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Mocellin S, Baretta Z, Roqué i Figuls M, Solà I, Martin-Richard M, Hallum S, Bonfill Cosp X.
Second-line systemic therapy for metastatic colorectal cancer.
Cochrane Database of Systematic Reviews 2017, Issue 1. Art. No.: CD006875.
DOI: [10.1002/14651858.CD006875.pub3](https://doi.org/10.1002/14651858.CD006875.pub3).

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[Intervention Review]

Second-line systemic therapy for metastatic colorectal cancer

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Editorial group: Cochrane Colorectal Cancer Group.

Publication status and date: Edited (conclusions changed), published in Issue 1, 2017.

Citation: Mocellin S, Baretta Z, Roqué i Figuls M, Solà I, Martin-Richard M, Hallum S, Bonfill Cosp X. Second-line systemic therapy for metastatic colorectal cancer. *Cochrane Database of Systematic Reviews* 2017, Issue 1. Art. No.: CD006875. DOI: [10.1002/14651858.CD006875.pub3](https://doi.org/10.1002/14651858.CD006875.pub3).

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ABSTRACT

Background

The therapeutic management of people with metastatic colorectal cancer (CRC) who did not respond to first-line treatment represents a formidable challenge.

Objectives

To determine the efficacy and toxicity of second-line systemic therapy in people with metastatic CRC.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library 2016, Issue 4), Ovid MEDLINE (1950 to May 2016), Ovid MEDLINE In-process & Other Non-Indexed Citations (1946 to May 2016) and Ovid Embase (1974 to May 2016). There were no language or date of publication restrictions.

Selection criteria

Randomized controlled trials (RCTs) assessing the efficacy (survival, tumour response) and toxicity (incidence of severe adverse effects (SAEs)) of second-line systemic therapy (single or combined treatment with any anticancer drug, at any dose and number of cycles) in people with metastatic CRC that progressed, recurred or did not respond to first-line systemic therapy.

Data collection and analysis

Authors performed a descriptive analysis of each included RCT in terms of primary (survival) and secondary (tumour response, toxicity) endpoints. In the light of the variety of drug regimens tested in the included trials, we could carry out meta-analysis considering classes of (rather than single) anticancer regimens; to this aim, we applied the random-effects model to pool the data. We used hazard ratios (HRs) and risk ratios (RRs) to describe the strength of the association for survival (overall (OS) and progression-free survival (PFS)) and dichotomous (overall response rate (ORR) and SAE rate) data, respectively, with 95% confidence intervals (CI).

Main results

Thirty-four RCTs (enrolling 13,787 participants) fulfilled the eligibility criteria. Available evidence enabled us to address multiple clinical issues regarding the survival effects of second-line systemic therapy of people with metastatic CRC.

1. Chemotherapy (irinotecan) was more effective than best supportive care (HR for OS: 0.58, 95% CI 0.43 to 0.80; 1 RCT; moderate-quality evidence); 2. modern chemotherapy (FOLFOX (5-fluorouracil plus leucovorin plus oxaliplatin), irinotecan) is more effective than outdated chemotherapy (5-fluorouracil) (HR for PFS: 0.59, 95% CI 0.49 to 0.73; 2 RCTs; high-quality evidence) (HR for OS: 0.69, 95% CI 0.51 to 0.94; 1 RCT; moderate-quality evidence); 3. irinotecan-based combinations were more effective than irinotecan alone (HR for PFS: 0.68, 95% CI 0.60 to 0.76; 6 RCTs; moderate-quality evidence); 4. targeted agents improved the efficacy of conventional chemotherapy both when considered together (HR for OS: 0.84, 95% CI 0.77 to 0.91; 6 RCTs; high-quality evidence) and when bevacizumab was used alone (HR for PFS: 0.67, 95% CI 0.60 to 0.75; 4 RCTs; high-quality evidence).

With regard to secondary endpoints, tumour response rates generally paralleled the survival results; moreover, higher anticancer efficacy was generally associated with worse treatment-related toxicity, with the important exception of bevacizumab-containing regimens, where the addition of the targeted agent to chemotherapy did not result in a significant increase in the rate of SAE. Finally, we found that oral (instead of intravenous) fluoropyrimidines significantly reduced the incidence of adverse effects (without compromising efficacy) in people treated with oxaliplatin-based regimens.

We could not draw any conclusions on other debated aspects in this field of oncology, such as ranking of treatments (not all possible comparisons have been tested and many comparisons were based on single trials enrolling a small number of participants) and quality of life (virtually no data available).

Authors' conclusions

Systemic therapy offers a survival benefit to people with metastatic CRC who did not respond to first-line treatment, especially when targeted agents are combined with conventional chemotherapeutic drugs. Further research is needed to define the optimal regimen and to identify people who most benefit from each treatment.

PLAIN LANGUAGE SUMMARY

Second-line therapy can increase survival of people with metastatic colorectal cancer who did not respond to a first treatment

Review question

We reviewed the ability of chemotherapy drugs (medicines used to treat cancer) to reduce tumour size and improve survival in people with metastatic colorectal cancer who had not responded to a prior treatment. We also looked at the side effects caused by the different drug regimens.

Background

People with metastatic colorectal cancer (cancer that has spread to sites other than the colon) and whose disease had progressed despite one prior chemotherapy (first-line treatment) treatment, and who can be offered a second therapy (second-line treatment) with the aim of improving their poor outcome (prognosis). The treatment regimens compared were systemic (administered intravenously (through a vein)).

Study characteristics

The evidence is current to May 2016. In this updated review, we identified 34 clinical trials that compared second-line therapy with either no chemotherapy (best supportive care) or an alternative second-line therapy, so addressing the issue of second-line therapy performance in people with metastatic colorectal cancer.

Main results

Available evidence seemed to support the use of second-line therapy because it improved survival expectations as compared to best supportive care, although this was reported in only one small trial and the result would need to be confirmed in further research. Moreover, we found that modern chemotherapy regimens were more effective than older ones that contained a drug called 5-fluorouracil, that combination chemotherapy was more effective than single agent chemotherapy and that targeted agents (so called 'smart drugs' that attack the cancer cells and do little damage to normal cells) increased the effectiveness of conventional chemotherapy. Generally, toxicity increased as effectiveness increased.

Quality of the evidence

The main conclusions of this review were based on moderate to high quality evidence. When the quality of the evidence was considered low or moderate, this was generally due to inconsistency in the main results (i.e. the result for progression-free survival (time from the start of second-line treatment to progression of the cancer) was not confirmed by overall survival (time from the start of second-line treatment to death from any cause)) and the low numbers of participants included in the analyses. Nevertheless, it should be remembered that

progression-free survival nowadays is considered a reliable surrogate of overall survival (which includes all deaths, not just cancer-related, and requires longer follow-up to obtain an accurate estimate) in the setting of second-line therapy for metastatic colorectal cancer. Most of the trials did not report quality of life, which prevented us formally investigating the balance between survival benefits provided by second-line systemic therapy and treatment-related toxicity.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Modern chemotherapy regimens compared with 5-fluorouracil

Modern chemotherapy regimens compared with 5-fluorouracil

Patient or population: people with metastatic CRC

Settings: second-line treatment

Intervention: modern CTX (FOLFOX or irinotecan)

Comparison: 5FU

Outcomes	Illustrative comparative risks*		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	5FU	Modern CTX				
Overall survival	800 per 1000	671 per 1000 (560 to 780)	HR 0.69 (0.51 to 0.94)	167 (1 RCT)	+++ - Moderate	Reason for downgrading: only 1 trial available
Progression-free survival	900 per 1000	749 per 1000 (669 to 818)	HR 0.59 (0.49 to 0.73)	470 (2 RCTs)	++++ High	-
Overall tumour response	34 per 1000	99 per 1000 (50 to 197)	RR 2.96 (1.66 to 5.27)	866 (3 RCTs)	++++ High	-
Severe adverse effects	450 per 1000	621 per 1000 (481 to 801)	RR 1.39 (1.22 to 1.58)	843 (3 RCTs)	+++ - Moderate	Reason for downgrading: between-study heterogeneity

*The basis for the **assumed risk** (median control group risk across studies) for survival outcomes is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

5FU: 5-fluorouracil; **CI:** confidence interval; **CRC:** colorectal cancer; **CTX:** chemotherapy; **FOLFOX:** fluorouracil + oxaliplatin + leucovorin; **HR:** hazard ratio; **RCT:** randomized controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

* Assumed risk in controls: 1-year progression-free survival rate = 10%; 1-year overall survival rate = 20%.

Summary of findings 2. Chemotherapy + bevacizumab compared with chemotherapy

Chemotherapy + bevacizumab compared with chemotherapy

Patient or population: people with metastatic CRC

Settings: second-line treatment

Intervention: bevacizumab + CTX

Comparison: CTX

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	CTX	Bevacizumab + CTX				
Overall survival	600 per 1000	515 per 1000 (474 to 554)	HR 0.79 (0.70 to 0.88)	1723 (4 RCTs)	++++ High	-
Progression-free survival	850 per 1000	720 per 1000 (680 to 759)	HR 0.67 (0.60 to 0.75)	1723 (4 RCTs)	++++ High	-
Overall tumour response	92 per 1000	158 per 1000 (113 to 223)	RR 1.72 (1.23 to 2.43)	1723 (4 RCTs)	++++ High	-
Severe adverse effects	585 per 1000	626 per 1000 (544 to 731)	RR 1.07 (0.93 to 1.25)	1708 (4 RCTs)	+- - Low	Reasons for downgrading: 95% CI crossed the null value and between-study heterogeneity

*The basis for the **assumed risk** (median control group risk across studies) for survival outcomes is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **CRC:** colorectal cancer; **CTX:** chemotherapy; **HR:** hazard ratio; **RCT:** randomized controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence

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Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

* Assumed risk in controls: 1-year progression-free survival rate = 15%; 1-year overall survival rate = 40%.

Summary of findings 3. Irinotecan-based regimens compared with irinotecan

Irinotecan-based regimens compared with irinotecan

Patient or population: people with metastatic CRC

Settings: second-line treatment

Intervention: irinotecan-based combination CTX

Comparison: irinotecan

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Irinotecan	Irinotecan combination				
Progression-free survival	850 per 1000	725 per 1000 (680 to 764)	HR 0.68 (0.60 to 0.76)	2615 (6 RCTs)	+++- Moderate	Reason for downgrading: results inconsistency (progression-free survival findings not supported by overall survival findings)
Overall survival	600 per 1000	565 per 1000 (515 to 614)	HR 0.91 (0.79 to 1.04)	2615 (6 RCTs)	++-- Low	Reasons for downgrading: results imprecision (95% CI crossed the null value) and inconsistency (moderate between-study heterogeneity; overall survival findings not supported by progression-free survival findings)
Overall tumour response	67 per 1000	192 per 1000 (141 to 263)	RR 2.87 (2.10 to 3.93)	2577 (6 RCTs)	++++ High	-

Severe adverse effects	480 per 1000	566 per 1000 (461 to 696)	RR 1.18 (0.96 to 1.45)	2510 (6 RCTs)	+++ - Moderate	Reason for downgrading: between-study heterogeneity
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*The basis for the **assumed risk** (median control group risk across studies) for survival outcomes is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **CRC:** colorectal cancer; **CTX:** chemotherapy; **HR:** hazard ratio; **RCT:** randomized controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence

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Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

* Assumed risk in controls: 1-year progression-free survival rate = 15%; 1-year overall survival rate = 40%.

Summary of findings 4. Irinotecan + oxaliplatin compared with irinotecan

Irinotecan + oxaliplatin compared with irinotecan

Patient or population: people with metastatic CRC

Settings: second-line treatment

Intervention: irinotecan + oxaliplatin (IROX)

Comparison: irinotecan

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Irinotecan	IROX				
Overall survival	600 per 1000	511 per 1000 (459 to 562)	HR 0.78 (0.67 to 0.90)	627 (1 RCT)	+++ - Moderate	Reason for downgrading: only 1 trial
Progression-free survival	900 per 1000	749 per 1000 (718 to 781)	HR 0.60 (0.55 to 0.66)	627 (1 RCT)	+++ - Moderate	Reason for downgrading: only 1 trial
Overall tumour response	221 per 1000	658 per 1000	RR 2.98	627	+++ -	Reason for downgrading: only 1 trial

	(422 to 1025)	(1.91 to 4.64)	(1 RCT)	Moderate	
Severe adverse effects	594 per 1000	725 per 1000	RR 1.22	627	+++ - Reason for downgrading: only 1 trial
	(647 to 814)	(1.09 to 1.37)	(1 RCT)	Moderate	

*The basis for the **assumed risk** (median control group risk across studies) for survival outcomes is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **CRC:** colorectal cancer; **HR:** hazard ratio; **RCT:** randomized controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

* Assumed risk in controls: 1-year progression-free survival rate = 10%; 1-year overall survival rate = 40%.

Summary of findings 5. Chemotherapy compared with best supportive care

Chemotherapy compared with best supportive care

Patient or population: people with metastatic CRC

Settings: second-line treatment

Intervention: CTX

Comparison: BSC

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	BSC	CTX				
Overall survival	850 per 1000	667 per 1000 (557 to 780)	HR 0.58 (0.43 to 0.80)	279 (1 RCT)	+++ - Moderate	Reason for downgrading: only 1 trial
Progression-free survival	-	-	-	-	-	-
Overall tumour response	-	-	-	-	-	-

Severe adverse effects	12 per 1000	14 per 1000 (12 to 17)	RR 1.19 (1.01 to 1.40)	279 (1 RCT)	+++ - Moderate	Reason for downgrading: only 1 trial
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*The basis for the **assumed risk** (median control group risk across studies) for survival outcomes is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

BSC: best supportive care; **CI:** confidence interval; **CRC:** colorectal cancer; **CTX:** chemotherapy; **RCT:** randomized controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

* Assumed risk in controls: 1-year overall survival rate = 15%.

Summary of findings 6. FOLFIRI + targeted therapy compared with FOLFIRI

FOLFIRI + targeted therapy compared with FOLFIRI

Patient or population: people with metastatic CRC

Settings: second-line treatment

Intervention: FOLFIRI + targeted agents

Comparison: FOLFIRI

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	FOLFIRI	FOLFIRI + targeted agents				
Overall survival	550 per 1000	488 per 1000 (459 to 516)	HR 0.84 (0.77 to 0.91)	3335 (6 RCTs)	++++ High	-
Progression-free survival	850 per 1000	772 per 1000 (740 to 808)	HR 0.78 (0.71 to 0.87)	3335 (6 RCTs)	++++ High	-

Overall tumour response	112 per 1000	232 per 1000 (147 to 367)	RR 2.07 (1.31 to 3.28)	3192 (6 RCTs)	+++ - Moderate	Reason for downgrading: between-study heterogeneity
Severe adverse effects	494 per 1000	642 per 1000 (578 to 716)	RR 1.30 (1.17 to 1.45)	3341 (6 RCTs)	+++ - Moderate	Reason for downgrading: between-study heterogeneity

*The basis for the **assumed risk** (median control group risk across studies) for survival outcomes is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **CRC:** colorectal cancer; **FOLFIRI:** fluorouracil + irinotecan + leucovorin; **HR:** hazard ratio; **RCT:** randomized controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

* Assumed risk in controls: 1-year progression-free survival rate = 15%; 1-year overall survival rate = 45%.

Summary of findings 7. FOLFOX + targeted therapy compared with FOLFOX

FOLFOX + targeted therapy compared with FOLFOX

Patient or population: people with metastatic CRC

Settings: second-line treatment

Intervention: FOLFOX + targeted agents

Comparison: FOLFOX

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	FOLFOX	FOLFOX + targeted agents				
Overall survival	600 per 1000	553 per 1000	HR 0.92 (0.82 to 1.04)	1432	+ - - -	Reasons for downgrading: results imprecision (95% CI crosses the null value) and inconsistency

	(453 to 654)			(2 RCTs)	Very low	(high between-study heterogeneity; overall survival findings not supported by progression-free survival findings)
Progression-free survival	900 per 1000	809 per 1000 (705 to 892)	HR 0.76 (0.66 to 0.86)	1432 (2 RCTs)	++ - - Low	Reasons for downgrading: results inconsistency (between-study heterogeneity and progression-free survival findings not conformed by overall survival data)
Overall tumour response	86 per 1000	227 per 1000 (147 to 349)	RR 2.64 (1.71 to 4.06)	578 (1 RCT)	+++ - Moderate	Reason for downgrading: only 1 trial available
Severe adverse effects	669 per 1000	803 per 1000 (756 to 856)	RR 1.20 (1.13 to 1.28)	1414 (2 RCTs)	++++ High	-

*The basis for the **assumed risk** (median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **CRC:** colorectal cancer; **FOLFIRI:** fluorouracil + irinotecan + leucovorin; **HR:** hazard ratio; **RCT:** randomized controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

* Assumed risk in controls: 1-year progression-free survival rate = 10%; 1-year overall survival rate = 40%.

Summary of findings 8. Irinotecan + targeted therapy compared with irinotecan

Irinotecan + targeted therapy compared with irinotecan

Patient or population: people with metastatic CRC

Settings: second-line treatment

Intervention: irinotecan + targeted therapy

Comparison: irinotecan

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				

	Irinotecan	Irinotecan + targeted therapy				
Overall survival	600 per 1000	596 per 1000 (553 to 603)	HR 0.99 (0.88 to 1.10)	1758 (2 RCTs)	++ - Low	Reasons for downgrading: results imprecision (95% CI crosses the null value) and inconsistency (overall survival findings not conformed by progression-free survival data)
Progression-free survival	900 per 1000	805 per 1000 (771 to 838)	HR 0.71 (0.64 to 0.79)	1758 (2 RCTs)	+++ - Moderate	Reason for downgrading: results inconsistency (progression-free survival findings not conformed by overall survival data)
Overall tumour response	61 per 1000	206 per 1000 (154 to 276)	RR 3.38 (2.53 to 4.52)	1758 (2 RCTs)	++++ High	-
Severe adverse effects	425 per 1000	612 per 1000 (557 to 676)	RR 1.44 (1.31 to 1.59)	1704 (2 RCTs)	++++ High	-

*The basis for the **assumed risk** (median control group risk across studies) for survival outcomes is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **CRC:** colorectal cancer; **HR:** hazard ratio; **RCT:** randomized controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

* Assumed risk in controls: 1-year progression-free survival rate = 10%; 1-year overall survival rate = 40%.

BACKGROUND

Description of the condition

Colorectal cancer (CRC) is one of the most common causes of cancer and cancer death worldwide and the third cause in Western countries (Ferlay 2015; Torre 2015). The World Health Organization (WHO) estimates that there are about one million cases annually worldwide, with almost 500,000 deaths (WHO 2003). About 50% of all newly diagnosed people have metastatic disease at presentation (so called synchronous metastasis) or will ultimately develop metastatic disease (metachronous metastasis), regardless of treatment (Cunningham 1998; Cunningham 2010; Saunders 2006). Except for selected people with liver only resectable metastatic disease where radical surgery can be followed by long survival times (Adam 2012; Schmoll 2012), systemic treatment is the treatment of choice in metastatic disease since it has proved to be effective in prolonging survival (Best 2000; Cunningham 2010; Gustavsson 2015; Kirstein 2014; Schmoll 2012).

Description of the intervention

Until the introduction of irinotecan and oxaliplatin in 2000, standard first-line chemotherapy treatment for metastatic CRC was based on regimens containing 5-fluorouracil (5FU) and leucovorin. Currently, the combination regimens FOLFOX (5FU plus leucovorin plus oxaliplatin) and FOLFIRI (5FU plus leucovorin plus irinotecan) are considered standard therapies in first-line treatment (Grothey 2006; NICE 2005). Moreover, so-called targeted therapies based on agents that selectively act on molecules that play a significant role in cancer progression (e.g. epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF)) have further improved life expectancy (Kirstein 2014; Marques 2014). However, most (if not all) people with metastatic disease will eventually present clinical failure (i.e. disease recurrence or progression) or lack of response to first-line treatment, thus becoming potential candidates for second-line systemic therapy (Arnold 2013; Cunningham 2010; Goldberg 2006; Gustavsson 2015; Kirstein 2014; Marques 2014; Rougier 2005).

Why it is important to do this review

The performance (i.e. efficacy and toxicity) of second-line systemic therapy is unclear. In particular, there is uncertainty about the efficacy of chemotherapy in this population (as compared to observation/best supportive care), the role of targeted agents (e.g. whether or not they increase the efficacy of conventional chemotherapy), the optimal regimen in terms of type and number of anticancer agents and the schedule of treatment delivery. The purpose of this systematic review was to summarize the available evidence on the performance of second-line systemic therapy in people with distant metastatic CRC.

OBJECTIVES

To determine the efficacy and toxicity of second-line systemic therapy in people with metastatic CRC.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs) in people with distant metastatic (or locally advanced unresectable) CRC, in which a second-line systemic therapy regimen is compared with placebo, best supportive care or another second-line systemic therapy regimen. Cluster-randomized trials and cross-over trials were not eligible.

Types of participants

People with distant metastatic or locally advanced unresectable CRC (that is, TNM stage IV disease) that had progressed, recurred or did not respond to first-line systemic therapy. People eligible for surgery (e.g. with resectable liver metastasis) were not included.

Types of interventions

Any second-line systemic therapy regimen (single agent or combinatory regimen). We considered the following comparisons:

- second-line systemic therapy versus control (placebo or best supportive care);
- comparisons of different second-line systemic therapy regimens.

Types of outcome measures

Primary outcomes

- Overall survival (OS, time from the start of second-line treatment to death by any cause).
- Progression-free survival (PFS, time from the start of second-line treatment to disease progression).

Secondary outcomes

- Overall tumour response rate (ORR (complete and partial response), according to WHO (WHO 1979), or Response Evaluation Criteria In Solid Tumours (RECIST) criteria (Therasse 2000)).
- Severe adverse events (SAE, treatment-related grade 3 to 5 toxicity in Common Terminology Criteria for Adverse Events (CTCAE) (CTCAE) scale, or equivalent).
- Quality of life (QoL, as assessed by dedicated questionnaires such as the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30).

Search methods for identification of studies

Electronic searches

We conducted a comprehensive literature search to identify all published and unpublished RCTs applying no language or date of publication restrictions. We searched the following electronic databases:

- Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library 2016, Issue 4) (Appendix 1);
- Ovid MEDLINE (1950 to May 2016) (Appendix 2);
- Ovid MEDLINE In-process & Other Non-Indexed Citations (1946 to May 2016) (Appendix 3); and

- Ovid EMBASE (1974 to May 2016) ([Appendix 4](#)).

We applied a sensitivity- and precision maximizing search filter to the MEDLINE search strategy in accordance with recommendations from Chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)).

Searching other resources

We checked the reference lists of relevant studies as well as those of both qualitative and quantitative reviews to identify additional trials.

Finally, we searched the following web-based electronic databases in May 2016: www.clinicaltrials.gov; www.clinicaltrialsregister.eu; www.eortc.org/clinical-trials, and www.cancerresearchuk.org.

Data collection and analysis

Selection of studies

Two authors (SM, ZB) independently screened the results of the bibliographic search, assessing studies against the inclusion criteria. We retrieved full copies of trial reports when necessary for a more thorough assessment. We resolved disagreements by discussion and consensus.

Data extraction and management

Two authors (SM, ZB) independently extracted the relevant data from the included trials. We resolved disagreements by discussion and consensus. We extracted information regarding trial quality, participants and disease features, study design and trial results. As regards trial findings, we retrieved and analyzed intention-to-treat data. For survival data, for each comparison we extracted the corresponding hazard ratio (HR) (and its 95% confidence interval (CI)) relative to the experimental versus control arm; when

these summary data were not reported in the study article, we calculated them from Kaplan-Meier survival curves (if available) as per [Parmar 1998](#). For dichotomous data (tumour response and toxicity), we extracted events and total number of participants from both experimental and control arm.

In order to evaluate whether the number of participants included in a trial (or meta-analysis of trials) was adequate to draw robust conclusions (i.e. based on adequately powered analyses) regarding the lack of difference between two treatments, we calculated that the minimum sample size needed to get an 80% statistical power (considering an alpha level of significance of 5%, a one-year survival rate in the control population of 20% and an expected HR of 0.75) was about 500.

Assessment of risk of bias in included studies

Two authors (SM, ZB) independently assessed the risk of bias according to the Cochrane 'Risk of bias' tool within the following domains ([Higgins 2011](#)):

- random allocation generation;
- allocation concealment;
- blinding of participants and personnel;
- blinding of outcome assessment;
- incomplete outcome data;
- selective reporting bias; and
- other biases (see [Appendix 5](#)).

Criteria for judging as low, high or unclear risk of bias within each domain were classified based on the 'Risk of bias' assessment tool (see [Appendix 5](#)) from Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). We summarized the risk of bias for each included study in [Figure 1](#) and [Figure 2](#).

Figure 1.

Figure 2.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias): Efficacy outcomes	Incomplete outcome data (attrition bias): Safety and QoL outcomes	Selective reporting (reporting bias)	Other bias?
Bendell 2013_folfiri	?	?	-	-	+	+	+	+
Bendell 2013_folfox	?	?	-	-	+	+	+	+
Bennouna 2013	+	+	-	-	+	+	+	+
Cao 2015	?	?	-	-	+	+	+	+
Clarke 2011	+	+	?	?	+	+	+	+
Cohn 2013_conat	+	+	+	?	+	+	+	+
Cohn 2013_ganit	+	+	+	?	+	+	+	+
Cunningham 1998	+	+	-	-	+	+	+	?
Élez 2015	?	+	-	-	+	+	+	+
Fuchs 2003	+	?	-	-	+	+	+	+
Giantonio 2007	?	?	-	-	+	+	+	+
Gibbs 2011	?	?	-	-	+	+	+	+
Graeven 2007	?	?	-	-	-	+	+	+
Haller 2008	+	+	-	-	+	+	+	+
Hecht 2015	?	?	-	-	+	+	+	+
Iwamoto 2015	+	+	-	-	+	+	+	+
Kim 2009	+	+	-	-	+	+	+	+
Liu 2015	?	?	-	-	+	+	+	+

Figure 2. (Continued)

Liu 2015	?	?	-	-	+	+	+	+
Masi 2015	?	?	-	-	+	+	+	+
Muro 2010	+	+	-	-	+	+	+	+
O'Neil 2014	?	?	-	-	+	+	+	+
Peeters 2010	?	?	-	-	+	+	+	+
Peeters 2013	+	+	+	?	+	+	+	+
Price 2014	+	+	-	-	+	+	+	+
Rothenberg 2003_folfox	?	+	?	?	+	+	?	+
Rothenberg 2003_oxa	?	+	?	?	+	?	?	+
Rothenberg 2008	+	?	?	?	+	+	+	+
Rougier 1998	+	?	?	?	+	+	+	+
Scheithauer 2002	+	+	?	+	+	+	?	+
Seymour 2013	+	+	-	-	+	+	+	+
Shoemaker 2004	?	+	-	-	?	+	?	+
Sobrero 2008	?	?	-	-	+	+	+	+
Tabernero 2015	+	+	+	?	+	+	+	+
Tsavaris 2003	+	+	?	?	+	+	+	+
Van Cutsem 2011	+	+	+	?	+	+	+	+
Van Cutsem 2012	+	+	+	?	+	+	+	+
Viéitez 2011	?	?	+	?	+	+	+	+

We resolved any disagreements by discussion or by involving a third author.

Measures of treatment effect

For each included trial, we measured treatment effects with HR for survival (time-to-event) data and risk ratio (RR) for dichotomous variables (i.e. ORR and SAE rate). We presented each effect estimate with its 95% confidence intervals (CIs) as a measure of uncertainty.

Unit of analysis issues

We did not encounter unit of analysis issues (we chose to exclude cluster-randomized trials and cross-over trials).

Dealing with missing data

The eligible articles did not report all outcomes of interest. We contacted the corresponding authors of these articles by email, but we could not retrieve the missing data either because the study had not been designed to collect those data or because we did not receive a reply. In case of dropouts, we considered the best-case and worse-case scenarios (for binary data only, as for time to event data this is unfeasible).

Assessment of heterogeneity

We assessed the consistency of results (effect sizes) across studies using the I^2 statistic (which indicates the percentage of the variability in effect estimates because of true between-study variance rather than sampling error (within-study variance)). Heterogeneity was considered low, moderate or high for I^2 values of less than 25%, 26% to 50% or greater than 50%, respectively (Higgins 2003).

Assessment of reporting biases

Funnel plot is usually utilized to detect the so-called 'small-study effect' (Sterne 2000). Publication and selection biases in meta-analysis are more likely to affect small studies, which also tend to be of lower methodological quality: this may lead to a smaller study effect, where the smaller studies in a meta-analysis show larger treatment effects. Funnel plot asymmetry is formally investigated with the Egger linear regression approach: to be more conservative, usually this test is considered statistically significant when the P value is less than 0.1. However, since the test is poorly reliable (due to low power to detect bias, if present) when the number of trials is

low (e.g. fewer than 10), we could not assess the small-study effect (all meta-analyses included fewer than 10 studies).

Data synthesis

When possible (at least two RCTs available), we pooled summary data for survival (OS, PFS) and dichotomous outcomes (ORR, SAE rate) obtained from relevant trials by means of meta-analysis using the random-effects model (inverse variance method). Since the estimation of between-study variance can be inaccurate when the number of trials is small, we adopted a fixed-effect model when fewer than four trials were available. Otherwise, we reported summary data (HRs, RRs along with their 95% CI) of single RCTs.

For survival and toxicity data, a ratio lower than 1 favours the intervention, whereas for tumour response data a ratio greater than 1 favours the intervention.

Finally, we calculated the event rates in the control and experimental groups in order to provide readers with information on the absolute effect of treatment on participants' outcomes. In the light of the multiple comparisons we considered, we limited these calculations to the primary outcomes (OS and PFS), on which the main conclusions are based; since primary outcomes are based on survival data, the event rates were calculated as per [Altman 1999](#).

Subgroup analysis and investigation of heterogeneity

We explored the potential sources of heterogeneity by means of subgroup analysis, which brings together RCTs more homogeneous

by one or more features such as drug regimen (e.g. with or without targeted anticancer agents), study design (e.g. open label versus double blind), participants' characteristics (e.g. performance status, mean age) or disease characteristics (e.g. tumour stage). Testing the statistical difference between subgroups can be useful to identify regimens with better efficacy (or lower toxicity) or subsets of participants who benefit most from a given treatment. Unfortunately, the limited number of RCTs and the frequent lack of information on all these aspects did not allow us to perform all the planned subgroup analyses. Finally, sensitivity analysis was also carried out to investigate heterogeneity (see [Sensitivity analysis](#)).

Effect differences across subgroups were formally tested using the Cochrane Q-test for heterogeneity, as performed by the Review Manager 5 software ([RevMan 2014](#)).

Sensitivity analysis

We used a sensitivity analysis to assess the impact of specific trials (e.g. those with doubts about the randomization process or those characterized by a high risk of bias) by excluding them from the meta-analysis (if at least two RCTs were available). This can help test the robustness of meta-analysis findings, especially in the presence of result uncertainty (e.g. in the presence of substantial between-study heterogeneity).

Evidence grading

We used the GRADE system to grade the quality of evidence (regarding primary outcome, that is, survival) into four levels ([Guyatt 2011](#)).

Grade	Definition
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence on the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

The quality of evidence can be downgraded by one (serious concern) or two (very serious concern) levels for the following reasons: risk of bias (see [Assessment of risk of bias in included studies](#)), inconsistency (unexplained heterogeneity, inconsistency of results), indirectness (indirect population, intervention, control, outcomes), imprecision (wide CIs, single trial) and risk of publication bias. The quality can also be upgraded by one level due to large summary effect (we chose HR less than 0.6).

RESULTS

Description of studies

Results of the search

We identified 1826 records through the electronic searches of the Cochrane Library (279 records), MEDLINE (332 records),

MEDLINE In-process & Other Non-indexed citations (548 records) and Embase (667 records). We excluded 791 duplicates and 968 clearly irrelevant records through reading titles and abstracts. We retrieved the remaining 67 records for further assessment. Upon full-text reading, we excluded 41 studies for reasons listed in the [Characteristics of excluded studies](#) table. We identified eight additional studies through scanning reference lists of the identified RCTs.

In total, 34 RCTs fulfilled the inclusion criteria. The study flow diagram is shown in [Figure 3](#).

Figure 3. Study flow diagram.

A list of abbreviations used in the text are reported in [Table 1](#).

Included studies

The main features of each of the 34 included trials (overall enrolling 13,787 participants; range: 55 to 1298; median: 247) are reported in the [Characteristics of included studies](#) table. One trial compared four arms ([Bendell 2013_folfiri](#)), four trials compared three arms ([Cohn 2013_conat](#); [Élez 2015](#); [O'Neil 2014](#); [Rothenberg 2003_folfox](#)), and the remaining 27 trials compared two arms. Only one trial compared a second-line chemotherapy regimen with best supportive care ([Cunningham 1998](#)). The other included studies compared two or more different second-line treatments.

All trials were comparable in terms of baseline characteristics (all participants enrolled had metastatic CRC and had not responded to a first-line treatment), except for the first-line regimens that could be different. As regards outcomes, OS, PFS, ORR and SAE data were reported in 31, 31, 30 and 34 trials, respectively.

The drug regimens tested were heterogeneous. In particular, 17 different anticancer agents (alone or in combination) were tested: seven chemotherapy agents (5FU, oxaliplatin,

irinotecan, mitomycin-C, raltitrexed, capecitabine, S-1) and 10 targeted agents (seven monoclonal antibodies: bevacizumab, cetuximab, panituzumab, abiraterone, conatumumab, ganitumab, ramucirumab; two small molecule inhibitors: vatalanib and gefitinib; and two recombinant blocking proteins: aflibercept and trebananib). The main features of these compounds are reported in [Table 2](#). Two compounds (leucovorin and hyaluronan) utilized in some RCTs have no anticancer activity per se, but increase (leucovorin) or are supposed to increase (hyaluronan) the anticancer activity of chemotherapy agents.

The RCTs tested the following 25 drug combinations: 1. FOLFOX (5FU plus leucovorin plus oxaliplatin), 2. FOLFIRI (5FU plus leucovorin plus irinotecan), 3. IRIS (S-1 plus irinotecan), 4. XELOX (capecitabine plus oxaliplatin), 5. bevacizumab plus FOLFIRI, 6. bevacizumab plus FOLFOX, 7. cetuximab plus irinotecan, 8. panitumumab plus FOLFIRI, 9. panitumumab plus irinotecan, 10. panitumumab plus bevacizumab plus FOLFIRI, 11. axitinib plus FOLFOX, 12. axitinib plus FOLFIRI, 13. conatumumab plus FOLFIRI, 14. ganitumab plus FOLFIRI, 15. hyaluronan plus irinotecan, 16. oxaliplatin plus irinotecan, 17. linifanib plus FOLFOX, 18. ramucirumab plus FOLFIRI, 19. vatalanib plus FOLFOX, 20.

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aflibercept plus FOLFIRI, 21. gefitinib plus raltitrexed, 22. mitomycin plus oxaliplatin, 23. mitomycin plus irinotecan, 24. trebananib plus FOLFIRI and 25. abtuzumab plus cetuximab plus irinotecan.

Only one trial used no anticancer treatment (best supportive care) as the control arm (the experimental arm was treatment with irinotecan) (Cunningham 1998).

Excluded studies

After reading the full text of 65 articles, we excluded 39 studies. Main reason for exclusion was that the trial did not focus on second-line therapy, rather the enrolment of people for first-line treatment or for third- or higher-line treatment.

Details regarding the reasons for exclusion of each study are reported in the [Characteristics of excluded studies](#) table.

Risk of bias in included studies

[Figure 1](#) and [Figure 2](#) show the risk of bias across trials and for each trial, respectively; details are reported in the 'Risk of bias' tables in the [Characteristics of included studies](#) table. Considering the risk of single biases across trials, a high risk was present in a significant proportion (greater than 50%) of trials only for performance and detection bias ([Figure 1](#)). However, it should be noted that performance bias was unavoidable in some circumstances (e.g. chemotherapy compared to best supportive care); moreover, it is unlikely that this type of bias had a significant impact on the trial results and ultimately on the findings of the meta-analysis. While evaluating the risk of bias we did not find any difference between different outcomes; therefore, the risk assessment across domains is reported as a single assessment for all outcomes.

Allocation

There was no high risk of selection bias, although the risk was unclear for about 50% of the trials ([Figure 1](#)).

Blinding

There was high risk of bias in 22 open-label trials due to the lack of blinding (performance bias) intrinsic to the study design.

Incomplete outcome data

There was a high risk of attrition bias (incomplete outcome data) in only one study due to the following reasons: 1. for survival outcome, neither the arm the two withdrawn participants belonged to, nor the reasons for withdrawal were reported; and 2. for tumour response, "39 patients were evaluable for response", therefore 16 participants were not evaluable ([Graeven 2007](#)).

Selective reporting

There was no high risk of reporting bias.

Other potential sources of bias

There was no high risk of other bias (e.g. baseline imbalances between arms).

Effects of interventions

See: [Summary of findings for the main comparison](#) Modern chemotherapy regimens compared with 5-fluorouracil; [Summary of findings 2](#) Chemotherapy + bevacizumab compared with

chemotherapy; [Summary of findings 3](#) Irinotecan-based regimens compared with irinotecan; [Summary of findings 4](#) Irinotecan + oxaliplatin compared with irinotecan; [Summary of findings 5](#) Chemotherapy compared with best supportive care; [Summary of findings 6](#) FOLFIRI + targeted therapy compared with FOLFIRI; [Summary of findings 7](#) FOLFOX + targeted therapy compared with FOLFOX; [Summary of findings 8](#) Irinotecan + targeted therapy compared with irinotecan

[Table 3](#) shows a synopsis of the results (in terms of OS, PFS, ORR and SAEs) generated by each included trial.

The included RCTs rarely tested the same drugs or drug regimens. Therefore, the results of the 34 eligible trials could not be pooled. Nevertheless, the available evidence provided us with the opportunity to group (and meta-analyze) RCTs addressing the same clinical issue (e.g. does the addition of targeted agents improve the efficacy of conventional chemotherapy?), although - singularly taken - they tested drug regimens that were not always identical (e.g. different targeted agents or different chemotherapy drugs).

Due to space considerations and in order to ease the interpretation of the wealth of data reported in this review, we reported forest plots and 'Summary of findings' tables only for the primary outcome (survival) in case of clinical practice changing results (i.e. for the comparisons on which the main conclusions of this review are based).

Nine out of 34 studies (26%) formally addressed QoL with participant compliance being 50% to 60% ([Clarke 2011](#); [Cunningham 1998](#); [Fuchs 2003](#); [Peeters 2010](#); [Price 2014](#); [Rougier 1998](#); [Seymour 2013](#); [Sobrero 2008](#); [Tabernero 2015](#)). Although most investigators used similar questionnaires, the (few) data could not be meta-analyzed since no article reported the actual scores (neither individual nor summary data). As regards single studies, six trials reported no significant differences in QoL ([Clarke 2011](#); [Fuchs 2003](#); [Peeters 2010](#); [Price 2014](#); [Rougier 1998](#); [Tabernero 2015](#)). QoL was better in participants treated with irinotecan compared to those treated with best supportive care ([Cunningham 1998](#)), irinotecan plus panitumumab versus irinotecan alone ([Seymour 2013](#)), and cetuximab plus irinotecan versus irinotecan alone ([Sobrero 2008](#)).

The available evidence enabled us to address the following clinical issues.

Modern chemotherapy regimens versus 5-fluorouracil

Two RCTs (726 participants) compared 5FU (the first chemotherapeutic agent to be associated with survival advantage in first-line treatment of people with metastatic CRC) with three different chemotherapy regimens (including more modern drugs): FOLFOX ([Rothenberg 2003_folfox](#)), oxaliplatin ([Rothenberg 2003_oxa](#)), and irinotecan ([Rougier 1998](#)).

Only one trial (167 participants) addressed OS and showed a significant advantage for participants treated with irinotecan (HR 0.69, 95% CI 0.51 to 0.94) ([Rougier 1998](#)). Both trials reported PFS: considering the single comparisons, both FOLFOX and irinotecan were better than 5FU, whereas oxaliplatin was not. By pooling the PFS data of the three comparisons, regimens other than 5FU alone performed better than 5FU alone (HR 0.84, 95% CI 0.73 to 0.96) ([Figure 4](#)), a finding characterized by a high between-study heterogeneity ($I^2 = 91\%$) sustained by the poor activity of

oxaliplatin alone. The 'leave-one-out' sensitivity analysis showed that heterogeneity reduced to 11% if the oxaliplatin versus 5FU comparison was excluded; in this case, FOLFOX and irinotecan showed a clinically relevant and statistically significant PFS

advantage compared to 5FU in second-line therapy of metastatic CRC (HR 0.59, 95% CI 0.49 to 0.73). Based on the GRADE system, we rated this evidence as high (no reason for downgrading) ([Summary of findings for the main comparison](#)).

Figure 4.

For tumour response data, at meta-analysis, ORR was significantly higher for other chemotherapy regimens compared to 5FU (RR 2.96, 95% CI 1.66 to 5.27), although this finding was not supported by the oxaliplatin versus 5FU comparison. Finally, the SAE rate was higher in participants treated with modern chemotherapy regimens (RR 1.39, 95% CI 1.22 to 1.58).

Irinotecan plus other anticancer agents versus irinotecan

Six trials assessed the effect of adding other anticancer agents (5FU, oxaliplatin, hyaluronan acid (a drug carrier), panitumumab, cetuximab) to irinotecan (2615 participants) ([Clarke 2011](#); [Gibbs 2011](#); [Graeven 2007](#); [Haller 2008](#); [Seymour 2013](#); [Sobrero 2008](#)).

Only one trial (627 participants) found a statistically significant advantage for overall OS (HR 0.78, 95% CI 0.67 to 0.90) and PFS (HR

0.60, 95% CI 0.55 to 0.66), when irinotecan was combined with oxaliplatin (also known as IROX regimen) ([Haller 2008](#)). The grade of evidence was moderate (because there was only one study) ([Summary of findings 4](#)).

When the results of the six studies were pooled together, there was no OS advantage (HR 0.91, 95% CI 0.79 to 1.04), with a non-negligible between-study heterogeneity (I² = 42%). In contrast, there was both a PFS advantage (HR 0.68, 95% CI 0.60 to 0.76) ([Figure 5](#)) and an ORR advantage (RR 2.87, 95% CI 2.10 to 3.93) for combination regimens, with no significant difference in terms of toxicity (RR 1.18, 95% CI 0.96 to 1.45); the grade of evidence was moderate (since the PFS findings were not confirmed by the OS data) ([Summary of findings 3](#)).

Figure 5.

Since the between-study heterogeneity was moderate to high for all outcomes, we searched for more homogeneous results by subgroup analysis. Pooling the data of two trials (144 participants)

comparing the same regimens (irinotecan versus FOLFIRI) found no OS, PFS, ORR or SAE differences ([Clarke 2011](#); [Graeven 2007](#)).

Heterogeneity was drastically reduced (I^2 less than 25%) when we meta-analyzed the data of the two trials (1758 participants) testing the hypothesis that the addition of targeted agents (panitumumab, cetuximab) might enhance the therapeutic efficacy of irinotecan (Seymour 2013; Sobrero 2008): both PFS (HR 0.71, 95% CI 0.64 to 0.79) and ORR (RR 3.38, 95% CI 2.52 to 4.53) were significantly better in the combination regimen; however, there was no significant OS difference (HR 0.99, 95% CI 0.88 to 1.10), and the rate of SAEs was significantly higher with the combination regimen (RR 1.44, 95% CI 1.31 to 1.59); the grade of evidence was moderate because the PFS findings were not confirmed by the OS data (Summary of findings 8).

Fractionated irinotecan versus single-dose irinotecan

Three RCTs compared irinotecan administered as single dose (every three weeks) with that of irinotecan fractionated (with different schedules) (Fuchs 2003, 391 participants; Shoemaker 2004, 85 participants; Tsavaris 2003, 120 participants). There were no statistically significant differences in terms of OS (HR 0.86, 95% CI 0.71 to 1.05; 2 RCTs) (Fuchs 2003; Tsavaris 2003), PFS (HR 0.90,

95% CI 0.71 to 1.14; 2 RCTs) (Fuchs 2003; Tsavaris 2003), ORR (RR 0.83, 95% CI 0.45 to 1.53; 2 RCTs) (Shoemaker 2004; Tsavaris 2003), and SAE (RR 0.97, 95% CI 0.87 to 1.10; 3 RCTs) (Fuchs 2003; Shoemaker 2004; Tsavaris 2003).

Bevacizumab plus chemotherapy versus chemotherapy

Four RCTs (1723 participants) addressed the addition of bevacizumab to chemotherapy (oxaliplatin- or irinotecan-based regimens) (Bennouna 2013; Cao 2015; Giantonio 2007; Masi 2015).

All four studies demonstrated a survival advantage for the combination arms, although this advantage was only statistically significant in two RCTs (Bennouna 2013; Giantonio 2007). Pooling the OS data from all four studies showed that bevacizumab can lead to a survival advantage (HR 0.79, 95% CI 0.70 to 0.88) (Figure 6), with no between-study heterogeneity ($I^2 = 0\%$). The four single trials reported even better results for PFS, which was confirmed by meta-analysis (HR 0.67, 95% CI 0.60 to 0.75) (Figure 7). Based on the GRADE system, we rated the evidence as high (no reason for downgrading) (Summary of findings 2).

Figure 6.

Figure 7.

ORR data were in line with survival data as the response rates were higher in the bevacizumab-containing regimens (RR 1.72, 95% CI 1.23 to 2.43). Interestingly, the addition of bevacizumab did not significantly increase the risk of SAEs (RR 1.07, 95% CI 0.93 to 1.25).

FOLFIRI plus targeted agents versus FOLFIRI

Six trials (3335 participants) tested the hypothesis that adding other anticancer agents to the FOLFIRI regimen (conventional chemotherapy drugs only) might increase therapeutic efficacy investigating seven different targeted drugs: conatumumab

(Cohn 2013_conat), ganitumab (Cohn 2013_ganit), panitumumab (Peeters 2010), bevacizumab (plus panitumumab) (Liu 2015), trebananib (Peeters 2013), ramucirumab (Tabernero 2015), and aflibercept (Van Cutsem 2012). Singularly taken, only three RCTs showed a significant improvement in OS (Liu 2015; Tabernero 2015; Van Cutsem 2012); pooling the data of all six trials, we found that the addition of targeted agents did increase life expectation (HR 0.84, 95% CI 0.77 to 0.91) (Figure 8). There were similar results when pooling PFS data (HR 0.78, 95% CI 0.71 to 0.87) (Figure 9) and ORR data (RR 2.07, 95% CI 1.31 to 3.28).

Figure 8.

Figure 9.

Importantly, the addition of targeted agents also significantly increased the incidence of SAEs (RR 1.30, 95% CI 1.17 to 1.45). At subgroup analysis, considering the three trials (2440 participants) that investigated targeted agents blocking exclusively the VEGF pathway (bevacizumab, ramucirumab, aflibercept), findings were even more homogeneous in terms of survival (OS: HR 0.82, 95% CI 0.74 to 0.90; PFS: HR 0.77, 95% CI 0.70 to 0.84).

Based on the GRADE system, we rated the evidence as high.

FOLFOX plus targeted agents versus FOLFOX

Two RCTs (1432 participants) tested the hypothesis that adding targeted agents (bevacizumab and vatalanib) to the FOLFOX regimen (chemotherapy drugs only) might increase therapeutic efficacy (bevacizumab: [Giantonio 2007](#); vatalanib: [Van Cutsem 2011](#)). The meta-analysis of the two trials showed a significantly improved PFS when targeted agents were added to FOLFOX (HR 0.76, 95% CI 0.66 to 0.86) ([Figure 10](#)), although there was a high degree of heterogeneity ($I^2 = 78\%$). Addition of targeted agents also improved OS, although this result did not reach statistical significance (HR 0.92, 95% CI 0.82 to 1.04).

Figure 10.

Finally, the incidence of SAEs was significantly higher among participants receiving the combination regimen (RR 1.2, 95% CI 1.13

to 1.28). Only one study reported ORR, which showed an advantage for the regimen including bevacizumab ([Giantonio 2007](#)).

Based on the GRADE system, we rated the evidence as low (due to high heterogeneity and PFS data not confirmed by OS data).

FOLFIRI plus bevacizumab versus FOLFIRI plus other targeted agents

Two trials (282 participants) compared the FOLFIRI chemotherapy regimen in combination with either bevacizumab or other targeted agents (axitinib or panitumumab) (Bendell 2013_folfiri; Hecht 2015). Neither study reported a significant OS difference between the two approaches, a result confirmed by data meta-analysis (HR 1.15, 95% CI 0.86 to 1.53). There were similar findings for PFS and ORR both in single studies and meta-analysis (PFS: HR 1.10, 95% CI 0.81 to 1.50; ORR: RR 1.44, 95% CI 0.94 to 2.20).

Toxicity findings favoured the bevacizumab-containing regimen (other agents versus bevacizumab comparison: RR 1.53, 95% CI 1.10 to 2.11). Due to the low number of participants randomized, any result should be interpreted with caution (due to low statistical power considerations).

Using the GRADE system, we rated the evidence as low (due to imprecision and low statistical power).

FOLFOX plus bevacizumab versus FOLFOX plus other targeted agents

Two trials (169 participants) compared the FOLFOX chemotherapy regimen in combination with either bevacizumab or other targeted agents (Axitinib or Linifanib) (Bendell 2013_folfox; O'Neil 2014). Neither study reported a significant OS difference between the two approaches, a result confirmed by data meta-analysis (HR 1.14, 95% CI 0.81 to 1.61). There were similar findings for PFS and ORR both in single studies and meta-analysis (PFS: HR 1.26, 95% CI 0.83 to 1.91; ORR: RR 0.77, 95% CI 0.46 to 1.29).

Toxicity findings favoured the bevacizumab-containing regimen (other agents versus bevacizumab comparison: RR 1.27, 95% CI 1.03 to 1.55). Due to the low number of participants randomized, any result should be interpreted with caution (due to low statistical power considerations).

Using the GRADE system, we rated the evidence as low (due to imprecision and low statistical power).

Other comparisons based on single trials

Single RCTs compared the following regimens (for details see [Characteristics of included studies](#) and [Table 3](#)).

Irinotecan versus best supportive care

This trial (279 participants) is particularly important because it showed that anticancer therapy (irinotecan) provided a significant OS advantage (HR 0.58, 95% CI 0.43 to 0.80) even in second-line (all enrolled participants were refractory to first-line 5FU) compared to best supportive care, although at the cost of a (predictable) higher incidence of SAEs (RR 1.19, 95% CI 1.01 to 1.40) (Cunningham 1998).

Using the GRADE system, we rated the evidence as moderate (since there was only one trial).

IRIS versus FOLFIRI

This trial (426 participants), which compared IRIS versus FOLFIRI (both contained irinotecan), found that the two regimens were very

similar in terms of survival, tumour response and toxicity outcomes (Muro 2010).

Using the GRADE system, we rated the evidence as low (due to imprecision and low statistical power).

XELOX versus FOLFOX

This study (627 participants), in which the two combination regimens basically differed by using oral (XELOX: capecitabine) instead of intravenous (FOLFOX: 5FU) fluoropyrimidine, suggested that the survival and tumour response results achieved with XELOX were similar to those with FOLFOX, but with the advantage of a lower incidence of SAEs (RR 0.75, 95% CI 0.68 to 0.82) (Rothenberg 2008).

Using the GRADE system, we rated the evidence as moderate (since there was only one trial).

FOLFOX versus irinotecan

This RCT (491 participants), which compared FOLFOX with single-agent irinotecan, found no significant difference in OS; however, participants who received FOLFOX showed better PFS and ORR, which were not associated with a significant increase in toxicity (Kim 2009).

Using the GRADE system, we rated the evidence as low (due to imprecision and low statistical power).

Mitomycin plus oxaliplatin versus mitomycin plus irinotecan

The investigators of this trial (64 participants) did not report survival outcomes. There were no statistically significant differences between the two chemotherapy regimens in tumour response and toxicity (Scheithauer 2002).

Using the GRADE system, we rated the evidence as very low (due to imprecision and very low statistical power).

Gefitinib plus raltitrexed versus raltitrexed

The addition of targeted agent gefitinib to chemotherapy agent raltitrexed did not improve OS, PFS or ORR (76 participants). There were no toxicity differences reported between the two study arms (Viéitez 2011).

Using the GRADE system, we rated the evidence as very low (due to imprecision and very low statistical power).

Different bevacizumab dosages

One trial (369 participants) compared two bevacizumab dosages (used in association with FOLFIRI) (Iwamoto 2015). Since there were no statistically significant differences in terms of OS, PFS, ORR or SAEs, the authors concluded that higher-dose bevacizumab did not perform better than lower-dose bevacizumab when associated with FOLFIRI.

Using the GRADE system, we rated the evidence as low (due to imprecision and low statistical power).

Panitumumab versus cetuximab

In this trial (999 participants), the investigators did not detect significant differences between the two targeted agents

panitumumab and cetuximab in terms of OS, PFS, ORR or SAEs (Price 2014).

Using the GRADE system, we rated the evidence as moderate (since there was only one trial available).

Abituzumab plus cetuximab plus irinotecan versus cetuximab plus irinotecan

The results of this RCT (216 participants) suggested that targeted agent abituzumab (both low and high dose) does not add any advantage (in terms of OS, PFS, ORR or SAEs) to the cetuximab plus irinotecan combination (Élez 2015).

Using the GRADE system, we rated the evidence as low (due to imprecision and low statistical power).

DISCUSSION

This is the first systematic review and meta-analysis addressing the issue of the performance (efficacy plus toxicity) of second-line systemic therapy in people with metastatic (TNM stage IV) CRC. Our findings are based on the data collected from 34 eligible RCTs enrolling 13,787 participants.

Since the included RCTs tested a variety of drug regimens, it was almost always impossible to pool results from identical comparisons. Nevertheless, we exploited the available evidence in order to answer clinically relevant broad questions, which implied the meta-analysis of RCTs addressing the same issue (e.g. do targeted drugs increase the efficacy of chemotherapy?) though - singularly taken - they tested different drug regimens (e.g. different targeted agents).

Summary of main results

The main findings of our work can be summarized as the answers to the following clinical questions.

- Is second-line chemotherapy effective in people with metastatic CRC?

Only one RCT addressed this issue. It demonstrated a significant survival advantage for people undergoing chemotherapy (irinotecan) compared to people treated with best supportive care. Obviously, chemotherapy was accompanied by a higher rate of toxicity. The level of evidence was moderate because this result was based on a single study.

- Are modern chemotherapy regimens superior to outdated 5FU?

The results of two RCTs showed that modern chemotherapy regimens (FOLFOX and irinotecan) were more effective than 5FU alone, although at the cost of a higher toxicity rate. The level of evidence was high.

- Are irinotecan-based regimens better than irinotecan alone?

In general, irinotecan-based regimens were better than irinotecan alone, although results were heterogeneous, which was probably linked to the variety of treatments included. When we looked at more homogeneous subgroups, two combinations were significantly associated with a better efficacy: irinotecan plus targeted agents (two RCTs testing anti-EGFR agents cetuximab and panitumumab; grade of evidence: moderate, since the PFS

finding was not supported by the OS finding) and irinotecan plus oxaliplatin (IROX regimen; one RCT; grade of evidence: moderate, as there was only one RCT). In both cases, improved efficacy was accompanied by a higher rate of SAEs. Of note, the combination regimen, FOLFIRI, was not superior to irinotecan alone.

- Does targeted agent bevacizumab increase the efficacy of chemotherapy?

Four RCTs addressed this issue and found that bevacizumab significantly increased the efficacy of chemotherapy (miscellany of regimens); interestingly, this benefit was not paralleled by a significant increase in toxicity rates. The grade of evidence was high.

- Do targeted agents increase the efficacy of FOLFIRI or FOLFOX?

The evidence from eight RCTs (FOLFIRI, 6 RCTs; FOLFOX, 2 RCTs) supported the superiority of combination regimens including targeted agents; however, the grade of evidence was high for FOLFIRI and low for FOLFOX (due to results heterogeneity and PFS data not confirmed by OS data). In both cases, improved efficacy was accompanied by a higher rate of SAEs.

Importantly, we would like to underscore that the answers to the last two questions strongly support the use of targeted agents in combination with chemotherapy for the treatment of people with metastatic CRC who did not respond to first-line treatment. Interestingly, the use of bevacizumab was associated with higher efficacy without increased toxicity, a common finding when dealing with regimens that show better anticancer activity (see the comparisons 'Modern chemotherapy regimens versus 5-fluorouracil', 'Irinotecan plus other anticancer agents versus irinotecan', and 'Irinotecan and best supportive care'). In particular, other widely used targeted agents, such as those targeting the EGFR pathway (e.g. cetuximab and panitumumab) which improve people's survival (when added to chemotherapy), are accompanied by a significantly worse tolerability (see comparison 'Irinotecan plus other anticancer agents versus irinotecan').

Regarding secondary endpoints, both response and toxicity rates are usually directly proportional to efficacy (i.e. the higher the efficacy, the higher the rates of both tumour shrinkage and SAEs); this was the case for the regimens compared with the exception of bevacizumab (which appeared to lead to higher response rates when combined with chemotherapy, without increasing toxicity). Another important clue comes from the comparison between oral and intravenous fluoropyrimidines (combined with oxaliplatin), which supports the use of oral administration due to similar efficacy, lower toxicity rates and easier route of administration (Rothenberg 2008).

Overall completeness and applicability of evidence

Although the above findings provide clinicians with some useful information, some unanswered questions remain. For instance, many comparisons showing no statistically significant difference between regimens were based on single trials enrolling a number of participants insufficient to obtain a satisfactory statistical power, which prevents us from drawing any definitive conclusions based on those results. Moreover, not all comparisons were available, which did not enable us to generate a full ranking of the variety of tested regimens. For example, thus far no RCT has investigated irinotecan plus bevacizumab (versus irinotecan alone), which

would be a potentially useful combination of two drugs with established efficacy when individually taken as second-line therapy for people with metastatic CRC.

Since they are based on moderate to high quality evidence, the main findings of this review could be helpful to guide clinicians for the routine clinical practice in the choice of second-line therapy for people with metastatic CRC.

Quality of the evidence

The main conclusions of this review (see [Summary of main results](#)) are based on moderate to high-quality evidence; the main reason for downgrading being inconsistency due to the fact that PFS findings were not confirmed by OS data. Nevertheless, it should be remembered that PFS is nowadays considered a reliable surrogate of OS (which includes disease-unrelated events and requires longer follow-ups) in the setting of second-line therapy for metastatic CRC ([Buyse 2007](#); [Giessen 2015](#)).

Potential biases in the review process

Although always possible, we believe it is unlikely that a significant bias was introduced in the search for trials. Moreover, we employed the high-quality Cochrane methods to evaluate trials and conducting data analysis.

Agreements and disagreements with other studies or reviews

Only one systematic review has so far been published on this subject ([Giessen 2015](#)); this work had the specific aim to investigate PFS and ORR as potential surrogate endpoints for OS and found 23 RCTs (our review identified 34 studies). Moreover, only one systematic review and meta-analysis has been published in this field ([Beretta 2013](#)), but its area of interest was limited to one treatment (FOLFIRI plus bevacizumab); the results of this work (based on both randomized and non-randomized trials) were in line with the findings of this review.

AUTHORS' CONCLUSIONS

Implications for practice

Systemic therapy offers a survival benefit to people with metastatic colorectal cancer (CRC) who did not respond to first-line treatment,

especially when targeted agents are combined with conventional chemotherapeutic drugs. This review provides clinicians with several clues on the choice of second-line therapy for people with metastatic CRC who have not responded to first-line treatment, such as the superiority of some chemotherapy regimens and the advantage of adding targeted agents to chemotherapy.

Implications for research

Our findings highlight the need for further research in order to address some issues, such as:

- the evidence on some treatments was based on single trials, which precludes any definitive conclusion on those regimens;
- considering the positive results yielded with targeted agents, then other compounds should be tested in this setting that are being successfully used against other tumour types (e.g. co-inhibitory molecule inhibitors);
- novel biomarkers predictive of tumour response are needed (besides KRAS mutational status for epidermal growth factor receptor (EGFR) pathway inhibitors) in order to improve our ability to select people with the highest likelihood of benefiting from a given therapy (personalized cancer medicine);
- data on the quality of life of people with cancer should become a mandatory item while designing and running a cancer trial in order to formally investigate the balance between survival benefits provided by second-line systemic therapy and treatment-related toxicity.

ACKNOWLEDGEMENTS

We truly thank Dr Marta Briarava (data manager of the Meta-Analysis Unit of the University of Padova, Padova, Italy) for her invaluable help with the setup and management of the dedicated database we used for the collection and analysis of the literature data.

We would also like to thank Juan-José López and the previous authors for their contribution to the first published version of this review.

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CHARACTERISTICS OF STUDIES
Characteristics of included studies *[ordered by study ID]*
[Bendell 2013_folfiri](#)

Methods	Parallel-group RCT (4-arm), open label, multicentre
Participants	People with metastatic CRC who did not respond to first-line therapy with oxaliplatin-containing regimens Mean age (years): 59 Males (%): 47
Interventions	Experimental group: axitinib + FOLFIRI (n = 49) Axitinib (small molecule tyrosine kinase inhibitor targeting VEGFR1-3, c-KIT and PDGFR): 5 mg to 10 mg twice daily, oral Control group: bevacizumab + FOLFIRI (n = 51) Bevacizumab (blocking monoclonal antibody targeting VEGF): 5 mg/kg every 2 weeks, i.v. Co-intervention: FOLFIRI (every 2 weeks, i.v.): irinotecan (180 mg/m ²) + 5FU (2800 mg/m ²) + leucovorin (400 mg/m ²)
Outcomes	OS, PFS, ORR, SAE
Notes	Same publication as Bendell 2013_folfox (data split for presentation purposes only) Country: international (Western countries) Dropouts: none reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unreported
Allocation concealment (selection bias)	Unclear risk	Unreported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias)	Low risk	We found no evidence of attrition bias

Second-line systemic therapy for metastatic colorectal cancer (Review)

Bendell 2013_folfiri (Continued)

Efficacy outcomes

Incomplete outcome data (attrition bias) Safety and QoL outcomes	Low risk	We found no evidence of attrition bias
Selective reporting (reporting bias)	Low risk	We found no evidence of reporting bias
Other bias?	Low risk	We found no evidence of other bias

Bendell 2013_folfox

Methods	Parallel-group RCT (4-arm), open label, multicentre, international	
Participants	People with metastatic CRC who did not respond to first-line therapy with irinotecan-containing regimens Mean age (years): 59 Males (%): 47	
Interventions	<p>Experimental group: axitinib + FOLFOX (n = 36)</p> <p>Axitinib (small molecule tyrosine kinase inhibitor targeting multiple receptors such as VEGFR1-3, c-KIT and PDGFR): 5 mg to 10 mg twice daily, oral</p> <p>Control group: bevacizumab + FOLFOX (n = 35)</p> <p>Bevacizumab (blocking monoclonal antibody targeting VEGF): 5 mg/kg every 2 weeks, i.v.</p> <p>Co-intervention: FOLFOX (every 2 weeks, i.v.): oxaliplatin (85 mg/m²) + 5FU (2800 mg/m²) + leucovorin (400 mg/m²)</p>	
Outcomes	OS, PFS, ORR, SAE	
Notes	Same publication as Bendell 2013_folfiri (data split for presentation purposes only) Country: international (Western countries) Dropouts: none reported	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unreported
Allocation concealment (selection bias)	Unclear risk	Unreported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial

Bendell 2013_folfox (Continued)

Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) Efficacy outcomes	Low risk	We found no evidence of attrition bias
Incomplete outcome data (attrition bias) Safety and QoL outcomes	Low risk	We found no evidence of attrition bias
Selective reporting (reporting bias)	Low risk	We found no evidence of reporting bias
Other bias?	Low risk	We found no evidence of other bias

Bennouna 2013

Methods	Parallel-group RCT, open label, multicentre, international
Participants	People with metastatic CRC who did not respond to first-line therapy with oxaliplatin- or irinotecan-containing regimen Mean age (years): 63 Males (%): 64
Interventions	Experimental group: bevacizumab + chemotherapy (n = 409) Bevacizumab (blocking monoclonal antibody targeting VEGF): 5 mg/kg every 2 weeks, i.v. Control group: chemotherapy (n = 411) Chemotherapy: irinotecan- or oxaliplatin-containing regimen (switch with first-line regimen)
Outcomes	OS, PFS, ORR, SAE
Notes	Country: international (Western countries) Dropouts: 4 (all in the combination regimen arm)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Permuted block randomization by second-order minimization algorithm
Allocation concealment (selection bias)	Low risk	Clinical and statistical teams were masked during the study
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial

Second-line systemic therapy for metastatic colorectal cancer (Review)

Bennouna 2013 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) Efficacy outcomes	Low risk	We found no evidence of attrition bias
Incomplete outcome data (attrition bias) Safety and QoL outcomes	Low risk	We found no evidence of attrition bias
Selective reporting (reporting bias)	Low risk	We found no evidence of reporting bias
Other bias?	Low risk	We found no evidence of other bias

Cao 2015

Methods	Parallel-group RCT, open label, multicentre, national
Participants	People with metastatic CRC who did not respond to first-line therapy with oxaliplatin-containing regimen Mean age (years): 62 Males (%): 62
Interventions	Experimental group: bevacizumab + FOLFIRI (n = 65) Bevacizumab (blocking monoclonal antibody targeting VEGF): 10 mg/kg, i.v. Control group: FOLFIRI (n = 77) FOLFIRI (i.v.): irinotecan (150 mg/m ²) + 5FU (2800 mg/m ²) + leucovorin (400 mg/m ²)
Outcomes	OS, PFS, ORR, SAE
Notes	Country: China Dropouts: none reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unreported
Allocation concealment (selection bias)	Unclear risk	Unreported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial

Cao 2015 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) Efficacy outcomes	Low risk	We found no evidence of attrition bias
Incomplete outcome data (attrition bias) Safety and QoL outcomes	Low risk	We found no evidence of attrition bias
Selective reporting (reporting bias)	Low risk	We found no evidence of reporting bias
Other bias?	Low risk	We found no evidence of other bias

Clarke 2011

Methods	Parallel-group RCT, multicentre, national
Participants	People with metastatic CRC who did not respond to first-line therapy with 5FU-containing regimen Mean age (years): unreported Males (%): 60
Interventions	Experimental group: FOLFIRI (n = 44) FOLFIRI (i.v., every 2 weeks): irinotecan (180 mg/m ²) + 5FU (2800 mg/m ²) + leucovorin (20 mg/m ²) Control group: irinotecan (n = 45) Irinotecan: 300 or 350 mg/m ² , i.v., every 3 weeks
Outcomes	OS, PFS, ORR, SAE, QoL
Notes	Country: Australia Dropouts: 4 (2 in each arm)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization by minimization method
Allocation concealment (selection bias)	Low risk	Participants were randomized centrally by telephone
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unreported

Clarke 2011 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unreported
Incomplete outcome data (attrition bias) Efficacy outcomes	Low risk	Only 1 participant explicitly asking not to be analyzed (irinotecan arm) was excluded
Incomplete outcome data (attrition bias) Safety and QoL outcomes	Low risk	We found no evidence of attrition bias
Selective reporting (reporting bias)	Low risk	We found no evidence of reporting bias
Other bias?	Low risk	We found no evidence of other bias

Cohn 2013_conat

Methods	Parallel-group RCT (3-arm), double blind, multicentre, international	
Participants	People with mutant KRAS metastatic CRC who did not respond to first-line therapy with oxaliplatin (with or without bevacizumab)-containing regimen Mean age (years): 59 Males (%): 51	
Interventions	Experimental group: conatumumab + FOLFIRI (n = 51) Conatumumab (agonistic monoclonal antibody targeting DR5 (death receptor 5)): 10 mg/kg, i.v., every 2 weeks Control group: placebo + FOLFIRI (n = 52) FOLFIRI: (i.v., every 2 weeks): irinotecan (180 mg/m ²) + 5FU (2800 mg/m ²) + leucovorin (400 mg/m ²)	
Outcomes	OS, PFS, ORR, SAE	
Notes	Same publication as Cohn 2013_ganit (data split for presentation purposes only) Country: international (mainly Western countries) Dropouts: none reported	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Permuted blocks randomization
Allocation concealment (selection bias)	Low risk	Centralized randomization (interactive voice response system)

Cohn 2013_conat (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind trial
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unreported
Incomplete outcome data (attrition bias) Efficacy outcomes	Low risk	We found no evidence of attrition bias
Incomplete outcome data (attrition bias) Safety and QoL outcomes	Low risk	We found no evidence of attrition bias
Selective reporting (reporting bias)	Low risk	We found no evidence of reporting bias
Other bias?	Low risk	We found no evidence of other bias

Cohn 2013_ganit

Methods	Parallel-group RCT (3-arm), double blind, multicentre, international
Participants	People with mutant KRAS metastatic CRC who did not respond to first-line therapy with oxaliplatin (with or without bevacizumab)-containing regimen Mean age (years): 59 Males (%): 51
Interventions	Experimental group: ganitumab + FOLFIRI (n = 51) Ganitumab (blocking monoclonal antibody targeting insulin-like growth factor 1 receptor (IGF1R)): 12 mg/kg, i.v., every 2 weeks Control group: placebo + FOLFIRI (n = 52) FOLFIRI: (i.v., every 2 weeks): irinotecan (180 mg/m ²) + 5FU (2800 mg/m ²) + leucovorin (400 mg/m ²)
Outcomes	OS, PFS, ORR, SAE
Notes	Same publication as Cohn 2013_conat (data split for presentation purposes only) Country: international (mainly Western countries) Dropouts: none reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Permuted blocks randomization

Cohn 2013_ganit (Continued)

Allocation concealment (selection bias)	Low risk	Centralized randomization (interactive voice response system)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind trial
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unreported
Incomplete outcome data (attrition bias) Efficacy outcomes	Low risk	We found no evidence of attrition bias
Incomplete outcome data (attrition bias) Safety and QoL outcomes	Low risk	We found no evidence of attrition bias
Selective reporting (reporting bias)	Low risk	We found no evidence of reporting bias
Other bias?	Low risk	We found no evidence of other bias

Cunningham 1998

Methods	Parallel-group RCT, open label, multicentre, international	
Participants	People with metastatic CRC who did not respond to first-line therapy with 5FU. Some participants (24%) had received ≥ 2 previous chemotherapy regimens Mean age (years): 61 Males (%): 66	
Interventions	Experimental group: irinotecan (n = 189) Irinotecan: 350 mg/m ² i.v. every 21 days Control group: best supportive care (n = 90)	
Outcomes	OS, SAE, QoL	
Notes	Country: international (Western countries) Dropouts: 10 (5 in each arm)	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random sequence was generated electronically

Cunningham 1998 (Continued)

Allocation concealment (selection bias)	Low risk	Centralized randomization
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) Efficacy outcomes	Low risk	We found no evidence of attrition bias
Incomplete outcome data (attrition bias) Safety and QoL outcomes	Low risk	We found no evidence of attrition bias
Selective reporting (reporting bias)	Low risk	We found no evidence of reporting bias
Other bias?	Unclear risk	"Characteristics were similar for both groups except for performance status (more patients having poor performance status in the supportive-care group) and anaemia."

Fuchs 2003

Methods	Parallel-group RCT, open label, multicentre, national	
Participants	People with metastatic CRC who did not respond to first-line therapy with 5FU Mean age (years): 62 Males (%): 61	
Interventions	Experimental group: irinotecan schedule-1 (n = 196) Irinotecan schedule-1 (single dose): 350 mg/m ² i.v. every 3 weeks Control group: irinotecan schedule-2 (n = 95) Irinotecan schedule-2 (fractionated): 125 mg/m ² weekly during 4 weeks every 6 weeks	
Outcomes	OS, PFS, SAE, QoL	
Notes	Country: USA Dropouts: none reported	
Risk of bias		
Bias	Authors' judgement	Support for judgement

Fuchs 2003 (Continued)

Random sequence generation (selection bias)	Low risk	Random sequence was generated electronically
Allocation concealment (selection bias)	Unclear risk	Unreported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) Efficacy outcomes	Low risk	We found no evidence of attrition bias
Incomplete outcome data (attrition bias) Safety and QoL outcomes	Low risk	"A total of seven patients, one on the weekly schedule and six on the every-3-weeks regimen, received no irinotecan and were excluded from the tolerability analysis." Reasons for not receiving treatment are described
Selective reporting (reporting bias)	Low risk	We found no evidence of reporting bias
Other bias?	Low risk	We found no evidence of other bias

Giantonio 2007

Methods	Parallel-group RCT, open label, multicentre, international
Participants	People with metastatic CRC who did not respond to first-line therapy with FOLFIRI Mean age (years): 60 Males (%): 60
Interventions	Experimental group: bevacizumab + FOLFOX4 (n = 286) Bevacizumab (blocking monoclonal antibody targeting VEGF): 10 mg/kg, i.v., every 2 weeks Control group: FOLFOX4 (n = 291) FOLFOX4 (i.v., every 2 weeks): oxaliplatin (85 mg/m ²) + 5FU (1000 mg/m ²) + leucovorin (200 mg/m ²)
Outcomes	OS, PFS, ORR, SAE
Notes	Country: international (mainly USA) Dropouts: 6 (number per arm: unreported)

Risk of bias

Bias	Authors' judgement	Support for judgement
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Giantonio 2007 (Continued)

Random sequence generation (selection bias)	Unclear risk	Unreported
Allocation concealment (selection bias)	Unclear risk	Unreported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) Efficacy outcomes	Low risk	We found no evidence of attrition bias
Incomplete outcome data (attrition bias) Safety and QoL outcomes	Low risk	We found no evidence of attrition bias
Selective reporting (reporting bias)	Low risk	We found no evidence of reporting bias
Other bias?	Low risk	We found no evidence of other bias

Gibbs 2011

Methods	Parallel-group RCT, open-label, multicentre, national
Participants	People with metastatic CRC who did not respond to first-line therapy with 5FU without oxaliplatin Mean age (years): 63 Males (%): 59
Interventions	Experimental group: hyaluronan-irinotecan (n = 41) Hyaluronan-irinotecan (i.v., every 3 weeks): hyaluronan (1000 mg/m ²) + irinotecan (350 mg/m ²) Control group: irinotecan (n = 35) Irinotecan: 350 mg/m ² , i.v., every 3 weeks
Outcomes	OS, PFS, ORR, SAE
Notes	Country: Australia Dropouts: none reported

Risk of bias

Bias	Authors' judgement	Support for judgement
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Gibbs 2011 (Continued)

Random sequence generation (selection bias)	Unclear risk	Unreported
Allocation concealment (selection bias)	Unclear risk	Unreported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) Efficacy outcomes	Low risk	We found no evidence of attrition bias
Incomplete outcome data (attrition bias) Safety and QoL outcomes	Low risk	We found no evidence of attrition bias
Selective reporting (reporting bias)	Low risk	We found no evidence of reporting bias
Other bias?	Low risk	We found no evidence of other bias

Graeven 2007

Methods	Parallel-group RCT, open-label, multicentre, national
Participants	People with metastatic CRC who did not respond to first-line therapy with 5FU without oxaliplatin Mean age (years): 66 Males (%): 64
Interventions	Experimental group: FOLFIRI (n = 28) FOLFIRI (i.v., every 7 weeks): irinotecan (80 mg/m ²) + leucovorin (500 mg/m ²) + 5FU (2000 mg/m ²) Control group: irinotecan (n = 27) Irinotecan: 125 mg/m ² , i.v., every 6 weeks
Outcomes	OS, PFS, ORR, SAE
Notes	Country: Germany Dropouts: none reported

Risk of bias

Bias	Authors' judgement	Support for judgement
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Graeven 2007 (Continued)

Random sequence generation (selection bias)	Unclear risk	Unreported
Allocation concealment (selection bias)	Unclear risk	Unreported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) Efficacy outcomes	High risk	"Efficacy analyses were based on an intent-to-treat population". 57 patients were enrolled into this multicentre study. 2 patients were withdrawn prior to the first administration. Therefore, the intent-to-treat population includes 55 patients. Overall survival and PFS are presented for 55 participants. Neither the arm the two patients belonged to, nor the reasons for withdrawal were reported "39 patients were evaluable for response", therefore the intention-to-treat population includes 16 no evaluable participants
Incomplete outcome data (attrition bias) Safety and QoL outcomes	Low risk	We found no evidence of attrition bias
Selective reporting (reporting bias)	Low risk	We found no evidence of reporting bias
Other bias?	Low risk	We found no evidence of other bias

Haller 2008

Methods	Parallel-group RCT, open-label, multicentre, international
Participants	People with metastatic CRC who did not respond to first-line therapy with 5FU or capecitabine without leucovorin Mean age (years): 62 Males (%): 60
Interventions	Experimental group: IROX (irinotecan + oxaliplatin) (n = 317) IROX (i.v., every 3 weeks): oxaliplatin (85 mg/m ²) + irinotecan (200 mg/m ²) Control group: irinotecan (n = 310) Irinotecan: 350 mg/m ² (i.v., every 3 weeks)
Outcomes	OS, PFS, ORR, SAE
Notes	Country: international (mainly Western countries)

Haller 2008 (Continued)

Dropouts: 14 (5 in IROX arm; 9 in irinotecan arm)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central randomization by interactive voice response system
Allocation concealment (selection bias)	Low risk	Central randomization by interactive voice response system
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) Efficacy outcomes	Low risk	We found no evidence of attrition bias
Incomplete outcome data (attrition bias) Safety and QoL outcomes	Low risk	We found no evidence of attrition bias
Selective reporting (reporting bias)	Low risk	We found no evidence of reporting bias
Other bias?	Low risk	We found no evidence of other bias

Hecht 2015

Methods	Parallel-group RCT, open-label, multicentre, national
Participants	People with wild-type KRAS metastatic CRC who did not respond to first-line therapy with FOLFOX + bevacizumab Mean age (years): 62 Males (%): 66
Interventions	Experimental group: panitumumab + FOLFIRI (n = 91) Panitumumab (blocking monoclonal antibody targeting EGFR): 6 mg/kg, i.v., every 2 weeks Control group: bevacizumab + FOLFIRI (n = 91) Bevacizumab (blocking monoclonal antibody targeting VEGF): 5 mg/kg to 10 mg/kg, i.v., every 2 weeks Co-intervention: FOLFIRI (i.v., every 2 weeks): irinotecan (180 mg/m ²) + 5FU (2800 mg/m ²) + leucovorin (400 mg/m ²)
Outcomes	OS; PFS, ORR, SAE

Hecht 2015 (Continued)

Notes Country: USA
Dropouts: none reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unreported
Allocation concealment (selection bias)	Unclear risk	Unreported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) Efficacy outcomes	Low risk	We found no evidence of attrition bias
Incomplete outcome data (attrition bias) Safety and QoL outcomes	Low risk	We found no evidence of attrition bias
Selective reporting (reporting bias)	Low risk	We found no evidence of reporting bias
Other bias?	Low risk	We found no evidence of other bias

Iwamoto 2015

Methods	Parallel-group RCT, open-label, multicentre, national
Participants	People with metastatic CRC who did not respond to first-line therapy with FOLFOX + bevacizumab Mean age (years): 66 Males (%): 56
Interventions	Experimental group: bevacizumab (low dose) + FOLFIRI (n = 181) Bevacizumab (blocking monoclonal antibody targeting VEGF) low dose: 5 mg/kg (i.v., every 2 weeks) Control group: bevacizumab (high dose) + FOLFIRI (n = 188) Bevacizumab (blocking monoclonal antibody targeting VEGF) high dose: 10 mg/kg (i.v., every 2 weeks) Co-intervention: FOLFIRI (i.v., every 2 weeks): irinotecan (150 mg/m ²) + 5FU (2800 mg/m ²) + leucovorin (200 mg/m ²)

Iwamoto 2015 (Continued)

Outcomes	OS, PFS, ORR, SAE
Notes	Country: Japan Dropouts: 4 (1 in low-dose arm; 3 in high-dose arm)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Dynamic randomization with minimization method
Allocation concealment (selection bias)	Low risk	Centralized randomization
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) Efficacy outcomes	Low risk	We found no evidence of attrition bias
Incomplete outcome data (attrition bias) Safety and QoL outcomes	Low risk	We found no evidence of attrition bias
Selective reporting (reporting bias)	Low risk	We found no evidence of reporting bias
Other bias?	Low risk	We found no evidence of other bias

Kim 2009

Methods	Parallel-group RCT, open-label, multicentre, national
Participants	People with metastatic CRC who did not respond to first-line therapy with 5FU Mean age (years): 63 Males (%): 62
Interventions	Experimental group: FOLFOX4 (n = 246) FOLFOX4 (i.v., every 2 weeks): oxaliplatin (85 mg/m ²) + 5FU (1000 mg/m ²) + leucovorin (200 mg/m ²) Control group: irinotecan (n = 245) Irinotecan: 350 mg/m ² , i.v., every 3 weeks

Kim 2009 (Continued)

Outcomes	OS, PFS, ORR, SAE
Notes	Country: USA
	Dropouts: 6 (3 per arm)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomly assigned to treatment through dynamic allocation designed to balance assignment for stratification factors"
Allocation concealment (selection bias)	Low risk	Remote registration and randomization through a website or by telephone
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) Efficacy outcomes	Low risk	We found no evidence of attrition bias
Incomplete outcome data (attrition bias) Safety and QoL outcomes	Low risk	We found no evidence of attrition bias
Selective reporting (reporting bias)	Low risk	We found no evidence of reporting bias
Other bias?	Low risk	We found no evidence of other bias

Liu 2015

Methods	Parallel-group RCT, open label, single centre
Participants	People with metastatic CRC who did not respond to first-line therapy with 5FU- or oxaliplatin-based regimen Mean age (years): 62 Males (%): 61
Interventions	Experimental group: panitumumab + bevacizumab + FOLFIRI (n = 65) Panitumumab (blocking monoclonal antibody targeting EGFR): 4 mg/kg, i.v., every 2 weeks Bevacizumab (blocking monoclonal antibody targeting VEGF): 4 mg/kg, i.v., every 2 weeks FOLFIRI: (i.v., every 2 weeks): irinotecan (180 mg/m ²) + 5FU (2800 mg/m ²) + leucovorin (400 mg/m ²)

Liu 2015 (Continued)

Control group: FOLFIRI (n = 77)

FOLFIRI: (i.v., every 2 weeks): irinotecan (180 mg/m²) + 5FU (2800 mg/m²) + leucovorin (400 mg/m²)

Outcomes	OS, PFS, ORR, SAE
Notes	Country: China Quality issue: outcome findings (effect size + confidence intervals) do not appear to coincide with Kaplan-Meier curves findings Dropouts: none reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unreported
Allocation concealment (selection bias)	Unclear risk	Unreported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) Efficacy outcomes	Low risk	We found no evidence of attrition bias
Incomplete outcome data (attrition bias) Safety and QoL outcomes	Low risk	We found no evidence of attrition bias
Selective reporting (reporting bias)	Low risk	We found no evidence of reporting bias
Other bias?	Low risk	We found no evidence of other bias

Masi 2015

Methods	Parallel-group RCT, open label, multicentre, national
Participants	People with metastatic CRC who did not respond to first-line therapy with bevacizumab-containing regimen Mean age (years): 64 Males (%): 60
Interventions	Experimental group: bevacizumab + chemotherapy (FOLFOX or FOLFIRI) (n = 92)

Second-line systemic therapy for metastatic colorectal cancer (Review)

Masi 2015 (Continued)

Bevacizumab (blocking monoclonal antibody targeting VEGF): schedule unreported

Chemotherapy: FOLFOX or FOLFIRI (based on first-line regimen)

Control group: chemotherapy (FOLFOX or FOLFIRI) (n = 92)

Chemotherapy: FOLFOX or FOLFIRI (based on first-line regimen)

Outcomes	OS, PFS, ORR, SAE
Notes	Country: Italy Dropouts: none reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unreported
Allocation concealment (selection bias)	Unclear risk	Unreported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) Efficacy outcomes	Low risk	We found no evidence of attrition bias
Incomplete outcome data (attrition bias) Safety and QoL outcomes	Low risk	We found no evidence of attrition bias
Selective reporting (reporting bias)	Low risk	We found no evidence of reporting bias
Other bias?	Low risk	We found no evidence of other bias

Muro 2010

Methods	Parallel-group RCT, open label, multicentre, national
Participants	People with metastatic CRC who did not respond to first-line therapy without irinotecan Mean age (years): 61 Males (%): 54
Interventions	Experimental group: IRIS (S-1 + irinotecan) (n = 213)

Muro 2010 (Continued)

IRIS: irinotecan (125 mg/m² every 14 days, i.v.) + S-1 (40 mg to 60 mg twice daily for 2 weeks from days 1 to 14 and then a 2-week pause; orally); S-1 is an oral fluoropyrimidine consisting of tegafur, 5-chloro-2,4-dihydropyridine (CDHP) and potassium oxonate, in which tegafur is a prodrug of fluorouracil

Control group: FOLFIRI (n = 213)

FOLFIRI (i.v., every 2 weeks): irinotecan (150 mg/m²) + 5FU (2800 mg/m²) + leucovorin (200 mg/m²)

Outcomes	OS, PFS, ORR, SAE
Notes	Country: Japan
	Trial acronym: FIRIS
	Dropouts: none reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomisation by a computer program, by use of a minimisation method"
Allocation concealment (selection bias)	Low risk	"Investigators provided the patient's details to the central registration centre through a web-based registration system. After an eligibility check, patients were randomly assigned to receive FOLFIRI or IRIS at the central. Assignment of patients was concealed from the investigator"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) Efficacy outcomes	Low risk	We found no evidence of attrition bias
Incomplete outcome data (attrition bias) Safety and QoL outcomes	Low risk	We found no evidence of attrition bias
Selective reporting (reporting bias)	Low risk	We found no evidence of reporting bias
Other bias?	Low risk	We found no evidence of other bias

O'Neil 2014

Methods	Parallel-group RCT (3-arm), open label, multicentre, international
Participants	People with metastatic CRC who did not respond to first-line therapy with irinotecan- or 5FU-containing regimen

O'Neil 2014 (Continued)

Mean age (years): 60

Males (%): 51

Interventions	<p>Experimental group: linifanib low dose + FOLFOX (n = 49)</p> <p>Linifanib low dose (small molecule tyrosine kinase inhibitor targeting VEGFR and PDGFR): 7.5 mg/day, oral</p> <p>Control group: bevacizumab + FOLFOX (n = 49)</p> <p>Bevacizumab (blocking monoclonal antibody targeting VEGF): 10 mg/kg (i.v., every 2 weeks)</p> <p>Co-intervention: FOLFOX (i.v., every 2 weeks): oxaliplatin (85 mg/m²) + 5FU (2800 mg/m²) + leucovorin (400 mg/m²)</p>
Outcomes	OS, PFS, ORR, SAE
Notes	<p>Country: international (Western countries)</p> <p>Dropouts: none reported</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unreported
Allocation concealment (selection bias)	Unclear risk	Unreported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) Efficacy outcomes	Low risk	We found no evidence of attrition bias
Incomplete outcome data (attrition bias) Safety and QoL outcomes	Low risk	We found no evidence of attrition bias
Selective reporting (reporting bias)	Low risk	We found no evidence of reporting bias
Other bias?	Low risk	We found no evidence of other bias

Peeters 2010

Methods	Parallel-group RCT, open label, multicentre, international
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Second-line systemic therapy for metastatic colorectal cancer (Review)

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Peeters 2010 (Continued)

Participants	<p>People with KRAS wild-type metastatic CRC who did not respond to first-line therapy with 5FU-containing regimen (neither irinotecan nor anti-EGFR drugs allowed)</p> <p>Mean age (years): 62</p> <p>Males (%): 61</p>
Interventions	<p>Experimental group: panitumumab + FOLFIRI (n = 303)</p> <p>Panitumumab (blocking monoclonal antibody targeting EGFR): 6 mg/kg (i.v., every 2 weeks)</p> <p>FOLFIRI (i.v., every 2 weeks): irinotecan (180 mg/m²) + 5FU (2800 mg/m²) + leucovorin (400 mg/m²)</p> <p>Control group: FOLFIRI (n = 294)</p> <p>FOLFIRI (i.v., every 2 weeks): irinotecan (180 mg/m²) + 5FU (2800 mg/m²) + leucovorin (400 mg/m²)</p>
Outcomes	OS, PFS, ORR, SAE, QoL
Notes	<p>Country: international (Western countries)</p> <p>Note: the trial originally included also 483 participants with KRAS mutated CRC: since no effect is expected in this population (as the authors acknowledge), only the results from participants with KRAS wild-type CRC are presented here (dropouts: none reported)</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unreported
Allocation concealment (selection bias)	Unclear risk	Unreported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) Efficacy outcomes	Low risk	We found no evidence of attrition bias
Incomplete outcome data (attrition bias) Safety and QoL outcomes	Low risk	We found no evidence of attrition bias
Selective reporting (reporting bias)	Low risk	We found no evidence of reporting bias
Other bias?	Low risk	We found no evidence of other bias

Peeters 2013

Methods	Parallel-group RCT, double blind, multicentre, international
Participants	People with metastatic CRC who did not respond to first-line therapy with FOLFOX regimen Mean age (years): 56 Males (%): 62
Interventions	Experimental group: trebananib + FOLFIRI (n = 95) Trebananib (anti-angiogenic fusion protein targeting the Tie2 receptor): 10 mg/kg, i.v., weekly Control group: placebo + FOLFIRI (n = 49) Co-intervention: FOLFIRI (i.v., every 2 weeks): irinotecan (180 mg/kg) + 5FU (2800 mg/kg) + leucovorin (400 mg/kg)
Outcomes	OS, PFS, ORR, SAE
Notes	Country: international Dropouts: none reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization by interactive voice response system
Allocation concealment (selection bias)	Low risk	Randomization by interactive voice response system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind trial
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unreported
Incomplete outcome data (attrition bias) Efficacy outcomes	Low risk	We found no evidence of attrition bias
Incomplete outcome data (attrition bias) Safety and QoL outcomes	Low risk	We found no evidence of attrition bias
Selective reporting (reporting bias)	Low risk	We found no evidence of reporting bias
Other bias?	Low risk	We found no evidence of other bias

Price 2014

Methods	Parallel-group RCT, open label, multicentre, international
Participants	People with wild-type KRAS metastatic CRC who did not respond to first-line therapy with FOLFOX + bevacizumab Mean age (years): 61 Males (%): 63
Interventions	Experimental group: panitumumab (n = 499) Panitumumab (blocking monoclonal antibody targeting EGFR): 6 mg/kg (i.v., every 2 weeks) Control group: cetuximab (n = 500) Cetuximab (blocking monoclonal antibody targeting EGFR): 400 mg/kg followed by 250 mg/kg (i.v., weekly) Study design: non-inferiority trial
Outcomes	OS, PFS, ORR, SAE, QoL
Notes	Country: international (Western and Eastern countries) Dropouts: 11 (7 in experimental arm; 4 in control arm)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization by interactive voice response system
Allocation concealment (selection bias)	Low risk	Randomization by interactive voice response system
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) Efficacy outcomes	Low risk	We found no evidence of attrition bias
Incomplete outcome data (attrition bias) Safety and QoL outcomes	Low risk	We found no evidence of attrition bias
Selective reporting (reporting bias)	Low risk	We found no evidence of reporting bias
Other bias?	Low risk	We found no evidence of other bias

Rothenberg 2003_folfox

Methods	Parallel-group RCT (3-arm), open label (?), multicentre, international
Participants	People with metastatic CRC who did not respond to first-line therapy with irinotecan-based regimen Mean age (years): 60 Males (%): 58
Interventions	Experimental group: FOLFOX (n = 152) FOLFOX (i.v., every 2 weeks): oxaliplatin (85 mg/m ²) + 5FU (2000 mg/m ²) + leucovorin (400 mg/m ²) Control group: 5FU (n = 151) 5FU (i.v., every 2 weeks): 5FU (2000 mg/m ²) + leucovorin (400 mg/m ²)
Outcomes	PFS, ORR, SAE
Notes	Country: international (North America) Dropouts: 10 (number per arm: unreported)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unreported
Allocation concealment (selection bias)	Low risk	Centralized randomization
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Open-label trial (?)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Open-label trial (?)
Incomplete outcome data (attrition bias) Efficacy outcomes	Low risk	Intention-to-treat efficacy analysis with 459 eligible participants out of 463 randomized participants. Reasons for ineligibility are described for these 4 participants, but not treatment group assignment
Incomplete outcome data (attrition bias) Safety and QoL outcomes	Low risk	Safety analysis performed with 445 participants that received treatment during the study out of 463 randomized participants. Group assignment and reasons for not receiving treatment are not described
Selective reporting (reporting bias)	Unclear risk	OS findings unreported
Other bias?	Low risk	We found no evidence of other bias

Rothenberg 2003_oxa

Methods	Parallel-group RCT (3-arm), open label (?), multicentre, international
Participants	People with metastatic CRC who did not respond to first-line therapy with irinotecan-based regimen Mean age (years): 60 Males (%): 58
Interventions	Experimental group: oxaliplatin (n = 156) Oxaliplatin (i.v., every 2 weeks): 85 mg/m ² Control group: 5FU (n = 151) 5FU (i.v., every 2 weeks): 5FU (2000 mg/m ²) + leucovorin (400 mg/m ²)
Outcomes	PFS, ORR, SAE
Notes	Country: international (North America) Dropouts: 10 (number per arm: unreported)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unreported
Allocation concealment (selection bias)	Low risk	Centralized randomization
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Open-label trial (?)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Open-label trial (?)
Incomplete outcome data (attrition bias) Efficacy outcomes	Low risk	Intention-to-treat efficacy analysis with 459 eligible participants out of 463 randomized participants. Reasons for ineligibility are described for these 4 participants, but not treatment group assignment
Incomplete outcome data (attrition bias) Safety and QoL outcomes	Unclear risk	Safety analysis performed with 445 participants that received treatment during the study out of 463 randomized participants. Group assignment and reasons for not receiving treatment are not described
Selective reporting (reporting bias)	Unclear risk	OS findings unreported
Other bias?	Low risk	We found no evidence of other bias

Rothenberg 2008

Methods	Parallel-group RCT, open label (?), multicentre, international
Participants	People with metastatic CRC who did not respond to first-line therapy with irinotecan-based regimen Mean age (years): 60 Males (%): 62
Interventions	Experimental group: XELOX (n = 313) XELOX (every 3 weeks): oxaliplatin (130 mg/m ² , i.v.) + capecitabine (1000 mg/m ² twice daily for 15 days) Control group: FOLFOX (n = 314) FOLFOX (i.v., every 2 weeks): oxaliplatin (85 mg/m ²) + 5FU (2000 mg/m ²) + leucovorin (400 mg/m ²)
Outcomes	OS, PFS, ORR, SAE
Notes	Country: international (Western countries) Study design: non-inferiority trial Dropouts: 8 (2 in XELOX arm; 6 in FOLFOX arm)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Dynamic randomization was used to assign patients to treatment"
Allocation concealment (selection bias)	Unclear risk	Unreported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Open-label trial (?)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Assessment of tumor response was made by an independent response review committee (IRC) that was blinded to treatment assignment"
Incomplete outcome data (attrition bias) Efficacy outcomes	Low risk	We found no evidence of attrition bias
Incomplete outcome data (attrition bias) Safety and QoL outcomes	Low risk	We found no evidence of attrition bias
Selective reporting (reporting bias)	Low risk	We found no evidence of reporting bias
Other bias?	Low risk	We found no evidence of other bias

Rougier 1998

Methods	Parallel-group RCT, open label (?), multicentre, international
Participants	People with metastatic CRC who did not respond to first-line therapy with 5FU-based regimen Mean age (years): 58 Males (%): 60
Interventions	Experimental group: irinotecan (n = 134) Irinotecan: 350 mg/m ² (i.v., every 3 weeks) Control group: 5FU (n = 133) 5FU (i.v., every 2 weeks): 5FU (2000 mg/m ²) + leucovorin (200 mg/m ²)
Outcomes	OS, PFS, ORR, SAE, QoL
Notes	Country: international (Europe) Dropouts: 10 (5 per arm)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization stratified by centre and performance status was done with a minimisation procedure"
Allocation concealment (selection bias)	Unclear risk	Unreported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Open-label trial (?)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Open-label trial (?)
Incomplete outcome data (attrition bias) Efficacy outcomes	Low risk	"Of 267 patients randomly allocated treatment, 256 received at least one cycle of treatment." The 11 dropout or withdrawn participants were balanced among treatment arms with regard to number and reason of exclusion All efficacy results were presented for 256 participants
Incomplete outcome data (attrition bias) Safety and QoL outcomes	Low risk	Safety results are presented for 256 participants
Selective reporting (reporting bias)	Low risk	We found no evidence of reporting bias
Other bias?	Low risk	"A significant difference in baseline was found for the percentage of patients with hyperleukocytosis, but the mean white-blood-cell counts in both groups were similar."

Rougier 1998 (Continued)

The review authors considered this imbalance as unimportant and not a source of bias

Scheithauer 2002

Methods	Parallel-group RCT, open label (?), multicentre, international
Participants	People with metastatic CRC who did not respond to first-line therapy with 5FU-based regimen Mean age (years): 66 Males (%): 44
Interventions	Experimental group: oxaliplatin + mitomycin (n = 33) Oxaliplatin (i.v.): 85 mg/m ² on days 1 + 15 Control group: irinotecan + mitomycin (n = 31) Irinotecan (i.v.): 120 mg/m ² on days 1 + 15 Co-intervention: mitomycin-C (i.v.): 8 mg/m ² every 4 weeks
Outcomes	ORR, SAE
Notes	Country: Austria Dropouts: none reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were stratified. [...] Balance across strata was attained using the method of Pocock and Simon"
Allocation concealment (selection bias)	Low risk	Centralized randomization
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Open-label trial (?)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Treatment efficacy evaluated by personnel blinded to treatment
Incomplete outcome data (attrition bias) Efficacy outcomes	Low risk	We found no evidence of attrition bias
Incomplete outcome data (attrition bias) Safety and QoL outcomes	Low risk	We found no evidence of attrition bias

Scheithauer 2002 (Continued)

Selective reporting (reporting bias)	Unclear risk	No survival data (hazard ratios or survival curves) reported
Other bias?	Low risk	We found no evidence of other bias

Seymour 2013

Methods	Parallel-group RCT, open label, multicentre, national
Participants	People with KRAS wild-type metastatic CRC who did not respond to first-line therapy with 5FU-based regimen (without oxaliplatin) Mean age (years): 64 Males (%): 69
Interventions	Experimental group: irinotecan + panitumumab (n = 230) Irinotecan: 350 mg/m ² (i.v., every 3 weeks) Panitumumab (blocking monoclonal antibody targeting EGFR): 9 mg/kg (i.v., every 3 weeks) Control group: irinotecan (n = 230) Irinotecan: 350 mg/m ² (i.v., every 3 weeks)
Outcomes	OS, PFS, ORR, SAE, QoL
Notes	Country: UK Dropouts: 12 (6 per arm)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization sequence
Allocation concealment (selection bias)	Low risk	An automated telephonic system was used
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) Efficacy outcomes	Low risk	We found no evidence of attrition bias
Incomplete outcome data (attrition bias)	Low risk	We found no evidence of attrition bias

Second-line systemic therapy for metastatic colorectal cancer (Review)

Seymour 2013 (Continued)

Safety and QoL outcomes

Selective reporting (reporting bias)	Low risk	We found no evidence of reporting bias
Other bias?	Low risk	We found no evidence of other bias

Shoemaker 2004

Methods	Parallel-group RCT, open label, multicentre, international
Participants	People with metastatic CRC who did not respond to first-line therapy with 5FU-based regimen Mean age (years): 61 Males (%): 58
Interventions	Experimental group: irinotecan schedule-1 (n = 41) Irinotecan schedule-1 (single dose): 350 mg/m ² , i.v., every 3 weeks Control group: irinotecan schedule-2 (n = 44) Irinotecan schedule-2 (fractionated): 125 mg/m ² , i.v. weekly for 4 weeks every 6 weeks
Outcomes	ORR, SAE
Notes	Country: international (Europe) Dropouts: 6 (number per arm: unreported)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unreported
Allocation concealment (selection bias)	Low risk	Centralized randomization
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) Efficacy outcomes	Unclear risk	174 participants entered the study. 168 received medication and comprised the intention-to-treat population. No information reported on the 6 participants who did not receive medication, and to which group they belonged to
Incomplete outcome data (attrition bias) Safety and QoL outcomes	Low risk	We found no evidence of attrition bias

Second-line systemic therapy for metastatic colorectal cancer (Review)

Shoemaker 2004 (Continued)

Selective reporting (reporting bias)	Unclear risk	No survival data (hazard ratios or survival curves) reported
Other bias?	Low risk	We found no evidence of other bias

Sobrero 2008

Methods	Parallel-group RCT, open label, multicentre, international
Participants	People with metastatic CRC who did not respond to first-line therapy with FOLFOX regimen Mean age (years): 62 Males (%): 63
Interventions	Experimental group: irinotecan + cetuximab (n = 648) Irinotecan: 350 mg/m ² (i.v., every 3 weeks) Cetuximab (blocking monoclonal antibody targeting EGFR): 400 mg/m ² followed by 250 mg/m ² (i.v., weekly) Control group: irinotecan (n = 650) Irinotecan: 350 mg/m ² (i.v., every 3 weeks)
Outcomes	OS, PFS, ORR, SAE, QoL
Notes	Country: international (Western countries) People were not selected based on the KRAS status (which is today mandatory for cetuximab administration because only KRAS wild-type tumours can respond to the drug) Dropouts: none reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unreported
Allocation concealment (selection bias)	Unclear risk	Unreported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) Efficacy outcomes	Low risk	We found no evidence of attrition bias

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Sobrero 2008 (Continued)

Incomplete outcome data (attrition bias) Safety and QoL outcomes	Low risk	We found no evidence of attrition bias
Selective reporting (reporting bias)	Low risk	We found no evidence of reporting bias
Other bias?	Low risk	We found no evidence of other bias

Taberner 2015

Methods	Parallel-group RCT, double blind, multicentre, international	
Participants	People with metastatic CRC who did not respond to first-line therapy with FOLFOX + bevacizumab regimen Mean age (years): 62 Males (%): 57	
Interventions	Experimental group: ramucirumab + FOLFIRI (n = 536) Ramucirumab (blocking monoclonal antibody targeting VEGFR2): 8 mg/kg (i.v., every 2 weeks) Control group: placebo + FOLFIRI (n = 536) Co-intervention: FOLFIRI (i.v., every 2 weeks): irinotecan (180 mg/m ²) + 5FU (2800 mg/m ²) + leucovorin (400 mg/m ²)	
Outcomes	OS, PFS, ORR, SAE, QoL	
Notes	Country: international (mainly Western countries) Dropouts: 15 (8 in experimental and 7 in control arm)	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerized randomization system
Allocation concealment (selection bias)	Low risk	Randomization by means of a voice response system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind trial
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unreported
Incomplete outcome data (attrition bias)	Low risk	We found no evidence of attrition bias

Taberner 2015 (Continued)

Efficacy outcomes

Incomplete outcome data (attrition bias) Safety and QoL outcomes	Low risk	We found no evidence of attrition bias
Selective reporting (reporting bias)	Low risk	We found no evidence of reporting bias
Other bias?	Low risk	We found no evidence of other bias

Tsavaris 2003

Methods	Parallel-group RCT, open label (?), multicentre, national
Participants	People with metastatic CRC who did not respond to first-line therapy with 5FU Mean age (years): 63 Males (%): 56
Interventions	Experimental group: irinotecan schedule-1 (n = 60) Irinotecan schedule-1 (single dose): 350 mg/m ² (i.v. every 3 weeks) Control group: irinotecan schedule-2 (n=60) Irinotecan schedule-2: (fractionated):175 mg/m ² (i.v. days 1 and 10 every 3 weeks)
Outcomes	OS, PFS, ORR, SAE
Notes	Country: Greece Dropouts: none reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were allocated to the two treatment groups by a simple randomization method (closed envelopes)."
Allocation concealment (selection bias)	Low risk	"Patients were allocated to the two treatment groups by a simple randomization method (closed envelopes)."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Open-label trial (?)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Open-label trial (?)
Incomplete outcome data (attrition bias) Efficacy outcomes	Low risk	We found no evidence of attrition bias

Second-line systemic therapy for metastatic colorectal cancer (Review)

Tsavaris 2003 (Continued)

Incomplete outcome data (attrition bias) Safety and QoL outcomes	Low risk	We found no evidence of attrition bias
Selective reporting (reporting bias)	Low risk	We found no evidence of reporting bias
Other bias?	Low risk	We found no evidence of other bias

Van Cutsem 2011

Methods	Parallel-group RCT, double blind, multicentre, international
Participants	People with metastatic CRC who did not respond to first-line therapy with FOLFIRI Mean age (years): 60 Males (%): 58
Interventions	Experimental group: FOLFOX + vatalanib (n = 426) Vatalanib (also known as PTK787; small molecule tyrosine kinase inhibitor targeting VEGFR): 1250 mg/day, orally Control group: FOLFOX + placebo (n = 429) Co-intervention: FOLFOX (i.v., every 2 weeks): oxaliplatin (85 mg/m ²) + 5FU (2000 mg/m ²) + leucovorin (400 mg/m ²)
Outcomes	OS, PFS, SAE
Notes	Country: international (Western countries) Dropouts: none reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization by means of an interactive voice response system
Allocation concealment (selection bias)	Low risk	Randomization by means of an interactive voice response system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind trial
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unreported
Incomplete outcome data (attrition bias)	Low risk	We found no evidence of attrition bias

Second-line systemic therapy for metastatic colorectal cancer (Review)

Van Cutsem 2011 (Continued)

Efficacy outcomes

Incomplete outcome data (attrition bias) Safety and QoL outcomes	Low risk	We found no evidence of attrition bias
Selective reporting (reporting bias)	Low risk	Response rates unreported
Other bias?	Low risk	We found no evidence of other bias

Van Cutsem 2012

Methods	Parallel-group RCT, double blind, multicentre, international
Participants	People with metastatic CRC who did not respond to first-line therapy with oxaliplatin-based regimen Mean age (years): 60 Males (%): 63
Interventions	Experimental group: FOLFIRI + aflibercept (n = 612) Aflibercept (also known as VEGF trap; blocking fusion protein targeting VEGF): 4 mg/kg (i.v., every 2 weeks) Control group: FOLFIRI + placebo (n = 614) Co-intervention: FOLFIRI (i.v., every 2 weeks): irinotecan (180 mg/m ²) + 5FU (2800 mg/m ²) + leucovorin (400 mg/m ²)
Outcomes	OS, PFS, ORR, SAE
Notes	Country: international (mainly Western countries) Dropouts: none reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization by means of an interactive voice response system
Allocation concealment (selection bias)	Low risk	Randomization by means of an interactive voice response system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind trial
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unreported

Van Cutsem 2012 (Continued)

Incomplete outcome data (attrition bias) Efficacy outcomes	Low risk	We found no evidence of attrition bias
Incomplete outcome data (attrition bias) Safety and QoL outcomes	Low risk	We found no evidence of attrition bias
Selective reporting (reporting bias)	Low risk	We found no evidence of reporting bias
Other bias?	Low risk	We found no evidence of other bias

Viéitez 2011

Methods	Parallel-group RCT, double blind, multicentre, national
Participants	People with metastatic CRC who did not respond to first-line therapy with 5FU-based regimen Mean age (years): 60 Males (%): 58
Interventions	Experimental group: raltitrexed + gefitinib (n = 38) Raltitrexed: 3 mg/m ² (i.v., every 3 weeks) Gefitinib: 250 mg/day (orally) Control group: raltitrexed (n = 38) Raltitrexed: 3 mg/m ² (i.v., every 3 weeks)
Outcomes	OS, PFS, ORR, SAE
Notes	Country: Spain Dropouts: none reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unreported
Allocation concealment (selection bias)	Unclear risk	Unreported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind trial
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unreported

Second-line systemic therapy for metastatic colorectal cancer (Review)

Viéitez 2011 (Continued)

Incomplete outcome data (attrition bias) Efficacy outcomes	Low risk	We found no evidence of attrition bias
Incomplete outcome data (attrition bias) Safety and QoL outcomes	Low risk	We found no evidence of attrition bias
Selective reporting (reporting bias)	Low risk	We found no evidence of reporting bias
Other bias?	Low risk	We found no evidence of other bias

Élez 2015

Methods	Parallel-group RCT (3-arm), open label, multicentre, international	
Participants	People with KRAS wild-type metastatic CRC who did not respond to first-line therapy with oxaliplatin-containing regimen Mean age (years): 60 Males (%): 61	
Interventions	Experimental group: abituzumab low dose + cetuximab + irinotecan (n = 73) Abituzumab (blocking monoclonal antibody targeting integrin- α V): 500 mg (i.v., every 2 weeks) Control group: cetuximab + irinotecan (n = 72) Irinotecan (i.v., every 2 weeks): 180 mg/m ² Co-intervention: cetuximab (blocking monoclonal antibody targeting EGFR): 400 (first dose) and then 250 mg/m ² (i.v., weekly)	
Outcomes	OS, PFS, ORR, SAE	
Notes	Country: international (Western countries) Dropouts: none reported	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unreported
Allocation concealment (selection bias)	Low risk	Centralized randomization
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial

Élez 2015 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) Efficacy outcomes	Low risk	We found no evidence of attrition bias
Incomplete outcome data (attrition bias) Safety and QoL outcomes	Low risk	We found no evidence of attrition bias
Selective reporting (reporting bias)	Low risk	We found no evidence of reporting bias
Other bias?	Low risk	We found no evidence of other bias

5FU: 5-fluorouracil; CRC: colorectal cancer; EGFR: epidermal growth factor receptor; FOLFIRI: 5FU plus leucovorin plus irinotecan; FOLFOX: 5FU plus leucovorin plus oxaliplatin; i.v.: intravenous; n: number of participants; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; QoL: quality of life; RCT: randomized controlled trial; SAE: severe adverse effect; VEGF: vascular endothelial growth factor; XELOX: capecitabine + oxaliplatin.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Amado 2008	Third (or higher)-line treatment (on results described in Van Cutsem 2007)
Aranda 1998	First-line treatment
Chau 2004	Subgroup analysis of Lal 2004 trial
Chibaudel 2016	Non-comparative study
Comella 2000	First-line treatment
Comella 2002	First-line treatment
Cunningham 2004	Third (or higher)-line treatment
Ducreux 2011	Comparison of first- to second-line sequence of regimens
Garrett 2013	Third (or higher)-line treatment
Grothey 2013	Third (or higher)-line treatment
Hendlisz 2010	Hepatic arterial infusion
Hurwitz 2004	First-line treatment
Jonker 2007	Third (or higher)-line treatment
Kabbinavar 2003	First-line treatment
Kemeny 1993	Hepatic arterial infusion

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Study	Reason for exclusion
Koopman 2007	Comparison of first- to second-line sequence of regimens
Labianca 2011	First-line treatment (continuous vs intermittent)
Lacouture 2010	Trial focusing on skin toxicity
Lal 2004	Only participants responding to second-line therapy were randomized to 2 different treatments
Levi 1997	First-line treatment
Lin 2014	Third (or higher)-line treatment
Mandalá 2009	First-line treatment
Maughan 2003	Only participants responding (or stable) after first-line treatment
Mayer 2015	Third (or higher)-line treatment
Muro 2016	No suitable data (abstract only)
Rao 2004	Third (or higher)-line treatment
Reidy 2010	Third (or higher)-line treatment
Rougier 2002	Third (or higher)-line treatment; no survival data
Saltz 2000	First-line treatment
Saltz 2007	Third (or higher)-line treatment
Seymour 2007	Comparison of first- to second-line sequence of regimens
Siu 2013	Third (or higher)-line treatment
Tournigand 2004	Comparison of first- to second-line sequence of regimens
Tournigand 2006	First-line treatment (continuous vs intermittent)
Tsavaris 2007	First-line treatment
Van Cutsem 2005	Comparison of standard dose irinotecan (350 mg/m ²) with a variable dosage (250 or 350 or 500 mg/m ²) according to participant tolerance
Van Cutsem 2007	Third (or higher)-line treatment
Van Cutsem 2012_bis	Randomization of a subgroup of participants (those with low toxicity after cetuximab administration)
Van Cutsem 2014	Third (or higher)-line treatment (most participants)
Yasui 2015	Duplicate of Muro 2010
Yoshino 2012	Third (or higher)-line treatment

DATA AND ANALYSES

Comparison 1. All

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival (OS)_modern chemotherapy (CTX) vs 5-fluorouracil (5FU)	1		Hazard Ratio (Random, 95% CI)	0.69 [0.51, 0.94]
2 Progression-free survival (PFS)_modern CTX vs 5FU	3		Hazard Ratio (Fixed, 95% CI)	0.84 [0.73, 0.96]
2.1 FOLFOX irinotecan (irino)	2		Hazard Ratio (Fixed, 95% CI)	0.59 [0.49, 0.73]
2.2 Oxaliplatin	1		Hazard Ratio (Fixed, 95% CI)	1.11 [0.93, 1.33]
3 Overall response rate (ORR)_modern CTX vs 5FU	3	866	Risk Ratio (IV, Fixed, 95% CI)	2.96 [1.66, 5.27]
4 Serious adverse events (SAE)_modern CTX vs 5FU	3	843	Risk Ratio (IV, Fixed, 95% CI)	1.39 [1.22, 1.58]
5 OS_irino combination (combo)	6		Hazard Ratio (Random, 95% CI)	0.91 [0.79, 1.04]
6 PFS_irino combo	6		Hazard Ratio (Random, 95% CI)	0.68 [0.60, 0.76]
7 ORR_irino combo	6	2577	Risk Ratio (IV, Random, 95% CI)	2.87 [2.10, 3.93]
8 SAE_irino combo	6	2510	Risk Ratio (IV, Random, 95% CI)	1.18 [0.96, 1.45]
9 OS_bevacizumab (beva) combo	4		Hazard Ratio (Random, 95% CI)	0.79 [0.70, 0.88]
10 PFS_beva combo	4		Hazard Ratio (Random, 95% CI)	0.67 [0.60, 0.75]
11 ORR_beva combo	4	1714	Risk Ratio (IV, Random, 95% CI)	1.72 [1.23, 2.43]
12 SAE_beva combo	4	1708	Risk Ratio (IV, Random, 95% CI)	1.07 [0.93, 1.25]
13 OS_FOLFIRI targeted	7		Hazard Ratio (Random, 95% CI)	0.84 [0.77, 0.91]
14 PFS_FOLFIRI targeted	7		Hazard Ratio (Random, 95% CI)	0.78 [0.71, 0.87]
15 ORR_FOLFIRI targeted	7	3192	Risk Ratio (IV, Random, 95% CI)	2.07 [1.31, 3.28]
16 SAE_FOLFIRI targeted	7	3341	Risk Ratio (IV, Random, 95% CI)	1.30 [1.17, 1.45]
17 OS_FOLFOX targeted	2		Hazard Ratio (Fixed, 95% CI)	0.92 [0.82, 1.04]
18 PFS_FOLFOX targeted	2		Hazard Ratio (Fixed, 95% CI)	0.76 [0.66, 0.86]
19 ORR_FOLFOX targeted	1	578	Risk Ratio (IV, Random, 95% CI)	2.64 [1.71, 4.06]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
20 SAE_FOLFOX targeted	2	1414	Risk Ratio (IV, Fixed, 95% CI)	1.20 [1.13, 1.28]
21 OS_irino fraction	2		Hazard Ratio (Fixed, 95% CI)	0.86 [0.71, 1.05]
22 PFS_irino fraction	2		Hazard Ratio (Fixed, 95% CI)	0.90 [0.71, 1.14]
23 ORR_irino fraction	2	205	Risk Ratio (IV, Fixed, 95% CI)	0.83 [0.45, 1.53]
24 SAE_irino fraction	3	489	Risk Ratio (IV, Fixed, 95% CI)	0.97 [0.87, 1.10]
25 OS_FOLFIRI + beva vs other targeted	2		Hazard Ratio (Fixed, 95% CI)	1.15 [0.86, 1.53]
26 PFS_FOLFIRI + beva vs other targeted	2		Hazard Ratio (Fixed, 95% CI)	1.10 [0.81, 1.50]
27 ORR_FOLFIRI + beva vs other targeted	2	267	Risk Ratio (IV, Fixed, 95% CI)	1.43 [0.94, 2.19]
28 SAE_FOLFIRI + beva vs other targeted	2	279	Risk Ratio (IV, Fixed, 95% CI)	1.53 [1.10, 2.11]
29 OS_FOLFOX + beva vs other targeted	2		Hazard Ratio (Fixed, 95% CI)	1.14 [0.81, 1.61]
30 PFS_FOLFOX + beva vs other targeted	2		Hazard Ratio (Fixed, 95% CI)	1.26 [0.83, 1.91]
31 ORR_FOLFOX + beva vs other targeted	2	170	Risk Ratio (IV, Fixed, 95% CI)	0.77 [0.46, 1.29]
32 SAE_FOLFOX + beva vs other targeted	2	169	Risk Ratio (IV, Fixed, 95% CI)	1.27 [1.03, 1.55]

Analysis 1.1. Comparison 1 All, Outcome 1 Overall survival (OS)_modern chemotherapy (CTX) vs 5-fluorouracil (5FU).

Study or subgroup	Modern CTX N	5FU N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Random, 95% CI	Weight	Hazard Ratio IV, Random, 95% CI
Rougier 1998	0	0	-0.4 (0.157)		100%	0.69[0.51,0.94]
Total (95% CI)					100%	0.69[0.51,0.94]
Heterogeneity: Not applicable						
Test for overall effect: Z=2.38(P=0.02)						
<div> <div>Favors modern CTX</div> <div>0.010.1110100</div> <div>Favours 5FU</div> </div>						

Analysis 1.2. Comparison 1 All, Outcome 2 Progression-free survival (PFS)_modern CTX vs 5FU. **Analysis 1.3. Comparison 1 All, Outcome 3 Overall response rate (ORR)_modern CTX vs 5FU.** **Analysis 1.4. Comparison 1 All, Outcome 4 Serious adverse events (SAE)_modern CTX vs 5FU.**

Analysis 1.5. Comparison 1 All, Outcome 5 OS_irino combination (combo).

Analysis 1.6. Comparison 1 All, Outcome 6 PFS_irino combo.

Analysis 1.7. Comparison 1 All, Outcome 7 ORR_irino combo.

Analysis 1.8. Comparison 1 All, Outcome 8 SAE_irino combo.

Analysis 1.9. Comparison 1 All, Outcome 9 OS_bevacizumab (beva) combo.

Analysis 1.10. Comparison 1 All, Outcome 10 PFS_beва combo.

Analysis 1.11. Comparison 1 All, Outcome 11 ORR_beва combo.

Analysis 1.12. Comparison 1 All, Outcome 12 SAE_beва combo.

Analysis 1.13. Comparison 1 All, Outcome 13 OS_FOLFIRI targeted.

Analysis 1.14. Comparison 1 All, Outcome 14 PFS_FOLFIRI targeted.

Analysis 1.15. Comparison 1 All, Outcome 15 ORR_FOLFIRI targeted.

Analysis 1.16. Comparison 1 All, Outcome 16 SAE_FOLFIRI targeted.

Analysis 1.17. Comparison 1 All, Outcome 17 OS_FOLFOX targeted.

Analysis 1.18. Comparison 1 All, Outcome 18 PFS_FOLFOX targeted.

Analysis 1.19. Comparison 1 All, Outcome 19 ORR_FOLFOX targeted.

Analysis 1.20. Comparison 1 All, Outcome 20 SAE_FOLFOX targeted.

Analysis 1.21. Comparison 1 All, Outcome 21 OS_irino fraction.

Analysis 1.22. Comparison 1 All, Outcome 22 PFS_irino fraction.

Analysis 1.23. Comparison 1 All, Outcome 23 ORR_irino fraction.

Analysis 1.24. Comparison 1 All, Outcome 24 SAE_irino fraction.

Analysis 1.25. Comparison 1 All, Outcome 25 OS_FOLFIRI + beva vs other targeted.

Analysis 1.26. Comparison 1 All, Outcome 26 PFS_FOLFIRI + beva vs other targeted.

Analysis 1.27. Comparison 1 All, Outcome 27 ORR_FOLFIRI + beva vs other targeted.

Analysis 1.28. Comparison 1 All, Outcome 28 SAE_FOLFIRI + beva vs other targeted.

Analysis 1.29. Comparison 1 All, Outcome 29 OS_FOLFOX + beva vs other targeted.

Analysis 1.30. Comparison 1 All, Outcome 30 PFS_FOLFOX + beva vs other targeted.

Analysis 1.31. Comparison 1 All, Outcome 31 ORR_FOLFOX + beva vs other targeted.

Analysis 1.32. Comparison 1 All, Outcome 32 SAE_FOLFOX + beva vs other targeted.

ADDITIONAL TABLES

Table 1. List of abbreviations

Acronym	Full name
5FU	5-fluorouracil
Ang1	Angiopoietin-1
Ang2	Angiopoietin-2
CRC	Colorectal cancer
CTX	Chemotherapy
DR5	Death receptor 5
EGFR	Epithelial growth factor receptor
FOLFIRI	Fluorouracil + irinotecan + leucovorin
FOLFOX	Fluorouracil + oxaliplatin + leucovorin
HR	Hazard ratio
IGF1R	Insulin-like growth factor 1 receptor
IRIS	S-1 + irinotecan
i.v.	Intravenous
KRAS	Name of a gene whose product acts downstream of EGFR
ORR	Overall response rate
OS	Overall survival
PDGFR	Platelet derived growth factor receptor
PFS	Progression-free survival

Table 1. List of abbreviations *(Continued)*

QoL	Quality of life
RCT	Randomized controlled trial
RR	Risk ratio
SAE	Severe adverse event
VEGF	Vascular endothelium growth factor
VEGFR	VEGF receptor
XELOX	Capecitabine + oxaliplatin

Table 2. Main features of anticancer agents

Name (abbreviation)	Class	Mechanism of action	Route of administration
5-fluorouracil (5FU)	Chemotherapy agent	Antimetabolite (pyrimidine analogue) inhibiting RNA synthesis and the enzyme thymidylate synthase (which converts dUMP to dTMP which in turn is needed for the synthesis of DNA)	Intravenous
Oxaliplatin	Chemotherapy agent	Alkylating agent binding covalently to DNA, which in turn inhibits DNA replication or causes DNA breaks	Intravenous
Irinotecan	Chemotherapy agent	Inhibits the enzyme topoisomerase-I, which is involved in DNA replication or transcription	Intravenous
Mitomycin-C	Chemotherapy agent	Alkylating agent binding covalently to DNA, which in turn inhibits DNA replication or causes DNA breaks	Intravenous
Raltitrexed	Chemotherapy agent	Antimetabolite that inhibits the enzyme thymidylate synthase (which converts dUMP to dTMP which in turn is needed for the synthesis of DNA)	Intravenous
Capecitabine	Chemotherapy agent	It is a prodrug of 5FU: one within the cells, it is transformed into the active drug	Oral
S-1	Chemotherapy agent	Antimetabolite (pyrimidine analogue) inhibiting RNA synthesis and the enzyme thymidylate synthase (which converts dUMP to dTMP which in turn is needed for the synthesis of DNA)	Oral
Bevacizumab	Targeted drug	Monoclonal antibody blocking VEGF (a ligand of VEGFR, a receptor involved in angiogenesis)	Intravenous
Cetuximab	Targeted drug	Monoclonal antibody blocking EGFR (a receptor involved in cell proliferation); best works against KRAS wild-type tumours	Intravenous
Panituzumab	Targeted drug	Monoclonal antibody blocking EGFR (a receptor involved in cell proliferation); best works against KRAS wild-type tumours	Intravenous
Conatumumab	Targeted drug	Monoclonal antibody activating DR5 (a receptor involved in cell apoptosis)	Intravenous

Table 2. Main features of anticancer agents (Continued)

Ganitumab	Targeted drug	Monoclonal antibody blocking IGF1R (a receptor involved in cell proliferation)	Intravenous
Ramucirumab	Targeted drug	Monoclonal antibody blocking VEGFR (a receptor involved in angiogenesis)	Intravenous
Abituzumab	Targeted drug	Monoclonal antibody blocking integrin- α v (a molecule involved in cell adhesion)	Intravenous
Trebananib	Targeted drug	Recombinant protein blocking Ang1 and Ang2 (ligands of Tie2, a receptor involved in angiogenesis)	Intravenous
Aflibercept	Targeted drug	Recombinant protein blocking VEGF (a ligand of VEGFR, a receptor involved in angiogenesis)	Intravenous
Vatalanib	Targeted drug	Small molecule inhibitor of multiple tyrosine kinases such as VEGFR (a receptor involved in angiogenesis) and PDGFR (a receptor involved in cell proliferation)	Oral
Gefitinib	Targeted drug	Small molecule inhibitor of tyrosine kinase EGFR (a receptor involved in cell proliferation); best works against EGFR mutated/KRAS wild-type tumours	Oral

Ang1: angiopoietin-1, Ang2: angiopoietin-2; DR5: death receptor 5; dTMP: deoxythymidine monophosphate; dUMP: deoxyuridine monophosphate; IGF1R: insulin-like growth factor 1 receptor; PDGFR: platelet-derived growth factor receptor; RNA: ribonucleic acid; VEGF: vascular endothelial growth factor; VEGFR: VEGF receptor.

Table 3. Summary of studies' results

Study	Comparison	OS (HR, 95% CI)	PFS (HR, 95% CI)	ORR (RR, 95% CI)	SAE (RR, 95% CI)
Bendell 2013_folfiri	Axitinib + FOLFIRI vs bevacizumab + FOLFIRI	1.36 (0.82 to 2.26)	1.27 (0.77 to 2.09)	1.11 (0.55 to 2.22)	2.09 (1.04 to 4.23)
Bendell 2013_folfox	Axitinib + FOLFOX vs bevacizumab + FOLFOX	0.69 (0.37 to 1.29)	1.04 (0.55 to 1.97)	0.97 (0.38 to 2.49)	1.94 (0.74 to 5.12)
Bennouna 2013	Bevacizumab + chemotherapy vs chemotherapy	0.81 (0.69 to 0.95)	0.68 (0.58 to 0.80)	1.38 (0.74 to 2.59)	1.11 (0.99 to 1.24)
Cao 2015	Bevacizumab + FOLFIRI vs FOLFIRI	0.78 (0.55 to 1.11)	0.71 (0.52 to 0.97)	1.67 (1.08 to 2.58)	0.84 (0.67 to 1.05)
Clarke 2011	FOLFIRI vs irinotecan	0.72 (0.46 to 1.13)	0.81 (0.52 to 1.26)	1.02 (0.32 to 3.28)	0.98 (0.63 to 1.52)
Cohn 2013_conat	Conatumumab + FOLFIRI vs FOLFIRI	0.89 (0.54 to 1.47)	0.69 (0.41 to 1.16)	7.14 (0.91 to 55.96)	1.53 (1.09 to 2.15)
Cohn 2013_ganit	Ganitumab + FOLFIRI vs FOLFIRI	1.27 (0.76 to 2.12)	1.01 (0.61 to 1.67)	4.00 (0.46 to 34.59)	1.17 (0.80 to 1.71)
Cunningham 1998	Irinotecan vs best supportive care	0.58 (0.43 to 0.80)	Not available	Not available	1.19 (1.01 to 1.40)

Table 3. Summary of studies' results (Continued)

Élez 2015	Abituzumab + cetuximab + irinotecan vs cetuximab + irinotecan	0.83 (0.54 to 1.28)	1.13 (0.78 to 1.64)	1.04 (0.61 to 1.78)	0.91 (0.60 to 1.38)
Fuchs 2003	Irinotecan schedule 1 vs irinotecan schedule 2	0.99 (0.73 to 1.34)	1.06 (0.76 to 1.47)	Not available	0.97 (0.81 to 1.17)
Giantonio 2007	Bevacizumab + FOLFOX vs FOLFOX	0.75 (0.60 to 0.94)	0.61 (0.48 to 0.78)	2.64 (1.71 to 4.06)	1.23 (1.10 to 1.38)
Gibbs 2011	Hyaluronan + irinotecan vs irinotecan	0.93 (0.49 to 1.76)	0.56 (0.33 to 0.95)	3.00 (0.33 to 26.99)	1.38 (0.87 to 2.20)
Graeven 2007	FOLFIRI vs irinotecan	1.31 (0.68 to 2.52)	0.87 (0.48 to 1.58)	0.96 (0.21 to 4.37)	0.34 (0.18 to 0.62)
Haller 2008	Oxaliplatin + irinotecan vs irinotecan	0.78 (0.67 to 0.90)	0.60 (0.55 to 0.66)	2.98 (1.91 to 4.64)	1.22 (1.09 to 1.37)
Hecht 2015	Panitumumab + FOLFIRI vs bevacizumab + FOLFIRI	1.06 (0.75 to 1.50)	1.01 (0.68 to 1.50)	1.67 (0.98 to 2.85)	1.40 (0.97 to 2.02)
Iwamoto 2015	Bevacizumab schedule 1 + FOLFIRI vs bevacizumab schedule 2 + FOLFIRI	1.08 (0.75 to 1.56)	0.95 (0.75 to 1.20)	1.04 (0.58 to 1.86)	1.07 (0.92 to 1.26)
Kim 2009	FOLFOX vs irinotecan	0.92 (0.79 to 1.07)	0.72 (0.60 to 0.88)	1.80 (1.26 to 2.56)	1.13 (0.99 to 1.29)
Liu 2015	Panitumumab + bevacizumab + FOLFIRI vs FOLFIRI	0.67 (0.47 to 0.96)	0.58 (0.35 to 0.95)	1.66 (1.03 to 2.67)	1.60 (1.30 to 1.99)
Masi 2015	Bevacizumab + chemotherapy vs chemotherapy	0.77 (0.56 to 1.06)	0.70 (0.52 to 0.94)	1.24 (0.70 to 2.19)	1.05 (0.75 to 1.47)
Muro 2010	IRIS vs FOLFIRI	0.91 (0.71 to 1.16)	1.08 (0.86 to 1.34)	1.13 (0.72 to 1.77)	1.00 (0.84 to 1.18)
O'Neil 2014	Linifanib + FOLFOX vs bevacizumab + FOLFOX	1.42 (0.94 to 2.15)	1.45 (0.83 to 2.53)	0.69 (0.37 to 1.29)	1.24 (1.01 to 1.53)
Peeters 2010	Panitumumab + FOLFIRI vs FOLFIRI	0.85 (0.70 to 1.03)	0.73 (0.59 to 0.90)	3.44 (2.36 to 5.02)	1.40 (1.23 to 1.60)
Peeters 2013	Trebananib + FOLFIRI vs FOLFIRI	0.90 (0.53 to 1.53)	1.23 (0.81 to 1.87)	13.02 (0.79 to 215.40)	0.94 (0.73 to 1.22)
Price 2014	Panitumumab vs cetuximab	0.97 (0.84 to 1.12)	1.00 (0.88 to 1.14)	1.11 (0.87 to 1.42)	1.06 (0.93 to 1.20)
Rothenberg 2003_folfox	FOLFOX vs 5FU	Not available	0.55 (0.43 to 0.70)	5.22 (1.83 to 14.83)	1.78 (1.43 to 2.22)
Rothenberg 2003_oxa	Oxaliplatin vs 5FU	Not available	1.11 (0.93 to 1.33)	1.29 (0.35 to 4.72)	1.14 (0.88 to 1.48)
Rothenberg 2008	XELOX vs FOLFOX	1.02 (0.86 to 1.22)	0.97 (0.83 to 1.13)	1.11 (0.60 to 2.07)	0.75 (0.68 to 0.82)

Table 3. Summary of studies' results (Continued)

Rougier 1998	Irinotecan vs 5FU	0.69 (0.51 to 0.94)	0.69 (0.49 to 0.97)	2.90 (1.27 to 6.62)	1.28 (1.05 to 1.55)
Scheithauer 2002	Mitomycin + oxaliplatin vs mitomycin + irinotecan	Not available	Not available	1.32 (0.47 to 3.71)	1.62 (0.93 to 2.83)
Seymour 2013	Panitumumab + irinotecan vs irinotecan	1.01 (0.83 to 1.23)	0.78 (0.64 to 0.95)	2.93 (1.97 to 4.35)	1.51 (1.24 to 1.84)
Shoemaker 2004	Single-dose irinotecan vs fractionated irinotecan	Not available	Not available	0.62 (0.11 to 3.53)	0.97 (0.72 to 1.30)
Sobrero 2008	Cetuximab + irinotecan vs irinotecan	0.98 (0.85 to 1.11)	0.69 (0.62 to 0.78)	3.94 (2.62 to 5.92)	1.42 (1.28 to 1.59)
Tabernero 2015	Ramucirumab + FOLFIRI vs FOLFIRI	0.84 (0.73 to 0.97)	0.79 (0.70 to 0.90)	1.07 (0.79 to 1.47)	1.15 (0.97 to 1.36)
Tsavaris 2003	Single-dose irinotecan vs fractionated irinotecan	0.78 (0.60 to 1.01)	0.75 (0.53 to 1.06)	0.87 (0.45 to 1.66)	0.98 (0.82 to 1.17)
Van Cutsem 2011	Vatalanib + FOLFOX vs FOLFOX	1.00 (0.87 to 1.15)	0.83 (0.71 to 0.97)	Not available	1.19 (1.10 to 1.28)
Van Cutsem 2012	Aflibercept + FOLFIRI vs FOLFIRI	0.82 (0.71 to 0.94)	0.76 (0.66 to 0.87)	1.78 (1.32 to 2.39)	1.34 (1.24 to 1.43)
Viéitez 2011	Gefitinib + raltitrexed vs raltitrexed	0.99 (0.55 to 1.78)	1.23 (0.81 to 1.87)	1.00 (0.15 to 6.74)	1.67 (0.43 to 6.49)

CI: confidence interval; FOLFIRI: fluorouracil + irinotecan + leucovorin; FOLFOX: fluorouracil + oxaliplatin + leucovorin; HR: hazard ratio; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; RR: risk ratio; SAE: severe adverse effects.

APPENDICES

Appendix 1. CENTRAL search strategy

CENTRAL search strategy 2016, Issue 4

#1 MeSH descriptor: [Colorectal Neoplasms] explode all trees

#2 (colorect* or colon* or rect* or anal* or anus* or intestin* or bowel*) near/3 (carcinom* or neoplas* or adenocarcinom* or cancer* or tumor* or tumour* or sarcom*):ti,ab,kw

#3 #1 or #2

#4 MeSH descriptor: [Chemotherapy, Adjuvant] explode all trees

#5 MeSH descriptor: [Salvage Therapy] explode all trees

#6 MeSH descriptor: [Drug Resistance] explode all trees

#7 chemotherap* or salvage therapy or drug resistance:ti,ab,kw

#8 MeSH descriptor: [Antibodies, Monoclonal, Humanized] explode all trees

#9 MeSH descriptor: [Receptor, Epidermal Growth Factor] explode all trees

#10 MeSH descriptor: [Receptors, Vascular Endothelial Growth Factor] explode all trees

Second-line systemic therapy for metastatic colorectal cancer (Review)

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#11 MeSH descriptor: [Protein Kinase Inhibitors] explode all trees

#12 MeSH descriptor: [Antineoplastic Combined Chemotherapy Protocols] explode all trees

#13 (vascular endothelial growth factor or VEGF or VEGFR or FGFR or fibroblast growth factor or target* therap* or antibod* or tyrosine kinase receptor inhibitor or oxaliplatin or cetuximab or irinotecan or camptothecin or protein kinase inhibitor or capecitabine or fluorouracil or leucovorin or conatumumab or panituzumab or bevacizumab or raltitrexed or aflibercept or sorafenib or cediranib or axitinib)

#14 #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13

#15 (second line or second-line)

#16 #14 and #15

#17 ((resistant or refractory) adj5 (cisplatin or carboplatin or anthracycline or doxorubicin or platinum))

#18 #16 or #17

#19 #3 and #18

Appendix 2. MEDLINE search strategy

Ovid MEDLINE 1950 to 18 May 2016

1. exp Colorectal Neoplasms/

2. ((colorect* or colon* or rect* or anal* or anus* or intestin* or bowel*) adj3 (carcinom* or neoplas* or adenocarcinom* or cancer* or tumor* or tumour* or sarcom*)).mp.

3. 1 or 2

4. exp Salvage Therapy/

5. exp Drug Resistance/

6. (chemotherap* or salvage therapy or drug resistance).mp.

7. Antibodies/ or exp Antibodies, Monoclonal, Humanized/

8. exp Epidermal Growth Factor/

9. exp Vascular Endothelial Growth Factors/

10. exp Protein Kinase Inhibitors/

11. exp Antineoplastic Combined Chemotherapy Protocols/

12. (vascular endothelial growth factor or VEGF or VEGFR or FGFR or fibroblast growth factor or epidermal growth factor or EGR or EGFR or ErbB-1 or HER1).mp.

13. (target* therap* or antibod* or tyrosine kinase receptor inhibitor or oxaliplatin or cetuximab or irinotecan or camptothecin or protein kinase inhibitor or capecitabine or fluorouracil or leucovorin or conatumumab or panituzumab or bevacizumab or raltitrexed or aflibercept or sorafenib or cediranib or axitinib).mp.

14. or/4-13

15. (second line or second-line).mp.

16. 14 and 15

17. ((resistant or refractory) adj5 (cisplatin or carboplatin or anthracycline or doxorubicin or platinum)).mp.

18. 16 or 17

19. 3 and 18

20. randomized controlled trial.pt.

Second-line systemic therapy for metastatic colorectal cancer (Review)

21. controlled clinical trial.pt.
22. randomized.ab.
23. placebo.ab.
24. clinical trials as topic.sh.
25. randomly.ab.
26. trial.ti.
27. 20 or 21 or 22 or 23 or 24 or 26
28. exp animals/ not humans.sh.
29. 27 not 28
30. 19 and 29

Appendix 3. MEDLINE In-process & Other Non-Indexed Citations search strategy

Ovid MEDLINE In-process & Other Non-indexed Citations 1946 to 18 May 2016

1. exp Colorectal Neoplasms/
2. ((colorect* or colon* or rect* or anal* or anus* or intestin* or bowel*) adj3 (carcinom* or neoplas* or adenocarcinom* or cancer* or tumor* or tumour* or sarcom*)).mp.
3. 1 or 2
4. exp Salvage Therapy/
5. exp Drug Resistance/
6. (chemotherap* or salvage therapy or drug resistance).mp.
7. Antibodies/ or exp Antibodies, Monoclonal, Humanized/
8. exp Epidermal Growth Factor/
9. exp Vascular Endothelial Growth Factors/
10. exp Protein Kinase Inhibitors/
11. exp Antineoplastic Combined Chemotherapy Protocols/
12. (vascular endothelial growth factor or VEGF or VEGFR or FGFR or fibroblast growth factor or epidermal growth factor or EGR or EGFR or ErbB-1 or HER1).mp.
13. (target* therap* or antibod* or tyrosine kinase receptor inhibitor or oxaliplatin or cetuximab or irinotecan or camptothecin or protein kinase inhibitor or capecitabine or fluorouracil or leucovorin or conatumumab or panituzumab or bevacizumab or raltitrexed or aflibercept or sorafenib or cediranib or axitinib).mp.
14. or/4-13
15. (second line or second-line).mp.
16. 14 and 15
17. ((resistant or refractory) adj5 (cisplatin or carboplatin or anthracycline or doxorubicin or platinum)).mp.
18. 16 or 17
19. 3 and 18
20. random* or placebo or trial or blind* or meta-analys* or meta analys*
21. 19 and 20

Appendix 4. EMBASE search strategy

Ovid EMBASE 1974 to 18 May 2016

1. exp colon tumor/
2. exp rectum tumor/
3. ((colorect* or colon* or rect* or anal* or anus* or intestin* or bowel*) adj3 (carcinom* or neoplas* or adenocarcinom* or cancer* or tumor* or tumour* or sarcom*)).mp.
4. 1 or 2 or 3
5. exp CHEMOTHERAPY/
6. exp salvage therapy/
7. exp drug resistance/
8. (chemotherap* or salvage therapy or drug resistance).mp.
9. exp monoclonal antibody/ or antibody/
10. exp epidermal growth factor/
11. (vascular endothelial growth factor or VEGF or VEGFR or FGFR or fibroblast growth factor or epidermal growth factor or EGR or EGFR or ErbB-1 or HER1).mp.
12. exp protein kinase inhibitor/
13. exp antineoplastic agent/
14. (target* therap* or antibod* or tyrosine kinase receptor inhibitor or oxaliplatin or cetuximab or irinotecan or camptothecin or protein kinase inhibitor or capecitabine or fluorouracil or leucovorin or conatumumab or panituzumab or bevacizumab or raltitrexed or aflibercept or sorafenib or cediranib or axitinib).mp.
15. or/5-14
16. (second line or second-line).mp.
17. 15 and 16
18. ((resistant or refractory) adj5 (cisplatin or carboplatin or anthracycline or doxorubicin or platinum)).mp.
19. 17 or 18
20. 4 and 19
21. CROSSOVER PROCEDURE.sh.
22. DOUBLE-BLIND PROCEDURE.sh.
23. SINGLE-BLIND PROCEDURE.sh.
24. (crossover* or cross over*).ti,ab.
25. placebo*.ti,ab.
26. (doubl* adj blind*).ti,ab.
27. allocat*.ti,ab.
28. trial.ti.
29. RANDOMIZED CONTROLLED TRIAL.sh.
30. random*.ti,ab.
31. 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30

32. (exp animal/ or exp invertebrate/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans or man or men or women).ti.)

33. 31 not 32

34. 20 and 33

Appendix 5. Criteria for judging risk of bias in the 'Risk of bias' assessment tool

Random sequence generation

Selection bias (biased allocation to interventions) due to inadequate generation of a randomized sequence.

Criteria for a judgement of 'low risk' of bias.	<p>The investigators describe a random component in the sequence generation process such as:</p> <ul style="list-style-type: none"> referring to a random number table; using a computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization*. <p>*Minimization may be implemented without a random element, and this is considered to be equivalent to being random.</p>
Criteria for the judgement of 'high risk' of bias.	<p>The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example:</p> <ul style="list-style-type: none"> sequence generated by odd or even date of birth; sequence generated by some rule based on date (or day) of admission; sequence generated by some rule based on hospital or clinic record number; Other non-random approaches happen much less frequently than the systematic approaches mentioned above and tend to be obvious. They usually involve judgement or some method of non-random categorization of participants, for example: allocation by judgement of the clinician; allocation by preference of the participant; allocation based on the results of a laboratory test or a series of tests; allocation by availability of the intervention.
Criteria for the judgement of 'unclear risk' of bias.	Insufficient information about the sequence generation process to permit judgement of 'low risk' or 'high risk'.

Allocation concealment

Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.

Criteria for a judgement of 'low risk' of bias.	<p>Participants and investigators enrolling participants could not foresee assignment because 1 of the following, or an equivalent method, was used to conceal allocation:</p> <ul style="list-style-type: none"> central allocation (including telephone, web-based and pharmacy-controlled randomization); sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes.
Criteria for the judgement of 'high risk' of bias.	<p>Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on:</p> <ul style="list-style-type: none"> using an open random allocation schedule (e.g. a list of random numbers);

(Continued)

- assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or nonopaque or not sequentially numbered);
- alternation or rotation;
- date of birth;
- case record number;
- any other explicitly unconcealed procedure.

Criteria for the judgement of 'unclear risk' of bias.

Insufficient information to permit judgement of 'low risk' or 'high risk'. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement - for example, if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.

Blinding of participants and personnel

Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.

Criteria for a judgement of 'low risk' of bias.

Any 1 of the following:

- no blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding;
- blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.

Criteria for the judgement of 'high risk' of bias.

Any 1 of the following:

- no blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding;
- blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.

Criteria for the judgement of 'unclear risk' of bias.

Any 1 of the following:

- insufficient information to permit judgement of 'low risk' or 'high risk';
- the study did not address this outcome.

Blinding of outcome assessment

Detection bias due to knowledge of the allocated interventions by outcome assessors.

Criteria for a judgement of 'low risk' of bias.

Any 1 of the following:

- no blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding;
- blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.

Criteria for the judgement of 'high risk' of bias.

Any 1 of the following:

- no blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding;
- blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.

Criteria for the judgement of 'unclear risk' of bias.

Any 1 of the following:

- insufficient information to permit judgement of 'low risk' or 'high risk';
- the study did not address this outcome.

Incomplete outcome data

Attrition bias due to amount, nature or handling of incomplete outcome data.

(Continued)

Criteria for a judgement of 'low risk' of bias.	<p>Any 1 of the following:</p> <ul style="list-style-type: none"> no missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods.
Criteria for the judgement of 'high risk' of bias.	<p>Any 1 of the following:</p> <ul style="list-style-type: none"> reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomization; potentially inappropriate application of simple imputation.
Criteria for the judgement of 'unclear risk' of bias.	<p>Any 1 of the following:</p> <ul style="list-style-type: none"> insufficient reporting of attrition/exclusions to permit judgement of 'low risk' or 'high risk' (e.g. number randomized not stated, no reasons for missing data provided); the study did not address this outcome.

Selective reporting

Reporting bias due to selective outcome reporting.

Criteria for a judgement of 'low risk' of bias.	<p>Any of the following:</p> <ul style="list-style-type: none"> the study protocol is available and all of the study's prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were prespecified (convincing text of this nature may be uncommon).
Criteria for the judgement of 'high risk' of bias.	<p>Any 1 of the following:</p> <ul style="list-style-type: none"> not all of the study's prespecified primary outcomes have been reported; 1 or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not prespecified; 1 or more reported primary outcomes were not prespecified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); 1 or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report does not include results for a key outcome that would be expected to have been reported for such a study.

(Continued)

Criteria for the judgement of 'unclear risk' of bias.	Insufficient information to permit judgement of 'low risk' or 'high risk'. It is likely that the majority of studies will fall into this category.
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Other bias

Bias due to problems not covered elsewhere in the table.

Criteria for a judgement of 'low risk' of bias.	The study appears to be free of other sources of bias.
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Criteria for the judgement of 'high risk' of bias.	<p>There is at least 1 important risk of bias. For example, the study:</p> <ul style="list-style-type: none"> • had a potential source of bias related to the specific study design used; or • has been claimed to have been fraudulent; or • had some other problem.
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Criteria for the judgement of 'unclear risk' of bias.	<p>There may be a risk of bias, but there is either:</p> <ul style="list-style-type: none"> • insufficient information to assess whether an important risk of bias exists; or • insufficient rationale or evidence that an identified problem will introduce bias.
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WHAT'S NEW

Date	Event	Description
18 May 2016	New citation required and conclusions have changed	New search performed and 27 new studies incorporated in the review.

HISTORY

Protocol first published: Issue 1, 2008

Review first published: Issue 2, 2009

Date	Event	Description
5 December 2008	Amended	Substantive amendment: review finalised
14 May 2008	Amended	Converted to new review format.
16 September 2007	New citation required and major changes	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Previous version: MR wrote the draft protocol; IS designed the search strategy; all authors helped design the review and write the review.

Current version: SM and ZB updated and expanded (including targeted therapies) the previous version.

DECLARATIONS OF INTEREST

None of the authors have any known conflicts of interest to declare.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Instituto de Salud Carlos III. PI04/2309, Spain.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The updated version included targeted therapies (which were excluded in the previous version of the protocol and review): overall, this led to the inclusion of 34 trials instead of the seven trials included in the previous version.

Future updates of this review will include targeted therapies.

INDEX TERMS

Medical Subject Headings (MeSH)

Antineoplastic Agents [*therapeutic use]; Antineoplastic Combined Chemotherapy Protocols [administration & dosage] [*therapeutic use]; Bevacizumab [administration & dosage]; Camptothecin [administration & dosage] [analogs & derivatives] [therapeutic use]; Colorectal Neoplasms [*drug therapy] [mortality] [pathology]; Fluorouracil [administration & dosage]; Irinotecan; Leucovorin [administration & dosage]; Organoplatinum Compounds [administration & dosage]; Randomized Controlled Trials as Topic; Survival Rate

MeSH check words

Humans