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Single-agent irinotecan or 5-fluorouracil and leucovorin (FOLFIRI) as second-line chemotherapy for advanced colorectal cancer; results of a randomised phase II study (DaVINCI) and meta-analysis

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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. The trial, amended from a larger factorial design, was terminated early due to slow recruitment. Results were also combined with other second-line irinotecan trials.

Findings: We randomised 44 patients to combination and 45 to single agent. Eight patients in the irinotecan arm and 4 in the combination arm had grade 3/4 diarrhoea ($P = 0.24$). 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

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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 reduces alopecia and diarrhoea without compromising efficacy on clinical outcomes. Both regimens remain as reasonable treatment options.

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1. 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 the 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 the 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 of Saltz et al[3], 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.

2. Methods

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

2.1. 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 a placebo to assess impacts on the quality of life and tumour response in 300 patients. The celecoxib arms were abandoned before the study began due to safety concerns about the 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 one prior chemotherapy regimen for advanced disease and/or after prior adjuvant therapy, provided that relapse had occurred within 6 months of that treatment. Required pre-treatment haematological parameters were: haemoglobin >10 g/dL, white blood count $>4.0 \times 10^9$/L, neutrophils $>1.5 \times 10^9$/L, and platelets $>100 \times 10^9$/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.

2.2. 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 versus 2), institution and, after the 2007 amendment, time to progression after previous chemotherapy (<6 months or $\geqslant$6 months).

2.3. 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.

2.4. 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]

2.5. 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 $\geqslant 1.5 \times 10^9$/L, the platelet count $\geqslant 75 \times 10^9$/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.

2.6. 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.

2.7. Statistical methods

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 end-points 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. All time points with available data per individual (from post-baseline to progression) were averaged and compared with baseline to estimate the effect of treatment. This phase II study was primarily designed to estimate the outcomes in the two groups rather than statistically compare them. However, with 100 planned patients, the trial had 80% power to detect a 12% reduction in rates of diarrhoea, the primary outcome, from 20% to 8.2%. With a final sample size of 89 this power was 75%.

2.8. 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.

2.9. Role of the funding source

The funder which provided a research grant for this trial had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data and had final responsibility to submit for publication.

3. Results

Between June 2005 and January 2008, 89 patients were randomised (Fig. 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 (Fig. 1). 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 the 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.

3.1. *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 significant 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 that for single-agent 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.

3.2. *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 the best response rate: 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 (Fig. 2 and Table 4). The median overall survival for the single-agent was 11.2 months and in the combination arm was 15.4 months (Fig. 3 and Table 4). There was no statistically significant difference between the treatment arms in progression-free survival ($P = 0.34$) or overall survival ($P = 0.14$).

3.3. *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

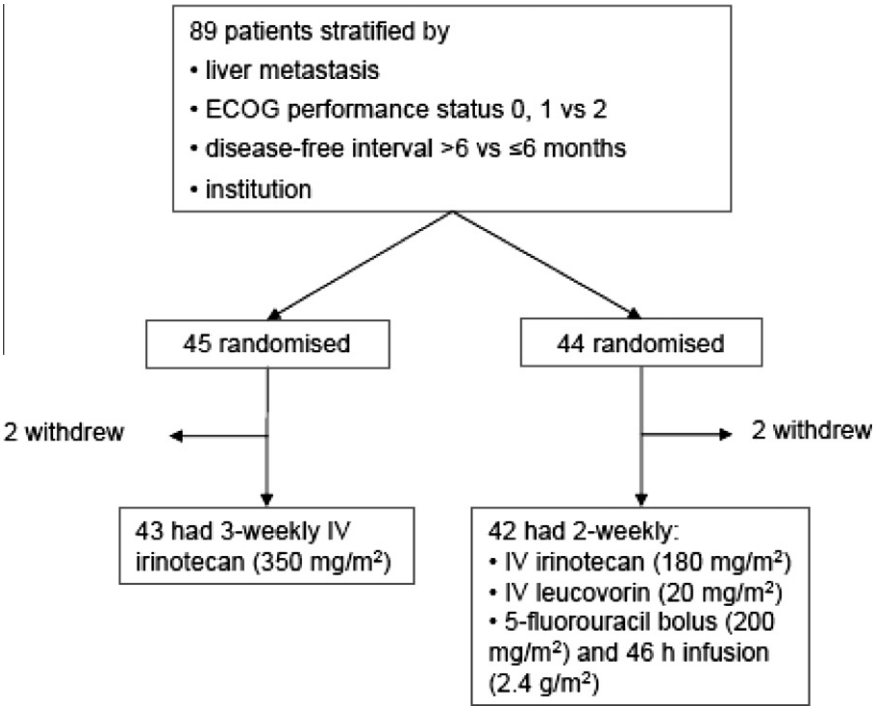


Fig. 1 – Enrolment and analysis of patients in the DaVINCI trial.

Table 1 – Baseline characteristics of DaVINCI patients, by treatment group.

Characteristics	Irinotecan % ($n = 44$[a])	Combination % ($n = 44$)
Sex		
Male	59	70
Female	41	30
ECOG performance status		
0 or 1	98	93
2	2	7
Chemotherapy-free > 6 months	20	15
Baseline diarrhoea [b]	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[c]		
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
Haemoglobin (g/dL)	13.5	12.8
Serum creatinine (×ULN)	0.70	0.75
Bilirubin (×ULN)	0.50	0.50

ULN – Upper limit of normal.
[a] 1 patient withdrew consent, not included in analysis.
[b] All grade 1.
[c] All patients had prior chemotherapy.

Table 2 – DaVINCI 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 (months)	3.2	4.4
Median treatment delay (days)	4.5	7.0
Any treatment delay	41	66

scores were similar in both groups except for worse diarrhoea (6.0 versus 15.7) and financial difficulties (8.6 versus 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 (Fig. 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.

3.4. *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

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

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[a]	16 (37)	6 (14)
Neutropenia, no infection	2 (5)	6 (14)
Febrile neutropenia	3 (7)	1 (2)

[a] Grade 2.

Table 4 – Primary and secondary end-points, by treatment group.

End-point	Irinotecan	Combination	Comparison (95% CI)	P Value
Diarrhoea, grade 3 or 4 (%)[a]	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

[a] Analysis adjusted for time on treatment: OR = 0.34 (0.10–1.13), $P = 0.08$.

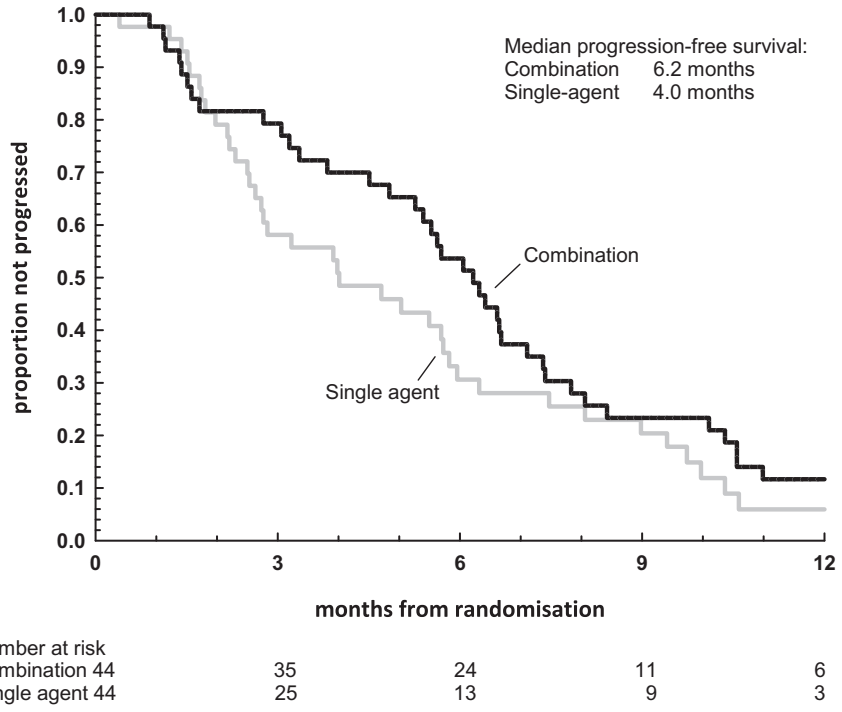
other studies using irinotecan-based therapy was hampered by substantial variation in doses and schedules of regimens used.

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) (Web Appendix).[38] The response rate for patients receiving the combination was higher (16.2 versus 10.7%), although this difference was not statistically significant. There was no difference in the progression-free survival (4.4 versus 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 versus 10.7%).[36] Response rates were similar (15.8 versus 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 Fig. 5).

4. Discussion

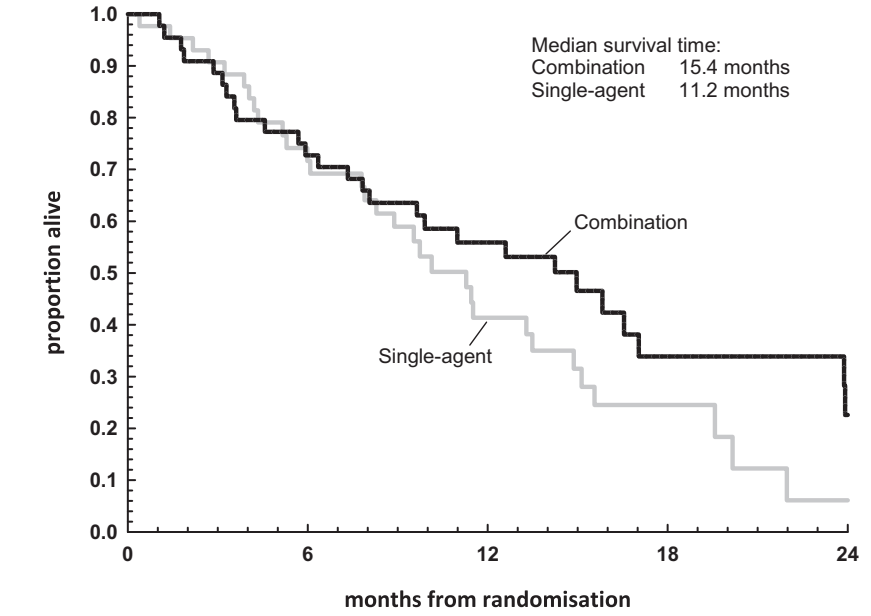
In the treatment of patients with metastatic colorectal cancer in the second line setting, combination treatment with irinotecan and 5-fluorouracil appears associated with less toxicity in terms of alopecia and diarrhoea than single-agent irinotecan, without compromising efficacy on key clinical outcomes.

In the DaVINCI trial the observed progression-free survival and overall survival rates slightly favoured the combination treatment. However, these differences were not statistically significant in this randomised phase II trial which was not powered for these outcomes. The DaVINCI results were 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



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

Fig. 2 – Kaplan–Meier graph of progression-free survival in the two study arms of DaVINCI trial.



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

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

Fig. 3 – Kaplan–Meier graph of overall survival in the two study arms of DaVINCI trial.

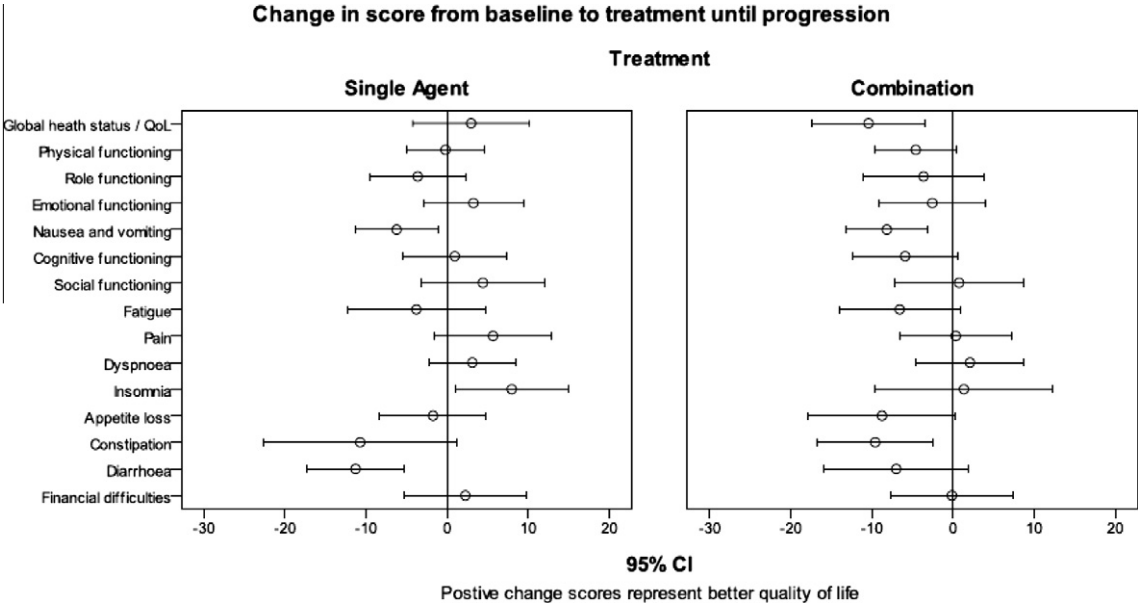


Fig. 4 – Quality of life. Change in score from baseline until treatment progression.

irinotecan combination arms.[38] When evidence from the three randomised trials was considered together, similar efficacy outcomes were seen amongst patients on either regimen, suggesting the combination therapy was at least as effective as the single agent.

In the DaVINCI trial, higher rates of diarrhoea and alopecia were observed in patients receiving single-agent irinotecan, but this was only statistically significant for alopecia. The higher rates in DaVINCI are consistent with those of other studies that assessed irinotecan with or without 5-fluorouracil plus leucovorin. Findings from our systematic review found a greater incidence of severe diarrhoea (approximately double) and alopecia in the single-agent arms, so the combined data are consistent with increased

Table 5 – Systematic review of DaVinci and two other randomised trials of irinotecan compared with combination therapy; and an additional 24 single-arm trials of either irinotecan or combination therapy.

	Treatment effects in 3 randomised trials[a]	Rates of toxicity (%) in all 27 trials, including single-arm trials	
No. of trials (total pts)[b]	3(693)	Irinotecan 24(4201)	Combination 6(468)
End-point	Estimate (95%CI)	Irinotecan	Combination
Diarrhoea, grade 3 or 4	OR = 0.45 (0.27–0.75)	23.5 (20–27)	8.4 (6–11)
Alopecia, grade 2[c]	OR = 0.28 (0.13–0.60)	38.9 (25–53)	11.7 (4–19)
Tumour response	OR = 0.68 (0.43–1.08)	12.5 (11–14)	14.2 (7–21)
Median progression-free survival at 3 months (%)	HR = 0.96 (0.84–1.09)	60.4 (55–66)	62.2 (51–73)
Median overall survival at 6 months (%)	HR = 0.92 (0.51–1.67)	71.4 (69–74)	76.1 (63–90)

[a] For irinotecan compared with combination therapy in three trials: [a]DaVINCI, [b]Seymour et al[1] and [c]Graeven et al[2]: Sample sizes of randomised trials. DaVINCI (89); Seymour et al (549 in irinotecan (364) or combination (185) arms); Graeven et al (55). Total 693 patients. Irinotecan dose of randomised trials: DaVINCI (irinotecan combination 180 mg/m^2 IV over 90 min, day 1, 2 weekly; irinotecan single-agent 350 mg/m^2 IV over 90 min, 3 weekly); Seymour et al (irinotecan combination 180 mg/m^2 IV over 30 min, day 1, 2-weekly; irinotecan single-agent 350 mg/m^2 IV over 30-90 min, 3-weekly); Graeven et al (irinotecan low dose 80 mg/m^2 IV over 60 min, day 1, weekly for 6 weeks then 1 week rest period; irinotecan high dose 125 mg/m^2 IV over 30-90 min, day 1, weekly) for 4 weeks then 2 weeks rest period).

[b] Not all studies reported estimates of all outcomes; the number of patients contributing to each estimate (with the exception of Alopecia) is at least 92% of the total.

[c] Alopecia data were only available for: 2 of the 3 randomised trials: [a]DaVINCI, [b]Seymour et al[1] (total 638 patients); for 13 (irinotecan) single-arm trials, and for 5 (combination) single-arm trials.

toxicity from single-agent irinotecan for both these outcomes.

When considering patient-reported quality of life in DaVINCI, some individual quality of life indices worsened over time from baseline for each treatment, but the relative impacts of treatment on quality of life did not appear to differ significantly between the two regimens. Hence, overall the combination treatment in DaVINCI was associated with a comparatively better toxicity profile than single-agent irinotecan, without significant worsening of clinical outcomes.

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 the second-line therapy, the response rate and time to progression were higher for the oxaliplatin combination.[7] The apparently greater synergy of oxaliplatin over irinotecan in combination with may relate either to greater activity of oxalipatin in combination or the lesser activity of this treatment when used as a single agent relative to irinotecan.. In spite of a simple design, DaVINCI accrued patients more slowly 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 might 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 might be confounded by irinotecan scheduling and dose – should not exclude the consideration of use of single-agent irinotecan as a treatment option.

In summary, there appears to be a modest therapeutic advantage to second line combination therapy based on these results, but both single-agent irinotecan and irinotecan in combination with infusional 5-fluorouracil remain as reasonable second-line treatments for patients with advanced or metastatic colorectal cancer.

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.

Conflict of interest statement

Authors recruiting patients received per patient payments from the coordinating centre. DR received travel funding from Roche. DG received advisory board honoraria from Pfizer,

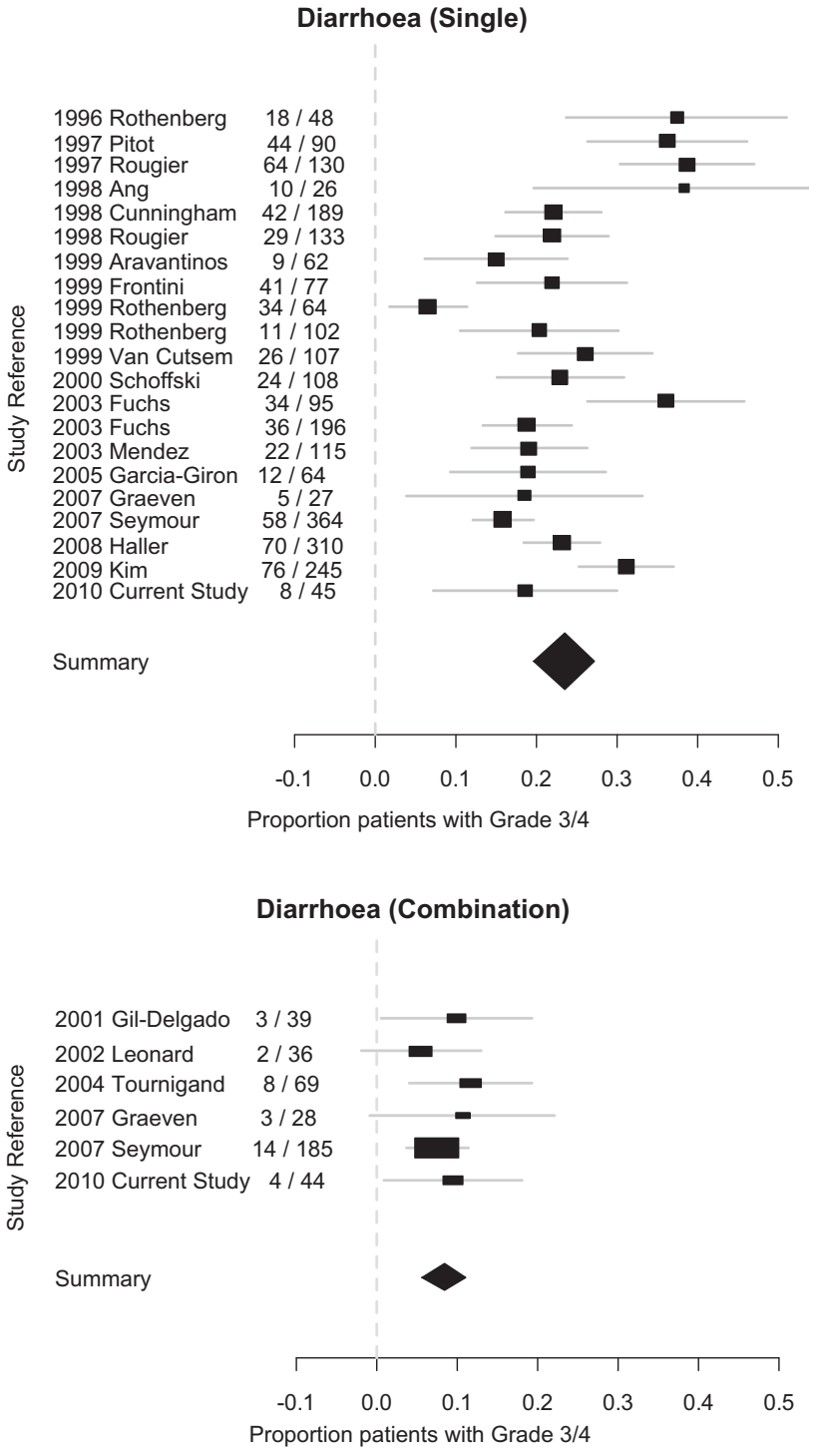


Fig. 5 – Summary of grade 3/4 diarrhoea estimates of trials from systematic review. Proportions of patients with grade 3 or 4 diarrhoea for single-arm trials of irinotecan (top panel) or combination therapy including irinotecan (bottom panel) in studies identified in systematic review. The number of patients with grade 3 or 4 diarrhoea and the total number enrolled are shown.

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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.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejca.2011.04.024.

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