Q11: WHAT IS THE CURRENT STANDARD FIRST LINE TREATMENT FOR METASTATIC INOPERABLE COLORECTAL CANCER?

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SCIENTIFIC REPORT

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1 INTRODUCTION

1.1 PICO

What is the current standard first line treatment for metastatic inoperable colorectal cancer?	
P (patient)	Metastatic colorectal cancer (resectable solitary liver or lung metastases excluded)
I (Intervention)	Any chemotherapy and/or targeted therapy
C (comparison)	Fluoropyrimidin-based chemotherapy + oxaliplatin or irinotecan
O (outcome)	PFS, OS

1.2 Summary Guidelines IKNL 2008 – NICE 2011 – SIGN 2011

Table 1 –First-line systemic treatment of metastatic colorectal cancer: summary of guidelines

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
IKNL 2008[1]	02-2006	In asymptomatic patients with irresectable, measurable disease, systemic therapy should not be delayed	3 RCTs	
		Combined fluoropyrimidine-based chemotherapy and bevacizumab is the standard first-line treatment for patients in good general condition (WHO PS 0-1) without contraindications for the use of bevacizumab	3 RCTs	
		Oral fluoropyrimines are preferred above IV 5-FU/LV as side effects are less common and oral administration is also safe in combination therapy	4 RCTs	
		Both oxaliplatin or irinotecan are considered valuble options for first line treatment. If 5FU is given in combination with irinotecan,it should be administered as continuous infusion and not as a bolus infusion as the latter is associated with increased toxicity.	Review based on 7 RCTs	
		Combination therapy of fluoropyrimidines with irinotecan or oxaliplatin has no significant benefit compared to sequential treatment with these agents.	2 prospective studies	
SIGN 2011[2]	February 2011	All patients with metastatic colorectal cancer should be considered for chemotherapy	Several SRs	1++
		Combination treatment with 5-FU/Leucovorin/oxaliplatin or capecitabine and oxaliplatin or 5-FU/leucovorin/irinotecan are the preferred options in patients with with good performance status and organ function	RCTs, MA	1+/1++
		Consider raltitrexed for patients with metastatic colorectal cancer who are intolerant to 5-FU and leucovorin, or for whom	RCT	1+

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
		these drugs are not suitable		
		Although the use of bevacizumab is associated with improved outcomes in patients with metastatic colorectal cancer , it is currently not recommended by the Scottish Medicines Consortium (due to insufficient evidence of cost effectiveness)		
NICE 2011[3]	February 2011	When offering multiple chemotherapy drugs to patients with advanced and metastatic colorectal cancer, consider one of the following sequences of chemotherapy unless they are contraindicated: FOLFOX as first-line treatment then single agent irinotecan as second line treatment OR FOLFOX as first-line treatment then FOLFIRI as second-line treatment OR XELOX as first-line treatment then FOLFIRI as second-line treatment	Mixed treatment comparison (indirect modelling)	
		Decide which combination and sequence of chemotherapy to use after full discussion of the side effects and the patient's preferences		
		Consider raltitrexed only for patients with advanced colorectal cancer who are intolerant to 5-FU and leucovorin, or for whom these drugs are not suitable (for example, patients who develop cardiotoxicity). Fully discuss the risk and benefits of raltitrexed with the patient	1 RCT with indirect evidence, one randomized phase II trial and some non-randomized phase II trials	
		Oral therapy with either capecitabine or tegafur with uracil (in combination with folinic acid) is recommended as an option for the first-line treatment of metastatic colorectal cancer	NICE technology appraisal 61 (2003)[$]	
		The choice of regimen (intravenous 5-fluorouracil and folonic acid or one of the oral therapies) should be made jointly by the		

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
		individual and the clinician(s) responsible for treatment. The decision should be made after an informed discussion between the clinician(s) and the patient; this discussion should take into account contraindications and the side-effect profile of the agents as well as the clinical condition and preferences of the individual		
		The use of capecitabine or tegafur with uracil to treat metastatic colorectal cancer should be supervised by oncologists who specialize in colorectal cancer.		
		Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine is not recommended for the treatment of metastatic colorectal cancer	NICE technology appraisal 212 (2010)[$]	

[$]*NICE technology appraisals formulate recommendations based on evidence reports submitted by the manufacturer.*

2 SEARCH FOR EVIDENCE

2.1 Search strategy

Evidence of the IKNL guideline was updated with literature search from 2006 onwards.

Initially, systematic reviews and meta-analyses were searched. Additional searches for randomized controlled trials (RCTs) were performed to update the selected reviews or to identify all high level evidence if no systematic review was available.

Systematic reviews and meta-analyses were searched in the following databases: OVID Medline and PreMedline, EMBASE, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA) database. RCTs were searched in: OVID Medline and PreMedline, EMBASE and CENTRAL. Searches were run between October and December 2012.

Additionally, guideline databases and websites of international oncology guideline developers were searched for evidence-based guidelines relevant to the subject.

The search strategy can be found in Appendix 1.

2.2 Study selection

All citations retrieved from the systematic literature search were screened based on title and abstracts. Possible citations of interest were further selected based on the full text article.

Study selection criteria for systematic reviews and randomized controlled trials are summarized in Table 10 and Table 11 respectively.

Search for systematic reviews and meta-analyses published between 2009 and 2012 retrieved 1109 citations after removal of duplicates. The further selection process is summarized in Figure 9.

To update the included systematic reviews, randomized controlled trials published in 2011 and 2012 were searched. After removal of duplicates, 405 citations were left for evaluation. Selection process of RCTs is summarized in Figure 10.

2.3 Critical appraisal

Selected systematic reviews were critical appraised using the AMSTAR checklist (see Table 12). To be included, the following criteria had to be fulfilled:

- Search strategy includes at least Medline and another database
- Characteristics of included studies reported
- Critical appraisal of included studies using prespecified criteria. Results should be reported

If one or more of these criteria were not fulfilled, AMSTAR checklist was not further completed.

For the quality appraisal of RCTs, the Cochrane Collaboration's tool for assessing risk of bias [4] was used (see Table 13). Judgement of each item includes three categories: 'low risk of bias', 'high risk of bias', and 'unclear risk of bias'. For each criterion the definitions as described in the Cochrane Handbook [4] were

used. If applicable, risk of bias for the items regarding detection bias and attrition bias were assessed per class of outcomes (e.g. subjective and objective outcomes).

Results of the critical appraisal of the individual papers are summarized in Table 14 and Table 15.

2.4 Statistical analysis

When new RCTs were found in addition to an existing meta-analysis, or in case subgroup analysis was needed for certain topics, meta-analysis was performed using Review Manager Version 5.

For progression-free survival (PFS) and overall survival (OS), a hazard ratio (HR) was extracted from the reported analyses. We used the extraction methods following Parmar et al.[5] All meta-analyses were performed using a generic inverse variance method, unless otherwise stated.

Heterogeneity was statistically assessed using χ^2test and I^2 statistic. If heterogeneity was present, a random-effects model was used instead of a fixed-effect model. Possible reasons for heterogeneity were explored post-hoc. Sensitivity analysis was performed by removing outliers from the analysis.

2.5 Grading of evidence

Data extraction was done by one reviewer using the standard KCE template for evidence tables (see Appendix 3).

The pooled results from included systematic reviews were extracted or newly identified RCTs were pooled if appropriate, and the quality of evidence was evaluated using GRADE methodology. A level of evidence was assigned to each conclusion using the GRADE system (Table 2).[6]

GRADE for guidelines was used, meaning that the evidence across all outcomes and across studies for a particular recommendation was assessed. The following quality elements for intervention studies were evaluated: study limitations, inconsistency, indirectness, imprecision and publication bias.

As only RCTs were considered in this review, quality rating was initially considered to be of high level. The rating was then downgraded if needed based on the judgement of the different quality elements. Each quality element considered to have serious or very serious risk of bias was rated down -1 or -2 points respectively. Judgement of the overall confidence in the effect estimate was also taken into account. We considered confidence in estimates as a continuum and the final rating of confidence could differ from that suggested by each separate domain.[7]

The general principles used to downgrade the quality rating are summarized in Table 3. Decisions on downgrading with -1 or -2 points were based on the judgement of the assessors. Reasons for (no) downgrading were summarized in the GRADE profiles.

Since upgrading of the level of evidence is primarily relevant to observational studies and our report focused on RCTs, upgrading was not considered applicable although theoretically possible.[8]

Table 2 – Levels of evidence according to the GRADE system

Quality level	Definition	Methodological Quality of Supporting Evidence
High	We are very confident that the true effect lies close to that of the estimate of the effect	RCTs without important limitations or overwhelming evidence from observational studies
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect	RCTs with very important limitations or observational studies or case series
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect	

Table 3 – Downgrading the quality rating of evidence using GRADE

Quality element	Reasons for downgrading
Limitations[9]	For each study reporting the selected outcome, possible risk of bias introduced by lack of allocation concealment, lack of blinding, lack of intention-to-treat analysis, loss of follow-up and selective outcome reporting were assessed. Additionally, other limitations such as stopping early for benefit and use of unvalidated outcome measures were taken into consideration. Level of evidence was downgraded if studies were of sufficiently poor quality. Downgrading was omitted if studies with low risk of bias were available that lead to similar conclusions as the studies with a high risk of bias.
Inconsistency[10]	Downgrading the level of evidence for inconsistency of results was considered in the following situations: point estimates vary widely across studies, confidence intervals show minimal or no overlap, the statistical test for heterogeneity shows a low p-value or the I^2 is large. If large variability in magnitude of effect remained unexplained, the quality of evidence was rated down. If the body of evidence included only a single study, rating was downgraded with -1 points as consistency of results cannot be judged and there is no proof that results are reproducible. The only exception was the availability of one large multicentre trial without heterogeneity across sites.
Indirectness[11]	Quality rating was downgraded for indirectness in case the trial population or the applied intervention differed significantly from the population or intervention of interest. Also, the use of surrogate outcomes could lead to downgrading. A third reason for downgrading for indirectness occurred when the studied interventions were not tested

Quality element	Reasons for downgrading
	in a head-to-head comparison.
Imprecision[12]	Evaluation of the imprecision of results was primarily based on examination of the 95%CI. Quality was rated down if clinical action would differ if the upper versus the lower boundary of the 95%CI represented the truth. In general, 95%CIs around relative effects were used for evaluation, except when the event rate was low in spite of a large sample size. To examine the 95%CIs, the clinical decision threshold (CDT) was defined. When the 95%CI crossed this clinical decision threshold, the quality level was rated down. A relative risk reduction (RRR) of 25% was defined as CDT by default and adapted if deemed appropriate e.g. in case of a low risk intervention. If the CIs included both appreciable benefit and appreciable harm, quality of evidence was downgraded by 2 levels. Even if 95%CIs appeared robust, level of evidence could be rated down because of fragility. To judge fragility of results, it is suggested to calculate the number of patients needed for an adequately powered (imaginary) single trial, also called the optimal information size (OIS). If the total number of patients included in a systematic review was less than the calculated OIS, rating down for imprecision was considered. For calculations, a RRR of 25% was used, unless otherwise stated. When the OIS could not be calculated, a minimum of 300 events for binary outcomes and a minimum of 400 participants for continuous outcomes were used as a rule of thumb.
Reporting bias[13]	Quality rating was downgraded for reporting bias if publication bias was suggested by analysis using funnel plots or searching of trial registries. Publication was also suspected if results came from small, positive industry-sponsored trials only.

3 SUMMARY OF THE EVIDENCE

NB:' First line chemotherapy' is defined as no prior systemic treatment for advanced or metastatic colorectal cancer. Many included studies however allow prior adjuvant chemotherapy after surgery of the primary tumour if completed at least six or twelve months before randomization.

3.1 Choice of chemotherapy agents

3.1.1 Oral versus IV fluoropyrimidines

Six meta-analyses[14-19] were published since 2009 on the comparison between oral fluoropyrimidines (capecitabine) with intravenous 5-fluorouracil, administered as a continued infusion or as a bolus (Table 16).

The meta-analyses of Montagnani[16] and Petrelli[17] were excluded based on AMSTAR criteria as no critical appraisal of included studies was performed. However, as both publications performed a comprehensive search strategy, reference lists were checked and two additional RCTs[20, 21] were included in the meta-analyses by KCE.

The review by Cao et al.[14] included all RCTs comparing oxaliplatin in combination with capecitabine or fluorouracil as first-line treatment of metastatic colorectal cancer. Search date was September 2008. No significant difference was seen for progression-free or overall survival (HR 1.08; 95%CI 0.98-1.18 and HR 1.04; 95%CI 0.95-1.14 respectively). Grade 3-4 thrombocytopenia and grade3-4 hand-foot syndrome were significantly more frequent in the capecitabine arm, whilst grade3-4 neutropenia was significantly more frequent in the 5FU arm.

All first-line studies included in the review of Zhao et al.[19] were also included in the review of Cao et al. except the study of Hochster et al. That study reported insufficient information on PFS and OS to be included in the meta-analysis. The study is summarized in Table 17.

The review of Ling et al.[15] included all studies comparing capecitabine with IV 5FU as monotherapy or in combination with oxaliplatin or irinotecan. Studies in the first-line, second-line and neo-adjuvant setting were included. Search date of the review was March 2010. Overall, Progression-free survival was in favour of capecitabine (WMD 1.24 months, p=0.04). No significant difference was seen for overall survival (WMD 0.29 months, p=0.75). The risk for severe adverse events was significantly lower for patients treated with capecitabine (OR 0.73; 95%CI 0.59-0.92).

The review of Zhang et al.[22] included all studies comparing capecitabine-oxaliplatin with 5FU-oxaliplatin. Search date of the review was April 2011. One additional study[23] was added to the meta-analysis by Cao et al. and also included in the updated meta-analysis (see below).

Search for RCTs published since 2011 retrieved 3 publications[24-26], comparing oral or intravenous fluoropyrimidines in combination with oxaliplatin, including one reporting updated survival results of the study of Cassidy et al. published in 2008. Two RCTs published in 2012 compared capecitabine and 5FU in combination with irinotecan and bevacizumab.[25, 26]

Oxaliplatin-based chemotherapy

The meta-analysis of Cao et al. including all first-line studies comparing oral and IV fluoropyridoxines and oxaliplatin was updated with the study of Ducreux et al.[27] and the updated survival results of Cassidy et al.[24]

Cassidy et al. enrolled 2034 patients who received XELOX or FOLFOX with or without bevacizumab. The trial was designed as a 2X2 design and was considered to have a low risk of bias. Overall, no significant difference was noted for overall survival (HR 0.95; 97.5%CI 0.85-1.06). Exclusion of patients who received bevacizumab led to the same conclusion (HR 0.95: 97.5%CI 0.83-1.09).

Ducreux et al. randomized 306 patients between XELOX and FOLFOX6. The trial was considered to have a low risk of bias. No significant difference between the two treatment arms was seen for overall (HR 1.02; 90%CI 0.81-1.30) or progression-free survival (HR 1.00; 90%CI 0.82-1.22).

Meta-analyses performed by KCE shows that there is no significant difference in progression-free or overall survival if capecitabine or intra-venous fluoro-uracil in combination with oxaliplatin are used as first-line treatment for unresectable metastatic colorectal cancer. Hazard ratios are 1.07 (95%CI 0.98-1.16) and 1.01 (95%CI 0.93-1.11) respectively (Figure 1 and Figure 2).

Study or Subgroup	log[Hazard Ratio]	SE	capectibine Total	IV 5FU Total	Weight	Hazard Ratio IV, Fixed, 95% CI
AIO (Porschen 2007)	0.157004	0.1009315	241	233	18.2%	1.17 [0.96, 1.43]
Ducreux 2011	0	0.1210067	156	150	12.6%	1.00 [0.79, 1.27]
NO16966 (Cassidy 2008)	0.039221	0.0570364	317	317	56.9%	1.04 [0.93, 1.16]
SICOS (Comella 2009)	0.113329	0.1230419	158	164	12.2%	1.12 [0.88, 1.43]
Total (95% CI)			**872**	**864**	**100.0%**	**1.07 [0.98, 1.16]**

Heterogeneity: Chi² = 1.48, df = 3 (P = 0.69); I² = 0%

Test for overall effect: Z = 1.50 (P = 0.13)

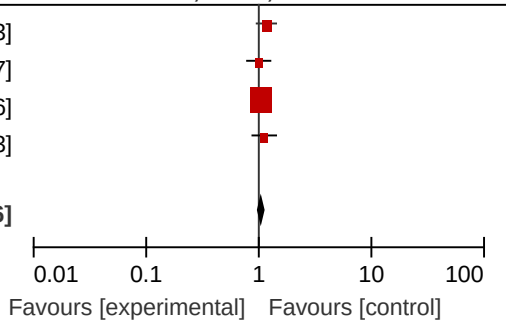

Figure 1 – Oral versus IV fluoropyrimidines + oxaliplatin: forest plot PFS

Study or Subgroup	log[Hazard Ratio]	SE	capecitabine Total	IV 5FU Total	Weight	Hazard Ratio IV, Fixed, 95% CI
AIO (Porschen 2007)	0.113329	0.1003624	241	233	19.6%	1.12 [0.92, 1.36]
Cassidy 2011	-0.05129	0.0602841	667	668	54.4%	0.95 [0.84, 1.07]
Ducreux 2011	0.019803	0.1405632	144	140	10.0%	1.02 [0.77, 1.34]
SICOS (Comella 2009)	0.00995	0.1587017	158	164	7.8%	1.01 [0.74, 1.38]
TTD (Diaz-Rubio 2007)	0.198851	0.1552099	171	171	8.2%	1.22 [0.90, 1.65]
Total (95% CI)			**1381**	**1376**	**100.0%**	**1.01 [0.93, 1.11]**

Heterogeneity: Chi² = 3.57, df = 4 (P = 0.47); I² = 0%

Test for overall effect: Z = 0.30 (P = 0.76)

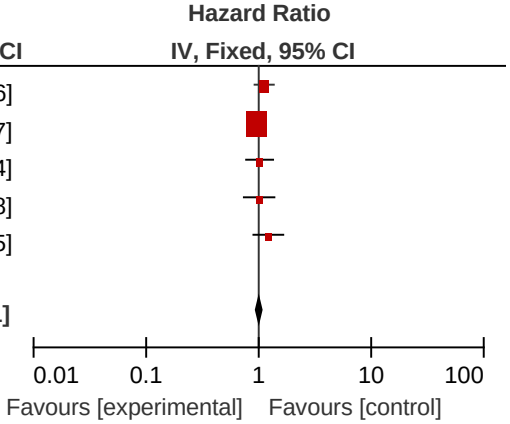

Figure 2 – Oral versus IV fluoropyrimidines + oxaliplatin: forest plot OS

Irinotecan-based chemotherapy

Capecitabine and 5FU in combination with irinotecan are compared in four randomized controlled trials.

Fuchs et al.[20] compared infusional 5FU, bolus 5FU and capecitabine in combination with irinotecan as first-line treatment for metastatic colorectal cancer. In the first phase of the trial, 430 patients were randomized. During the second phase, bevacizumab was added to the two IV arms and the capecitabine-irinotecan arm was closed due to increased toxicity compared with 5FU. Discontinuation of treatment due to unacceptable toxicity occurred in 25.5% of capecitabine treated patients and 14.6% and 13.9% in the two 5FU-based treatment schedules. Analysis based on 430 patients showed a higher risk for progression or death in the capecitabine-treated patients compared to FOLFIRI-treated patients (HR 1.36; 95%CI 1.04-1.80).

The EORTC 40015 study[21] published by Köhne et al. investigated the same comparison in a 2X2 factorial design with the comparison celecoxib or placebo. The study was closed early due to seven toxic deaths of which five in the capecitabine-based arm. Survival analysis based on 85 patients shows a statistically non-significant difference in PFS in favour of FOLFIRI (HR 0.76; 95%CI 0.48-1.21). Median overall survival was 19.9 months in the 5FU-treated patients and 14.75 months in the capecitabine-treated patients and this difference reached statistical significance (HR 0.31; 95%CI 0.14-0.71).

The study published by Pectasides et al[25] compared XELIRI-bevacizumab with FOLFIRI-bevacizumab as first-line treatment for metastatic colorectal cancer. Median progression-free survival was 10.2 and 10.8 months in the XELIRI and the FOLFIRI group respectively. Median overall survival was 20 months and 25.3 months respectively. The trial of Pectasides could not be included in the meta-analysis due to insufficiently reported results.

Souglakos et al[26] randomized 333 patients with unresectable metastatic colorectal cancer who were treated with capecitabine-irinotecan-bevacizumab or folinic aced-5-fluorouracil-irinotecan-bevacizumab. No significant differences were seen for PFS and OS (HR 0.99: 95%CI 0.90-1.09 and HR 1.08: 95%CI 0.94-1.24 respectively.

Meta-analysis performed by KCE shows a non-significant advantage in PFS for patients treated with 5FU and irinotecan. Removing the study of Souglakos et al., which included bevacizumab in both treatment arms, removes heterogeneity between studies and results in a statistically significant increase of PFS for the 5FU-treated patients (HR 1.35; 95%CI 1.07-1.70).

			capecitabine	IV 5FU		Hazard Ratio	Hazard Ratio
Study or Subgroup	**log[Hazard Ratio]**	**SE**	**Total**	**Total**	**Weight**	**IV, Random, 95% CI**	**IV, Random, 95% CI**
Fuchs 2007	0.307485	0.1368694	145	144	31.8%	1.36 [1.04, 1.78]	
Köhne 2008	0.277632	0.236715	44	41	17.2%	1.32 [0.83, 2.10]	
Souglakos 2012	0.00995	0.0476183	143	142	51.0%	1.01 [0.92, 1.11]	
Total (95% CI)			**332**	**327**	**100.0%**	**1.16 [0.92, 1.47]**	

Heterogeneity: Tau² = 0.03; Chi² = 5.17, df = 2 (P = 0.08); I² = 61%

Test for overall effect: Z = 1.28 (P = 0.20)

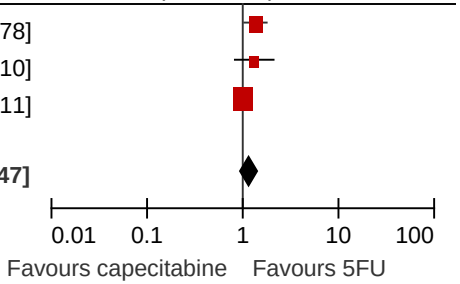

Figure 3 – Oral versus IV fluoropyrimidines + irinotecan: forest plot PFS

For overall survival, he study of Fuchs et al. contained insufficient data to be included in a meta-analysis. Combining the study of Köhne et al. and Souglakos et al. was considered not meaningful given the heterogeneity.

Table 4 – Oral versus IV fluoropyrimidines: GRADE profiles

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Oral versus IV pyrimidines + oxaliplatin								
Progression-free survival HR 1.07; 95%CI 0.98-1.16	4	-1	0	0	-1	0	1: blinding in none of the studies 4: CI includes significant benefit for 5FU (HR > 1.1)	Low
Overall survival HR 1.01; 95%CI 0.93-1.11	5	0	0	0	-1	0	4: CI includes significant benefit for 5FU (HR > 1.1)	Moderate
Oral versus IV pyrimidines + irinotecan								
Progression-free survival HR 1.35; 95%CI 1.07-1.70	2	-2	0	0	-1	0	1: both trials closed early 4: CI includes no significant effect and appreciable benefit 5FU	Very low

Conclusions

- There are indications that there is no significant difference in progression-free survival if fluoropyrimidines are administered orally or intravenously in combination with oxaliplatin as first-line treatment for metastatic colorectal cancer (Cao 2010, Ducreux 2011, Cassidy 2011; Low level of evidence).
- It is plausible that there is no significant difference in overall survival if fluoropyrimidines are administered orally or intravenously in combination with oxaliplatin as first-line treatment for metastatic colorectal cancer (Cao 2010, Ducreux 2011, Cassidy 2011; Moderate level of evidence).
- There are indications that oral administration of fluoropyrimidines shortens progression-free survival compared to intravenous fluoropyrimidines if combined with irinotecan as first-line treatment for metastatic colorectal cancer (Fuchs 2007, Köhne 2008; Very low level of evidence)

3.1.2 *Oxaliplatin versus irinotecan*

As recognized in the IKNL 2008, SIGN 2011 and NICE 2011 guidelines[2, 3], fluoropyrimidines in combination with oxaliplatin or irinotecan are valuable options for the first-line treatment of unresectable metastatic colorectal cancer. When oxaliplatin and a fluoropyrimidine are compared against irinotecan combinations the results are not significantly different in the majority of trials, albeit with differing toxicities.[3]

However, a meta-analysis of seven RCTs published in 2010 by Liang et al.[28] (Table 18) shows a survival benefit of approximately 2 months in favour of the oxaliplatin-fluorouracil combination (WMD -2.04; 95%CI -3.54 to -0.54). The quality of included studies was judged to be poor as allocation concealment was unclear in all studies and no studies used blinding procedures. Search date of the systematic review was January 2010. The meta-analysis published by Zhuang et al.[18] was based on a systematic review of the literature performed in May 2088; all studies were included in the paper of Liang et al.

No additional RCTs comparing oxaliplatin-based with iriniotecan-based chemotherapy in a first-line setting were identified in the NICE guideline or in the literature published since 2011.

Table 5 – Oxaliplatin-based versus irinotecan-based chemotherapy: GRADE profiles

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Overall survival WMD -2.04 months; 95%CI -3.54 to -0.54 months	6	-1	-1	0	-1	0	1: allocation concealment unclear in all studies 2: heterogeneity visible on forest plot 4: upper boundary of CI includes clinically no significant effect	Very low

Conclusions

- There are indications that first-line treatment of metastatic colorectal cancer with the combination oxaliplatin-fluoropyrimidines results in longer overall survival compared to first-line treatment with the combination irinotecan-fluoropyrimidines (Liang 2010; Very low level of evidence).

In the NICE 2011 guideline[3], 10 different combinations of first- and second-line therapy including FOLFOX, XELOX, FOLFIRI, XELIRI and irinotecan monotherapy were compared using mixed and indirect treatment comparison techniques as no head-to-head comparisons are available. Efficacy data, quality of life and cost-effectiveness considerations are taken into account. The following three sequences are recommended:

- FOLFOX as first-line treatment then single agent irinotecan as second-line treatment
- FOLFOX as first-line treatment then FOLFIRI as second-line treatment

- XELOX as first-line treatment then FOLFIRI as second-line treatment

Patient-specific factors, such as prior oxaliplatin-containing adjuvant chemotherapy, are not considered in the comparison.

3.2 Sequential versus combined chemotherapy

The IKNL 2008 guideline and the NICE 2011 guideline identified two RCTs comparing sequential versus combination chemotherapy for first-line treatment of metastatic colorectal cancer. In 2011, one additional RCT on the same comparison was published. The three trials are summarized in Table 19. All trials are considered to have a low risk of bias.

Although the three trials used different treatment schedules and sequences, in none of the trials a significant difference in overall survival was seen between sequential and combination therapy.

Koopman et al.[29] randomized 820 patients with metastatic colorectal cancer between sequential treatment (first-line treatment with capecitabine, second-line with irinotecan and third line capecitabine and oxaliplatin) or combination treatment (first-line treatment with capecitabine plus irinotecan and second-line with capectiabine with oxaliplatin). Treatment in both arms was continued for at least 6 months or until disease progression or unacceptable toxicity, whichever came first. Before a patient entered the next line of treatment, initial eligibility criteria had to be met. No significant difference in overall survival was seen (HR 0.92; 95%CI 0.79-1.08).

Seymour et al.[30] randomized 2135 patients with advanced colorectal cancer starting treatment with non-curative intent. The trial contained multiple comparisons. Patients in the control arm (arm A) were treated with single-agent 5FU until treatment failure, then single agent irinotecan. In treatment arm B, the deferred combination arm, patients were treated with single agent 5FU first, then with 5FU-irinotecan or 5-FU-oxaliplatin as determined by a second randomization. In treatment arm C, the first-line combination arm, patients also underwent a second randomization and were treated immediately with combined 5FU-irinotecan or 5-FU-oxaliplatin. Treatments were continued until treatment failure; breaks were not allowed in the first three months and were restricted to 4 weeks during the second three months. Median survival was slightly longer for all groups of treatment arm B and C compared to treatment arm A, but the difference was only significant for the group treated with first-line 5FU-irinotecan. A non-inferiority analysis for group B versus group C (considered standard treatment at the end of the trial period) was added post-hoc. HR for overall survival was 1.06; 90%CI 0.97-1.17, which was within the predetermined non-inferiority boundary of HR=1.18.

In the trial of Ducreux et al.[31] 410 patients were randomly assigned to either sequential therapy consisting of monotherapy 5FU followed by FOLFOX6 and then FOLFIRI or combination therapy consisting of FOLFOX6 followed by FOLFIRI. Further lines of therapy were at the investigator's discretion. There was no significant difference between the two treatment arms in terms of progression-free survival after two lines of therapy (HR 0.95; 95%CI 0.77-1.16) or overall survival (HR 1.02; 95%CI 0.82-1.27).

Meta-analysis for overall survival performed by KCE shows a hazard ratio of 1.01; 95%CI 0.93-1.10 (Figure 4).

Study or Subgroup	log[Hazard Ratio]	SE	sequential Total	combination Total	Weight	Hazard Ratio IV, Random, 95% CI
Ducreux FFCD 2011	0.019803	0.113539	205	205	14.9%	1.02 [0.82, 1.27]
Koopman 2007	-0.08338	0.0777249	410	410	29.9%	0.92 [0.79, 1.07]
Seymour 2007	0.058269	0.0541025	712	713	55.3%	1.06 [0.95, 1.18]
Total (95% CI)			**1327**	**1328**	**100.0%**	**1.01 [0.93, 1.10]**

Heterogeneity: Tau² = 0.00; Chi² = 2.24, df = 2 (P = 0.33); I² = 11%

Test for overall effect: Z = 0.23 (P = 0.82)

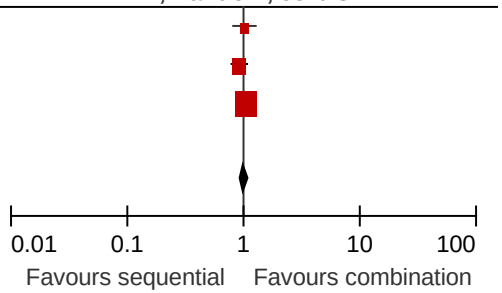

Figure 4 – Sequential versus combined first-line chemotherapy for mCRC: forest plot OS

Table 6 – Sequential versus combined first-line chemotherapy for mCRC: GRADE profile

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Overall survival HR 1.01; 95%CI 0.93-1.11	3	0	0	0	0	0		High

Conclusions

- It is demonstrated that sequential and combination first-line chemotherapy result in similar overall survival for patients with metastatic colorectal cancer (Koopman 2007, Seymour 2007, Ducreux 2011; High level of evidence).

3.3 Targeted therapy

3.3.1 Anti-VEGF therapy: bevacizumab

Eight meta-analyses[32-39] and one RCT[40] were identified in the literature addressing the addition of bevacizumab to first line chemotherapy in patients suffering from advanced colorectal cancer (Table 20 and Table 21). Only studies comparing identical chemotherapy with or without bevacizumab were included.

Three meta-analyses[37-39] were excluded based on critical appraisal (no comprehensive literature search, no quality assessment of included studies).

The most recent meta-analysis by Macedo et al.[34] includes 4 phase III and phase II RCTs adding bevacizumab to first-line chemotherapy in patients suffering from metastatic cancer. Search date of the review was March 2011. Risk of bias of the review was considered to be low. Two studies studied bevacizumab in combination with irinotecan-based chemotherapy, one with oxaliplatin-based chemotherapy and three with single agent fluorouracil. Overall, adding bevacizumab to first-line chemotherapy appeared to improve both PFS and OS at the cost of increased rates of hypertension, proteinuria, bleeding and thromboembolic events. Also a slight increase of treatment interruptions (HR 1.47; 95%CI 1.19-1.83) was seen. Other meta-analyses included only first-line studies that were also included in the publication of Macedo et.al.[34]

One more recent RCT was found. In the study by Guan et al.[40], 214 Chinese patients were randomized to receive irinotecan, leucovorin bolus and 5FU intravenous infusion with or without bevacizumab. The trial was considered to be low risk of bias. Treatment was continued until documented progressive disease, death or unacceptable toxicity. Hazard ratios for progression-free and overall survival were 0.44; 95%CI 0.31 to 0.63 and 0.62; 95%CI 0.41 to 0.95 respectively, in favour of bevacizumab.

The meta-analysis of Macedo et al. was updated with the data of the Guan trial. Overall, adding bevacizumab to first-line chemotherapy improves progression-free and overall survival (HR 0.59; 95%CI 0.46 to 0.74 and 0.82; 95%CI 0.71 to 0.94 respectively) as summarized in Figure 5 and Figure 6. There was substantial in-between study heterogeneity for the PFS outcome, which disappeared when the only study using oxaliplatin-based chemotherapy was removed from the analysis. Removal of the study by Saltz et al. did not significantly alter the results (PFS HR 0.55; 95%CI 0.48 to 0.62). This study by Saltz et al. shows a more modest effect of bevacizumab when added to oxaliplatin-based chemotherapy.

Study or Subgroup	log[Hazard Ratio]	SE	Experimental Total	Control Total	Weight	Hazard Ratio IV, Random, 95% CI
Guan 2011	-0.82098	0.1786747	139	64	15.1%	0.44 [0.31, 0.62]
Hurwitz 2004	-0.61619	0.0903	402	411	20.3%	0.54 [0.45, 0.64]
Kabinnavar 2003	-0.61619	0.283162	68	36	10.0%	0.54 [0.31, 0.94]
Kabinnavar 2005	-0.69315	0.196767	104	105	14.1%	0.50 [0.34, 0.74]
Saltz 2008	-0.18633	0.0585586	699	701	21.7%	0.83 [0.74, 0.93]
Tebutt 2010	-0.46204	0.1179141	156	156	18.7%	0.63 [0.50, 0.79]
Total (95% CI)			**1568**	**1473**	**100.0%**	**0.59 [0.46, 0.74]**

Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 27.56$, df = 5 ($P < 0.0001$); $I^2 = 82\%$

Test for overall effect: Z = 4.49 ($P < 0.00001$)

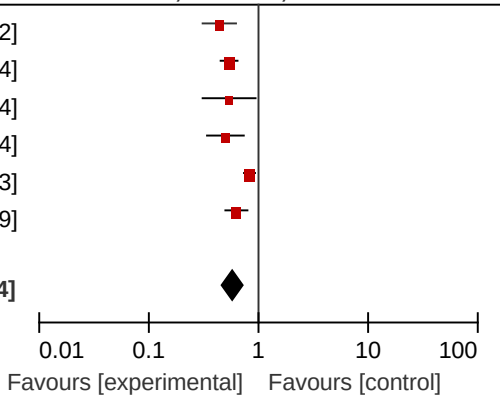

Figure 5 – Adding bevacizumab to first-line chemotherapy for mCRC: forest plot PFS

Study or Subgroup	log[Hazard Ratio]	SE	chemotherapy bevacizumab Total	chemotherapy Total	Weight	Hazard Ratio IV, Random, 95% CI
Guan 2011	-0.47804	0.21100118	142	72	8.5%	0.62 [0.41, 0.94]
Hurwitz 2004	-0.41552	0.102383	402	411	19.8%	0.66 [0.54, 0.81]
Kabinnavar 2003	-0.15082	0.3419172	68	36	3.8%	0.86 [0.44, 1.68]
Kabinnavar 2005	-0.23572	0.1755593	104	105	11.0%	0.79 [0.56, 1.11]
Saltz 2008	-0.11653	0.06731	699	701	25.8%	0.89 [0.78, 1.02]
Stathopoulos 2010	0.04879	0.1324037	114	108	15.5%	1.05 [0.81, 1.36]
Tebutt 2010	-0.12783	0.1315455	156	156	15.6%	0.88 [0.68, 1.14]
Total (95% CI)			**1685**	**1589**	**100.0%**	**0.82 [0.71, 0.94]**

Heterogeneity: Tau² = 0.02; Chi² = 11.43, df = 6 (P = 0.08); I² = 47%

Test for overall effect: Z = 2.77 (P = 0.006)

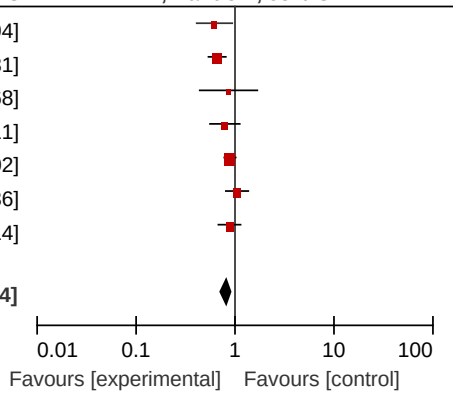

Figure 6 – Adding bevacizumab to first-line chemotherapy for mCRC: forest plot OS

Table 7 – Adding bevacizumab to first-line chemotherapy for mCRC: GRADE profiles

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Progression-free survival HR 0.59; 95%CI 0.46 to 0.74	6	-1	0	0	0	0	1: no blinding, no ITT in 3/6 studies	Moderate
Overall survival HR 0.82; 95%CI 0.71 to 0.94	7	0	0	0	-1	0	1: blinding considered as not introducing risk of bias for OS 4: CI includes clinical decision threshold (0.94 clinically non-significant effect)	Moderate

1. Limitations 2. Inconsistency 3. Indirectness 4. Imprecision 5. Reporting bias

Conclusions

- It is plausible that the addition of bevacizumab to first-line chemotherapy for metastatic colorectal cancer improves progression-free survival (Macedo 2012, Guan 2011; Moderate level of evidence).
- It is plausible that the addition of bevacizumab to first-line chemotherapy for metastatic colorectal cancer improves overall survival (Macedo 2012, Guan 2011; Moderate level of evidence).

3.3.2 Anti-EGFR therapy: cetuximab and panitumumab

NB: two monoclonal antibodies (MAbs) directed at the epidermal growth factor receptor (EGFR) are registered with the European Medicines Agency (EMA) for the treatment of metastatic colorectal cancer: cetuximab and panitumumab.[41, 42] Both agents are authorized for use in tumours containing wild-type (WT) KRAS genes. Therefore, only results for patients having a wild-type KRAS tumour are reported.

Fourteen systematic reviews on the efficacy of anti-EGFR therapy in the treatment of metastatic colorectal cancer, of which eight were excluded based on critical appraisal[43-50] (no search in at least two databases or absence of quality appraisal of included studies).

The most recent systematic review with meta-analysis published in 2012 by Vale et al.[51] included all RCTs comparing chemotherapy with or without cetuximab in patients with advanced colorectal cancer (Table 22). He review was considered to have a low risk of bias. Fourteen eligible trails were included, of which seven in the first line setting. Results were primarily reported for wild type (WT) KRAS tumours. Three trials did not report by KRAS status and were included only in an additional sensitivity analysis. Also the trials including bevacizumab in the two treatment arms were added in a separate analysis.

In trials of first or second line treatment, there was benefit of anti-EGFR MAbs in patients with WT KRAS tumours, for both PFS and OS (HR 0.83; 95%CI 0.76 to 0.90 for PFS, HR 0.89; 95%CI 0.82 to 0.97 for OS). Where reported, baseline characteristics for the subset of patients in whom KRAS status was assessed were similar to those for all randomised patients suggesting a low risk of patient selection bias in the KRAS tested population. For progression-free survival, there was significant heterogeneity between trials (P=0.02, I^2=60%), most probably explained by the choice of fluoropyrimidines. Analysis confined to trials using 5FU based chemotherapy, HR for PFS was 0.77; 95%CI 0.70-0.85. Also for OS, benefit appeared to be confined to trials using 5FU (HR 0.86; 95%CI 0.78-0.95). For PFS, adding the results for all randomised patients from three trials where KRAS subgroup data is not available did not change the conclusions.

Meta-analysis of the WT KRAS patients treated in two trials adding bevacizumab to both arms shows a better PFS and OS for patients treated with chemotherapy and bevacizumab only (HR 1.27; 95%CI 1.06-1.51 and HR 1.51; 95%CI 0.74-3.08 respectively).

All first-line studies included in the other five systematic reviews, were also included in the analysis of Vale et al.

Two more recent RCTs[52, 53] were retrieved from the literature, of which one was a publication on updated results of the CRYSTAL trial[53], already included in the meta-analysis of Vale et al.

The CRYSTAL trial compared FOLFIRI with or without cetuximab in 1217 patients with previously untreated metastatic colorectal cancer. In the updated report, median follow-up time was 46 months. KRAS status was known for 88% of participants (45% in the original publication). Baseline characteristics and survival data for patients with known KRAS status were similar to the overall population. For patients with wild-type KRAS tumours, a benefit in progression-free survival and overall survival was confirmed for treatment with cetuximab and chemotherapy compared to chemotherapy alone (HR 0.696; 95%CI 0.558-0.867 and HR 0.796; 95%CI 0.670-0.946 respectively).

Tveit et al.[52] published the results of the NORDIC-VII study in 2012. Patients were randomized to receive either standard Nordic FLOX (bolus 5FU + folinic acid + oxaliplatin) or cetuximab and FLOX or cetuximab with intermittent FLOX. In the first two arms, treatment was continued until disease progression or intolerable toxicity. In the third arm, FLOX was stopped after 16 weeks of treatment, cetuximab was continued in case of objective response. When progressive disease was reported, FLOX was reintroduced. Comparing the first two arms, with identical chemotherapy, no significant advantage was seen for cetuximab in terms of progression-free or overall survival (HR 1.07; 95%CI 0.79-1.45 and HR 1.14; 95%CI 0.80-1.61).

A meta-analysis was performed including all first-line trials included in the MA of Vale et al. and the two recent publications. Only data for wild-type KRAS tumours were included. In the majority of studies, oxaliplatin-based chemotherapy was used, only in the CRYSTAL study and part of the PACCE study, chemotherapy was irinotecan-based.

Overall, a statistically significant benefit was seen if cetuximab was added to chemotherapy in terms of progression-free survival (HR 0.82; 95%CI 0.69-0.96) and overall survival (HR 0.89; 95%CI 0.80-0.99). For progression-free survival, there was evidence of heterogeneity between studies which disappeared if the two studies using oral (COIN Xelox) or bolus IV (Nordic VII) fluoropyrimidines were removed. Analysis limited to studies using continuous IV administration of 5FU only shows a HR of 0.74; 95%CI 0.66-0.84 (data not shown).

If cetuximab was added to combined chemotherapy and bevacizumab, shows a shorter PFS for patients treated with the cetuximab (HR 1.27; 95%CI 1.06-1.51). For overall survival, differences were not statistically significant (HR 1.51; 95%CI 0.74-3.08).

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
4.1.1 cetuximab - panitumimab + chemotherapy				
COIN Ox5FU (Maughan)	-0.2634	0.1379	11.7%	0.77 [0.59, 1.01]
COIN XELOX(Maughan)	0.0561	0.0961	13.7%	1.06 [0.88, 1.28]
CRYSTAL (Van Cutsem)	-0.36241	0.1127504	12.9%	0.70 [0.56, 0.87]
NORDIC VII (Tveit)	-0.0645918	0.155028	10.9%	0.94 [0.69, 1.27]
OPUS (Bokemeyer)	-0.5621	0.2366	7.6%	0.57 [0.36, 0.91]
PRIME (Douillard)	-0.2231	0.0982	13.6%	0.80 [0.66, 0.97]
Subtotal (95% CI)			**70.5%**	**0.82 [0.69, 0.96]**
Heterogeneity: Tau² = 0.02; Chi² = 12.37, df = 5 (P = 0.03); I² = 60%				
Test for overall effect: Z = 2.47 (P = 0.01)				
4.1.2 cetuximab - panitumumab + chemotherapy + bevacizumab				
CAIRO 2 (Tol)	0.1458	0.129	12.2%	1.16 [0.90, 1.49]
PACCE Iri (Hecht)	0.4055	0.3096	5.5%	1.50 [0.82, 2.75]
PACCE Ox (Hecht)	0.3075	0.1357	11.8%	1.36 [1.04, 1.77]
Subtotal (95% CI)			**29.5%**	**1.27 [1.06, 1.51]**
Heterogeneity: Tau² = 0.00; Chi² = 1.07, df = 2 (P = 0.59); I² = 0%				
Test for overall effect: Z = 2.66 (P = 0.008)				
Total (95% CI)			**100.0%**	**0.93 [0.78, 1.11]**
Heterogeneity: Tau² = 0.05; Chi² = 30.01, df = 8 (P = 0.0002); I² = 73%				
Test for overall effect: Z = 0.83 (P = 0.41)				
Test for subgroup differences: Chi² = 13.16, df = 1 (P = 0.0003), I² = 92.4%				

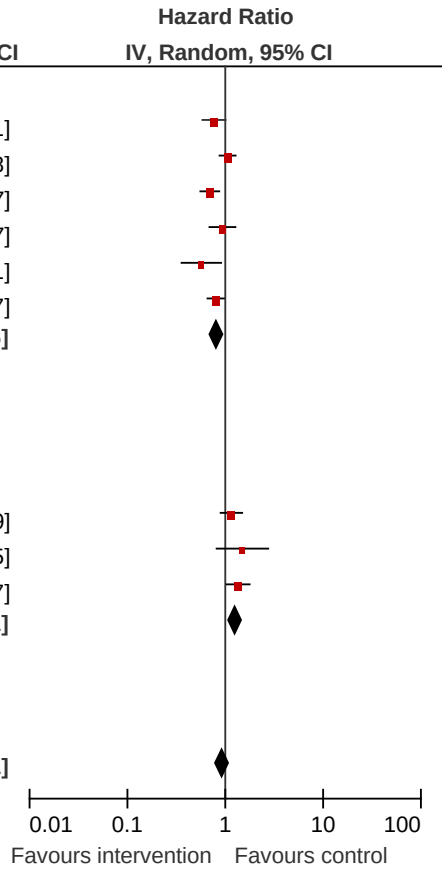

Figure 7 – Adding cetuximab or panitumumab to first-line chemotherapy +/- bevacizumab for mCRC: forest plot PFS

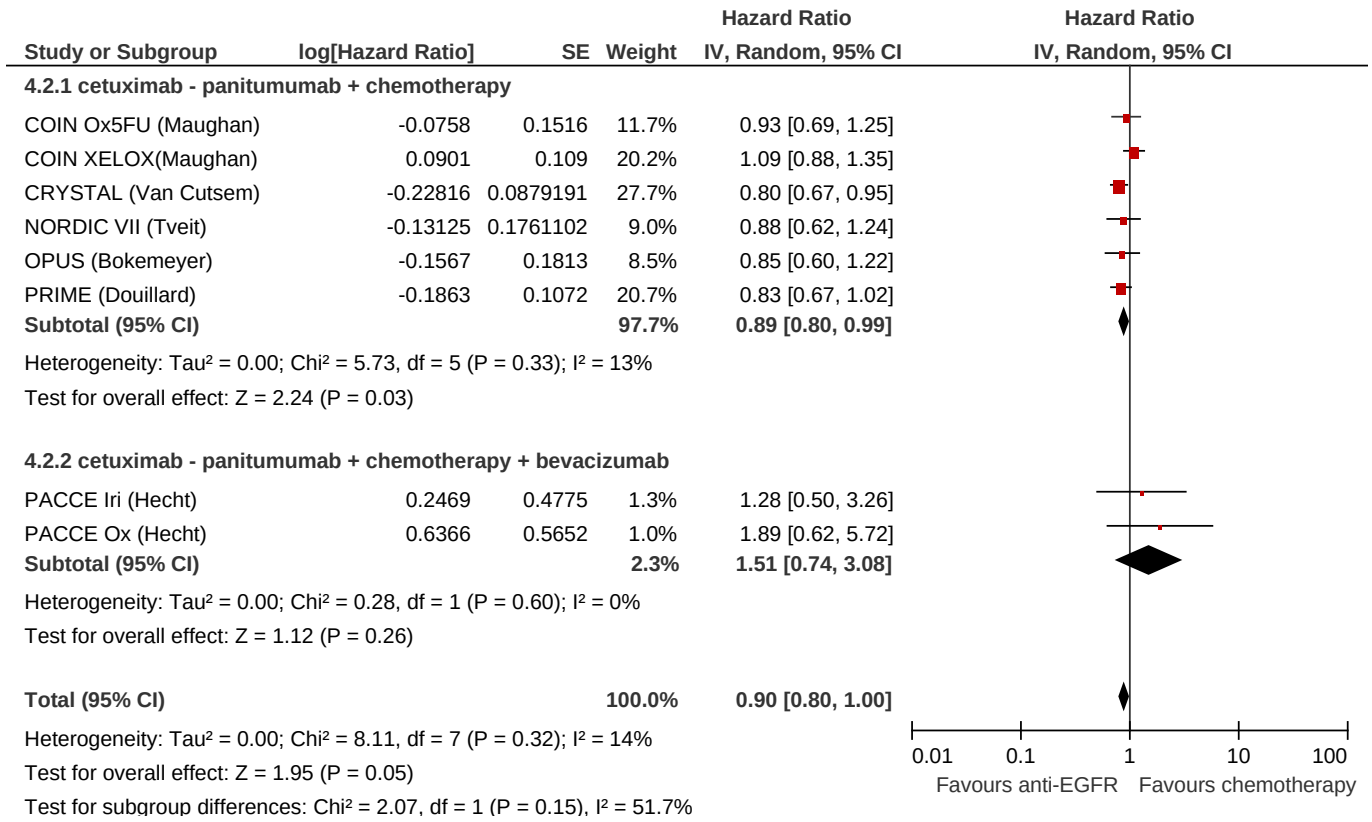

Figure 8 – Adding cetuximab or panitumumab to first-line chemotherapy +/- bevacizumab for mCRC: forest plot OS

Table 8 – Adding cetuximab or panitumumab to first-line chemotherapy +/- bevacizumab for mCRC: GRADE profiles

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Cetuximab added to chemotherapy								

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Progression-free survival HR 0.82; 95%CI 0.69-0.96	6	-1	0	0	-1	0	1: No blinding in all studies, possible selection bias for KRAS status 2: statistical heterogeneity but explained 4: CI includes clinical decision threshold	Low
Overall survival HR 0.89; 95%CI 0.80-0.99	6	-1	0	0	-1	0	1: possible selection bias for KRAS status 4: CI includes clinical decision threshold	Low
Cetuximab added to chemotherapy + bevacizumab								
Progression-free survival HR 1.27; 95%CI 1.06-1.51	3	-2	0	0	0	0	1: unclear allocation concealment and no blinding in both studies, possible selection bias for KRAS status	Low
Overall survival HR 1.51; 95%CI 0.74-3.08	2	-1	0	0	-2	0	1: unclear allocation concealment, possible selection bias for KRAS status 4: CI includes appreciable harm and appreciable benefit	Very low

Conclusions

- There are indications that the addition of cetuximab to first-line chemotherapy for wild-type KRAS metastatic colorectal cancer improves progression-free survival (Vale 2012, Van Cutsem 2011, Tveit 2012; low level of evidence).
- There are indications that the addition of cetuximab to first-line chemotherapy for wild-type KRAS metastatic colorectal cancer improves overall survival (Vale 2012, Van Cutsem 2011, Tveit 2012; low level of evidence).
- There are indications that the addition of cetuximab to chemotherapy and bevacizumab as first-line treatment for wild-type KRAS metastatic colorectal cancer shortens progression-free survival (Vale 2012; low level of evidence).

- For the addition of cetuximab to chemotherapy and bevacizumab as first-line treatment for wild-type KRAS metastatic colorectal cancer, neither significant harm nor significant benefit in terms of overall survival could be excluded (Vale 2012; very low level of evidence).

APPENDICES

APPENDIX 1. SEARCH FOR EVIDENCE

Appendix 1.1. Search strategy

Table 9 – Date	22-10-2012
Database	Medline via OVID
Search Strategy	1 exp Colorectal Neoplasms/ (135940) 2 (colo$ adj5 cancer$).tw. (79753) 3 (colo$ adj5 neoplas$).tw. (5380) 4 (colo$ adj5 carcin$).tw. (32908) 5 (colo$ adj5 tumo$).tw. (22654) 6 (colo$ adj5 metasta$).tw. (15633) 7 (colo$ adj5 malig$).tw. (4638) 8 1 or 2 or 3 or 4 or 5 or 6 or 7 (169031) 9 exp Neoplasm Metastasis/ (145333) 10 stage IV.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (12982) 11 advanced.ab,ti. (212865) 12 metasta$.tw. (269810) 13 9 or 10 or 11 or 12 (519270) 14 8 and 13 (43636) 15 exp Antineoplastic Protocols/ (96176) 16 drug therapy, combination/ or antineoplastic combined chemotherapy protocols/ (225835) 17 exp molecular targeted therapy/ (4215) 18 exp Antineoplastic Agents/ (761288)

19	exp Antibodies, Monoclonal/ (168243)
20	exp Angiogenesis Inhibitors/ (30624)
21	exp Protein Kinase Inhibitors/ (41474)
22	chemother$.mp. (284983)
23	(systemic therap$ or systemic treatment).mp. (10406)
24	(5-fluorouracil$ or 5-FU).mp. (26744)
25	oxaliplatin$.mp. (4640)
26	irinotecan.mp. (6349)
27	capecitabin$.mp. (3037)
28	FOLFOX$.mp. (1168)
29	FOLFIRI$.mp. (514)
30	XELOX.mp. (177)
31	XELIRI$.mp. (27)
32	(target$ adj3 therap$).mp. (71201)
33	(target$ adj3 treatment).mp. (14951)
34	(target$ adj3 agent$).mp. (10766)
35	EGFR$.mp. (21741)
36	VEGF.mp. (32494)
37	angiogen$.mp. (68039)
38	cetuximab.mp. (2999)
39	bevacizumab.mp. (6461)
40	panitumumab.mp. (600)
41	regorafinib.mp. (0)
42	Colorectal Neoplasms/dt, th [Drug Therapy, Therapy] (10848)
43	15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 (1298249)
44	14 and 43 (18900)
45	exp animals/ not humans.sh. (3797751)
46	44 not 45 (17956)

	47 limit 46 to yr="2006 -Current" (8061) 48 meta-analysis.mp,pt. or review.pt. or search:.tw. (1892967) 49 47 and 48 (1750)
Note	Search for RCTs performed on 29 November 2012 using the following filters: 47 randomized controlled trial.pt. (342334) 48 controlled clinical trial.pt. (85694) 49 randomized.ab. (244919) 50 placebo.ab. (136550) 51 clinical trials as topic.sh. (163815) 52 randomly.ab. (175193) 53 trial.ti. (105840) 54 47 or 48 or 49 or 50 or 51 or 52 or 53 (791543) 55 46 and 54 (3283) 56 limit 55 to yr="2011 -Current" (319)

Date	**05-12-2012**
Database	Premedline via Ovid
Search Strategy	1 (colo$ adj5 cancer$).tw. (4814) 2 (colo$ adj5 neoplas$).tw. (240) 3 (colo$ adj5 carcin$).tw. (1254) 4 (colo$ adj5 tumo$).tw. (984) 5 (colo$ adj5 metasta$).tw. (978) 6 (colo$ adj5 malig$).tw. (273) 7 stage IV.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (595) 8 advanced.ab,ti. (15343)

9 metasta$.tw. (17839)

10 disseminated.tw. (1633)

11 1 or 2 or 3 or 4 or 5 or 6 (6266)

12 7 or 8 or 9 or 10 (32956)

13 11 and 12 (1924)

14 chemother$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (12473)

15 (systemic therap$ or systemic treatment).mp. (739)

16 (5-fluorouracil$ or 5-FU$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (1187)

17 oxaliplatin$.mp. (400)

18 irinotecan.mp. (338)

19 capecitabin$.mp. (267)

20 FOLFOX$.mp. (128)

21 FOLFIRI$.mp. (68)

22 XELOX.mp. (27)

23 XELIRI$.mp. (7)

24 (target$ adj3 therap$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (7152)

25 (target$ adj3 treatment).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (1494)

26 (target$ adj3 agent$).mp. (1123)

27 EGFR$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (1980)

28 VEGF$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (2644)

29 angiogen$.mp. (3906)

30 cetuximab.mp. (261)

31 bevacizumab.mp. (779)

32 panitumumab.mp. (73)

	33 regorafinib.mp. (0) 34 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 (27869) 35 13 and 34 (782)
Note	

Date	**29 October 2012**
Database	EMBASE via Embase.com
Search Strategy	'large intestine cancer'/exp OR colo* NEAR/ cancer OR colo* NEAR/5 neoplas* OR colo* NEAR/5 carcin* OR colo* NEAR/5 tumo* OR colo* NEAR/5 metasta* OR colo* NEAR/5 malig* AND ('metastasis'/exp OR advanced OR 'stage iv' OR metasta* OR disseminated) AND ('molecularly targeted therapy'/exp OR 'protein kinase inhibitor'/exp OR '5 fluorouracil' OR '5 fu' OR irinotecan OR oxaliplatin* OR capecitabin* OR folfox* OR xelox OR xeliris OR egfr OR vegf OR angiogen* OR cetuximab OR bevacizumab OR panitumumab OR regorafinib OR 'cancer chemotherapy'/exp) AND ([cochrane review]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim OR [systematic review]/lim) AND [humans]/lim AND [2006-2013]/py
Note	Search for RCTs performed on 6 December 2012 using the following filters: [controlled clinical trial]/lim OR [randomized controlled trial]/lim) AND [humans]/lim AND [2011-2013]/py

Date	**25-10-2012**

Database	Cochrane Library	
Search Strategy	#1	MeSH descriptor: [Colorectal Neoplasms] explode all trees
	#2	colo* near/5 cancer*:ti,ab
	#3	colo* near/5 neoplas*:ti,ab
	#4	colo* near/5 carcin*:ti,ab
	#5	colo* near/5 tumo*:ti,ab
	#6	colo* near/5 metasta*:ti,ab
	#7	colo* near/5 malig*:ti,ab
	#8	#1 or #2 or #3 or #4 or #5 or #6 or #7
	#9	MeSH descriptor: [Colorectal Neoplasms] explode all trees and with qualifiers: [Drug therapy - DT]
	#10	MeSH descriptor: [Antineoplastic Agents] explode all trees
	#11	MeSH descriptor: [Drug Therapy] this term only
	#12	MeSH descriptor: [Drug Administration Schedule] this term only
	#13	MeSH descriptor: [Antineoplastic Protocols] explode all trees
	#14	MeSH descriptor: [Molecular Targeted Therapy] explode all trees
	#15	MeSH descriptor: [Maintenance Chemotherapy] explode all trees
	#16	chemother*.ti,ab
	#17	systemic therap* or systemic treatment:ti,ab
	#18	5-fluorouracil* or 5-FU:ti,ab,kw
	#19	oxaliplatin*:ti,ab,kw
	#20	irinotecan:ti,ab,kw
	#21	capecitabin:ti,ab,kw
	#22	FOLFOX*:ti,ab,kw
	#23	FOLFIRI:ti,ab,kw
	#24	XELOX:ti,ab,kw
	#25	XELIRI*:ti,ab,kw
	#26	target* near/3 therap*:ti,ab
	#27	target* near/3 treatment:ti,ab
	#28	target* near/3 agent*:ti,ab

	#29	EGFR:ti,ab
	#30	VEGF:ti,ab
	#31	angiogen*:ti,ab
	#32	cetuximab:ti,ab
	#33	bevacizumab:ti,ab
	#34	panitumumab:ti,ab
	#35	regorafinib:ti,ab
	#36	MeSH descriptor: [Neoplasm Metastasis] explode all trees
	#37	stage IV:ti,ab,kw (Word variations have been searched)
	#38	advanced:ti,ab,kw (Word variations have been searched)
	#39	metasta*:ti,ab,kw (Word variations have been searched)
	#40	MeSH descriptor: [Antibodies, Monoclonal] explode all trees
	#41	#36 or #37 or #38 or #39
	#42	#8 and #41
	#43	MeSH descriptor: [Protein Kinase Inhibitors] explode all trees
	#44	#9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #40 or #43
	#45	#42 and #44 from 2006 to 2012
Note	Search repeated for RCTs on 6 December 2012 from 2011 to 2012	

Appendix 1.2. Study selection

Table 10 – Study selection criteria for systematic reviews and meta-analyses

Review question:	**What is the current standard first line treatment for metastatic inoperable colorectal cancer?**	
Selection criteria	***Inclusion criteria***	***Exclusion criteria***
Population	Patients with newly diagnosed stage IV colorectal cancer (adenocarcinoma) not eligible for local treatment of lung or liver metastastases OR patients with recurrent colorectal cancer without previous treatment with chemotherapy or radiotherapy	Prior chemotherapy or targetted treatment for colorectal cancer. Studies including rectal cancer patients only. Studies including other cancers without seperate results for colorectal cancer (except for adverse events).
Intervention	1st line chemotherapy and/or targeted therapy	regional chemotherapy, radiotherapy, surgery, supportive care, alternative therapies, (neo)adjuvant chemotherapy, vaccine therapy
Outcome	OS, PFS, selected predictive factors	tumour response, prognostic factors, biomarkers, methodologic considerations, costs, other outcomes
Design	systematic review, meta-analysis, evidence based guidelines	narrative review, editorial, letter, primary research, consensus based guidelines, abstract only.
Language	English, Dutch, French, german	other languages
Full text not available	no	yes
duplicate	no	yes

Table 11 – Study selection criteria for RCTs

Review question:	**What is the current standard first line treatment for metastatic inoperable colorectal cancer?**	
Selection criteria	***Inclusion criteria***	***Exclusion criteria***
Population	Patients with newly diagnosed stage IV colorectal cancer (adenocarcinoma) not eligible for local treatment of lung or liver metastastases OR patients with recurrent colorectal cancer without previous treatment with chemotherapy or radiotherapy	Prior chemotherapy or targetted treatment for colorectal cancer. Studies including rectal cancer patients only. Studies including other cancers without seperate results for colorectal cancer (except for adverse events).
Intervention	1st line chemotherapy and/or targeted therapy	regional chemotherapy, radiotherapy, surgery, supportive care, alternative therapies, (neo)adjuvant chemotherapy, vaccine therapy
Outcome	OS, PFS	tumour response, prognostic factors, biomarkers, methodologic considerations, costs, other outcomes
Design	Randomized controlled trial	Non-randomized trials, observational studies, cross-sectional studies, case reports, editorial, letter, abstract only.
Language	English, Dutch, French, german	other languages
Full text not available	no	yes
duplicate	no	yes

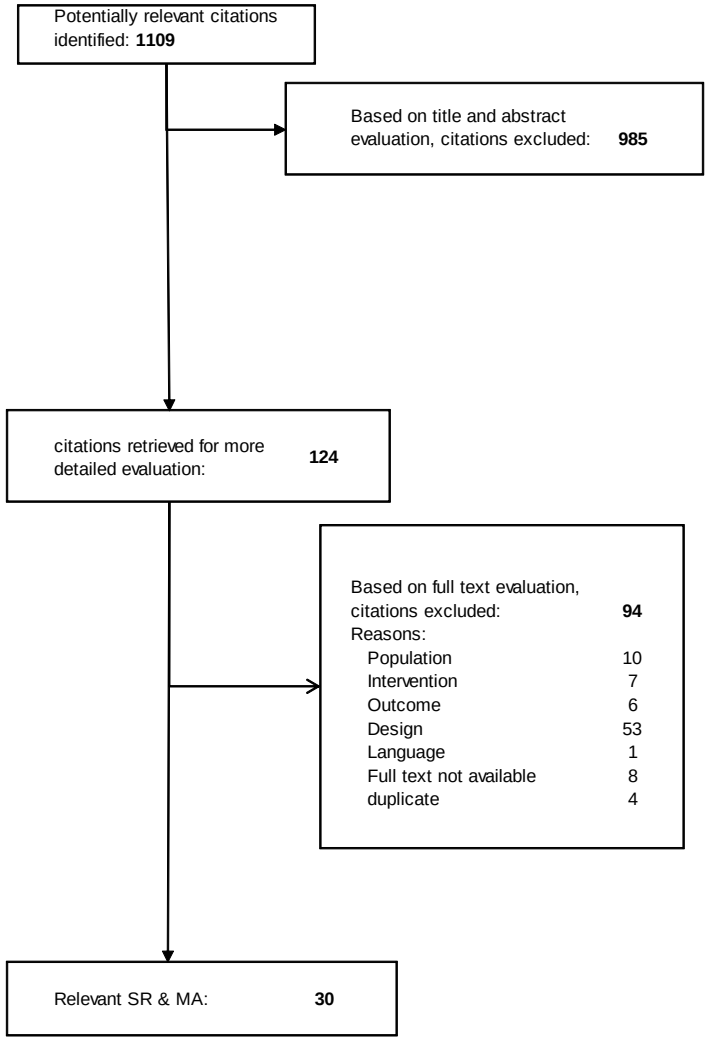
Potentially relevant citations identified: 1109
Based on title and abstract evaluation, citations excluded: 985
citations retrieved for more detailed evaluation: 124
Based on full text evaluation, citations excluded: 94
Reasons:
Population 10
Intervention 7
Outcome 6
Design 53
Language 1
Full text not available 8
duplicate 4
Relevant SR & MA: 30

Figure 9 – Selection of systematic reviews: flow chart

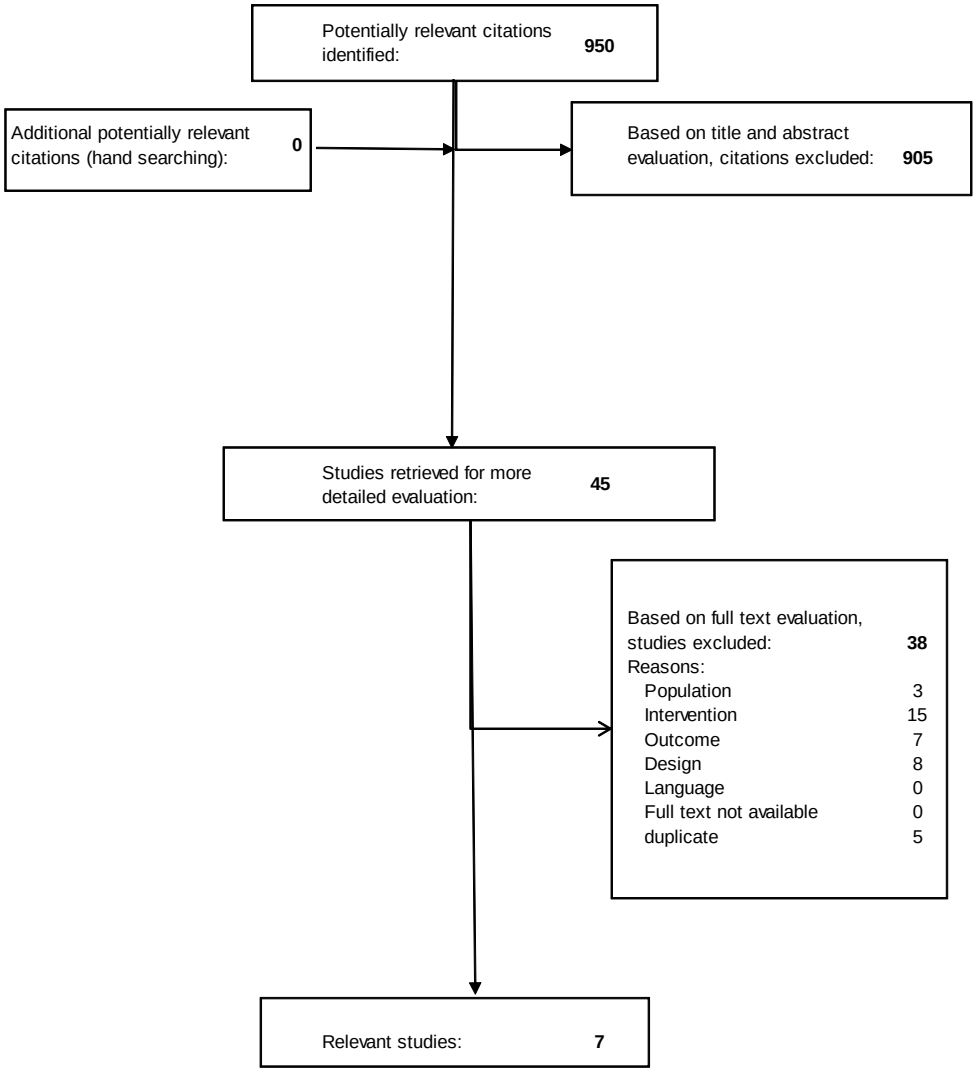
Potentially relevant citations identified: 950
Additional potentially relevant citations (hand searching): 0
Based on title and abstract evaluation, citations excluded: 905
Studies retrieved for more detailed evaluation: 45
Based on full text evaluation, studies excluded: 38
Reasons:
Population 3
Intervention 15
Outcome 7
Design 8
Language 0
Full text not available 0
duplicate 5
Relevant studies: 7

Figure 10 – Selection of randomized controlled trials: flow chart

APPENDIX 2. CRITICAL APPRAISAL

Appendix 2.1. AMSTAR checklist

Table 12 – AMSTAR checklist

Question	Answer
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of the review.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided.	☐ Yes ☐ No ☐ Can't answer

Question	Answer
	☐ Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable

Appendix 2.2. Cochrane Collaboration's tool for assessing risk of bias

Table 13 – Cochrane Collaboration's tool for assessing risk of bias

Domain	Support for judgement	Review authors' judgement
Selection bias		
1. Random sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups	Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence
2. Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment
Performance bias		
3. Blinding of participants and personnel Assessments should be made for each main outcome (or class of outcomes)	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study
Detection bias		
4. Blinding of outcome assessment Assessments should be made for each main outcome (or class of outcomes)	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Detection bias due to knowledge of the allocated interventions by outcome assessors
Attrition bias		
5. Incomplete outcome data Assessments should be made for each main outcome (or class of outcomes)	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for	Attrition bias due to amount, nature or handling of incomplete outcome data

Domain	Support for judgement	Review authors' judgement
	attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors	
Reporting bias		
6. Selective reporting	State how the possibility of selective outcome reporting was examined by the review authors, and what was found	Reporting bias due to selective outcome reporting
Other bias		
7. Other sources of bias	State any important concerns about bias not addressed in the other domains in the tool If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry	Bias due to problems not covered elsewhere in the table

Appendix 2.3. Critical appraisal of systematic reviews

Table 14 – Critical appraisal systematic reviews: results

AMSTAR question[§]	1	2	3	4	5	6	7	8	9	10	11	Included
Oral vs IV fluoropyrimidines												
Zhao 2010	yes	yes	**yes**	yes	no	**yes**	**yes**	yes	yes	no	no	yes
Montagnani 2010	no	yes	**yes**	yes	no	**no**	**no**		yes	no	no	no
Cao 2010	yes	yes	**yes**	yes	yes	**yes**	**yes**	yes	yes	no	no	yes
Ling 2011	yes	yes	**yes**	yes	no	**yes**	**yes**	no	yes	Can't answer	no	yes
Zhang 2012	yes	yes	**yes**	yes	no	**yes**	**yes**	yes	yes	no	no	yes
Petrelli 2012	yes	no	**yes**	yes	no	**yes**	**no**		yes	no	no	no
Oxaliplatin vs												

AMSTAR question[§]	1	2	3	4	5	6	7	8	9	10	11	Included
irinotecan												
Liang 2010	yes	yes	**No**[$]	no	no	**yes**	**yes**	yes	yes	no	no	yes
Zhuang 2010	Can't answer	yes	**yes**	no	no	**yes**	**yes**	no	yes	yes	no	yes
Bevacizumab												
Cao 2009	yes	yes	**yes**	no	yes	**yes**	**yes**	yes	yes	Can't answer	no	yes
Wagner 2009	yes	yes	**yes**	yes	yes	**yes**	**yes**	yes	yes	yes	yes	yes
Welch 2010	yes	yes	**yes**	no	no	**yes**	**yes**	yes	yes	no	no	yes
Loupakis 2010			**no**				**no**					no
Heinemann 2010		no	**no**	no			**no**					no
Galfrascoli 2011	yes	yes	**yes**	yes	yes	**yes**	**yes**	no	yes	no	no	yes
Hompes 2011			**no**	no			**no**					no
Macedo 2012	yes	yes	**yes**	yes	no	**yes**	**yes**	yes	yes	no	yes	yes
Anti-EGFR therapy												
Nie 2009	yes	yes	**yes**	yes	yes	**yes**	**yes**	Can't answer	yes	yes	no	yes
Liu 2010	yes	yes	**yes**	yes	no	**yes**	**yes**	yes	yes	no	no	yes
Tol 2010	Can't answer	Can't answer	**no**	no			**no**					no
Ibrahim 2010		no	**yes**	yes			**no**					no
Qiu 2010			**yes**			**yes**	**no**					no
Petrelli 2011			**no**				**no**					no
Zhang 2011	yes	no	**No**[$]	no	no	**yes**	**yes**	no	yes	no	no	yes
Ibrahim 2011			**yes**			**yes**	**no**					no
Dahabreh 2011	yes	yes	**yes**	no	no	**yes**	**yes**	no	yes	yes	no	yes

AMSTAR question[§]	1	2	3	4	5	6	7	8	9	10	11	Included
Adelstein 2011			**yes**			**yes**	**no**					no
Lin AY 2011			**no**				**no**					no
Loupakis 2012			**no**									no
Vale 2012	yes	Can't answer	**yes**	yes	no	**yes**	**yes**	yes	yes	no	no	yes
Wang 2012	yes	Can't answer	**yes**	yes	no	**yes**	**Can't answer**		yes	yes	no	yes

[§] *as listed in Table 12*

Table 15 – Critical appraisal randomized controlled trials: results

RoB tool question[§]	1	2	3	4	5	6	7
Guan 2011	low	low	high	high	high	low	No ITT analysis
Fuchs 2007	low	low	high	high	low	unclear	sponsored by Pfizer, early closure of capeIRI arm, 3X2 design with simultaneous testing of celecoxib
Köhne 2008	low	low	high	high	low	unclear	sponsored by Roche, Pfizer, Aventis
Cassidy 2011	low	low	high	high	low	low	sponsored by Roche. Cross-over allowed, censored in analysis.
Pectasides 2012	low	low	high	high	unclear	unclear	no ITT analysis
Souglakos 2012	low	low	high	high	unclear	unclear	no ITT analysis
Hochster 2008	low	low	high	high	unclear	unclear	sponsored by Sanofi-aventis
Ducreux 2011	low	low	high	high	unclear	unclear	sponsored by Roche
Van Cutsem 2011	low	low	high	low	high	low	19 untreated patients (reasons unspecified) not included in ITT. KRAS status known for 1063/1198 pts. Sponsored by

RoB tool question[§]	1	2	3	4	5	6	7
							Merck
Tveit 2012	low	unclear	high	high	high	low	KRAS status known for 88% of patients only. 5 ineligible patients excluded from ITT. Sponsored by Merck serono and Sanofi-Aventis
Ducreux 2011 (S vs C)	low	low	high	high	low	low	early closure due to slow accrual after the introduction of bevacizumab
Koopman 2007	low	low	high	high	low	low	Sonsored by Sanofi-Aventis, Roche and pfizer. 17 ineligible patients excluded from analysis
Seymour 2007	low	low	high	high	low	low	Sponsored by Sanofi-synthelabo, Aventis, Wyeth-Lederle, Baxter

[§] *as listed in Table 13*

APPENDIX 3. EVIDENCE TABLES

Table 16 – Treatment metastatic colorectal cancer: SRs oral versus IV fluoropyrimidines 0

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Zhang 2012	• Design: SR and MA • Sources of funding: not stated • Search date: April 2011 • Searched	• Eligibility criteria: RCTs published in English. Histologically confirmed CRC. Experimental arm consists of cpecitabine plus	• Intervention: XELOX or CAPOX or OXXEL • Comparator: FOLFOX(4)(6)	• OS: no meta-analysis performed • PFS: no meta-analysis performed •	• Overall response rate (5 trials): OR 0.85; 95%CI 0.70-1.02 • Complete response (4 trials): OR 0.78; 95%CI 0.47-1.31 • Partial response (4	Results critical appraisal: • none of the trials had any description of concealment allocation and blinding

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	databases: CENTRAL, Pubmed, Ovid Sciencedirect, EBSCO, EMBASE and conference proceedings • Included study designs: RCTs • Number of included studies: 7 • Included studies: Rothenberg 2008 Porschen 2007 Ducreux 2010 Van Cutsem 2009 Diaz-Rubio 2007 Comella 2009 Cassidy 2008	oxaliplatin • Patients characteristics: mean age between 59-66 years. • Median FU: not stated			trials): OR 0.81; 95%CI 0.65-1.00	methods. • Publication bias not assessed, possible conflicts of interest not reported • Unclear if all trials included first-line patients only.
Cao, 2010	• Design: SR and MA • Sources of funding: not stated • Search date: September	• Eligibility criteria: RCTs including patients with metastatic colorectal cancer or advanced colorectal cancer. Capecitabine plus oxaliplatin versus	• Intervention: Capecitabine plus oxaliplatin • Comparator: FU plus oxaliplatin	• Overall survival (4 trials): HR 1.04; 95%CI 0.95-1.14 • Progression-free survival (3 trials): HR 1.08; 95%CI 0.98-	• Time to treatment failure: HR 1.10; 95%CI 1.01-1.20 • Overall response rate: OR 0.87; 95%CI 0.73-1.03	Results critical appraisal: • publication bias not assessed, possible conflicts of interest not

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	2008 • Searched databases: Pubmed, Embase, Cochrane library, abstracts of ASCO meetings • Included study designs: RCTs • Number of included studies: 6 • Included studies: Cassidy 2008 Diaz-Rubio 2007 Porschen 2007 Martoni 2007 Comella 2009 Bennouna 2007	FU plus oxaliplatin for first line treatment • Patients characteristics: median age between 61-67 years • Median FU: between 12.3-29.7 months		1.18	• Toxicity: • Grade 3-4 thrombocytopenia: OR 1.87; 95%CI 1.24-2.81 (p=0.003) • Grade 3-4 neutropenia: OR 0.20; 95%CI 0.07-0.53 (p=0.001) • Grade 3-4 hand-foot syndrome: OR 3.90; 95%CI 2.13-7.12 (p<0.001)	reported • Generation of sequence of randomization described in only 3 out of 6 trials, only one study double blind
Ling, 2011	• Design: SR and MA based on individual patient data • Sources of funding:	• Eligibility criteria: phase III RCT including metastatic CRC, trials in adjuvant setting excluded. Trials comparing	• Intervention: capecitabine-based chemotherapy • Comparator: infusional 5-FU-	• Overall survival: WMD 0.29 months (p=0.75) • Progression-free survival: WMD 1.24 months	• Response rate: OR 1.02; 95%CI 0.90-1.14 • Response rate for trials comparing oxaliplatin	Results critical appraisal: • funnel plots for assessment of publication bias not reported.

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	Shanghai Municipal Education Committee, Shanghai Municipal natural Science Foundation • Search date: March 2010 • Searched databases: Medline CENTRAL, Highwire press, conference proceedings ASCO - ECCO • Included study designs: phase III RCT • Number of included studies: 10 • Included trials: Kohne 2008 Eduardo 2007 Van Cutsem 2001 Skof 2009 Cassidy 2008 Rothenberg	capecitabine-based chemotherapy and infusional 5-FU-based chemotherapy with ITT analysis • Patients characteristics: advanced or metastatic CRC undergoing first-line treatment except in Skof 2009 (neoadjuvant) and Rothenberg 2008 (2nd line); Median age between 60.5-67 years. • Median FU: not stated	based chemotherapy	(p=0.04) (in favour of capecitabine)	combinations: OR 0.93; 95%CI 0.82-1.06 • Response rate capecitabine monotherapy versus 5-FU monotherapy: OR 1.56; 95%CI 1.16-2.06 • Severe adverse events: OR 0.73: 95%CI 0.59-0.92 (p=0.007) in favour of capecitabine	Possible conflicts of interest for included trials not reported. • Unclear if trials reporting on neoadjuvant chemotherapy or second line treatment are included in survival analysis.

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	2008 Martoni 2006 Comella 2009 Hoff 2001 Porschen 2007					

Petrelli 2012[17]: no critical appraisal of included studies, second line study included in meta-analysis. Reference list checked for additional studies: Fuchs 2007 included in meta-analysis KCE.

Montagnani 2010[16]: no critical appraisal of included studies, study in neo-adjuvant setting included in meta-analysis. Fuchs 2007 and Köhne 2008 included in meta-analysis KCE

Table 17 – Treatment metastatic colorectal cancer: RCTs oral versus IV fluoropyrimidines

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Fuchs, 2007	• Design: RCT • Sources of funding: Pfizer • Setting: multicentre, USA, Canada, Australia, New Zealand • Sample size: 430 patients • Duration: February 2003-December 2004	• Eligibility criteria: histologically confirmed metastatic colorectal adenocarcinoma with measurable disease, ECOG PS 0-1, adequate organ function, no previous chemotherapy for metastatic disease, prior adjuvant chemotherapy completed 12	• Intervention(s): FOLFIRI (infusional 5FU + irinotecan) versus mIFL (bolus 5FU + irinotecan) versus CapeIRI (capecitabin + irinotecan)	**Median PFS** • FOLFIRI 7.6 months • mIFL: 5.9 months • CapeIRI 5.8 months • FOLFIRI versus mIFL: HR 1.51; 95%CI 1.16-1.97 (p=0.004) • FOLFIRI versus CapeIRI : HR 1.36 ; 95%CI 1.04-1.80 (p=0.015) • mIFL versus CapeIRI : HR 1.05 ; 95%CI 0.81-1.38 (p=0.46) **Median OS**	**Tolerability**: • discontinuation of study treatment for unacceptable toxicity: CapeIRI 25.5%, FOLFIRI 14.6% mIFL 13.9% • Death rates within the first 60 days of treatment: FOLFIRI 3.6%, mIFL 5.1%, CapeIRI 3.5%	• Dropouts: not stated • Results critical appraisal: early closure of CapeIRI arm due to toxicity and introduction of bevacizumab for second episode of the trial. Trial designed as 3X2 randomization

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
		months befor includion. CNS metastases excluded, cardiovascular comorbidity excluded. • Patients characteristics: median age 61-62y, primary tumour colonca 64.5-71% • Median FU: 34 months		• FOLFIRI 23.1 months • mIFL 17.6 months • CapeIRI 18.9 months • These differences in OS between chemotherapy arms did not achieve statistical significance (p=0.09 for FOLFIRI versus mIFL)		with simultaneous evaluation of celecoxib versus placebo. No blinding of patients, carers or outcome assessors.
Köhne, 2008	• Design: RCT • Sources of funding: Roche, Pfizer, Aventis • Setting: Multicentre, Belgium, Germany, Hungary • Sample size: 85 • Duration: May 2003 – April 2004	• Eligibility criteria: previously untreated metastatic, histologically verified colorectal adenocarcinoma. WHO PS 0-2. • Patients characteristics: 62% male; 52% coloncancer; Median age 64.0y (range 42-78) • Median FU: 14.6 months	• Intervention(s): CAPIRI (capecitabine + irinotecan) • Comparator(s): FOLFIRI (infusional 5FU + irinotecan) • 2X2 design with comparison celecoxib versus placebo	• Median PFS: CapIRI 5.85 months versus FOLFIRI 9.6 months HR 0.76; 95%CI 0.48-1.21 in favour of FOLFIRI • Median OS: CapIRI 14.75 months versus FOLFIRI 19.9 months HR 0.31; 95%CI 0.14-0.71 in favour of FOLFIRI	• Frequency of grade 3/4 adverse events: CAPIRI 74% versus FOLFIRI 49%	• Dropouts: 3 patients did not receive study drugs, excluded from safety analysis • Results critical appraisal: early closure after randomization of 85 (planned 692 patients) due to seven toxic deaths, five in the CAPIRI arm and two in the FOLFIRI arm.
Cassidy,	• Design: RCT	• Eligibility criteria:	• Intervention(s):	• Median overall survival:	• Frequency of grade	• Dropouts: ITT

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
2011	• Sources of funding: Roche • Setting: multicentre, worldwide • Sample size: 2034 pts • Duration: July 2003 – May 2004	histologically confirmed, unresectable metastatic colorectal cancer, ECOG PS 0-1, life expectancy > months. No previous systemic therapy for metastatic disease. Adequate organ function. Excluded: clinically detectable ascites, known CNS metastases • Patients characteristics: median age between 60-62y, primary coloncancer between 63-67% • Median FU: 14.6 months	XELOX (capecitabine + oxaliplatin) • Comparator(s): FOLFOX4 (5FU + oxaliplatin) • 2X2 design with comparison bevacizumab versus placebo (second phase of trial) • Treatment continued until disease progression or for 48 weeks. (continuation in post-study phase or surgery allowed)	(all) XELOX 19.8 months versus (all) FOLFOX4 19.5 months. HR 0.95; 97.5%CI 0.85-1.06) • Median overall survival bevacizumab patients excluded: XELOX 19.0 months versus FOLFOX4 18.9 months. HR 0.95: 97.5%CI 0.83-1.09 • Median overall survival chemotherapy-bevacizumab: XELOX-bevacizumab 21.6 months versus FOLFOX4-bevacizumab 21.0 months. HR 0.95; 97.5%CI 0.78-1.15	3/4 adverse events: XELOX 72% versus FOLFOX4 78% • Frequency of grade 3/4 adverse events XELOX-bevacizumab 75% versus FOLFOX4-bevacizumab 85%	analysis performed but no info on loss of follow-up • Results critical appraisal: no blinding reported. Study insufficiently powered for overall survival as primary outcome PFS (non-inferiority design).
Ducreux, 2011	• Design: RCT • Sources of funding: Roche • Setting: multicentre, France	• Eligibility criteria: previously untreated, histologically confirmed mCRC, measurable disease. ECOG PS	• Intervention(s): XELOX (oxaliplatin+ capecitabine) • Comparator(s): FOLFOX6 (oxaliplatin +	• Progression-free survival: HR 1.00; 90%CI 0.82-1.22 • Overall survival HR 1.02; 90%CI 0.81-1.30	• 20% of XELOX- and 22% of FOLFOX6-treated patients discontinued treatment due to toxicity • Grade 3/4 adverse	• Dropouts: 22 ineligible patients included in ITT population. No information on loss of follow-

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	• Sample size: 306 pts • Duration:May 2003-August 2004	0-2. Prior (neo)adjuvant chemotherapy allowed if completed at least 6 months prior to enrolment. Adequate organ function. • Patients characteristics: median age 66-64y. Male 64-60%. Primary site colon cancer 60-63%. • Median FU: 18.8 months	leucovorin + IV 5FU) *Treatment was continued for maximum 24 weeks*		events: XELOX associated with significantly less grade3/4 neuropathy, neutropenia, and febrile neutropenia but more diarrhoea and thrombocytopnia	up • Results critical appraisal: sample size calculation for response rate as primary outcome. No blinding reported.
Pectasides, 2012	• Design: RCT • Sources of funding: Hellenic Cooperative Oncology Group for translational research • Setting: multicentre, Greece • Sample size: 302 (285) • Duration:	• Eligibility criteria: histologically or cytologically confirmed stage IV CRC with measurable disease. Previous adjuvant treatment should be completed at least 4 months before enrolment. ECOG PS 0-2. Adequate organ function • Patients characteristics:	• Intervention(s): Bevacizumab + irinotecan + capecitabine • Comparator(s): bevacizumab + irinotecan + capecitabine *Bevacizumab was not administered if a contra-indication was present and optionally in elderly patients > 75 years old*	• Median PFS: XELIRI-bev 10.2 months versus FOLFIRi-bev 10.8 months (p=0.74) Median OS: XELIRI-bev 20 months versus FOLFIRi-bev 25.3 months (p=0.099	Toxicity: • Neutropenia more frequent in the FOLFIRI-bev group (13% versus 22%; p=0.053) • Diarrhoea more frequent in the XELIRI group (19% versus 11%; p=0.082) • Vomiting more frequent in the XELIRI group (5% versus 0%; p=0.014)	• Dropouts: 17 ineligible patients excluded from analysis • Results critical appraisal: no blinding. Only 117pts in the intervention group and 120 pts in the control group received bevacizumab

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	January 2006 – January 2008	• Median FU: 42 months				
Souglakos 2012	• Design: RCT • Sources of funding: non stated • Setting: multicentre, Greece • Sample size:336 • Duration: June 2005 – June 2008	• Eligibility criteria: Untreated patients with mCRC, adjuvant treatment completed at least 6 months before study enrolment. ECOG PS 0-2. Measurable disease, adequate organ function. Excluded: liverM+ > 50% of the livern chronic diarrhoea, contraindication for bevacizumab • Patients characteristics: median age 66-67y. Male 62-66%. Primary tumour location colon 74-80% • Median FU: 32 months	• Intervention(s): CAPIRI-bev (capecitabine, irinotecan, bevacizumab) • Comparator(s): bolus 5FU + FA, irinotecan, bevacizumab • Treatment continued until disease progression or unacceptable toxicity	• Median PFS: FOLFIRI-bev 10.0 months versus CAPIRI-Bev 8.9 months. HR 0.99: 95%CI 0.90-1.09 (p=0.85) • Median OS: FOLFIRI-bev 25.7 months versus CAPIRI-Bev 27.5 months. HR 1.08: 95%CI 0.94-1.24 (p=0.30)	• Toxicity: patients treated with CAPIRI-Bev had a significantly higher incidence of grade ¾ febrile neutropenia (p<0.001), diarrhoea (p=003) and hand-foot skin reaction (p=0.03). • Death rates within the first 60 days of treatment were 2.4% for FOLFIRI-Bev patients and 4.1% for CAPIRI-Bev patients (p=0.42)	• Dropouts: 3 ineligible patients excluded from the analysis • Results critical appraisal: no blinding reported.
Hochster, 2008	• Design: RCT • Sources of	• Eligibility criteria: histologically	• Treatment arms TREE 1:	Median overall survival: • mFOLFOX6 19.2	• Incidence of Grade3-4 AE during the first	• Dropouts: not reported • Results critical

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	funding: sanofi-aventis • Setting: multicentre, USA • Sample size: 150+223 • Duration: December 2002 – November 2003 and November 2003 – April 2004	documented mCRC or recuurent CRC without prior chemotherapy for metastatic cancer. Prior adjuvant chemotherapy allowed if completed at least 6 months prior to enrolment. ECOG PS 0-1. Measurable disease. Adequate organ function. • Patients characteristics: median age 57-64y, male 57-65%primary coloncancer 55-75% • Median FU: not stated	mFOLFOX6 versus bFOL versus CapeOx • Treatment arms TREE 2: mFOLFOX6-bev + bFOL-bev + CapeOc-bev	months (95%CI 14.2-24.9 months) • bFOL 17.9 months (95%CI 11.5-24.6) • CapeOX 17.2 months (95%CI 12.5-22.3 months) • mFOLFOX6-bev 26.1 months (95%CI 18.0 to NE months) • bFOL-bev 20.4 months (95%CI 18.4-25.3 months) • CapeOX-bev 24.6 months (21.4-31.6 months) Median TTP: • mFOLFOX6 8.7 months (95%CI 6.5-9.8 months) • bFOL 6.9 months (95%CI 4.2-8.0) • CapeOX 5.9 months (95%CI 5.1-7.4 months) • mFOLFOX6-bev 9.9 months (95%CI 7.9-11.7 months) • bFOL-bev 8.3 months (95%CI 6.6-9.9 months) • CapeOX-bev 10.3 months (8.6-12.5	12 weeks of treatment • mFOLFOX6 76% (95%CI 61-87%) • bFOL 44% (95%CI 30-59%) • CapeOx 73% (95%CI 58-85%) • mFOLFOX-bev: 65% (95%CI 53-76%) • bFOL-bev: 60% (95%CI 48-72%) • CapeOx 58% (95%CI 46-70%)	appraisal: no blinding reported. Completeness of follow-up unclear. No conclusions on survival data, insufficient reporting for inclusion in meta-analysis.

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
				months)		

Table 18 – First-line treatment metastatic colorectal cancer: oxaliplatin versus irinotecan based chemotherapy

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Liang, 2010	• Design: SR and MA • Sources of funding: not stated • Search date: January 2010 • Searched databases: Medline, OVID, Springer, Cochrane Controlled Trials register, Chinese Biology and Medicine disc • Included study designs: RCT • Number of included	• Eligibility criteria: metastatic colorectal cancer diagnosed by pathological examination. First-line studies. Outcomes: clinical efficacy, adverse effects. ITT. • Patients characteristics: comparable between treatment arms • Median FU: not stated •	• Intervention: irinotecan in combination with fluorouracil/leucovorin • Comparator: oxaliplatin in combination with fluorouracil/leucovorin	Overall survival: • WMD -2.04 months; 95%CI -3.54 to -0.54 months (p=0.008) in favour of oxaliplatin-based chemotherapy Time to progression: • -1.07 months; 95%CI 0.70 to 0.26 months (p=0.12)	Response rate: • RR 0.82; 95%CI 0.70-0.96 (p=0.01) in favour of oxaliplatin-based chemotherapy Grade 3-4 toxicity: • Diarrhoea: RR 1.71; 95%CI 1.22-3.09 • Neurotoxicity: RR 0.06; 95%CI 0.03-0.14 • Neutropenia: RR 0.70; 95%CI 0.55-0.91 • Thrombocytopenia: RR 0.18; 95%CI 0.05-0.61 • Alopecia: RR 14.56; 95%CI 4.11-51.66	Results critical appraisal: • Several databases were searched but no 'additional search strategy' such as checking reference lists, search of trial databases or consultation of experts • Included studies considered to be of poor quality as no blinding and allocation

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	studies: 7 • Included studies: Goldberg 2004 Tournigand 2004 Delaunoit 2004 Kalofonos 2005 Comella 2005 Colucci 2005 Goldberg 2006					concealment unclear in all trials.

Zhuang 2010: search date may 2008; all studies included in meta-analysis Liang 2010

Table 19 – First-line treatment of metastatic colorectal cancer: RCTs sequential versus combination therapy

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Koopman, 2007	• Design: RCT • Sources of funding: Dutch Cancer Foundation, Roche, Aventis, Sanofi and Pfizer • Setting: multicentre, the Netherlands • Sample size: 820	• Eligibility criteria: histologically proven colorectal cancer, advanced stage not amenable to surgery. Measurable disease. No prior chemotherapy for metastatic disease, previous adjuvant	• Intervention(s): Sequential treatment = capecitabine, then irinotecan, then capecitabine + oxaliplatin • Comparator(s): combination therapy =	• Overall survival: HR 0.92; 95%CI 0.79-1.08	• PFS after first line treatment: HR 0.77; 95%CI 0.67-0.89 in favour of the combination group	• Dropouts: 17 ineligible patients excluded from analysis. • Results critical appraisal: no blinding.

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	pts • Duration: January 2003-December 2004	chemotherapy allowed if las administration at least 6 months before randomization; WHO PS 0-2. Adequate organ function. • Patients characteristics: median age 63 years, 63% male, 60% primary colon cancer • Median FU: 31.5 months	capecitabine + irinotecan then capectiabine + oxaliplatin Treatment was continued until disease progression or intolerable toxicity for at least six months.			
Seymour, 2007	• Design: RCT • Sources of funding: UK Medical research council, sanofi-synthelabo, Aventis, Wyeth-Lederle, Baxter • Setting: multicentre, UK + Cyprus • Sample size: 2135 pts • Duration: May	• Eligibility criteria: histologically confirmed colorectal cancer with inoperable locoregional or metastatic disease. Measurable disease. WHO PS 0-2. No prior chemotherapy for metastatic disease. Adequate organ function.	• Strategy A: 5FU until treatment failure then irinotecan • Strategy B: 5FU until treatment failure then 5FU + irinotecan (B-Ir) or 5FU + oxaliplatin (B-Ox) • Strategy C: 5FU + irinotecan (C-Ir) or 5FU +	• Overall survival: HR 1.06; 95%CI 0.97-1.17 for strategy B versus C (non-inferiority analysis).		• Dropouts: • Results critical appraisal: no blinding

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	2000-December 2003	• Patients characteristics: 66-70% male, median age 63-64 years, 65-69% primary colon cancer • Median FU: 26.5 months	oxaliplatin (C-Ox) All strategies could be followed by salvage chemotherapy			
Ducreux, 2011	• Design: RCT • Sources of funding: Sanofi-Aventis • Setting: multicentre, France • Sample size: 410 pts • Duration:February 2002 – February 2006	• Eligibility criteria: histologically proven metastatic colorectal cancer with measurable disease. WHO PS 0-2. No prior chemotherapy for metastatic disease, adjuvant chemotherapy allowed if ended 6 months before enrolment. • Patients characteristics: 60-63% male, median age 66-68y. 76-79% primary colon cancer • Median FU: 36 months	• Intervention(s): Sequential treatment = 5FU continued until treatment failure, then FOLFOX6 until treatment failure then FOLFIRI until treatment failure. • Comparator(s): combination treatment = FOLFOX6 until treatment failure, then FOLFIRI until treatment failure. Further lines in both treatment groups were at the investigator's	• Overall survival: HR 1.02; 95%CI 0.82-1.27	• PFS after first line treatment: HR 0.70; 95%CI 0.57-0.85 in favour of combination treatment • PFS after first and second-line treatment: HR 0.95; 95%CI 0.77-1.16 • PFS after first, second and third line of treatment: HR 0.95; 95%CI 0.77-1.16	• Dropouts: 9 pts (2%) lost of follow-up • Results critical appraisal: no blinding. Early closure due to low accrual after the approval of bevacizumab

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
			discretion			

Table 20 – Treatment metastatic colorectal cancer: SRs chemotherapy +/- bevacizumab

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Macedo 2012	• Design: SR and MA • Sources of funding: • Search date: March 2011 • Searched databases: Pubmed, Embase, Lilacs, Cochrane library, Meeting websites ASCE, ESMO, World congress on GI cancer • Included study designs: RCTs • Number of included studies: 6	• Eligibility criteria: RCTs comparing chemotherapy with or without bevacizumab in previously untreated patients with metastatic colorectal cancer. Studies including other targeted agents were excluded. • Patients characteristics: first line treatment, 2 two trials exclusively elderly patients.	• Intervention: Chemotherapy + bevacizumab • Comparator: chemotherapy	• Overall survival: HR 0.84; 95%CI 0.77-0.91 (p=0.04) • Progression-free survival: HR 0.72; 95%CI 0.66-0.78 (p=0.01) • Overall response rate: OR 1.12; 95%CI 0.94-1.33 (p=0.21) • Treatment interruptions: HR 1.47; 95%CI 1.19-1.83 • Treatment related mortality: OR 1.00; 95%CI 0.61-1.63 Toxicity • Hypertension (grade 3-	Irinotecan based chemotherapy • Overall survival: HR 0.78; 95%CI 0.68-0.89 • Progression-free survival: HR 0.66; 95%CI 0.58-0.76 Oxaliplatin based chemotherapy • Overall survival: HR 0.89; 95%CI 0.79-1.00 • Progression-free survival: HR 0.83; 95%CI 0.74-0.93 Fluorouracil	• Results critical appraisal: No results of tests for publication bias reported.

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	Phase II Kabinnavar 2003 Kabinnavar 2005 **Phase III** Hurwitz 2004 Stathopoulos 2010 Saltz 2008 Tebutt 2010	• Median FU: not stated		5): OR 4.90; 95%CI 2.16-11.11 • Bleeding: OR 1.78; 95%CI 1.07-2.95 • Perforation: OR 1.80; 95%CI 0.78-4.17 • Tromboembolic events: OR 1.30; 95%CI 1.01-1.67	monotherapy • Overall survival: HR 0.84; 95%CI 0.69-1.03 • Progression-free survival: HR 0.58; 95%CI 0.49-0.70	

Welch 2010: all first-line studies included in Macedo et al.

Galfrascoli 2011: all first-line studies included in Macedo et al.

Cao 2009: all first-line studies included in Macedo et al.

Table 21 – Treatment metastatic colorectal cancer: RCTs chemotherapy +/- bevacizumab

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Guan, 2011	• Design: RCT • Sources of funding: Sponsored by Shangai Roche Pharmaceuticals • Setting: Multicentre, China • Sample size:	• Eligibility criteria: unresectable, histologically proven, measurable mCRC ECOG PS 0-1, no previous therapy for metastatic disease, life expectancy ≥ 3 months, adequate organ function. • Exclusion criteria:	• Intervention(s): Bevacizumab + irinotecan + 5FU/LV • Comparator(s): irinotecan + 5FU/LV • Treatment continued until documented progressive disease, death or	• PFS rate at six months: 62.6% (95%CI 54.5-70.6%) in the intervention group versus 25.0% (95%CI 14.4-35.6%) in the comparator group (p<0.001) • Median PFS: 8.3 months (95%CI 7.4-8.9 months) in the intervention group	• Incidence of grade 3-4 adverse events: 69% intervention group versus 61% control group	• Dropouts: 11 patients excluded due to no tumour assessment or survival information (7) or not received study treatment (4) • Results critical appraisal: no

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	214 pts • Duration:July 2007-August 2008	previous irinotecan or anti-VEGF therapy, untreated brain metastases or evidence of central nervous system disease, clinically significant cardiovascular disease. • Patients characteristics:median age 50-53 years, colon cancer 48%, 35.9-41.7% single metastatic site • Median FU: not stated	unacceptable toxicity	versus 4.2 months (95%CI 3.7-4.9) months in the comparator group • Risk of death: HR 0.62; 95%CI 0.41-0.95 (p=0.014)		ITT analysis

Table 22 – First-line treatment metastatic colorectal cancer: SRs chemotherapy +/- anti-EGFR therapy

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Vale 2012	• Design: SR and MA • Sources of funding: UK Medical	• Eligibility criteria: completed RCTs comparing chemotherapy + cetuximab or panitumumab with	• Intervention: Anti-EGFR MAbs + chemotherapy • Comparator: identical	• Overall survival first and second line KRAS wild type patients: HR 0.89; 95%CI 0.82-0.97	• Progression-free survival first and second line KRAS wild type patients, including trials using bevacizumab +	• Results critical appraisal: publication bias not assessed, possible conflict of

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	Research Council • Search date: not stated • Searched databases: Medline, CENTRAL, PDQ, clinicaltrials.gov and conference proceedings ASCO, ASCO GI, ESMO, ECCO, World GI congress) • Included study designs: completed RCTs • Number of included studies: 5+2 • Included first-line RCTs: CRYSTAL (Van Cutsem 2008) OPUS (Bokemeyer 2008) PRIME (Douillard 2009 COIN (Maughan	the same standard treatment alone in patients of any age with advanced colorectal cancer. Separate analysis for first –line trials as reported here. Trials including bevacizumab (CAIRO2, PACCE) included in the sensitivity analysis only. • Patients characteristics: Median age between 61-63y, % male between 54-66% • Median FU: not stated	chemotherapy alone	• Progression-free survival first and second line KRAS wild type patients: HR 0.83; 95%CI 0.76-0.90 • Progression-free survival for patients with wild-type KRAS status, including results for all randomized patients from three trials where KRAS subgroup data are unavailable: HR 0.78; 95%CI 0.72-0.863	chemotherapy + anti-EGFR therapy: HR 1.27; 95%CI 1.06-1.51 (poorer PFS associated with the addition of bevacizumab)	interest of included studies not stated. Risk of bias for included trials low or unclear. • Baseline characteristics for the subset of patients in whom KRAS status was assessed were similar to those for all randomised patients (low risk of selection bias)

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	2011) • Nordic VII (Tveit 2010) • CAIRO2 (Tol 2009) • PACCE (Hecht 2009					

NB: as cetuximab and panitumumab are registered in Europe for wild type KRAS advanced colorectal cancer only, results are reported exclusively for this group of patients

Wang 2012: all first-line trials included in Vale et al.

Dahabreh 2011: reports HR of patients with KRAS wild type tumours versus KRAS mutated tumours. No data on treatment outcome within the KRAS wild type group

Zhang 2011: all first-line trials included in Vale et al.

Nie 2009: all first-line trials included in Vale et al.

Liu 2010: all first-line trials included in vale et al.

Table 23 – First-line treatment metastatic colorectal cancer: RCTs chemotherapy +/- anti-EGFR therapy

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Van Cutsem, 2011 (updated results CRYSTAL, Van Cutsem 2009)	• Design: RCT • Sources of funding: Merck • Setting: multicentre, Europe - Asia • Sample size: 1217 pts	• Eligibility criteria: histologically confirmed colorectal adenocarcinoma with EGFR expression, unresectable disease at first occurrence of	• Intervention(s): Cetuximab + FOLFIRI • Comparator(s): FOLFIRI	For WT KRAS tumours: • PFS: HR 0.696; 95%CI 0.558-0.867 (p=0.0012) • OS: HR 0.796; 95%CI 0.670-0.946 (p=0.0093)	For WT KRAS tumours: • Overall response rate: OR 2.096; 95%CI 1.515-2.826 (p=0.0093)	• Dropouts: 19 untreated patients (reasons unspecified) excluded from the ITT • Results critical appraisal: no

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	• Duration: July 2004 – November 2005	metastatic disease. ECOG PS 0-2. No prior therapy for metastatic disease. • Patients characteristics KRAS WT pts: 60.3-62.0% male, median age 59-61y. 84.3-87.7% M+ at one or two sites, 20.6-21.5% confined to liver • Median FU: 46 months				ITT. No blinding of patients and carers but blinding of oucome assessors. Incomplete outcome data as KRAS status known for 1063/1198 patients only (baseline characteristics comparable to overall population).
Tveit, 2012	• Design: RCT • Sources of funding: Merck Serono, Sanofi-Aventis, Norwegian Cancer Society, Swedish Cancer Society • Setting: multicentre, Northern Europe • Sample size:	• Eligibility criteria: previously untreated metastatic colorectal adenocarcinoma, measurable disease, ECOG PS 0-2. FU-based adjuvant chemotherapy allowed if ended more than six months before inclusion • Patients characteristics for KRAS WT population: median	• Intervention A: Continued bolus FU + folinic acid + oxaliplatin + • Intervention B: continued bolus FU + folinic acid + oxaliplatin + continued cetuximab • Intervention C: intermittent bolus FU + folinic acid + oxaliplatin + continued cetuximab	For KRAS wild-type patients: • Overall survival: arm B versus A: HR 1.14; 95%CI 0.80-1.61 arm C versus A : HR 1.08 ; 95%CI 0.77-1.52 • Progression-free survival: arm B versus A: HR 1.07; 95%CI 0.79-1.45	For KRAS wild type: • Overall response rate: HR 0.96; 95%CI 0.55-1.69	• Dropouts: 5 ineligible patients excluded from ITT. KRAS status known for 88% of patients only • Results critical appraisal: unclear allocation concealment (although probably central randomization),

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	571 pts • Duration: May 2005 – October 2007	age 60y, 51-66% male, 64-57% colon cancer • Median FU:	Continued: treatment continued until progressive disease or unacceptable toxicity Intermittent: stopped after 16 weeks of treatment and reintroduced after recording progressive disease			no blinding.

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