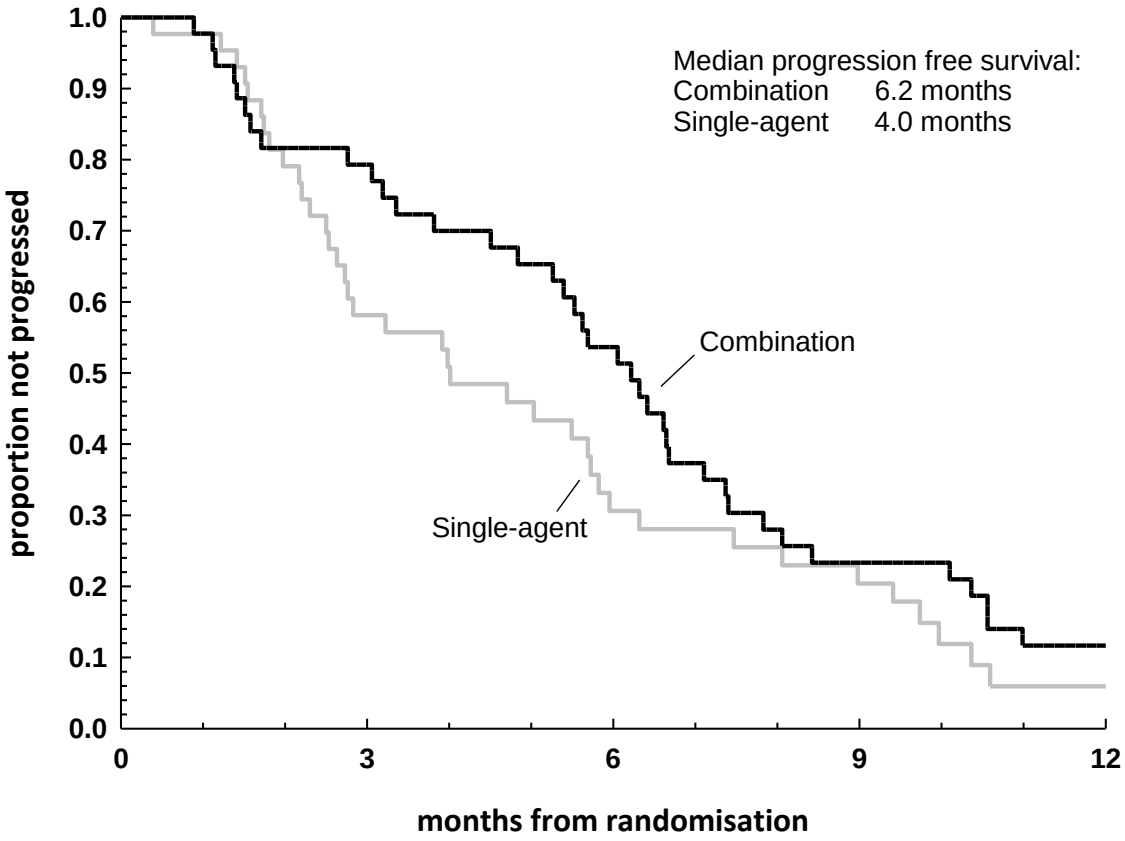


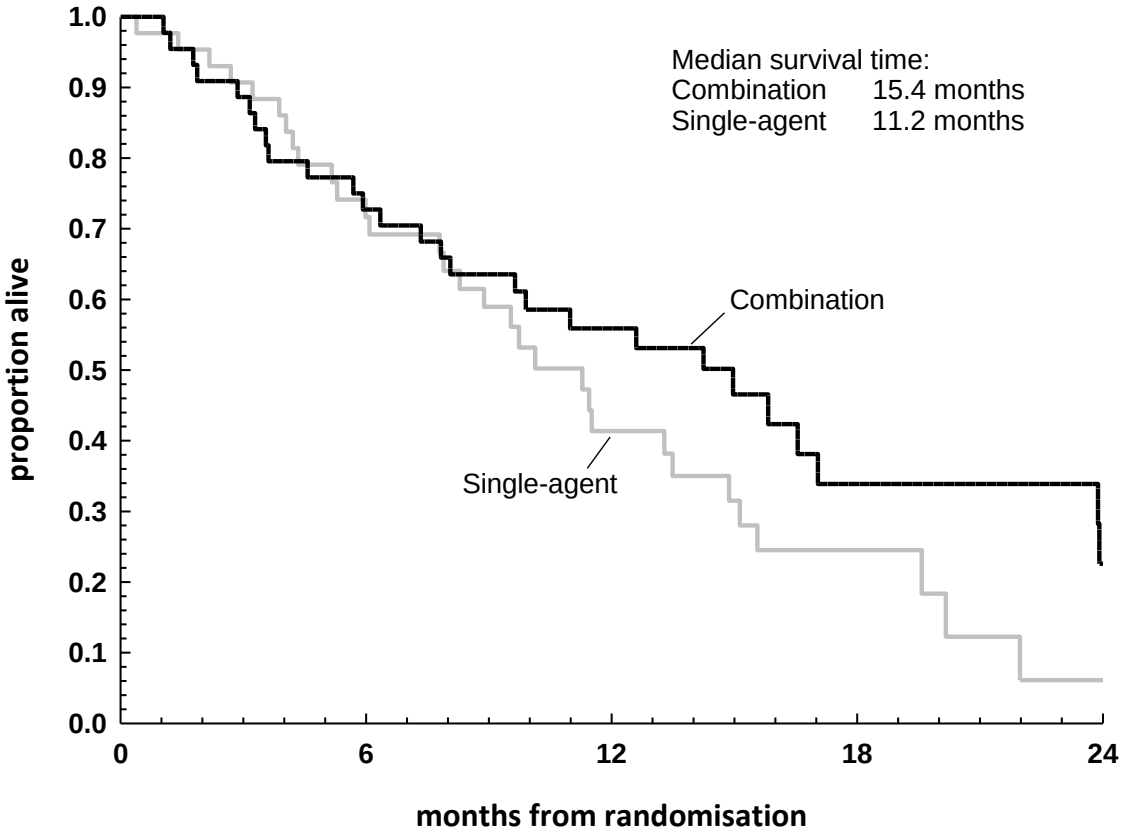
Figure 2 - DaVinci Progression-free survival



Number at Risk				
Combination 44	35	24	11	6
Single-agent 44	25	13	9	3

Time from randomisation to progression or death. HR=0.81 (0.52–1.25) p=0.34

Figure 3 - Da Vinci Overall Survival



Number at Risk				
Combination 44	33	26	18	12
Single-agent 44	46	18	10	7

Time from randomisation to death by any cause. HR = 0.72 (0.46–1.12), p=0.14**.**

Figure 4 - Quality of life

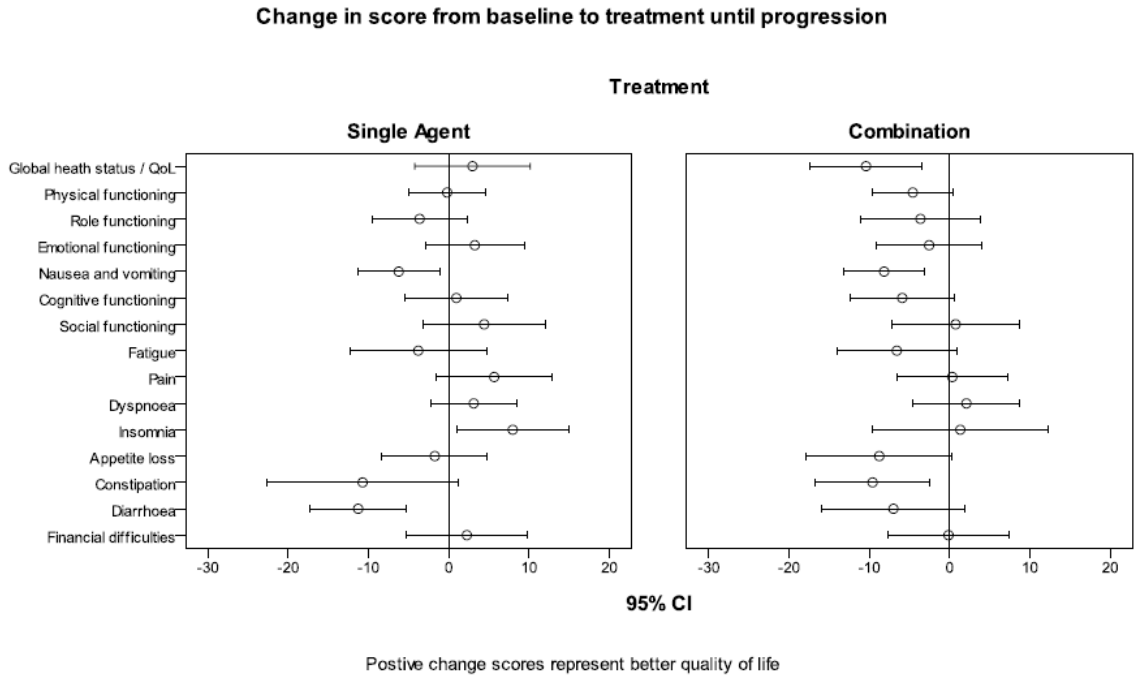
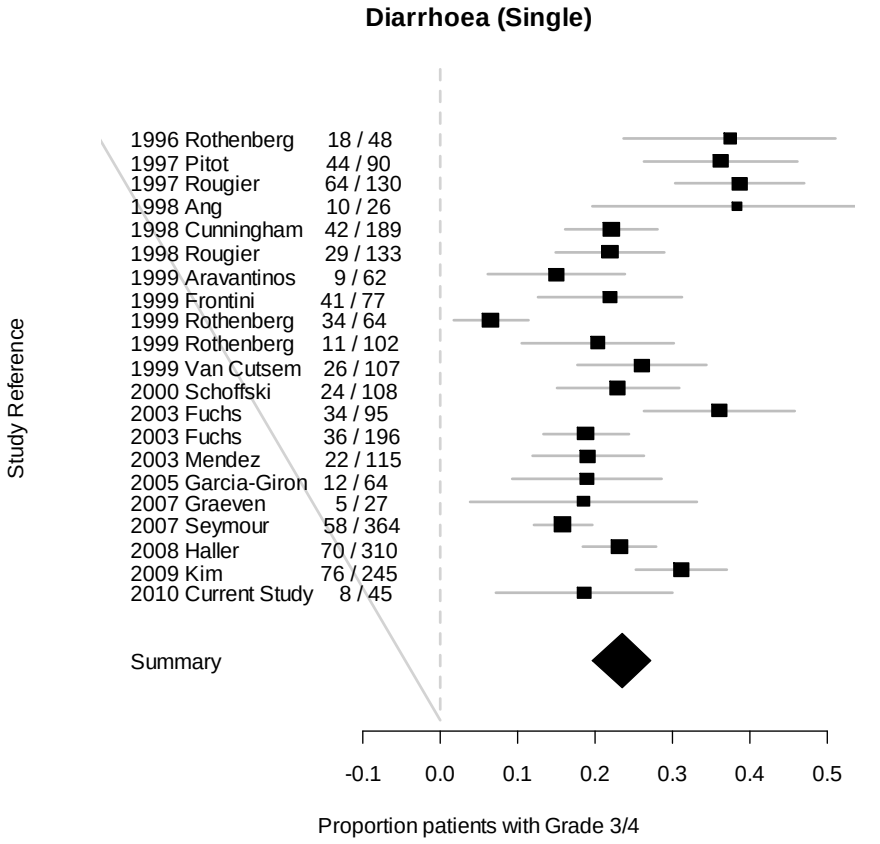
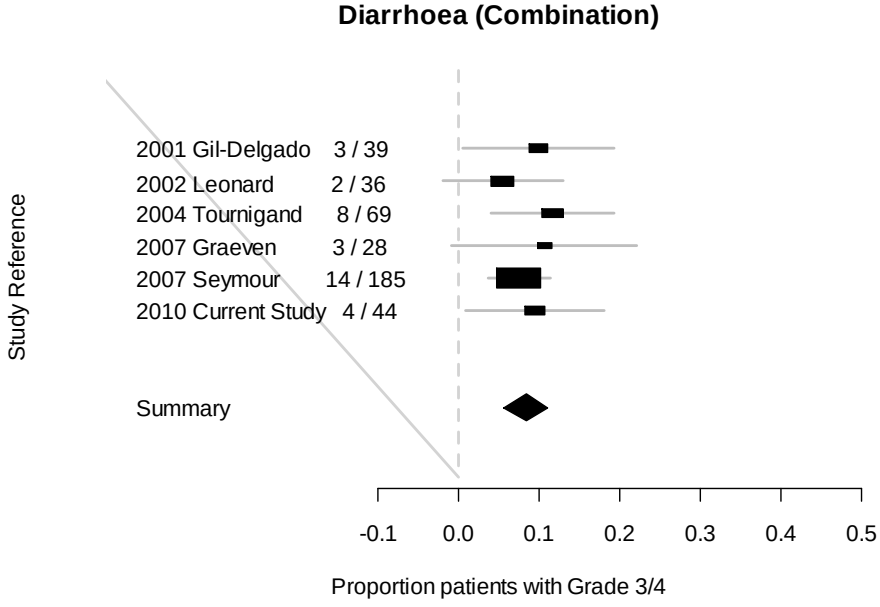
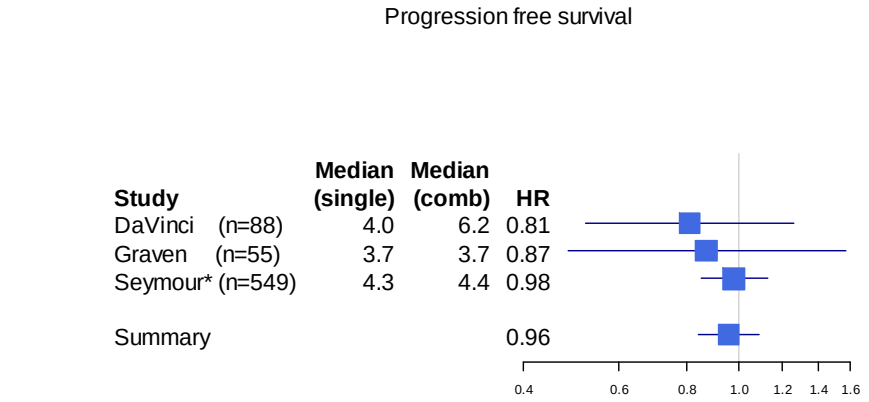


Figure 5 – Summary of study grade 3/4 diarrhoea estimates





Web Appendix Figure 6



* HR estiamted from medians, CI estiamted from published test statistic.