NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

Cetuximab (review of TA176) and panitumumab (partial review of TA240) for the first line treatment of metastatic colorectal cancer ID794

Committee papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

MULTIPLE TECHNOLOGY APPRAISAL

Cetuximab (review of TA176) and panitumumab (partial review of TA240) for the first line treatment of metastatic colorectal cancer [ID794]

Contents:

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Any information supplied to NICE which has been marked as confidential, and which is not related to the patient access scheme, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Cetuximab (review of TA176) and panitumumab (partial review of TA240) for the first line treatment of metastatic colorectal cancer

This premeeting briefing highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Key issues for consideration

Clinical effectiveness

Generalisability

- Considering the information below, are the clinical trials generalisable to the population and current practice in England?
  - Trials included subsequent treatments that are not widely used in England.
  - Average age of trial populations was 59–65 years and the majority of participants had an ECOG performance status of <2, meaning that people were younger and fitter than the UK population of people with metastatic colorectal cancer.
  - The Assessment Group assumed that the diagnostic tests for RAS wild-type status used in the clinical trials had the same accuracy as the tests used in NHS practice (page 307 assessment report). It suggested that if the test were less accurate in clinical practice than in the trials, this would likely increase the ICERs for cetuximab and panitumumab.
- Are the diagnostic tests for RAS wild-type status available to all patients in the NHS?

- How important are uncertainties and potential for bias in the clinical evidence?
  - Evidence in people with RAS wild-type status tumours is mainly based on post hoc subgroup analyses, not full intention-to-treat trial populations (the subgroup analysis was pre-planned in 1 trial: PEAK). There are limitations associated with interpreting subgroup data (for example, no minimising bias by stratification or randomisation) and reduced power to show statistical significance.
  - The sample size of people with metastases confined to the liver was small and analyses were post hoc, increasing uncertainty and further reducing power of studies to show statistical significance.
  - The subgroup data are the only available data for the RAS wild-type sub-population. The European Medicines Agency used these data to inform the recent change to the licensed indications for the technologies.
  - Trials were open-label design (participants and outcomes assessors were not blinded). However, 2 studies (OPUS and CRYSTAL) performed a blinded retrospective review of radiological assessment, progression, and best objective response rate, and 1 study (PRIME) did so for objective response rate In addition, in 1 study (PRIME) an independent data monitoring committee reviewed interim analyses of safety and progression free survival. The PEAK trial did not include any independent assessments.

Treatment pathway

- Patients with colorectal cancer may undergo surgery to resect liver metastases; for some patients, they are considered for resection only after first line chemotherapy shrinks the hepatic metastases.
  - Are all patients considered for resection of liver metastases in clinical practice or only people with metastases confined to the liver?
  - What is the evidence for increased survival after resection of liver metastases?

Robustness of clinical effectiveness estimates

- The Assessment Group performed a network meta-analysis to compare cetuximab plus chemotherapy with chemotherapy alone, panitumumab plus

chemotherapy with chemotherapy alone, and lastly cetuximab plus chemotherapy with panitumumab plus chemotherapy. Did the Assessment Group use robust methods and assumptions in its network meta-analysis?

- Was it appropriate for the Assessment Group to use a fixed effect model in its network meta-analysis?
- The Assessment Group generated 2 discrete networks: 1 evaluating FOLFOX-containing chemotherapy regimens and the second comparing FOLFIRI-containing chemotherapy regimens. Was this appropriate, based on the trial data available (it excluded the CALGB-80405 trial)?

Comparators

- Was it appropriate for the Assessment Group to exclude some comparators from its base case?
  - Which FOLFOX regimen (FOLFOX4 or FOLFOX6) is more commonly used in clinical practice in England? The Assessment Group used FOLFOX4 in its base case and FOLFOX6 in a scenario analysis.
  - Is XELOX used in clinical practice in England and is it a relevant comparator?
  - The Assessment Group also excluded the following comparators from its base case: bevacizumab, capecitabine monotherapy, tegafur, folinic acid and fluorouracil.
- The Assessment Group assumed that XELOX had equal efficacy compared with FOLFOX but that XELOX was cheaper. Is this appropriate, given the tolerability profile of XELOX?

Cost effectiveness

Generalisability

- The Assessment Group used an every other week dosing schedule for cetuximab in its base case model, although the trials use weekly dosing. NICE cannot issue guidance outside of the marking authorisation for cetuximab (which stipulates weekly dosing). The Assessment Group did a scenario analysis using weekly dosing of cetuximab; the results are presented in Table 7 and Figures 3–6.

  - [redacted]

- For the subgroup analysis of people with metastases confined to the liver, the following parameters were the same as used for the full population who had metastases not confined to the liver: time of resection, overall survival for patients who have not undergone resection, overall survival post-resection, progression-free survival post-resection, utilities, costs, and adverse events. Parameters that were unique to the subgroup of people with only liver metastases were: proportion of people who had surgical resection, progression-free survival for patients who have not undergone resection and treatment duration. Is this clinically realistic?
- The Assessment Group used an average body surface area of 1.85m^2 for people in its model, meaning that everyone would be treated with the highest dosage of cetuximab. Does this accurately reflect the distribution of patients?

Treatment duration

- Above all, treatment duration is the most critical issue to explain the difference in cost effectiveness estimates between the Merck model and Assessment Group model; the ICERs increase substantially using the Assessment Group estimates.
  - Treatment duration affected the total mean cost of drug acquisition and administration, which were critical drivers of cost effectiveness because they were by far the largest cost items.
  - The Assessment Group ICERs were very sensitive to changes in treatment duration (deterministic sensitivity analysis).
  - ICERs were impacted in a scenario analysis in which the Assessment Group modelled overall survival from trial data, which in turn changed treatment duration estimates (pages 379–382 of the assessment report).

  Was the Assessment Group's method of estimating treatment duration (presented on pages 284–298 of the assessment report) appropriate? Merck acknowledged that it underestimated treatment duration and submitted revised estimates to reflect the actual mean treatment durations from the CRYSTAL and OPUS studies

(pages 11–12 of Merck's comments on the assessment report); these have not been fully critiqued by the Assessment Group because they were submitted as consultation comments but the Assessment Group noted that Merck did not explain its method for calculating mean treatment duration in CRYSTAL and OPUS.

Costs

- The cost of drug administration (comprising drug delivery, pharmacy costs, infusion pump and line maintenance) was one of the largest cost items and is affected by another key issues: treatment duration. Did the Assessment Group use NHS Reference costs appropriately to estimate the cost of drug administration? Refer to page 322–329 of the assessment report and page 8 of Merck's consultation comments (which have not been critiqued by the Assessment Group).
- Did the Assessment Group use an appropriate estimate for the cost of resection surgery? Costs were estimated as follows:
  - Merck: £2707
  - Assessment Group: £10,440
  - NICE technology appraisal 176: £8929.

Proportion of patients who undergo resection

- What is the likely proportion of patients who undergo surgical resection in clinical practice? The Assessment Group's ICERs were very sensitive to changes in this parameter (deterministic sensitivity analysis).
  - The Assessment Group considered that the company (Merck) estimates were not appropriate (see table 92 of the assessment report).
  - The Assessment Group stated that its estimated proportion of patients who undergo resection with CET+FOLFOX [redacted] is subject to uncertainty because it is based on an indirect comparison (pages 251–258 of the assessment report). Is it realistic to assume that the proportion of patients who undergo resection with CET+FOLFOX [redacted] is higher than the proportion with PAN+FOLFOX [redacted]?

- In Merck's consultation comments on the assessment report (which have not been critiqued by the Assessment Group), it referred to data which suggests that a higher proportion of patients undergo surgical resection in clinical practice than in clinical trials (including the CELIM trial by Folprecht et al, the Ye et al study and the Adam et al study). It noted that during NICE technology appraisal 176, clinical specialists stated that a realistic rate for potentially curative resection with chemotherapy in general was approximately 12–15%, which could rise to approximately 30–35% with the addition of cetuximab.

Overall survival and progression-free survival

- The Assessment Group ICERs were very sensitive to changes in the post-resection overall survival and progression-free survival estimates (deterministic sensitivity analysis). In addition, the Assessment Group acknowledged a number of uncertainties in their progression-free survival estimates (see section 5.8).
  - In its base-case model, the Assessment Group assumed that survival after first line progression is independent of first line treatment (that is to say, treatment effect from first line drugs stopped when disease progressed). Is this appropriate?
  - Was it appropriate for the Assessment Group to use the Weibull model to extrapolate post-resection progression due to any other cause? See pages 260–265 of the assessment report for details.
  - Was it appropriate for the Assessment Group to use the log logistic model to extrapolate overall survival post-resection? It rejected the Weibull model because progression free survival exceeded overall survival after 13 years, which is not possible. See pages 260–266 of the assessment report for details.
  - Was it appropriate for the Assessment Group to use the French study by Adam et al. 2004 to estimate progression-free survival and overall survival post-resection? How generalisable is the population in the Adam et al. study?
- Was the Assessment Group's method of estimating progression-free survival for patients who did not undergo resection appropriate (pages 273–277 of the assessment report)?

Utility values

- Are the Assessment Group's utility values appropriate (Table 1)? Although the utility values are derived from trial-based EQ-5D data, the data were from the broader KRAS wild-type population (not specific to RAS wild-type patients). Note that changing the utility values had little impact on the ICERS.

Table 1. Base case utility values in company (Merck) and Assessment Group model (table 83 and 111 assessment report)

Parameter	Company	Assessment Group	Assessment Group source
1st line (PFS)	0.778	0.767	Bennett et al. (2011); average of the PAN+FOLFOX and FOLFOX arms of the PRIME trial (EQ-5D data)
2nd line	0.769	0.762	Bennett et al. (2011) l FOLFIRI arm of the PRIME trial (EQ-5D data)
3rd line (PD)	0.663	0.6407	Wang et al. (2011); people receiving BSC who are in disease progression from the PRIME study (EQ-5D data)
PFS post resection	0.789	0.831 (age 63)	Age related general population utility (method by Ara and Brazier 2010, updated to use Health Survey for England 2012 data)
PD post resection disutility	0.107	0.142	Average of 2nd and 3rd line utilities, weighted by time spent in 2nd or 3rd line
Key: PD, progressive disease; PFS, progression free survival			

Cost-effectiveness results

- Do cetuximab and panitumumab meet the NICE criteria for end of life treatments?
- Cetuximab in combination with FOLFOX or FOLFIRI was shown to be cost effective in the previous appraisal (with ICERS of £26,700–£33,300 and £23,500 per QALY compared with FOLFOX or FOLFIRI alone, respectively). What explains the differences in the ICERs in the current appraisal? Refer to pages 417–423 of the assessment report for a comparison of the 2 models.

1 Remit and decision problem(s)

1.1 The remit from the Department of Health for this appraisal was: To appraise the clinical and cost effectiveness of cetuximab and panitumumab within their licensed indications for previously untreated metastatic colorectal cancer (review of technology appraisal 176 and partial review of technology appraisal 240). This appraisal considers 2 populations:

- everyone with RAS wild-type metastatic colorectal cancer eligible for first-line treatment, and
- a subgroup of people with metastases confined to the liver (note that current NICE guidance TA176 recommends cetuximab only in people whose metastases are confined to the liver).

Approximately 26% of patients in the 5 pivotal clinical trials for cetuximab and panitumumab had metastases only in their liver. Refer to Table 2 below for a summary of the final scope, and Appendix A of the assessment report for the full protocol.

Table 2. Final scope issued by NICE, with Assessment Group comments

	Final scope issued by NICE	Additional comments or specifications in the Assessment Group's protocol
Population	Adults with previously untreated, RAS wild-type mCRC. If evidence allows, consideration may be given to subgroups based on the location of metastases (inside and/or outside the liver).	Subgroup: people with metastases confined to the liver
Intervention	• Cetuximab, in combination with FOLFOX (CET+FOLFOX) or irinotecan-based chemotherapy • Panitumumab, in combination with fluorouracil-containing regimens (PAN+FOLFOX or PAN+FOLFIRI)	Assessment Group did not identify any evidence for PAN+FOLFIRI as a first line treatment in people with RAS wild-type mCRC

Comparator	The interventions should be compared with each other, and with: • FOLFOX • XELOX • FOLFIRI • Capecitabine • Tegafur, folinic acid and fluorouracil • Bevacizumab, in combination with oxaliplatin- or irinotecan-based chemotherapy (not recommended by NICE but funded via the Cancer Drugs Fund)	The Assessment Group used FOLFOX4 in its base case and FOLFOX6 in a scenario analysis (page 385 assessment report and page 19 confidential appendix). The Assessment Group did not include bevacizumab or XELOX in its base case analysis, but included included them as comparators in scenario analyses. • Bevacizumab-based first line treatment for mCRC was delisted from the Cancer Drugs Fund in March 2015. • There were no head-to-head studies comparing cetuximab or panitumumab with XELOX in the RAS wild-type subgroup, and the data for XELOX (compared with FOLFOX) contained many uncertainties. The Assessment Group did do not consider capecitabine monotherapy or tegafur, folinic acid and flourouracil as comparators in the base case or scenarios as these single fluoropyrimidine regimens are typically only used for patients for whom combination chemotherapies would be unsuitable and therefore these patients would not be eligible to receive cetuximab or panitumumab. It did not consider tegafur/uracil because it was discontinued in 2013.
Outcomes	• Overall survival • Progression-free survival • Response rate • Rate of resection of metastases • Adverse events • HRQoL	-
Key: FOLFIRI, folinic acid+fluourouracil+irinotecan; FOLFOX, folinic acid+fluourouracil+oxaliplatin; HRQoL, health-related quality of life; mCRC, metastatic colorectal cancer; RAS, rat sarcoma; XELOX, capectiabine+oxaliplatin		

2 Background: clinical need and practice

2.1 Colorectal cancer usually develops slowly over a period of 10 to 15 years. Metastatic colorectal cancer (mCRC) refers to disease that has spread beyond the large intestine and nearby lymph nodes. This type of cancer most often spreads first to the liver, but metastases may also occur in other parts of the body including the peritoneum, lungs, brain, and bones. Approximately 25% of people present with metastases at initial diagnosis and almost 50% of people with colorectal cancer will develop metastases. The 1-year survival rate in England and Wales is approximately 75%, and the 5-year survival rate is under 60%.

2.2 Treatment of metastatic colorectal cancer may involve a combination of surgery, chemotherapy, radiotherapy and supportive care. When possible, surgical removal (resection) of the primary tumour and metastases may be considered, but usually only when there are no metastases outside of the liver. Chemotherapy may be recommended before surgery, to make the tumour(s) smaller and suitable for resection. For people with metastases only in their liver, complete resection appears to offer the best chance of long-term survival; up to 30% of people may be cured if liver metastases can be resected.

2.3 NICE clinical guideline 131 recommends chemotherapy options including:

1. fluorouracil and folinic acid in combination with oxaliplatin (FOLFOX),
2. tegafur in combination with fluorouracil and folinic acid,
3. capecitabine in combination with oxaliplatin (XELOX), and
4. capecitabine alone.

In practice, fluorouracil and folinic acid may also be used in combination with irinotecan (FOLFIRI) in some people for whom oxaliplatin is not suitable.

2.4 Chemotherapy may be combined with biological agents such as:

1. cetuximab (recommended for 16 weeks only, in people whose metastases are confined to the liver, in technology appraisal 176)
2. panitumumab (available through the Cancer Drugs Fund)
3. bevacizumab (available through the Cancer Drugs Fund).

3 Technologies

3.1 Cetuximab and panitumumab appear to be more effective for treating tumours without mutations (known as 'wild-type') in genes in the RAS family (specifically KRAS and NRAS) than those with mutations. Since the previous NICE technology appraisals of cetuximab and panitumumab, the European Medicines Agency updated the marketing authorisations of both drugs to reflect a new stricter definition of RAS wild-type status so that the drugs are now licensed for a smaller population than previously. The original marketing authorisations applied only to people with metastatic colorectal cancer who did not have mutations in a single part of the KRAS gene (exon 2). The current, updated marking authorisations are restricted to people without any mutations in any of the RAS genes (known as RAS wild-type status, see Table 3). Approximately half of people with metastatic colorectal cancer have RAS wild-type tumours. NICE therefore agreed to review technology appraisal 176 and partially review technology appraisal 240 to appraise the drugs within their revised marketing authorisations.

Table 3. Summary description of technologies under appraisal

	Cetuximab (Erbitux, Merck Serono)	Panitimumab (Vectibix, Amgen)
Marketing authorisation	Indicated for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing, RAS wild-type metastatic colorectal cancer • in combination with irinotecan-based chemotherapy, • in first-line in combination with FOLFOX, • as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan.	Indicated for the treatment of adult patients with wild-type RAS metastatic colorectal cancer (mCRC): • in first-line in combination with FOLFOX or FOLFIRI. • in second-line in combination with FOLFIRI for patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan). • as monotherapy after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens
NICE guidance	NICE TA 176: Cetuximab in combination with FOLFOX, within its licensed indication, is recommended for the first-line treatment of metastatic colorectal cancer only when all of the following criteria are met: (1) the primary colorectal tumour has been resected or is potentially operable (2) the metastatic disease is confined to the liver and is unresectable (3) the person is fit enough to undergo surgery to resect the primary colorectal tumour and to undergo liver surgery if the metastases become resectable after treatment with cetuximab (4) the manufacturer rebates 16% of the amount of cetuximab used on a per patient basis. Cetuximab in combination with FOLFIRI, within its licensed indication, is recommended for the first-line treatment of metastatic colorectal cancer only when all of the following criteria are met:	NICE TA 240: NICE was unable to recommend the use of panitumumab in combination with chemotherapy for the treatment of mCRC because no evidence submission was received from the manufacturer.

	Cetuximab (Erbitux, Merck Serono)	Panitimumab (Vectibix, Amgen)
	(1) The primary colorectal tumour has been resected or is potentially operable. (2) The metastatic disease is confined to the liver and is unresectable. (3) The patient is fit enough to undergo surgery to resect the primary colorectal tumour and to undergo liver surgery if the metastases become resectable after treatment with cetuximab. (4) The patient is unable to tolerate or has contraindications to oxaliplatin. Patients who meet the criteria should receive treatment with cetuximab for no more than 16 weeks. At 16 weeks, treatment with cetuximab should stop and the patient should be assessed for resection of liver metastases.	
Administration	Administered through intravenous infusion once a week. The initial dose is 400 mg cetuximab per m^2 body surface area. All subsequent weekly doses are 250 mg cetuximab per m^2.	6 mg/kg of bodyweight given through intravenous infusion once every two weeks.
Acquisition cost (BNF 2015)	20 ml vial (5 mg/ml): £178.10 100 ml vial (5 mg/ml): £890.50 A patient access scheme makes cetuximab available to the NHS at a lower cost: £114.66 for the 20 ml vial and £573.30 for the 100 ml vial (a 35.6% discount).	5 ml vial (20 mg/ml): £379.29 20 ml vial (20 mg/ml): £1,517.16 A confidential patient access scheme makes panitumumab available to the NHS at a lower cost.
Key: FOLFIRI, folinic acid+fluourouracil+irinotecan; FOLFOX, folinic acid+fluourouracil+oxaliplatin		

4 Clinical-effectiveness evidence

4.1 The Assessment Group included 3 key clinical trials of cetuximab and panitumumab in its base case model: OPUS, CRYSTAL, and PRIME (Table 4). The Assessment Group included data from other randomised clinical trials in scenario analyses, for example the PEAK trial which compared PAN+FOLFOX with BEV+FOLFOX. Full details of the clinical evidence for cetuximab and panitumumab are presented on pages 88–130 of the assessment report.

Table 4. Summary of clinical trials included in Assessment Group base case model

	Trial	Intention to treat population	People with RAS wild-type	Intervention	Comparator
CET	OPUS[a]	337	87	CET+FOLFOX	FOLFOX
	CRYSTAL	1198	367	CET+FOLFIRI	FOLFIRI
PAN	PRIME[a]	1183	512	PAN+FOLFOX	FOLFOX

[a] The Assessment Group used PRIME as the baseline trial for the FOLFOX network in their base case cost-effectiveness model, because PRIME was larger than OPUS.
Key: CET, cetuximab; FOLFIRI, folinic acid+fluourouracil+irinotecan; FOLFOX, folinic acid+fluourouracil+oxaliplatin; PAN, panitumumab

4.2 The Assessment Group performed a network meta-analysis to compare cetuximab plus chemotherapy with chemotherapy alone, panitumumab plus chemotherapy with chemotherapy alone, and lastly cetuximab plus chemotherapy with panitumumab plus chemotherapy. The results of the network meta-analysis are summarised in Table 5. It was not possible for the Assessment Group to construct a complete network based on the trials identified, so it generated 2 discrete networks: 1 evaluating FOLFOX-containing chemotherapy regimens (known as the FOLFOX network) and the second comparing FOLFIRI-containing chemotherapy regimens (known as the FOLFIRI network). Merck constructed a complete network using the CALGB-80405 trial, which compared cetuximab plus FOLFOX or FOLFIRI with bevacizumab plus FOLFOX or FOLFIRI. The

Assessment Group excluded this trial did not randomly allocate patients to FOLFOX or FOLFIRI, and the trial is only available as an abstract (see page 169 of the assessment report). Results from the Assessment Group's 2 discrete networks are not directly comparable.

- There was no evidence to suggest that CET+FOLFOX is any more effective than FOLFOX alone, BEV+FOLFOX or PAN+FOLFOX at improving overall survival or progression-free survival.
- The Assessment Group noted that there was some evidence to show that CET+FOLFOX improved overall response rate compared with PAN+FOLFOX, and
- The Assessment Group noted that there was some evidence to show that CET+FOLFOX was associated with fewer adverse events compared with PAN+FOLFOX.
- Direct trial evidence and the results of the network meta-analysis suggested that CET+FOLFIRI is more effective than FOLFIRI at improving overall survival, progression-free survival and overall response rate.

Full details of the network meta-analysis are presented on pages 131–153 of the assessment report.

4.3 The Assessment Group noted methodological differences between its network meta-analysis and the submissions from the 2 companies that make cetuximab and panitumumab. However, it noted that the overall results of all 3 network meta-analyses were similar, but that all 3 were subject to substantial uncertainty. The Assessment Group stated that, in its view, the main limitation of the clinical evidence was that the clinical evidence was all based on subgroup analyses. The trials were analysed post-hoc after re-evaluating tumour samples from people with KRAS wild-type exon 2 tumours, reclassifying them by RAS wild-type status as currently defined. The Assessment Group noted that there were a low number of samples available for re-analysis and missing data which

reduced the power of some studies to find a statistical difference. The Assessment Group stated that the trial populations were generally balanced which minimised the potential for confounding bias.

Table 5. Summary of results from Assessment Group's network meta-analysis (fixed effect model) to compare chemotherapy-based cetuximab and panitumumab regimens with each other, and with chemotherapy alone: efficacy outcomes (table 54 on page 152 of the assessment report)

	***RAS* wild-type**			***RAS* wild-type with only liver metastases at baseline**		
	PFS, HR (95%CrI)	**OS, HR (95% CrI)**	**Complete resection rate, OR (95% CrI)**	**PFS, HR (95% CrI)**	**OS, HR (95% CrI)**	**Complete resection rate, OR (95% CrI)**
Intervention: CET+FOLFOX compared with						
FOLFOX	0.53 (0.27, 1.04)[a]	0.94 (0.56, 1.57)[a]	NE	0.35 (0.06, 1.96)[a]	0.90 (0.33, 2.43)[a]	4.63 (0.20, 104.60)[a]
PAN+FOLFOX	0.74 (0.36, 1.49)	1.22 (0.71, 2.11)	NE	0.44 (0.07, 2.66)	1.29 (0.42 3.94)	2.09 (0.08, 56.28)
Intervention: PAN+FOLFOX compared with						
FOLFOX	0.72 (0.58, 0.90)[b]	0.77 (0.64, 0.93)[b]	[redacted]	0.79 (0.49, 1.27)[b]	0.69 (0.42, 1.15)[b]	2.20 (0.80, 6.07)[b]
Intervention: CET+FOLFIRI compared with						
FOLFIRI	0.56 (0.41, 0.76)[d]	0.69 (0.54, 0.88)[d]	NE	NE	NE	NE

[a] direct evidence from OPUS; [b] direct evidence from PRIME; [c] direct evidence from PEAK; [d] direct evidence from CRYSTAL; [e] direct evidence from FIRE-3
Key: BEV, bevacizumab; CET, cetuximab; CrI, credible interval; FOLFIRI, folinic acid+fluorouracil+irinotecan; FOLFOX, folinic acid+fluorouracil+oxaliplatin; HR, hazard ratio; NE, not evaluable (no data available); OR, odds ratio; OS, overall survival; PAN, panitumumab; PFS, progression free survival; RAS, rat sarcoma

5 Cost-effectiveness evidence

5.1 Amgen, the manufacturer of panitumumab, did not include an economic model in its submission. Merck, the manufacturer of cetuximab, submitted an economic model which the Assessment Group critiqued on pages 188–236 of the assessment report. The Assessment Group's independent economic assessment is described on page 237 onwards. The Assessment Group model simulates a cohort of people with RAS wild-type metastatic colorectal cancer starting on first line treatment (Figure 1). It uses a cycle length of 1 month and a time horizon of 30 years; virtually everyone in the model is predicted to have died 20 years from start of treatment.

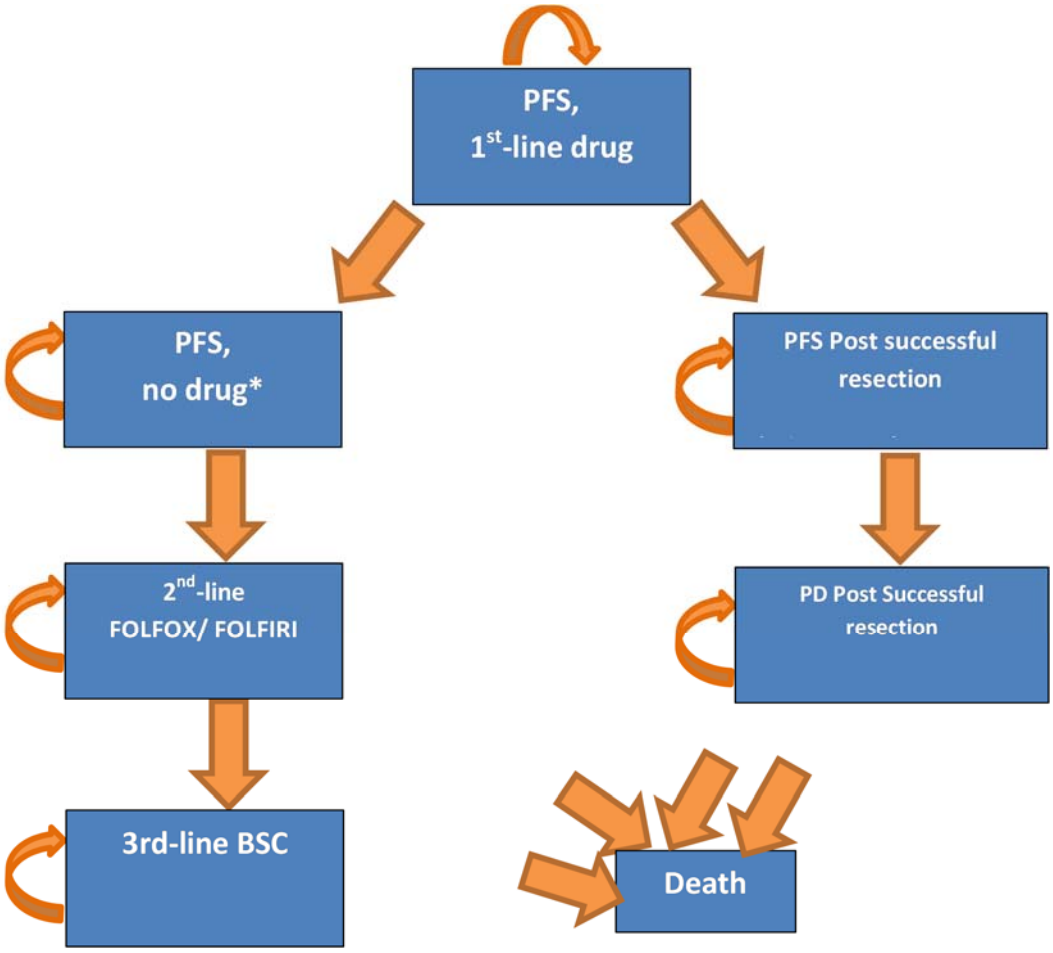
5.2 The Assessment Group assumed a certain proportion of patients receiving treatment then become suitable for resection of their liver metastases; the Assessment Group calculated this separately for each treatment arm. For patients who undergo resection, the Assessment Group modelled progression-free survival and progressive disease post-resection. In the model, life expectancy after resection was substantially greater than for patients without resection. For patients who do not undergo resection, the Assessment Group modelled first line progression-free survival for each therapy, second line treatment with FOLFOX or FOLFIRI and third line treatment with best supportive care. The Assessment Group did not model second-line treatment with panitumumab, cetuximab or bevacizumab, although they were used extensively in the relevant clinical trials, because:

- NICE have recommended none of these treatments
- the CDF have recommended only second line BEV+FOLFOX, not panitumumab nor cetuximab
- these treatments are not commonly used in current practice in England.

5.3 Differences in clinical effectiveness between first line drug treatments are represented by the differences between:

- first line progression-free survival on treatment
- proportion of patients who undergo surgical resection
- incidence of adverse events.

Figure 1. Structure of the Assessment Group cost-effectiveness model



* PFS, no drug: in the randomised controlled trials relevant to this appraisal, mean time on first line treatment is less than mean time in PFS for CET+FOLFIRI and FOLFIRI. Because the Assessment Group assume that patients start second line treatment at the time of progression, there is therefore a period in first line PFS during which patients are on no active drug treatment. For patients who have not undergone resection in the CET+FOLFIRI and FOLFIRI arms, first line PFS is therefore split in to 2 states: on drug, and not on drug. For all other treatments, patients were assumed to receive first line treatment for the complete duration of first line PFS.
Key: BSC, best supportive care; PD, progressive disease; PFS, progression-free survival

5.4 The Assessment Group's base-case analysis assumed that survival after first line progression is independent of first line treatment, that is to say any treatment effect from first line drugs stopped when disease progressed. By contrast, in the randomised controlled trials overall survival reflected response to both first and subsequent lines of treatment. However, the Assessment Group considered it inappropriate to use this assumption in its model because the trials included second line drugs that are not commonly used in the NHS (including second-line panitumumab, cetuximab and bevacizumab), and these second line treatments may affect survival. It also noted that second line treatments differed across the trial arms, and therefore the arms are not balanced. The Assessment Group explored the impact of the alternative survival assumption in a scenario analysis.

5.5 Refer to page 251–341 of the assessment report for full details of the model parameters and assumptions, including:

- utilities (pages 308–314)
- costs (pages 315–338)
- adverse event-related disutilities and costs (pages 338–341).

For the subgroup analysis of people with metastases in their liver **only**, the Assessment Group assumed that the following parameters have the same values in the subgroup as for the full population (who, if they have liver metastases, also have metastases elsewhere):

- time of resection of liver metastases
- overall survival for patients who did not have surgical resection
- overall survival post-resection
- progression-free survival post-resection
- utilities
- costs

- adverse events.

Parameters that were unique to the subgroup of people with only liver metastases were:

- proportion of patients who undergo surgical resection
- progression-free survival for patients who did not have surgical resection
- treatment duration.

5.6 The Assessment Group predicted slightly longer life expectancy in the liver metastases subgroup (1.8–3.0 years) compared with all patients (1.7–2.4 years), because it predicted a higher proportion of patients would undergo resection of liver metastases for the subgroup [redacted] compared with all patients [redacted]

5.7 The Assessment Group noted 8 key differences between its model and the model submitted by Merck, resulting in different ICERs for cetuximab plus chemotherapy compared with chemotherapy alone:

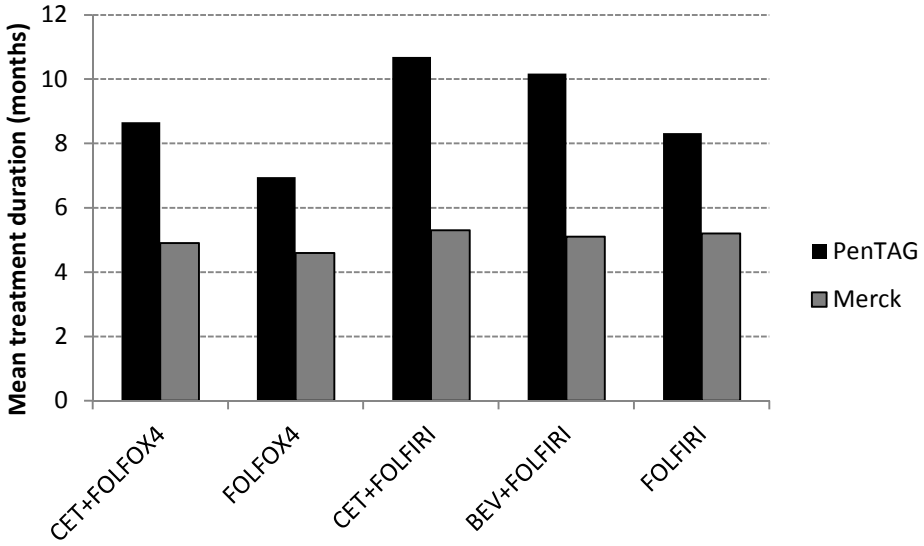
1. **Treatment duration**: the Assessment Group considered that Merck underestimated mean treatment durations. This resulted in lower drug acquisition costs and subsequently lower ICERs than the Assessment Group (see Figure 2 below, and pages 202–203, 222–224 and 284–298 of the assessment report). The Assessment Group noted that treatment duration was the most important issue explaining the difference between the results of the Merck model and the Assessment Group's model. Refer to pages 11–12 of Merck's comments on the assessment report for revised treatment duration estimates, which inform Merck's revised ICERs on page 23 of the comment document (note that these comments and revised ICERs have not been critiqued by the Assessment because they were submitted as consultation comments).

2. **Progression-free survival in patients who did not undergo resection of liver metastases:** the Assessment Group considered that the Merck model overestimated this parameter, which resulted in lower ICERs than the Assessment Group (see page 200–203 of the assessment report).
3. **Post resection progression-free survival:** Merck assumed shorter durations, and therefore estimated higher ICERs, than the Assessment Group (pages 199 and 260 of the assessment report).
4. **Duration of progressive disease:** Merck assumed shorter durations, and therefore estimated higher ICERs, than the Assessment Group (pages 199 and 260 of the assessment report)
5. **Proportion of patients who undergo resection:** Merck assumed a lower proportion of patients who have resection with CET+FOLFOX than the Assessment Group, which increased Merck's ICERs compared with the Assessment Group's estimates (pages 198 and 251 of the assessment report).
6. **Drug administration unit costs:** Merck assumed lower costs, which reduced the ICERs compared with the Assessment Group (see page 231–233, 208 and 322–359 of the assessment report).
7. **Drug acquisition costs**: Merck assumed lower costs for cetuximab and therefore lower ICERs than the Assessment Group. Merck used higher costs for FOLFOX and FOLFIRI than the Assessment Group, which doesn't impact cost effectiveness because both treatment arms are affected in a similar way (pages 205–207, 226–231 and 316–322 of the assessment report).
8. **Cost of a resection operation cost:** Merck assumed a lower cost, which resulted in lower ICERs compared with the Assessment Group (see page 210, 234, and 330–333 of the assessment report).
9. **Monthly cost of post-resection progressive disease:** Merck assumed lower costs, which reduced the ICERs compared with the

Assessment Group (see page 210–211, 233–234 and 335–337 of the assessment report).

When the Assessment Group applied their preferred assumptions to Merck's model, the results were similar to the results of their own model (see table 146 and the figures on pages 404–409 of the assessment report).

Figure 2. Mean durations of first line drug treatment: comparison of company model and Assessment Group's model (PenTAG) (Figure 17 of the assessment report)



5.8 The Assessment Group highlighted a number of uncertainties in its own model:

- **Estimates of progression-free survival:**
  - Evidence for cetuximab was not as strong as panitumumab, because the OPUS trial of cetuximab had fewer RAS wild-type patients (n=87) than the PRIME trial of panitumumab (n=512).
  - Because the Assessment Group did not have access to individual patient data, it could only approximately estimate how progression-free survival differs between patients who do or do not undergo resection (pages 267–282 of the assessment report).
  - The Assessment Group used a study by Adam et al. to estimate progression-free survival and overall survival post-resection, but acknowledged that these data are several years old, and that no patients in the study had received either cetuximab or panitumumab (pages 260–263 of the assessment report). Merck cited some more recent references in its comments on the assessment report (pages 19–20); these have not been critiqued by the Assessment Group because they were submitted as consultation comments.
  - The Assessment Group noted that the subgroup analysis of people with metastases only in their liver is subject to even more uncertainty because it had to make additional assumptions to estimate progression-free survival in these patients.
- **Treatment effect:** the Assessment Group assumed that any treatment effect from first line drugs stopped when disease progressed. The Assessment Group did not model overall survival from the randomised controlled trials because it considered that the data were not mature enough, so modelled only progression-free survival from the trials. It estimated overall survival from the times on first, second and third line treatment for patients who had not undergone resection, and from overall survival for patients who had undergone resection. It acknowledged that this introduced uncertainty in the model, and

explored the use of trial survival data in a scenario analysis (see pages 379–382 of the assessment report for results of the scenario analysis: the ICER for CET+FOLFOX compared with FOLFOX increased, and the ICERS for CET+FOLFORI and PAN+FOLFOX compared with chemotherapy alone decreased).

- **Proportion of patients who undergo resection:** the Assessment Group stated that its estimated proportion of patients who undergo resection with CET+FOLFOX ([redacted]) is subject to uncertainty because it is based on an indirect comparison (pages 251–258 of the assessment report).

Assessment Group base case results

5.9 In the Assessment Group's analysis of all patients, cetuximab and panitumumab generated more QALYs than for chemotherapy alone: 0.15–0.35 more QALYs compared with FOLFOX and 0.30 QALYs compared with FOLFIRI. However the additional costs were substantial: more than £35,000 for cetuximab or panitumumab compared with FOLFOX or FOLFIRI in the Assessment Group's base case.

5.10 The Assessment Group's base-case analysis used a fortnightly dosing regimen for cetuximab, which is not included in its marketing authorisation in the UK. Using a weekly dosing regimen increased the incremental costs for cetuximab plus chemotherapy compared with chemotherapy alone, which in turn increased the ICERs for cetuximab.

5.11 Regardless of dosing regimen for cetuximab, the ICERs for cetuximab or panitumumab combined with chemotherapy compared with chemotherapy alone were all over £100,000 per QALY gained, using the list price for both cetuximab and panitumumab. When the Assessment Group used the discounted prices for panitumumab (discount commercial in confidence) and cetuximab, the ICERs were substantially above £50,000 per QALY gained compared with chemotherapy alone (Table 6, Table 7, Figure 3–6). Table 7 and Figures 3–6 use the weekly dosing regimen for cetuximab.

Table 6. Cost-effectiveness result from company (Merck, manufacturer of cetuximab) and Assessment Group base case analyses: fortnightly dosing of cetuximab (dosing not included in the marketing authorisation for cetuximab in the UK)

	COMPANY ICERs (£/QALY)		AG ICERs (£/QALY)	
	List price	Updated (new assumptions & PAS) NOT CRITIQUED BY AG	List price	PAS for CET and confidential PAS for PAN
ALL PATIENTS				
CET+FOLFOX vs PAN+FOLFOX	Not reported	Not reported	£12,792 (but CET+FOLFOX extendedly dominates PAN+FOLFOX)	[redacted]
CET+FOLFOX vs FOLFOX	£46,503	£44,916	£109,820	£80,182
PAN+FOLFOX vs FOLFOX	Not reported	Not reported	£239,007	[redacted]
CET+FOLFIRI vs FOLFIRI	£55,971	£74,139	£149,091	£105,588
PATIENTS WITH METASTASES CONFINED TO THE LIVER				
CET+FOLFOX vs PAN+FOLFOX	NR	NR	£173,505	[redacted]
CET+FOLFOX vs FOLFOX	£28,230	£42,793 or £22,669[a]	£104,045	£77,043
PAN+FOLFOX vs FOLFOX	Not reported	Not reported	£89,673	[redacted]
CET+FOLFIRI vs FOLFIRI	£39,545	£66,113 or £22,527[a]	£106,707	£78,292

[a] Using the TA176 treatment duration. Source: Assessment report pages 213–221 and confidential appendix, Merck submission pages 60–61
Key: AG, Assessment Group; CET, cetuximab; FOLFIRI, folinic acid+fluorouracil+irinotecan; FOLFOX, folinic acid+fluorouracil+oxaliplatin; ICER, incremental cost-effectiveness ratio; PAN, panitumumab; PAS, patient access scheme; QALY, quality-adjusted life year

Table 7. Cost-effectiveness result from company (Merck, manufacturer of cetuximab) and Assessment Group scenario analyses: weekly dosing of cetuximab (dosing consistent with the marketing authorisation for cetuximab in the UK)

	COMPANY ICERs (£/QALY)	AG ICERs (£/QALY)	
	List price	List price	PAS for CET and confidential PAS for PAN
ALL PATIENTS			
CET+FOLFOX vs PAN+FOLFOX	Not reported	£110,276 (but CET+FOLFOX extendedly dominates PAN+FOLFOX)	[redacted]
CET+FOLFOX vs FOLFOX	£61,894	£165,491	£135,380
PAN+FOLFOX vs FOLFOX	Not reported	£239,007	[redacted]
CET+FOLFIRI vs FOLFIRI	£74,212	£227,381	£183,314
PATIENTS WITH METASTASES CONFINED TO THE LIVER			
CET+FOLFOX vs PAN+FOLFOX	Not reported	£467,857	[redacted]
CET+FOLFOX vs FOLFOX	Not reported	£154,508	£127,166
PAN+FOLFOX vs FOLFOX	Not reported	£89,673	[redacted]
CET+FOLFIRI vs FOLFIRI	Not reported	£157,649	[redacted]

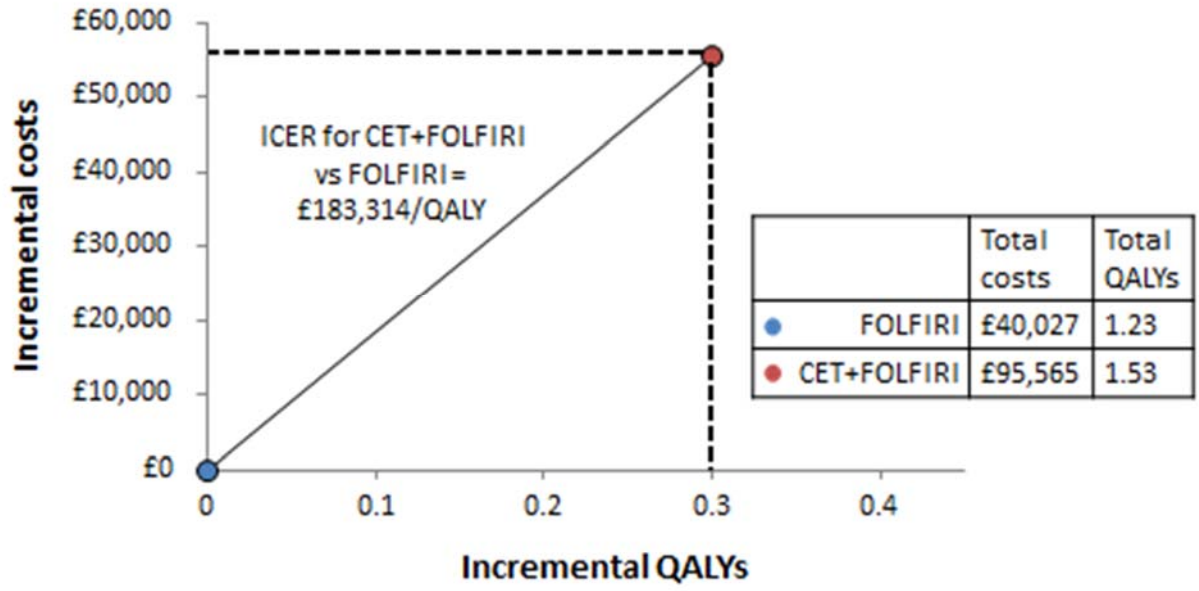
Source: Assessment report pages 385 and confidential appendix, Assessment Group model (Excel file), Merck submission pages 60–61
Key: AG, Assessment Group; CET, cetuximab; FOLFIRI, folinic acid+fluorouracil+irinotecan; FOLFOX, folinic acid+fluorouracil+oxaliplatin; ICER, incremental cost-effectiveness ratio; PAN, panitumumab; PAS, patient access scheme; QALY, quality-adjusted life year

Figure 3. Assessment Group base case results using discounted prices for panitumumab (discount commercial in confidence) and cetuximab and weekly dosing for cetuximab: all patients, FOLFOX network

[redacted]

Source: Assessment report confidential appendix
CET, cetuximab; FOLFOX, folinic acid+fluorouracil+oxaliplatin; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life year

Figure 4. Assessment Group base case results using discounted price and weekly dosing for cetuximab: all patients, FOLFIRI network

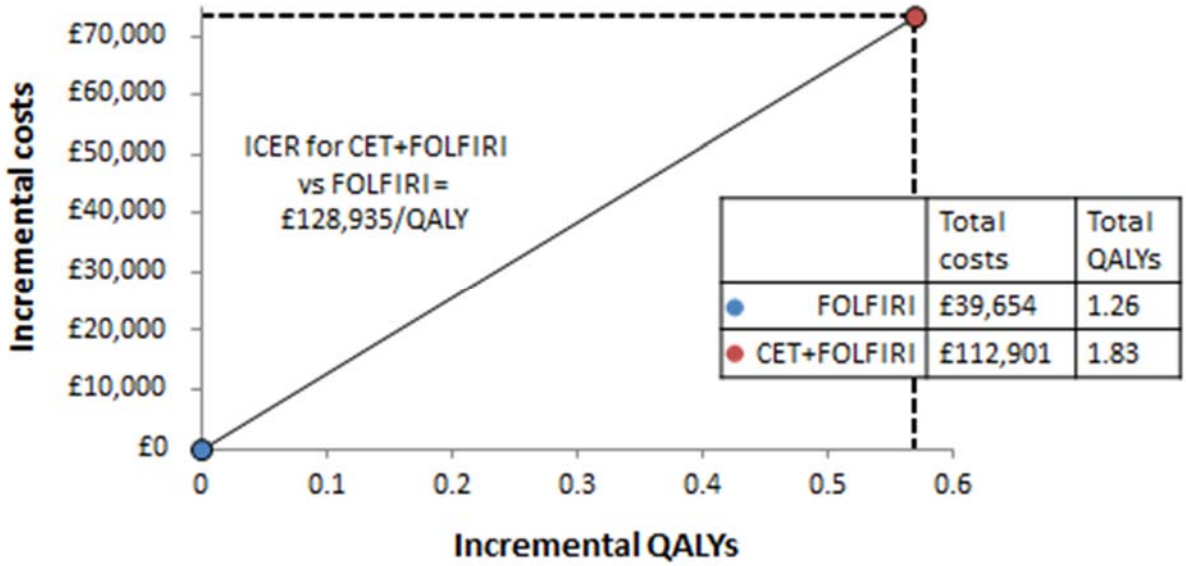


Source: Assessment report confidential appendix
CET, cetuximab; FOLFIRI, folinic acid+fluorouracil+irinotecan; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life year

Figure 5. Assessment Group base case results using discounted prices for panitumumab (discount commercial in confidence) and cetuximab and weekly dosing for cetuximab: patients with metastases confined to liver, FOLFOX network

Source: Assessment report confidential appendix
CET, cetuximab; FOLFOX, folinic acid+fluorouracil+oxaliplatin; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life year

Figure 6. Assessment Group base case results using discounted price and weekly dosing for cetuximab: patients with metastases confined to liver, FOLFIRI network



Source: Assessment report confidential appendix
CET, cetuximab; FOLFIRI, folinic acid+fluorouracil+irinotecan; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life year

5.12 In the base case analysis of all patients, most of the incremental QALYs for CET+FOLFOX compared with FOLFOX came from progression-free survival post-resection. The Assessment Group explained that this is largely because of the high expected proportion of patient who undergo resection for CET+FOLFOX ([redacted]) compared to FOLFOX ([redacted]). The incremental QALYs for PAN+FOLFOX were lower than for CET+FOLFOX, because the Assessment Group model predicted a lower proportion of patients undergoing resection for PAN+FOLFOX ([redacted]), compared to CET+FOLFOX. For CET+FOLFIRI, most incremental QALYs came from progression-free survival in patients who either underwent resection or who did not, but post-resection QALYs were less important than for CET+FOLFOX because of the low proportion of patients undergoing resection with CET+FOLFIRI (7.3%) and FOLFIRI (2.1%). In the subgroup analysis of people with metastases confined to their liver, most incremental QALYs in the FOLFOX network came from progression-free survival and progressive disease post-resection. In the FOLFIRI network QALYS came from progression-free survival both in patients who did or did not undergo resection.

5.13 The probability that the treatments are cost-effective at a willingness to pay threshold of £30,000 per QALY (using list prices for cetuximab and panitumumab) are:

- FOLFOX or FOLFIRI: 78%
- CET+FOLFOX: 22%
- PAN+FOLFOX: 0%
- CET+FOLFIRI: 0%.

Results were similar in the subgroup whose metastases are confined to the liver. See figures 60 and 61 of the assessment report for cost-effectiveness acceptability curves.

5.14 When the Assessment Group set the prices of cetuximab and panitumumab to zero, the ICERs were:

- CET+FOLFOX compared with FOLFOX: £27,000 per QALY
- PAN+FOLFOX compared with FOLFOX: £50,000 per QALY
- CET+FOLFIRI compared with FOLFIRI: £27,000 per QALY.

The Assessment Group suggested that the reason that CET+FOLFOX, PAN+FOLFOX and CET+FOLFIRI were associated with high ICERS is that total costs of administering the combination treatments far exceeds the costs of either FOLFOX or FOLFIRI, which is because the Assessment Group predict that patients take the combination treatments for longer than chemotherapy alone (9–11 months compared with 7–8 months). See pages 392–394 of the assessment report for more detail.

5.15 In the Assessment Group's deterministic sensitivity analysis (pages 387–392 of the assessment report), the ICERs were very sensitive to the:

- proportion of patients who undergo resection
- length of progression-free survival after resection
- life expectancy (overall survival) after resection
- progression-free survival for patients who do not undergo resection
- treatment duration.

ICERs were also sensitive to:

- discounting
- cost of administration for first line drugs.

5.16 The Assessment Group's scenario analyses are presented on pages 376–387 of the assessment report.

6 End-of-life considerations

6.1 Table 8 and Table 9 summarise the End of Life criteria, as presented in the assessment report. The Assessment Group cautioned that the life extension estimates were not robust. Merck provided additional considerations on End of Life criteria in the comments on the assessment report (pages 15–18); these have not been critiqued by the Assessment Group because they were submitted as consultation comments. Note that the indications in the marketing authorisations for cetuximab and panitumumab differ: cetuximab is also approved for treating squamous cell cancer of the head and neck which determines the population size.

Table 8. Assessment of cetuximab against NICE End of Life criteria (table 148 of assessment report)

End of Life criteria	CET+FOLFOX compared with FOLFOX	CET+FOLFIRI compared with FOLFIRI
Treatment is indicated for patients with a short life expectancy, normally less than 24 months	Mean 22.3 months on FOLFOX based on Assessment Group model (page 343 assessment report).	Mean 21.0 months on FOLFIRI based on Assessment Group model (page 343 assessment report).
	However, mean 26.7 months based on PRIME RCT	However, mean 24.9 months based on CRYSTAL RCT
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Mean 6.6 months extension to life expectancy based on Assessment Group model (page 343 assessment report).	Mean 5.5 months extension to life expectancy based on Assessment Group model (page 343 assessment report).
	However, mean 0.5 months based on OPUS RCT alone.	However, mean 8.8 months based on CRYSTAL RCT alone.

End of Life criteria	CET+FOLFOX compared with FOLFOX	CET+FOLFIRI compared with FOLFIRI
Technology is licensed or otherwise indicated, for small patient populations normally not exceeding a cumulative total of 7000 for all licensed indications in England[a]	Estimated by the Assessment Group as: • 8,807 (based on data considered in previous technology appraisal TA282 for KRAS WT population, including other indications for cetuximab and updated to reflect subgroup of RAS WT patients, in England only) • 7,567 (based on data submitted by Merck for this appraisal, updated to reflect all indications for cetuximab using data from TA272, in England only) • 11,349 (based on data cited in assessment report for current appraisal, pages 63–64 and 410)	

[a] Note that the indications in the marketing authorisations for cetuximab and panitumumab differ: cetuximab is also approved for treating squamous cell cancer of the head and neck

Table 9. Assessment of panitumumab against NICE End of Life criteria (table 149 of assessment report)

End of Life criteria	PAN+FOLFOX compared with FOLFOX
Treatment is indicated for patients with a short life expectancy, normally less than 24 months	Mean 22.3 months on FOLFOX based on Assessment Group model (page 343 assessment report). However, mean 26.7 months based on PRIME RCT
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Mean 2.6 months extension to life based on Assessment Group model (page 343 assessment report). However, mean 5.7 months based on PRIME RCT alone.
Technology is licensed or otherwise indicated, for small patient populations normally not exceeding a cumulative total of 7000 for all licensed indications in England[a]	Estimated by the Assessment Group as: • 5,968 (based on data considered in previous technology appraisal TA282 for KRAS WT population, updated to reflect subgroup of RAS WT patients, in England only) • 4,728 (based on data submitted by Merck for this appraisal, updated to reflect England only) • 8,511 (based on data cited in assessment report for current appraisal, pages 63–64 and 410)

[a] Note that the indications in the marketing authorisations for cetuximab and panitumumab differ: cetuximab is also approved for treating squamous cell cancer of the head and neck

7 Equality issues

7.1 No equality issues were identified during the scoping process or submissions.

8 Authors

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Appendix A: Supporting evidence

Related NICE guidance

Published

- Cetuximab, bevacizumab and panitumumab for the treatment of metastatic colorectal cancer after first-line chemotherapy (review of TA150 and part review of TA118). NICE technology appraisal guidance 242 (2012)
- Panitumumab in combination with chemotherapy for the treatment of metastatic colorectal cancer (terminated appraisal). NICE technology appraisal guidance 240 (2011)
- Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for the treatment of metastatic colorectal cancer. NICE technology appraisal guidance 212 (2010)
- Cetuximab for the first-line treatment of metastatic colorectal cancer'. NICE technology appraisal guidance 176 (2009)
- Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer. NICE technology appraisal guidance 118 (2007)
- The diagnosis and management of colorectal cancer'. NICE clinical guideline 131 (2011)
- Selective internal radiation therapy for non-resectable colorectal metastases in the liver. NICE interventional procedure guidance 401 (2011)
- Radiofrequency ablation for colorectal liver metastases. NICE interventional procedure guidance 327 (2009)
- Preoperative high dose rate brachytherapy for rectal cancer. NICE interventional procedure guidance 201 (2006)

NICE pathways

- There is a NICE pathway on Colorectal cancer, which is available from http://pathways.nice.org.uk/pathways/colorectal-cancer.

Appendix B: European public assessment report

Cetuximab: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000558/WC500160158.pdf

Panitumumab: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000741/WC500187313.pdf

NICE National Institute for Health and Care Excellence

Cetuximab for the first-line treatment of metastatic colorectal cancer

Issued: August 2009

NICE technology appraisal guidance 176

guidance.nice.org.uk/ta176

Contents

1 Guidance

1.1 Cetuximab in combination with 5-fluorouracil (5-FU), folinic acid and oxaliplatin (FOLFOX), within its licensed indication, is recommended for the first-line treatment of metastatic colorectal cancer only when all of the following criteria are met:

- The primary colorectal tumour has been resected or is potentially operable.
- The metastatic disease is confined to the liver and is unresectable.
- The patient is fit enough to undergo surgery to resect the primary colorectal tumour and to undergo liver surgery if the metastases become resectable after treatment with cetuximab.
- The manufacturer rebates 16% of the amount of cetuximab used on a per patient basis.

1.2 Cetuximab in combination with 5-FU, folinic acid and irinotecan (FOLFIRI), within its licensed indication, is recommended for the first-line treatment of metastatic colorectal cancer only when all of the following criteria are met:

- The primary colorectal tumour has been resected or is potentially operable.
- The metastatic disease is confined to the liver and is unresectable.
- The patient is fit enough to undergo surgery to resect the primary colorectal tumour and to undergo liver surgery if the metastases become resectable after treatment with cetuximab.
- The patient is unable to tolerate or has contraindications to oxaliplatin.

1.3 Patients who meet the criteria in 1.1 and 1.2 should receive treatment with cetuximab for no more than 16 weeks. At 16 weeks, treatment with cetuximab should stop and the patient should be assessed for resection of liver metastases.

1.4 People with metastatic colorectal cancer with metastatic disease confined to the liver who receive cetuximab should have their treatment managed only by multidisciplinary teams that involve highly specialised liver surgical services.

2 The technology

2.1 Cetuximab (Erbitux, Merck Serono) is a recombinant monoclonal antibody that blocks the human epidermal growth factor receptor (EGFR) and therefore inhibits the proliferation of cells that depend on EGFR activation for growth. Cetuximab is indicated for the treatment of patients with EGFR-expressing, Kirsten rat sarcoma (KRAS) wild-type metastatic colorectal cancer:

- in combination with chemotherapy
- as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan.

2.2 One common adverse effect of cetuximab treatment is the development of skin reactions, which occur in more than 80% of patients and mainly present as an acne-like rash or, less frequently, as pruritus, dry skin, desquamation, hypertrichosis or nail disorders (for example, paronychia). The majority of skin reactions develop within the first 3 weeks of treatment. The summary of product characteristics (SPC) notes that if a patient experiences a grade 3 or 4 skin reaction, cetuximab treatment must be stopped, with treatment being resumed only if the reaction resolves to grade 2. Other common adverse effects of cetuximab include mild or moderate infusion-related reactions such as fever, chills, nausea, vomiting, headache, dizziness or dyspnoea that occur soon after the first cetuximab infusion. For full details of adverse effects and contraindications, see the SPC.

2.3 The acquisition cost of cetuximab is £159.02 for a 5-mg/ml, 20-ml vial (excluding VAT; 'British national formulary' [BNF] edition 57). The manufacturer has agreed with the Department of Health that the NHS price will be £136.50 for a 20-ml vial (the previous list price) until NICE next reviews the guidance on cetuximab for this indication. All calculations are based on this price. The initial dose is 400 mg/m^2 body surface area. Subsequent weekly doses are 250 mg/m^2 each. The SPC states that cetuximab treatment is recommended until there is progression of the underlying disease. A person with a body surface area of 1.75 m^2 would receive seven vials per loading dose and five vials per maintenance dose, equating to a cost of £955.50 for the loading dose and £682.50 for each maintenance dose. Patients in the key clinical trials received

cetuximab for approximately 8 months, equating to an average total cost of £22,796 per patient. Costs may vary in different settings because of negotiated procurement discounts.

3 The manufacturer's submission

The Appraisal Committee (appendix A) considered evidence submitted by the manufacturer of cetuximab and a review of this submission by the Evidence Review Group and the Decision Support Unit (ERG and DSU; appendix B).

Clinical effectiveness

3.1 In the submission, the manufacturer compared a regimen of cetuximab in combination with FOLFIRI with the FOLFIRI chemotherapy regimen alone, and a regimen of cetuximab in combination with FOLFOX with the FOLFOX chemotherapy regimen alone.

3.2 The main evidence on the efficacy of cetuximab in the manufacturer's submission was derived from two randomised controlled trials:

- CRYSTAL (n = 1198), a phase III, multicentre, open-label randomised controlled trial, which compared cetuximab in combination with FOLFIRI with FOLFIRI alone, and examined progression-free survival as the primary outcome.
- OPUS (n = 336), a phase II, multicentre, open-label randomised controlled trial, which compared cetuximab in combination with FOLFOX with FOLFOX alone, and examined response rate as the primary outcome.

  The participants in both trials were patients with previously untreated metastatic colorectal cancer with non-resectable metastases and an Eastern Cooperative Oncology Group (ECOG) performance status of less than or equal to 2 at study entry. The planned treatment duration in both trials was until demonstration of progressive disease by computed tomography (CT) or magnetic resonance imaging (MRI), withdrawal of consent, or occurrence of unacceptable adverse events (CRYSTAL only) or toxicity (OPUS only).

3.3 In the submission, the manufacturer presented data for the full analysis set (people with KRAS wild-type metastatic colorectal cancer and KRAS mutations) for both trials. However, the main data in the submission focused on the post hoc analysis of the KRAS wild-type subgroup (n = 348 for the

CRYSTAL trial; n = 134 for the OPUS trial), which was requested by the regulatory agencies and reflects the licensed indication.

3.4 In response to ACD consultation, the manufacturer submitted updated overall survival data from the CRYSTAL trial (described in sections 3.5 and 3.7) and additional clinical evidence on the rates of liver resection (described in sections 3.12 and 3.13).

3.5 The results of the full analysis set for the CRYSTAL study showed an improved progression-free survival for cetuximab in combination with FOLFIRI compared with FOLFIRI alone (p = 0.0479) with a hazard ratio (HR) of 0.85 (95% confidence interval [CI] 0.726 to 0.998). In the manufacturer's additional evidence, the overall survival (median follow-up 30 months) was 19.9 months (95% CI 18.5 to 21.3) for cetuximab in combination with FOLFIRI compared with 18.6 months (95% CI 16.6 to 19.8) for FOLFIRI alone (HR = 0.93, 95% CI 0.81 to 1.07). This was not statistically significant (p = 0.30).

3.6 In the OPUS study, for the full analysis set, the best overall response rate for cetuximab in combination with FOLFOX was 45.6% compared with 36.0% for FOLFOX alone. The chance for a best overall response of either complete response or partial response increased by 50% in the cetuximab in combination with FOLFOX group, which was not statistically significant (p = 0.064).

3.7 The results of the CRYSTAL trial for the KRAS wild-type subgroup showed a statistically significant increase in progression-free survival with a median progression-free survival of 9.9 months (95% CI 8.7 to 14.6) for cetuximab in combination with FOLFIRI compared with 8.7 months (95% CI 7.4 to 9.9) for FOLFIRI alone (HR = 0.684, p = 0.0167). Cetuximab in combination with FOLFIRI was also associated with a statistically significant increase in response rate compared with FOLFIRI alone (59.3%, 95% CI 51.6 to 66.7 versus 43.2%, 95% CI 35.8 to 50.9, respectively; p = 0.0028). The rate of potentially curative liver metastases resection for cetuximab in combination with FOLFIRI was 3.5% (n = 6) compared with 2.3% (n = 4) for FOLFIRI alone (statistical significance was not reported for this outcome). In the additional evidence, the overall survival (median follow-up 30 months) was 24.9 months

(95% CI 22.2 to 27.8) for cetuximab in combination with FOLFIRI compared with 21.0 months (95% CI 19.2 to 25.7) for FOLFIRI alone (HR = 0.84, 95% CI 0.64 to 1.11). This was not statistically significant (p = 0.22).

3.8 The OPUS trial results for the KRAS wild-type subgroup also showed a statistically significant increase in progression-free survival, with a median progression-free survival of 7.7 months (95% CI 7.1 to 12.0) for cetuximab in combination with FOLFOX compared with 7.2 months (95% CI 5.6 to 7.4) for FOLFOX alone (HR = 0.570, p = 0.0163). Cetuximab in combination with FOLFOX was also associated with a statistically significant increase in response rate compared with FOLFOX alone (60.7%, 95% CI 47.3 to 72.9 versus 37.0%, 95% CI 26.0 to 49.1, p = 0.011). The rate of potentially curative liver metastases resection for cetuximab in combination with FOLFOX was 11.5% (n = 7) compared with 4.1% (n = 3) for FOLFOX alone (statistical significance was not reported for this outcome).

3.9 The CRYSTAL trial also reported results for people in the KRAS wild-type subgroup who had metastatic disease confined to the liver (n = 67). The addition of cetuximab to FOLFIRI increased the median progression-free survival from 9.5 months to 14.6 months. However, this difference was not statistically significant (HR = 0.724, p = 0.437). Cetuximab in combination with FOLFIRI was associated with a statistically significant increase in response rate compared with FOLFIRI alone (77.1%, 95% CI 59.9 to 89.6 versus 50.0%, 95% CI 31.9 to 68.1, p = 0.0246).

3.10 Quality of life was assessed in the CRYSTAL study using the QLQ-C30 and the EuroQol (EQ-5D) questionnaires. In the KRAS wild-type subgroup, some measures of the QLQ-C30 showed statistically significant differences between the two treatment groups in favour of the FOLFIRI-only group (mean change from baseline to worst physical functioning score, and dyspnoea scores). Only 37 patients completed evaluable baseline EQ-5D questionnaires; therefore, no formal statistical analyses were performed. A summary utility value was calculated for all patients, pooling all values at each visit. This provided a utility value representative of patients receiving first-line chemotherapy of 0.77 (standard deviation 0.22, n = 128). The OPUS study did not collect any quality of life data.

3.11 The majority of adverse events in the KRAS wild-type subgroup were in line with the existing SPC for cetuximab or 5-FU with folinic acid in combination with irinotecan or oxaliplatin. In the CRYSTAL trial, the adverse events that occurred more frequently with cetuximab in combination with FOLFIRI compared with FOLFIRI alone (a difference of 5% or more between groups) were neutropenia, constipation, dyspepsia, dyspnoea, dysgeusia, injection site reaction, erythema, hypotension, hypertrichosis and cheilitis. In the KRAS wild-type population of both the CRYSTAL and OPUS trials, the frequency of palmar-plantar erythrodysaesthesia syndrome was higher with cetuximab in combination with FOLFIRI compared with FOLFIRI alone (16.2% versus 2.8% [28 versus 5 patients]) and with cetuximab in combination with FOLFOX compared with FOLFOX alone (13.1% versus 4.1% [8 versus 3 patients]).

3.12 The manufacturer submitted data from the CELIM trial (n = 114), a phase II, multicentre, open-label, randomised trial that compared cetuximab in combination with FOLFOX with cetuximab in combination with FOLFIRI, and examined tumour response as the primary outcome. Secondary endpoints included liver resection rates, progression-free survival, disease-free survival and overall survival. The participants in the trial were patients with non-resectable colorectal liver metastases (defined as patients with five or more liver metastases, or patients with liver metastases that are technically non-resectable) and a Karnofsky performance status score of 80 or more. Patients received 8 cycles (approximately 4 months) of treatment.

3.13 The results of the interim analysis of the data from the CELIM trial showed that the liver resection rate for cetuximab in combination with FOLFIRI (n = 53) was 43% compared with 40% for cetuximab in combination with FOLFOX (n = 52). For all patients in the trial (n = 105) the liver resection rate was 42%, and for the KRAS wild-type subgroup (n = 67) it was 43%. For those patients who had technically non-resectable liver metastases at baseline (n = 57) the liver resection rate was 40%.

3.14 The ERG considered that there were a number of limitations with the evidence in the manufacturer's submission. It noted that the KRAS wild-type analysis was carried out post hoc and was likely to have been underpowered. It also noted that the differences in progression-free survival of 1.2 months and

0.5 months for the CRYSTAL and OPUS trials' KRAS wild-type populations, respectively, were statistically significant in favour of cetuximab but not clinically meaningful. The ERG was also uncertain of the accuracy of the KRAS test in clinical practice.

3.15 The ERG identified a number of limitations with the evidence from the CELIM study. It was concerned that the study was not a randomised assessment of cetuximab compared with no cetuximab. Therefore the ERG was uncertain whether the higher rates of resection were because of cetuximab treatment or other factors in the study such as those associated with patient care, surgical practice and patient characteristics. The ERG noted that inclusion criteria for the study specified patients with non-resectable liver metastases, with 55% of patients having technically non-resectable metastases at baseline and 45% having five or more liver metastases. In addition, the ERG commented that the sample size in the trial was relatively small, with approximately 55 patients in each arm.

Cost effectiveness

3.16 The manufacturer developed a semi-Markov model to simulate the disease progression and survival of a cohort of patients with EGFR-expressing, KRAS wild-type metastatic colorectal cancer throughout first and subsequent lines of treatment (second- and third-line) including longer-term survival after successful curative surgery. The model had a cycle length of 1 week and estimated costs and benefits over a lifetime horizon (approximately 23 years).

3.17 The analysis looked at two treatment strategies: cetuximab in combination with FOLFIRI compared with FOLFIRI alone, and cetuximab in combination with FOLFOX compared with FOLFOX alone. The economic evaluation focused on a population with the following characteristics:

- Good performance status (the majority of KRAS wild-type patients in the CRYSTAL and OPUS trials [96% and 90%, respectively] had an ECOG performance status of 0 or 1, so this was reflected in the modelled cohort).
- Suitable for irinotecan- or oxaliplatin-containing chemotherapy.

- Metastatic disease confined to the liver, excluding people whose liver metastases were resectable at presentation.

3.18 The analysis assessed the impact of cetuximab in combination with FOLFIRI or FOLFOX on the rates of potentially curative resection among people whose tumours became resectable during first-line treatment. The first-line treatment regimens were as set out in the CRYSTAL and OPUS trial protocols and administered as recorded in the trial data sets. The second-line treatment regimens of FOLFIRI or FOLFOX were taken from the published evidence, dependent on first-line treatment. If FOLFIRI was used in the first line, then FOLFOX was used in the second line, and vice versa. In the third-line setting, people received best supportive care. In the model, people were considered to be tumour-free following successful curative resection. Based on other published evidence, people were assumed to have an increase in their estimated mean life expectancy of 4.76 years, with an observed median survival time of 3.23 years. Following a successful curative liver resection, people did not receive any further treatment with cetuximab. However, people who had an unsuccessful curative liver resection or did not undergo a liver resection were treated with cetuximab until disease progression.

3.19 Subsequent lines of treatment were modelled because neither clinical trial had generated mature overall survival data at the time of the manufacturer's original submission. Extrapolation techniques were used in the economic model to estimate survival benefits in the base case. These were varied in the scenario analyses.

3.20 The manufacturer considered the liver resection rates from the CRYSTAL and OPUS trials (3.5% [n = 6] for cetuximab in combination with FOLFIRI versus 2.3% [n = 4] for FOLFIRI alone; 11.5% [n = 7] for cetuximab in combination with FOLFOX versus 4.1% [n = 3] for FOLFOX alone) to be low compared with current clinical practice in the NHS. Data from a published study were therefore used to estimate possible resection rates for patients with metastatic disease confined to the liver from the response rates. The correlation observed between response rates and resection rates was used to model resection rates in the base case and different scenarios in the model. The value for the failure rate of liver resection used in the model was 27.8%, which was taken from the

full analysis set from the CRYSTAL trial. This rate was applied to all arms in the model.

3.21 The cost data were taken from the BNF edition 55 (2008) and the NHS National Tariff (2006). The cost of the KRAS test included in the model was £300 per test. This was provided verbally by a manufacturer of the test to the manufacturer of cetuximab, based on ad hoc patient testing. The analysis took into account testing of the whole patient population. The model used a weighted average cost per liver resection surgery of £2271 calculated from four liver healthcare resource groups: G02 (liver – complex procedures), G03 (liver – very major procedures), G04 (liver – major procedures, patient aged over 69 years with complications and/or comorbidities) and G05 (liver – major procedures, patient aged under 70 years without complications and/or comorbidities). This cost was assumed to occur only once, at 16 weeks.

3.22 Health-related utility weights were applied to the time lived with disease at different stages of disease progression in the Markov model. Heath-related utilities were taken from clinical trials in the first- and third-line settings and estimated for the second-line setting. The utility in the period following curative resection took into account utility in patients free of disease and patients with recurrent disease. It was assumed that patients free of disease had health-related utility equal to that of the general population. In patients with progressive disease, the utility was estimated as the weighted average of utilities in the second- and third-line setting.

3.23 The economic analysis results included in the manufacturer's original submission have since been superseded by updated analyses (see sections 3.29, 3.31 and 3.32).

3.24 The ERG identified a number of limitations with the manufacturer's economic model. It was concerned that the model focused on a much smaller patient population (people with KRAS wild-type metastatic colorectal cancer who had metastases confined to the liver and had a good performance status) than the population defined in the appraisal scope (people with untreated metastatic colorectal cancer) and was therefore concerned about the applicability of the results to clinical practice. The ERG was also concerned that no evidence was

provided by the manufacturer to support the assumptions in the model that all patients who are suitable for cetuximab treatment are identified and treated with cetuximab (those who are KRAS wild-type) and that patients who are not suitable for cetuximab treatment (those with KRAS mutations) are not treated with cetuximab. Given the importance of estimating the outcomes for those treated incorrectly in reaching a conclusion on the cost effectiveness of the treatment, the ERG considered that this omission was a flaw in the model design.

3.25 The ERG was uncertain how accurate the effectiveness estimates used within the economic model were, given that they were derived from small post hoc subgroup analyses of trial results, and whether all relevant costs had been included within the model.

Revised economic analyses

3.26 In response to ACD consultation, revised economic analyses were provided amending the following parameters: the time at which patients were referred for liver resection, liver resection rates and failure rates of liver resection. The manufacturer also submitted revised analyses for cetuximab in combination with FOLFOX compared with FOLFOX alone that incorporated a patient access scheme, a 16-week stopping rule for cetuximab and revised costs of liver resection.

Liver resection rates

3.27 The revised economic analysis used a 43% liver resection rate for both cetuximab in combination with FOLFIRI and cetuximab in combination with FOLFOX, taken from the CELIM trial (KRAS wild-type subgroup). The CELIM trial did not include FOLFIRI or FOLFOX alone as a direct comparator. Therefore, in the revised economic analysis the manufacturer assumed a liver resection rate of 9% for FOLFIRI alone and 22% for FOLFOX alone (taken from published evidence [GERCOR study]), based on the recommendation of clinical specialists as being the most robust data for resection rates for FOLFIRI and FOLFOX. The model was also adjusted so that patients were

referred for curative liver resection surgery at 16 weeks rather than 12 weeks, to reflect the data from the CELIM trial.

Failure rates of liver resection

3.28 In addition, the manufacturer obtained clinical opinion on the 27.8% liver resection failure rate used in the original analysis. Clinical advice suggested that this rate was high for patients who have a liver resection in a specialist centre, and suggested that this rate was more likely to be 5%. The manufacturer used the revised value of 5% for the revised economic analyses.

3.29 The results of the revised analysis (updated liver resection rates, 5% failure rate of liver resection and lifetime horizon) for cetuximab in combination with FOLFIRI compared with FOLFIRI alone gave an ICER of £23,456 per QALY gained. The results for cetuximab in combination with FOLFOX compared with FOLFOX alone gave an ICER of £29,891.

Patient access scheme

3.30 Details of a patient access scheme were provided by the manufacturer based on a 16% rebate of the amount of cetuximab used when given in combination with FOLFOX for people with KRAS wild-type metastatic colorectal cancer who have metastases confined to the liver. The scheme requires that patients are treated according to the final NICE guidance and that data should be provided to the manufacturer to show that the NICE guidance has been followed. Cetuximab would normally be rebated in the form of free stock at a rate of 16% for all patients in the scheme on a per patient basis, with an option for rebate via credit note or cash. The patient access scheme was incorporated into the economic analysis for the comparison of cetuximab in combination with FOLFOX compared with FOLFOX alone.

Stopping rule

3.31 The manufacturer incorporated a stopping rule for treatment with cetuximab when analysing cetuximab in combination with FOLFOX compared with FOLFOX alone. A scenario was explored in which the cost of treatment with cetuximab was stopped at 16 weeks (the point at which people were assessed

for curative resection) for all people in the analysis. No amendments were made to the progression-free survival of cetuximab after stopping treatment with cetuximab at 16 weeks. The result of this 16-week analysis incorporating the patient access scheme, liver resection rates of 43% for cetuximab in combination with FOLFOX and 22% for FOLFOX alone, and a 5% failure rate of liver resection, gave an ICER for cetuximab in combination with FOLFOX compared with FOLFOX alone of £18,660 per QALY gained. The manufacturer performed a sensitivity analysis around the liver resection rate for cetuximab in combination with FOLFOX, and when the rate was varied to 35% and 30%, the ICER for cetuximab in combination with FOLFOX compared with FOLFOX alone increased to £24,610 and £31,006 per QALY gained, respectively.

Cost of liver resection

3.32 The manufacturer also revised the costs of liver resection by calculating a new weighted average cost of £8929, based on the proportion of people receiving different surgical techniques from a published study and assigning the healthcare resource groups G02 (liver – complex procedures) and G03 (liver – very major procedures). Incorporating this revised cost of liver resection in the 16-week analysis gave an ICER for cetuximab in combination with FOLFOX compared with FOLFOX alone of £21,056 per QALY gained. Varying the liver resection rate for cetuximab in combination with FOLFOX to 35% and 30%, the ICER for cetuximab in combination with FOLFOX compared with FOLFOX alone increased to £26,662 and £32,688 per QALY gained, respectively.

Decision Support Unit report

3.33 The Decision Support Unit (DSU) commented that although the manufacturer had removed the direct costs of cetuximab after 16 weeks in the 16-week analysis, it had not altered the progression-free survival and therefore the probabilities of progression after 16 weeks of treatment with cetuximab. The DSU considered this to be the most optimistic method of implementing a stopping rule. The DSU conducted an exploratory analysis implementing a more conservative stopping rule in which the patients in the cetuximab in combination with FOLFOX arm followed the cetuximab progression-free survival curve for 16 weeks, after which they then switched to follow the

progression-free survival curve for the FOLFOX-alone arm. Incorporating the DSU's 16-week stopping rule (in addition to the patient access scheme, the £8929 revised cost of liver resection, 43% liver resection rate for cetuximab in combination with FOLFOX, 22% liver resection rate for FOLFOX alone and a 5% failure rate of liver resection), the ICER for cetuximab in combination with FOLFOX compared with FOLFOX alone increased from £21,056 (estimated by the manufacturer) to £24,022 per QALY gained. When varying the liver resection rate for cetuximab in combination with FOLFOX to 35% and 30%, the ICER increased from £26,662 to £33,291 and from £32,688 to £45,604, respectively.

3.34 Full details of all the evidence are in the manufacturer's submissions, the ERG reports and the DSU report.

4 Consideration of the evidence

4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of cetuximab for the first-line treatment of metastatic colorectal cancer, having considered evidence on the nature of the condition and the value placed on the benefits of cetuximab by people with metastatic colorectal cancer, those who represent them, and clinical specialists. It was also mindful of the need to take account of the effective use of NHS resources.

4.2 The Committee noted that the marketing authorisation for cetuximab limits its use to people with KRAS wild-type metastatic colorectal cancer, a narrower indication than outlined in the scope. The Committee acknowledged that the scope pre-dated the marketing authorisation for cetuximab, which placed this restriction on use. It heard from the clinical specialists that the marketing authorisation for cetuximab reflects increasing evidence that KRAS mutation status is predictive of response to treatment and that people whose tumours have KRAS mutations are unlikely to respond to treatment with cetuximab. The Committee also heard from the clinical specialists that KRAS testing accurately identifies people with wild-type KRAS status. The test can be carried out on 95% of tissue samples and is currently only conducted in two NHS centres (Leeds and Cardiff), although the tests are becoming more widely available through the NHS for people with metastatic colorectal cancer. Commercial companies offer KRAS testing, but these are understood to be more expensive than the tests carried out within the NHS.

4.3 The Committee reviewed the clinical-effectiveness results from the two clinical trials; one that compared cetuximab in combination with FOLFIRI with FOLFIRI alone and another that compared cetuximab in combination with FOLFOX with FOLFOX alone in the KRAS wild-type subgroup. It noted the statistically significant improvements in progression-free survival and response rates associated with cetuximab. However, it was aware that the improvement in median progression-free survival was 1.2 months and 0.5 months respectively in the two trials and concluded that the effectiveness of cetuximab at improving progression-free survival was therefore limited. In addition, the Committee noted that the difference in the overall survival of 3.9 months from the CRYSTAL trial was not statistically significant. The Committee was also

concerned that the KRAS wild-type subgroup analysis was based on small sample sizes and was carried out post hoc (at the request of the European Medicines Agency; EMEA). However, the Committee was reassured by the clinical specialists that differential response based on KRAS status had biological plausibility given current understanding of the pathology of metastatic colorectal cancer.

4.4 The Committee heard from the clinical specialists that cetuximab combined with chemotherapy had an important potential role in shrinking secondary liver metastases, to enable potentially curative resection in people with KRAS wild-type metastatic colorectal cancer. The clinical specialists reported that, of people whose disease responds sufficiently to cetuximab to enable resection of liver metastases, approximately 90% would do so within 12 weeks of treatment with cetuximab. The duration of treatment with cetuximab in clinical practice for KRAS wild-type metastatic colorectal cancer patients with liver-only metastases would not normally exceed 16 weeks. Patients for whom liver resection was not possible (for example, because of the distribution of liver metastases) or who were not well enough to undergo potentially curative liver resection would not be treated with cetuximab, and would receive standard chemotherapy only. The Committee noted that in people who have undergone primary colorectal surgery with curative intent and whose liver metastases are rendered resectable following a successful response to chemotherapy, the 5- and 10-year survival rate is approximately 30% and 20% respectively.

4.5 The Committee considered the evidence for the effect of treatment with cetuximab on the rate of potentially curative resection of liver metastases. The results of the clinical trials showed that very few patients with KRAS wild-type metastatic colorectal cancer went on to receive potentially curative resection (cetuximab in combination with FOLFIRI 3.5%, FOLFIRI alone 2.3%; cetuximab in combination with FOLFOX 11.5%, FOLFOX alone 4.1%) and the Committee noted that no statistical significance was reported for these differences. It heard from the clinical specialists that the number of patients receiving potentially curative liver resection in the CRYSTAL and OPUS trials was lower than that seen in UK clinical practice, which is based on management by multidisciplinary teams involving highly specialised liver surgical services. The clinical specialists stated that a more realistic rate for

potentially curative resection with chemotherapy in general was approximately 12–15%, which could rise to approximately 30–35% with the addition of cetuximab. The Committee also heard from the clinical specialists that the current UK standard chemotherapy approach for shrinking liver metastases was to use the FOLFOX regimen, which in practice enables a resection rate of approximately 20%. The Committee acknowledged the importance of liver resection rates as an endpoint in assessing the effectiveness of cetuximab.

4.6 The Committee reviewed the additional clinical data submitted by the manufacturer on the liver resection rates. It noted that the CELIM trial was not a randomised assessment of cetuximab in combination with chemotherapy compared with chemotherapy alone, had a relatively small sample size and had not been peer-reviewed. The Committee was initially concerned that only 55% of patients were described as having technically non-resectable liver metastases at baseline; however, the Committee then noted that the remaining 45% had at least five or more liver metastases at baseline, and were therefore also non-resectable. It noted that the subgroup analysis for these two groups of patients indicated a liver resection rate of 40% and 44% respectively, but that this subgroup analysis was for all patients and not just those with KRAS wild-type metastatic colorectal cancer. The Committee heard from the clinical specialists that the 43% liver resection rate for patients with KRAS wild-type metastatic colorectal cancer who were treated with cetuximab was an encouraging result, but it also noted that this was higher than the 30–35% rate originally considered likely by the clinical specialists (see section 4.5). The Committee was concerned that the 22% liver resection rate for FOLFOX was taken from an older study (GERCOR, Tournigand et al. 2004), but noted that the clinical specialists suggested that a liver resection rate of approximately 20% for FOLFOX was appropriate for current UK clinical practice (see section 4.5).

4.7 The Committee discussed the failure rate of liver resection. It noted that the 27.8% failure rate used in the original analysis appeared high for current practice. The Committee heard from the clinical specialists that a 5% failure rate of liver resection was a more appropriate reflection of current practice in UK specialist centres. The Committee agreed that this low rate reflected

improvements in preoperative assessment and surgical technique and was appropriate to be used in the model.

4.8 The Committee discussed the adverse effects related to cetuximab. The clinical specialists advised the Committee that cetuximab is associated with an increase in an acne-like rash affecting a person's upper trunk, gastrointestinal adverse effects such as diarrhoea, and fatigue. The clinical specialists and patient experts explained that the acne-like rash may be indicative of response to cetuximab treatment and would not usually cause admission to hospital. Therefore, it is often interpreted by people as a positive effect because it suggests that the drug is working, outweighing any negative effects of the rash.

4.9 The Committee considered the results of the economic analysis submitted by the manufacturer. The Committee noted that the manufacturer had not provided an economic analysis that included the entire population for which cetuximab is licensed. The economic model focused on a subgroup of patients with a good performance status and metastatic disease confined to the liver. The Committee was persuaded that, in this group of patients, the aim of treatment with cetuximab was to reduce the size of metastases so they were resectable. Therefore the most appropriate comparator was FOLFOX (see section 4.5), considered over a lifetime horizon. The Committee heard from the clinical specialists that in current UK clinical practice, all patients would normally stop receiving treatment with cetuximab at the time of the assessment for possible liver resection (that is, after approximately 12–16 weeks), and noted the impact of incorporating a 16-week stopping rule for cetuximab on the economic analysis. In addition, the Committee was aware of the patient access scheme details provided by the manufacturer for cetuximab in combination with FOLFOX, and the impact of the scheme on the results of the economic analysis. The Committee concluded that the most appropriate analysis for consideration was that which incorporated the 16-week stopping rule for cetuximab and the patient access scheme.

4.10 The Committee was aware that in the manufacturer's new 16-week analysis (incorporating a 5% failure rate of liver resection, 43% liver resection rate, lifetime horizon and the patient access scheme), the ICER for cetuximab in combination with FOLFOX compared with FOLFOX alone was £18,700 per

QALY gained (see section 3.31). The Committee was concerned about the limited methodology used for estimating the resection rates in the model, in that single arms from two separate studies were used to provide the data for the two groups in the model; the CELIM study for cetuximab in combination with FOLFOX and the GERCOR study for FOLFOX alone. The Committee considered that exploration of the different populations and evaluation of possible selection biases between the trials had not been done to a satisfactory level. Therefore, the Committee expressed caution about the results produced by the new analysis using a 43% resection rate for cetuximab in combination with FOLFOX, as the relative difference in resection rates was assumed from unrelated studies without any adjustments. It noted the sensitivity analysis requested from the manufacturer, which used resection rates of 35% and 30% for cetuximab in combination with FOLFOX (assuming a 22% resection rate for FOLFOX alone), resulted in ICERs of £24,600 and £31,000 per QALY gained, respectively. The Committee agreed that a 35% liver resection rate for cetuximab in combination with FOLFOX compared with the 22% for FOLFOX alone more closely reflected the 10–15% relative difference in resection rates for these two comparators considered to be realistic by the clinical specialists and was a more appropriate value to use in the economic analysis.

4.11 The Committee discussed the cost of liver resection included in the economic analysis. It noted that the manufacturer had originally used a weighted average of a range of healthcare resource groups for all liver procedures giving an average cost of £2300 for liver resection surgery, and that this only occurred once in the model. The Committee considered that this cost could be low compared with current UK clinical practice because a proportion of patients may undergo more than one operation to achieve complete resection of metastases. In addition, the Committee heard from the clinical specialists that liver resection costs £7000 per case. The Committee discussed the additional analysis requested from the manufacturer, which used a new weighted average based on the surgical technique employed by Adam et al. (2004) giving an average cost of £8900 for liver resection surgery. The Committee agreed that this weighted cost was a more accurate reflection of current UK clinical practice. Using this liver resection cost, the ICER for cetuximab in combination with FOLFOX compared with FOLFOX alone increased from

£18,700 to £21,100 per QALY gained for the scenario with a liver resection rate of 43%. Varying the resection rate to 35% (considered by the Committee to be more likely than 43%) increased the ICER from £24,600 to £26,700 per QALY gained. Using a resection rate of 30% (considered by the Committee to be a conservative estimate) increased the ICER from £31,000 to £32,700 per QALY gained.

4.12 The Committee noted that the 16-week analysis provided by the manufacturer only explored stopping the costs of cetuximab treatment at 16 weeks. The manufacturer made no amendments to the efficacy of cetuximab in terms of progression-free survival after the decision to resect the liver metastases and stop cetuximab treatment, due to the lack of evidence for progression-free survival following 16 weeks of treatment. The Committee considered this to be the most optimistic scenario. The Committee then discussed the alternative 16-week analysis provided by the DSU which took a more conservative view and also changed the efficacy of cetuximab after 16 weeks to equal that of the FOLFOX-alone arm. It noted that incorporating the revised cost of liver resection (£8900) and a 43% resection rate, the ICER for cetuximab in combination with FOLFOX compared with FOLFOX alone increased from £21,100 to £24,000 per QALY gained. The result of the sensitivity analysis which used the Committee's preferred resection rate of 35% showed an increase in the ICER from £26,700 to £33,300 per QALY gained.

4.13 The Committee agreed that the most likely ICER for cetuximab in combination with FOLFOX compared with FOLFOX alone was between £26,700 (estimated by the manufacturer) and £33,300 per QALY gained (estimated by the DSU), and that this was within a range that could be considered a cost-effective use of NHS resources. The Committee was mindful that people with liver-only metastases form a subgroup of the population within the marketing authorisation, and that the manufacturer had submitted economic evidence only for this subgroup. On the basis of its considerations of the clinical evidence, the Committee thought that the QALYs gained for the whole population would be substantially lower than that of the subgroup, while the incremental costs would not be any lower. Therefore, the Committee felt that the cost effectiveness for the whole population had not been demonstrated. The Committee noted that for patients who are not well enough to have

surgery to remove liver metastases, adding cetuximab to their chemotherapy would not help in enabling a curative operation. It therefore concluded that the addition of cetuximab is only appropriate for patients who have had the primary colorectal tumour resected, or if that is not the case, where the primary colorectal tumour is potentially operable and the patient is fit enough to undergo colorectal surgery. The patient also needs to be fit enough to undergo liver surgery if their metastases become resectable after treatment with cetuximab. The Committee noted that the suitability for undergoing such surgery was determined in different ways in the clinical trials underpinning the evidence base. Therefore the Committee considered it appropriate that fitness for surgery be decided on an individual basis following discussion between patients and their clinicians. The Committee concluded that cetuximab in combination with FOLFOX should be recommended for the first-line treatment of metastatic colorectal cancer when the following criteria are met:

- The primary colorectal tumour has been resected or is potentially operable.
- The metastatic disease is confined to the liver and is unresectable.
- The patient is fit enough to undergo surgery to resect the primary colorectal tumour and to undergo liver surgery if the metastases become resectable after treatment with cetuximab.
- The manufacturer rebates 16% of the amount of cetuximab used on a per patient basis.
- The duration of treatment with cetuximab is restricted to 16 weeks.

4.14 The Committee then discussed cetuximab in combination with FOLFIRI as a first-line treatment option for patients with metastatic colorectal cancer. The Committee had earlier noted that the most appropriate comparator for patients with liver-only metastases was FOLFOX (see section 4.9); therefore adding cetuximab to this chemotherapy regimen with the intention of reducing the size of liver metastases would be the combination of choice for this population. However, the Committee was aware that there may be some patients who are unable to tolerate, or have a contraindication to oxaliplatin, and it agreed that for these patients, the most appropriate comparator would be FOLFIRI. The Committee discussed the analysis presented by the manufacturer for

cetuximab in combination with FOLFIRI compared with FOLFIRI alone. It noted that this analysis did not include the 16-week stopping rule and the revised cost of liver resection. Assuming resection rates of 43% for cetuximab in combination with FOLFIRI and 9% for FOLFIRI alone, and a liver resection cost of £2300, the ICER for cetuximab in combination with FOLFIRI compared with FOLFIRI alone was £23,500 per QALY gained. Although the precise value of the ICER that incorporated the 16-week stopping rule for cetuximab, the revised cost of liver resection (£8900) and the preferred 35% resection rate for cetuximab was not known, the Committee accepted that the ICER would likely be within a range considered to be a cost-effective use of NHS resources. The Committee therefore concluded that cetuximab in combination with FOLFIRI should be recommended for first-line treatment of metastatic colorectal cancer when the following criteria are met:

- The primary colorectal tumour has been resected or is potentially operable.
- The metastatic disease is confined to the liver and is unresectable.
- The patient is fit enough to undergo surgery to resect the primary colorectal tumour and to undergo liver surgery if the metastases become resectable after treatment with cetuximab.
- The patient is unable to tolerate or has contraindications to oxaliplatin.
- The duration of treatment with cetuximab is restricted to 16 weeks.

4.15 The Committee was aware that, in current UK clinical practice, the treatment of patients with metastatic colorectal cancer receiving potentially curative resection of metastases confined to the liver is managed by multidisciplinary teams involving highly specialised liver surgical services. The Committee concluded that current practice for this population was the most appropriate approach, and that patients should continue to be managed in this way.

5 Implementation

5.1 The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website. The NHS is not required to fund treatments that are not recommended by NICE.

5.2 NICE has developed tools to help organisations implement this guidance (listed below).

- Costing report and costing template to estimate the savings and costs associated with implementation.
- Audit support for monitoring local practice.

6 Recommendations for further research

6.1 The Committee noted the following ongoing clinical trial related to this appraisal:

- NCT00182715 is a phase III randomised controlled trial evaluating first-line use of cetuximab for metastatic colorectal cancer (COIN trial). It aims to determine whether the addition of cetuximab to continuous oxaliplatin plus fluoropyrimidine chemotherapy improves overall survival when compared with either continuous or intermittent oxaliplatin plus fluoropyrimidine chemotherapy.

7 Related NICE guidance

- Cetuximab for the treatment of metastatic colorectal cancer following failure of oxaliplatin-containing chemotherapy (terminated appraisal). NICE technology appraisal 150 (2008). [replaced by NICE technology appraisal guidance 242]
- Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer.NICE technology appraisal guidance 118 (2007). [replaced by NICE technology appraisal guidance 242]
- Capecitabine and oxaliplatin in the adjuvant treatment of stage III (Dukes' C) colon cancer. NICE technology appraisal guidance 100 (2006).
- Irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer (review of technology appraisal 33). NICE technology appraisal guidance 93 (2005). [Replaced by NICE clinical guideline 131]
- Improving outcomes in colorectal cancers manual update. NICE cancer service guidance (2004
- Guidance on the use of capecitabine and tegafur with uracil for metastatic colorectal cancer. NICE technology appraisal guidance 61 (2003).
- Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for the treatment of metastatic colorectal cancer. NICE technology appraisal guidance 212 (2010)
- Colorectal cancer: The diagnosis and management of colorectal cancer. NICE clinical guideline 131 (2011).

8 Review of guidance

8.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider whether the technology should be reviewed. This decision will be taken in the light of information gathered by the Institute, and in consultation with consultees and commentators.

8.2 The guidance on this technology will be considered for review in August 2012.

Andrew Dillon
Chief Executive
August 2009

Appendix A: Appraisal Committee members and NICE project team

A Appraisal Committee members

The Appraisal Committee is a standing advisory committee of the Institute. Its members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. The Appraisal Committee meets three times a month except in December, when there are no meetings. The Committee membership is split into three branches, each with a chair and vice chair. Each branch considers its own list of technologies, and ongoing topics are not moved between the branches.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Professor Keith Abrams
Professor of Medical Statistics, University of Leicester

Dr Ray Armstrong
Consultant Rheumatologist, Southampton General Hospital

Dr Jeff Aronson
Reader in Clinical Pharmacology, University Department of Primary Health Care, University of Oxford

Dr Darren Ashcroft
Reader in Medicines Usage and Safety, School of Pharmacy and Pharmaceutical Sciences, University of Manchester

Professor David Barnett (Chair)
Professor of Clinical Pharmacology, University of Leicester

Dr Peter Barry
Consultant in Paediatric Intensive Care, Leicester Royal Infirmary

Professor John Cairns
Public Health and Policy, London School of Hygiene and Tropical Medicine

Dr Mark Chakravarty
External Relations Director – Pharmaceuticals & Personal Health, Oral Care Europe

Professor Jack Dowie
Health Economist, London School of Hygiene and Tropical Medicine

Dr Martin Duerden
Medical Director, Conwy Local Health Board

Ms Lynn Field
Nurse Director, Pan Birmingham Cancer Network

Dr Fergus Gleeson
Consultant Radiologist, Churchill Hospital, Oxford

Ms Sally Gooch
Independent Nursing and Healthcare Consultant

Mrs Eleanor Grey
Lay Member

Mr Sanjay Gupta
Former Service Manager in Stroke, Gastroenterology, Diabetes and Endocrinology, Basildon and Thurrock University Hospitals Foundation NHS Trust

Mr Terence Lewis
Lay Member, Mental Health Consultant, National Institute for Mental Health in England

Professor Gary McVeigh
Professor of Cardiovascular Medicine, Queens University, Belfast

Dr Ruairidh Milne
Senior Lecturer in Public Health, National Coordinating Centre for Health Technology

Dr Neil Milner
General Practitioner, Tramways Medical Centre, Sheffield

Dr Rubin Minhas
General Practitioner, CHD Clinical Lead, Medway PCT

Dr John Pounsford
Consultant Physician, Frenchay Hospital, Bristol

Dr Rosalind Ramsay
Consultant Psychiatrist, Adult Mental Health Services, Maudsley Hospital

Dr Stephen Saltissi
Consultant Cardiologist, Royal Liverpool University Hospital

Dr Lindsay Smith
General Practitioner, East Somerset Research Consortium

Mr Roderick Smith
Finance Director, West Kent Primary Care Trust

Mr Cliff Snelling
Lay Member

Professor Ken Stein
Professor of Public Health, Peninsula Technology Assessment Group (PenTAG), University of Exeter

Professor Andrew Stevens
Professor of Public Health, Department of Public Health and Epidemiology, University of Birmingham

Dr Rod Taylor
Associate Professor in Health Services Research, Peninsula Medical School, Universities of Exeter and Plymouth

Ms Nathalie Verin
Health Economics Manager, Boston Scientific UK and Ireland

Dr Colin Watts
Consultant Neurosurgeon, Addenbrookes Hospital

Mr Tom Wilson
Director of Contracts and Information Management and Technology, Milton Keynes PCT

B NICE project team

Each technology appraisal is assigned to a team consisting of one or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Helen Knight
Technical Lead

Helen Chung
Technical Adviser

Jeremy Powell
Project Manager

Appendix B: Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by West Midlands Health Technology Assessment Collaboration – University of Birmingham:

- Meads C, Round J, Tubeuf S, et al. Cetuximab for the first-line treatment of metastatic colorectal cancer, July 2008

B. Additional evidence for this appraisal was prepared by West Midlands Health Technology Assessment Collaboration – University of Birmingham:

- Critical appraisal of additional material on the CELIM randomised controlled trial submitted by Merck Serono for the Cetuximab STA
- Comment on additional material submitted by Merck Serono in relation to cetuximab for metastatic colorectal cancer
- Cetuximab CRC STA – Additional briefing document required for third committee meeting

C. Additional evidence for this appraisal was also prepared by the Decision Support Unit, School of Health and Related Research – University of Sheffield:

- Cetuximab for the first line treatment of metastatic colorectal cancer – report by the Decision Support Unit

D. The following organisations accepted the invitation to participate in this appraisal. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to give their expert views. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I) Manufacturer/sponsor:

- Merck Serono

II) Professional/specialist and patient/carer groups:

- Association of Coloproctology of Great Britain and Ireland
- Beating Bowel Cancer
- Bowel Cancer UK
- British Association of Surgical Oncology
- Cancer Research UK
- Macmillan Cancer Relief
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians, Medical Oncology Joint Special Committee
- UK Oncology Nursing Society

III) Other consultees:

- Department of Health
- Islington PCT
- Nottinghamshire County PCT
- Welsh Assembly Government

IV) Commentator organisations (did not provide written evidence and without the right of appeal):

- Department of Health, Social Services and Public Safety for Northern Ireland
- Institute of Cancer Research
- National Collaborating Centre for Cancer
- NHS Quality Improvement Scotland
- Pfizer
- Roche Diagnostics

- Roche Products
- Sanofi-Aventis

E. The following individuals were selected from clinical specialist and patient advocate nominations from the non-manufacturer/sponsor consultees and commentators. They gave their expert personal view on cetuximab by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Mr Ian Beaumont, nominated by Bowel Cancer UK patient expert
- Dr Rob Glynne-Jones, Clinical Oncologist, Mount Vernon Hospital, nominated by Bowel Cancer UK clinical specialist
- Professor Timothy Maughan, Consultant Clinical Oncologist and Professor of Cancer Studies, Cardiff University, nominated by the Royal College of Physicians clinical specialist
- Mr Goff Norrington, nominated by Beating Bowel Cancer patient expert
- Mr Graeme Poston, nominated by the British Association of Surgical Oncology clinical specialist

Changes after publication

February 2014: minor maintenance

March 2012: minor maintenance

About this guidance

NICE technology appraisal guidance is about the use of new and existing medicines and treatments in the NHS in England and Wales.

This guidance was developed using the NICE single technology appraisal process.

The recommendations from this guideline have been incorporated into a NICE Pathway. We have produced a summary of this guidance for patients and carers. Tools to help you put the guidance into practice and information about the evidence it is based on are also available.

Your responsibility

This guidance represents the views of NICE and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

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The clinical effectiveness and cost-effectiveness of cetuximab (review of TA176) and panitumumab (partial review of TA240) for previously untreated metastatic colorectal cancer: a systematic review and economic evaluation

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Date completed: 7 August 2015

Declared competing interests of authors: None

Rider on responsibility for this report::	The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.
This report should be referenced as follows:	Huxley N, Crathorne L, Varley-Campbell J, Tikhonova I, Snowsill T, Briscoe S, Peters J, Bond M, Napier M, Hoyle M. The clinical effectiveness and cost-effectiveness of cetuximab (review of TA176) and panitumumab (partial review of TA240) for previously untreated metastatic colorectal cancer: a systematic review and economic evaluation (2015) PenTAG, University of Exeter Medical School (Report for NICE)

Contributions of authors

Nicola Huxley	Provided project management (Feb 2015 to Aug 2015), and led the review of published cost-effectiveness studies and critique of the manufacturer submission of cost-effectiveness. Contributed to the parameterisation and checking of the PenTAG independent economic assessment. Contributed to the writing and editing of the report.
Louise Crathorne	Provided project management (Nov 2014 to Feb 2015), and led the systematic review of clinical effectiveness, including assessment of all abstracts and titles for possible inclusion. Wrote the Background, Decision Problem, and Section 3 (Clinical Effectiveness Review).. Contributed to the writing and editing of the report.
Jo Varley-Campbell	Screened titles, abstracts and papers for inclusion in the systematic review Contributed to the writing of the clinical effectiveness section and corresponding sections within the executive summary, discussion and appendices. Contributed to the editing of the report.
Irina Tikhonova	Contributed to the critique of the submission by Merck Serono, parameterisation and checking of the PenTAG independent economic assessment and writing and editing of the report.
Tristan Snowsill	Contributed to the critique of the submission by Merck Serono, parameterisation and checking of the PenTAG independent economic assessment and writing and editing of the report.
Simon Briscoe	Designed and carried out literature searches for the systematic reviews and identification of model parameters, and contributed to the writing and editing of the report

Jaime Peters	Carried out the network meta-analyses and contributed to the writing of the clinical effectiveness section.
Mary Bond	Screened titles, abstracts and papers for inclusion in the systematic review and commented on the draft report
Mark Napier	Provided clinical input into the design of the model, and advised on clinical matters.
Martin Hoyle	Led the design and parameterisation of the PenTAG economic model and implemented the model in Excel, wrote the sections on the design, parameterisation and results of the economic model (Chapter 6). Contributed to the critique of the submission by Merck Serono. Contributed to the writing and editing of the report. Overall Director and Guarantor of the report.

Acknowledgments: The authors are pleased to acknowledge Mrs Sue Whiffin and Ms Jenny Lowe who provided administrative support.

Mr Christopher Bowles (Royal Devon and Exeter Hospital), Mr Neil Atkey (Sheffield Children's NHS Foundation Trust), Dr Michelle Wood (Institue of Medical Genetics, University Hospital of Wales), Dr Marie Westwood (Kleijnen Systematic Reviews Ltd) who provided information about *RAS* mutation testing

Dr Sandi Deans (UK NEQAS) who contacted UK genetic laboratories on our behalf

Dr Paul Tappenden (University of Sheffield) who commented on the draft report.

Professor Chris Hyde who commented on the draft report and provided senior management support.

All 'commercial in confidence' and 'academic in confidence' data provided by companies, and specified as such, has been redacted, for example: [redacted]. All confidential data used in the cost-effectiveness models has been replaced with dummy data.

The Peninsula Technology Assessment Group (PenTAG) is part of the Evidence Synthesis and Modelling for Health Improvement (ESMI) group based at the University of Exeter Medical School. PenTAG was established in 2000 and carries out independent Health Technology Assessments (HTAs) for the NIHR HTA Programme, systematic reviews and

economic analyses for other local and national decision-makers. The group is multi-disciplinary and draws on individuals' backgrounds in public health, health services research, computing and decision analysis, systematic reviewing, statistics and health economics. The Institute of Health Research is made up of discrete but methodologically related research groups, among which HTA is a strong and recurring theme.

Health technology assessment projects in 2014/2015 included:

- Immunosuppressive therapy for kidney transplantation in children (review of technology appraisal guidance 99)
- Immunosuppressive therapy for kidney transplantation in adults (review of technology appraisal guidance 85)
- Ofatumumab in combination with chlorambucil or bendamustine for previously untreated chronic lymphocytic leukaemia
- Obinutuzumab for previously untreated chronic lymphocytic leukaemia
- The effectiveness and cost-effectiveness of erythropoiesis-stimulating agents (epoetin and darbepoetin) for treating cancer-treatment induced anaemia (including review of TA142): a systematic review and economic model

For a full list of previous projects please see
http://medicine.exeter.ac.uk/esmi/workstreams/pentaghealthtechnologyassessment/

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Abbreviations

AEs	adverse events
BEV	Bevacizumab
BNF	British National Formulary
CAP	Capecitabine
CDF	Cancer Drugs Fund
CET	Cetuximab
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CRC	colorectal cancer
CR	complete response
CRD	Centre for Reviews and Dissemination
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EQ-5D	EuroQol 5-Dimensions
FOLFIRI	folinic acid + fluorouracil + irinotecan
FOLFOX	folinic acid + fluorouracil + oxaliplatin
HRAS	Harvey rat sarcoma

HRQoL	health-related quality of life
ICER	Incremental cost-effectiveness ratio
IRIN	Irinotecan
KRAS	kirsten rat sarcoma
LLD	liver limited disease
mCRC	metatstatic colorectal cancer
MTA	multiple technology appraisal
MTC	mixed treatment comparison
mths	Months
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NRAS	neuroblastoma rat sarcoma
ORR	objective response rate
OS	overall survival
OX	Oxaliplatin
PAN	Panitumumab
PD	progressive disease
PFS	progression free survival
PR	partial response

PS	performance status
PSSRU	Personal Social Services and Resource Use
QALY	quality-adjusted life year
RAS	rat sarcoma
RCT	randomised controlled trial
SAEs	serious adverse events
sd	standard deviation
SD	stable disease
SE	standard error
SPC	Summary of Product Characteristics
SR	systematic review
STA	single technology appraisal
TA	technology appraisal
wks	Weeks
WT	wild type
XELOX	capecitabine + oxaliplatin
yrs	Years

Glossary

Epidermal growth factor receptor (EGFR)	The protein encoded by this gene is a transmembrane glycoprotein that is a member of the protein kinase superfamily. This protein is a receptor for members of the epidermal growth factor family. EGFR is a cell surface protein that binds to epidermal growth factor. Binding of the protein to a ligand induces receptor dimerization and tyrosine autophosphorylation and leads to cell proliferation. Mutations in this gene are associated with lung cancer. Multiple alternatively spliced transcript variants that encode different protein isoforms have been found for this gene
Kirsten rat sarcoma (*KRAS*)	The *KRAS* gene belongs to a class of genes known as oncogenes. When mutated, oncogenes have the potential to cause normal cells to become cancerous. These proteins play important roles in cell division, cell differentiation, and the self-destruction of cells (apoptosis).
Neuroblastoma rat sarcoma (*NRAS*)	The *NRAS* gene belongs to a class of genes known as oncogenes. When mutated, oncogenes have the potential to cause normal cells to become cancerous. These proteins play important roles in cell division, cell differentiation, and the self-destruction of cells (apoptosis).
Rat sarcoma (*RAS*)	Gene family consisting of *HRAS*, neuroblastoma rat sarcoma (*NRAS*), and kirsten rat sarcoma (*KRAS*)

Wild type (WT)	The normal, non-mutated version of a gene common in nature

Abstract

Background: Colorectal cancer is the fourth most commonly diagnosed cancer in the UK after breast, lung and prostate cancer. People with metastatic disease who are sufficiently fit are usually treated with active chemotherapy as first- or second-line therapy. Targeted agents are available, including the anti-epidermal growth factor receptor (EGFR) agents cetuximab and panitumumab.

Objective: To investigate the clinical effectiveness and cost-effectiveness of panitumumab in combination with chemotherapy and cetuximab in combination with chemotherapy for rat sarcoma (*RAS*) wild-type (WT) patients for the first-line treatment of metastatic colorectal cancer.

Data sources: The assessment comprises a systematic review of clinical effectiveness and cost-effectiveness studies, a review and critique of manufacturer submissions and a de novo cohort-based economic analysis. For the assessment of effectiveness, a literature search was conducted in a range of electronic databases, including MEDLINE, EMBASE and The Cochrane Library.

Review methods: Studies were included if they were randomised controlled trials (RCTs) or systematic reviews of RCTs of cetuximab or panitumumab in participants with previously untreated metastatic colorectal cancer with *RAS* WT status. All steps in the review were performed by one reviewer and checked independently by a second. Narrative synthesis and network meta-analyses (NMA) were conducted for outcomes of interest. An economic model was developed focusing on first-line treatment and with a 30 year time horizon to capture costs and benefits. Costs and benefits were discounted at 3.5% per annum. Scenario analyses and probabilistic and univariate deterministic sensitivity analyses were performed.

Results: The searches identified 2,811 titles and abstracts. Five clinical trials were included. Additional data from these trials was provided by the manufacturers. No data were available for panitumumab plus irnotecan based chemotherapy (FOLFIRI) in previously untreated patients. Studies reported results for *RAS* WT subgroups. First line treatment with anti-EGFR therapies in combination with chemotherapy appears to have statistically significant benefits for patients who are *RAS* WT. For the economic evaluation, four studies met the inclusion criteria. The base-case incremental cost-effectiveness ratio (ICER) for *RAS* WT patients for cetuximab plus oxaliplatin based chemotherapy (FOLFOX) compared with FOLFOX is £109,820 per quality-adjusted life-year (QALY) gained, for panitumumab plus FOLFOX compared with FOLFOX is £239,007 per QALY gained and for cetuximab FOLFIRI

compared with FOLFIRI is £106,707 per QALY gained. All ICERs are sensitive to treatment duration, progression free survival, overall survival (resected patients only) and resection rates.

Limitations: The trials only include *RAS* WT populations as subgroups. No evidence was available for panitumumab plus FOLFIRI. Two networks were used for the NMA and the model, based on the different chemotherapies (FOLFOX and FOLFIRI) as no evidence was available to connect these networks.

Conclusions: Although cetuximab and panitumumab in combination with chemotherapy appear to be clinically beneficial for *RAS* WT patients compared with chemotherapy alone, they are likely to represent poor value for money when judged by cost-effectiveness criteria currently used in the UK. It would be useful to conduct a RCT for patients with *RAS* WT.

Funding: The National Institute for Health Research Health Technology Assessment programme

Word count: 497

Plain English Summary

Colorectal cancer is any cancer that affects the large bowel or rectum. Metastatic colorectal cancer occurs when this cancer spreads to other parts of the body. This type of cancer most often spreads first to the liver, but may also occur in other parts of the body including the lungs, brain and bones.

Metastatic colorectal cancer is often treated with chemotherapy and where possible, surgery is performed to remove cancerous tumour tissue.

It is suggested that targeted therapies such as cetuximab and panitumumab, used in combination with chemotherapies, may improve health outcomes for some people. These people are selected through genetic testing, and can receive treatment with these targeted therapies if they do not have specific mutations.

This report considered the costs and benefits of these targeted therapies when adding them to standard chemotherapy treatment.

This report found some benefit to health outcomes when using these targeted therapies compared to chemotherapy alone. However, costs of these therapies were shown to be very high.

Word count: 163

Executive summary

Background

Colorectal cancer (CRC) is a malignant tumour arising from the lining of the large intestine (colon and rectum). Metastatic colorectal cancer (mCRC) refers to disease that has spread beyond the large intestine and nearby lymph nodes. This type of cancer most often spreads first to the liver, but metastases may also occur in other parts of the body including the lungs, brain and bones

Colorectal cancer is the fourth most common cancer in the UK behind breast, lung, and prostate cancer. In 2011, there were 34,000 people diagnosed with CRC in England. Approximately 25% of people with CRC have metastatic disease when first diagnosed, and approximately 50% of people who have surgery for early stage disease will eventually develop metastases.

For the majority of people, surgery with curative intent is not an option due to the widespread nature of their disease and/or their poor suitability for surgery. National Institute for Health and Care Excellence (NICE) clinical guideline 131 recommends chemotherapy which may be combined with biological agents such as cetuximab (currently recommended for people satisfying criteria specified in NICE technology appraisal [TA] 176 and available subject to satisfaction of eligibility criteria via the Cancer Drugs Fund), panitumumab (NICE guidance not currently available [TA 240], but available subject to satisfaction of eligibility criteria via the Cancer Drugs Fund [CDF]), and bevacizumab (not recommended by NICE but funded via the CDF until March 2015).

The choice and effectiveness of some treatments for mCRC may be influenced by genetic markers. Inhibitors of epidermal growth factor receptor (EGFR), such as cetuximab and panitumumab, appear to be less effective for treating tumours with mutations in genes in the rat sarcoma (*RAS*) family. The *RAS* gene is often mutated in mCRC. Kirsten rat sarcoma (*KRAS*) mutations are the most common, with mutations in codons 12 and 13 of Exon 2 of the *KRAS* gene predictive of treatment resistance to anti-EGFR therapy. However, recent research suggests that other mutations in genes of the *RAS* family (*KRAS* Exon 3 and 4 and *NRAS* Exon 2, 3 and 4), are also associated with reduced response to anti-EGFR. Approximately 50% of people with CRC have *RAS* mutations.

These research developments have led the European Medicines Agency (EMA) to update the marketing authorisations for cetuximab and panitumumab so that they are licensed for a more targeted population based on *RAS* wild-type (WT) status. While this MTA review aims

to update previous guidance, the population in the scope differs from that specified in TA 176 and TA 240 as it is restricted to people with *RAS* WT tumours in line with the developments in research and the amendments to the product licences.

Objective

The key objectives of this report are two-fold. These include estimating the clinical effectiveness of two interventions for first-line treatment of *RAS* WT mCRC, and establishing the cost effectiveness of these interventions.

The following question is addressed by this technology assessment report: "What is the clinical effectiveness and cost-effectiveness of cetuximab (review of TA176) and panitumumab (partial review of TA240) for previously untreated mCRC?"

Methods

The assessment comprises a systematic review of clinical and cost-effectiveness studies, a review and critique of manufacturer submissions, and a *de novo* economic analysis.

Clinical effectiveness systematic review

Evidence for the clinical effectiveness of the interventions outlined in the NICE scope (cetuximab and panitumumab) was assessed by conducting a systematic review of published research evidence. The review was undertaken following the general principles published by the Centre for Reviews and Dissemination (CRD).

As research into understanding the impact of *RAS* mutations on the effectiveness of EGFR inhibitors has progressed, the pivotal studies for both cetuximab and panitumumab have been re-evaluated and the licensed population for both cetuximab and panitumumab has recently been updated by the EMA to reflect these research developments. In line with recent changes in licensing, the population eligible for inclusion in this current multiple technology appraisal (MTA) specifies people with *RAS* WT mCRC, whereas the scope for TA176 specified people with EGFR-expressing mCRC. Given these differences, although the majority of trials evaluating cetuximab were included in the previous appraisal (TA176) only data from subgroup analyses of the *RAS* WT population from these RCTs are relevant to this review as specified in the final scope issued by NICE . As such, all data included in this update review for both cetuximab and panitumumab were identified by the PenTAG searches.

Identification of studies

Literature searching for clinical effectiveness studies was conducted in January 2015 and updated on 27th April 2015.

The following bibliographic and ongoing trials databases were searched: MEDLINE (Ovid); MEDLINE In-Process and Other Non-Indexed Citations (Ovid); EMBASE (Ovid); The Cochrane Library including the Cochrane Systematic Reviews Database, CENTRAL, DARE and HTA databases; Web of Science (Thomson Reuters); ClinicalTrials.gov; UK Clinical Research Network's (UKCRN) portfolio; International Standard Randomised Controlled Trials Number (ISRCTN) registry; WHO International Clinical Trials Registry Platform (ICTRP). All searches were limited to English language studies where possible, and randomised controlled trials. No date limits were used.

After the reviewers completed the screening process, the bibliographies of included papers were scrutinised for further potentially includable studies. The manufacturers' submissions were assessed for unpublished data.

Study selection

The population was defined as adults expressing *RAS* wild-type (WT) mCRC. The interventions of interest were cetuximab in combination with FOLFOX (folinic acid + fluorouracil + oxaliplatin) or irinotecan-based chemotherapy, and panitumumab in combination with fluorouracil-containing regimens. These were compared with each other and with: FOLFOX; XELOX (capecitabine + oxaliplatin); FOLFIRI (folinic acid + fluorouracil + irinotecan); capecitabine; tegafur, folinic acid and fluouracil; and bevacizumab, in combination with oxaliplatin- or irinotecan-based chemotherapy. Evidence on the following outcome measures was considered: overall survival (OS), progression free survival (PFS); response rate (including overall response rate [ORR], complete response [CR], partial response [PR], progressive disease [PD], stable disease [SD]); adverse effects (AEs) of treatment; and, health-related quality of life (HRQoL).

Titles and abstracts returned by the search strategy were examined independently by two researchers and screened for possible inclusion against the predefined inclusion criteria. Disagreements were resolved by discussion. Full texts of potentially relevant studies were ordered. Full publications were assessed independently by two reviewers for inclusion or exclusion against pre-specified criteria, with disagreements resolved by discussion. The quality of the clinical effectiveness data was assessed by two independent reviewers and

checked for agreement. The study quality was assessed according to recommendations by the NHS CRD and Cochrane Handbook for Systematic Reviews of Interventions.

Data synthesis

Extracted data and quality assessment for each study were presented in structured tables and as a narrative summary. Network meta-analyses were undertaken within a Bayesian framework in WinBUGS (version 1.4.3).

Cost-effectiveness systematic review

Literature searching was conducted in January 2015 and updated on 27th April 2015.

The following databases were searched for economic studies: MEDLINE (Ovid); MEDLINE In-Process and Other Non-Indexed Citations (Ovid); EMBASE (Ovid); NHS EED (via Cochrane Library); EconLit (EBSCO); Web of Science (Thomson Reuters). A supplementary search for health utilities was run in the following databases: MEDLINE (Ovid); MEDLINE In-Process and Other Non-Indexed Citations (Ovid); EMBASE (Ovid); PsycINFO (Ovid); Web of Science (Thomson Reuters); ScHARR Health Utilities Database. All searches were limited to English language studies where possible, and no date limits were used.

After the reviewer completed the screening process, the bibliographies of included papers were scrutinised for further potentially includable studies. The manufacturers' submissions were assessed for unpublished data.The inclusion criteria for population, intervention and comparators were the same as for the clinical effectiveness review, with study design as full cost-effectiveness studies. Cost studies were only considered if they were UK based.

Studies were critiqued using summary tables and narrative synthesis and full papers were quality appraised using the Evers et al. (2005)[1] and Philips et al. (2006) [2] checklists.

Critique of manufacturers' submissions

Amgen submitted a review of clinical effectiveness, but did not submit cost-effectiveness evidence.

Merck Serono submitted a review of clinical effectiveness, cost-effectiveness evidence and utilities.

Merck Serono submitted a cost-effectiveness review that was generally appropriate for this project, but limited to cetuximab studies so missed evidence on panitumumab. The separate review for utilities appeared to give appropriate includes.

Merck Serono submitted two versions of a total population (not restricted to liver metastases) model. We have critiqued the most recent version, which was received on 16th June 2015. We compared the results of the Merck Serono model to the PenTAG model by inputting our preferred parameters into the Merck Serono model.

PenTAG de novo cost-utility model

Comparator treatments

In our base case, we consider two treatment networks:

"FOLFOX network"

- Cetuximab plus FOLFOX (CET+FOLFOX),
- Panitumumab plus FOLFOX (PAN+FOLFOX)
- FOLFOX.

"FOLFIRI network"

- Cetuximab plus FOLFIRI (CET+FOLFIRI),
- FOLFIRI.

Two networks are considered as no randomised evidence that connects the networks was identified.

These treatments are all widely used within the NHS.

In scenario analyses, we also consider bevacizumab+FOLFOX in the FOLFOX network, and bevacizumab+FOLFIRI in the FOLFIRI network, even though bevacizumab containing treatment for 1st-line mCRC was delisted from the Cancer Drugs Fund in March 2015.

In another scenario analysis, we also consider XELOX in place of FOLFOX.

We consider FOLFOX4 in our base case and FOLFOX6 in a scenario analysis.

Although comparators in the NICE Scope, we do not consider capecitabine monotherapy or tegafur, folinic acid and flourouracil as comparators in the model as these single fluoropyrimidine regimens are typically only used for patients for whom combination chemotherapies would be unsuitable and therefore these patients would not be eligible to receive cetuximab or panitumumab. Furthermore, tegafur/uracil has been discontinued in the UK and no alternatives have been identified.

Patient population & liver metastases subgroup

In common with Merck Serono and the NICE scope, we consider two patient populations:

- All 1st line patients with *RAS* wild-type mCRC.
- Subgroup of these patients with liver metastases confined to their liver, the "Liver metastases subgroup" , approximately 26% of all patients.

The following parameters are uniquely altered for the liver metastases subgroup:

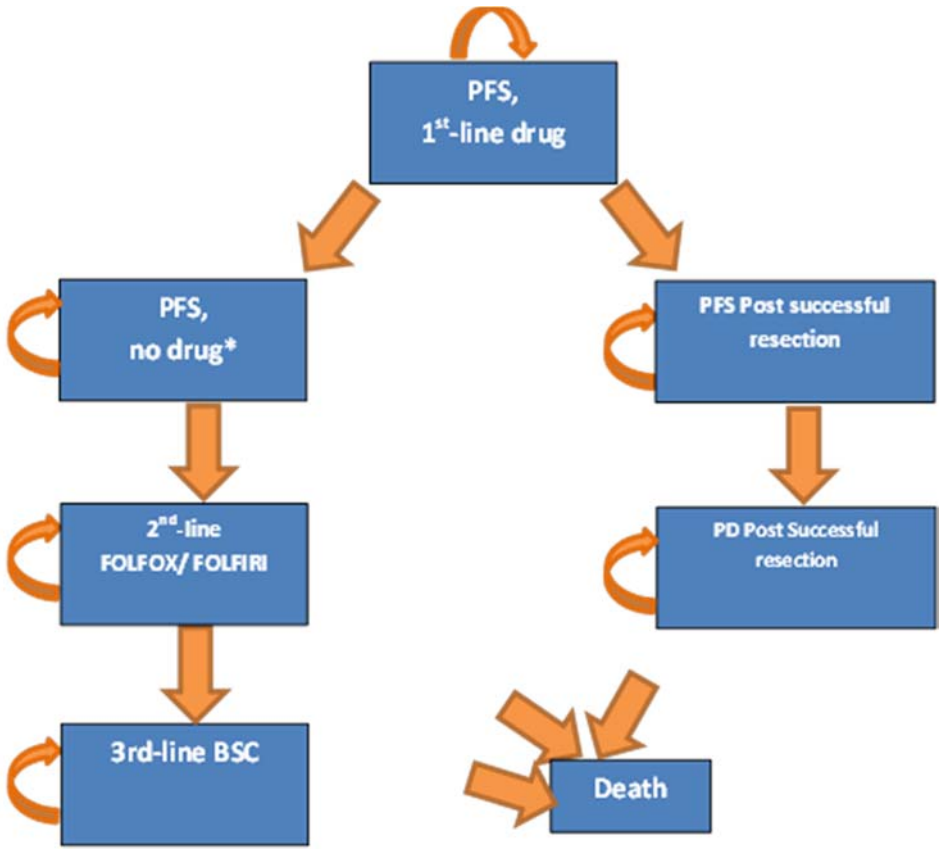
- Resection rates,
- PFS for unresected patients.
- Treatment duration

All other parameters are unchanged from the total population analysis.

Model structure

The PenTAG cost-effectiveness model, implemented in Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA), simulates a cohort of people with *RAS* WT mCRC starting on 1st-line line treatment (see Figure A).

Figure A. Structure of PenTAG cost-effectiveness model



Key: BSC = best supportive care; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; PD = progressive disease; PFS = progression free survival
Notes: * For CET+FOLFIRI and FOLFIRI only

We have identified two candidate model structures: Structures 1 and 2.

Structure 1 assumes that the PFS benefits of the 1st-line drugs translate into OS benefits if the subsequent lines of treatment are balanced between treatment arms. Expressed differently, we assume that survival after 1st-line progression is independent of 1st-line treatment, which seems plausible, given lack of evidence to the contrary. As Merk Serono, we use Structure 1 in our base case analysis.

Conversely, Structure 2 assumes OS is a product of responses to both 1st and subsequent lines of treatment, as experienced in the RCTs. We consider Structure 2 in a scenario analysis in which we model OS as well as PFS from the RCTs. We make the implicit assumption that the costs of the subsequent lines of treatment from the RCTs are equal between treatment arms.

Both Structures have been used in many previous NICE appraisals.

We assume a certain proportion of patients become suitable for resection of liver metastases, separately for each treatment arm. For resected patients, we model PFS and PD post-resection, and for unresected patients, 1st-line PFS, 2nd-line treatment with FOLFOX or FOLFIRI and 3rd-line BSC (see Figure A).

As with Merck Serono's model, differences in clinical effectiveness between 1st-line drug treatments are represented by the differences between:

- 1st-line PFS,
- Resection rates,
- Incidences of adverse events.

In the base case, in the FOLFOX network, clinical effectiveness data was taken from the OPUS RCT of CET+FOLFOX vs. FOLFOX and the PRIME RCT of PAN+FOLFOX vs. FOLFOX. In the FOLFIRI network, data was taken from the CRYSTAL RCT of CET+FOLFIRI vs. FOLFIRI.

For each treatment arm, OS is estimated as the average of OS for resected patients and the sum of time on 1st-line PFS, 2nd-line and 3rd-line treatments for unresected patients, weighted by the proportion of patients that are resected. Life expectancy after successful resection is substantially greater than for patients without successful resection.

Model parameters

In common with Merck Serono, PFS and OS for patients post-resection were taken from a study by Adam et al. (2004). [3]

Also, in common with Merck Serono, we based our estimates of 1st-line PFS for unresected patients on the data from the pivotal RCTs. However, Merck Serono estimate PFS for non-resected patients directly from the RCTs of all patients (resected and non-resected). We believe that this over-estimates PFS for non-resected patients, given that some patients in the RCTs are resected and that PFS for these patients is substantially longer than for non-resected patients. Instead, we estimated PFS for unresected patients by starting with PFS for resected + unresected patients in the RCTs of 1st-line drugs, and then attempting to subtract off the PFS that we expect in the RCTs in respect of resected patients.

We make further assumptions to estimate PFS for unresected patients in the liver metastases subgroup.

The mean times on 1st-line drug treatment are extremely important quantities because they affect the total mean cost of drug acquisition and administration per person, which are critical drivers of cost-effectiveness.

We estimate the mean treatment duration for each 1st-line treatment in the following Steps:

A. Estimate the mean treatment duration for each 1st-line treatment in each of the pivotal RCTs.

B. Estimate mean treatment duration for each 1st-line treatment by simple indirect comparison, using CRYSTAL and PRIME as baseline RCTs.

C. For each treatment, compare the estimated mean treatment duration with the estimated mean 1st-line PFS for unresected patients. Usually, mean treatment duration is greater than mean 1st-line PFS for unresected patients. Given that we use only PFS, not OS from the RCTs, we assume no, or equal treatment effects across treatment arms post-progression. Therefore, we should not model 1st-line treatment after 1st-line PFS for unresected patients. If we did, we would incur the costs of 1st-line drug treatment after progression, but gain no clinical benefit from this, which is clearly inappropriate. Therefore:

- If mean treatment duration was estimated less than mean 1st-line PFS for unresected patients, our estimate of mean treatment duration was left unaltered.
- Otherwise, mean treatment duration was capped at mean 1st-line PFS for unresected patients.

The mean total cost of drug acquisition per patient is estimated as the product of the drug price per unit time, the mean treatment duration and the mean dose intensity.

We make further assumptions to estimate treatment duration for the liver metastases subgroup.

Published literature (Westwood et al., 2014)[4] suggests that a link between different tests for *KRAS* mutations and the effectiveness of the treatment strategy based on the outcome of the test cannot be confirmed, such that the method used to diagnose *KRAS* WT patients suitable to receive cetuximab or panitumumab is not shown to significantly alter the efficacy of the treatment. Therefore, the difference in test accuracy between tests conducted in trials and those conducted in clinical practice cannot be proven to have a significant impact on the cost- effectiveness of cetuximab and panitumumab. As such, our model assumes the same accuracy in practice as in the trials that inform the effectiveness estimates.

The utilities search was supplemented with utility data from existing economic evaluations. The population of interest was not restricted to *RAS* WT, but similar populations, such as *KRAS* WT were preferred. One study presenting EQ-5D data from two trials with *KRAS* WT populations (one first line and one second line) was used to inform first and second line utility values (0.767 and 0.762 respectively).[5] Third line utility of 0.641 was also taken from published literature.[6] These sources were the same as those used in Merck Serono's submission, though different values were chosen by Merck Serono as more appropriate.

No literature specific to post resection utilities was identified. Instead we used the same approach as Merck Serono: age related population utility in PFS post successful resection (0.831) and a disutility based on a weighted average of second and third line utilities for PD post successful resection (0.142). Our PFS value was informed by recent Health Survey for England data and the Ara and Brazier study.[7, 8]

We now turn to the costs in our economic analysis.

In our base case, we used the list prices of cetuximab, panitumumab and bevacizumab. This yielded the following monthly costs of drug acquisition:

- Cetuximab: £3,859
- Panitumumab: £4,109
- Bevacizumab: £2,003

In our base case, we used the discounted prices of FOLFOX and FOLFIRI, taken from the Commercial Medicines Unit Electronic market information tool (CMU eMit) to reflect the true cost to the NHS. This yielded the following monthly costs of drug acquisition.

- FOLFOX4: £86
- FOLFIRI: £128

Drug administration costs comprises the costs of chemotherapy delivery, pharmacy costs, infusion pumps and line maintenance. In the CRYSTAL and OPUS RCTs, cetuximab was given weekly. However, in our economic analysis, in common with Merck Serono, we assumed that cetuximab is administered fortnightly, to coincide with FOLFOX/FOLFIRI administration. Fortnightly administration is common clinical practice in the NHS. Further, Merck Serono argue on the basis of an open-label RCT and a literature review that 500mg/m² fortnightly administration is is as effective as induction 400 mg/m² followed by weekly 250 mg/m² administration. We consider that this is justified by the clinical evidence. Fortnightly administration is not included in the summary of product characteristics of

cetuximab. [redacted].

Our estimated total monthly drug administration costs are:

- CET/PAN/BEV+FOLFOX: £2,473
- FOLFOX4: £2,348
- CET/BEV+FOLFIRI: £1,759
- FOLFIRI: £1,634

In a sensitivity analysis, we assume cetuximab is given weekly, consistent with the CRYSTAL and OPUS RCTs. Then, the estimated monthly drug administration costs are substantially higher:

- CET + FOLFOX: £4,714
- CET + FOLFIRI: £4,000

We estimate the cost of resection surgery as £10,440, substantially higher than Merck Serono's estimate of £2,707. Once we allow for the probability of a successful operation and the mean number of operations per person, we estimate a cost of approximately £17,600 per person who is successfully operated.

Medical management costs were assumed in 1st-line PFS, 2nd-line and 3rd-line, and in PFS and PD post-resection.

The costs of treatment of adverse events and disutilities due to adverse events are modelled.

Results

Clinical effectiveness systematic review

Number and quality of effectiveness studies

Of 2,811 titles/abstracts screened, five *RAS* WT subgroup analyses from RCTs met the inclusion criteria for the clinical effectiveness systematic review. Three subgroup analyses provided data for the effectiveness of cetuximab and two provided evidence for the effectiveness of panitumumab. Efficacy and safety outcomes were tabulated and discussed

in a narrative review. All included studies provided evidence for the network meta-analysis (NMA) where data were available for the outcome of interest.

The risk of bias was high but generally similar between studies with respect to randomisation, allocation concealment, blinding, outcome reporting and loss to follow-up. The main consideration with respect to quality is that currently available data for both cetuximab and panitumumab are taken only from a subgroup of the intention to treat (ITT) trial population. To set this in context, the rationale for this is based on tumour biology; research has shown a treatment interaction for RAS and EGFR inhibitors. In response to this, the EMA have recently revised the licensed indication for these products based on the subgroup data from the ITT populations of the trials. Currently the only available data demonstrating efficacy in people with *RAS* WT mCRC is from subgroup analyses (prespecified in one included trial, PEAK); we did not identify any RCT evidence where there was an ITT *RAS* WT population.

Despite this the limitations associated with the interpretation of subgroup data still apply. Given the use of subgroup data all comparisons were made without protection by stratification/randomisation. Instead, allocation to subgroups was based on *RAS* analysis of tumour samples from the *KRAS* WT Exon 2 trial participants; the *RAS* ascertainment rate was 61% minimising the potential for significant ascertainment bias (missing data largely resulted from unavailable tumour samples or inconclusive *RAS* test results). In addition, although imbalances in baseline characteristics between groups were expected, no major differences were observed mimimising the potential for selection bias. Due to the retrospective nature of the *RAS* analysis there were a low number of samples available for analysis reducing the power of the studies to show statistical significance.

Summary of benefits and risks

In total, five subgroup analyses were included in the clinical effectiveness review presented in this report. Given the differences in the eligible population between this current MTA review (cetuximab and panitumumab for previously untreated mCRC [in people with *RAS* WT tumours]), and the previous STA reviews (cetuximab for firstline treatment of mCRC [TA176] and panitumumab and chemotherapy for the treatment of mCRC [TA240; terminated appraisal]), the evidence included in this submission was identified by the Assessment Group's searches. The included subgroup analyses all contributed to network meta-analyses. It was not possible to construct a complete network as no studies were identified comparing FOLFOX with FOLFIRI in the *RAS* WT population to link the networks. Two

discrete networks were generated, one evaluating FOLFOX-containing chemotherapy regimens and the second comparing FOLFIRI-containing chemotherapy regimens.

Cetuximab

Two trials (OPUS and CRYSTAL), provided evidence for the effectiveness of cetuximab in combination with chemotherapy (FOLFOX4 [FOLFOX may be administered in different regimens, most commonly FOLFOX4 and FOLFOX6, the main difference is in the administration of these regimens] or FOLFIRI) compared with chemotherapy alone (FOLFOX4 or FOLFIRI). These trials included a total of 1,535 participants in the ITT population. Of these, 548 were evaluable for RAS status and 82.8% had *RAS* WT tumours. The median age of participants in these trials was >59.0 years (24–79 years in OPUS and 19–82 years in CRYSTAL), and the majority were male 61% . In both trials, the majority of participants (96%) had Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–1. Twenty-six percent of the *RAS* WT sub-population had liver metastases at baseline.

Evidence consistently suggests a treatment effect in favour of the addition of cetuximab to chemotherapy (FOLFOX4 or FOLFIRI) compared with chemotherapy alone (FOLFOX4 or FOLFIRI) for the outcomes of interest. The addition of cetuximab to FOLFOX4 (**Tejpar *et al.* (2015)** (OPUS)) was associated with a 47% reduction in the risk of progression in people with *RAS* WT tumours (HR 0.53 [95% CI 0.27, 1.04]), similarly, the addition of cetuximab to FOLFIRI (**Van Cutsem *et al.* (2015)** (CRYSTAL)) was associated with a 44% reduction (HR 0.56 [95% CI 0.41, 0.76]). For OS the addition of cetuximab to FOLFOX4 showed no significant evidence of improvement compared to FOLFOX4 alone (HR 0.94 [95% CI 0.56, 1.56]) however, the addition of cetuximab to FOLFIRI resulted in a 31 % reduction in OS (HR 0.69 [95% CI 0.54, 0.88]). Tumour response rates in the experimental arm ranged from 58% in the **Tejpar *et al.* (2015)** (OPUS) study to 66% in the **Van Cutsem *et al.* (2015)** (CRYSTAL) study vs 29% to 60% in the same respective studies for the control arms. In people with liver metastases at baseline, results in terms of improvement in OS and PFS were consistent with results for overall *RAS* WT population. Of these people 13.3% in the **Tejpar *et al.* (2015)** (OPUS) study to 16.3 % in the **Van Cutsem *et al.* (2015)** (CRYSTAL) study had complete resection in the experimental arms. Overall, clinical safety was consistent with results for *KRAS* WT population in all the trials. The most common events were diarrhoea, haematotoxiticity, neutropenia and skin reactions.

One trial (FIRE-3 trial [**Heinemann *et al.,* 2014**]), provided evidence for the effectiveness of cetuximab in combination with chemotherapy (FOLFIRI) compared with bevacizumab with

chemotherapy (FOLFIRI). This trial included 592 participants in the ITT population. Of these, 542 were evaluable for *RAS* status and 63.1% had *RAS* WT tumours. The median age of participants in FIRE-3 was >64.0 years (33–76 years), and the majority were male 69.8% with ECOG PS 0–1 *(98.5%). Thirty-five percent of the *RAS* WT sub-population had liver metastases at baseline. PFS was similar between the treatment groups (HR 1·06, 95% CI 0·88–1·26; p=0·55). The proportion of people who achieved an objective response were also similar between the cetuximab plus FOLFIRI and bevacizumab plus FOLFIRI. However, results show longer OS suggesting a benefit with cetuximab plus FOLFIRI (HR 0.70, 95% CI 0.53, 0.92).

Panitumumab

One trial (PRIME), provided evidence for the effectiveness of panitumumab in combination with chemotherapy (FOLFOX) compared with chemotherapy alone (FOLFOX). This trial included 1,183 participants in the ITT population. Of these, 1,060 were evaluable for *RAS* status and 48.3% had *RAS* WT tumours. The median age of participants in PRIME was >61.0 years (24–82 years) and the majority (>65%) were male with ECOG PS 0–1 (94%). Eighteen percent of the *RAS* WT sub-population had liver metastases at baseline. No evidence was identified comparing panitumumab plus FOLFIRI with FOLFIRI.

Evidence consistently suggests a treatment effect in favour of the addition of panitumumab to FOLFOX4 compared with FOLFOX4. Overall, clinical safety was consistent with results for *KRAS* WT population in all the trials. The most common events were diarrhoea, haematotoxiticity, neutropenia and skin reactions. The addition of panitumumab to FOLFOX4 was associated with a reduction in risk of progression of 28% (HR 0.72 [95% CI 0.58, 0.9]) (**Douillard *et al.,* 2013** [PRIME]).. Similarly, for OS the HR were 0.77 (95% CI 0.64, 0.94), favouring the panitumumab plus FOLFOX4 treatment group. Tumour response rates in the experimental arm were [redacted] compared with [redacted] in the control arm (**Data on File: Amgen UK, 2015** [PRIME]). In people with liver metastases at baseline results in terms of improvement in OS and PFS were consistent with results for the overall *RAS* WT population. Of these people, [redacted] in the experimental arm compared with [redacted] in the control arm had complete resection.

One trial (PEAK), provided evidence for the effectiveness of panitumumab in combination with chemotherapy (modified FOLFOX6 [mFOLFOX6]) compared with bevacizumab with chemotherapy (mFOLFOX6). This trial included 285 participants in the ITT population. Of these, 285 were evaluable for *RAS* status and 59.6% had *RAS* WT tumours. The median age of participants in PEAK was >60 years (23–82 yrs) and the majority (>67%) were male

with ECOG PS 0–1 (99%). Twenty-six percent of the *RAS* WT sub-population had liver metastases at baseline. The proportion of people who achieved an ORR were similar between the cetuximab plus mFOLFOX6 and bevacizumab plus mFOLFOX6. For PFS the addition of panitumumab to mFOLFOX6 was associated with a 35% reduction in risk of progression compared with bevacizumab plus mFOLFOX6. In addition, a trend towards OS benefit with panitumumab plus mFOLFOX6 was observed (HR 0.63; 95% CI 0.39, 1.02).

Network meta-analysis: FOLFOX network

The network meta-analysis (NMA) provided no statistically significant evidence to suggest that cetuximab plus FOLFOX was any more effective than FOLFOX, bevacizumab plus FOLFOX or panitumumab plus FOLFOX to increase the time to death or the time to progression or death.

Direct evidence suggests that panitumumab plus FOLFOX was more effective at increasing time to progression or death than FOLFOX and bevacizumab plus FOLFOX. Panitumumab plus FOLFOX was also estimated to be more effective at increasing survival than FOLFOX.

There was limited evidence to suggest that cetuximab plus FOLFOX is more effective at improving overall response rate than panitumumab plus FOLFOX.

There was little evidence that cetuximab plus FOLFOX was associated with fewer adverse events (AEs) than panitumumab plus FOLFOX, however some of these analyses were limited by the small number of events recorded in the treatment arms.

Network meta-analysis: FOLFIRI network

Evidence from the NMA suggests that cetuximab plus FOLFIRI and bevacizumab plus FOLFIRI are more effective than FOLFIRI at increasing time to progression or death, and ORR.

Direct evidence suggests that cetuximab plus FOLFIRI was more effective than FOLFIRI and bevacizumab plus FOLFIRI at increasing survival.

Cost effectiveness

Published economic evaluations

Of 1,979 search results, four studies were identified and reviewed: 1 full paper, 2 conference abstracts with accompanying posters and 1 conference abstract whose accompanying poster could not be retrieved.

One study was UK based, and compared cetuximab plus chemotherapy to chemotherapy alone. [9] This study was only reported as a conference abstract and poster. As this study was related to a SMC appraisal, additional details were sought from the SMC report.[10]

The full paper compared panitumumab in combination with FOLFOX to bevacizumab in combination with FOLFOX and was conducted in France, so the results were of limited generalisability to the UK. One other conference abstract also looked at this comparison for the Greek healthcare perspective.

The final abstract with accompanying poster reported the *RAS* WT population as a scenario analysis and was conducted from a healthcare perspective.

As the majority of included studies were not full papers, the quality of reporting was limited. One important note from the quality assessment was that all studies had at least one author employed by a manufacturer.

No studies completely answered the decision problem in this HTA and as such highlights the need for a *de novo* cost-effectiveness model.

Appraisal of Merck Serono's economic analysis

Merck Serono conducted a cost-effectiveness review and two executable models: one for the overall *RAS* WT population and one for a liver limited disease subgroup. As Merck Serono sent us their liver subgroup model very late in the review period, and as we were unable to reconcile the subgroup analysis with the overall population model, we did not critique this subgroup analysis.

The model was generally poorly reported: there were several discrepancies between the parameters in the report and model and the sources of some parameters were incorrectly given. A second iteration of the total population model and report were received to solve discrepancies between the results reported in the first submission.

In common with us, in their base case, Merck Serono assume fortnightly administration of cetuximab. They estimate the ICERs for the two key comparisons related to cetuximab:

- CET+FOLFOX vs. FOLFOX: £47,000 per QALY,
- CET+FOLFIRI vs. FOLFIRI: £56,000 per QALY.

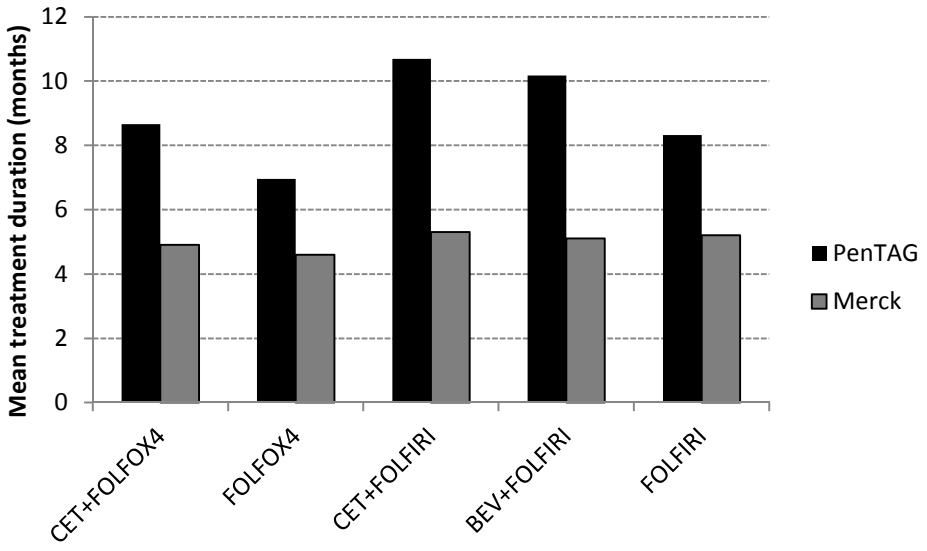
The model itself contained some minor errors and inconsistencies, but we found no major wiring errors.

The general structure of Merck Serono's model is similar to our own. Further, we are satisfied with the great majority of parameter values in Merck Serono's model.

However, we have identified 8 items that differ between our model and Merck Serono's model which have an important impact on cost-effectiveness, as discussed below. Most importantly, we believe that Merck Serono have underestimated mean treatment durations (Figure B). This has the important effect that Merck Serono estimate far lower drug acquisition costs (Figure C), and hence far lower ICERs than us.

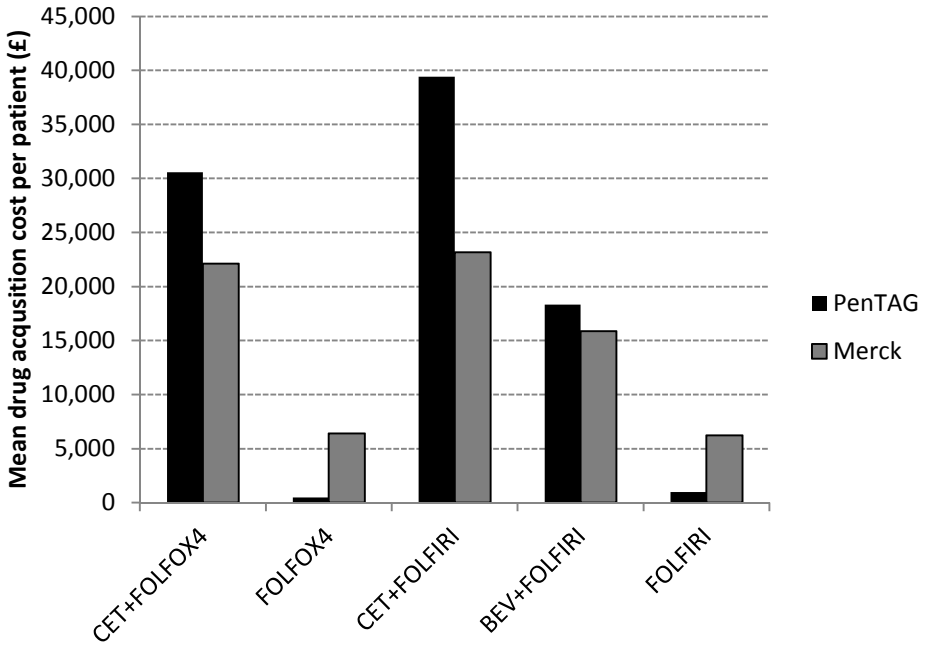
Merck Serono assume that no 1st-line drugs are given after a certain cut-off time, which varies slightly by treatment arm. Strangely, they provide no justification for the cut-off. Further, we note that Merck Serono assumed a similar cut-off time in their model for cetuximab and cetuximab+irinotecan for subsequent lines of treatment for mCRC, NICE TA242, in 2011.

Figure B. Mean durations of 1st-line line drugs: PenTAG vs. Merck Serono



Key: BEV = bevacizumab; CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin

Figure C. Mean cost of 1st-line drug acquisition: PenTAG vs. Merck Serono



Key: BEV = bevacizumab; CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin

PenTAG model

Our base case results for the FOLFOX and FOLFIRI networks are given in Table A and Table B below.

Table A. PenTAG base case summary cost-effectiveness results: All patients, FOLFOX network

				CET+FOLFOX vs.	PAN+FOLFOX vs.
	CET+FOLFOX	**PAN+FOLFOX**	**FOLFOX**	**FOLFOX**	**FOLFOX**
Life years (mean, undiscounted)	2.41	2.08	1.86	0.55	0.22
QALYs (mean, discounted)	1.61	1.41	1.26	0.35	0.15
Total costs (mean, discounted)	£77,262	£74,705	£38,825	£38,437	£35,880
ICER (Cost / QALY) vs. FOLFOX				**£109,820**	**£239,007**
ICER (Cost / QALY) on efficiency frontier	**£109,820**	Extended dominated	Reference		

Key: BEV = bevacizumab; CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

Table B. PenTAG base case summary cost-effectiveness results: All patients, FOLFIRI network

			CET+FOLFIRI vs.
	CET+FOLFIRI	FOLFIRI	FOLFIRI
Life years (mean, undiscounted)	2.21	1.75	0.46
QALYs (mean, discounted)	1.53	1.23	0.30
Total costs (mean, discounted)	£85,197	£40,027	£45,170
ICER (Cost / QALY)			£149,091

Key: BEV = bevacizumab; CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

We predict that for the comparison CET+FOLFOX vs. FOLFOX, most incremental QALYs come from PFS post-resection. This is largely due to the high expected resection rate for CET+FOLFOX ([redacted]) compared to FOLFOX ([redacted]). Total incremental QALYs for PAN+FOLFOX vs. FOLFOX are far lower than for CET+FOLFOX vs. FOLFOX. This is mostly because we predict a lower resection rate for PAN+FOLFOX ([redacted]), compared to CET+FOLFOX.

For the comparison CET+FOLFIRI vs. FOLFIRI, most incremental QALYs come from PFS non-resected and PFS post-resection (Figure 51). Post-resection QALYs are less important than for CET+FOLFOX vs. FOLFOX, as we predict low rates of resection for CET+FOLFIRI (7.3%) and FOLFIRI (2.1%).

The expected absolute 1st-line drug acquisition costs and 1st- and 2nd-line drug administration costs are by far the largest cost items. Incremental 1st-line drug acquisition costs dominate. 1st-line drug administration costs also make an important contribution to total incremental costs.

We believe that the ICERs are subject to substantial uncertainty, only some of which is captured in the PSA. On the plus side, the PFS data for 1st-line treatment is of high quality, as it comes directly from RCTs. However, we note that the evidence of CET+FOLFOX is not as strong as for PAN+FOLFOX, as the OPUS trial of CET+FOLFOX vs. FOLFOX had far fewer RAS WT patients (87) than the PRIME RCT of PAN+FOLFOX vs. FOLFOX. On the

minus side, we make several important assumptions that are associated with substantial uncertainty, including:

- We adjusted PFS from the RCTs of 1st-line drugs by removing patients who are resected. However, without access to the underlying individual patient data from the RCTs, we concede that our method is only approximate.
- We assume that any treatment effect from 1st-line drugs stops on progression. This is because we do not model OS from the RCTs, but instead only PFS. We explore the use of OS from the RCTs in a scenario analysis below.

- Given lack of data to suggest otherwise, we assume the same accuracy of the *RAS* test in clinical practice as in the 1st-line RCTs. Any differences are likely to result in even higher ICER estimates for cetuximab and panitumumab.
- Our estimate of resection rates for CET+FOLFOX = [redacted] is uncertain because it is estimated by an indirect comparison, and cost-effectiveness is very sensitive to resection rates. By comparison, we have confidence in our estimated rates of resection for the FOLFIRI network (CET+FOLFIRI = 7.3%, FOLFIRI = 2.1%). Also, our resection rate estimates for the FOLFOX network of PAN+FOLFOX = [redacted], FOLFOX = [redacted] are reliable, as they are taken directly from PRIME.

Probabilistic sensitivity analyses predicts the probabilities that the following treatments are most cost-effective at a willingness to pay threshold of £30,000 per QALY are:

- CET+FOLFOX: 22%.
- PAN+FOLFOX: 0%
- FOLFOX: 78%

- CET+FOLFIRI: 0%.
- FOLFIRI: 100%

We now discuss the liver metastases subgroup. Our base case results for the FOLFOX and FOLFIRI networks are given in Tables C and D below.

Table C PenTAG base case summary cost-effectiveness results: Liver metastases subgroup, FOLFOX network

				CET+FOLFOX vs.	PAN+FOLFOX vs.
	CET+FOLFOX	**PAN+FOLFOX**	**FOLFOX**	**FOLFOX**	**FOLFOX**
Life years (mean, undiscounted)	2.98	2.86	2.21	0.76	0.65
QALYs (mean, discounted)	1.97	1.89	1.49	0.49	0.40
Total costs (mean, discounted)	£94,008	£79,579	£43,537	£50,471	£36,042
ICER (Cost / QALY) vs. FOLFOX				£104,045	£89,673
ICER (Cost / QALY) on efficiency frontier	**£173,505 (vs. PAN+FOLFOX)**	**£89,673 (vs. FOLFOX)**	**Reference**		

Key: BEV = bevacizumab; CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

Table D. PenTAG base case summary cost-effectiveness results: Liver metastases subgroup, FOLFIRI network

			CET+FOLFIRI vs.
	CET+FOLFIRI	**FOLFIRI**	**FOLFIRI**
Life years (mean, undiscounted)	2.69	1.83	0.86
QALYs (mean, discounted)	1.83	1.26	0.57
Total costs (mean, discounted)	£100,274	£39,654	£60,620
ICER (Cost / QALY)			**£106,707**

Key: BEV = bevacizumab; CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

We predict slightly longer life expectancy for the liver mets subgroup (1.8 – 3.0 years) compared to all patients (1.7 – 2.4 years). This is because we also predict greater resection rates for the liver mets subgroup ([redacted]) than for all patients ([redacted]), and life expectancy is substantially greater for patients after resection compared to without resection.

Our estimated ICERs are highly uncertain, indeed more uncertain than for all patients combined, as, in addition to all the uncertainties for all patients combined, PFS for unresected patients is more uncertain than for all patients because additional assumptions are required to estimate this quantity.

Probabilistic sensitivity analyses predict the probabilities that the following treatments are most cost-effectivet at a willingness to pay threshold of £30,000 per QALY are:

- CET+FOLFOX: 2%.
- PAN+FOLFOX: 0%.
- FOLFOX: 98%

- CET+FOLFIRI: 0%.
- FOLFIRI: 100%

We now discuss the impact of some of the key scenario analyses on cost-effectiveness for all patients combined. The impact for the liver metastases subgroup is explained in the main text.

We find that BEV+FOLFOX is dominated by FOLFOX. When we include BEV+FOLFIRI as a comparator, the ICER for CET+FOLFIRI vs. BEV+FOLFIRI is £290,000 per QALY, greater than the ICER for CET+FOLFIRI vs. FOLFIRI.

When we include XELOX as a comparator, we predict that the ICERs for CET+FOLFOX vs. XELOX and PAN+FOLFOX vs. XELOX are higher than the corresponding ICERs vs. FOLFOX. This is because we estimate a lower drug administration cost for XELOX than for FOLFOX.

In our base case analysis, we model only PFS from the RCTs. OS is estimated from the times on 1st-, 2nd and 3rd-line of treatment for unresected patients, and for OS for resected patients. In a sensitivity analysis, we model OS, in addition to PFS, from the RCTs. The three differences in the scenario analysis versus the base case are:

- The modelled mean treatment duration for each treatment arm is set equal to the treatment duration from the RCTs. Unlike in the base case, we do not cap treatment duration as the mean time in 1st-line PFS for unresected patients. The rationale for removing the cap is that OS from the RCTs is likely to be affected (probably lengthened), by 1st-line drugs taken post-progression.

- We estimate the proportions of patients taking cetuximab- and panitumumab-based treatments 2nd-line from the limited data from the RCTs. From this, we estimate the total costs of drug acquisition and administration of these 2nd-line treatments.
- The time on 3rd-line best supportive care (BSC) for unresected patients is changed in such a way as to yield the OS curves from the RCTs (after subtracting patients post-resection, and after the indirect comparisons). The times in all other health states are unaltered.

- The cost-effectiveness of CET+FOLFOX vs. FOLFOX increases substantially so that CET+FOLFOX is now dominated by FOLFOX.
- The cost-effectiveness of PAN+FOLFOX vs. FOLFOX decreases substantially from £239,000 to £100,000 per QALY.
- The ICER for CET+FOLFIRI vs. FOLFIRI decreases from £149,000 to £101,000 per QALY.

When we assume that cetuximab is given weekly, as opposed to fortnightly in our base case, the monthly administration cost of cetuximab increases greatly and the ICERs increase substantially:

- CET+FOLFOX vs. FOLFOX: from £110,000 to £165,000 per QALY.
- CET+FOLFIRI vs. FOLFIRI: from £149,000 to £227,000 per QALY.

We now discuss the deterministic sensitivity analyses. Cost-effectiveness is very sensitive to:

- Resection rates.
- PFS and OS post-resection.
- PFS for unresected patients.
- Treatment duration.

Cost-effectiveness is quite sensitive to:

- discounting
- cost of administration of 1st-line drugs.

We find the following ICERs, when the prices of cetuximab and panitumumab are set to £0:

- CET+FOLFOX vs. FOLFOX: £27,000 per QALY.
- PAN+FOLFOX vs. FOLFOX: £50,000 per QALY.
- CET+FOLFIRI vs. FOLFIRI: £27,000 per QALY.

In other words, none of the combination treatments are cost-effective at the £20,000 per QALY threshold. This is largely because the total costs of administration of the combination treatments far exceed those of either FOLFOX or FOLFIRI. This in turn is because we predict that the combination treatments are taken for longer than FOLFOX or FOLFIRI, and because the monthly costs of administration are high.

Now turning to NICE's End of Life (EoL) criteria. Merck Serono claim that cetuximab satisfies these criteria. However, we disagree, as we believe that:

- The eligible patient population is too large,
- The estimated extension to life is not robust.
- We are not sure whether life expectancy on FOLFOX and FOLFIRI is less than the required 24 months
- We are not sure whether the extension to life is greater than the required 3 months.

We believe that panitumumab probably does not meet EoL as:

- The extension to life is not robust.
- We are unsure whether the patient population is sufficiently small,
- We are unsure whether life expectancy on FOLFIRI is less than the required 24 months,
- We are unsure whether the extension to life is greater than the required 3 months.

Results of pricing under the Patient Access Schemes for panitumumab and cetuximab can be found in Appendix K.

Comparison of the PenTAG and Merck Serono cost-effectiveness results

There are many similarities between our model and Merck Serono's model. For example, we assume:

- The same overall model structure, that is we both use only resection rates and PFS, but not OS, from the trials of 1st-line drugs. In scenario analyses, we both also model OS from the RCTs.

- Similar utilities.
- The same source for estimation of PFS and OS after resection.
- The same prices of cetuximab, panitumumab and bevacizumab. We assume far lower prices for FOLFOX and FOLFIRI, but this affects cost-effectiveness little.
- Similar times and treatment duration in 2nd-line FOLFOX and FOLFIRI.

Yet, there are several important differences between our models which act to yield very different estimates of cost-effectiveness of cetuximab.

The PenTAG ICERs:

- CET+FOLFOX vs. FOLFOX = £110,000 per QALY,
- CET+FOLFIRI vs. FOLFIRI = £149,000 per QALY.

are much higher than Merck Serono's ICERs:

- CET+FOLFOX vs. FOLFOX = £47,000 per QALY,
- CET+FOLFIRI vs. FOLFIRI = £55,000 per QALY.

In total, we have identified 8 items that differ between our model and Merck Serono's model which have an important impact on cost-effectiveness.

For the FOLFOX network, treatment duration and PFS for unresected patients are the most important items (Figure D). The ICER from Merck Serono's model increases substantially when both are independently changed to our estimate, because we assume substantially greater treatment durations than Merck Serono, and we assume substantially smaller differences between mean PFS for unresected patients for CET+FOLFOX vs. FOLFOX than do Merck Serono. This itself is because we estimate PFS for unresected patients by subtracting off PFS for resected patients from the PFS data for resected+unresected patients from the RCT, whereas Merck Serono do not.

For the FOLFIRI network, treatment duration is clearly the most important item. The ICER from Merck Serono's model increases substantially when durations are changed to our estimates. Unlike for the FOLFOX network, the ICER for CET+FOLFIRI vs. FOLFIRI increases only slightly when we use our estimates of PFS for unresected patients, even though we again subtract off PFS for resected patients from PFS for resected+unresected patients from the RCTs. This is because we estimate substantially lower resection rates for the FOLFIRI network compared to the FOLFOX network.

Above all, treatment duration is the most critical issue in the current HTA with regards to explaining the difference in cost-effectiveness as produced by our model and Merk Serono's model.

We assume a far longer duration in PFS and PD post-resection for than Merck Serono. This substantially improves the cost-effectiveness of CET+FOLFOX vs. FOLFOX and CET+FOLFIRI vs. FOLFIRI (Figure D).

For the FOLFOX network, we assume far higher resection rates than Merck Serono. This also substantially improves the cost-effectiveness of CET+FOLFOX vs. FOLFOX. We assume the same resection rates as Merck Serono for CET+FOLFIRI and FOLFIRI.

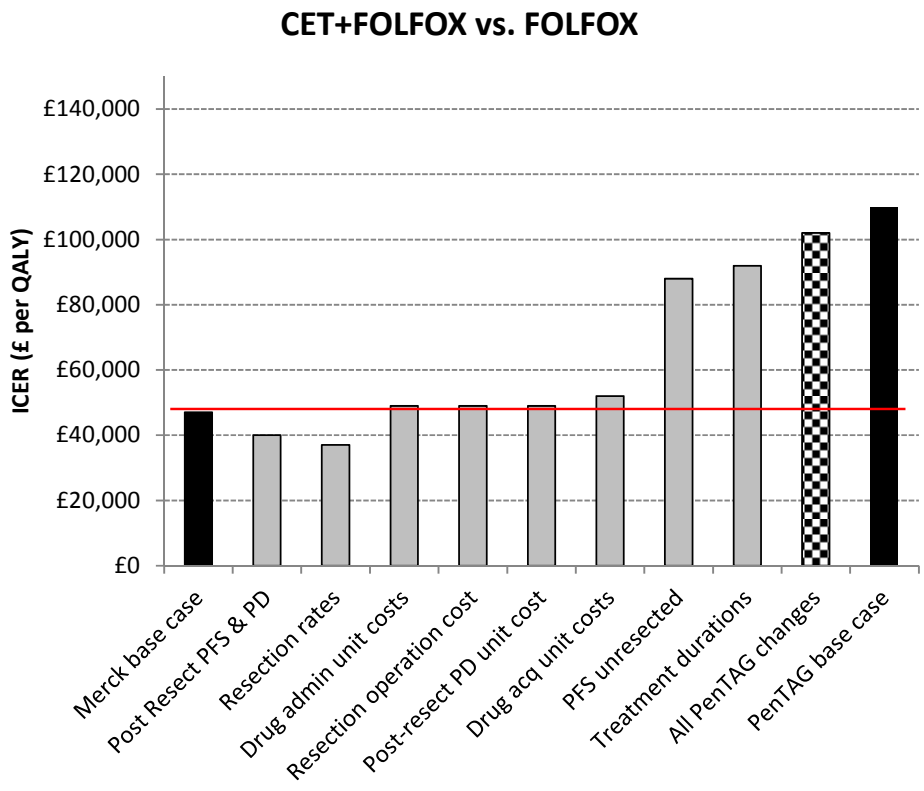
There are four other factors which contribute to the PenTAG model having higher ICERs than Merck Serono's model:

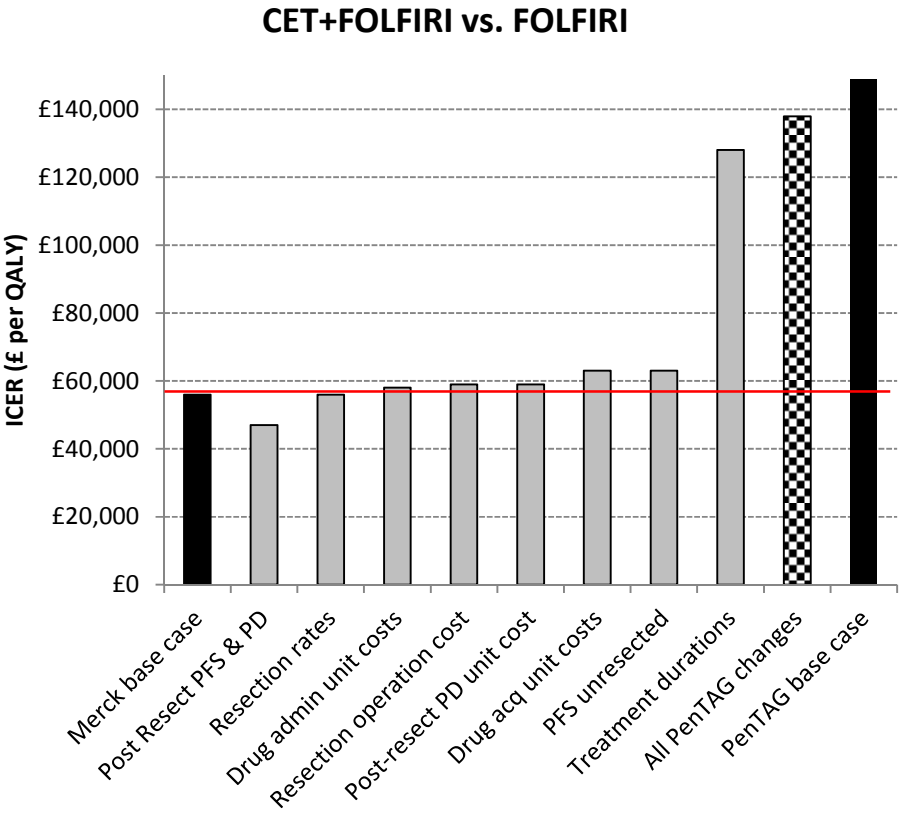
- We assume far higher unit costs of drug administration than Merck Serono. Our values yield slightly higher ICERs because we assume that patients are on treatment for longer on CET+FOLFOX than FOLFOX and for longer on CET+FOLFIRI than FOLFIRI.
- We assume a far higher cost for resection operation than do Merck Serono. This acts to worsen cost-effectiveness, as the resection rate is higher for CET+FOLFOX than FOLFOX and for CET+FOLFIRI than FOLFIRI.
- We assume a higher cost per month for treating patients in PD post-resection. This acts to increase the ICERs, again as the resection rate is higher for CET+FOLFOX than FOLFOX and for CET+FOLFIRI than FOLFIRI.
- We assume different costs of drug acqusiton per month. This acts to increase the ICERs, as we assume a slightly higher cost of acquisition of cetuximab per month than Merck Serono (£3,859 vs. £3,478). Our estimates of the monthly cost of acquisition of FOLFOX and FOLFIRI are much lower than those of Merck Serono. However, cost-effectiveness is insensitive to these differences because they affect both treatment arms similarly in treatment comparison pairs.
- We assume a higher monthly acquisition cost of cetuximab than Merck Serono because we assume a slightly larger body surface area, 1.85m2 vs. 1.79m2, and the dose of cetuximab depends on body surface area.

When we amend Merck Serono's model for all eight changes simultaneously, the resulting ICERs are similar to the base case ICERs in our model (Figure D). We find no remaining large differences in incremental mean life years, QALYs and costs between Merck's

amended model and our model. We conclude that there are no further differences between our model and Merck Serono's model that have a large impact on cost-effectiveness.

Figure D. ICERs from Merck Serono model with PenTAG changes applied independently or in combination





Comparison of the current MTA to previous STAs (TA176, TA240)

Although this MTA seeks to update previous guidance from two single technology appraisals (STAs) (TA176 and TA240),[11, 12] there are some important differences between the scope for the previous STA reviews and this current MTA review (ID794). The main difference is in the patient population. The current scope specifies people with *RAS* WT mCRC, whereas previous STA reviews specified EGFR-expressing mCRC (TA 176) [11], and *KRAS* WT mCRC (TA240)[12].

TA240 aimed to assess the effectiveness and cost-effectiveness of firstline panitumumab in combination with chemotherapy for metastatic colorectal cancer patients, but was terminated when no evidence was received from the manufacturers. As such no comparison can be madebetween TA240 and the current assessment can be made.

TA176 assessed the effectiveness and cost-effectiveness of firstline cetuximab in combination with chemotherapy for metastatic colorectal cancer patients. Comparisons can only be made between TA176 and the current MTA for the OPUS and CRYSTAL trials, since FIRE-3 is new to the current appraisal. In line with research developments, effect estimates (where reported) for OS, PFS and ORR were either similar or point estimates were slightly decreased in the *RAS* WT subgroup compared with the *KRAS* WT population suggesting reduced risk of progression or death in the *RAS* WT population. However, these results should be interpreted with caution, as the analyses are based on subgroup analyses and as sample sizes (for some studies) were small reducing the power of the studies to show statistical significance. No comparison could be made in respect of HRQoL data as the current HTA did not identify any data for HRQoL among the *RAS* WT population. Variability in the reporting of AEs between TA 176 and the current MTA; e.g. summary AEs, AEs in ≥5% of participants; or AEs >5% difference between treatment arms made it difficult to draw comparison where data were reported

Both TA176 and the current assessment include a *de novo* economic analysis provided by Merck Serono. The structure and data sources for this model are similar to those presented in the current assessment and therefore our crticisms of the current Merck Serono model also apply to that submitted for TA176.

TA176 presented two comparisons based on head to head trial data:

- CET+FOLFOX versus FOLFOX, informed by OPUS
- CET+FOLFIRI versus FOLFIRI, informed by CRYSTAL

The ICERs reported in TA176 are £63,245 per QALY gained for CET+FOLFOX versus FOLFOX and £69,287 per QALY gained for CET+FOLFIRI versus FOLFIRI, lower than the current PenTAG model results. As with the current Merck Serono assessment, the differences are primarily driven by difference in costs of first line treatment. As we do not have the original model for TA176, it is not possible to confirm which parameters differed.

Discussion

The systematic reviews of clinical and cost-effectiveness were conducted by an independent, experienced research team using the latest evidence and working to a pre-specified protocol (PROSPERO CRD42015016111). This technology assessment builds on existing secondary research and economic evaluations

Strengths and limitations of the systematic review of effectiveness studies

A strength of this report is that a systematic review of RCTs for cetuximab and panitumumab in people with mCRC with *RAS* WT tumours, and a network meta-analysis (NMA) has been conducted to evaluate relative efficacy. In the absence of head-to-head RCTs, an NMA was conducted to assess relative efficacy of panitumumab in combination with chemotherapy and cetuximab in combination with chemotherapy.

However, there are some important sources of uncertainty that may impact on the conclusions:

- Currently available data providing evidence for the effectiveness of cetuximab and panitumumab are taken from subgroups of the ITT trial populations.The rationale is based on developments in tumour biology research (i.e. research demonstrating an interaction between *RAS* and EGFR inhibitors [specifically the negative implications of *RAS* mutations on the effectiveness of EGFR inhibitors]). Of note, the recent change to the licensed indication by the EMA is based on these same subgroup data and treatment effect estimates for both cetuximab and panitumumab are in the expected direction and consistent across trial populations.

- Given the use of subgroup data all comparisons were made without protection by stratification/randomisation. Instead, allocation to subgroups was based on re-evaluating tumour samples from the *KRAS* WT Exon 2 population for *RAS* status. While this minimised the potential for ascertainment bias, there were missing data for some of the trials (either the tumour was not evaluable for *RAS* status or the results were

inconclusive). No significant imbalances between the trial populations were observed minimising the potential for selection bias. Of note, none of the included subgroup analyses reported the results of a test for treatment interaction. Due to the retrospective nature of the *RAS* analysis, for some studies, e.g. the OPUS RCT, there were a low number of samples available for analysis, reducing the power of the studies to show statistical significance

- No evidence was identified to estimate the effectiveness of panitumumab plus FOLFIRI (licence approved for panitumumab plus FOLFIRI for the first-line treatment of adults with *RAS* WT metastatic colorectal cancer [mCRC] in Q1 2015).

- The subgroup analyses all contributed to network meta-analyses. However, it was not possible to construct a complete network and two discrete networks were generated, one evaluating FOLFOX-containing chemotherapy regimens and the second comparing FOLFIRI-containing chemotherapy regimens. It was therefore not possible to make comparison between FOLFOX-containing and FOLFIRI-containing regimens.

- Although there were some reporting omissions in the publications of the subgroup analyses, the Assessment Group were able to confirm estimates via other sources; e.g. European Medicines Agency (EMA) reports or via the companies.

- The timepoint at which ORR was measured was unclear for all of the trials. Objective response rate was measured at either six- or eight-week intervals (according to methods reported in the primary publications). Given this uncertainty results reported for the *RAS* WT population for this outcome should be treated with caution.

- Small sample sizes for the subgroup of the *RAS* WT population with liver metastases at baseline increased the level of uncertainty; there was a lack of statistical power and limitations with precision and validity. However, subgroup data provide the only available evidence. In addition the effect estimates are consistent across all studies. Although one trial – FIRE-3 (which contributed evidence for the effectiveness of cetuximab plus FOLFIRI compared with FOLFIRI) did not report data for all outcomes for this subgroup.

- None of the included trials reported HRQoL estimates for the *RAS* WT population.

- We are aware of other cetuximab trials; for example, COIN and NORDIC VII for which there is currently no *RAS* WT subgroup data available.

- Data comparing cetuximab plus FOLFOX with panitumumab plus FOLFOX was only available from the network meta-analysis. The limitations regarding the data for the *RAS* WT population (above), also apply to the network meta-analysis, and as such results should also be interpreted with caution.

Generalisability of the findings

The study arm populations had, median/mean ages of between 59 and 65 years and the majority of participants had an ECOG performance status of <2, meaning that people were younger and fitter than the UK population of people with mCRC. This is a recurrent problem, however, in the findings of trials of therapies for mCRC to the UK population. All of the included studies were multicentre studies (including European centres), and evaluated the study drugs in line with their licensed indications.

Importantly, however, data for the *RAS* WT population were only available from subgroup analyses rather than ITT analyses, and, as such, sample sizes were often small and results are subject to a high degree of uncertainty. While subject to the uncertainties outlined above, these subgroup data are currently the only available data for the RAS WT sub-population. We did not identify any RCTs with an ITT by RAS WT status, and only one of the included trials prespecified the extended RAS analysis. Of note, the EMA's recent change to the licensed indication was based on subgroup data from trials that inform this current assessment, and while subgroup analyses were defined post-hoc the rationale was based on research developments into tumour biology and results were in line with the expected direction of effect and consistent across included studies

Published economic evaluations are from a range of settings, only one of which being UK based, and they have varying levels of reporting, the majority being conference abstracts/posters. All evaluations have issues of generalisability that concern the estimates of effectiveness.

Hence the extent to which the results of included trials can provide a reasonable basis for generalization to the UK NHS population of people with mCRC is unclear.

Strengths and limitations of the de novo *economic analysis*

A strength of the PenTAG model is that is an independent model, not sponsored by any of the manufacturers producing cetuximab or panitumumab. It uses up-to-date clinical effectiveness data, which has been acquired through a systemic review of current evidence.

Drug acquisition costs were obtained, where possible, from the Commercial Medicines Unit eMit database, which reflects the true cost to the NHS of acquiring these drugs as it includes discounts obtained by hospital pharmacies. For other drugs the list price from the BNF was used, as in the NICE reference case.

We have explored areas of uncertainty through scenario analyses and sensitivity analyses (deterministic and probabilistic). Though ICERs for anti-EGFR therapies versus chemotherapy alone altered quite substantially in some analyses, none fell below a willingness to pay threshold of £20,000 per QALY gained.

The model is subject to the same limitations as the clinical effectiveness review as these are carried through into the modelling. There are also several areas of uncertainty, including:

- The evidence is poor for the accuracy and effectiveness of companion diagnostic for testing *RAS* mutation status, with no trials presenting effectiveness of treatment following diagnosis for all tests used in clinical practice. We have assumed, due to the the evidence available, that this is the same in practice as it is in the trials, but this may not be true and would likely result in lower effectiveness for cetuximab and panitumumab in practice.
- Some drugs (those for which the BNF price was used) may be obtained at lower costs than assumed due to locally procured discounts. There is no indication what these costs might be, and the NICE reference case has been adhered to in this regard.
- It has been assumed that fortnightly cetuximab will be used in the NHS as this is believed to be current clinical practice and is less costly and burdensome for patients. It was assumed that clinical effectiveness would be unchanged going from weekly to fortnightly on the basis of a single non-inferiority trial. It remains possible that there is in fact a difference in effectiveness between the schedules, although on the basis of current evidence there is unlikely to be a substantial difference. This also adds complexity to the decision process, since to achieve the ICER reported in the PenTAG base case might require NICE to issue guidance outside the current marketing authorisation
- The PFS data for 1st-line treatment is of high quality, as it comes directly from RCTs, but we note that the evidence of CET+FOLFOX is not as strong as for PAN+FOLFOX, as the OPUS trial of CET+FOLFOX vs. FOLFOX had far fewer *RAS* WT patients (87) than the PRIME RCT of PAN+FOLFOX vs. FOLFOX (512). This is demonstrated in the probabilistic sensitivity analysis, where the

CET+FOLFOX versus FOLFOX results are much more uncertain than PAN+FOLFOX versus FOLFOX.

- As there were two trials to base the effectiveness of FOLFOX on, one had to be chosen for the base case. Due to its larger size, we based our effectiveness estimates for FOLFOX on the PRIME trial. In a scenario analysis where OPUS is chosen to base the effectiveness estimates the ICERs for PAN+FOLFOX versus FOLFOX do decrease substantially, particularly for the liver metastases subgroup.
- We adjusted the PFS from the RCTs of 1st-line drugs by subtracting patients who are resected to calculate PFS for unresected patients. As the underlying individual patient data from the RCTs was not available, this method is only approximate.
- We estimated survival post-resection from a study that is now several years old, where no patients received either cetuximab or panitumumab. [3] It is therefore possible that survival post-resection for patients initially treated with these drugs could differ from Adam et al. (2004).
- Treatment effect from 1st-line drugs was assumed to stop following disease progression. This is because we do not model OS from the RCTs, only PFS. We explore the use of OS from the RCTs in a scenario analysis where the ICERs for CET+FOLFOX significantly increases versus FOLFOX; PAN+FOLFOX ICERs significantly decreased versus FOLFOX; CET+FOLFIRI versus FOLFIRI ICER decreases. These changes are driven by the treatment duration which is now calculated directly from the RCTs.
- For the liver metastases subgroup PFS is even more uncertain as direct evidence was unavailable so adjustments to PFS for all patients was made. Furthermore, we were forced to estimate PFS for unresected patients from PFS for resected + unresected patients for the liver metastases subgroup using a different, and arguably less rigorous, method compared to all patients.

Conclusions

Clinical effectiveness evidence in this review suggests there is some clinical benefit from anti-EGFR therapies in comparison to standard chemotherapy treatments and mixed clinical benefit in comparison to anti-VEGF therapies: e.g. direct evidence suggests that panitumumab plus FOLFOX is more effective at increasing time to progression or death than FOLFOX and bevacizumab plus FOLFOX. Panitumumab plus FOLFOX is also estimated to be more effective at increasing time to death than FOLFOX. Evidence suggests that cetuximab plus FOLFIRI and bevacizumab plus FOLFIRI are more effective than FOLFIRI at increasing time to progression or death, and ORR.

There is limited evidence to draw conclusions over which anti-EGFR therapy has most clinical benefit. There is no evidence to suggest that cetuximab plus FOLFOX is any more effective than panitumumab plus FOLFOX to increase the time to death or the time to progression or death and there is limited evidence to suggest that cetuximab plus FOLFOX is more effective at improving ORR than panitumumab plus FOLFOX.

Estimates of cost-effectiveness currently suggest poor value for money at willingness to pay thresholds of £30,000. Our results currently indicate that the cost of administering these treatments is what drives this poor value for money, as even when reducing the cost to £0, ICERs remain above a £30,000 per QALY gained willingness to pay threshold. Probabilistic sensitivity analyses further demonstrate that anti-EGFR therapies are unlikely to be cost-effective at a willingness to pay threshold of £30,000 per QALY gained: for the FOLFOX network, FOLFOX has 78% likelihood of being most cost-effective treatment; and for the FOLFIRI network, FOLFIRI has 100% likelihood of being the most cost-effective treatment.

In summary, there is potential for clinical benefit from anti-EGFR therapies, but cost of administering these therapies is substantial.

Suggested research priorities

- We recommend that the economic analysis should be repeated when the PFS and OS data from the RCTs is more mature. Given sufficiently mature data, we would no longer need to use PFS and OS related to patients post-resection, with all the associated uncertainty, as we do currently.

- The RCTs of 1st-line drugs included subsequent treatments that are not widely used in the UK NHS. Therefore, the economic analysis would benefit from RCTs with subsequent treatments in line with those widely used in the NHS. However, given the substantial costs of conducting trials, we appreciate that this is unlikely to happen.

- Given lack of data to suggest otherwise, we assume the same accuracy of the *RAS* test in clinical practice as in the 1st-line RCTs. Any differences are likely to render higher ICERs for cetuximab and panitumumab. Therefore, we would welcome further research in to the relative accuracies of the tests as used in the trials and in clinical practice.

- Our economic analysis is desgined for the NHS in England & Wales. However, it could easily be adapted for the healthcare systems of other countries.

- CET+FOLFOX, CET+FOLFIRI and PAN+FOLFOX are all given intravenously. Our economic analysis suggests that the administration of these treatments is expensive, and

it highlights that there is a strong economic incentive to develop oral treatments for mCRC.

- The cost-effective of treatments for the liver metastases subgroup are very uncertain, partly due to the small numbers of patients in the trials. Therefore, if there is further interest in giving these treatments to this subgroup of patients, then we need better quality and quantity of clinical evidence.

1. Background

1.1. Description of the health problem

1.1.1. Aetiology and pathology

Colorectal cancer (CRC), also referred to as bowel cancer, is any cancer that affects the colon (large bowel) and rectum. It usually develops slowly over a period of 10 to 15 years. The tumour typically begins as a noncancerous polyp. A polyp is a growth of tissue that develops on the lining of the large intestine (colon or rectum) that can become cancerous. Metastatic colorectal cancer (mCRC) refers to disease that has spread beyond the large intestine and nearby lymph nodes.[13] This type of cancer most often spreads first to the liver, but metastases may also occur in other parts of the body including the lungs, brain and bones.[13]

The pathology of the tumour is usually determined by analysis of tissue taken from a biopsy or surgery. The extent to which the cancer has spread is described as its stage.[14] Staging is essential in determining the choice of treatment and in assessing prognosis.[14] The pathology of the tumour is usually determined by analysis of tissue taken from a biopsy or surgery.[14] More than one system is used for the staging of cancer. Colorectal cancer stage can be described using the modified Dukes staging system (based on postoperative findings – a pathological staging based on resection of the tumour and measuring the depth of invasion through the mucosa and bowel wall), or the more precise TNM staging system which is based on the depth of tumour invasion (T), nodal involvement (N), and metastatic spread (M) assessed pre-operatively by radiological examination (Table 1).[14] Metastatic disease is classified as Stage IV or Modified Duke's Stage D.

Table 1. Staging of colorectal cancer

Staging group	TNM staging and sites involved	Modified Dukes stage
Stage 0	Carcinoma in situ (Tis, N0, M0)	
Stage I	No nodal involvement, no distant metastases	A
	Tumour invades submucosa (T1, N0, M0)	
	Tumour invades muscularis propria (T2, N0, M0)	
Stage II	No nodal involvement, no distant mestastases	B
	Tumour invades muscularis propria into pericolorectal tissues (T3, N0, M0)	
	Tumour penetrates surface of visceral peritoneum or directly invades or is adherent to other organs or structures (T4a/b, N0, M0)	
Stage III	Nodal involvement, no distant metastases	C
	(Any T, Any N, M0)	
Stage IV	Distant metastases	D
	(Any T, Any N, M1a/M1b)	

Key: T0, no evidence of tumour; Tis, tumour in situ (abnormal cells present but may spread to neighbouring tissue, sometimes referred to as preinvasive cancer); T1, T2, T3, T4, stage of cancer; N0, no regional lymph node involvement; M0, no distant metastasis; M1, distant metastasis is present
Source: National Institute for Health and Care Excellence. NICE Pathways: Staging colorectal cancer. London: NICE, 2015[14]

1.1.2. Epidemiology

1.1.2.1. Incidence and prevalence

In terms of incidence, CRC is the fourth most common cancer in the UK behind breast, lung and prostate cancer, accounting for 13% of all new cases.[15] It is the third most common cancer in both men (14% of the total for men) and women (11%) separately.[15] Table 2 summarises the number of new cases and incidence rates in the UK.

Table 2. Number of new cases, crude and European age-standardised incidence rates per 100,000 population, UK (2011)

		England	Wales	Scotland	Northern Ireland	UK
Male	Cases	18,971	1,297	2,239	664	23,171
	Crude rate	72.6	86.2	87.9	74.7	74.6
	AS rate (95% CI)	56.7 (55.9, 57.5)	60.2 (57.0, 63.5)	67.4 (64.6, 70.2)	66.4 (61.3, 71.4)	58.0 (57.3, 58.8)
Female	Cases	15,073	1,046	1,756	535	18,410
	Crude rate	55.9	67.1	64.9	57.8	57.2
	AS rate (95% CI)	36.8 (36.2, 37.4)	40.6 (38.2, 43.1)	41.9 (39.9, 43.9)	42.9 (39.3, 46.5)	37.6 (37.1, 38.2)
Persons	Cases	34,044	2,343	3,995	1,199	41,581
	Crude rate	64.1	76.5	76.0	66.1	65.8
	AS rate (95% CI)	46.0 (45.5, 46.5)	49.6 (47.6, 51.6)	53.3 (51.7, 55.0)	53.5 (50.5, 56.5)	47.0 (46.6, 47.5)

Key: AS = age standardised; CI = confidence interval; UK = United Kingdom
Notes: The ICD codes for cancer incidence and mortality are ICD-10 C18-C20 (which includes cancers of the colon, rectum and rectosigmoid junction)
Source: Adapted from Cancer Research UK, Bowel Cancer Incidence Statistics, 2011[15]

Approximately two thirds (66%) of cancer cases affect the colon and over one third (34%) affect the rectum, though this distribution varies by sex.[15] The crude incidence rate shows that there are 46 and 41 new colon cancer cases for every 100,000 men and women in the UK, respectively.[15] The crude rates also show there are around 29 and 17 new rectal cancer cases for every 100,000 men and women in the UK, respectively.[15]

Approximately 25% of people present with metastases at initial diagnosis and almost 50% of people with CRC will develop metastases.[16]

Prevalence refers to the number of people who have previously received a diagnosis of cancer and who are still alive at a given time point. Some people will have been cured of their disease and others will not. In the UK, more than 143,000 people were still alive at the end of 2006, up to ten years after being diagnosed with CRC (Table 3).[15]

Table 3. Colorectal cancer (C18–20): one, five and 10 year prevalence, UK (2006)

Cases	1 year prevalence	5 year prevalence	10 year prevalence
Male	14,635	51,183	78,483
Female	11,415	40,594	65,075
Persons	26,050	91,777	143,558

Source: Adapted from Cancer Research UK, Bowel Cancer Incidence Statistics, 2011[15]

1.1.2.2. Risk factors

Risk factors include age and family history. In the UK between 2009 and 2011, an average 43% of bowel cancer cases were diagnosed in people aged 75 years and over, and 95% were diagnosed in those aged 50 years-plus.[15] The lifetime risk of developing bowel cancer in the UK is 1 in 14 for men and 1 in 19 for women.[15]

1.1.2.3. Mortality

Colorectal cancer is the second most common cause of cancer death in the UK (2012), accounting for 10% of all deaths from cancer.[17] In 2012, there were 16,187 deaths from CRC in the UK (Table 4). The crude mortality rate shows that there are 28 CRC deaths for every 100,000 men in the UK, and 23 for every 100,000 women.[17]

Around six in 10 (61%) CRC deaths are due to cancers of the colon, and around four in 10 (39%) are due to cancers of the rectum.[17] Almost a fifth (18%) of CRC deaths occur in people aged 60-69 years.[17]

Table 4. Colorectal cancer (C18-C20), number of deaths, crude and European age-standardised mortality rates per 100,000 population, UK (2012)

		England	Wales	Scotland	Northern Ireland	UK
Male	Cases	7,200	525	837	233	8,795
	Crude rate	27.3	34.8	32.5	26.0	28.1
	AS rate (95% CI)	20.0 (19.5, 20.4)	23.0 (21.1, 25.0)	23.3 (21.7, 24.8)	22.2 (19.3, 25.0)	20.5 (20.1, 20.9)
Female	Cases	6,0.36	387	784	185	7,392
	Crude rate	22.2	24.7	28.7	19.9	22.8
	AS rate (95% CI)	12.6 (12.3, 12.9)	13.1 (11.8, 14.4)	16.2 (15.1, 17.4)	12.8 (10.9, 14.6)	13.0 (12.7, 13.3)
Persons	Cases	13,236	912	1,621	418	16,187
	Crude rate	24.7	29.7	30.5	22.9	25.4
	AS rate (95% CI)	15.9 (15.7, 16.2)	17.6 (16.5, 18.7)	19.2 (18.3, 20.1)	17.0 (15.3, 18.6)	16.3 (16.1, 16.6)

Key: AS = age standardised; CI = confidence interval; UK = United Kingdom
Notes: The ICD codes for cancer incidence and mortality are ICD-10 C18-C20 (which includes cancers of the colon, rectum and rectosigmoid junction)
Source: Adapted from Cancer Research UK, Bowel Cancer Mortality Statistics, 2012[17]

1.1.2.4. Survival and prognosis

Approximately 77% of men survive CRC for at least one year, and this is predicted to fall to 59% surviving for five years or more, as shown by age-standardised net survival for people diagnosed with CRC during 2010-2011 in England and Wales.[18] Survival for women at one and five years is slightly lower, with 74% surviving for one year or more, and 58% predicted to survive for at least five years.[18]

Survival is, however, highly dependent upon the stage of disease at diagnosis. Survival by stage is not yet routinely available for the UK due to inconsistencies in the collecting and recording of staging data in the past. However, published estimates suggest that approximately 90% of people diagnosed at the earliest stage while fewer than 10% of people diagnosed with distant metastases will survive for more than five years.[19] In general, the earlier the diagnosis the higher the chances of survival.[19]

1.1.3. Impact of health problem

Colorectal cancer is a significant cause of morbidity and mortality.[20] When treating people with mCRC, the main aims of treatment are to relieve symptoms and to improve health-related quality of life (HRQoL) and survival.[13]

1.1.4. Measurement of disease

The outcome endpoints of CRC can be measured in a variety of ways:

- Overall survival (OS): defined as the time from randomisation to death from any cause.[21]
- Progression-free survival (PFS): defined as time from randomisation until disease progression or death.[21]
- Objective response rate (ORR): defined as either a partial response (PR) or complete response (CR). The number of CRs and PRs are important as the benefits from CRs tend to be greater.
  - complete response (CR): all detectable tumour has disappeared
  - partial response (PR): roughly corresponds to at least a 50% decrease in the total tumour volume but with evidence of some residual disease still remaining
  - stable disease (SD) includes either a small amount of growth (typically less than 20 or 25%) or a small amount of shrinkage
  - progressive disease (PD): means the tumour has grown significantly or that new tumours have appeared. The appearance of new tumours is always PD regardless of the response of other tumours. Progressive disease normally means the treatment has failed.
- Health-related quality of life (HRQoL): How a person's well-being is affected by treatment.

1.2. Current service provision

National Institute for Health and Care Excellence (NICE) guidance is available on the diagnosis and management of mCRC,[13] and first line chemotherapeutic treatments for mCRC (see Sections 1.2.2.1, 1.2.2.2 and 1.2.2.3).[11, 12, 22] NICE guidance on the use of second line or subsequent treatments is also available, however, it is not discussed in detail in this report as it is beyond the scope for this multiple technology appraisal (MTA).[23]

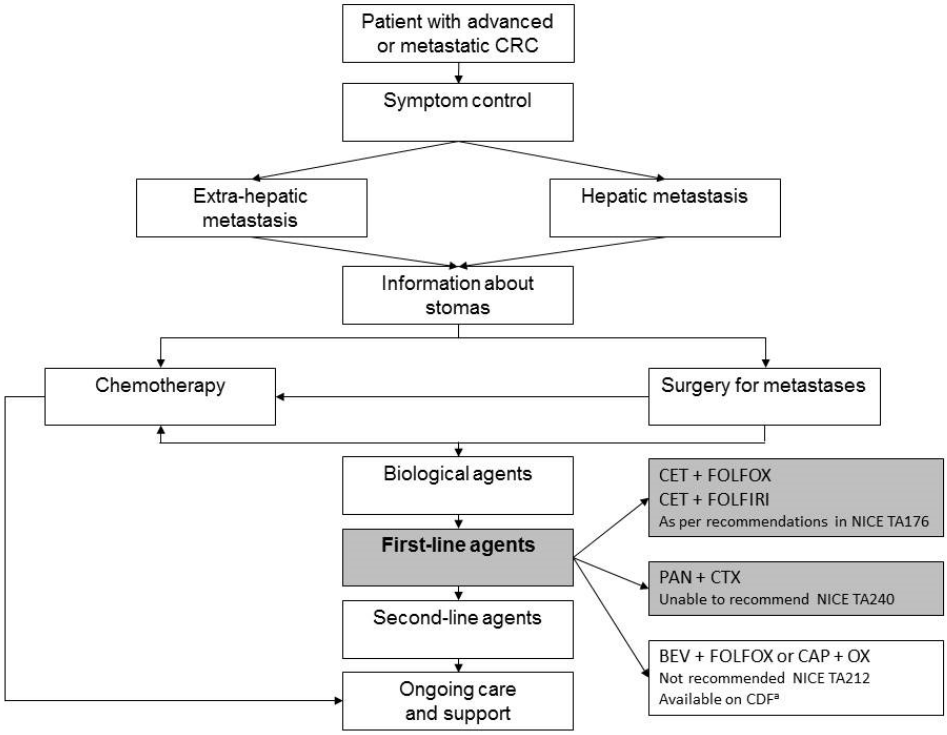
1.2.1. Management of disease

Treatment of mCRC may involve a combination of surgery, chemotherapy, radiotherapy, and supportive care (Figure 1).

The majority of people with metastatic disease are not initially suitable for potentially curative resection.[13, 16] Up to 30% of people may be cured if metastases in the liver can be resected.

In order for surgery to be considered, there must be no evidence of cancer outside of the liver, and there must be an adequate amount of normal liver left behind after the resection to sustain life.[13] Surgical skill is crucial to outcomes and there is evidence of wide variation between survival rates operated on by individual surgeons.[24] Chemotherapy may be recommended before surgery in some cases, even if the metastatic disease appears confined to the liver.[13, 16] This approach may help a person who is a borderline candidate for surgery (due to size or location of tumours) to become suitable for resection after a response has been achieved with combination chemotherapy.[13, 16]

Figure 1. Managing advanced and metastatic colorectal cancer (NICE Pathways)



Key: BEV = bevacizumab; CAP = capecitabine; CDF = Cancer Drugs Fund; CET = cetuximab; CRC = colorectal cancer; CTX = chemotherapy; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; NICE = National Institute for Health and Care Excellence; OX = oxaliplatin; TA = technology appraisal

Notes: Bevacizumab is not recommended by NICE (TA212).At the time of scoping BEV was available (subject to satisfying criteria for access) via the CDF; however, this drug was delisted for the indication under review in this TA in March 2015

Source: Adapted from NICE Pathways: Managing Advanced and Metastatic Colorectal Cancer[25]

For the majority of people however, surgery with curative intent is not an option due to the widespread nature of their disease and/or their poor suitability for surgery.[13] These people are treated with palliative intent using a combination of specialist treatments: palliative surgery (e.g. in cases where the tumour is causing an obstruction), chemotherapy, or radiotherapy to improve both the duration and the quality of the individual's remaining life.[13]

NICE clinical guideline 131 recommends chemotherapy options including fluorouracil and folinic acid in combination with oxaliplatin (FOLFOX), tegafur in combination with fluorouracil and folinic acid, capecitabine in combination with oxaliplatin (XELOX), and capecitabine alone.[13] In practice, fluorouracil and folinic acid may also be used in combination with irinotecan (FOLFIRI) in some people for whom oxaliplatin is not suitable.[13] FOLFOX may be administered in different regimens, most commonly FOLFOX4 and FOLFOX6. The differences in drug acquisition and administration of these regimens are discussed in Section 6.1.4.12, p.316, but in effectiveness they are widely considered by the clinical community to be equal. Single agent fluoropyrimidine regimens (tegafur, folinic acid and fluorouracil and capacitabine monotherapy) are generally given to patients for who combination therapy is not suitable (expert opinion, Dr Mark Napier, Merck Serono submission Table 4, p.22)

Folinic acid (FA), is also known as leucovorin (LV) and is given alongside fluorouracil to improve the response rate versus fluorouracil alone. It is given as calcium folinate (also known as leucovorin calcium), or less frequently as disodium folinate. [26]Folinic acid (and salts calcium and disodium folinate), unless otherwise stated, are racemic mixtures (with equal amounts of left- and right-handed enantiomers), in which only the levoisomer (left-handed form) is pharmacologically active. [27] The levoisomer, levoleucovorin, has marketing authorisation in the UK (as calcium levofolinate and disodium levofolinate), and is administered at half the dose of standard (racemic) leucovorin. There appears to be no significant difference between levoleucovorin and leucovorin in terms of efficacy or adverse events, but levoleucovorin is significantly more expensive than leucovorin at present. [27]

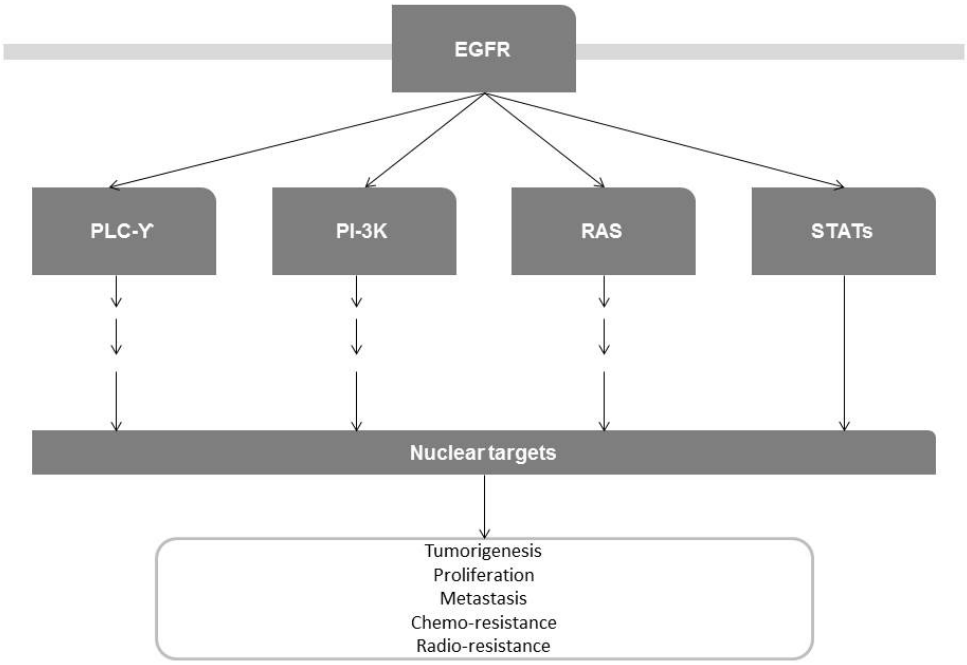
Chemotherapy may be combined with biological agents such as cetuximab (currently recommended for people satisfying criteria specified in NICE Technology Appraisal (TA) 176 [see Section 1.2.2.1]), panitumumab (see Section 1.2.2.2), and bevacizumab (see Section 1.2.2.3). Although bevacizumab is included in the final scope for this TA it is not recommended by NICE (TA 212). It was available subject to satisfaction of criteria for access via the Cancer Drugs Fund, but has recently (March 2015) been delisted for the indication under review in this TA. As of 17th July 2015, bevacizumab remains delisted for this indication.

1.2.1.1. Personalised treatment

Normal cell behaviour in multicellular organisms is controlled by a complex network of signalling pathways that ensures that cells proliferate only when they are required to; e.g. in wound healing.[28] Cancer occurs when normal growth regulation breaks down, usually because of defects within these signalling mechanisms.[28] The rat sarcoma (*RAS*) genes play

an important role in the epidermal growth factor receptor (EGFR) pathway; a complex signalling cascade that is involved in the development and progression of cancer (Figure 2).[29] Signals are passed protein to protein along several different pathways. Disruption of the signals via mutation of the *RAS* gene is involved in many tumour types.

Figure 2. EGFR signalling pathway



Key: EGFR = epidermal growth factor receptor; PI-3K - phosphoinositide 3-kinase; PLC-Y = Phospholipase-C; RAS = rat sarcoma; STATs = signal transducers and activators of transcription
Source: Adapted from Lo HW, Hung MC. British journal of cancer. 2006;94(2):184-8[30]

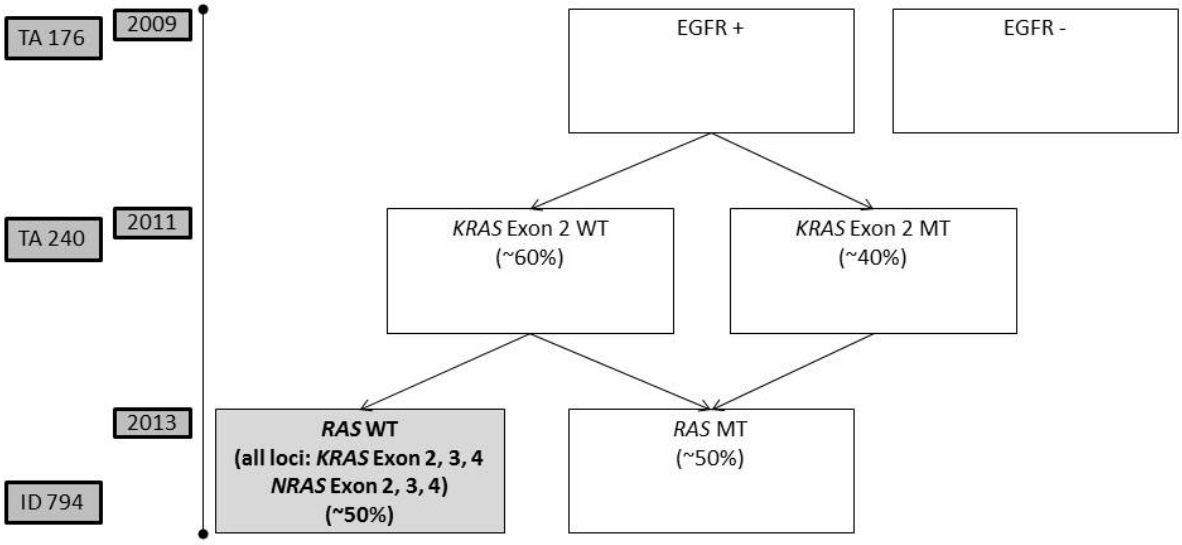
The three *RAS* genes: Kirsten rat sarcoma [*KRAS*]; Harvey rat sarcoma [*HRAS*]; and, neuroblastoma rat sarcoma [*NRAS*]) are the most common oncogenes in human cancer.[28, 29] All three are widely expressed, with *KRAS* expressed in almost all cell types.[28] Published research has demonstrated that mutations in codons 12 and 13 of Exon 2 of the *KRAS* gene are predictive of response to anti-EGFR therapies in mCRC.[31-38] For this reason, only people with *KRAS* Exon 2 wild type (WT) tumours were initially approved for treatment with this class of agents.[39-41]

More recently it has been shown that that other mutations in genes of the *RAS* family (*NRAS* mutations and *KRAS* mutations outside Exon 2: codon 61 of exon 3 and codon 117 and 146 of exon 4 of *KRAS* and exons 2, 3 and 4 of *NRAS*), are also associated with reduced response to anti-EGFR therapy.[16, 35, 37, 38, 42, 43] These developments led the European Medicines Agency (EMA) to update the marketing authorisations for cetuximab and

panitumumab in 2013 by restricting the indication in mCRC to the treatment of people with *RAS* WT tumours (Sections 1.3.1.1 and 1.3.1.2).[44-49]

Exon 2 mutations occur in approximately 40% of CRC cases, and other *KRAS* and *NRAS* mutations occur in approximately 10% of people with mCRC (Figure 3).[31, 35, 42, 50-53] Approximately 50% of people do not have *RAS* mutations and are classified as *RAS* WT.

Figure 3. Grouping of molecular characteristics of tumours: research progress



Key: EGFR = epidermal growth factor receptor; ID = identification; *KRAS* = Kirsten rat sarcoma; MT = mutant; *RAS* = rat sarcoma; TA = Technology Appraisal; WT = wild type

RAS mutation testing

A biomarker test is a simple way of looking at the type and status of particular genes of interest in a cancer. Biomarkers have been found for many different types of cancer such as colorectal, breast and lung cancer, and have an increasingly important role in helping physicians to tailor care and treatment on an individual basis, known as 'personalised medicine'. *RAS* − a predictive biomarker − is a group of genes that includes *KRAS* and *NRAS* and can be used to help select the most appropriate therapy for each individual mCRC.

Methods for *RAS* mutation testing whose use in the UK has been identified by a previous Diagnostic Assessment Report[4] and by the Assessment Group are summarised in Table 5.[4] Additional techniques have been developed and are in use internationally including:

Sequenom® (San Diego [CA], USA), Randox (Randox Laboratories Ltd., Crumlin, Co. Antrim, Ireland), SNaPshot® Multiplex kit (Applied Biosystems, Foster City, CA).

Many techinques and products reported are assays associated with polymerase chain reaction (PCR) or require PCR prior to their implementation. Additionally, some laboratories offer their own in house variant of real-time PCR. [4].

Table 5. Methods used for *RAS* mutation testing

KRAS	NRAS	Limit of detection	Source
Sanger Sequence		10–20%	Wong et al J Clin Pathol 2014[54]
Pyrosequence		5%	Wong et al J Clin Pathol 2014[54]
High resolution melt (HRM)		1–5%	Wong et al J Clin Pathol 2014[54]
StripAssay® (ViennaLab, Vienna, Austria)		1%	ViennaLab product brochure[55]
Next Generation Sequencing (NGS)		~5%	Westwood et al. (2014) [4].
Cobas® (Roche Diagnostics Limited, Rotkreuz, Switzerland)		5%	Wong et al J Clin Pathol 2014[54]
Therascreen® (Qiagen, KJ Venlo, The Netherlands)		1–5%	Wong et al J Clin Pathol 2014[54]
Peptide Nucleic Acid (PNA) Clamp® (Panagene, Daejeon, Korea)		1%	Panagene website[56]

Key: CE-SSCA = Capillary electrophoresis single-strand conformation analysis; DNA = deoxyribosenucleic acid; HRM = high resolution melt; *KRAS* = kirsten rat sarcoma; NGS = next generation sequencing; *NRAS* = neuroblastoma rat sarcoma; PCR = polymerase chain reaction; PNA = peptide nucleic acid

Currently, there are no NICE recommendations as to which mutation test should be used in the NHS.[57] A NICE diagnostics review of *KRAS* mutation testing for identifying adults with mCRC was suspended in 2013, following notification of potential changes to clinical practice as to who may benefit from first-line treatment with cetuximab or panitumumab.[57] [57] This review did demonstrate that evidence linking test accuracy with treatment effects is unavailable for most techniques currently in use. It concluded that there were 'no clear differences in the treatment effects… regardless of which *KRAS* mutation test was used to select patients'.[4] Further discussion of the tests available and their impact on this review is reported in Appendix I.

1.2.2. Current NICE guidelines, biological agents (first line)

1.2.2.1. NICE TA 176: Cetuximab for the first-line treatment of metastatic colorectal cancer

In the previous assessment (TA176):

- **Cetuximab** in combination with 5-fluorouracil (5-FU), folinic acid and oxaliplatin (FOLFOX), within its licensed indication, is recommended for the first-line treatment of mCRC only when all of the following criteria are met:

  (1) the primary colorectal tumour has been resected or is potentially operable

  (2) the metastatic disease is confined to the liver and is unresectable

  (3) the person is fit enough to undergo surgery to resect the primary colorectal tumour and to undergo liver surgery if the metastases become resectable after treatment with cetuximab

  (4) the manufacturer rebates 16% of the amount of cetuximab used on a per patient basis.[11]

- **Cetuximab** in combination with 5-FU, folinic acid and irinotecan (FOLFIRI), within its licensed indication, is recommended for the first-line treatment of mCRC only when all of the following criteria are met:

  (1) the primary colorectal tumour has been resected or is potentially operable

  (2) the metastatic disease is confined to the liver and is unresectable

  (3) the patient is fit enough to undergo surgery to resect the primary colorectal tumour and to undergo liver surgery if the metastases become resectable after treatment with cetuximab

  (4) the patient is unable to tolerate or has contraindications to oxaliplatin.[11]

People who meet the criteria above should receive treatment with cetuximab for no more than 16 weeks.[11] At 16 weeks, treatment with cetuximab should stop and the patient should be assessed for resection of liver metastases.[11]

1.2.2.2. NICE TA 240: Panitumumab for the first-line treatment of metastatic colorectal cancer

The appraisal of panitumumab in combination with chemotherapy for the treatment of mCRC (NICE technology appraisal 240) was ended because no evidence submission was received from the manufacturer or sponsor of the technology.[12] Therefore NICE was unable to make a recommendation about the use in the NHS of panitumumab in combination with chemotherapy for the treatment of mCRC.[12]

1.2.2.3. NICE TA 212: Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for the treatment of metastatic colorectal cancer

Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine is not recommended by NICE for the treatment of mCRC.[22]

1.2.2.4. Current usage in the NHS

Currently only cetuximab is recommended by NICE and is available for use on the NHS in England subject to satisfaction of criteria set out in TA 176 (see Section 1.2.2.1). For people with mCRC not meeting criteria set out in TA176, cetuximab is available via the CDF.[58]

NICE was unable to make a recommendation about the use in the NHS of panitumumab in combination with chemotherapy for the treatment of mCRC (TA 240 [see Section 1.2.2.2]).[12] Panitumumab is currently available for the first line treatment of mCRC via the CDF.[59]

Bevacizumab was not recommended by NICE (TA 212 [see Section 1.2.2.3]).[22] At the time of scoping bevacizumab was available (subject to satisfaction of eligibility criteria) via the CDF; however, it was delisted in March 2015.[60]

Almost one third of people receive cetuximab or panitumumab in combination with oxaliplatin or irinotecan based chemotherapy (Table 6).

Table 6. Estimated current usage of regimens

	Estimated current proportion of first line mCRC patients in UK	Estiamted proportion of first line mCRC patients in UK if CET/PAN/BEV no longer available on CDF and not recommended by NICE
FOLFOX[a]	30%	60%
FOLFIRI[b]	10%	20%
Tegafur, FA + FU, capecitabine[c]	20%	20%
BEV + OX- or IRIN-based CTX	10%	NA
CET/PAN + OX- or IRIN-based CTX	30%	NA

Key: 5-FU = 5 fluorouracil; BEV = bevacizumab; CDF = Cancer Drugs Fund; CET = cetuximab; CTX = chemotherapy; FA = folinic acid; FOLFIRI = fluorouracil + folinic acid + irinotecan; FOLFOX = fluorouracil + folinic acid + oxaliplatin; FU = fluourouracil; IRIN = irinotecan; mCRC = metastatic colorectal cancer; NA = not applicable; OX = oxaliplatin; PAN = panitumumab; UK = United Kingdom

Notes: a 5-FU and capecitabine (XELOX [capecitabine + oxaliplatin]) used interchangeably (5-FU is an oral pro-drug of 5-FU); b 5-FU and capecitabine (XELIRI [capecitabine + irinotecan]) used interchangeably (5-FU is an oral pro-drug of 5-FU); c tegafur/uracil was discontinued in 2013 (Merck Serono submission, Section 1.2, p.19)

Source: Clinical advisor, Dr Mark Napier (personal communication), informed by Exeter South West Regional Gastro Oncology Meeting

1.2.3. Current service cost

Treatment costs can include the following: cost of first line chemotherapy drugs (cetuximab, panitumumab, irinotecan or oxaliplatin, folinic acid, 5- fluorouracil), cost of administration in the first line, cost of curative intent liver surgery, cost of post-resection therapy in people who had curative result of the liver metastases operation, cost of management of adverse events in the first line, cost of treatments in second line, cost of treatment in third line, and the cost of *RAS* screening.

1.3. Description of technology under assessment

1.3.1. Interventions considered in the scope of this assessment

The scope of this review is to ascertain the clinical and cost-effectiveness of two interventions for previously untreated metastatic colorectal cancer (mCRC). These interventions are: cetuximab and panitumumab.

1.3.1.1. Cetuximab (Erbitux®, Merck Serono)

Cetuximab (Erbitux®, Merck Serono) is a recombinant monoclonal antibody that blocks the human EGFR and therefore inhibits the proliferation of cells that depend on EGFR activation for growth.[44]

Previously, cetuximab was indicated for use in people with EGFR-expressing, *KRAS* WT mCRC.[39, 40, 61, 62] In November 2013, in response to new biomarker data, the Committee for Medicinal Products for Human Use (CHMP) changed the indication to clarify the particular genetic makeup of the cancer that must be present before treatment with cetuximab is initiated.[46, 48] Based on this recommendation, cetuximab is now indicated for the treatment of people with EGFR-expressing, *RAS* WT mCRC:

- in combination with irinotecan-based chemotherapy
- in first-line in combination with FOLFOX
- as a single agent in people who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan.[44]

In this label change, the combination of cetuximab with oxaliplatin-containing chemotherapy is now contraindicated for people with *RAS* mutant mCRC or for whom *RAS* status is unknown.[44]

Prior to the first infusion, premedication with an antihistamine and a corticosteroid at least one hour prior to the administration of cetuximab should be given.[44] This premedication is recommended prior to all subsequent infusions.[44] Cetuximab is administered once a week.[44] The initial dose is 400 mg cetuximab per m^2 body surface area.[44] All subsequent weekly doses are 250 mg cetuximab per m^2 each.[44]

One common adverse effect (AE) of cetuximab treatment is the development of skin reactions, which occur in more than 80% of people and mainly present as an acne-like rash or, less frequently, as pruritus, dry skin, desquamation, hypertrichosis or nail disorders (for example, paronychia).[44] The majority of skin reactions develop within the first three weeks of treatment.[44] The summary of product characteristics (SPC) notes that if a person experiences a Grade 3 or 4 skin reaction, cetuximab treatment must be stopped, with treatment being resumed only if the reaction resolves to Grade 2.[44] Other common AEs of cetuximab include mild or moderate infusion-related reactions such as fever, chills, nausea, vomiting, headache, dizziness or dyspnoea that occur soon after the first cetuximab infusion.[44]

1.3.1.2. Panitumumab (Vecitibix®, Amgen)

Panitumumab is a recombinant monoclonal antibody which targets the EGFR receptor, thereby inhibiting the growth of EGFR-expressing tumours.[45]

In June 2013, the CHMP also adopted a change to the indication for the use of panitumumab for the treatment of mCRC,[47, 49] restricting use to the treatment of adults with *RAS* WT mCRC:

- in first-line in combination with FOLFOX or FOLFIRI
- in second-line in combination with FOLFIRI for people who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan)
- as monotherapy after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.[45]

In this label change, the combination of panitumumab with oxaliplatin-containing chemotherapy is now contraindicated for people with *RAS* mutant mCRC or for whom *RAS* mCRC status is unknown.[45]

The recommended dose of panitumumab is 6 mg/kg of bodyweight given once every two weeks.[45] Prior to infusion, panitumumab should be diluted in 0.9% sodium chloride injection to a final concentration not to exceed 10 mg/ml.[45]

Panitumumab is contraindicated in people with a history of severe or life-threatening hypersensitivity reactions to the active substance or to any of the excipients.[45] Skin toxicities, hypomagnesaemia, and diarrhoea were the most common treatment-related toxicities observed.[45] The most common AEs (incidence ≥20%) are skin toxicities (i.e. erythema, dermatitis acneiform, pruritus, exfoliation, rash and fissures), paronychia, hypomagnesemia, fatigue, abdominal pain, nausea, diarrhoea and constipation.[45]

Recent research (Section 1.2.1.1, p.69) has resulted in the CHMP adopting a change to the licensed indication for both cetuximab and panitumumab, restricting use to people with *RAS* WT mCRC. These developments and resultant changes to the licensed indications provide the rationale for this MTA review.

1.3.2. ID 794: Cetuximab and panitumumab for previously untreated metastatic colorectal cancer (review of TA176 and partial review of TA240)

Although this MTA seeks to update previous guidance (TA 176 and TA 240), it is important to note the differences between the scope for the previous STA reviews and this current MTA review (ID794). The main difference is in the population criterion. The current scope specifies people with *RAS* WT mCRC, whereas previous STA reviews specified EGFR-expressing mCRC (TA 176), and *KRAS* WT mCRC (TA 240).[12, 63] A summary of all the differences

between the scopes for the reviews alongside a summary of how the product licences have changed is provided in Table 7.

Table 7. Comparison of NICE scope (TA 176 and TA 240), CHMP positive opinion, and the scope for the current MTA

	CET		PAN		CET	PAN	CET + PAN
	CHMP[39, 40, 61, 62]	TA 176[63]	CHMP[41, 64]	TA 240[12]	CHMP[46, 48]	CHMP[47, 49]	Current MTA ID 794[23]
Year	2008, 2011	2009	2011	2011	2013	2013	2014-16
NICE Appraisal Method	NA	STA	NA	STA	NA	NA	MTA
NICE Guidance	NA	TA176	NA	TA 240 [suspended[a]]	NA	NA	Due 2016
Population	*KRAS* WT mCRC	Untreated mCRC, first line palliative	*KRAS* WT mCRC	NA	*RAS* WT expressing mCRC	*RAS* WT expressing mCRC	*RAS* WT expressing mCRC
Metastases	Any location	Untreated, any location	Any location	NA	Any location	Any location	Untreated, any location (subgroup of interest liver metastases)[23]
Intervention (firstline)	CET+FOLFOX4 or IRIN-based CTX	CET + CTX[63]	PAN+FOLFOX	NA	CET + FOLFOX or CET+FOLFIRI	PAN+FOLFOX	CET + FOLFOX or IRIN- based regimens PAN + FOLFOX regimens
Comparators	NA	Ox-based CTX; IRIN-based CTX[63]	NA	NA	NA	NA	FOLFOX; XELOX; FOLFIRI; CAP; TEG + FA + FU; BEV + OX- or IRIN-based CTX[b]
Supporting Trials	CRYSTAL, OPUS, COIN, NORDIC VII	CRYSTAL, OPUS	*KRAS* WT subgroup from PRIME	NA	*RAS* WT subgroup from OPUS, CRYSTAL, FIRE-3	*RAS* WT subgroup from PEAK. PRIME,	*RAS* WT subgroup from CRYSTAL, OPUS, PRIME, PEAK, FIRE-3

Key: BEV = bevacizumab; CET = cetuximab; CHMP = Committee for Medicinal Products for Human Use; CTX = chemotherapy; FA = folinic acid; FOLFOX = folinic acid + fluorouracil + oxaliplatin; FOLFIRI = folinic acid + fluorouracil + irinotecan; FU = fluorouracil; IRIN = irinotecan; *KRAS* = kirsten rat sarcoma; mCRC = metastatic colorectal cancer; MTA = multiple technology appraisal; NA = not applicable; NICE = National Institute for Health and Clinical Excellence; OX = oxaliplatin; PAN = panitumumab; *RAS* = rat sarcoma; STA = single technology appraisal; WT = wild type

Notes: a NICE was unable to recommend the use in the NHS of PAN + CTX for the treatment of mCRC because no evidence submission was received from the manufacturer or sponsor of the technology; b Bevacizumab is not recommended by NICE (TA212).At the time of scoping BEV was available (subject to satisfying criteria for access) via the CDF; however, this drug was delisted in March 2015 for the indication under review in this technology appraisal

2. Definition of the decision problem

2.1. Decision problem

Previously, cetuximab and panitumumab (interventions of interest to this appraisal) were separately evaluated in 2009 (technology appraisal [TA] 176), and 2011 (TA 240) (see Section 1.2.2).[11, 12]

At the time of technology appraisal 176 (2009), rat sarcoma (*RAS*) wild-type (WT) status was defined based on a single part ('exon') of the *KRAS* gene, and testing typically focused on *KRAS* codons 12 and 13.[65] However, subsequent research has suggested that mutations in other *KRAS* codons and other genes downstream of EGFR may also confer drug resistance explaining why some individuals with *KRAS* codon 12 and 13 WT tumours did not respond to therapy.[65] The absence of mutations in the *NRAS* gene and in 2 further exons (3 and 4) of *KRAS* was found to improve the effectiveness of cetuximab and panitumumab.[65] These developments led the European Medicines Agency (EMA) to update the marketing authorisations for cetuximab and panitumumab in 2013 by restricting the indication in colorectal cancer (CRC) to the treatment of people with *RAS* WT tumours.[48, 49] It is this change to the licensed indications for these products that provides the rationale for this appraisal.[23]

2.2. Population including subgroups

The population specified in the final scope issued by NICE is people with previously untreated, *RAS* WT mCRC.[23]

Subgroup of interest, based on the location of metastases, specifically liver and non-liver limited disease.[23]

2.3. Interventions

This technology report considers two interventions:

- Cetuximab (Erbitux®, Merck Serono) is a recombinant monoclonal antibody that blocks the human epidermal growth factor receptor (EGFR), inhibiting the growth of tumours expressing EGFR.[44] Cetuximab has a UK marketing authorisation for the treatment of people with EGFR-expressing, *RAS* WT mCRC, either in combination with FOLFOX

(FOL [folinic acid;F [Fluorouracil, 5-FU], OX [Oxaliplatin, Eloxatin]), or irinotecan-based chemotherapy.[11]

- Panitumumab (Vectibix®, Amgen) is a recombinant, fully human immunoglobulin (Ig) G2 monoclonal antibody that binds to EGFR, blocking its signalling pathway and inhibiting the growth of tumours.[45] It has a UK marketing authorisation for use in combination with FOLFOX, for treating previously untreated, *RAS* WT mCRC.[45] Panitumumab is also licensed for use second-line in combination with FOLFIRI for people who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan), although clinical trials have also measured the effectiveness of panitumumab in combination with FOLFIRI for previously untreated mCRC.[45]

2.4. Comparators

The scope issued by NICE specifies that the interventions should be compared with each other, and with:[23]

- FOLFOX
- XELOX
- FOLFIRI
- Capecitabine
- Tegafur, folinic acid and fluorouracil
- Bevacizumab, in combination with oxaliplatin- or irinotecan-based chemotherapy

The Assessment Group notes that tegafur/uracil was discontinued in 2013 (Merck Serono submission, Section 1.2, p.19). Capecitabine and folinic acid plus fluorouracil, are typically preferred for patients with poor performance status (expert opinion and Merck Serono submission).

2.5. Outcomes

The outcomes of interest considered in this review included:[23]

- overall survival (OS)
- progression-free survival (PFS)

- response rate (including overall response rate [ORR], complete response [CR], partial response [PR], progressive disease (PD), stable disease [SD])
- rate of resection of metastases
- adverse effects of treatment
- health-related quality of life (HRQoL).

2.6. Overall aims and objectives of assessment

The aim of this project is to review the clinical effectiveness and cost effectiveness of cetuximab and panitumumab in a multiple technology appraisal (MTA). This includes a review of TA176 (cetuximab), and a part review of TA240 (panitumumab) for adults with previously untreated metastatic colorectal cancer (mCRC) expressing RAS WT status. The medical benefit and risks associated with these treatments are assessed and compared across the treatments and against available standard drug treatments. The review also assesses whether these drugs are likely to be considered good value for money for the NHS.

3. Assessment of clinical effectiveness

3.1. Methods for reviewing effectiveness

Evidence for the clinical effectiveness of cetuximab and panitumumab for people with previously untreated rat sarcoma (*RAS*) wild type (WT) metastatic colorectal cancer (mCRC) was assessed by conducting a systematic review of published research evidence. The review was undertaken following the general principles published by the Centre for Reviews and Dissemination (CRD).[66] The project was undertaken in accordance with a protocol (PROSPERO number CRD42015016111 [see Appendix A]). There were no major departures from this protocol.

Individuals respond differently to some drugs.[67, 68] Genotype is an important determinant of both the response to treatment and the susceptibility to adverse reactions for a wide range of drugs;[69, 70] for example, response to EGFR inhibitors has been shown to be dependent on gene expression in colon cancer; studies have demonstrated a treatment interaction between *RAS* status and the effectiveness of EGFR inhibitors.[71-73] In line with research developments evaluating the negative impact of RAS mutations on the effectiveness of EGFR inhibitors, approval for the use of anti-EGFR antibodies has now been limited to people with mCRC with *RAS* WT tumours. Tumour samples from trial populations supporting the original licensed indications were evaluated retrospectively for RAS status. Importantly, therefore, data supporting this recent licence change and this NICE assessment are not from the intention to treat (ITT) population for any of the included studies but from a subgroup of people contained within the original RCTs and results are therefore subject to uncertainty. However, no RCTs with an ITT population by *RAS* WT status were identified.

Previously, NICE has appraised cetuximab (TA176) for the treatment of people with EGFR-expressing mCRC; in line with the licensed indication at the time. Although two of the identified cetuximab trials were included in the last appraisal, only data from the subgroup of people evaluated as *RAS* WT from those trials are relevant to the scope of this review as set out in the final scope from NICE (see Section 2.2). The appraisal of panitumumab in combination with chemotherapy for the treatment of mCRC (NICE technology appraisal 240) was ended because no evidence submission was received from the manufacturer or sponsor of the technology. As such, NICE was unable to make recommendations relating to the use of panitumumab in the NHS. All data included in this update review for both cetuximab and panitumumab have been identified by the Assessment Group's searches.

3.1.1. Identification of studies

The search strategy for clinical effectiveness studies included the following search methods:

- Searching of bibliographic and ongoing trials databases.
- Searching of conference proceedings.
- Contact with experts in the field.
- Scrutiny of bibliographies of retrieved papers and company submissions.

The following bibliographic and ongoing trials databases were searched for clinical effectiveness studies: MEDLINE (Ovid); MEDLINE In-Process and Other Non-Indexed Citations (Ovid); EMBASE (Ovid); The Cochrane Library including the Cochrane Systematic Reviews Database, CENTRAL, DARE and HTA databases; Web of Science (Thomson Reuters); ClinicalTrials.gov; UK Clinical Research Network's (UKCRN) portfolio; International Standard Randomised Controlled Trials Number (ISRCTN) registry; WHO International Clinical Trials Registry Platform (ICTRP).

The bibliographic database searches were developed and run by an information specialist (SB) in January 2015. Search filters were used to limit the searches to randomised controlled trials, where appropriate, and all searches were limited to English language studies where possible. No date limits were used. An update search was carried out on 27 April 2015. No papers or abstracts published after this date were included in the review. The ongoing trials databases were searched by a reviewer in March 2015. The search strategies for each database are detailed in Appendix B.

In addition to the clinical effectiveness searches, the Health Management Information Consortium (HMIC, Ovid) was searched for grey literature; this produced no new studies.

The following websites were searched for conference proceedings:

- National Cancer Research Institute http://conference.ncri.org.uk/
- American Association for Cancer Research http://aacrmeetingabstracts.org/
- American Society of Clinical Oncology http://meetinglibrary.asco.org/abstracts

The bibliographic search results were exported to, and de-duplicated using Endnote (X7). De-duplication was also performed using manual checking. Titles and abstracts returned by the search strategy were examined independently by two researchers (LC and MB) and

screened for possible inclusion. Disagreements were resolved by discussion. Full texts of potentially relevant studies were ordered. Full publications were assessed independently by two reviewers (LC and MB) for inclusion or exclusion against pre-specified criteria, with disagreements resolved by discussion.

After the reviewers completed the screening process, the bibliographies of included papers were scrutinised for further potentially includable studies. The manufacturers' submissions were assessed for unpublished data.

3.1.2. Eligibility criteria

Inclusion and exclusion criteria for the selection of clinical effectiveness and safety evidence were defined according to the decision problem outlined in the NICE scope (Section 2); criteria are summarised in Table 8.[23]

Table 8. Inclusion criteria (based on the decision problem) for studies evaluating clinical effectiveness

Population	Adults with previously untreated, *RAS* WT[a] mCRC
Intervention	Cetuximab, in combination with FOLFOX or irinotecan-based chemotherapy
	Panitumumab, in combination with fluorouracil-containing regimens
Comparator	FOLFOX
	XELOX
	FOLFIRI
	Capecitabine
	Tegafur, folinic acid and fluorouracil
	Bevacizumab, in combination with oxaliplatin- or irinotecan-based chemotherapy
Outcomes	Overall survival
	Progression-free survival
	Response rate
	Rate of resection of metastases
	Adverse events
	Health-related quality of life
Study design	Randomised controlled trials
	Systematic reviews of randomised controlled trials[b]

Key: FOLFIRI = fluorouracil + folinic acid + irinotecan; FOLFOX = fluorouracil + folinic acid + oxaliplatin; *KRAS* = kirsten rat sarcoma; mCRC = metastatic colorectal cancer; *NRAS* = neuroblastoma rat sarcoma; *RAS* = rat sarcoma; XELOX = capecitabine in combination with oxaliplatin; WT = wild type

Notes: a *RAS* WT = *KRAS* WT and *NRAS* WT Exons 2, 3 and 4; b Systematic reviews of randomised controlled trials were used as potential sources of additional references for efficacy evidence (they were not formally included in the review)

The systematic review of clinical effectiveness was based on randomised controlled trial (RCT) evidence. Studies published as abstracts or conference presentations were only included if sufficient details were presented to allow both an appraisal of the methodology and an assessment of the results to be undertaken. Systematic reviews of RCTs (although not formally included in the systematic review) were used as potential sources of additional references of efficacy evidence. A systematic review was defined as having:

- a focused research question
- explicit search criteria that are available to review, either in the document or on application; explicit inclusion/exclusion criteria, defining the population(s), intervention(s), comparator(s), and outcome(s) of interest
- a critical appraisal of included studies, including consideration of internal and external validity of the research
- a synthesis of the included evidence, whether narrative or quantitative.

The following study types were also excluded: animal models; preclinical and biological studies; narrative reviews, editorials, opinions; non-English language papers.

3.1.3. Data extraction and management

Included papers were split between two reviewers for the purposes of data extraction using a standardised data specification form, and checked independently by another. Information extracted and tabulated included details of the study's design and methodology, baseline characteristics of participants and results including any adverse events if reported. Where information on key data was incomplete, we attempted to contact the study's authors to gain further details. Discrepancies were resolved by discussion. Where multiple publications of the same study were identified, data were extracted and reported as a single study. In addition, the companies were approached via NICE to provide missing data for the *RAS* WT population; this information was provided as commercial in confidence (CiC).

3.1.4. Assessment of risk of bias

The methodological quality of each included study was assessed by one reviewer and checked by a second reviewer, using criteria based on those proposed by the NHS Centre for Reviews and Dissemination for RCTs (Table 9).[66] The potential generalisability of the study was also assessed, as well as the judged applicability to the current organisation, clinical pathways and practices of the NHS in England.

Table 9. Quality assessment

Treatment allocation	1. Was the assignment to the treatment groups really random?
	2. Was treatment allocation concealed?
Similarity of groups	3. Were the groups similar at baseline in terms of prognostic factors?
Implementation of masking	4. Were the care providers blinded to the treatment allocation?
	5. Were the outcome assessors blinded to the treatment allocation?
	6. Were the participants blinded to the treatment allocation?
Completeness of trial	7. Were all a priori outcomes reported?
	8. Were complete data reported, e.g. was attrition and exclusion (including reasons) reported for all outcomes?
	9. Did the analyses include an ITT analysis?
Generalisability	10. Are there any specific limitations which might limit the applicability of this study's findings to the current NHS in England?

Key: ITT = intention-to-treat; NHS = National Health Service
Source: Centre for Reviews and Dissemination (University of York), 2009

3.1.5. Methods of data analysis/synthesis

Details of results on clinical effectiveness and quality assessment for each included study are presented in structured tables and as a narrative summary. The possible effects of study quality on the clinical effectiveness data and review findings are discussed.

3.1.6. Network meta-analysis

Network meta-analyses were undertaken within a Bayesian framework in WinBUGS (version 1.4.3). Where prior distributions were used these were defined to be as vague as possible. The network meta-analyses could have been conducted outside of WinBUGS (especially because of the low number of RCTs); however, the approach taken here allows calculation of the probability that each treatment is the most effective compared to all others within the network.

Two networks were analysed: those using FOLFOX regimens and those using FOLFIRI regimens. For the FOLFOX regimens network, the treatment FOLFOX was the baseline treatment, while FOLFIRI was the baseline treatment in the FOLFIRI regimens network.

For the analysis of PFS, OS and ORR models with a normal likelihood and identify link were used.[74] Analysis of AEs used a model with a binomial likelihood and logit link.[74] For the analysis of the AEs, where there are no events reported in a study arm, a continuity correction of 0.5 was added to every cell for that particular study to allow analysis to be conducted.[74]

Analyses were run with 3 chains, an initial burn-in of 50,000 iterations, followed by an additional 100,000 iterations on which the results were based. Due to the small number of RCTs contributing to each network, only fixed effects models were used. Convergence of the models was assessed visually using the autocorrelation, density and trace plots for all monitored variables, and checking that each chain was sampling from the same posterior distribution. The posterior means and 95% credibility intervals (CrIs) from these analyses are reported. The probability that each treatment in the network was ranked as the most effective (Rank 1), down to the least effective (Rank 4) was also calculated and is presented in the results (Section 3.2).

3.2. Results

The results of the included studies are discussed in the sections that follow. Initially, a summary of the quantity and quality of the evidence is provided, together with a table presenting an overview of the included trials. Additionally, a more detailed narrative description, together with an overview of trial quality, for each included trial is presented. A narrative description of population baseline characteristics and potential imbalances are discussed for each trial. Clinical effectiveness results are reported by outcome (OS, PFS, ORR, resection rate, health-related quality of life [HRQoL], and adverse effects). Within the efficacy outcomes of OS, PFS, and ORR, results are presented separately for cetuxuimab and panitumumab.

3.2.1. Studies identified

We screened the titles and abstracts of 2,636 unique references identified by the PenTAG searches and additional sources, and retrieved 52 papers for detailed consideration. Of these, 49 were excluded (a list of these items with reasons for their exclusion can be found in Appendix C). Of the excluded items, four abstracts were identified as relevant to the review (**Ciardiello et al.**, **2015** [OPUS]; **Van Cutsem et al., 2015** [CRYSTAL]; **Douillard et al., 2014** [PRIME], **Peeters et al., 2013** [PRIME]) (see Appendix D), but were excluded as there was not enough information was available to adequately quality appraise. Authors of the abstracts were contacted which led to the identification of an additional two full papers (**Tejpar et al.**, **2015** [OPUS]; and, **Van Cutsem et al., 2015** [CRYSTAL. In total, post hoc analyses from five randomised controlled trials (RCTs) (OPUS [**Tejpar et al., 2015**]; CRYSTAL [**Van Cutsem et al., 2015**], FIRE-3 [**Heinemann et al., 2014**], PRIME [**Douillard et al., 2013**], and PEAK [**Schwartzberg et al., 2014**]), met the inclusion criteria (see Table 8 and Appendix A). In assessing titles and abstracts, agreement between the two reviewers

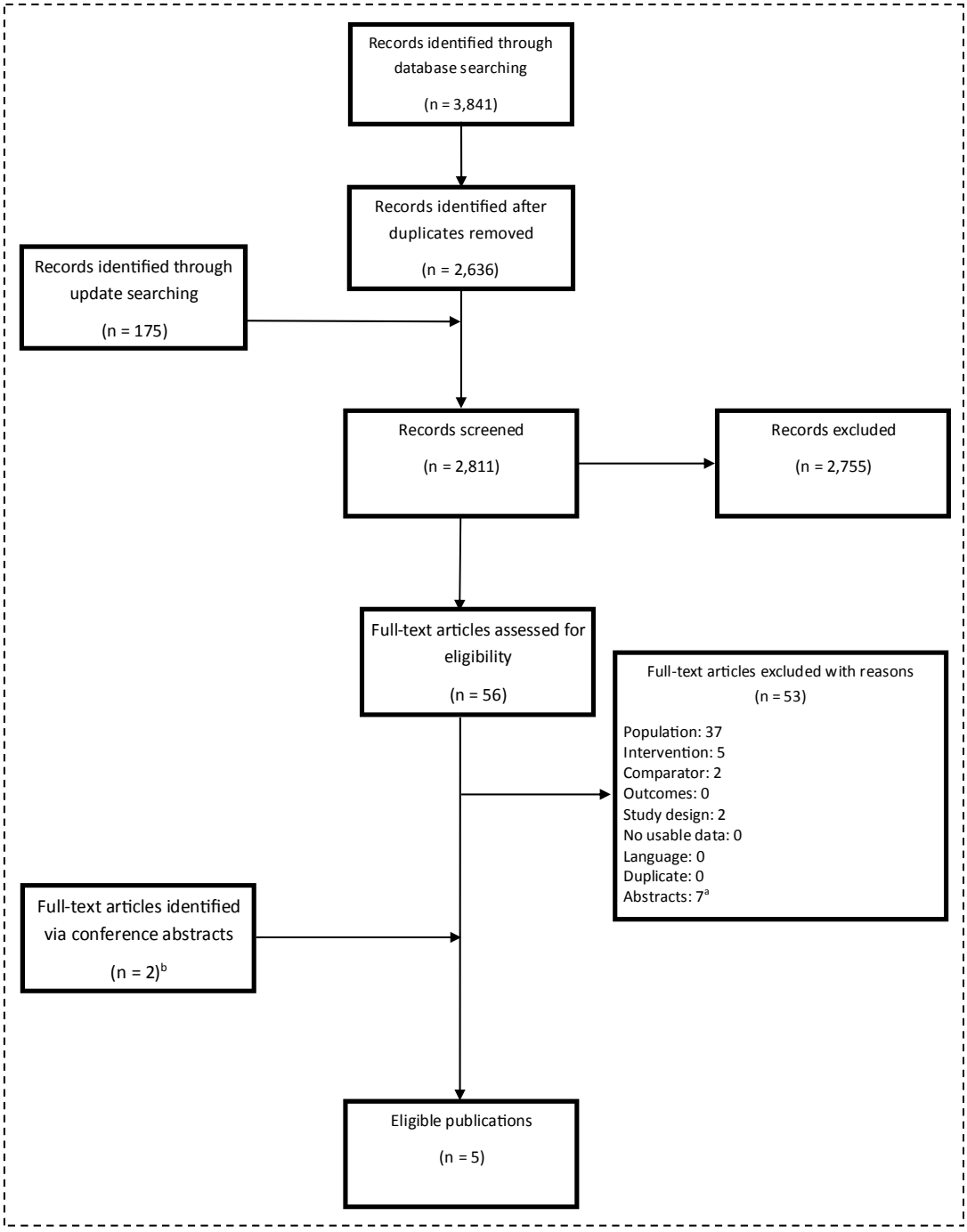
was substantial (κ=0.801). At the full-text stage, agreement was good (κ=0.636]). At both stages, initial disagreements were easily resolved by consensus.

Update searches were conducted on 27 April 2015 using the same methodology as described earlier. A total of 175 records were screened by two reviewers (LC and JVC) and four records were selected for full-text retrieval. Of these, none were formally included in the review although three were considered to meet the eligibility criteria for the review they were only available in abstract format and, as such, could not be quality appraised (**Rivera et al., 2015** [PEAK], **Siena et al., 2015** [PRIME], and **Wang et al., 2015** [PRIME]) (see Appendix D).

No studies comparing either cetuximab or panitumumab with the following comparators: XELOX; capecitabine monotherapy; and tegafur+folinic acid+5-FU (specified in the NICE scope) met the eligibility criteria for this review. In addition, no studies evaluating panitumumab plus FOLFIRI met the eligibility criteria for this review (see Section 3.1.2, p.85).

The study selection process is outlined in Figure 4.

Figure 4. PRISMA flow chart for studies included and excluded from the clinical effectiveness review



Notes: a Seven abstracts presenting data from four trials (OPUS [Ciardiello et al., 2015]; CRYSTAL [Van Cutsem et al., 2015]; PRIME [Douillard et al., 2014; Peeters et al., 2013; Siena et al., 2015; and, Wang et al., 2015]; and PEAK [Rivera et al., 2015]) were considered relevant to the review. Authors of the abstracts were contacted leading to the identification of an additional two papers (OPUS [Tejpar et al., 2015] and CRYSTAL [Van Cutsem et al., 2015]); b Two papers were identified via the authors (OPUS [Tejpar et al., 2015; provided as academic in confidence] and CRYSTAL [Van Cutsem et al., 2015])

3.2.2. Cetuximab

3.2.2.1. Study characteristics

The 2009 single technology appraisal (STA) review (TA176) identified two RCTs investigating the effectiveness of the addition of cetuximab to either oxaliplatin-based (FOLFOX) or irinotecan-based chemotherapy (FOLFIRI), those reported by Van Cutsem et al. *(*2009) (CRYSTAL),[33] and Bokemeyer et al. (2009) (OPUS).[32] As research into the impact of *KRAS* and *NRAS* tumour mutations on the effectiveness of EGFR inhibitors developed, the ITT population from the pivotal trials were re-evaluated forming the basis for the revision of the licensed population.

A total of three subgroup analyses from three randomised, open-label trials (OPUS, **Tejpar et al., 2015**; CRYSTAL, **Van Cutsem et al., 2015;** and, FIRE-3, **Heinemann et al., 2014**), were included in the update review.[37, 52, 75] Of note, in the FIRE-3 (**Heinemann et al., 2014**) trial there was a protocol amendment made restricting eligibility for the ITT population to people with *KRAS* WT Exon 2 tumours, due to the emerging evidence on the negative predictive value of *KRAS* Exon 2 mutations, and the subsequent changes to the licence for cetuximab.[37] However, in all of the included trials the extended *RAS* subgroup analysis of interest to this review was conducted retrospectively.[52, 75]

Of the included trials, two evaluated the addition of cetuximab to background chemotherapy (FOLFOX [OPUS, **Tejpar et al., 2015**] or FOLFIRI [CRYSTAL, **Van Cutsem et al., 2015**]), and one trial evaluated the addition of cetuximab or bevacizumab to background chemotherapy (FOLFIRI [**Heinemann et al., 2014**]). All trials evaluated the same dose and administration of cetuximab (Table 10).

All of the included trials (OPUS, **Tejpar et al., 2015**; CRYSTAL, **Van Cutsem et al., 2015**; and FIRE-3, **Heinemann et al., 2014**), measured the following outcomes: objective response rate (ORR); progression free survival (PFS); overall survival (OS); secondary resection of liver metastases with curative intent; and, safety and tolerability (including the incidence and type of adverse events [AEs]).[37, 52, 75]

In two of the included trials (OPUS, **Tejpar et al., 2015** and FIRE-3, **Heinemann et al., 2014**),[37, 75] the primary endpoint was the proportion of participants who had an objective response rate. In the OPUS trial (**Tejpar et al., 2015**),[75] tumour response was assessed by an independent review committee according to modified World Health Organisation (WHO) criteria, whereas in the FIRE-3 trial (**Heinemann et al., 2014**) tumour response was measured according to the Response Evaluation Criteria in Solid Tumours (RECIST)

Version 1.0, as assessed by the study investigators.[37] The independent review committee conducted a blinded review of images and clinical data. In the CRYSTAL trial (**Van Cutsem et al., 2015**), the primary end point PFS time, defined as the time from randomisation to disease progression or death from any cause within 60 days after the last tumour assessment or after randomisation.[52] No data were identified for HRQoL for the *RAS* WT population from either of the included trials.

Median follow-up was not reported in the OPUS (**Tejpar et al., 2015**) or CRYSTAL (**Van Cutsem et al., 2015**) trials.[52, 75] In the FIRE-3 trial (**Heinemann et al., 2014)** median follow-up was 33.0 months (IQR 19.0, 55.4) in the cetuximab plus FOLFIRI arm vs. 39.0 (IQR 22.5, 56.9) in the bevacizumab plus FOLFIRI arm.[37]

Study characteristics for the included studies are summarised in Table 10.

3.2.2.2. Population characteristics

Baseline demographic and disease characteristics for the *RAS* WT subgroup are reported in Table 11.

For the ITT population for each of the included trials the baseline demographic and disease characteristics were well matched. In all studies, existing DNA samples from *KRAS* exon 2 WT tumours were re-analysed for other *RAS* mutations in four additional *KRAS* codons (exons 3 and 4) and six *NRAS* codons (exons 2, 3, and 4). Mutation status was evaluable in 796 (73.0%) of 1,090 trial participants with *KRAS* exon 2 WT tumours (Table 10). Details of the proportions of study participants evaluated to be *RAS* WT are summarised in Table 10. In all trials, the baseline and disease characteristics were comparable with those seen for the *KRAS* WT population (see Appendix E for baseline and disease characteristics for the *KRAS* WT population).

Participants were similar in terms of age, gender distribution and site of primary cancer. However, as is usually the case with cancer trials, the study populations were significantly younger than the general population presenting with mCRC, where the peak in number of cases in the UK, for example, is between 70 and 79 years of age for men and 75- to 85 years-plus for women, compared with a median of 59–65 years shown in Table 11.

Table 10. Overview of included studies: Cetuximab trials

Author, Year Trial NCT Study design	Included in TA176a	Included in update review	Inclusion criteria	ITT (N)	RAS WT (n) / analysed (N)	Randomisation stratification factors	Interventions evaluated Dose	Primary endpoint	Median treatment duration, mths (IQR)	Median follow-up, mths (IQR)
Tejpar, 2015 OPUS NCT00125034 Retrospective subgroup analysis	N[b]	Y	≥18 yrs; ECOG ≤2; first occurrence metastatic disease	337	87/[redacted]	ECOG PS 0–1 or 2	CET+FOLFOX4 vs FOLFOX4 CET: Day 1, 400 mg/m^2, then 250 mg/m^2/wk FOLFOX: Q2W as IV OX 85 mg/m*2* Day 1 + folinic acid 200 mg/m^2 IV infusion (over 2 hrs) on Days 1 & 2 Q2W + FU 400 mg/m^2 bolus IV infusion (2–4 mins) then 600 mg/m^2 infusion (during 22 hrs) on Days 1 & 2	ORR	5.7 (NR) CET+FOLFOX4 vs 4.7 (NR) FOLFOX4	NR
Van Cutsem, 2015 CRYSTAL NCT00154102 Retrospective subgroup analysis	N[b]	Y	≥18 yrs; ECOG ≤2; first occurrence metastatic disease	1,198	367/430	ECOG PS 0–1 or 2; region (Western Europe vs. Eastern Europe vs. outside Europe)	CET+FOLFIRI vs FOLFIRI CET: Day 1, 400 mg/m^2, then 250 mg/m^2/wk FOLFIRI: 30–90 min infusion IRIN 180 mg/m^2 + 120-min infusion of racemic leucovorin 400 mg/m^2 or l-leucovorin 200 mg/m^2 + FU bolus 400 mg/m^2 then cont. infusion for 46 hrs 2,400 mg/m^2	PFS	7.41 (NR) CET+FOLFIRI vs 5.77 mths (NR) FOLFIRI	NR
Heinemann FIRE-3 NCT00433927 Retrospective subgroup analysis	N	Y	≥18 yrs; ECOG ≤2; first occurrence metastatic disease	592	342/542	ECOG PS 0–1 or 2; no. of metastatic sites (=1 or >1); white blood cell count	CET+FOLFIRI vs BEV+FOLFIRI CET: Day 1, 400 mg/m^2, then 250 mg/m^2/wk BEV: Day 1, 90-min infusion 5 mg/kg, 2 wks later 60-min infusion 5 mg/kg; over 30 mins every 2 wks thereafter FOLFIRI: 60–90 min infusion IRIN 180 mg/m^2 + 120-min infusion of racemic leucovorin 400 mg/m^2 + FU bolus 400 mg/m^2 then cont. infusion for 46 hrs 2,400 mg/m^2	ORR	NR	33.0 (19.0, 55.4) CET+FOLFIRI vs 39.0 (22.5, 56.9) BEV + FOLFIRI

Key: BEV = bevacizumab; CET = cetuximab; ECOG = Eastern Cooperative Oncology Group; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; FU = fluorouracil; hrs., = hours; IRIN = irinotecan; ITT = intention to treat; IV = intravenous; mins., = minute(s); NCT = National Clinical Trial; ORR = objective response rate; OX = oxaliplatin; PFS = progression free survival; PS = performance status; Q2w = every 2 weeks; *RAS* = rat sarcoma TA = Technology Appraisal; vs. = versus; wks., = week(s); WT = wild type; Y = yes; yrs., = year(s

Notes: (a) TA 176 was a single technology appraisal. The current scope specifies people with *RAS* WT mCRC, whereas TA176 specified EGFR-expressing mCRC. The papers identified by the PenTAG searches report results from the post-hoc subgroup analysis for the OPUS and CRYSTAL studies and were not included in the previous STA review (TA 176)

Sources: Tejpar et al., Eur J Cancer, 2015 (OPUS [also referred to Bokemeyer et al. 2009; Bokemeyer et al. 2014]); Data on File (OPUS), Merck Serono UK Ltd; Van Cutsem et al., J Clin Oncol, 2015 (CRYSTAL); Data on File (CRYSTAL), Merck Serono UK Ltd; Heinemann et al., Lancet Oncol, 2014 (FIRE-3); Data on File (FIRE-3), Merck Serono UK Ltd

Table 11. Baseline characteristics (*RAS* WT [all loci]): Cetuximab trials

Author, year Trial Name	Intervention	N	Age, yrs (median (range))	Male n/N (%)	ECOG PS n/N (%)	No. metastatic sites n/N (%)	Primary tumour diagnosis n/N (%)	LLD n/N (%)
Tejpar, 2015 OPUS	CET+FOLFOX4	38	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15/38 (39.5)
	FOLFOX4	49	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	12/49 (24.5)
Van Cutsem, 2014 CRYSTAL	CET+FOLFIRI	178	60.0 (24.0–79.0)	109/178 (61.2)	0: 97/178 (54.5) 1: 76/178 (42.7) 2: 5/178 (2.8)	≤2: 157/178 (88.2) ≥2: 17/178 (9.6) Other[a]: 4/178 (2.2)	Colon: 106/178 (59.6) Rectum: 68/178 (38.2) Colon & rectum: 4/178 (2.2) Missing: 0/178 (0)	43/178 (24.2)
	FOLFIRI	189	59.0 (19.0–82.0)	120/189 (63.5)	0: 114/189 (60.3) 1: 68/189 (36.0) 2: 7/189 (3.7)	≤2: 161/189 (85.2) ≥2: 25/189 (13.2) Other[a]: 3/189 (1.6)	Colon: 117/189 (61.9) Rectum: 70/189 (37.0) Colon & rectum: 2/189 (1.1) Missing: 0/189 (0)	46/189 (24.3)
Heinemann, 2014 FIRE-3	CET+FOLFIRI	171	64.0 (41.0–76.0)	125/171 (73.1)	0: 87/171 (50.9) 1: 82/171 (48.0) 2: 2/171 (1.2)	1: 75/171 (43.9) 2: 56/171 (32.7) ≥3: 38/171 (22.2)	Colon: 106/171 (62) Rectum: 55/171 (32.2) Colon & rectum: 7/171 (5.8) Missing: 3/171 (1.8)	62/171 (36.3)
	BEV+FOLFIRI	171	65.0 (33.0–76.0)	114/171 (66.7)	0: 87/171 (50.9) 1: 81/171 (47.4) 2: 3/171 (1.8)	1: 76/171 (44.4) 2: 54/171 (31.6) ≥3: 41/171 (24.0)	Colon: 105/171 (61.4) Rectum: 59/171 (34.5) Colon & rectum: 7/171 (4.1) Missing: 0/171 (0)	58/171 (33.9)

Key: BEV = bevacizumab; CET = cetuximab; ECOG = Eastern Cooperative Oncology Group; FOLFIRI = folinic acid + flurouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; LLD = liver limited disease; NA = not applicable; NR = not reported; PS = performance status

Notes: a Missing or unknown

Sources: Tejpar et al., Eur J Cancer, 2015 (OPUS [also referred to Bokemeyer et al., 2014]); Data on File (OPUS), Merck Serono UK Ltd; Van Cutsem et al., J Clin Oncol, 2015 (CRYSTAL); Heinemann et al., Lancet Oncol, 2014 (FIRE-3); Data on File (FIRE-3), Merck Serono UK Ltd

3.2.3. Panitumumab

3.2.3.1. Study characteristics

The appraisal of panitumumab in combination with chemotherapy for the treatment of mCRC (NICE Technology Appraisal 240) was suspended as no evidence submission was received from the manufacturer or sponsor of the technology. As such, all data included in this update review for panitumumab were identified by the Assessment Group's searches. It is also important to consider that, as for cetuximab, the ITT population from the pivotal trials for panitumumab were re-evaluated in line with research developments on the impact of *RAS* mutations on the effectiveness of EGFR inhibitors.

For this MTA review, a total of two subgroup analyses of the *RAS* WT population from two RCTs (PRIME, **Douillard et al., 2013** and PEAK, **Schwartzberg et al., 2014**), evaluating panitumumab were eligible for inclusion. In the PEAK study (**Schwartzberg et al., 2014**) the extended *RAS* subgroup analysis was pre-specified.[38] In the PRIME study, extended *RAS* subgroup analysis was noted alongside a protocol amendment restricting the analysis of the ITT population to compare PFS and OS according to *KRAS* status.

Of the two included trials, one evaluated the addition of panitumumab to background chemotherapy (FOLFOX4 [PRIME, **Douillard et al., 2013**]),[53] and one evaluated the addition of panitumumab or bevacizumab to background chemotherapy (mFOLFOX6 [PEAK, **Schwartzberg et al., 2014**]).[38] All trials evaluated the same dose and administration of panitumumab (Table 12). No clinical evidence assessing the effectiveness of panitumumab in conjunction with FOLFIRI was identified.

Both of the included trials (PRIME, **Douillard et al., 2013** and PEAK, **Schwartzberg et al., 2014**),[38, 53] measured the following outcomes: ORR; PFS; OS; secondary resection of liver metastases with curative intent; and, safety and tolerability (including the incidence and type of adverse events [AEs]). The primary end point in both trials was PFS, defined as the time from randomisation to disease progression or death from any cause within 60 days after the last tumour assessment or after randomisation. No data were identified for HRQoL for the *RAS* WT population from the included trials.

Median follow-up in the PRIME trial (**Douillard et al., 2013**) was 22.31 months (IQR 10.12, 35.65) for the panitumumab plus FOLFOX4 treatment group compared with 17.71 months (IQR 8.74, 32.20) in the FOLFOX4 alone treatment group.[53] In the PEAK trial (**Schwartzberg et al., 2014**) median follow-up was 14.97 months (IQR 8.83, 22.81) in the

cetuximab plus mFOLFOX6 treatment group compared with 14.93 (IQR 8.76, 21.39) in the bevacizumab plus mFOLFOX6 treatment group.[38]

Study characteristics for the included studies are summarised in Table 12.

3.2.3.2. Population characteristics

Baseline demographic and disease characteristics for the *RAS* WT subgroup are reported in Table 13.

In all studies, existing DNA samples from *KRAS* exon 2 WT tumours were re-analysed for other *RAS* mutations in four additional *KRAS* codons (exons 3 and 4) and six *NRAS* codons (exons 2, 3, and 4). Mutation status was evaluable in 882 (65.6%) of 1,345 trial participants with *KRAS* exon 2 WT tumours (Table 12). Details of the proportions of study participants evaluated to be *RAS* WT are summarised in Table 12. In all trials, the baseline demographic and disease characteristics were comparable with those seen for the *KRAS* WT population (see Appendix E for baseline and disease characteristics for the *KRAS* WT population).

Participants were similar in terms of age, gender distribution, and site of primary cancer (Table 11). However, as is usually the case with cancer trials, the study populations were significantly younger than the general population presenting with mCRC, where the peak in number of cases in the UK, for example, is between 70 and 79 years of age for men and 75- to 85-plus for women, as opposed to a median of 60–62 shown in Table 13.

Table 12. Overview of included studies: Panitumumab trials

Author, Year Trial NCT Study design	Included in TA176a	Included in update review	Inclusion criteria	ITT (N)	RAS WT (n) / analysed (N)	Randomisation stratification factors	Interventions evaluated & dose	Primary endpoint	Median treatment duration, mths (IQR)	Median follow-up, mths (IQR)
Douillard, 2013 PRIME NCT00364013 Retrospective subgroup analysis	N[b]	Y	≥18 yrs; ECOG ≤2; first occurrence of metastatic disease	1,183	512/1,060	ECOG PS (0–1 vs 2); region (Western Europe, Canada, and Australia vs Rest of World)	PAN+FOLFOX4 vs FOLFOX4 PAN: 60-min IV infusion, 6 mg/kg Q2W on Day 1 FOLFOX4: Q2W as IV OX 85 mg/m^2 Day 1 + racemic leucovorin 200 mg/m^2 IV infusion on Days 1 & 2 + FU 400 mg/m^2 IV bolus followed by a 600 mg/m^2 infusion over 22 hrs on Days 1 & 2	PFS	6.47 (3.68, 11.40) PAN+FOLFOX4 vs. NR FOLFOX4	22.31 (10.12, 35.65) PAN+FOLFOX4 vs. 17.71 (8.74, 32.20) FOLFOX4
Schwartzberg, 2014 PEAK NCT00819780 Prospective subgroup analysis	N[b]	Y	≥18 yrs; ECOG ≤2; first occurrence of metastatic disease	285	170/285	Prior adjuvant OX therapy	PAN+mFOLFOX6 vs BEV+mFOLFOX6 PAN: 60-min IV infusion, 6 mg/kg Q2W on Day 1 BEV: Day 1, 90-min infusion 5 mg/kg, 2 wks later 60-min infusion 5 mg/kg; over 30 mins every 2 wks thereafter mFOLFOX6: Q2W as OX 85 mg/m^2 IV infusion (over 2 hrs) Day 1 + leucovorin 400 mg/m^2 IV infusion (over 2 hrs)+ FU 400 mg/m^2 IV bolus (over 2–4 mins) Day 1 followed by a 2,400 mg/m^2 ambulatory pump (46–48 hrs)	PFS	7.45 (3.91, 11.66) PAN+mFOLFOX6 vs. 5.86 (3.13, 9.57) BEV+mFOLFOX6	14.97 (8.83, 22.81) PAN+mFOLFOX6 vs. 14.93 (8.76, 21.39) BEV+mFOLFOX6

Key: BEV = bevacizumab; ECOG = Eastern Cooperative Oncology Group; FOLFOX = folinic acid + fluorouracil + oxalipaltin; mFOLFOX = modified folinic acid + fluorouracil + oxaliplatin; FU = fluourouacil; hrs., = hour(s); ITT = intention to treat; IV = intravenous; mins., =minute(s); N = no; NCT = National Clinical Trial; OX = oxaliplatin; PAN = panitumumab; PFS = progression free survival; PS = performance status; Q2W = every two weeks; *RAS* = rat sarcoma; TA = Technology Appraisal; vs. = versus; wks., = week(s); WT = wild type; Y = yes; yrs., = year(s)

Notes: (a) The appraisal of panitumumab in combination with chemotherapy for the treatment of mCRC (NICE Technology Appraisal 240) was suspended because no evidence submission was received from the manufacturer or sponsor of the technology

Sources: Douillard et al. N Engl J Med, 2013 (PRIME); Data on File (PRIME), Amgen UK Ltd; Schwartzberg et al. J Clin Oncol, 2014 (PEAK); Data on File (PEAK), Amgen UK Ltd;

Table 13. Baseline characteristics (*RAS* WT [all loci]): Panitumumab trials

Author, year Trial Name	Intervention	N	Age, yrs (median (range))	Male n/N (%)	ECOG PS n/N (%)	No. metastatic sites n/N (%)	Primary tumour diagnosis n/N (%)	LLD n/N (%)
Douillard, 2013 Data on File, Amgen Ltd	PAN+FOLFOX4	253[b]	61 (27–81)	170 (67)	0: 150/253 (59) 1: 88/253 (35) 2: 15/253 (6)	1: 56/253 (22) 2: 92/253 (36) ≥3: 104/253 (41)	Colon: 165/253 (65) Rectum: 88/253 (35)	48/253 (19)
PRIME	FOLFOX4	252[b]	61 (24–82)	158 (63)	0: 137/252 (54) 1: 98/252 (39) 2: 16/252 (6)	1: 50/252 (20) 2: 93/252 (37) ≥3: 109/252 (43)	Colon: 164/252 (65) Rectum: 88/252 (35)	41/252 (16)
Schwartzberg, 2014 PEAK	PAN+ mFOLFOX6	88	62 (23–82)	58/88 (66)	0: 53/88 (60) 1: 35/88 (40) Other[a]: NA	1: 32/88 (36) 2: 28/88 (32) ≥3: 28/88 (32) Other[a]: 0/88 (0)	Colon: 64/88 (73) Rectum: 24/88 (27)	23/88 (26)
	BEV+ mFOLFOX6	82	60 (39–82)	56/82 (68)	0: 52/82 (63) 1: 29/82 (35) Other[a]: 1/82 (1)	1: 33/82 (40) 2: 29/82 (35) ≥3: 19/82 (23) Other[a]: 1/82 (1)	Colon: 57/82 (70) Rectum: 28/82 (30)	22/82 (27)

Key: BEV = bevacizumab; ECOG = Eastern Cooperative Oncology Group; FOLFIRI = folinic acid + flurouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; LLD = liver limited disease; m = modified; NA = not applicable; NR = not reported; PAN = panitumumab; PS = performance status

Notes: a Missing or unknown; b Baseline characteristics were not reported in Douillard et al., 2013 but provided by the Company. The total N reported in Douillard et al., 2013 is 512 but baseline characteristics data provided by the Company were for total n = 505

Sources: Data on File (PRIME), Amgen UK Ltd; Douillard et al., N Engl J Med, 2013 (PRIME); Schwartzberg et al. J Clin Oncol, 2014 (PEAK)

3.2.4. Quality appraisal

We appraised the five identified subgroup analyses. On occasion, however, we referred to the original trials to clarify issues relating to study design or methods. The reason for this was to put identified limitations associated with subgroup analyses into context for this appraisal. Quality assessments of included trials are presented in Table 14.

Overall, the risk of bias was similar between studies in respect of treatment allocation, allocation concealment, blinding, outcome reporting and loss to follow-up.

3.2.5. Treatment allocation

The method of random allocation, including the method of sequence generation, was clearly stated and adequate for all of the included trials. All trials used a stratified permuted block procedure. Stratification factors varied between the studies but were predominantly based on ECOG performance status (0 or 1 vs. 2) and region (Eastern or Western Europe vs. outside of Europe and Western Europe, Canada, Australia vs. rest of world).

However, data for people with *RAS* WT mCRC were only available from subgroup analyses and not the ITT trial population for any of the included trials. In response to research developments demonstrating a treatment interaction of *RAS* and EGFR inhibitors (specifically the negative impact of *RAS* mutations on the effectiveness of EGFR inhibitors), tumour samples from participants of the original RCTs were re-evaluated for *RAS* status. None of the included studies stratified randomisation by *RAS* status; this was because the impact of *RAS* mutations on the effectiveness of EGFR inhibitors was not known at the protocol development phase. For four of the trials (OPUS, CRYSTAL, FIRE-3 and PRIME) the subgroup analyses were retrospective. However, for two of these trials (PRIME and FIRE-3) protocol amendments were made in line with research developments. The only trial in which the extended *RAS* WT subgroup analysis was pre-specified was the PEAK trial.

Tumour samples from participants in the ITT population identified as *KRAS* Exon 2 WT were re-evaluated for *RAS* mutations and either allocated to subgroups *RAS* WT or *RAS* mutant. The methods used to detect *RAS* mutations varied between studies, minimising the potential for ascertainment bias. The *RAS* ascertainment rate was 61% (1,478/2,435), the missing data largely resulted from unavailable tumour samples or inconclusive *RAS* test results.Of note, none of the included subgroup analyses reported the results of a test for treatment interaction.

3.2.5.1. Similarity of groups

Three of the included trials fully reported baseline characteristics for the *RAS* WT population (OPUS, CRYSTAL, and PEAK). While two of the trials (PRIME and FIRE-3) did not report baseline characteristics for the subgroup of interest in the trial publication we were able to confirm these via the companies. Of note, however, baseline characteristics provided by the manufacturer for the PRIME study were for a total 505 participants whereas the Douillard et al. (2013) paper reports a total of 512 participants in the *RAS* WT subgroup.

Given the use of subgroup data, all comparisons were made without protection by stratification/randomisation increasing the risk of selection bias. However, from the evidence provided (published and unpublished) we were able to confirm evidence that the treatment groups were adequately similar at baseline on a range of prognostic factors for the *RAS* WT population. Moreover, characteristics were similar to those for both the ITT and *KRAS* WT populations suggesting a low risk of selection bias in the *RAS* tested trial population.

3.2.5.2. Implementation of masking

The trials were open-label design and as such participants and outcomes assessors were not blinded. There was, however, a blinded retrospective review of radiological assessment and clinical data for progression and best objective response rate in two of the studies (OPUS and CRYSTAL), and objective response rate for one study (PRIME). In addition, in one study (PRIME) an independent data monitoring committee reviewed interim analyses of safety and one descriptive interim analysis of PFS. No independent assessment was performed in either the PEAK or FIRE-3 trial.

3.2.5.3. Completeness of trial data

With regards to the reporting of *a priori* outcomes, all included trials were rated as unclear. This was because the original trial reports for the ITT population failed to explicitly state whether all outcomes defined in the study protocol were reported. Therefore, we were by default unable to assess whether all *a priori* outcomes had been reported for the *RAS* WT population. Summary data, including event numbers and denominators were reported for the majority of expected outcomes for the *RAS* WT population, and where not reported we were able to confirm data (predominantly ORR and resection rates) using secondary sources; e.g., European Medicines Agency (EMA) documents or via the manufacturer.

Withdrawals and dropouts were adequately reported in all of the original trial publications (by providing numbers and reasons by treatment group in the form of a CONSORT flow

diagram) for the ITT population. Loss to follow-up was, however, unclear. With respect to the *RAS* WT population missing data largely resulted from unavailable tumour samples or inconclusive *RAS* test results.

Currently available data on the effectiveness of both cetuximab and panitumumab in the *RAS* WT population are from subgroup analyses not from the ITT trial population and, as such, intention-to-treat (ITT) analysis was not conducted and results were not available. Due to the retrospective nature of the *RAS* analysis there were a low number of samples available for analysis reducing the power of the studies to show statistical significance.

3.2.5.4. Applicability to the NHS in England

The population evaluated is in line with that specified in the licensed indication and the NICE final scope. The study arm populations had, median/mean ages of between 59 and 65 years and the majority of participants had an ECOG performance status of <2, meaning that people were younger and fitter than the UK population of people with mCRC. This is a recurrent problem, however, in the findings of trials of therapies for mCRC to the UK population. All of the included studies were multicentre studies (including European centres), and evaluated the study drugs in line with their licensed indications. Importantly, however, data for the *RAS* WT population were only available from subgroup analyses rather than ITT analyses, and, as such, sample sizes were often small and results are subject to a high degree of uncertainty.

The rationale for the use of subgroup data is based on research developments which have demonstrated that genotype is an important determinant of both the response to treatment and the susceptibility to adverse reactions for a wide range of drugs.[69, 70] In colorectal cancer response to EGFR inhibitors has been shown to be dependent on gene expression; studies have demonstrated a treatment interaction between *RAS* status and the effectiveness of EGFR inhibitors.[71-73] It was in line with these research developments evaluating the negative impact of *RAS* mutations on the effectiveness of EGFR inhibitors, that tumour samples from trial populations supporting the original licensed indications were evaluated retrospectively for *RAS* status. Therefore data are not from the ITT population for any of the included studies, but from a subgroup of people contained within the original RCTs.

While subject to the uncertainties outlined above, these subgroup data are currently the only available data for the *RAS* WT sub-population. The Assessment Group did not identify any RCTs with an ITT population by *RAS* WT status, and .only one of the included trials prespecified the extended *RAS* analysis. Of note, the EMA's recent change to the licensed

indication was based on subgroup data from trials that inform this current assessment, and while subgroup analyses were defined post-hoc the rationale was based on research developments into tumour biology and results were in line with the expected direction of effect and consistent across included studies. Hence the extent to which the results of included trials can provide a reasonable basis for generalization to the UK NHS population of people with mCRC is unclear.

Table 14. Quality assessment: *RAS* WT subgroup

Study, year	Random allocation	Allocation concealment	Baseline similarity	Care providers blinded	Outcome assessors blinded	Patients blinded	All a priori outcomes reported	Complete data reported	ITT	Applicability
Van Cutsem, 2015 CRYSTAL	Inadequate[a]	Unclear[e]	Adequate	Inadequate[f]	Inadequate[f,g]	Inadequate[f]	Unclear[h]	Inadequate[i]	Inadequate[j]	Inadequate[k]
Bokemeyer, 2015 OPUS	Inadequate[a]	Unclear[e]	Adequate	Inadequate[f]	Inadequate[f,g]	Inadequate[f]	Unclear[h]	Inadequate[i]	Inadequate[j]	Inadequate[k]
Heinemann, 2014 FIRE-3	Inadequate[a,b]	Unclear[e]	Adequate	Inadequate[f]	Inadequate[f]	Inadequate[f]	Unclear[h]	Inadequate[i]	Inadequate[j]	INadequate[k]
Douillard, 2013 PRIME	Inadequate[a,c]	Unclear[e]	Adequate	Inadequate[f]	Inadequate[f,g]	Inadequate[f]	Unclear[h]	Inadequate[i]	Inadequate[j]	Inadequate[k]
Schwartzberg, 2014 PEAK	Inadequate[a,d]	Unclear[e]	Adequate	Inadequate[f]	Inadequate[f,g]	Inadequate[f]	Unclear[h]	Inadequate[i]	Inadequate[j]	Inadequate[k]

Key: CET = cetuximab; ECOG = Eastern Cooperative Oncology Group; IDMC = Independent Data Monitoring Committee; ITT = intention to treat; OS = overall survival; PAN = panitumumab; PFS = progression free survival; PS = performance status; RAS = rat sarcoma; WT = wild type

Notes: a Although in the main trial population random allocation was considered adequate via stratified permuted block procedure, the data relevant to this review were from a subgroup analysis by RAS status. The KRAS WT Exon 2 population from the original trials were re-evaluated for RAS status following research developments into the negative impact of RAS mutations on EGFR inhibitors and changes to the licence for CET and PAN. Allocation to subgroups is based on biological assessment; ascertainment was 62% minimising the potential for ascertainment bias. The biological rationale for the re-evaluation by RAS status supports the validity of the effect estimates; b Protocol amendment to eligibility criteria people with mCRC with KRAS WT Exon 2 tumours (and to note the intention to conduct subgroup analysis by RAS status); c Protocol amendment to restrict statistical analysis for endpoints PFS and OS to participants with mCRC with KRAS WT Exon 2 tumours (and to note the intention to conduct subgroup analysis by RAS status); d Subgroup analysis by RAS status was pre-specified; e Not reported; f The trials were open-label design; g Blinded review for progression and objective response rate (OPUS & CRYSTAL) and for objective response rate (PRIME). In addition, an IDMC reviewed interim analyses of safety and one descriptive interim analysis of PFS (PRIME). No independent assessments were performed in either FIRE-3 or PEAK; h The primary trial publications did not explicitly state whether all outcomes defined in the trial protocol were reported as such we were not able to determine for the RAS WT population; i Missing data largely resulted from unavailable tumour samples or inconclusive RAS test results; j In the primary publications data analyses were conducted for all of the included trials for the intention-to-treat population. However, as the population of relevance to this review was people with mCRC with RAS WT status effectiveness estimates were determined via subgroup analysis; k Currently, available data on the effectiveness of both CET and PAN are only available from subgroup analyses from RCTs. While we note the uncertainties associated with effect estimates from subgroup analyses; e.g. ascertainment bias and selection bias we note that the potential for these is minimised. Lack of statistical power is also an issue with subgroup analyses but we also note the underlying rationale of tumour biology, and consistency of effect estimates for both CET and PAN support the validity of effect estimates

Sources: Tejpar et al., Eur J Cancer, 2015 (OPUS); Van Cutsem et al., J Clin Oncol, 2015 (CRYSTAL); Heinemann et al., Lancet Oncol, 2014 (FIRE-3); Douillard et al. N Engl J Med, 2013 (PRIME); Schwartzberg et al. J Clin Oncol, 2014 (PEAK). In addition, primary sources referred to: Bokemeyer et al., J Clin Oncol, 2009 (OPUS); Van Cutsem et al., N Engl J Med, 2015 (CRYSTAL); Douillard et al., J Clin Oncol, 2010 (PRIME)

3.2.6. Assessment of effectiveness

The following outcomes have been assessed:

- Progression free survival (PFS)
- Overall survival (OS)
- Objective response rate (ORR)
- Resection rate

We also sought HRQoL outcome data from included RCTs. However, none was reported.

Due to an insufficient number of RCTs, meta-analysis was not undertaken and publication bias was not investigated using funnel plots.

The results of the assessment of clinical effectiveness are presented as follows:

- An overview of the quantity and quality of available evidence together with a table summarising all included trials and a summary table of key quality indicators
- A critical review of the available evidence for each of the stated research questions covering:
  - the quantity and quality of available evidence
  - a summary table of the study characteristics
  - a summary table of the baseline population characteristics
  - comparison of the baseline populations in the included trials
  - study results presented in narrative and tabular form
  - comparison of the results in terms of effectiveness and safety
- A summary of evidence for clinical effectiveness used in the manufacturers' submissions.

3.2.6.1. Cetuximab

Progression-free survival

All of the included cetuximab trials reported PFS (**Tejpar et al., 2015** [OPUS]; **Van Cutsem et al., 2015** [CRYSTAL]; **Heinemann et al., 2014** [FIRE-3]).[37, 52, 75] Of these, one trial reported PFS as a primary outcome (**Van Cutsem et al., 2015** [CRYSTAL]**)**.[52] The definition of disease progression appears relatively consistent across the three trials. In each case PFS was defined as the interval from random assignment of treatment to radiologic evidence of disease progression or death from any cause. Radiologic assessment of pregression was

assessed according to either RECIST criteria (FIRE-3 [**Heinemann et al., 2014**]), or modified WHO criteria (OPUS [**Tejpar et al., 2015**] and CRYSTAL [**Van Custem et al., 2015**]). The time-to-event data were summarised by stratified hazard ratio (HR). A HR of <1 indicates an improvement in PFS for treatment (cetuximab) compared with control.

Cetuximab plus FOLFOX4 vs. FOLFOX4

Tejpar et al., (2015 [reported in abstract form in Bokemeyer et al., 2014]**)** (OPUS) reported median PFS as 12 months (95% CI 5.8, NR) and 5.8 months (95% CI 4.7, 7.9) for the cetuximab plus FOLFOX4 vs FOLFOX4 arms, respectively (Table 15).[75] The addition of cetuximab to FOLFOX4 was associated with a 47% reduction in the risk of progression in people with *RAS* WT tumours (HR 0.53 [95% CI 0.27, 1.04]) (Table 15).[75]

Cetuximab plus FOLFIRI vs. FOLFIRI

Van Cutsem et al. (2015) (CRYSTAL) reported median PFS as 11.4 months (95% CI 10, 14.6) and 8.4 months (95% CI 7.4, 9.4) for the cetuximab plus FOLFIRI vs FOLFIRI arms, respectively (Table 15).[52] The addition of cetuximab to FOLFIRI was associated with a 44% reduction in the risk of progression in people with *RAS* WT tumours (HR 0.56 [95% CI 0.41, 0.76]) (Table 15).[52]

Cetuximab plus FOLFIRI vs. bevacizumab plus FOLFIRI

In the FIRE-3 trial (**Heinemann et al., 2014**), median PFS was similar between the treatment groups 10.4 months (95% CI 9.5, 12.2) and 10.2 months (95% CI 9.3, 11.5) in the cetuximab plus FOLFIRI and bevacizumab plus FOLFIRI arms respectively; HR 0.93 (95% CI 0.74, 1.17) (Table 15).[37]

Table 15. Progression free survival (*RAS* WT [all loci]): Cetuximab trials

Author, year, TRIAL	Experimental (n/N) Median mths (95% CI)	Control (n/N) Median mths (95% CI)	HRa (95% CI)
Tejpar, 2015	CET+FOLFOX4 (13/38)	FOLFOX4 (29/49)	0.53 (0.27, 1.04)
OPUS[a]	12 (5.8, NR)	5.8 (4.7, 7.9)	
Van Cutsem, 2015	CET+FOLFIRI (73/178)	FOLFIRI (99/189)	0.56 (0.41, 0.76)
CRYSTAL[a]	11.4 (10, 14.6)	8.4 (7.4, 9.4)	
Heinemann, 2014	CET+FOLFIRI (144/171)	BEV+FOLFIRI (143/171)	0.93 (0.74, 1.17)
FIRE-3[a]	10.4 (9.5, 12.2)	10.2 (9.3, 11.5)	

Key: BEV = bevacizumab; CET = cetuximab; FOLFOX = folinic acid + fluorouracil + oxaliplatin; FOLFIRI = folinic acid + fluorouracil + irinotecan; HR= hazard ratio; LCL = lower confidence limit; mFOLFOX – modified folinic acid + fluorouracil = oxaliplatin; mths = months; PAN = panitumumab; UCL = upper confidence limit

Notes: a Stratified hazard ratio (HR). Random assignment was stratified by (i) ECOG performance status (0 or 1 vs. 2) (OPUS), (ii) ECOG performance status (0 or 1 vs. 2) and region (sites in Western Europe vs.Eastern Europe vs. outside Europe) (CRYSTAL); (iii) ECOG performance status (0–1 or 2), number of metastatic sites (1 or >1), white blood cell count (<8 × 10^9 cells per L or ≥8 × 10^9 cells per L) and alkaline phosphatase con centration (<300 units per L or ≥300 units per L) (FIRE-3)

Sources: Tejpar et al., Eur J Cancer, 2015 (OPUS [also reported in abstact form in Bokemeyer et al., 2014]); Van Cutsem et al., J Clin Oncol, 2015 (CRYSTAL); Heinemann et al., Lancet Oncol, 2014 (FIRE-3)

Overall survival

All of the included cetuximab trials reported overall survival (OS) (**Tejpar et al., 2015** [OPUS]; **Van Cutsem et al., 2015** [CRYSTAL]; **Heinemann et al., 2014** [FIRE-3]**)**.[37, 52, 75] In each of the trials OS was defined as the interval from random assignment of treatment to death. The time-to-event data were summarised by stratified hazard ratio (HR). A HR of <1 indicates an improvement in OS for treatment compared with control.

Cetuximab plus FOLFOX4 vs. FOLFOX4

In the OPUS trial (**Tejpar et al., 2015** [also reported in abstract form in Bokemeyer et al. 2014]), median OS was 19.8 months (95% CI 16.6, 25.4) in the cetuximab plus FOLFOX4 group compared with 17.8 months (95 % CI 13.8, 23.9) FOLFOX4 (HR 0.94 [95% CI 0.56, 1.56]) (Table 16).[75]

Cetuximab plus FOLFIRI vs. FOLFIRI

In the CRYSTAL trial (**Van Cutsem et al., 2015**), median OS was 28.4 months (95% CI 24.7, 31.6) in the cetuximab plus FOLFIRI group compared with 20.2 months (95% CI 17, 24.5) for FOLFIRI (HR 0.69 [95% CI 0.54, 0.88]) (Table 16).[52]

Cetuximab plus FOLFIRI vs. bevacizumab plus FOLFIRI

In the FIRE-3 trial (**Heinemann et al., 2014**), median OS was 33.1 months (95% CI 24.5, 39.4) in the cetuximab plus FOLFIRI group compared with 25.6 months (95% CI 22.7, 28.7) bevacizumab (HR 0.7 [95% CI 0.53, 0.92]) (Table 16).[37]

Table 16. Overall survival (*RAS* WT [all loci]): Cetuximab trials

Author, year, TRIAL	Experimental (n/N) Median mths (95% CI)	Control (n/N) Median mths (95% CI)	HRa (95% CI)
Tejpar, 2015	CET+FOLFOX4 (27/38)	FOLFOX4 (36/49)	0.94 (0.56, 1.56)
OPUS[a]	19.8 (16.6, 25.4)	17.8 (13.8, 23.9)	
Van Cutsem, 2015	CET+FOLFIRI (130/178)	FOLFIRI (154/189)	0.69 (0.54, 0.88)
CRYSTAL[a]	28.4 (24.7, 31.6)	20.2 (17, 24.5)	
Heinemann, 2014	CET+FOLFIRI (91/171)	BEV+FOLFIRI (110/171)	0.7 (0.53, 0.92)
FIRE-3[a]	33.1 (24.5, 39.4)	25.6 (22.7, 28.7)	

Key: BEV = bevacizumab; CET = cetuximab; FOLFOX = folinic acid + fluorouracil + oxaliplatin; FOLFIRI = folinic acid + fluorouracil + irinotecan; HR= hazard ratio; LCL = lower confidence limit; mFOLFOX – modified folinic acid + fluorouracil = oxaliplatin; mths = months; PAN = panitumumab; UCL = upper confidence limit

Notes: a Stratified hazard ratio (HR). Random assignment was stratified by (i) ECOG performance status (0 or 1 vs. 2) (OPUS), (ii) ECOG performance status (0 or 1 vs. 2) and region (sites in Western Europe vs.Eastern Europe vs. outside Europe) (CRYSTAL); (iii) ECOG performance status (0–1 or 2), number of metastatic sites (1 or >1), white blood cell count (<8 × 10^9 cells per L or ≥8 × 10^9 cells per L) and alkaline phosphatase con centration (<300 units per L or ≥300 units per L) (FIRE-3)

Sources: Tejpar et al., Eur J Cancer, 2015 (OPUS [also reported in abstact form in Bokemeyer et al., 2014]); Van Cutsem et al., J Clin Oncol, 2015 (CRYSTAL); Heinemann et al., Lancet Oncol, 2014 (FIRE-3)

Objective response rate

Data for objective response rate (ORR) were available from the three included studies (**Tejpar et al., 2015** [OPUS]; **Van Cutsem et al., 2015** [CRYSTAL]; and **Heinemann et al., 2014** [FIRE-3]).[37, 52, 75]

In all of the cetuximab trials (**Tejpar et al., 2015** [OPUS]; **Van Cutsem et al., 2015** [CRYSTAL]; and **Heinemann et al., 2014** [FIRE-3]),[37, 52, 75] response rate was defined as the percentage of study participants that achieved a partial or complete response as the best ORR according to radiological assessment.

In two of the analyses (**Tejpar et al., 2015** [OPUS]; and **Heinemann et al., 2014** [FIRE-3]), ORR was evaluated using Response Evaluation Criteria in Solid Tumours (RECIST) (Version 1.0); no independent review was performed.[37, 75] Tumour response evaluation was performed every six weeks (± 7 days) in the OPUS trial (**Tejpar et al., 2015**), and every eight weeks (± 7 days) in the FIRE-3 trial (**Heinemann et al., 2014**), and treatment was continued until disease progression, unacceptable toxicities, death, withdrawal of consent, or investigator decision, whichever was earlier. In the CRYSTAL analysis (**Van Cutsem et al.,**

2015), tumour response including disease progression was assessed by an independent review committee according to modified World Health Organisation (WHO) criteria. The independent review committee conducted a blinded review of images and clinical data using a common set of pre-specified criteria.[52]

The WHO criteria for response rate are older than the current standard RECIST criteria (see Appendix G). It can be seen that the two sets of criteria do not fully match; WHO criteria are multidimensional and the RECIST criteria are unidimensional. This is not necessarily important when considering a single trial but where there are several trials and some use one set of criteria and some use the other, the results cannot easily be compared.

The effect of treatment on response was measured as an odds ratio (i.e. odds of a response with cetuximab versus odds of a response without cetuximab).

Best available response rate (i.e. complete response [CR], partial response [PR], stable disease [SD], progressed disease [PD]) is reported in Appendix H.

Cetuximab plus FOLFOX4 vs. FOLFOX4

Tejpar et al. (2015) (OPUS [also reported in abstract form in Bokemeyer et al., 2014]) reported confirmed complete or partial tumour responses in 22 people (58%) receiving cetuximab plus FOLFOX4 and in 14 people (29%) receiving FOLFOX4 alone (**Error! eference source not found.**).[75] The adjusted odds ratio for a tumour response with the cetuximab plus FOLFOX4, as compared with FOLFOX4 alone, was 3.33 (95% CI 1.36, 8.17) favouring the cetuximab plus FOLFOX4 arm (Table 17).[75]

Cetuximab plus FOLFIRI vs. FOLFIRI

Van Cutsem et al. (2015) (CRYSTAL) reported confirmed complete or partial tumour responses in 118 people (66%) receiving cetuximab plus FOLFIRI and in 73 people (39%) receiving FOLFIRI alone (Table 17).[52] The adjusted odds ratio for a tumour response with the cetuximab plus FOLFIRI, as compared with FOLFIRI alone, was 3.11 (95% CI 2.03, 4.78), favouring the cetuximab plus FOLFIRI arm (Table 17).[52]

Cetuximab plus FOLFIRI vs. bevacizumab plus FOLFIRI

Heinemann et al. (2014) (FIRE-3) reported confirmed complete or partial tumour responses in 112 people (66%) receiving cetuximab plus FOLFIRI and in 102 people (60%) receiving bevacizumab plus FOLFIRI (Table 17).[37] The adjusted odds ratio for a tumour response with

the cetuximab plus FOLFIRI, as compared with bevacizumab plus FOLFIRI, was 1.28 (95% CI 0.83, 1.99), favouring the cetuximab plus FOLFIRI arm (Table 17).[37]

Table 17. Response rate (*RAS* WT [all loci]): Cetuximab trials

Author, year Trial	Experimental	n/N (% [95% CI])	Control	n/N (%, 95% CI)	OR[a] (95% CI)
Tejpar, 2015 OPUS[b]	CET+FOLFOX4	22/38 (58 [41, 74])	FOLFOX4	14/49 (29 [17, 43])	3.33 (1.36, 8.17)
Van Cutsem, 2015 CRYSTAL[b]	CET+FOLFIRI	118/178 (66 [59, 73])	FOLFIRI	73/189 (39 [32, 46])	3.11 (2.03, 4.78)
Heinemann, 2014 FIRE-3[c]	CET+FOLFIRI	112/171 (65.5 [58, 73])	BEV+FOLFIRI	102/171 (60 [52, 67])	1.28 (0.83, 1.99)

Key: BEV = bevacizumab; CET = cetuximab; CI = confidence interval; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; OR = odds ratio

Notes: a Stratified odds ratio (OR). Random assignment was stratified by (i) ECOG performance status (0 or 1 vs. 2) (OPUS), (ii) ECOG performance status (0 or 1 vs. 2) and region (sites in Western Europe vs.Eastern Europe vs. outside Europe) (CRYSTAL); (iii) ECOG performance status (0–1 or 2), number of metastatic sites (1 or >1), white blood cell count (<8 × 10^9 cells per L or ≥8 × 10^9 cells per L) and alkaline phosphatase con centration (<300 units per L or ≥300 units per L) (FIRE-3); b Assessed every eight weeks, median follow-up not reported; c Assessed 28 days from last treatment cycle (tumour evaluations had to be performed at least six weeks after first administration of therapy

Sources: Tejpar et al., Eur J Cancer, 2015 (OPUS [also reported in abstact form in Bokemeyer et al., 2014]); Van Cutsem et al., J Clin Oncol, 2015 (CRYSTAL); Heinemann et al., Lancet Oncol, 2014 (FIRE-3)

Rate of complete resection

Data for rate of complete resection with curative intent before disease progression were available from one of the included cetuximab trials (CRYSTAL [**Van Cutsem et al., 2015**]).[52]

Rate of surgery with curative intent (with complete resection of all lesions [R0]) was defined as the number of subjects with any resection of metastasis of curative intent and all lesions completely resected to R0, divided by all subjects qualifying for the ITT population. The effect of treatment on the likelihood of complete resection was measured as an odds ratio.

Cetuximab plus FOLFOX4 vs. FOLFOX4

No data were reported for the rate of complete resection from the OPUS trial (**Tejpar et al., 2015***)* for this comparison for the *RAS* WT population.[75]

Cetuximab plus FOLFIRI vs. FOLFIRI

No data were reported for the rate of complete resection in the CRYSTAL trial publication (**Van Cutsem et al., 2015** [CRYSTAL]**)**; however, data were provided as commercial in

confidence (CiC) by the manufacturer. The rate of complete resection with curative intent before disease progression was higher in the cetuximab plus FOLFIRI group than in the FOLFIRI group (7.3% vs. 2.1%; OR 3.11; 95% CI 2.03, 4.78; p=NR).[52]

Cetuximab plus FOLFIRI vs. bevacizumab plus FOLFIRI

No data were available for the rate of complete resection from the FIRE-3 trial (**Heinemann et al., 2014**) for this comparison for the *RAS* WT population.[37]

Table 18. Rate of complete resection (*RAS* WT [all loci]): Cetuximab trials

Author, year Trial	Experimental	n/N (%)	Control	n/N (%)	ORa (95% CI)
Tejpar, 2015 OPUS	CET+FOLFOX4	NR	FOLFOX4	NR	NR
Data on File, Merck Serono Ltd, 2015 CRYSTAL[b]	CET+FOLFIRI	13/178 (7.3)	FOLFIRI	4/189 (2.1)	3.11 (2.03, 4.78)
Heinemann, 2014 FIRE-3	CET+FOLFIRI	NR	BEV+FOLFIRI	NR	NR

Key: BEV = bevacizumab; CET = cetuximab; CI = confidence interval; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; NR = not reported; OR = odds ratio
Notes: a Stratified odds ratio (OR). Random assignment was stratified by (i) ECOG performance status (0 or 1 vs. 2) (OPUS), (ii) ECOG performance status (0 or 1 vs. 2) and region (sites in Western Europe vs.Eastern Europe vs. outside Europe) (CRYSTAL); (iii) ECOG performance status (0–1 or 2), number of metastatic sites (1 or >1), white blood cell count (<8 × 10^9 cells per L or ≥8 × 10^9 cells per L) and alkaline phosphatase con centration (<300 units per L or ≥300 units per L) (FIRE-3); b Median follow-up not reported
Sources: Tejpar et al., Eur J Cancer, 2015 (OPUS); Data on File (CRYSTAL), Merck Serono UK Ltd; Heinemann et al., Lancet Oncol, 2014 (FIRE-3)

Subgroup analyses: liver metastasis at baseline

There were no planned subgroup analyses in the *RAS* WT population as the data for this population was obtained retrospectively. However, data for people with liver metastasis at baseline were available from two of the included cetuximab trials (provided as CiC data by the manufacturer), (**Tejpar et al., 2015** [OPUS]; **Van Cutsem et al., 2015** [CRYSTAL]) and are presented below.[52, 75]

Cetuximab plus FOLFOX4 vs. FOLFOX4

Among the *RAS* WT subgroup a total of 27 (31.0%) participants in the OPUS trial (**Tejpar et al., 2015**) had metastasis to the liver at baseline.[75] Results are summarised in Table 18.

Complete resection was performed in two of 15 (13.3%) participants in the cetuximab plus FOLFOX4 arm and none (0/12; 0%) participants in the FOLFOX4 alone arm.

Cetuximab plus FOLFIRI vs. FOLFIRI

Among the *RAS* WT subgroup a total of 89 (24.3%) participants in the CRYSTAL trial (**Van Cutsem et al., 2015**) had metastasis to the liver at baseline.[52] Results are summarised in Table 19.

Complete resection was performed in seven of 43 (16.3%) participants in the cetuximab plus FOLFOX arm and three of 46 (6.5%) participants in the FOLFOX alone arm (OR. 2.68 [95% CI 0.63, 11.43]).

Cetuximab plus FOLFIRI vs. bevacizumab plus FOLFIRI

No data were available for people with liver metastasis at baseline from the FIRE-3 trial (**Heinemann et al., 2014**).[37]

Table 19. Subgroup analyses by liver metastases (*RAS* WT [all loci]): Cetuximab trials

	OPUS		CRYSTAL		FIRE-3	
	CET+FOLFOX4 (n=15)	FOLFOX4 (n=12)	CET+FOLFIRI (n=43)	FOLFIRI (n=46)	CET+FOLFIRI (n=NR)	BEV+FOLFIRI (n=NR)
PFS						
Progression/death events (n/N, %)	NR	NR	NR	NR	NR	NR
Median PFS, months (95% CI)	NR	7.4 (NR)	14.0 (NR)	8.1 (NR)	NR	NR
Stratified hazard ratio (95% CI)[a]		0.35 (0.06, 1.91)		0.21 (0.09, 0.49)	NR	
OS						
Deaths (n/N, %)	NR	NR	NR	NR	NR	NR
Median OS (95% CI)	23.9 (NR)	24.8 (NR)	29.8 (NR)	29.5 (NR)	NR	NR
Stratified hazard ratio (95% CI)[a]		0.90 (0.33, 2.42)		0.65 (0.38, 1.10)	NR	
ORR						
n/N, %	11/15 (73.3%)[b]	5/12 (41.7)[b]	36/43[b] (83.7%)	17/46[b] (37.0)	NR	NR
Stratified odds ratio (95% CI)[a]		3.30 (0.63, 17.16) [a]		8.99 (3.17, 25.52)	NR	
Resection rate						
Surgical resection rate, n/N (%)	NR	NR	NR	NR	NR	NR
Stratified odds ratio (95% CI)[a]	NR		NR		NR	
Complete R0 resection rate, n/N (%)	2/15 (13.3)	0/12 (0)	7/43 (16.3)	3/46 (6.5)	NR	NR
Stratified odds ratio (95% CI)[a]	NE			2.68 (0.63, 11.43)	NR	

Key: BEV = bevacizumab; CET = cetuximab; CI = confidence interval; FOLFIRI = 5-fluorouracil + folinic acid + irinotecan; FOLFOX = 5-fluorouracil + folinic acid + oxaliplatin; HR = hazard ratio; NE = not evaluable; NR = not reported; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; *RAS* = rat sarcoma; WT wild type

Notes: a Stratified hazard ratio (HR) / odds ratio (OR). Random assignment was stratified by (i) ECOG performance status (0 or 1 vs. 2) (OPUS), (ii) ECOG performance status (0 or 1 vs. 2) and region (sites in Western Europe vs.Eastern Europe vs. outside Europe) (CRYSTAL); (iii) ECOG performance status (0–1 or 2), number of metastatic sites (1 or >1), white blood cell count (<8 × 10^9 cells per L or ≥8 × 10^9 cells per L) and alkaline phosphatase con centration (<300 units per L or ≥300 units per L) (FIRE-3); b Assumption made that total N was total population with liver metastasis at baseline

Sources: Data on File (OPUS), Merck Serono UK Ltd; Data on File (CRYSTAL), Merck Serono UK Ltd; Heinemann et al., Lancet Oncol, 2014 (FIRE-3)

3.2.6.2. Panitumumab

Progression-free survival

Both of the included panitumumab trials reported progression free survival (PFS) in the *RAS* WT subgroup (**Douillard et al., 2013** [PRIME]; **Schwartzberg et al., 2014** [PEAK]).[38, 53] The definition of disease progression appears relatively consistent in both trials. In each case PFS was defined as the interval from random assignment of treatment to radiologic evidence of disease progression or death from any cause. Radiologic assessment of progression was assessed according to RECIST criteria (PRIME [**Douillard et al., 2013**]), AND peak [**Schwartzberg et al., 2014**]). The time-to-event data were summarised by stratified HR. A HR of <1 indicates an improvement in PFS for treatment compared with control.

Panitumumab plus FOLFOX4 vs. FOLFOX4

Douillard et al. (2013) (PRIME) reported median PFS as 10.1 months (95% CI 9.3, 12) and 7.9 months (95% CI 7.2, 9.3) for the panitumumab plus FOLFOX4 and FOLFOX4 arms respectively. The addition of panitumumab to FOLFOX4 was associated with a reduction in risk of progression of 28% (HR 0.72 [95% CI 0.58, 0.9]) (Table 20).[53]

Panitumumab plus mFOLFOX6 vs. bevacizumab plus mFOLFOX6

Schwartzberg et al. (2014) (PEAK) reported median PFS as 13 months (95% CI 10.9, 15.1) and 9.5 months (95% CI 9, 12.7) for the panitumumab plus mFOLFOX6 and bevacizumab plus FOLFOX4 arms respectively. The addition of panitumumab to mFOLFOX6 was associated with a reduction in risk of progression of 35% (HR 0.65 [95% CI 0.44, 0.96]) (Table 20).[38]

Table 20. Progression free survival (*RAS* WT [all loci]): Panitumumab trials

Author, year, TRIAL	Experimental (n/N) Median mths (95% CI)	Control (n/N) Median mths (95% CI)	HRa (95% CI)
Douillard, 2013 PRIME[a,b]	PAN+FOLFOX4 (156/259) 10.1 (9.3, 12)	FOLFOX4 (170/253) 7.9 (7.2, 9.3)	0.72 (0.58, 0.9)
Schwartzberg, 2014 PEAK[a]	PAN+mFOLFOX6 (50/88) 13 (10.9, 15.1)	BEV+mFOLFOX6 (60/82) 9.5 (9, 12.7)	0.65 (0.44, 0.96)

Key: BEV = bevacizumab; CI = confidence interval; FOLFOX = folinic acid + fluorouracil + oxaliplatin; FOLFIRI = folinic acid + fluorouracil + irinotecan; HR= hazard ratio; mFOLFOX – modified folinic acid + fluorouracil = oxaliplatin; mths = months; PAN = panitumumab; RAS = rat sarcoma; WT = wild type

Notes: a Stratified hazard ratio (HR). Random assignment was stratified by (i) ECOG performance status (0 or 1 vs. 2) and region (sites in Western Europe, Canada, and Australia vs. rest of world (PRIME); (ii) prior adjuvant oxaliplatin therapy (PEAK); (b) Data cut-off date (primary analysis), 30 September 2008; c Amgen also report results from an updated analysis 2 Aug 2010 in the company submission as academic in confidence: [redacted]

Sources: Douillard et al. N Engl J Med, 2013 (PRIME); Schwartzberg et al. J Clin Oncol, 2014 (PEAK)

Overall survival

Both of the included panitumumab trials reported OS for the *RAS* WT subgroup (**Douillard et al., 2014** [PRIME]; **Schwartzberg et al., 2014** [PEAK]).[38, 53] In each case OS was defined as the interval from random assignment of treatment to death. The time-to-event data were summarised by stratified HR. A HR of <1 indicates an improvement in OS for treatment compared with control.

Panitumumab plus FOLFOX4 vs. FOLFOX4

Douillard et al. (2013) (PRIME) reported median OS as 25.8 months (95% CI 21.7, 29.7) and 20.2 months (95% CI 17.6, 23.6) for the panitumumab plus FOLFOX4 and FOLFOX4 arms respectively; HR 0.77 (95% CI 0.64, 0.94), favouring the panitumumab plus FOLFOX4 treatment group (Table 21).[53]

Panitumumab plus mFOLFOX6 vs. bevacizumab plus mFOLFOX6

Schwartzberg et al. (2014) (PEAK) reported median OS as 41.3 months (95% CI 28.8, 41.3) and 28.9 months (95% CI 23.9, 13.1) for the panitumumab plus mFOLFOX6 and bevacizumab plus mFOLFOX6 arms respectively; HR 0.63 (95% CI 0.39, 1.02), favouring the panitumumab plus mFOLFOX6 treatment group (Table 21).[38]

Table 21. Overall survival (*RAS* WT [all loci]): Panitumumab trials

Author, year, Trial	Experimental (n/N) Median mths (95% CI)	Control (n/N) Median mths (95% CI)	HRa (95% CI)
Douillard, 2013	PAN+FOLFOX4 (204/259)	FOLFOX4 (218/253)	0.77 (0.64, 0.94)
PRIME[a,b]	25.8 (21.7, 29.7)	20.2 (17.6, 23.6)	
Schwartzberg, 2014	PAN+mFOLFOX6 (30/88)	BEV+mFOLFOX6 (40/82)	0.63 (0.39, 1.02)
PEAK[a]	41.3 (28.8, 41.3)	28.9 (23.9, 31.3)	

Key: BEV = bevacizumab; CI = confidence interval; FOLFOX = folinic acid + fluorouracil + oxaliplatin; FOLFIRI = folinic acid + fluorouracil + irinotecan; HR= hazard ratio; mFOLFOX – modified folinic acid + fluorouracil = oxaliplatin; mths = months; PAN = panitumumab; RAS = rat sarcoma; ET = wild type

Notes: a Stratified hazard ratio (HR). Random assignment was stratified by (i) ECOG performance status (0 or 1 vs. 2) and region (sites in Western Europe, Canada, and Australia vs. rest of world (PRIME); (ii) prior adjuvant oxaliplatin therapy (PEAK); b OS update analysis (descriptive), data cut-off date 24 January 2013; c Amgen also report results from the final analysis 2 August 2010 in the company submission as academic in confidence: [redacted]

Sources: Douillard et al. N Engl J Med, 2013 (PRIME); Schwartzberg et al. J Clin Oncol, 2014 (PEAK)

Objective response rate

Data for objective response rate (ORR) were available from both included studies (**Douillard et al., 2014** [PRIME] and **Schwartzberg et al., 2014** [PEAK]). [38, 53]

Overall response rate was defined as the percentage of participants that achieved a partial or complete response as the best overall response according to radiological assessments. In both trials (**Douillard et al., 2014** [PRIME] and **Schwartzberg et al., 2014** [PEAK]), ORR was evaluated using Response Evaluation Criteria in Solid Tumours (RECIST) (Version 1.0); no independent review was performed.[38, 53] Tumour response evaluation was performed every eight weeks (± 7 days), and treatment was continued until disease progression, unacceptable toxicities, death, withdrawal of consent, or investigator decision, whichever was earlier.

The effect of treatment on response was measured as an odds ratio.

Best available response rate (i.e., CR, PR, SD, PD) is reported in Appendix H.

Panitumumab plus FOLFOX4 vs. FOLFOX4

Douillard et al. (**2014)** (PRIME) reported confirmed complete or partial tumour responses in [redacted] people ([redacted]) receiving panitumumab plus FOLFOX4 and in [redacted] people ([redacted]) receiving FOLFOX4 alone (Table 22). The adjusted odds ratio for a tumour response with the panitumumab plus FOLFOX4, as compared with FOLFOX4 alone, was [redacted]) (Table 22).[53]

Panitumumab plus mFOLFOX6 vs. bevacizumab plus mFOLFOX6

Schwartzberg et al. (2014) (PEAK) reported confirmed complete or partial tumour responses in 56 people (64%) receiving panitumumab plus mFOLFOX6 and in 49 people (61%) receiving FOLFOX alone (Table 22). The adjusted odds ratio for a tumour response with the panitumumab plus FOLFOX, as compared with mFOLFOX6 alone, was 1.08 (95% CI 0.55, 2.12) (Table 22).[38]

Table 22. Response rate (*RAS* WT [all loci]): Panitumumab trials

Author, year Trial	Experimental	n/N (% [95% CI])	Control	n/N (%, 95% CI)	OR[a] (95%CI)
Data on File, Amgen UK Ltd PRIME[a,b]	PAN+FOLFOX4	[redacted]	FOLFOX4	[redacted]	[redacted]
Schwartzberg, 2014 PEAK[a,b]	PAN+mFOLFOX6	56/88 (64 [53, 74])	BEV+mFOLFOX6	49/81 (61 [49, 71])	1.08 (0.55, 2.12)

Key: BEV = bevacizumab; CI = confidence interval; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; m= modified; OR = odds ratio; PAN = panitumumab
Notes: a Stratified hazard ratio (HR). Random assignment was stratified by (i) geographic region (Western Europe, Canada, and Australia v rest of the world) and ECOG PS (0 or 1 v 2) (PRIME); (ii) prior adjuvant oxaliplatin therapy (PEAK); b Timepoint measured not reported. Median duration follow-up: 22.31 (10.12, 35.65) months and 17.71 (8.74, 32.20) months for PAN+FOLFOX vs FOLFOX respectively (PRIME), and 14.97 (8.83, 22.81) months vs 14.93 (8.76, 21.39) months for PAN+FOLFOX vs BEV+FOLFOX respectively (PEAK); c Company submission uses slightly different data for the PAN+FOLFOX4 arm, 59% (95% CI 52% to 65%). Adjusted odds ratio was 1.63 (995% CI 1.13 to 2.38) in favour of PAN+FOLFOX 30 Sept 2008 data cut off. Data inTable 22 were prvided to the Assessment Group by Amgen.
Sources: Data on File (PRIME), Amgen UK Ltd; Schwartzberg et al. J Clin Oncol, 2014 (PEAK)

Rate of complete resection

Data for rate of complete resection with curative intent before disease progression were available from both of the included panitumumab trials (**Douillard et al., 2014** [PRIME] and **Schwartzberg et al., 2014** [PEAK]).[38, 53]

Rate of surgery with curative intent (with complete resection of all lesions [R0]) was defined as the number of subjects with any resection of metastasis of curative intent and all lesions completely resected to R0, divided by all subjects qualifying for the ITT population.

The effect of treatment on the likelihood of complete resection was measured as an odds ratio.

Panitumumab plus FOLFOX4 vs. FOLFOX4

No data were reported for the rate of complete resection in the PRIME trial publication (**Douillard et al., 2014** [PRIME]); however, data were provided as AiC by the manufacturer

(Table 23). The rate of R0 resection with curative intent before disease progression for metastases was higher in the panitumumab plus FOLFOX4 group ([redacted]) than in the FOLFOX4 group ([redacted]); OR [redacted]).[53]

Panitumumab plus mFOLFOX6 vs. bevacizumab plus mFOLFOX6

No data were reported for the rate of complete resection in the PEAK trial publication (**Schwartzberg et al., 2014** [PEAK]); however, data were provided as CiC by the manufacturer (Table 23). The rate of R0 resection with curative intent before disease progression for metastases was higher in the panitumumab plus mFOLFOX6 group (13%) than in the mFOLFOX6 group (11%); OR for panitumumab plus mFOLFOX6, 1. 61; 95% CI 0.45, 2.96; p=NR).[38]

Table 23. Rate of complete resection (*RAS* WT [all loci]): Panitumumab trials

Author, year Trial	Experimental	n/N (% [95%CI])	Control	n/N (% [95%CI]	OR[a] (95% CI)
Data on File, Amgen UK Ltd PRIME[b]	PAN+FOLFOX4	[redacted]	FOLFOX4	[redacted]	[redacted]
Schwartzberg, 2014 PEAK[b]	PAN+mFOLFOX6	11/88 (13 [6, 21])	BEV+mFOLFOX6	9/82 (11 [5, 20])	1.16 (0.45, 2.96)

Key: BEV = bevacizumab; CI = confidence interval; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; m = modified; OR = odds ratio; PAN = panitumumab
Notes: a Stratified hazard ratio (HR). Random assignment was stratified by (i) geographic region (Western Europe, Canada, and Australia v rest of the world) and ECOG PS (0 or 1 v 2) (PRIME); (ii) prior adjuvant oxaliplatin therapy (PEAK); b Timepoint measured not reported. Median duration follow-up: 22.31 (10.12, 35.65) months and 17.71 (8.74, 32.20) months for PAN+FOLFOX vs FOLFOX respectively (PRIME), and 14.97 (8.83, 22.81) months vs 14.93 (8.76, 21.39) months for PAN+FOLFOX vs BEV+FOLFOX respectively (PEAK)
Sources: Data on File (PRIME), Amgen UK Ltd; Data on File (PEAK), Amgen UK Ltd

Subgroup analyses: liver metastases at baseline

There were no planned subgroup analyses in the *RAS* WT population as the data for this population was obtained retrospectively. However, data for people with liver metastases at baseline were available from both of the included panitumumab trials (provided by the manufacturer), (**Douillard et al., 2014** [PRIME]; **Schwartzberg., 2014** [PEAK]).

Panitumumab plus FOLFOX4 vs. FOLFOX4

Among the *RAS* WT subgroup a total of 89 (17.6%) participants in the PRIME trial (**Douillard et al., 2014**) had metastasis to the liver at baseline. Results are summarised in Table 24. Complete resection was performed in 15/48 (31%) participants in the panitumumab plus FOLFOX4 arm and 7/41 (17%) participants in the FOLFOX4 alone arm;

odds ratio for panitumumab plus FOLFOX4 2.2 (95% CI 0.80, 6.10), favouring panitumumab plus FOLFOX4.

Panitumumab plus FOLFOX4 vs. bevacizumab plus FOLFOX4

Among the *RAS* WT subgroup a total of 45 (26.5%) participants in the PEAK trial (**Schwartzberg et al., 2014**) had metastasis to the liver at baseline. Results are summarised in Table 24. Complete resection was performed in [redacted] participants in the panitumumab plus mFOLFOX6 arm and [redacted] participants in the bevacizmab plus mFOLFOX6 arm; odds ratio for panitumumab plus mFOLFOX6 [redacted].

Table 24. Subgroup analyses by liver metastases (*RAS* WT [all loci]): Panitumumab trials

	PRIME		**PEAK**	
	PAN+FOLFOX4	FOLFOX4	PAN+mFOLFOX6	BEV+ mFOLFOX6
	(n=48)[c]	(n=41)[c]	[redacted]	[redacted]
PFS				
Progression/death events, n/N (%)	38/48 (79)	37/41 (90)	[redacted]	[redacted]
Median PFS, months (95% CI)	11.3 (9.4, 21.3)	9.9 (7.2, 12.9)	[redacted]	[redacted]
Stratified hazard ratio (95% CI)[a,b]	0.75 (0.48, 1.19)		[redacted]	
OS				
Deaths, n/N (%)	32/48 (67)	31/41 (76)	[redacted]	[redacted]
Median OS (95% CI)	40.7 (26.6, 51.7)	33.4 (19.4, 46.8)	[redacted]	[redacted]
Stratified hazard ratio (95% CI)[a,b]	0.71 (0.43, 1.16)		[redacted]	
ORR				
n/N, (%)	38/47 (81)	27/41 (66)	[redacted]	[redacted]
Stratified odds ratio (95% CI)[a,b]	2.18 (0.75, 6.41)		[redacted]	
Resection rate				
Surgical resection rate, n/N (%)	16/48 (33)	10/41 (24)	[redacted]	[redacted]
Stratified odds ratio (95% CI)[a,b]	1.55 (0.61, 3.94)		[redacted]	
Complete resection rate, n/N (%)	15/48 (31)	7/41 (17)	[redacted]	[redacted]
Stratified odds ratio (95% CI)[a,b]	2.2 (0.80, 6.10)		[redacted]	

Key: BEV = bevacizumab; CI = confidence interval; FOLFIRI = 5-fluorouracil + folinic acid + irinotecan; FOLFOX = 5-fluorouracil + folinic acid + oxaliplatin; HR = hazard ratio; m = modified; NE = not evaluable; NR = not reported; OR = odds ratio; ORR = objective response rate; OS = overall survival; PAN = panitumumab; PFS = progression-free survival; *RAS* = rat sarcoma; WT wild type

Notes: a Stratified hazard ratio (HR) / odds ratio (OR). Random assignment was stratified by (i) geographic region (Western Europe, Canada, and Australia v rest of the world) and ECOG PS (0 or 1 v 2), (ii) prior adjuvant oxaliplatin therapy; b Timepoint measured not reported. Median duration follow-up: 22.31 (10.12, 35.65) months and 17.71 (8.74, 32.20) months for PAN+FOLFOX vs FOLFOX respectively (PRIME), and 14.97 (8.83, 22.81) months vs 14.93 (8.76, 21.39) months for PAN+FOLFOX vs BEV+FOLFOX respectively (PEAK); c Company submission uses data cut-off 28 Aug 2009 data: N=90 15/49 (31%) people vs 7/41 (17%). Adjusted odds ratio 2.31 (95% CI 0.74, 7.66). Data in Table 24 were provided to the Assessment Group by Amgen

Sources: Data on File (PRIME), Amgen UK Ltd; Peeters et al. Markers in Cancer, 2013 Brussels Belgium; Data on File (PEAK), Amgen UK Ltd

3.2.7. Adverse events

Data for adverse events (AEs) from the *RAS* WT subgroup from the individual trials are reported below. Within each trial, the safety population comprised study participants who had received at least one dose of study drug. The most frequently reported AEs were as expected for the individual treatments based on the Summary of Product Characteristics (SmPC) for the interventions of interest for this review (cetuximab and panitumumab).

Adverse events in the included trials were coded using versions of the Medical Dictionary for Regulatory Activities (MedDRA). The National Cancer Institute Common Terminology Criteria (NCI-CTC) (see Table 25), frequently used by trials to report drug toxicities, was used to grade severity. For each AE, grades are assigned using a scale from 0 to 5. Grade 0 is defined as absence of AE or within normal limits for values. Grade 5 is defined as death associated with an AE. All of the included cetuximab and panitumumab trials used NCI-CTC AEs Version 3.0; see Table 25

Table 25. NCI-CTC for AEs

Grade	Description
0	No AE or within normal limits
1	Mild AE
2	Moderate AE
3	Severe AE
4	Life threatening or disabling AE
5	Death related to an AE

Key: AE, adverse event; NCI-CTC = National Cancer Institute Common Terminology Criteria
Source: Common Terminology Criteria for Adverse Events, National Cancer Institute, 2006

3.2.7.1. Cetuximab

All of the included trials reported AEs. Two trials reported any AEs and any serious AEs, (**Tejpar et al., 2015** [OPUS]; **Van Cutsem et al., 2015** [CRYSTAL]) one reported any Grade 1 or 2 events (**Van Cutsem et al., 2015** [CRYSTAL]) and all three trials reported any Grade 3 or 4 events (**Tejpar et al., 2015** [OPUS]; **Van Cutsem et al., 2015** [CRYSTAL]; **Heinemann et al., 2014** [FIRE-3]).

As *RAS* mutation status refers to the tumour only, the EMA concluded in their report that there were no good reasons to postulate differences in safety profiles related to *RAS* status other than from the perspective that people with *RAS* WT tumours would be treated for

longer periods of time. Taking small sample sizes into account, the assumption that safety is independent of tumour *RAS* status was considered to be in-line with reported data.[48]

Cetuximab plus FOLFOX4 vs. FOLFOX4

In the OPUS trial (**Tejpar et al., 2015**)[75] all AEs were recorded between the onset of or after the first day of study medication up to six weeks after the end of the last administration of study treatment. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) (Version 10.0), and summarised by worst severity per patient according to the National Cancer Institute Common Terminology Criteria (NCI-CTC) for AEs (Version 3.0). Only AEs with a frequency of ≥5% in either treatment group were reported.

Incidences of any AEs were the same in both treatment arms (100% in each arm) (Table 26). However, both Grade 3 or 4 AEs and serious AEs were more commonly reported in the cetuximab plus FOLFOX4 arm (79% and 39.5% respectively) when compared to the FOLFOX4 arm (63% and 16% respectively). More specifically, commonly reported Grade 3 and 4 AEs included; diarrhoea, leukopenia, neutropenia, paraesthesia, peripheral sensory neuropathy, rash, any skin reactions and acne-like rash skin reaction. Incidences of which, were similar between treatment arms except for the skin reactions (any and acne-like) which were higher in the cetuximab plus FOLFOX4 arm (skin reaction any,13% vs 0%; skin reaction acne-like, 8% vs 0%) and paresthesia which was higher in the FOLFOX4 arm (0% vs 6%).

All AEs reported were noted as likely to occur by the SmPC and consistent with the known safety profile of cetuximab.

Cetuximab plus FOLFIRI vs. FOLFIRI

In the CRYSTAL trial (**Van Cutsem et al., 2015**) [52] AEs were recorded continuously and categorised according to the MedDRA Version 10.0. The severity of AEs were assessed according to the NCI-CTC AEs (Version 3.0).[33] Only AEs with a frequency of ≥5% in either treatment group were reported.

Incidences of any AEs were slightly higher in the cetuximab plus FOLFIRI (100%) when compared to FOLFIRI arm (98.9%; Table 27). Any Grade 1 or 2 AEs were more frequently reported in the FOLFIRI arm (41.8%) in comparison to the cetuximab plus FOLFIRI arm (19.1%). Whereas both Grade 3 or 4 AEs and serious AEs were more commonly reported in the cetuximab plus FOLFIRI arm (80.9% and 38.8% respectively) when compared to the

FOLFIRI arm (58.2% and 32.8% respectively). More specifically, commonly reported Grade 3 and 4 AEs included; deep vein thrombosis, dermatitis acneiform, diarrhoea, fatigue, leukopenia, neutropenia, infusion-related reaction, any skin reactions and acne-like rash skin reaction. Incidences of which, were all higher in the cetuximab plus FOLFIRI arm when compared to the FOLFIRI arm. Incidences were most notably higher for any skin reactions (20.8% vs 0.5%); skin reaction acne-like (16.9% vs 0 %); neutripenua (30.9% vs 20.1%) and rash (9% vs 0%).

All AEs reported were noted as likely to occur by the SmPC and consistent with the known safety profile of cetuximab.

Cetuximab plus FOLFIRI vs. bevacizumab plus FOLFIRI

In the FIRE-3 trial (**Heinemann et al., 2014**)[37] AEs were recorded continuously from enrolment to the end of the final study visit and were coded by the MedDRA (Version 13.1), and classified and graded according to the NCI-CTC AEs. Only AEs with a frequency of ≥5% in either treatment group were reported. Information on the safety population definition was not available.

Incidences of any Grade 3 or 4 AEs were similar between cetuximab plus FOLFIRI (69.0%) and bevacizumab plus FOLFIRI (67.3%), other subcategories for AEs were not reported. More specifically, commonly reported Grade 3 and 4 AEs included; acneiform/exanthema, desquamation, diarrhoea, haematotoxicity, hepatotoxicity, hypertension, hypokalemia, infection, mucositis/stomatitis, nail changes/paronychia, nausea, pain, skin reactions, thromboembolic events and thrombosis (any). Incidences of which, were all comparable between the two arms except for the following AEs which were higher in the cetuximab plus FOLFIRI arm when compared to bevacizumab plus FOLFIRI: skin reactions (28.7% vs. 2.9%); nail changes/paronychia (7.0% vs. 0%); desquamation (7% vs. 0.6%) and acneiform/exanthema (19.3 % vs. 0%).

Specific AEs which were classified as Grade 1 or 2 in severity were also available for **Heinemann et al., 2014** (FIRE-3)**,** a summary of which is provided in Appendix H.

Table 26. Adverse events (reported at a frequency of ≥5% in either treatment group) (*RAS* WT [all loci]): Cetuximab trials

	OPUS[a,c,d]		**CRYSTAL**[a,c]		**FIRE-3**[b,d]	
	CET+FOLFOX4 (n=38)	FOLFOX4 (n=49)	CET+FOLFIRI (n=178)	FOLFIRI (n=189)	CET+FOLFIRI (n=171)	BEV+FOLFIRI (n=171)
Any AE, n/N (%)	38/38 (100)	49/49 (100)	178/178 (100)	187/189 (98.9)	NR	NR
Worst grade of 3, n/N (%)	NR	NR	NR	NR	NR	NR
Worst grade of 4, n/N (%)	NR	NR	NR	NR	NR	NR
Worst grade of 5, n/N (%)	NR	NR	NR	NR	NR	NR
Any Grade 1 or 2 event, n/N (%)	NR	NR	34/178 (19.1)	79/189 (41.8)	NR	NR
Any Grade 3 or Grade 4 event, n/N (%)	30/38 (79)	31/49 (63)	144/178 (80.9)	110/189 (58.2)	118/171 (69)	115/171 (67.3)
Any serious AE, n/N (%)	15/38 (39.5)	8/49 (16)	69/178 (38.8)	62/189 (32.8)	NR	NR

Key: AE = adverse event; BEV = bevacizumab; CET = cetuximab; CTC = Common Terminology Criteria; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; MedDRA = Medical Dictionary for Regulatory Activities; NR = not reported; *RAS* = rat sarcoma; Vn = Version; WT = wild type

Notes: a Participants were observed for safety 30 days after last study drug administration; b Participants were observed for safety approximately 6 months after randomisation; c MedDRA Vn 10.0 terms, with special emphasis on Grade 3 and 4 toxic effects according to the National Cancer Institute – CTC for AEs, Vn 3.0; b MedDRA Vn 12.0 terms (except composite categories which use MedDRA Vn 10.0 terms), with special emphasis on Grade 3 and 4 toxic effects according to the National Cancer Institute – CTC for AEs Vn 2.0; d MedDRA Vn 13.1 preferred terms, with special emphasis on Grade 3 and 4 toxic effects according to the National Cancer Institute – CTC for AEs Vn 3.0

Sources: Tejpar et al., Eur J Cancer, 2015 (OPUS); Data on File (OPUS), Merck Serono UK Ltd; Van Cutsem et al., J Clin Oncol, 2015 (CRYSTAL); Data on File (CRYSTAL), Merck Serono UK Ltd; Data on File (FIRE-3), Merck Serono UK Ltd

Table 27. Incidence of Grade 3 or 4 adverse events (reported at a frequency of ≥5% in either treatment group) (*RAS* WT [all loci]): Cetuximab trials[a]

	OPUS[a,b]		CRYSTAL[a,c]		FIRE-3[a,d]	
	CET+FOLFOX4 (n=38)	FOLFOX4 (n=49)	CET+FOLFIRI (n=178)	FOLFIRI (n=189)	CET+FOLFIRI (n=171)	BEV+FOLFIRI (n=171)
Acneiform/Exanthema, n/N (%)	–	–	–	–	33/171 (19.3)	0/171 (0)
Deep vein thrombosis, n/N (%)	–	–	11/178 (6.2)	1/189 (0.5)	–	–
Dermatitis acneiform, n/N (%)	–	–	9/178 (5.1)	0/189 (0)	–	–
Desquamation, n/N (%)	–	–	–	–	12/171 (7.0)	1/171 (0.6)
Diarrhoea, n/N (%)	[redacted]	[redacted]	26/178 (14.6)	18/189 (9.5)	18/171 (10.5)	24/17 (14.0)
Fatigue, n/N (%)	–	–	12/178 (6.7)	9/189 (4.8)	–	–
Haematotoxicity, n/N (%)	–	–	–	–	47/171 (27.5)	37/171 (21.6)
Hepatotoxicity, n/N (%)	–	–	–	–	9/171 (5.3)	9/171 (5.3)
Hypertension, n/N (%)	–	–	–	–	11/171(6.4)	12/171 (7.0)
Hypokalemia, n/N (%)	–	–	–	–	17/171 (9.0)	7/171 (4.1)
Infection, n/N (%)	–	–	–	–	16/171 (9.4)	15/171 (8.8)
Leukopenia, n/N (%)	1/38 (3)	3/49 (6)	15/178 (8.4)	7/189 (3.7)	–	–
Mucositis/Stomatitis, n/N (%)	–	–	–	–	8/171 (4.7)	6/171 (3.5)
Nail Changes / Paronychia, n/N (%)	–	–	–	–	12/171 (7.0)	0/171 (0)
Nausea, n/N (%)	–	–	–	–	6/171 (3.5)	9/171 (5.3)
Neurotoxicity, n/N (%)	[redacted]	[redacted]	–	–	–	–
Neutropenia, n/N (%)	[redacted]	[redacted]	55/178 (30.9)	38/189 (20.1)	–	–
Pain, n/N (%)	[redacted]	[redacted]	–	–	6/171 (3.5)	10/171 (5.7)

	OPUS[a,b]		CRYSTAL[a,c]		FIRE-3[a,d]	
	CET+FOLFOX4 (n=38)	FOLFOX4 (n=49)	CET+FOLFIRI (n=178)	FOLFIRI (n=189)	CET+FOLFIRI (n=171)	BEV+FOLFIRI (n=171)
Paresthesia, n/N (%)	[redacted]	[redacted]	–	–	–	–
Rash, n/N (%)	[redacted]	[redacted]	16/178 (9.0)	0/189 (0)	–	–
Skin reactions, n/N (%)	–	–	–	–	49/171 (28.7)	5/171 (2.9)
Thromboembolic event, n/N (%)	–	–	–	–	8/171 (4.7)	12/171 (7.0)
Thrombosis (any), n/N (%)	–	–	–	–	10/171 (5.8)	13/171 (7.6)
COMPOSITE CATEGORIES						
Infusion-related reaction, n/N (%)	–	–	4/178 (2.2)	0/189 (0)	–	–
Skin reactions						
any, n/N (%)	5/38 (13)	0/49 (0)	37/178 (20.8)	1/189 (0.5)	–	–
acne-like rash, n/N (%)	3/38 (8)	0/49 (0)	30/178 (16.9)	0/189 (0)	–	–

Key: AE = adverse event; BEV = bevacizumab; CET = cetuximab; CTC = Common Terminology Criteria; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; MedDRA = Medical Dictionary for Regulatory Activities; NR = not reported; RAS = rat sarcoma; Vn = Version; WT = wild type

Notes: a For trials OPUS and CRYSTAL: data reported for most common Grade 3 or 4 adverse events reported at a frequency of ≥5% in either treatment group according to composite categories of special interest, and for FIRE-3 data reported for Grade 3 or 4 adverse events reported at a frequency of ≥5% in either treatment group; b MedDRA Vn 10.0 terms, with special emphasis on Grade 3 and 4 toxic effects according to the National Cancer Institute – CTC, Vn 2.0; c MedDRA Vn 12.0 terms (except composite categories which use MedDRA Vn 10.0 terms), with special emphasis on Grade 3 and 4 toxic effects according to the National Cancer Institute – CTC, Vn 2.0; d MedDRA Vn 13.1 preferred terms, with special emphasis on Grade 3 and 4 toxic effects according to the National Cancer Institute – CTC, Vn 3.0

Sources: Tejpar et al., Eur J Cancer, 2015 (OPUS); Van Cutsem et al., J Clin Oncol, 2015 (CRYSTAL); Data on File (PEAK), Amgen UK Ltd

3.2.7.2. Panitumumab

Data were available for AEs from both the PRIME and PEAK trials (**Douillard et al., 2013** [PRIME],and **Schwartzberg et al., 2014** [PEAK]).[38, 53] Both trials reported any AEs, AEs with a worst Grade of 3, AEs with a worst Grade of 4, AEs with a worst Grade of 5, any Grade 1 or 2 AEs, any Grade 3 or 4 AEs and any serious adverse events (SAEs). Adverse events with a worst Grade of 1 or 2 and AEs with a worst Grade of 3 or 4 were available from the PEAK trial (**Schwartzberg et al., 2014**) but not from the PRIME trial (**Douillard et al., 2013**).[38, 53]

The EMA concluded that no new safety concerns were identified for the safety profile of panitumumab in people with *RAS WT* tumour status as these people were indistinguishable from people with *KRAS* WT tumour status.

Panitumumab plus FOLFOX4 vs. FOLFOX4

In the PRIME trial (**Douillard et al., 2013**) [53] people were followed for safety 30 days after the last study drug administration. Adverse events were coded using the MedDRA (Version 15.0), and were graded for severity using the NCI-CTC AEs (Version3.0) with modifications for specific skin- and nail-related toxicities. The safety population comprised of people who received at least one dose of the protocol therapy. Only AEs with a frequency of ≥5% in either treatment group were reported.

Similar incidences were found between the arms panitumumab plus FOLFOX4 and FOLFOX4 (Table 28), for any AEs (100 % vs 99%), AEs with a worst Grade of 3 (57% vs 50%), AEs with a worst Grade of 4 (28% vs 20%), AEs with a worst Grade of 5 (5% vs 6%), any Grade 1 or 2 events (10% vs. 22%), any Grade 3 or 4 AEs (85% vs 70%) and any SAEs (43% vs 37%). More specifically, commonly reported Grade 3 and 4 AEs included (Table 29); abdominal pain, anaemia, asthenia, dermatitis acneiform, diarrhoea, fatigue, hypokalemia, hypomagnesemia, mucosal inflammation, neuropathy peripheral, neutropenia, paraesthesia, rash and stomatitis. Incidences of which, were similar between treatment arms except for the following AEs which were higher in the panitumumab plus FOLFOX4 arm when compared to the FOLFOX4 arm: dermatitis acneiform ([redacted] diarrhoea ([redacted] and rash ([redacted]) the skin reactions (any and acne-like).

Specific Grade 1 or 2 AEs were also available for **Douillard et al. (2013)** (PRIME)**,** a summary of which is provided in Appendix H.

Panitumumab plus mFOLFOX6 vs. Bevacizumab plus mFOLFOX6

In the PEAK trial (**Schwartzberg et al., 2014**)[38] people were followed for safety 30 days after the last study drug administration. Adverse events were coded using the MedDRA (Version 15.0), and were graded for severity using the NCI-CTC AEs (Version 3.0) with modifications for specific skin- and nail-related toxicities. The safety population was comprised of people who received at least one dose of the protocol therapy. Only AEs with a frequency of ≥5% in either treatment group were reported. [38]

Incidences of any AEs and any Grade 1 and 2 AEs were the same in both treatment arms (100% in each). Similar incidences were also found between the arms panitumumab plus mFOLFOX6 and bevacizumab plus mFOLFOX6 (Table 28) for: AEs with a worst Grade of 3 (70% vs 54%), AEs with a worst Grade of 4 (20% vs. 19%), AEs with a worst Grade of 5 (5% vs 9%), worst Grade 1 or 2 AEs (6% vs. 19%), worst Grade 3 or 4 AEs (90% vs. 73%), any Grade 3 or 4 AEs (93% vs. 81%) and any SAEs (43% vs. 39%). More specifically, commonly reported Grade 3 and 4 AEs included (Table 29); asthenia, decreased appetite, deep vein thrombosis, dehydration, diarrhoea, fatigue, hypertension, hypokalemia, hypomagnesemia, mucosal inflammation, neuropathy peripheral, neutropenia, paraesthesia, periperhal sensory neuropathy, polyneuropathy, pulmonary embolism, rash, skin disorders and stomatitis. Incidences of which, were similar between treatment arms except for the following AEs which were higher in the panitumumab plus mFOLFOX6 arm when compared to the bevacizumab plus mFOLFOX6 arm: rash (14% vs. 0%) and skin disorders (34% vs. 1%).

Specific Grade 1 or 2 AEs were also available for **Schwartzberg et al. (2014)** (PEAK)**,** a summary of which is provided in Appendix H.

Table 28. Adverse events (reported at a frequency of ≥5% in either treatment group) (*RAS* WT [all loci]): Panitumumab trials

	PRIME[a,b,c]		**PEAK**[a,b]	
	PAN+FOLFOX4 (n=250)	FOLFOX4 (n=250)	PAN+mFOLFOX6 (n=86)	BEV+mFOLFOX6 (n=80)
Any AE, n/N (%)	250/250 (100)	247/249 (99)	86/86 (100)	80/80 (100)
Worst Grade of 3, n/N (%)	142/250 (57)	125/249 (50)	60/86 (70)	43/80 (54)
Worst Grade of 4, n/N (%)	70/250 (28)	50/249 (20)	17/86 (20)	15/80 (19)
Worst Grade of 5, n/N (%)	13/250 (5)	16/249 (6)	4/86 (5)	7/80 (9)
Worst Grade 1 or 2 event, n/N (%)	NR	NR	5/86 (6)	15/80 (19)
Worst Grade 3 or Grade 4 event, n/N (%)	NR	NR	77/86 (90)	58/80 (73)
Any Grade 1 or 2 event, n/N (%)	25/250 (10)	56/249 (22)	86/86 (100)	80/80 (100)
Any Grade 3 or Grade 4 event, n/N (%)	212/250 (85)	175/249 (70)	80/86 (93)	65/80 (81)
Any serious AE, n/N (%)	108/250 (43)	92/249 (37)	37/86 (43)	31/80 (39)

Key: AE = adverse event; BEV = bevacizumab; CTC = Common Terminology Criteria; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX4 = folinic acid + fluorouracil + oxaliplatin; mFOLFOX6 = modified folinic acid + fluorouracil + oxaliplatin; MedDRA = Medical Dictionary for Regulatory Activities; NR = not reported; PAN = panitumumab; *RAS* = rat sarcoma; Vn = Version; WT = wild type

Notes: a Participants were observed for safety 30 days after the last study drug administration; b Adverse events were coded using MedDRA Vn 15.0, severity graded according to the National Cancer Institute – CTC for Adverse Events (Vn 3.0) with modifications for specific skin- and nail-related toxicities. Fatal adverse events were classified as Grade 5; c Data cut-off date 24 January 2013

Sources: Data on File (PRIME), Amgen UK Ltd; Schwartzberg et al. J Clin Oncol, 2014 (PEAK); Data on File (PEAK), Amgen UK Ltd

Table 29. Incidence of Grade 3 or 4 adverse events (reported at a frequency of ≥5% in either treatment group) (*RAS* WT [all loci]): Panitumumab trials

	PRIME[a,b]		PEAK[a,b]	
	PAN+FOLFOX4 (n=250)	FOLFOX4 (n=249)	PAN+mFOLFOX6 (n=86)	BEV+mFOLFOX6 (n=80)
Abdominal pain, n/N (%)				
Anaemia, n/N (%)				
Asthenia, n/N (%)				
Decreased appetite, n/N (%)				
Deep vein thrombosis, n/N (%)				
Dehydration, n/N (%)				
Dermatitis acneiform, n/N (%)				
Diarrhoea, n/N (%)				
Fatigue, n/N (%)				
Hypertension, n/N (%)				
Hypokalemia, n/N (%)				
Hypomagnesemia, n/N (%)				
Mucosal inflammation, n/N (%)				
Neuropathy peripheral, n/N (%)				
Neutropenia, n/N (%)				
Paraesthesia, n/N (%)				
Peripherhal sensory neuropathy, n/N (%)				
Polyneuropathy, n/N (%)				

	PRIME[a,b]		PEAK[a,b]	
	PAN+FOLFOX4 (n=250)	**FOLFOX4 (n=249)**	**PAN+mFOLFOX6 (n=86)**	**BEV+mFOLFOX6 (n=80)**
Pulmonary embolism, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Rash, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Skin disorders[c], n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Stomatitis, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]

Key: AE = adverse event; BEV = bevacizumab; CTC = Common Terminology Criteria; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX4 = folinic acid + fluorouracil + oxaliplatin; mFOLFOX6 = modified folinic acid + fluorouracil + oxaliplatin; MedDRA = Medical Dictionary for Regulatory Activities; NR = not reported; PAN = panitumumab; *RAS* = rat sarcoma; Vn = Version; WT = wild type

Notes: * Of Grade 3 or 4 AEs reported in at ≥5% participants in either treatment arm, * indicates a difference >5% between treatment arms; a Participants were observed for safety 30 days after the last study drug administration; b Adverse events were coded using MedDRA Vn 15.0, severity graded according to the National Cancer Institute – CTC for Adverse Events (Vn 3.0) with modifications for specific skin- and nail-related toxicities. Fatal adverse events were classified as Grade 5; c Skin disorders includes multiple terms from the skin and subcutaneous tissue disorders system organ class per MedDRA Vn 15.0

Sources: Data on File (PRIME). Amgen UK Ltd; Schwartzberg et al.J Clin Oncol, 2014 (PEAK); Data on File (PEAK), Amgen UK Ltd.

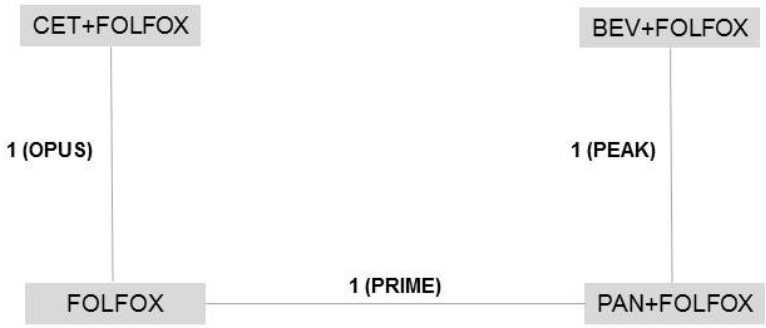
3.3. Network meta-analysis

To inform the decision problem, a network-meta-analysis (NMA) was carried out. Based on trials identified, it was not possible to construct a complete network. Two discrete networks were generated, one evaluating FOLFOX-containing chemotherapy regimens and the second comparing FOLFIRI-containing chemotherapy regimens. It should be stressed that results from the two discrete networks are not directly comparable.

3.3.1. FOLFOX regimens

Three RCTs (PRIME [**Douillard et al., 2014**], PEAK [**Schwartzberg et al., 2014**], and OPUS [**Tejpar et al., 2014**]), contributed to estimating the effectiveness of four treatments (FOLFOX, bevacizumab plus FOLFOX [BEV+FOLFOX], panitumumab plus FOLFOX [PAN+FOLFOX], and cetuximab plus FOLFOX [CET+FOLFOX]). As there was no direct evidence for CET+FOLFOX vs PAN+FOLFOX, the network meta-analysis allowed indirect estimation of this comparison. The network diagram – including which trials informed the network meta-analysis for each outcome of interest – is shown in Figure 5.

Figure 5. Network diagram for the FOLFOX network



		PFS	OS	ORR	Resection rate	Any Grade 1/2 AE	Any Grade 3/4 AE	SAE	AE by type
RAS WT	OPUS	✓	✓	✓	X	X	✓	✓	✓[a]
	PRIME	✓	✓	✓	✓	✓	✓	✓	✓[a]
	PEAK	✓	✓	✓	✓	X	✓	✓	✓[a]
RAS WT + liver metastasis at baseline	OPUS	✓	✓	✓	X	X	X	X	X
	PRIME	✓	✓	✓	✓[b]	X	X	X	X
	PEAK	✓	✓	✓	✓[b]	X	X	X	X

Key: AE = adverse event; BEV = bevacizumab; CET = cetuximab; FOLFOX = folinic acid + fluorouracil + oxaliplatin; OS = overall survival; ORR = overall response rate; PFS = progression-free survival; *RAS* = rat sarcoma; SAE = serious adverse event; WT = wild type

Notes: Adverse events based on incidence rates reported in the trials (occurring in ≥5% participants in either treatment arm); For the purposes of the network meta-analysis skin conditions included: acneiform exanthema, dermatitis acneiform, desquamation, nail changes/paronychia, skin reactions, and skin disorders based on rates reported in the included trials. Rash was treated separately. As composite reactions appeared to include conditions also reported by specialist preferred term these were excluded from the analysis. Incidence rates are reported in Section 3.2.7.1 (p120; cetuximab), and Section 3.2.7.2 (p126; panitumumab); a All trials (OPUS, PRIME and PEAK) informed the network meta-analysis for: Grade 3/4 neutropenia, paresthesia, rash, and skin conditions occurring in ≥5% participants in either treatment arm; and, Two trials (PRIME and PEAK) informed the network meta-analysis for Grade 3/4 diarrhoea, hypokalemia, hypomagnesemia, mucositis/stomatitis, mucosal inflammation, fatigue, neuropathy, and asthenia occurring in ≥5% participants in either treatment arm; b Data available to inform network meta-analysis for both surgical resection rate (partial and complete resection) and complete resection rate

3.3.1.1. Progression free survival

All three RCTs contributed to the estimation of PFS. The network meta-analysis found no evidence to suggest that CET+FOLFOX is any more effective than PAN+FOLFOX at increasing the time to progression or death (HR 0.74 (95% CrI 0.36, 1.49), see Table 30); however, CET+FOLFOX had a high probability (80%) of being the most effective treatment compared to the other treatments. Nevertheless, as the upper 95% CrI for CET+FOLFOX compared to all of the other treatments are >1, it is possible that CET+FOLFOX could be associated with greater progression or death than FOLFOX, BEV+FOLFOX or PAN+FOLFOX.

The direct evidence from PRIME and PEAK suggest that PAN+FOLFOX is more effective than FOLFOX (HR 0.72 (95% CrI 0.58, 0.90)) and BEV+FOLFOX (HR 0.65 (95% CrI 0.44, 0.96)).

Table 30. Hazard ratio* (and 95% CrI) for progression or death from a fixed effects network meta-analysis model

	Comparator treatment			Probability ranked			
Intervention treatment	FOLFOX	BEV+FOLFOX	PAN+FOLFOX	1st	2nd	3rd	4th
FOLFOX				<1%	2%	66%	32%
BEV+FOLFOX	1.11 (0.71, 1.73)			<1%	4%	29%	67%
PAN+FOLFOX	0.72 (0.58, 0.90)**	0.65 (0.44, 0.96)***		20%	79%	1%	<1%
CET+FOLFOX	0.53 (0.27, 1.04)****	0.48 (0.21, 1.07)	0.74 (0.36, 1.49)	80%	15%	3%	2%

Key: BEV = bevacizumab; CET = cetuximab; CrI = credible interval; FOLFOX = folinic acid + fluorouracil + oxaliplatin; HR = hazard ratio; PAN = panitumumab
Notes: * HR <1 favours 'Intervention' treatment; ** direct evidence from PRIME; *** direct evidence from PEAK; ****direct evidence from OPUS

3.3.1.2. Overall survival

All three RCTs contributed to the estimation of OS. The analysis suggests that there is no evidence that PAN+FOLFOX is more effective than CET+FOLFOX (HR 1.22 (95% CrI 0.71, 2.11), Table 31) since the upper 95% CrI is greater than 1.

The direct evidence from PRIME suggests that PAN+FOLFOX is more effective than FOLFOX (HR 0.77 (95% CrI 0.64, 0.93)).

Table 31. Hazard ratio* (and 95% CrI) for death from a fixed effects network meta-analysis model

	Comparator treatment			Probability ranked			
Intervention treatment	FOLFOX	BEV+FOLFOX	PAN+FOLFOX	1st	2nd	3rd	4th
FOLFOX				<1%	32%	55%	13%
BEV+FOLFOX	1.22 (0.73, 2.05)			2%	12%	18%	67%
PAN+FOLFOX	0.77 (0.64, 0.93)**	0.63 (0.39, 1.02)***		74%	25%	<1%	<1%
CET+FOLFOX	0.94 (0.56, 1.57)****	0.77 (0.37, 1.59)	1.22 (0.71, 2.11)	24%	31%	26%	19%

Key: BEV = bevacizumab; CET = cetuximab; CrI = credible interval; FOLFIRI = folinic acid + fluourouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; PAN = panitumumab
Notes: * HR <1 favours 'Intervention' treatment; ** direct evidence from PRIME; *** direct evidence from PEAK; ****direct evidence from OPUS

3.3.1.3. Objective response rate

All three RCTs contributed to the estimation of ORR. Objective response rate was measured at either six- or eight-week intervals (according to methods reported in the primary publications). However, due to differences in the reporting of the timing of ORR in each study it is unclear whether the timings are entirely comparable across studies. Given this uncertainty, results reported for the RAS WT population for this outcome should be treated with caution.

The network meta-analysis suggests that there is little evidence that CET+FOLFOX is any more effective than PAN+FOLFOX for overall response rate (HR 1.90 (95% CrI 0.72, 5.02), see Table 32).

Table 32. Odds ratio* (and 95% CrI) for ORR from a fixed effects network meta-analysis model

	Comparator treatment			Probability ranked			
Intervention treatment	FOLFOX	BEV+FOLFOX	PAN+FOLFOX	1st	2nd	3rd	4th
FOLFOX				<1%	<1%	11%	88%
BEV+FOLFOX	1.62 (0.75, 3.51)			9%	34%	46%	11%
PAN+FOLFOX	[redacted]	1.08 (0.55, 2.12)***		6%	57%	37%	<1%
CET+FOLFOX	3.33 (1.36, 8.12)****	2.05 (0.63, 6.70)	1.90 (0.72, 5.02)	85%	9%	6%	<1%

Key: BEV = bevacizumab; CET = cetuximab; CrI = credible interval; FOLFOX = folinic acid + fluorouracil + oxaliplatin; OR = odds ratio; ORR = overall response rate; PAN = panitumumab
Notes: * OR >1 favours 'Intervention' treatment; ** direct evidence from PRIME; *** direct evidence from PEAK; ****direct evidence from OPUS

3.3.1.4. Resection rates

Only data from the PRIME and PEAK trials are available to analyse resection rates, therefore a comparison with CET+FOLFOX cannot be made. The data suggests there is little difference in resection rates between the treatments as the 95% CrIs all include 1 (Table 33).

Table 33. Odds ratio* (and 95%CrI) for resection rate calculated from a fixed effects network meta-analysis model

	Comparator treatment		Probability ranked		
Intervention treatment	FOLFOX	BEV+FOLFOX	1st	2nd	3rd
FOLFOX			18%	35%	46%
BEV+FOLFOX	1.04 (0.35, 3.10)		35%	21%	44%
PAN+FOLFOX	[redacted]	1.61 (0.45, 2.98)***	47%	44%	9%

Key: BEV = bevacizumab; CrI = credible interval; FOLFOX = folinic acid + fluorouracil + oxaliplatin; OR = odds ratio; ORR = overall response rate; PAN = panitumumab
Notes: * OR >1 favours 'Intervention' treatment; ** direct evidence from PRIME; *** direct evidence from PEAK;

3.3.1.5. Adverse events

The indirect evidence suggests no difference in the odds ratios (ORs) for any Grade 3/4 AEs or any serious AEs between CET+FOLFOX and PAN+FOLFOX (see Table 34 and Table 35). However, PAN+FOLFOX is estimated (from direct evidence) to be associated with more

Grade 3/4 AEs than FOLFOX or BEV+FOLFOX. However, the evidence is less clear for CET+FOLFOX vs FOLFOX or BEV+FOLFOX since the 95% CrIs include 1 (see Table 34).

Table 34. Odds ratio* (and 95% CrI) for any Grade 3/4 AEs[a] from a fixed effects network meta-analysis model

	Comparator treatment			Probability ranked			
Intervention treatment	FOLFOX	BEV+FOLFOX	PAN+FOLFOX	1st	2nd	3rd	4th
FOLFOX				34%	63%	3%	0%
BEV+FOLFOX	0.81 (0.24, 2.43)			64%	28%	8%	<1%
PAN+FOLFOX	2.58 (1.59, 4.30)**	3.20 (1.21, 9.56)***		0%	<1%	40%	60%
CET+FOLFOX	2.24 (0.85, 6.24)****	2.80 (0.64, 13.34)	0.86 (0.29, 2.69)	2%	9%	49%	40%

Key: AEs = adverse events; BEV = bevacizumab; CET = cetuximab; CrI = credible interval; FOLFOX = folinic acid + fluorouracil + oxaliplatin; OR = odds ratio; PAN = panitumumab
Note: * OR <1 favours 'Intervention' treatment; ** OR calculated from study arm data from PRIME; *** OR calculated from study arm data from PEAK; **** OR calculated from study arm data from OPUS; a Reported in ≥5% participants in either treatment arm

Table 35. Odds ratio* (and 95% CrI) for any serious AEs[a] from a fixed effects network meta-analysis model

	Comparator treatment			Probability ranked			
Intervention treatment	FOLFOX	BEV+FOLFOX	PAN+FOLFOX	1st	2nd	3rd	4th
FOLFOX				57%	37%	6%	<1%
BEV+FOLFOX	1.09 (0.53, 2.23)			40%	31%	26%	2%
PAN+FOLFOX	1.30 (0.91, 1.86)**	1.19 (0.64, 2.24)***		2%	31%	64%	2%
CET+FOLFOX	3.45 (1.28, 9.88)****	3.18 (0.94, 11.33)	2.66 (0.93, 8.05)	<1%	1%	3%	95%

Key: AEs = adverse events; BEV = bevacizumab; CET = cetuximab; CrI = credible interval; FOLFIRI = folinic acid + fluourouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; OR = odds ratio; PAN = panitumumabNote: * OR <1 favours 'Intervention' treatment; a Reported in ≥5% participants in either treatment arm

The results of analyses of specific Grade 3/4 AEs are shown below. The available information allows estimation of the ORs for CET+FOLFOX versus PAN+FOLFOX for neutropenia (Table 36), paresthenia (Table 37), rash (Table 38), and skin conditions (Table

39). The estimated ORs (and 95% CrIs) suggest that there is little difference between the number of individuals experiencing those AEs for CET+FOLFOX and PAN+FOLFOX. Note that for the outcomes of rash and skin conditions, the 95% CrIs are very wide due to the low number of events reported in all three RCTs.

Table 36. Odds ratio* (and 95% CrI) for Grade 3/4 neutropenia[a] from a fixed effects network meta-analysis model

	Comparator treatment			Probability ranked			
Intervention treatment	FOLFOX	BEV+FOLFOX	PAN+FOLFOX	1st	2nd	3rd	4th
FOLFOX				28%	38%	26%	8%
BEV+FOLFOX	1.07 (0.50, 2.26)			31%	17%	22%	30%
PAN+FOLFOX	1.08 (0.75, 1.54)**	1.01 (0.52, 1.95)***		12%	32%	38%	18%
CET+FOLFOX	1.15 (0.45, 2.94)****	1.08 (0.32, 3.57)	1.07 (0.39, 2.90)	30%	13%	14%	44%

Key: AEs = adverse events; BEV = bevacizumab; CET = cetuximab; CrI = credible interval; FOLFOX = folinic acid + fluorouracil + oxaliplatin; HR = hazard ratio; OR = odds ratio; PAN = panitumumab
Note: * OR <1 favours 'Intervention' treatment; ** OR calculated from study arm data from PRIME; *** OR calculated from study arm data from PEAK; **** OR calculated from study arm data from OPUS; a Reported in ≥5% participants in either treatment arm

Table 37. Odds ratio* (and 95% CrI) for Grade 3/4 paresthesia[a] from a fixed effects network meta-analysis model

	Comparator treatment			Probability ranked			
Intervention treatment	FOLFOX	BEV+FOLFOX	PAN+FOLFOX	1st	2nd	3rd	4th
FOLFOX				3%	54%	34%	10%
BEV+FOLFOX	1.21 (0.24, 5.76)			5%	35%	22%	38%
PAN+FOLFOX	1.44 (0.73, 2.94)**	1.19 (0.29, 5.21)***		<1%	7%	43%	50%
CET+FOLFOX	0.09 (0.01, 1.45)****	0.07 (0.01, 1.92)	0.06 (0.01, 1.10)	92%	4%	2%	2%

Key: AEs = adverse events; BEV = bevacizumab; CET = cetuximab; CrI = credible interval; FOLFOX = folinic acid + fluorouracil + oxaliplatin; HR = hazard ratio; OR = odds ratio; PAN = panitumumab
Note: * OR <1 favours 'Intervention' treatment; ** OR calculated from study arm data from PRIME; *** OR calculated from study arm data from PEAK; **** OR calculated from study arm data from OPUS; a Reported in ≥5% participants in either treatment arm

Table 38. Odds ratio* (and 95% CrI) for Grade 3/4 rash[a] from a fixed effects network meta-analysis model

	Comparator treatment			Probability ranked			
Intervention treatment	FOLFOX	BEV+FOLFOX	PAN+FOLFOX	1st	2nd	3rd	4th
FOLFOX				53%	45%	2%	0%
BEV+FOLFOX	1.34 (0.01, 82.99)			44%	38%	18%	<1%
PAN+FOLFOX	74.61 (13.2, 1958)**	56.33 (4.71, 16540)***		0%	<1%	24%	76%
CET+FOLFOX	13.06 (0.67, 5480)****	13.12 (0.06, 36870)	0.17 (0.01, 86.72)	3%	17%	56%	24%

Key: AEs = adverse events; BEV = bevacizumab; CET = cetuximab; CrI = credible interval; FOLFIRI = folinic acid + fluourouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; HR = hazard ratio; OR = odds ratio; PAN = panitumumab

Note: * OR <1 favours 'Intervention' treatment; ** OR calculated from study arm data from PRIME; *** OR calculated from study arm data from PEAK; **** OR calculated from study arm data from OPUS; a Reported in ≥5% participants in either treatment arm

Table 39. Odds ratio* (and 95% CrI) for Grade 3/4 skin conditions[a,b] from a fixed effects network meta-analysis model

	Comparator treatment			Probability ranked			
Intervention treatment	FOLFOX	BEV+FOLFOX	PAN+FOLFOX	1st	2nd	3rd	4th
FOLFOX				54%	44%	2%	0%
BEV+FOLFOX	1.32 (0.03, 43.18)			43%	42%	15%	0%
PAN+FOLFOX	135.90 (24.97, 2660)**	103.1 (18.17, 2906)***		0%	0%	18%	82%
CET+FOLFOX	13.22 (0.66, 69.02)****	11.93 (0.10, 13540)	0.09 (0.01, 60.23)	3%	14%	64%	18%

Key: AEs = adverse events; BEV = bevacizumab; CET = cetuximab; CrI = credible interval; FOLFOX = folinic acid + fluorouracil + oxaliplatin; HR = hazard ratio; OR = odds ratio; PAN = panitumumab

Note: * OR <1 favours 'Intervention' treatment; ** OR calculated from study arm data from PRIME; *** OR calculated from study arm data from PEAK; **** OR calculated from study arm data from OPUS; a Reported in ≥5% participants in either treatment arm; b For the purposes of the network meta-analysis skin conditions included: acneiform exanthema, dermatitis acneiform, desquamation, nail changes/paronychia, skin reactions, and skin disorders based on rates reported in the included trials. Rash was treated separately. As composite reactions appeared to include conditions also reported by specialist preferred term these were excluded from the analysis. Incidence rates are reported in Section 3.2.7.1 (p120; cetuximab), and Section 3.2.7.2 (p126; panitumumab)

For the remaining AEs, the OPUS study did not provide the required information and so no comparison can be made between CET+FOLFOX and PAN+FOLFOX for diarrhoea,

hypokalemia, hypomagnesemia, mucositis/stomatitis, musosal inflammation, fatigue, neuropathy peripheral or asthenia. Instead these analyses are reported to allow the indirect comparison of BEV+FOLFOX vs FOLFOX (see Appendix H). Note that due to small numbers of events for hypomagnesemia, mucositis/stomatitis and musosal inflammation, the 95% CrIs are wide.

3.3.1.6. Subgroup analyses by liver metastases at baseline

Restricting the evidence to the subgroup of people with liver metastases at baseline has little impact on the overall conclusions: there is limited evidence to suggest any difference between CET+FOLFOX and PAN+FOLFOX for progression free survival (Table 40), overall survival (Table 41) and overall response rate (Table 42) as the 95% CrIs include 1.

Table 40. Hazard ratio* (and 95% CrI) for progression or death (liver metastases subgroup) from a fixed effects network meta-analysis model

	Comparator treatment			**Probability ranked**			
Intervention treatment	FOLFOX	BEV+FOLFOX	PAN+FOLFOX	1st	2nd	3rd	4th
FOLFOX				2%	17%	42%	39%
BEV+FOLFOX	1.04 (0.42, 2.59)			6%	21%	24%	49%
PAN+FOLFOX	0.79 (0.49, 1.27)**	[redacted]		13%	56%	28%	4%
CET+FOLFOX	0.35 (0.06, 1.96)****	0.34 (0.05, 2.37)	0.44 (0.07, 2.66)	79%	6%	6%	8%

Key: AEs = adverse events; BEV = bevacizumab; CET = cetuximab; CrI = credible interval; FOLFOX = folinic acid + fluorouracil + oxaliplatin; HR = hazard ratio; PAN = panitumumab
Note: * HR <1 favours 'Intervention' treatment; ** direct evidence from PRIME; *** direct evidence from PEAK; ****direct evidence from OPUS

Table 41. Hazard ratio* (and 95% CrI) for death (liver metastases subgroup) from a fixed effects network meta-analysis model

	Comparator treatment			Probability ranked			
Intervention treatment	FOLFOX	BEV+FOLFOX	PAN+FOLFOX	1st	2nd	3rd	4th
FOLFOX				3%	41%	53%	2%
BEV+FOLFOX	1.95 (0.35, 10.79)			<1%	2%	10%	88%
PAN+FOLFOX	0.69 (0.42, 1.15)**	[redacted]		65%	30%	5%	0%
CET+FOLFOX	0.90 (0.33, 2.43)****	0.46 (0.06, 3.39)	1.29 (0.42, 3.94)	32%	27%	31%	10%

Key: BEV = bevacizumab; CET = cetuximab; CrI = credible interval; FOLFOX = folinic acid + fluorouracil + oxaliplatin; HR = hazard ratio; OS = overall survival; PAN = panitumumab
Note: * HR <1 favours 'Intervention' treatment; ** direct evidence from PRIME; *** direct evidence from PEAK; ****direct evidence from OPUS

Table 42. Odds ratio* (and 95% CrI) for ORR (liver metastases subgroup) from a fixed effects network meta-analysis model

	Comparator treatment			Probability ranked			
Intervention treatment	FOLFOX	BEV+FOLFOX	PAN+FOLFOX	1st	2nd	3rd	4th
FOLFOX				<1%	10%	45%	45%
BEV+FOLFOX	0.98 (0.16, 5.80)			6%	15%	29%	49%
PAN+FOLFOX	2.18 (0.74, 6.36)**	[redacted]		29%	55%	14%	<1%
CET+FOLFOX	3.30 (0.63, 17.10)****	3.35 (0.30, 38.24)	1.51 (0.21, 10.80)	64%	19%	12%	5%

Key: BEV = bevacizumab; CET = cetuximab; CrI = credible interval; FOLFOX = folinic acid + fluorouracil + oxaliplatin; OR = odds ratio; ORR = overall response rate; PAN = panitumumab
Note: * OR >1 favours 'Intervention' treatment; ** direct evidence from PRIME; *** direct evidence from PEAK; ****direct evidence from OPUS

Only data from two RCTs (PRIME and PEAK) are available for the analysis of surgical resection rates (Table 43) for the liver mets subgroup. Since OPUS does not report this outcome, no comparison can be made between CET+FOLFOX and PAN+FOLFOX. However, the available data suggests that there is little evidence of a difference in surgical and complete resection rates between FOLFOX, BEV+FOLFOX and PAN+FOLFOX.

For completion resection, all three RCTs report relevant evidence and so a comparison between PAN+FOLFOX and CET+FOLFOX can be made. However, there is very little evidence to say that one treatment is associated with a greater number of complete resections than any other (Table 44), although these analyses are based on a small number of participants.

Table 43. Odds ratio* (and 95% CrI) for surgical resection rate calculated from a fixed effects network meta-analysis model

	Comparator treatment		**Probability ranked**		
Intervention treatment	FOLFOX	BEV+FOLFOX	1st	2nd	3rd
FOLFOX			8%	19%	72%
BEV+FOLFOX	2.18 (0.42, 11.43)		66%	18%	36%
PAN+FOLFOX	1.55 (0.61, 3.93)**	[redacted]	26%	62%	33%

Key: BEV = bevacizumab; CrI = credible interval; FOLFOX = folinic acid + fluorouracil + oxaliplatin; OR = odds ratio; PAN = panitumumab
Note: *OR >1 favours 'Intervention' treatment; ** direct evidence from PRIME; *** direct evidence from PEAK

Table 44. Odds ratio* (and 95% CrI) for complete resection rate calculated from a fixed effects network meta-analysis model

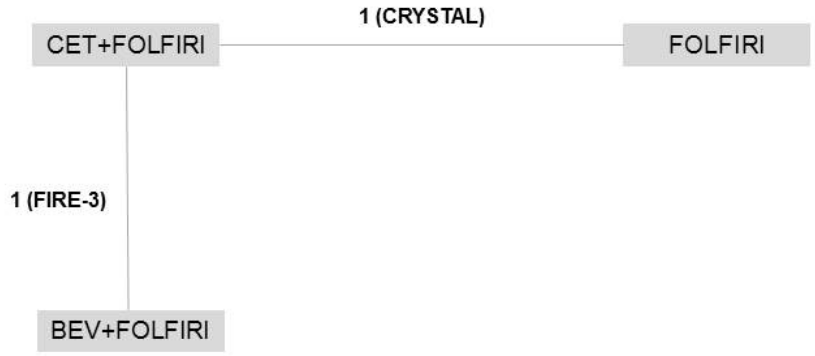
	Comparator treatment			**Probability ranked**			
Intervention treatment	FOLFOX	BEV+FOLFOX	PAN+FOLFOX	1st	2nd	3rd	4th
FOLFOX				<1%	3%	23%	73%
BEV+FOLFOX	4.22 (0.58, 30.68)			43%	39%	12%	6%
PAN+FOLFOX	2.20 (0.80, 6.07)**	[redacted]		7%	39%	49%	4%
CET+FOLFOX	4.63 (0.20, 104.60)****	1.09 (0.03, 44.34)	2.09 (0.08, 56.28)	50%	19%	15%	16%

Key: BEV = bevacizumab; CET = cetuximab; CrI = credible interval; FOLFOX = folinic acid + fluorouracil + oxaliplatin; OR = odds ratio; PAN = panitumumab
Note: *OR >1 favours 'Intervention' treatment; ** direct evidence from PRIME; *** direct evidence from PEAK; ****direct evidence from OPUS

3.3.2. FOLFIRI regimens

Two RCTs (CRYSTAL [**Van Cutsem et al., 2015**], and FIRE-3 [**Heinemann et al., 2014**]) contribute to the estimation of the effectiveness of three treatments (FOLFIRI, bevacizumab plus FOLFIRI [BEV+FOLFIRI] and cetuximab plus FOLFIRI [CET+FOLFIRI]). Even though there is no evidence on the effectiveness of panitumumab plus FOLFIRI (PAN+FOLFIRI) in this network, the network meta-analysis was conducted to allow estimation of the evidence that was available, i.e. to inform the indirect comparison of BEV+FOLFIRI vs FOLFIRI. The network diagram – including which trials informed the network meta-analysis for each outcome of interest – is shown in Figure 6.

Figure 6. Network diagram for the FOLFIRI network



		PFS	OS	ORR	Resection rate	Any Grade 1/2 AE[a]	Any Grade 3/4 AE[a]	SAE[a]	AE by type[a]
RAS WT	CRYSTAL	✓	✓	✓[b]	✓	✓	✓	✓	✓[c]
	FIRE-3	✓	✓	✓[b]	X	X	X	X	X
RAS WT + liver metastasis at baseline	CRYSTAL	✓	✓	✓	✓[d]	X	X	X	X
	FIRE-3	X	X	X	X	X	X	X	X

Key: AE = adverse event; BEV = bevacizumab; CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; OS = overall survival; ORR = overall response rate; PFS = progression-free survival; *RAS* = rat sarcoma; SAE = serious adverse event; WT = wild type

Notes: a Adverse events based on incidence rates reported in the trials (occurring in ≥5% participants in either treatment arm); b The CRYSTAL trial used World Health Organisation (WHO) criteria and the FIRE-3 trial used Response Criteria in Solid Tumours (RECIST) to assess response; c Grade 3/4 skin conditions occurring in ≥5% participants in either treatment arm, and Grade 3/4 diarrhoea occurring in ≥5% participants in either treatment arm. (For the purposes of the network meta-analysis skin conditions included: acneiform exanthema, dermatitis acneiform, desquamation, nail changes/paronychia, skin reactions, and skin disorders based on rates reported in the included trials. Rash was treated separately. As composite reactions appeared to include conditions also reported by specialist preferred term these were excluded from the analysis. Incidence rates are reported in Section 3.2.7.1 [p120; cetuximab], and Section 3.2.7.2 [p126; panitumumab]); d Surgical resection rate (partial and complete resection)

3.3.2.1. Progression free survival

The network meta-analysis suggests that BEV+FOLFIRI is more effective than FOLFIRI at increasing time to progression or death (HR 0.60 (0.41, 0.88), see Table 45), while evidence from CRYSTAL suggests that CET+FOLFIRI is more effective than FOLFIRI. Evidence from the FIRE-3 RCT suggests that CET+FOLFIRI is no more effective than BEV+FOLFIRI (see Table 45).

Table 45. Hazard ratio* (and 95% CrI) for progression or death from a fixed effects network meta-analysis model

	Comparator treatment		**Probability ranked**		
Intervention treatment	**FOLFIRI**	**BEV+FOLFIRI**	**1st**	**2nd**	**3rd**
FOLFIRI			<1%	<1%	99%
BEV+FOLFIRI	0.60		27%	73%	<1%
	(0.41, 0.88)				
CET+FOLFIRI	0.56**	0.93***	73%	27%	<1%
	(0.41, 0.76)**	(0.74, 1.17)***			

Key: BEV = bevacizumab; CET = cetuximab; CrI = credible interval; FOLFIRI = folinic acid + fluourouracil + irinotecan; HR = hazard ratio
Note: * HR <1 favours 'Intervention' treatment; ** direct evidence from CRYSTAL; *** direct evidence from FIRE-3

3.3.2.2. Overall survival

The network meta-analysis suggests that there is no evidence that BEV+FOLFIRI is more effective than FOLFIRI at increasing time to death, however evidence from CRYSTAL and FIRE-3 indicate that CET+FOLFIRI is more effective than both FOLFIRI and BEV+FOLFIRI (see Table 46).

Table 46. Hazard ratio* (and 95% CrI) for death from a fixed effects network meta-analysis model

	Comparator treatment		**Probability ranked**		
Intervention treatment	FOLFIRI	BEV+FOLFIRI	1st	2nd	3rd
FOLFIRI			<1%	47%	53%
BEV+FOLFIRI	0.99		<1%	53%	47%
	(0.68, 1.42)				
CET+FOLFIRI	0.69	0.70	99%	<1%	<1%
	(0.54, 0.88)**	(0.53, 0.92)***			

Key: BEV = bevacizumab; CET = cetuximab; CrI = credible interval; FOLFIRI = folinic acid + fluourouracil + irinotecan; HR = hazard ratio
Note: * HR <1 favours 'Intervention' treatment; ** direct evidence from CRYSTAL; *** direct evidence from FIRE-3

3.3.2.3. Objective response rate

Two RCTs contributed to the estimation of objective response rate (ORR) in the FOLFIRI network. However, due to differences in the reporting of the timing of ORR in each study it is unclear whether the timings are entirely comparable across studies. Given this uncertainty, results reported for the *RAS* WT population for this outcome should be treated with caution.

The network meta-analysis suggests that BEV+FOLFIRI and CET+FOLFIRI are both more effective than FOLFIRI for ORR; however, the evidence that CET+FOLFIRI is any more effective than BEV+FOLFIRI for ORR is uncertain due to the wide 95% CrI (OR 1.28 (95%CrI 0.83, 1.99), see Table 47.

Table 47. Odds ratio* (and 95% CrI) for ORR from a fixed effects network meta-analysis model

	Comparator treatment		Probability ranked		
Intervention treatment	**FOLFIRI**	**BEV+FOLFIRI**	**1st**	**2nd**	**3rd**
FOLFIRI			0%	13%	87%
BEV+FOLFIRI	2.43 (1.32, 4.48)		<1%	87%	13%
CET+FOLFIRI	3.11** (2.03, 4.77)	1.28*** (0.83, 1.99)	100%	<1%	0%

Key: BEV = bevacizumab; CrI = credible interval; FOLFIRI = folinic acid + fluourouracil + irinotecan; OR = odds ratio; ORR = objective response rate; PAN = panitumumab
Notes: *OR>1 favours 'Intervention' treatment; ** direct evidence from CRYSTAL; *** direct evidence from FIRE-3

3.3.2.4. Adverse events

The network meta-analysis suggests that BEV+FOLFIRI and CET+FOLFIRI are associated with greater Grade 3/4 AEs than FOLFIRI (Table 48), and that CET+FOLFIRI is associated with greater skin conditions than FOLFIRI or BEV+FOLFIRI (Table 49). For diarrhoea the evidence is unclear as to whether one treatment is associated with more cases than the other treatments (Table 50).

Table 48. Odds ratio* (and 95% CrI) for any Grade 3/4 AEs[a] from a fixed effects network meta-analysis model

	Comparator treatment		Probability ranked		
Intervention treatment	FOLFIRI	BEV+FOLFIRI	1st	2nd	3rd
FOLFIRI			99%	<1%	0%
BEV+FOLFIRI	2.82		<1%	64%	36%
	(1.46, 5.49)				
CET+FOLFIRI	3.06	1.09	0%	36%	64%
	(1.91, 4.95)**	(0.69, 1.72)***			

Key: BEV = bevacizumab; CET = cetuximab; CrI = credible interval; FOLFIRI = folinic acid + fluourouracil + irinotecan; OR = odds ratio

Note: * OR <1 favours 'Intervention' treatment; ** OR calculated from study arm data from CRYSTAL; *** OR calculated from study arm data from FIRE-3; a Reported in ≥5% participants in either treatment arm

Table 49. Odds ratio* (and 95% CrI) for Grade 3/4 skin conditions[a.b] from a fixed effects network meta-analysis model

	Comparator treatment		Probability ranked		
Intervention treatment	FOLFIRI	BEV+FOLFIRI	1st	2nd	3rd
FOLFIRI			72%	28%	0%
BEV+FOLFIRI	2.67		28%	72%	0%
	(0.18, 1177)				
CET+FOLFIRI	127.60	47.60	0%	0%	100%
	(11.12, 53970)**	(21.30, 129.40)***			

Key: BEV = bevacizumab; CET = cetuximab; CrI = credible interval; FOLFIRI = folinic acid + fluourouracil + irinotecan; OR = odds ratio

Note: * OR <1 favours 'Intervention' treatment; ** OR calculated from study arm data from CRYSTAL; *** OR calculated from study arm data from FIRE-3; a Reported in ≥5% participants in either treatment arm; b For the purposes of the network meta-analysis skin conditions included: acneiform exanthema, dermatitis acneiform, desquamation, nail changes/paronychia, skin reactions, and skin disorders based on rates reported in the included trials. Rash was treated separately. As composite reactions appeared to include conditions also reported by specialist preferred term these were excluded from the analysis. Incidence rates are reported in Section 3.2.7.1 (p120; cetuximab), and Section 3.2.7.2 (p126; panitumumab)

Table 50. Odds ratio* (and 95% CrI) for Grade 3/4 Diarrhoea[a] from a fixed effects network meta-analysis model

	Comparator treatment		Probability ranked		
Intervention treatment	FOLFIRI	BEV+FOLFIRI	1st	2nd	3rd
FOLFIRI			85%	11%	4%
BEV+FOLFIRI	2.04 (0.82, 5.20)		4%	13%	82%
CET+FOLFIRI	1.46 (0.77, 2.82)**	0.72 (0.37, 1.38)***	10%	76%	14%

Key: BEV = bevacizumab; CET = cetuximab; CrI = credible interval; FOLFIRI = folinic acid + fluourouracil + irinotecan; OR = odds ratio
Note: * OR <1 favours 'Intervention' treatment; ** OR calculated from study arm data from CRYSTAL; *** OR calculated from study arm data from FIRE-3; a Reported in ≥5% participants in either treatment arm

Sensitivity analyses

Addition of FIRE-3 data (taken from the manufacturer's submission; see also Appendix H) to the estimation of HRs for progression or death (Table 51), HRs for death (Table 52), and ORs for ORR (Table 53). However, inclusion of these data had very little difference on the overall conclusions for the FOLFIRI network.

Table 51. Hazard ratio* (and 95% CrI) for progression or death from a fixed effects network meta-analysis model

	Comparator treatment		Probability ranked		
Intervention treatment	FOLFIRI	BEV+FOLFIRI	1st	2nd	3rd
FOLFIRI			<1%	<1%	100%
BEV+FOLFIRI	0.58 (0.40, 0.84)		39%	61%	<1%
CET+FOLFIRI	0.56 (0.41, 0.76)**	0.97 (0.78, 1.20)***	61%	39%	<1%

Key: BEV = bevacizumab; CET = cetuximab; CrI = credible interval; FOLFIRI = folinic acid + fluourouracil + irinotecan; HR = hazard ratio
Note: * HR <1 favours 'Intervention' treatment; ** direct evidence from CRYSTAL; *** direct evidence from FIRE-3

Table 52. Hazard ratio* (and 95% CrI) for death from a fixed effects network meta-analysis model

	Comparator treatment		Probability ranked		
Intervention treatment	FOLFIRI	BEV+FOLFIRI	1st	2nd	3rd
FOLFIRI			<1%	47%	53%
BEV+FOLFIRI	0.99 (0.69, 1.40)		<1%	53%	47%
CET+FOLFIRI	0.69 (0.54, 0.88)**	0.70 (0.54, 0.90)***	100%	<1%	<1%

Key: BEV = bevacizumab; CET = cetuximab; CrI = credible interval; FOLFIRI = folinic acid + fluourouracil + irinotecan; HR = hazard ratio
Note: * HR <1 favours 'Intervention' treatment; ** direct evidence from CRYSTAL; *** direct evidence from FIRE-3

Table 53. Odds ratio* (and 95% CrI) for objective response rate from a fixed effects network meta-analysis model

	Comparator treatment		Probability ranked		
Intervention treatment	**FOLFIRI**	**BEV+FOLFIRI**	**1st**	**2nd**	**3rd**
FOLFIRI			0%	8%	92%
BEV+FOLFIRI	2.34 (1.29, 4.22)		<1%	91%	8%
CET+FOLFIRI	3.11** (2.03, 4.76)	1.33*** (0.89, 2.00)	>99%	<1%	0%

Key: BEV = bevacizumab; CET = cetuximab; CrI = credible interval; FOLFIRI = folinic acid + fluourouracil + irinotecan; HR = hazard ratio
Note: * OR >1 favours 'Intervention' treatment; ** OR calculated from study arm data from CRYSTAL; *** OR calculated from study arm data from FIRE-3

3.4. Summary

3.4.1. Summary of clinical effectiveness systematic review

- Of 2,811 titles/abstracts screened, five RAS WT subgroup analyses from randomised controlled trials (RCTs) met the inclusion criteria for the clinical effectiveness systematic review.
- Research has demonstrated a treatment interaction between *RAS* and EGFR inhibitors. Tumour samples from trial populations were re-evaluated for *RAS* status. In response to these research developments the EMA has recently amended the licence for cetuximab and panitumumab to restrict use to people with *RAS* WT mCRC. Importantly, currently available data for the effectiveness of EGFR inhibitors

in people with *RAS* WT mCRC are from a subgroup of the ITT trial populations for both cetuximab and panitumumab. Reported data were in line with the expected direction of effect across all of the include studies. No RCTs with a ITT population by *RAS* status were identified in the Assessment Group's searches.

- The risk of bias was high but generally similar between studies in respect of randomisation, allocation concealment, blinding, outcome reporting and loss to follow-up. The main limitation in terms of interpretation and validity was that all of the included studies were subgroup analyses of ITT trial populations. Allocation to subgroups was based on re-evaluating tumour samples from the *KRAS* WT Exon 2 population for *RAS* status. While this minimised the potential for ascertainment bias, there were missing data for some of the trials (either the tumour was not evaluable for *RAS* status or the results were inconclusive). No significant imbalance between the trial populations were observed minimising the potential for selection bias. Due to the retrospective nature of the *RAS* analysis, for some studies, there were a low number of samples available for analysis reducing the power of the studies to show statistical significance. Despite these limitations, these are currently the only available data evaluating the effectiveness in people with mCRC with *RAS* WT tumour status in line with the recently revised licensed indication and the NICE final scope.

3.4.1.1. Cetuximab

- Two trials provided evidence for the effectiveness of cetuximab in combination with chemotherapy (FOLFOX or FOLFIRI) compared with chemotherapy alone (FOLFOX or FOLFIRI). Evidence consistently suggests a treatment effect in favour of the addition of cetuximab to chemotherapy compared with chemotherapy alone.
  - Median PFS ranged from 11.4 months in the **Van Cutsem et al., 2015** (CRYSTAL) study to 12 months in the **Tejpar et al. (2015)** (OPUS) study for the experimental arms, and from 5.8 months to 8.4 months, respectively in the control arms.
  - Median OS ranged from 19.8 months in the **Van Cutsem et al., 2015** (CRYSTAL) study to 20.4 months in the in the **Tejpar et al. (2015)** (OPUS) study for the experimental arms, and from 17.8 months to 20.2 months, respectively in the control arms.
  - Tumour response rates in the experimental arm ranged from 58% in the **Tejpar et al. (2015)** (OPUS) study to 66% in the **Van Cutsem et al. (2015)**

(CRYSTAL) study vs 29% to 60% in the same respective studies for the control arms.

  - In people with liver metastases at baseline results in terms of improvement in OS and PFS were consistent with results for the overall *RAS* WT population. Of these people 13.3% in the **Tejpar et al. (2015)** (OPUS) study to 16.3 % in the **Van Cutsem et al. (2015)** (CRYSTAL) study had complete resection in the experimental arms.
  - Overall, clinical safety data for the *RAS* WT population were consistent with results for *KRAS* WT population in all the trials. The most common events were diarrhoea, haematotoxiticity, neutropenia and skin reactions.
- One trial provided evidence for the effectiveness of cetuximab in combination with chemotherapy (FOLFIRI) compared with bevacizumab with chemotherapy (FOLFIRI).
  - The proportion of people who achieved an objective response was similar between the cetuximab plus FOLFIRI and bevacizumab plus FOLFIRI. However, the association with longer overall survival suggests a benefit with cetuximab plus FOLFIRI (HR 0.70, 95% CI 0.53, 0.92).

3.4.1.2. Panitumumab

- One trial provided evidence for the effectiveness of panitumumab in combination with chemotherapy (FOLFOX4) compared with chemotherapy alone (FOLFOX4). No evidence was identified comparing panitumumab plus FOLFIRI with FOLFIRI. Evidence consistently suggests a treatment effect in favour of the addition of panitumumab to FOLFOX4 compared with FOLFOX4.
  - Median PFS was 10.1 months for the experimental arm, and 7.9 months in the control arm (**Douillard et al., 2013** [PRIME]).
  - Median OS was 25.8 months for the experimental arm, and 20.2 months in the control arm (**Douillard et al., 2013** [PRIME]).
  - Tumour response rates in the experimental arm were [redacted] compared with [redacted] in the control arm (**Douillard et al., 2013** [PRIME]).
  - In people with liver metastases at baseline results in terms of improvement in OS and PFS were consistent with results at baseline. Of these people, [redacted] in the experimental arm compared with [redacted] in the control arm had complete resection.

  - Overall, clinical safety data for the *RAS* WT population were consistent with results for *KRAS* WT population in all the trials. The most common events were diarrhoea, haematotoxiticity, neutropenia and skin reactions.
- One trial provided evidence for the effectiveness of panitumumab in combination with chemotherapy (mFOLFOX6) compared with bevacizumab with chemotherapy (mFOLFOX6).
  - The proportion of people who achieved an objective response were similar between the panitumumab plus mFOLFOX6 and bevacizumab plus mFOLFOX6. For PFS the addition of panitumumab to mFOLFOX6 was associated with a 35% reduction in risk of progression compared with bevacizumab plus mFOLFOX6. In addition, a trend towards OS benefit with panitumumab plus mFOLFOX6 was observed (HR 0.63; 95% CI 0.39, 1.02).

3.4.1.3. Summary of network meta-analysis

- A network meta-analysis was also conducted based on trials identified, it was not possible to construct a complete network. Two discrete networks were generated, one evaluating FOLFOX-containing chemotherapy regimens and the second comparing FOLFIRI-containing chemotherapy regimens.

FOLFOX network

- Three RCTs (PRIME [**Douillard et al., 2014**], PEAK [**Schwartzberg et al., 2014**], and OPUS [**Tejpar et al., 2014**]), contributed to estimating the effectiveness of four treatments (FOLFOX, bevacizumab plus FOLFOX [BEV+FOLFOX], panitumumab plus FOLFOX [PAN+FOLFOX], and cetuximab plus FOLFOX [CET+FOLFOX]).
- There is no evidence to suggest that cetuximab plus FOLFOX is any more effective than FOLFOX, bevacizumab plus FOLFOX or panitumumab plus FOLFOX to increase the time to death or the time to progression or death.
- Direct evidence suggests that panitumumab plus FOLFOX is more effective at increasing time to progression or death than FOLFOX and bevacizumab plus FOLFOX. Panitumumab plus FOLFOX is also estimated to be more effective at increasing time to death than FOLFOX.
- There is limited evidence to suggest that cetuximab plus FOLFOX is more effective at improving overall response rate than panitumumab plus FOLFOX.

- There is little evidence than cetuximab plus FOLFOX is associated with fewer AEs than panitumumab plus FOLFOX, however some of these analyses are limited by the small number of events recorded in the treatment arms.

FOLFIRI network

- No evidence was identified comparing panitumumab plus FOLFIRI with FOLFIRI.
- Two RCTs (CRYSTAL [**Van Cutsem et al., 2015**], and FIRE-3 [**Heinemann et al., 2014**]) contribute to the estimation of the effectiveness of three treatments (FOLFIRI, bevacizumab plus FOLFIRI [BEV+FOLFIRI] and cetuximab plus FOLFIRI [CET+FOLFIRI]).
- Evidence suggests that cetuximab plus FOLFIRI and bevacizumab plus FOLFIRI are more effective than FOLFIRI at increasing time to progression or death, and objective response rate.
- Direct evidence suggests that cetuximab plus FOLFIRI is more effective than FOLFIRI and bevacizumab plus FOLFIRI at increasing the time to death.

3.4.2. Summary results tables (clinical effectiveness)

A summary of results (direct and indirect evidence) for cetuximab plus FOLFOX, cetuximab plus FOLFIRI, and panitumumab plus FOLFOX compared with interventions of interest are provided for efficacy (PFS, OS, ORR, complete resection rate), and safety outcomes in Table 54 and Table 55. Note that for Grade 3 or 4 AEs by type (reported in ≥5% of participants in either treatment arm) only those analyses in the NMA are included in the summary results tables. A more complete summary of Grade 3 or 4 AEs by type is provided in Section 3.2.7.1 (p.120) and Section 3.2.7.2 (p.126).

Table 54. Results summary (direct and indirect evidence): Efficacy outcomes (*RAS* WT population and *RAS* WT with liver metastases at baseline)

	***RAS* WT**				***RAS* WT with liver metastases at baseline**			
	PFS HR (95%CrI)	**OS** HR (95% CrI)	**ORR** OR (95% CrI)	**Complete resection rate** OR (95% CrI)	**PFS** HR (95%CrI)	**OS** HR (95% CrI)	**ORR** OR (95% CrI)	**Complete resection rate[h]** OR (95% CrI)
Intervention: CET+FOLFOX vs.								
FOLFOX	0.53 (0.27, 1.04)[a]	0.94 (0.56, 1.57)[a]	3.33 (1.36, 8.12)[a]	NE	0.35 (0.06, 1.96)[a]	0.90 (0.33, 2.43)[a]	3.30 (0.63, 17.10)[a]	4.63 (0.20, 104.60)[a]
PAN+FOLFOX	0.74 (0.36, 1.49)	1.22 (0.71, 2.11)	1.90 (0.72, 5.02)	NE	0.44 (0.07, 2.66)	1.29 (0.42 3.94)	1.51 (0.21, 10.80)	2.09 (0.08, 56.28)
BEV+FOLFOX	0.48 (0.21, 1.07)	0.77 (0.37, 1.59)	2.05 (0.63, 6.70)	NE	0.34 (0.05, 2.37)	0.46 (0.06, 3.39)	3.35 (0.30, 38.24)	1.09 (0.03, 44.34)
Intervention: PAN+FOLFOX vs.								
FOLFOX	0.72 (0.58, 0.90)[b]	0.77 (0.64, 0.93)[b]	[redacted]	[redacted]	0.79 (0.49, 1.27)[b]	0.69 (0.42, 1.15)[b]	2.18 (0.74, 6.36)[b]	2.20 (0.80, 6.07)[b]
BEV+FOLFOX	0.65 (0.44, 0.96)[c]	0.63 (0.39, 1.02)[c]	1.08 (0.55, 2.12)[c]	1.61 (0.45, 2.98)[c]	[redacted]	[redacted]	[redacted]	[redacted]
Intervention: CET+FOLFIRI vs.								
FOLFIRI	0.56 (0.41, 0.76)[d]	0.69 (0.54, 0.88)[d]	3.11 (2.03, 4.77)[e]	NE	NE	NE	NE	NE
PAN+FOLFIRI	NE	NE	NE	NE	NE	NE	NE	NE
BEV+FOLFIRI	0.93 (0.74, 1.17)[e,f]	0.70 (0.53, 0.92)[e,g]	1.28 (0.83, 1.99)[f]	NE	NE	NE	NE	NE
Intervention: PAN+FOLFIRI vs.								
FOLFIRI	NE	NE	NE	NE	NE	NE	NE	NE
BEV+FOLFIRI	NE	NE	NE	NE	NE	NE	NE	NE

Key: BEV = bevacizumab; CET = cetuximab; CrI = credible interval; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; HR = hazard ratio; NE = not evaluable; OR = odds ratio; ORR = objective response rate; OS = overall survival; PAN = panitumumab; PFS = progression free survival; *RAS* = rat sarcoma; SAEs = serious adverse events; vs. = versus; WT = wild type

Notes: Fixed effects model; NE = indicates no data available; **Bold** text indicates direct evidence; HR <1 favours intervention; OR >1 favours intervention; a direct evidence from OPUS; b direct evidence from PRIME; c direct evidence from PEAK; d direct evidence from CRYSTAL; e direct evidence from FIRE-3; f Estimate for HR for progression or death using unpublished data HE 0.97 (95% CrI 0.78, 1.20); g Estimate for HR for death using unpublished data HR 0.70 (95% CrI 0.54, 0.90); h Note that surgical resection rate is also reported for PRIME and PEAK studies for the subgroup of *RAS* WT participants with liver metastases at baseline, see Section 3.3.1.6, Table 43, p.141)

Table 55. Results summary (direct and indirect evidence): Safety outcomes

	Any Grade 3/4 AEs[f] OR (95% CrI)	Any SAEs[f] OR (95% CrI)	Grade 3/4 neutropenia[f] OR (95% CrI)	Grade 3/4 paresthesia[f] OR (95% CrI)	Grade 3/4 rash[f] OR (95% CrI)	Grade 3/4 skin conditions[f] OR (95% CrI)	Grade 3/4 Diarrhoea[f] OR (95% CrI)
Intervention: CET+FOLFOX vs.							
FOLFOX	**2.24 (0.85, 6.24)a**	**3.45 (1.28, 9.88)a**	**1.15 (0.45, 2.94)a**	**0.09 (0.01, 1.45)a**	**13.06 (0.67, 5480)a**	**13.22 (0.66, 69.02)a**	NE
PAN+FOLFOX	0.86 (0.29, 2.69)	2.66 (0.93, 8.05)	1.07 (0.39, 2.90)	0.06 (0.01, 1.10)	0.17 (0.01, 86.72)	11.93 (0.10, 13540)	NE
BEV+FOLFOX	2.80 (0.64, 13.34)	3.18 (0.94, 11.33)	1.08 (0.32, 3.57)	0.07 (0.01, 1.92)	13.12 (0.06, 36870)	0.09 (0.01, 60.23)	NE
Intervention: PAN+FOLFOX vs.							
FOLFOX	**2.58 (1.59, 4.30)b**	**1.30 (0.91, 1.86)b**	**1.08 (0.75, 1.54)b**	**1.44 (0.73, 2.94)b**	**74.61 (13.2, 1958)b**	**135.90 (24.97, 2660)b**	NE
BEV+FOLFOX	**3.20 (1.21, 9.56)c**	**1.19 (0.64, 2.24)c**	**1.01 (0.52, 1.96)c**	**1.19 (0.29, 5.21)c**	**56.33 (4.71, 16540)c**	**103.1 (18.17, 2906)c**	NE
Intervention: CET+FOLFIRI vs.							
FOLFIRI	3.06 (1.91, 4.95)[d]	NE	NE	NE	NE	127.60 (11.12, 53970)[d]	1.46 (0.77, 2.82)[d]
PAN+FOLFIRI	NE	NE	NE	NE	NE	NE	NE
BEV+FOLFIRI	1.09 (0.69, 1.72)[e]	NE	NE	NE	NE	47.60 (21.30, 129.40)[e]	0.72 (0.37, 1.38)[e]
Intervention: PAN+FOLFIRI vs.							
FOLFIRI	NE	NE	NE	NE	NE	NE	NE
PAN+FOLFIRI	NE	NE	NE	NE	NE	NE	NE

Key: AEs = adverse events; BEV = bevacizumab; CET = cetuximab; CrI = credible interval; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; HR = hazard ratio; OR = odds ratio; ORR = objective response rate; OS = overall survival; PAN = panitumumab; PFS = progression free survival; *RAS* = rat sarcoma; SAEs = serious adverse events; vs. = versus; WT = wild type

Notes: Fixed effects model; NE = indicates no data available; **Bold** text indicates direct evidence; HR <1 favours intervention; OR >1 favours intervention; a OR calculated from study arm level data from OPUS; b OR calculated from study arm level data from PRIME; c OR calculated from study arm level data from PEAK; d Any Grade 3/4 AEs occurring in ≥5% participants in either treatment arm

3.5. Ongoing trials

Searches of ClinicalTrials.gov, WHO (ICTRP), UK Clinical Research Network and ISRCTN were conducted (see Appendix B for the search strategy used). All searches were carried out in March 2015. Ten trials were considered as relevant to this review (see Appendix I for information of the trials), and were investigated further. Seven trials were identified as ongoing (ongoing n=2, ongoing not recruiting n=2, active, not recruiting n=1, or recruiting n=2). Three trials were completed and included in this review (OPUS, CRYSTAL and PRIME).

3.6. Manufacturers' reviews of clinical effectiveness

Both manufacturers – Amgen and Merck Serono – submitted clinical evidence for consideration for this MTA.

3.6.1. Amgen

Amgen carried out literature searches for clinical evidence in MEDLINE, MEDLINE-in-Process and EMBASE, via Ovid, and the Cochrane Central Register of Controlled Trials (CENTRAL), via the Cochrane library (Amgen Submission, Section 1.2, pp11-12). They also carried out a rapid appraisal search in the Cochrane library to identify existing systematic reviews and protocols in the topic area. The search strategies combine free-text and index terms for relevant cancers with free-text and index terms for relevant interventions (Amgen Submission, Appendix 2, pp86-114). The Cochrane randomized controlled trial publication filter was used to limit the search results to RCTs. No language or date limits were applied.

Amgen also searched grey literature resources, including trials registries, online conference proceedings, and the websites of national guideline and regulatory agencies (Amgen Submission, Section 1.2, pp12-13).

The Amgen literature searches use an appropriate range of databases and grey literature resources for the topic. The choice of free-text and index terms is also appropriate, and the searches have an appropriate balance of sensitivity and specificity. The search strategies are reproduced in the appendices, including the number of hits retrieved per search and the dates the searches were carried out (Amgen Submission, Appendix 2, pp86-114).

The submission set out to identify the evidence available from randomised controlled trials (RCTs) evaluating the efficacy and safety of panitumumab and other therapies for the

treatment of people with previously untreated mCRC. The review identified two panitumumab trials (PRIME and PEAK) of which one (PRIME, [Douillard et al., 2013]) was considered to meet the criteria set out in the decision problem specified in the final scope (Table 56). The PRIME trial was also included in the PenTAG systematic review. In addition, the PenTAG review included the PEAK trial (Schwartzberg et al., 2014) which evaluated the efficacy of panitumumab in combination with mFOLFOX6 compared with bevacizumab in combination with mFOLFOX6. This trial was excluded from the Amgen submission as bevacizumab is no longer available via the Cancer Drugs Fund but information from the trial was provided as supporting evidence (Amgen Submission, Section 4.6, p44).

Table 56. Amgen submission: Included panitumumab studies

Trial acronym	First author, year	Included in PenTAG review	Reason for exclusion
PRIME	Douillard et al., 2013	Y	NA
(PAN+FOLFOX4 vs. FOLFOX4)	Reference also made in Section 4.4 to the Amgen Submission,, Section 4.4 to Siena et al. 2015 and Wang et al., 2015	N	Identified and listed in Appendix D (both only available in abstract format; not enough information to quality appraise

Key: NA = not applicable; *RAS* = rat sarcoma; vs. = versus; WT = wild type; Y= Yes
Sources: Douillard JYet al. New Engl J Med. 2013;369:1023-34 (PRIME); Siena S et al. 2015 Gastrointestinal Cancers Symposium San Francisco, CA United States. 2015;33 (3 SUPPL. 1.); Wang J et al. 2015 Gastrointestinal Cancers Symposium San Francisco, CA United States. 2015;33 (3 SUPPL. 1.)

Health-related quality of life (HRQoL) data from the PRIME trial (EQ-5D health state index [HSI] and overall health rating [OHR]; Siena et al. 2015 [abstract][76]), were included in the Amgen submission (see Amgen submission, Section 4.4, p31). An analysis of quality-adjusted survival in participants with *RAS* WT tumours using the quality-adjusted time without symptoms of disease or toxicity (Q-TWiST) method was also completed (see Amgen submission, Section 4.4, p31). No HRQoL data were identified for inclusion in the Assessment Group's review; however, two abstracts were identified (Siena et al., 2015 and Wang et al., 2015 [listed in Appendix D; not formally included as there was not enough information to conduct quality appraisal][76, 77]). Amgen reported a summary of AEs, patient incidence of AEs of interest, AEs occurring in ≥10% of participants in either treatment arm, and AEs with >5% difference in incidence between treatment arms (see Amgen submission, Section 4.7, pp49–51; Appendix VI Table 1 and Table 2). For AEs, the Assessment Group reported a summary of AEs, and Grade 3/4 AEs occurring in ≥5% participants in either treatment arm.

In Section 4.6 of the Amgen Submission (pp44-45), the company present 'Supporting evidence of panitumumab in combination with FOLFIRI' and note the data used to obtain regulatory approval. We have listed these data for information in the table below (see Table 57).

Table 57. Amgen submission: Supporting evidence referenced for panitumumab plus FOLFIRI

Trial acronym	First author, year	Included in PenTAG review	Reason for exclusion
PLANET (PAN+FOLFIRI vs. FOLFIRI)	Abad, ESMO, 2014 [abstract, ESMO]	N	Published as abstract only (see Appendix D; not enough information to conduct quality appraisal), reports data predominantly for *KRAS* WT population for response rate for *RAS* WT population
Study 20060314 (PAN+FOLFIRI)	Data on File, Amgen Ltd (CSR *RAS* analysis), October 2014	N	Not identified in searches as unpublished information; study design (single arm)
Study 20050181 (PAN+FOLFIRI vs FOLFIRI)	Peeters et al., Gastrointestinal Cancers Symposium, 2014	N	Population (previously treated; not first-line)
Study 20080763 (ASPECCT) (PAN vs CET)	Price et al., 2014	N	Population (previously treated [not first-line] and not *RAS* WT); Intervention (PAN or CET as monotherapy)

Key: CET = cetuximab; CSR = clinical study report; ESMO = Euorpean Society of Medical Oncology; FOLFIRI = folinic acid + 5-fluourouracil + irinotecan; FOLFOX = folinic acid + 5-fluourouracil + oxaliplatin; *KRAS* = Kirsten rat sarcoma; N = no; PAN = panitumumab; *RAS* = rat sarcoma; vs. = versus; WT = wild type; Y= Yes
Sources: Abad A et al. ESMO 16th World Congress on Gastrointestinal Cancer (25–28 June); 2014; Amgen Ltd (CSR *RAS* analysis), October 2014; Barcelona, Spain; Peeters M et al. Gastrointestinal Cancers Symposium; 2014; San Francisco (CA), USA; Data on File, Price TJ, et al. Lancet Oncology. 2014;15:569-79.

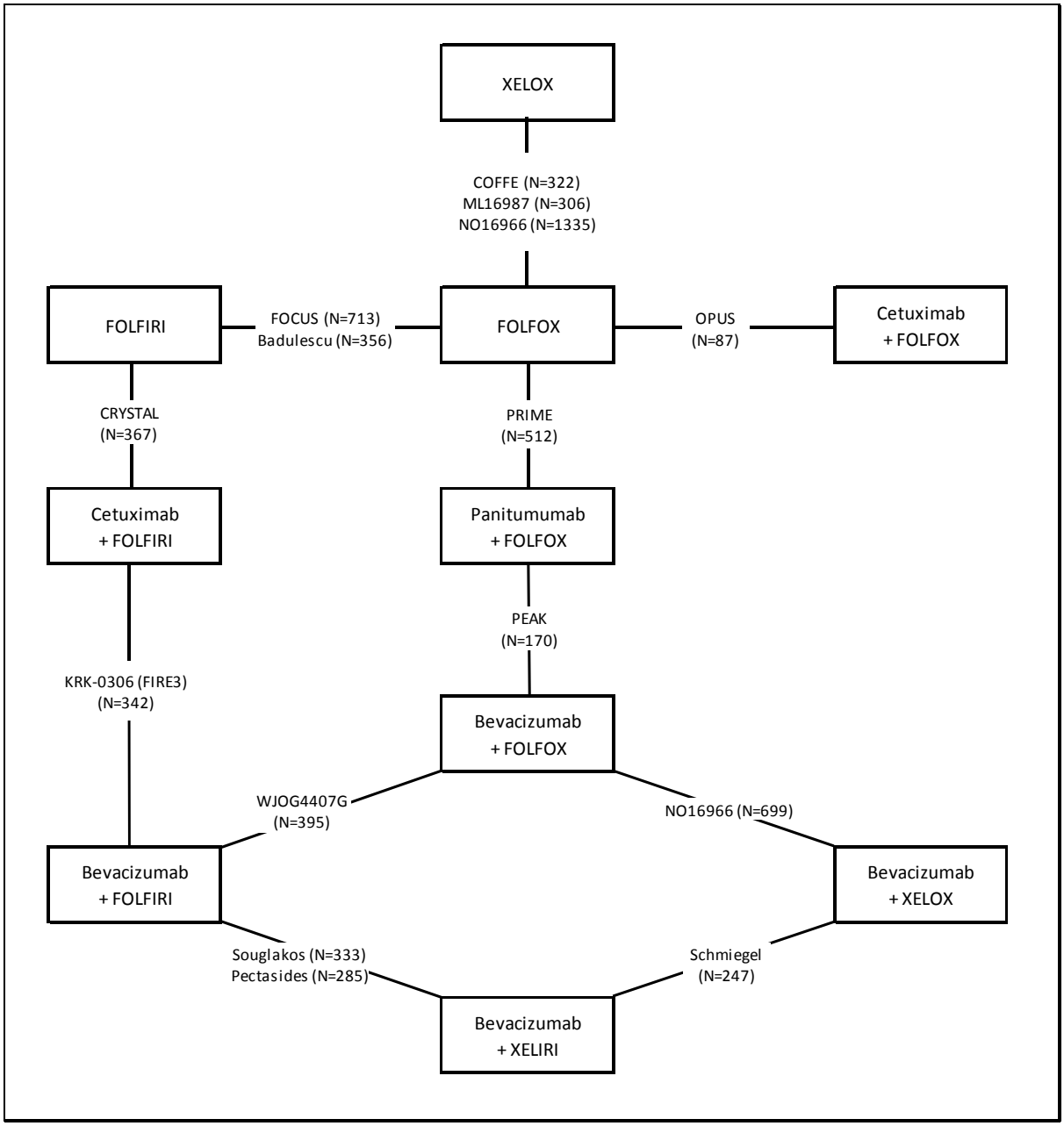
3.6.1.1. Network meta-analysis

Amgen performed a network meta-analysis (NMA) to compare panitumumab in combination with FOLFOX with other identified comparators in the scope (see Section 2.1, p80).

The company conducted a systematic review: the search strategy combined 'drug names' with 'disease terms' and 'study design terms' (the search strategy was provided as an appendix). Inclusion criteria for the NMA were in line with the PICO criteria specified in the NICE scope (see Section 2.1, p80).

Evidence informing the NMA comprised a total of 21 RCTs (reported in 23 publications [Ducreux et al., 2013; Badulescu et al., 2009; Hong et al., 2013; Cornella et al., 2009; Ciardiello et al., 2014; Seymour et al., 2007; Seymour et al., 2011; Heinemann et al., 2014; Ducreux et al., 2011; Cassidy et al., 2011; Saltz et al., 2008; Bokemeyer et al. 2014; Schwartzberg et al., 2014; Karthaus et al., 2014; Douillard et al., 2013; Amgen, 2013; Pectasides et al., 2012; Porschen et al., 2007; Rosati et al., 2010; Schmiegel et al., 2013; Souglakos et al., 2012; Hochster et al., 2008; and Yamazaki et al., 2014]).[37, 38, 42, 43, 53, 78-95] Four trials (Hong et al., 2013; Seymour et al., 2011; Porschen et al., 2007; Rosati et al., 2010),[85, 88, 89, 93] were excluded from the primary analysis due to population differences or differences in treatment regimen administered. Based on the 17 RCTs, Amgen built one network (Figure 7). Studies excluded from the company's primary analysis were included in a sensitivity analysis. Sensitivity analyses included: clinically similar chemotherapy (FOLFOX / XELOX and FOLFIRI / XELIRI), and the inclusion of relevant comparators (FOLFOX, XELOX, XELIRI and cetuximab plus FOLFOX/FOLFIRI). There were insufficient data to perform a NMA comparing panitumumab plus FOLFOX or FOLFIRI with the comparators of interest in the subgroup of people with liver metastases.

Figure 7. Amgen NMA diagram



Key: FOLFIRI = folinic acid+5-fluorouracil+irinotecan+irinotecan; FOLFOX = folinic acid+5-fluorouracil+oxaliplatin; NMA = network meta-analysis; XELIRI = capecitabine+irinotecan; XELOX = capecitabine+oxaliplatin

The study designs of the included studies were comparable; however, not all studies reported all outcomes of interest (OS, PFS, or ORR), hence not all studies contributed to the analysis for each outcome (see Amgen Submission, Appendix 8: Network meta-analysis: Methods and Results, pp27–35). In addition, disease progression and response rate were not assessed using the same method in all of the included studies, but it was assumed that this had no impact on the comparative treatment effect of the PFS or ORR endpoints. Population characteristics were assumed to be the same; however, the studies evaluating a non-EGFR inhibitor included people with mixed or unknown *RAS* status.

The company used meta-analysis techniques (random effects with fixed effects examined in sensitivity analysis) to pool direct comparisons using SAS Vn 9.2 software. For indirect comparison, the company used the Bucher method.[96] The indirect estimate of panitumumab versus comparator was adjusted according to the results of their direct comparisons with a common control using both fixed and random effects meta-analysis. Each indirect comparison was estimated separately within the IC framework. Within the indirect comparison, the underlying assumptions of homogeneity, similarity and consistency were reviewed according to guidelines by Song et al.[97] Details of implementation of the meta-analysis and indirect comparison are given in the Amgen submission (see Amgen Submission, Appendix 8: Network meta-analysis: Methods and Results).

For the NMA, a Bayesian framework with Markov chain Monte Carlo (MCMC) simulation was taken using methodology outlined by Ades et al (2006).[98] Analyses were performed using SAS Version 9.3. Non-informative priors were used. Analyses were run with an initial burn-in of 10,000 iterations followed by an additional 50,000 iterations. To address the potential for auto-correlation, it was necessary to thin the samples that are generated through SAS (a thinning factor of 40 was used). The posterior mean/median and 95% credible interval were reported together with the probability that each treatment was better (more effective) than the others. Within the indirect comparison, the underlying assumptions of homogeneity, similarity and consistency were reviewed according to guidelines by Song et al. (2009).[97] Convergence of the models was examined and Amgen note that, in some cases, the models for the treatment arm level analyses did not converge to a stationary distribution, showing a high level of autocorrelation between draws of the Markov chain, even with thinning factors of 100 or more and a burn-in period of over 1,000,000 iterations attempted. The results for these models were not shown; the company note that this is due to their unsuitability. Details of the implementation of the MTC are given in the Amgen submission (see Amgen Submission, Appendix 8: Network meta-analysis: Methods and Results).

Point estimates for relative effectiveness (including 95% CrI and the probability of being the better treatment), are reported in full in the Amgen submission (see Amgen Submission, Appendix 8: Network meta-analysis: Methods and Results, pp41-42 and pp87-97). Table 58 summarises the results for OS, PFS, and ORR for PAN+FOLFOX versus relevant comparators. Full results (including results of the sensitivity analyses conducted) are reported in the Amgen submission (see Amgen Submission, Appendix 8: Network meta-analysis: Methods and results, pp87–97). Amgen's NMA was not used to analyse liver resection rates or adverse events.

Table 58. Relative effectiveness results for PAN+FOLFOX vs. relevant comparators: Amgen NMA

	PFS HR (95% CrI) [P(HR >1]	OS HR (95% CrI) [P(HR >1]	ORR RR (95% CrI) [P(RR <1]
FOLFOX	[redacted]	[redacted]	[redacted]
XELOX	[redacted]	[redacted]	[redacted]
FOLFIRI	[redacted]	[redacted]	[redacted]
CET+FOLFOX	[redacted]	[redacted]	[redacted]
CET+FOLFIRI	[redacted]	[redacted]	[redacted]

Key: CET = cetuximab; CrI = credible interval; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; HR = hazard ratio; ORR = objective response rate; OS = overall survival; P = probability; PAN = panitumumab; PFS = progression-free survival; RR = relative risk; XELOX = capecitabine + oxaliplatin

Notes: HR <1 favours panitumumab plus FOLFOX; RR >1 favours panitumumab + FOLFOX; statistical significance is indicated by P<0.025 or P>0.975

Source: Amgen submission, Table 15, p41

The following limitations of the NMA were acknowledged: (1) data for non-EGFR inhibitors were from populations with mixed or unspecified *RAS* status; and, (2) data for the *RAS* WT population was not the protocol defined population for any of the EGFR inhibitor studies and results are not for the intention-to-treat (ITT) population but a retrospective subgroup.

Comparison with the Assessment Group's NMA

Of the studies included in Amgen's NMA (n=21 [reported in 23 publications]), 18 studies were not included in the Assessment Group's NMA (Ducreux et al., 2013; Badulescu et al., 2009; Hong et al., 2013; Cornella et al., 2009; Seymour et al., 2007; Seymour et al., 2011; Ducreux et al., 2011; Cassidy et al., 2011; Saltz et al., 2008; Pectasides et al., 2012; Porschen et al., 2007; Rosati et al., 2010; Schmiegel et al., 2013; Souglakos et al., 2012; Hochster et al., 2008; Karthaus et al., 2014; Amgen, 2013; and Yamazaki et al., 2014).[78-95] The reason for their exclusion was that these studies did not evaluate the effectiveness of the interventions in the *RAS* WT population. In addition to the abstracts for the OPUS and CRYSTAL trials (Bokemeyer et al., 2014 and Ciardiello et al., 2014) included in the Amgen NMA the Assessment Group identified the full publications (Tejpar et al., 2015 [provided to the Assessment Group by the lead author as AiC] and Van Cutsem et al., 2015).

Evidence from the included studies enabled the company to construct a complete network. The study Badulescu et al. (2009)[79] compared FOLFOX and FOLFIRI and enables the complete network approach based on the assumption that there was little difference between FOLFOX and FOLFIRI in terms of effectiveness. The NMA conducted by the Assessment Group comprised two separate networks (FOLFOX and FOLFIRI) as none of the included studies provided evidence to link the two networks; the two networks in the *RAS* WT population

Assumptions regarding the similarity between the included trials in terms of the study and design of the included studies were considered by the Assessment Group to be appropriate. However, in terms of population characteristics although data included in the NMA for panitumumab and cetuximab were restricted to the *RAS* WT population in line with the population specified in the NICE scope, data for non-EGFR inhibitors were not available for the *RAS* WT population given that efficacy is not contingent on the expression of the *RAS* genotype. While the Assessment Group consider this to be a logical approach it should be noted that data included in the NMA for non-EGFR inhibitor treatments came from study populations with mixed or unspecified *RAS* status. The likely impact of which would be to increase the uncertainty surrounding the effect estimates.

Analyses were conducted for outcomes PFS, OS, ORR, CR and PR. Time to event data were analysed using study level data (HR), and response rate data were analysed using study level data (RR). The company also note there were insufficient data to perform a NMA for PAN+FOLFOX vs. CET+FOLFOX or CET+FOLFIRI in the subgroup of people with liver metastases.

The methods used in Amgen's NMA were in line with guidance set out in the publication by Ades et al., 2006.[98]

Despite the broader approach taken the results for PAN+ FOLFOX versus FOLFOX were similar to the Assessment Group's NMA for OS and PFS. The effect estimates for this comparison for all outcomes showed a greater effect of PAN+FOLFOX vs FOLFOX but the 95% CrI were wider in the Assessment Group's results. There was no evidence to suggest that time to progression or death or time to death was any more effective for PAN+FOLFOX than for CET+FOLFOX. All results, however, are subject to uncertainty as a result of the acknowledged limitations. As the Assessment Group's NMA focused entirely on the RAS WT population no comparison could be made with Amgen's comparison of PAN+FOLFOX versus XELOX, and given that the Assessment Group's approach to the NMA resulted in two

networks no comparison of results could be made with the company's NMA for PAN+FOLFOX versus either FOLFIRI or CET+FOLFIRI.

3.6.2. Merck Serono

Merck Serono also carried out literature searches for clinical evidence in MEDLINE, MEDLINE-in-Process and EMBASE, via Ovid, and the Cochrane Central Register of Controlled Trials (CENTRAL), via the Cochrane library (Merck Serono Submission, Section 3.1.2.1, p11). As per Amgen, the searches combine free-text and index terms for relevant cancers with free-text and index terms for relevant interventions; however, unlike Amgen, the cancer search terms are combined with RAS search terms to further refine the results (Merck Serono Submission, Appendix A, pp44-49). A publication filter is used to limit the results to randomised controlled trials and observational studies. No language or date limits were applied.

Merck Serono also searched grey literature resources, including an online trials registry - ClinicalTrials.gov - and several online conference proceedings (Merck Serono Submission, Section 3.1.2.1, p12).

The Merck Serono literature searches use an appropriate range of bibliographic databases and grey literature resources for the topic, albeit they search fewer grey literature resources than Amgen. Their choice of free-text and index terms is also appropriate, and there is no evidence that the balance of sensitivity and specificity is compromised by the inclusion of RAS search terms. The database search strategies are reproduced in the appendices, including the number of hits retrieved per search (Merck Serono Submission, Appendix A, pp44-49). The dates the searches were carried out are reported elsewhere in the submission (Merck Serono Submission, Section 3.1.2.1, p11). The grey literature search strategies are not reproduced in the appendices, but the numbers of hits retrieved are reported in the PRISMA flow diagrams (Merck Serono Submission, Section 4.1, pp22-25).

The submission set out to identify the relevant efficacy and safety evidence for the interventions of interest in first-line treatment of people was *RAS* WT mCRC. Seven studies were identified that evaluated cetuximab. Of these, four studies were included in the systematic review presented by Merck Serono (Table 59). Three of the studies were included in the PenTAG systematic review; however, only the studies reporting results for the *RAS* WT population were considered relevant to the scope for this review and, as such, the other related publications were excluded on population. The CALGB-80405 study (Lenz et al., 2014) was not identified in the PenTAG searches. This was because we did not search the

ESMO conference database instead checking the ASCO database in line with published recommendations on searching for HTA reviews.[99] This study would have been excluded from our review, as while the CALGB-80405 trial randomised participants to cetuximab or bevacizumab, participants were not randomised to the background chemotherapy (FOLFOX or FOLFIRI), which could introduce bias into the analysis. In addition, the data are only published as an abstract and not available as a full paper and, as such, not enough information to conduct quality appraisal.

Table 59. Merck Serono submission: Included cetuximab studies

Trial acronym	First author, year	Included in PenTAG review	Reason for exclusion
CRYSTAL (CET+FOLFIRI vs. FOLFIRI)	Van Cutsem et al., 2009 (primary study reference); Van Cutsem et al., 2011; Ciardiello et al., 2014; Van Cutsem et al., 2015	Y (only data for the *RAS* WT population, Van *Cutsem* et al., 2015)	Van Cutsem et al., 2009 (no data for *RAS* WT population); Van Cutsem et al., 2011 (no data for *RAS* WT population); Ciardiello et al., 2014 (abstract)
OPUS (CET+FOLFOX vs. FOLFOX4)	Bokemeyer et al., 2009 (primary study reference); Tejpar et al., 2015	Y (only data for *RAS* WT population, Tejpar et al., 2015)	Bokemeyer et al., 2009 (no data for *RAS* WT population);
FIRE-3 (CET+mFOLFOX6 vs. BEV+mFOLFOX6)	Heinemann et al., 2013 (primary study reference); Stintzing et al., 2014a; Heinemann et al., 2014	Y (only data for *RAS* WT population, Heinemann et al., 2014)	Heinemann et al., 2013 [abstract of Heinemann et al., 2014]; Stintzing et al., 2014 [no data for *RAS* WT population; abstract]
CALGB-80405 (CET+CTX[a] vs. BEV+CTX[a])	Lenz et al., 2014	N	Study not identified in searches [no indexed in EMBASE or MEDLINE]. Participants only randomised to cetuximab or bevacizumab and not to the background chemotherapy. Study published in abstract format (presented at ESMO, 2014) and not enough information to quality appraise.

Key: ESMO = European Society of Medical Oncology; N = No; NA = not applicable; *RAS* = rat sarcoma; vs. = versus; WT = wild type; Y= Yes

Notes: a Chemotherapy was either FOLFOX or FOLFIRI at physician's discretion and randomised to cetuximab or bevacizumab

Sources: Bokemeyer C et al. J Clin Oncol 2009; 27(5): 663-71Ciardiello F et al. 2014 Annual Meeting of the American Society of Clinical Oncology, ASCO Chicago, IL United States. 2014;32 (15 SUPPL. 1.); Heinemann V et al. Jahrestagung der Deutschen, Osterreichischen und Schweizerischen Gesellschaften fur Hamatologie und Onkologie 2013 Wien Austria. 2013;36:10; Heinemann V et al.. Lancet Oncol. 2014; 15(10): 1065-1075; Lenz HJ et al. European Society of Medical Oncology (ESMO); 2014; Madrid (Spain): Abstr LBA3; Stintzing S et al. (Abstract 445). Gastrointestinal Cancers Symposium; 2014; San Francisco (CA), USA: J Clin Oncol; Tejpar S et al.. Eur J Cancer. 2015 (in press); Van Cutsem E et al, New Engl J Med 2009; 360(14): 1408-9; Van Cutsem E etal. J Clin Oncol 2011; 29(15): 2011-2019; Van Cutsem Eet al. J Clin Oncol. 2015; 33(7): 692-700;

Health-related quality of life (HRQoL) data from the OPUS trial (EORTC QLQ-C30 Global Health Status; unpublished data), and the CALGB-80405 trial (EORTC QLQ-C30 and Dermatology Specific Quality of Life [DSQLQ] scale), were also included in the Merck Serono submission (see Merck Serono submission, Section 2.1.3.3, pp34–35). No HRQoL data were identified for inclusion in the Assessment Group's review. Merck Serono reported a summary of AEs, Grade 3 /4 AEs by special AE category, and a comparison of the frequency of Grade 3/4 AEs (number of subjects) known for cetuximab (see Merck Serono submission, Section 2.1.4, pp36–40). For AEs, the Assessment Group reported a summary of AEs, and Grade 3/4 AEs occurring in ≥5% participants in either treatment arm.

Data reported for the FIRE-3 trial in the Merck Serono submission are different to those in the analysis condicted by the Assessment Group (values as reported in the **Heinemann et al. (2014)** paper. It is possible that the data reported in the Merck Serono submission are from a more recent data cut, as the number of participants evaluated as *RAS* WT is 199 in the cetuximab plus FOLFIRI treatment group and 201 in the bevacizumab plus FOLFIRI treatment group compared with 171 participants in each treatment group in the published paper. These unpublished data were analysed in the NMA as a sensitivity analysis (see Sensitivity analyses, p146). Although the results change slightly this difference does not impact the direction of effect.

3.6.2.1. Network meta-analysis

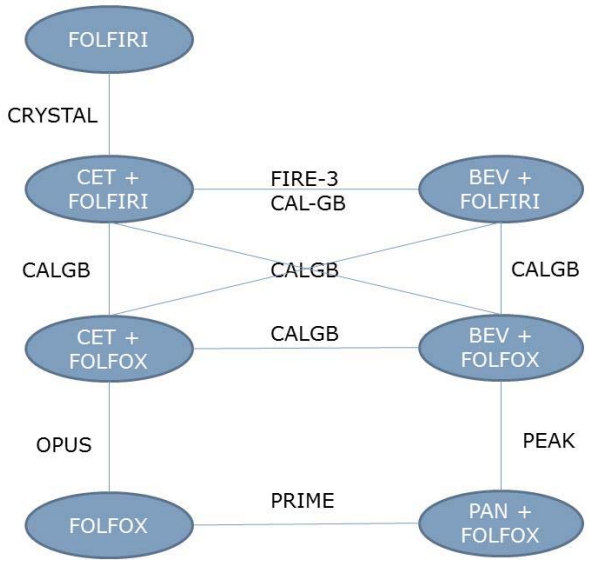
Merck Serono performed a network meta-analysis (NMA) to compare cetuximab plus chemotherapy (FOLFOX or FOLFIRI) for the treatment of *RAS* WT mCRC with other comparators specified in the NICE scope (see Section 2, p80).

The company conducted a systematic review: the search strategy combined 'drug names' with 'disease terms' and 'study design terms' (the search strategy was provided as an appendix). Inclusion criteria for the NMA were in line with the PICO criteria specified in the NICE scope (see Section 2.1, p80).

Six trials were included in the NMA (OPUS, CRYSTAL, FIRE-3, PRIME, PEAK and CALGB-80405).[37, 38, 52, 53, 75, 100] Evidence from these studies enabled one complete network for outcomes OS and PFS (Figure 8). This was possible as the CALGB-80405 trial compared cetuximab plus FOLFOX or FOLFIRI with bevacizumab plus FOLFOX or FOLFIRI, reporting separate Kaplan-Meier curves for each of the possible combination therapies. Within the global network, a sensitivity analysis was also conducted with FOLFOX and FOLFIRI grouped as generic chemotherapy ('chemo') (Figure 9). The complete network approach was

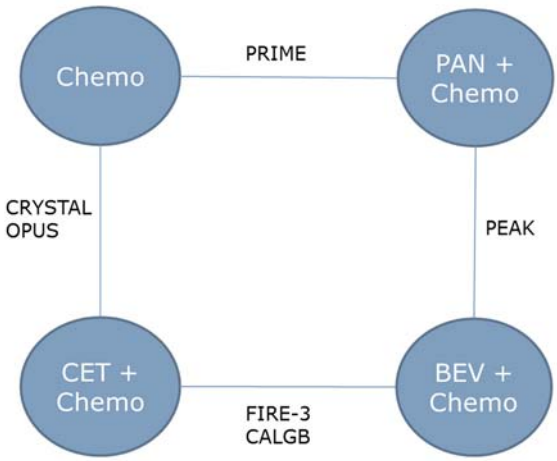
not possible for ORR as neither the PEAK nor CALGB-80405 study reported ORR and, as a result, only a FOLFIRI network was possible for this outcome. It was also not possible to include CALGB-80405 in any safety outcome network due to lack of reporting. Therefore two separate networks, one for FOLFOX and one for FOLFIRI were created to allow an indirect treatment comparison for safety outcomes.

Figure 8. Merck Serono NMA: Global evidence base network – split network



Key: BEV= bevacizumab; CET = cetuximab; FOLFIRI = folinic acid + fluourouacil + irinotecan; FOLFOX = folinic acid + fluourouracil+oxaliplatin; PAN = panitumumab

Figure 9. Merck Serono NMA: Global network for pooled analysis for OS and PFS



Key: BEV= bevacizumab; CET = cetuximab; Chemo = chemotherapy (FOLFOX and FOLFIRI); FOLFIRI = folinic acid + fluourouacil + irinotecan; FOLFOX = folinic acid + fluourouracil+oxaliplatin; PAN = panitumumab

The study designs of the included studies were comparable. While Merck Serono noted that disease progression was not assessed using the same method in all of the included studies, it was assumed that this had no impact on the comparative treatment effect of the PFS endpoint. For the safety outcomes, in the absence of reported data for the RAS WT population in the PRIME trial Merck Serono used data reported for the KRAS WT population. Although the company pre-specified safety outcomes of interest not all could be analysed due to limited reporting in several trials.

Population characteristics were assumed to be the same, although for some trials, baseline characteristics for the RAS WT population were not reported (PRIME) or very little published information was available (CALGB-80405), and data from the KRAS WT population was used as a proxy. Merck Serono highlight differences with respect to disease progression (ECOG PS ≤2 in four of the trials [OPUS, CRYSTAL, FIRE-3, PRIME] vs 0 or 1 in two of the included trials [PEAK and CALGB-80405]). However, the proportion of participants with ECOG PS equal to two in the OPUS and PRIME studies was low and as such was not considered to have an impact on the comparative treatment effect. It was assumed that both FOLFOX regimens (FOLFOX4 and mFOLFOX6) have a comparable effect.

Network meta-analyses were undertaken using a Bayesian approach with Markov chain Monte Carlo (MCMC) simulation in WinBUGS. Non-informative prior distributions were used. For the analysis of PFS, OS and ORR models with a normal likelihood and identify link were used. In addition, survival data extracted from the Kaplan-Meier curves were also analysed using a binomial or log likelihood and log link using a fractional polynomial model. Analysis of AEs used a model with a binomial likelihood and logit link. Analyses were run with an initial burn-in of 10,000 iterations (30,000 for the fractional polynomial models), followed by an additional 80,000 iterations (30,000 for fractional polynomials), and convergence of the samples was examined visually. Monte Carlo error was checked to ensure it was ≤5% of the posterior SD for the parameters examined. Both fixed and random effects models were used. Deviance information criteria (DIC) were used to compare the fixed and random effects models to determine goodness-of-fit; DIC values were reported for both models); where a difference of <5 was observed a fixed effects model was reported and results of the random effects model were reported in appendices (see Appendix B, Merck Serono submission). The posterior mean/median and 95% credible interval were reported together with the probability that each treatment was better (more effective) than the others.

Point estimates for relative effectiveness (including 95% CrI and the probability of being the better treatment), are reported in full in the Merck Serono submission (pp51–82). Table 60 summarises the results for OS, PFS and ORR for CET+FOLFOX and CET+FOLFIRI vs.

relevant comparators. In terms of AEs (not shown here), CET+FOLFIRI was associated with more events than FOLFIRI alone for Grade 3-4 venous thromboembolism, skin reactions, acne-like rash, mucositis, neutropenia, hypokalemia, hypomagnesemia and paronychia. Compared to BEV+FOLFIRI, CET+FOLFIRI was worse for skin reactions, acne-like rash, hypokalemia, hypomagnesemia and paronychia. However, CET+FOLFIRI was better than BEV+FOLFIRI for nausea (all grades) and vomiting (all grades). For the FOLFOX network, CET+FOLFOX, was worse than FOLFOX alone for Grades 3–4 pulmonary embolism and skin reactions. Compared to PAN+FOLFOX, CET+FOLFOX was worse for Grades 3-4 skin reactions.

Table 60. Relative effectiveness results for CET+FOLFIRI and CET+FOLFOX vs. relevant comparators[a]: Merck Serono NMA

CET+FOLFIRI vs.	OS[b] HR (95% CrI; P[better])	PFS[b] HR (95% CrI; P[better])	ORR[c] OR (95% CrI; P[better])
FOLFIRI	0.69 (0.54, 0.88; >99%)	0.56 (0.41, 0.76; >99%)	3.14 (2.07, 4.85; >99%)
BEV+FOLFIRI	0.80 (0.64, 1.01; 97%)	0.98 (0.81, 1.19; 58%)	1.29 (0.83, 2.00; 87%)
FOLFOX	0.96 (0.61, 1.52; 56%)	0.95 (0.61, 1.47; 60%)	NA[d]
CET+FOLFOX	0.98 (0.73, 1.31; 56%)	1.04 (0.81, 1.35; 37%)	NA[d]
PAN+FOLFOX	1.26 (0.80, 1.99; 16%)	1.39 (0.92, 2.11; 6%)	NA[d]
BEV+FOLFOX	0.83 (0.60; 1.13; 88%)	1.08 (0.85, 1.39; 26%)	NA[d]
CET+FOLFOX vs.	OS[b]	PFS[b]	ORR[c]
FOLFOX	0.99 (0.67, 1.45; 53%)	0.91 (0.61, 1.36; 68%)	NA[d]
PAN+FOLFOX	1.29 (0.87, 1.91; 10%)	1.33 (0.91, 1.95; 7%)	NA[d]
BEV+FOLFOX	0.85 (0.64, 1.12; 88%)	1.04 (0.84, 1.259; 37%)	NA[d]
FOLFIRI	0.71 (0.48, 1.04; 96%)	0.54 (0.36, 0.80; >99%)	NA[d]
BEV+FOLFIRI	0.82 (0.61, 1.11; 90%)	0.94 (0.72, 1.22; 68%)	NA[d]
CET+Chemo[e] vs.	OS[b]	PFS[b]	ORR[c]
Chemo[e]	0.76 (0.62, 0.94; >99%)	0.67 (0.53, 0.85; >99%)	–
PAN+Chemo[e]	1.02 (0.79, 1.32; 43%)	1.05 (0.80, 1.37; 38%)	–
BEV+Chemo[e]	0.79 (0.67, 0.94; >99%)	0.98 (0.85, 1.13; 61%)	–

Key: BEV= bevacizumab; CET = cetuximab; Chemo = chemotherapy (FOLFOX and FOLFIRI, see note e below); CrI = credible interval; FOLFIRI = folinic acid+fluourouacil+irinotecan; FOLFOX = folinic acid+fluourouracil+oxaliplatin; HR = hazard ratio; NA = not applicable; NMA = network meta-analysis; OR = odds ratio; ORR = objective response rate; OS = overall survival; P = probability; PAN = panitumumab; PFS = progression free survival; vs. = versus

Notes: a Based on results from fixed effects meta-analysis; b Hazard ratio (mean survival also analysed); c Odds ratio; d The complete network approach was not possible for ORR as neither the PEAK nor CALGB-80405 study reported this outcome and, as a result, only a FOLFIRI network was possible; e Chemo = pooled FOLFOX and FOLFIRI, conducted as a sensitivity analysis for the complete network for outcomes OS and PFS only

The following limitations of the NMA were noted: (1) due to the retrospective nature of the *RAS* analysis, for some studies, there were a low number of samples available for analysis reducing the power of the studies to show statistical significance; and, (2) limited data were available on safety for the CALGB-80405 study, resulting in many of the indirect comparison analyses having very wide confidence intervals and making interpretation from the indirect comparison difficult.

Comparison with the Assessment Group's NMA

Of the studies included in the NMA only CALGB-80405 was not included in the NMA conducted by the Assessment Group. CALGB-80405 compared cetuximab plus FOLFOX or FOLFIRI with bevacizumab FOLFOX or FOLFIRI; however, participants were only randomised to the cetuximab or bevacizumab component of the treatment, with the background chemotherapy (FOLFOX or FOLFIRI) chosen at the physicians' discretion. In addition, the CALGB-80405 trial is currently only available as an abstract. For these reasons this study was excluded from the Assessment Group's systematic review and NMA. No trials were identified analysing the effectiveness of panitumumab plus FOLFIRI versus any of the comparators specified in the NICE scope.

Using the CALGB-80405 enabled the company to construct a complete network for outcomes PFS and OS. The company conducted two analyses. One analysis used data from participants in the trial according to chemotherapy received; however, in this approach randomisation is broken and could introduce bias into the analysis. The second, a sensitivity analysis pooled results for FOLFOX and FOLFIRI as generic chemotherapy ('chemo') based on the assumption that there was little difference between FOLFOX and FOLFIRI in terms of effectiveness based on evidence reported in the Colucci et al., (2005) trial.[101] For ORR, and analysis of safety outcomes required two separate networks (one for FOLFOX and one for FOLFIRI). The Assessment Group's NMA used two separate networks (FOLFOX and FOLFIRI) for the analysis of all outcomes in the *RAS* WT population, as none of the included studies provided evidence to link the two networks.

Assumptions regarding the similarity between trials in terms of the study and population characteristics of the included studies were considered by the Assessment Group to be appropriate.

Absence of reported data for the PRIME and PEAK trials meant that ORR could not be conducted for the FOLFOX network, and analysis of all-grade AEs analyses could also not be performed for the FOLFOX network. The Assessment Group, however, had access to

unpublished data from the PRIME and PEAK trials and were able to analyse safety outcomes for any Grade 3/4 AEs, serious adverse events (SAEs), as well as Grade 3–4 AEs by type occurring in ≥5% participants in either treatment arm. The Assessment Group also conducted NMA for outcomes resection rates and also for the subgroup of patients with liver metastases at baseline.

The methods used in Merck Serono's NMA were in line with guidance from the NICE Decision Support Unit (DSU) guidance).[74]

Despite the slight differences in approach between the Merck Serono NMA and the Assessment Group's NMA the overall results were similar, with both analyses subject to significant uncertainty.

4. Assessment of cost effectiveness

4.1. Systematic review of existing cost-effectiveness studies

The cost-effectiveness of cetuximab (CET) and panitumumab (PAN) for people with previously untreated rat sarcoma (RAS) wild type (WT) metastatic colorectal cancer (mCRC) was assessed by conducting a systematic review of published research evidence.

4.1.1. Objectives

The objectives of this systematic review were to:

- gain insights into the key drivers of cost-effectiveness in this disease area.
- get an overview of the alternative modelling approaches that have been adopted in this disease and treatment area.
- provide a summary of the findings of previous relevant cost-utility, cost-effectiveness, and cost-benefit studies generalisable to the UK.

4.1.2. Methods

4.1.2.1. Study identification

The search strategy for economic studies included the following search methods:

- Searching of bibliographic and ongoing trials databases.
- Searching of conference proceedings.
- Scrutiny of bibliographies of retrieved papers and company submissions.

The following databases were searched for economic studies: MEDLINE (Ovid); MEDLINE In-Process and Other Non-Indexed Citations (Ovid); EMBASE (Ovid); NHS EED (via Cochrane Library); EconLit (EBSCO); Web of Science (Thomson Reuters).

A supplementary search for health utilities was run in the following databases: MEDLINE (Ovid); MEDLINE In-Process and Other Non-Indexed Citations (Ovid); EMBASE (Ovid); PsycINFO (Ovid); Web of Science (Thomson Reuters); ScHARR Health Utilities Database.

The searches were developed and run by an information specialist (SB) in January 2015. Search filters were used to limit the searches to economic or health utilities studies as appropriate, and searches were limited to English language studies where possible. No date limits were used. An update search was carried out on 27th April 2015. No papers or abstracts published after this date were included in the review. Ongoing trials databases were searched by a reviewer in March 2015. The search strategies for each database are detailed in Appendix B.

The database search results were exported to, and de-duplicated using Endnote (X7). De-duplication was also performed using manual checking. After the reviewer completed the screening process, the bibliographies of included papers were scrutinised for further potentially includable studies. The manufacturers' submissions were assessed for unpublished data.

Titles and abstracts returned by the search strategy were examined by one researcher (NH) and screened for possible inclusion. Full texts of potentially relevant studies were ordered. Full publications were assessed by the same reviewer (NH) for inclusion or exclusion against prespecified criteria.

4.1.2.2. Eligibility criteria

Inclusion and exclusion criteria were identical to the clinical effectiveness systematic review (Section 3.1.2, pp.85-86), with the following exceptions (as specified in the appraisal protocol):

- Non-randomised studies were included (e.g., decision model based analyses or analyses of patient-level cost and effectiveness data alongside observational studies).
- Full cost-effectiveness analyses, cost-utility analyses, cost-benefit analyses and cost consequence analyses were included. (Economic evaluations which only report average cost-effectiveness ratios were only included if the incremental ratios could be easily calculated from the published data).
- Studies that measure only costs but not health benefits were excluded except for stand alone cost analyses from the perspective of the UK NHS.

4.1.2.3. Data extraction

Study characteristics and results were abstracted by one reviewer (NH). In addition, parameters which could be used in the construction of an independent economic model were identified and noted.

The evidence base was assessed using narrative synthesis supported by summary data extraction tables.

4.1.3. Critical appraisal

Selected studies were quality assessed using the checklist developed by Evers et al. (2005) [1] by one reviewer (NH). Where there was insufficient information available in the article to assess quality the item was marked "No".

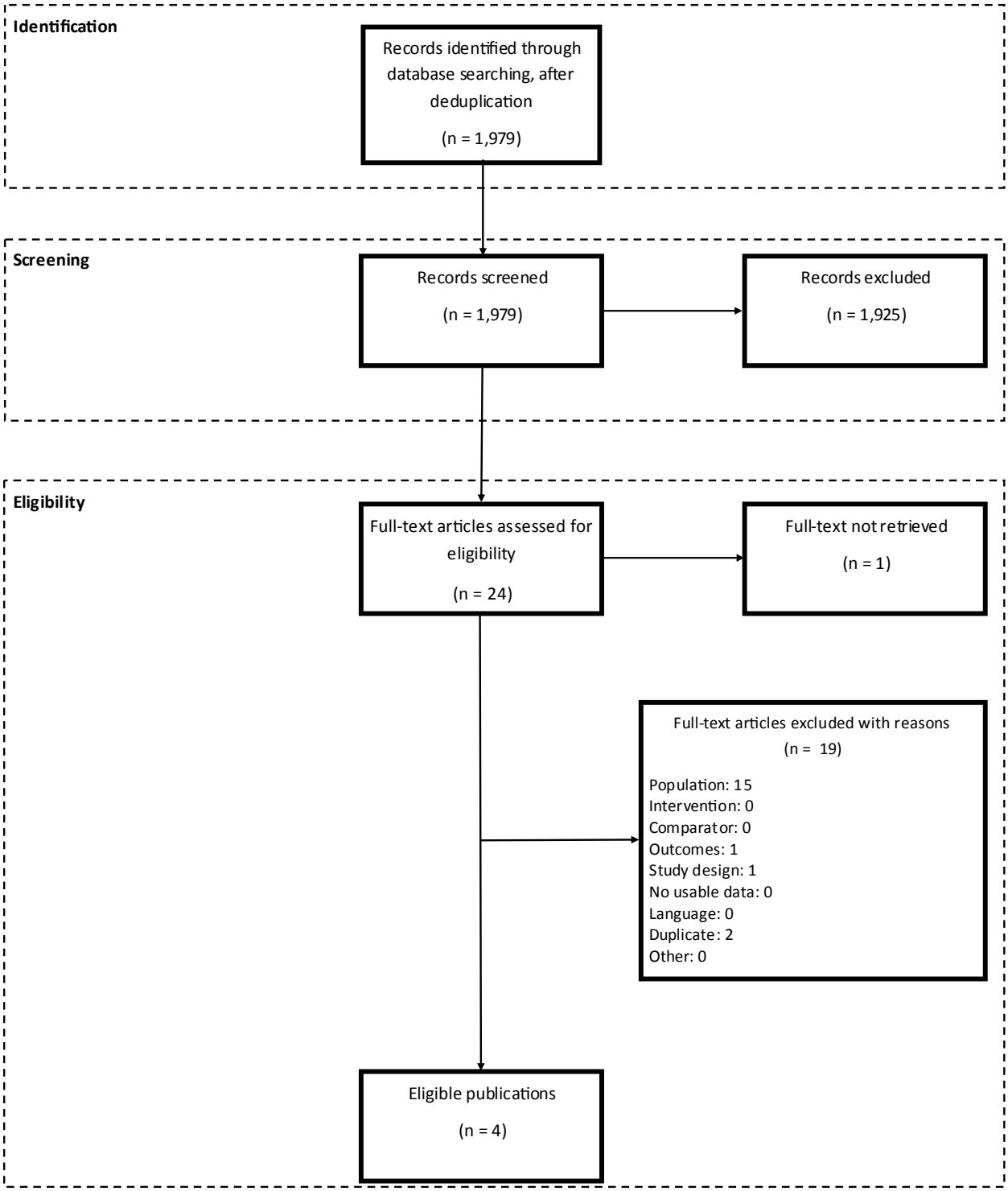
Where these studies were based on decision models, they were further quality assessed using the checklist developed by Philips et al. (2006).[2]

4.1.4. Results

Figure 10 shows the study flow diagram of this update review. The electronic database search for cost-effectiveness evidence identified 1,979 records after deduplication. All were screened by title and abstract. Of these 24 were identified for full-text screening, 5 were conference abstracts and 1 full-text could not be retrieved. 18 full texts were retrieved and assessed for eligibility. Of the 5 conference abstracts, 1 was a duplicate and 1 was a duplicate of a full paper.

Of the 19 full texts assessed for eligibility, 1 was deemed to meet the eligibility criteria. This study and the 2 abstracts for which posters were available, were assessed in full. The poster for the remaining abstract could not be identified. This study could therefore not be assessed in full, but the summary information is presented here.

Figure 10. PRISMA flow diagram for cost-effectiveness papers.



4.1.4.1. Characteristics of identified cost utility studies

Details of the included studies are given in Table 61 and Table 62. Theses tables show that none of the included studies compared both cetuximab and panitumumab. The comparator arms were either bevacizumab in combination chemotherapy agents or chemotherapy alone. The range of chemotherapies differed across studies. One study (Jarrett et al., 2014)[9] was based in the UK, but from the perspective of the Scottish National Health Service. This study only considered cetuximab in combination with chemotherapy (FOLFOX and FOLFIRI).

All studies used Markov or semi-Markov models and included resection and subsequent lines of treatment as health states, though the overall number of health states varied.

Jarrett et al. reported the smallest estimate of life years gained, which may be a consequence of a shorter time horizon in the model: 10 years as opposed to 20 years in the Graham et al. (2014) and nonspecified 'lifetime' in the other studies.

Table 61. Characteristics of included cost-effectiveness studies.

First author and year published	Setting, perspective	Population	Study purpose	Study approach	Comparators
Graham et al. (2014)	French health collective perspective	Adults >=18 years with RAS WT mCRC	Cost-effectiveness of 1st-line PAN+FOLFOX compared with BEV+FOLFOX	Semi-Markov decision model Lifetime horizon (<= 20 years), 2 week cycle length	PAN+FOLFOX BEV+FOLFOX
Jarrett et al. (2014)	Scottish National Health Service	RAS WT mCRC patients	Cost-effectiveness of 1st-line cetuximab in combination with chemotherapy compared to currently available treatments	Markov cohort decision model Lifetime horizon (10 years), 1 month cycles	CET+FOLFOX/FOLFIRI FOLFOX/FOLFIRI alone
Kourlaba et al. (2014)	Greek health care perspective	RAS WT mCRC patients	Cost-effectiveness of 1st-line PAN+FOLFOX compared with BEV+FOLFOX	Semi-Markov decision model	PAN+FOLFOX BEV+FOLFOX
Ortendahl et al. (2014)	US payer	US adults with previously untreated RAS WT mCRC	Cost-effectiveness of 1st-line CET+FOLFIRI compared to BEV+FOLFIRI	Markov cohort decision model Lifetime horizon	CET+FOLFIRI BEV+FOLFIRI

Key: BEV = bevacizumab; CET = cetuximab; FOLFIRI = folinic acid + flurouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; mCRC = metastatic colorectal cancer; PAN = panitumumab; WT; wild type
Sources: Graham et al. 2014;[102] Jarrett et al. 2014;[9] Kourlaba et al. 2014;[103] Ortendahl et al. 2014.[104]

Table 62. Results of included cost-effectiveness studies.

First author and year published	Outcomes measured	Discount rate	Base results	Sensitivity analysis approach	Main sensitivity analysis results
Graham et al. (2014)	Costs, LYs QALYs ICERs: €/LYG, €/QALY gained	4.0% costs and benefits	PAN+FOLFOX: 3.58 LYs, 2.68 QALYs, €97,203 BEV+FOLFOX: 2.73 LYs, 2.05 QALYs, €74,440 ICERs vs. BEV+FOLFOX: €26,918 per LYG, €36,577 per QALY gained	Scenario analysis, 1-way sensitivity analysis and probabilistic sensitivity analysis	Most notable scenario: all patients receive BSC after 1st-line (ICER €50,390 per QALY gained). 1-way sensitivity analysis: model most sensitive to drug acquisition costs, BSC costs and costs of subsequent treatments. PSA: PAN+FOLFOX most likely to be cost-effective at WTP threshold of €40,000.
Jarrett et al. (2014)	Costs, LYs, QALYs ICERs: £/LYG, ICERs £/QALY gained	NR	CET+FOLFIRI: 1.79 LYs, 1.30 QALYs, £41,015 FOLFIRI 1.45 LYs, 1.05 QALYs, £28,301 ICER vs. FOLFIRI £39,631 per LYG, £52,802 per QALY gained. CET+FOLFOX: 1.81 LYs, 1.32 QALYs, £39,612 FOLFOX: 1.50 LYs, 1.08 QALYs, £27,685. ICERS vs. FOLFOX: £38,936 per LYG, £50,894 per QALY gained	Scenario analysis, one way sensitivity analysis	Scenario analysis: no vial sharing increased ICERS to £58,220 (FOLFIRI), £56,520 (FOLFOX) per QALY gained. 1-way sensitivity analysis: model sensitive to treatment duration, body surface area, progression HR, proportion referred for curative resection.

First author and year published	Outcomes measured	Discount rate	Base results	Sensitivity analysis approach	Main sensitivity analysis results
Kourlaba et al. (2014)	Costs, LYs, QALYs ICERs €/QALY gained	NR	Incremental LYs 0.87, QALYs 0.65 PAN+FOLFOX vs. BEV+FOLFOX Incremental costs PAN+FOLFOX vs. BEV+FOLFOX €22,464. ICER vs BEV+FOLFOX: €34,644 per QALY gained	PSA	PSA: PAN+FOLFOX 81.5% likely to be cost-effective at WTP threshold of €51,000 per QALY gained
Ortendahl et al. (2014)	Costs, LYs, QALYs ICERs: £/LYG, $/QALY gained	NR	CET+FOLFIRI: 4.04 Lys, 3.11 QALYs, $305,727 BEV+FOLFIRI: 3.17 Lys, 2.43 QALYs, $238,255 ICERs vs BEV+FOLFIRI $77,380 per LYG, $99,636 per QALY gained	NR for *RAS* WT subgroup	NR for *RAS* WT subgroup

Key: BEV= bevacizumab; CET = cetuximab; FOLFIRI = folinic acid + flurouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; LYs = life years; mCRC = metastatic colorectal cancer; mFOLFOX6 = modified FOLFOX6; NR = not reported; PAN = panitumumab; PSA = probabilistic sensitivity analyses; QALYs = quality adjusted life years; WT = wild type; WTP = willingness to pay

Sources: Graham et al. (2014);[102] Jarrett et al. (2014);[9] Kourlaba et al. (2014);[103] Ortendahl et al. (2014)[104]

We now report the methods and results for the four included studies. As bevacizumab is no longer on the Cancer Drugs Fund (CDF), focus is given to those studies that report other comparator treatments.

Jarrett et al. (2014)

In this study the authors based their model population on the *RAS* wild type (WT) subset of patients who were retrospectively identified in the CRYSTAL and OPUS trials of cetuximab in combination with FOLFOX4 (or FOLFIRI) versus FOLFOX4 (or FOLFIRI) alone. Further details of these studies can be found in Section 3.2, pp.91-95. The authors used a Markov cohort model with five states to conduct a cost-utility analysis of cetuximab plus FOLFOX4 (CET+FOLFOX4) versus FOLFOX4 alone and cetuximab plus FOLFIRI (CET+FOLFIRI) versus FOLFIRI alone, from the Scottish National Health Service perspective.

The model included states such as first line (progression free), second and third line progressed disease states, post curative resection and death states. Progression free survival (PFS) was based on parametric survival curves estimated using the CRYSTAL data, using Weibull distributions. Resection transition probabilities were based on the CRYSTAL trial and death post resection was based on trial overall survival (OS) data. Transition probabilities for subsequent treatment were based on a study by Tournigand et al. Transition to death following 3rd line therapy was based on Jonker et al.

Unit cost data was based on Scottish sources or UK national sources when Scottish specific sources were not available. Resource use for post-resection was taken from Adam et al. and validated by a clinical expert in Scotland. The full reference for this is not reported. Other resource use was based on a systematic literature review.

Utilities were based on a systematic literature review. The sources were identified through the SMC report of this study as Bennett et al. (2011),[5] Wang et al. (2011)[6] (both also identified by our review) and Petrou and Hockley (2005),[105] which looked at the validity of EQ-5D and SF-6D.[10]

In this study, CET+FOLFOX4 resulted in 1.81 life years (1.32 quality adjusted life years, QALYs), compared to 1.50 life years (1.08 QALYs) when FOLFOX4 was used alone. Similarly, CET+FOLFIRI resulted in 1.79 life years (1.30 quality adjusted life years, QALYs), compared to 1.45 life years (1.05 QALYs) when FOLFIRI is used alone. The costs of cetuximab in combination with chemotherapy worked out to be roughly £12,000 more expensive than chemotherapy alone. This led to ICERs of more than £50,000 per QALY gained for cetuximab plus chemotherapy versus chemotherapy alone.

A scenario analysis where full vial wastage was assumed, which may be closer to general practice, increased the ICERs by more than £5,000. Sensitivity analyses showed that the model was sensitive to cost and effect of treatment with cetuximab: duration of treatment, body surface area, progression hazard rate and proportion of cohort referred for curative resection had large impacts on the ICER.

The poster claims that this analysis shows that cetuximab plus chemotherapy is a cost-effective treatment, especially in light of meeting the SMC's end-of-life criteria. According to the SMC report, cetuximab was accepted for this patient population, but only after a Patient Access Scheme (PAS) was applied to demonstrate cost-effectiveness. A further analysis of CET+FOLFOX4 versus CAPOX (XELOX) was requested by the SMC, assuming that XELOX and FOLFOX had similar efficacy, which resulted in an ICER of over £70,000 per QALY gained (without the PAS).[106]

This study is the most relevant to our review, as it is UK based and compares the intervention with chemotherapy agents available on the NHS. It does not include bevacizumab as a comparator, but with bevacizumab no longer on the CDF for this indication, this analysis may still be relevant. However, it does not assess panitumumab in a similar context and therefore does not answer the entire scope of our review.

Graham et al. (2014)

In this study the authors based their model population on the *RAS* wild type (WT) subset of patients who were retrospectively identified in the PEAK trial. In summary, these were patients at least 18 years old, who were diagnosed with previously untreated RAS WT metastatic colorectal cancer (mCRC). Further details of the PEAK population can be found in the clinical effectiveness review, see Section 3.2.3.2, p.96. The authors used a semi-Markov model with seven states to conduct a cost-utility analysis of panitumumab plus mFOLFOX6 (PAN+mFOLFOX6) versus bevacizumab plus FOLFOX (BEV+mFOLFOX6), from the perspective of the French health collective.

The model included states such as progression free and progressive disease with subsequent therapy or best supportive care (BSC) as well as separate states for attempted resection and post-resection disease states. Progression free survival (PFS) and overall survival (OS) were based on parametric survival curves estimated using the PEAK patient level data, using Weibull distributions. These were converted to transition probabilities to disease progression and death states. Resection transition probabilities were based on the

PEAK trial and a study by Adam et al. (2004).[3] Transition probabilities for subsequent treatment were also based on the PEAK trial.

Drug acquisition costs were estimated using French Health National Insurance costs and dose intensity and frequency were calculated from PEAK data. Other costs, including adverse events, *RAS* mutation testing, drug administration, chemotherapy, physician visits, diagnostic tests, resection, subsequent treatment and best supportive care were taken from literature and French healthcare cost sources. Costs were reported in 2013 Euros.

Utilities were based on the EQ-5D responses from the *RAS* WT patients in the PRIME trial. For subsequent lines of treatment, the patient population was assumed to be similar to that of patients who are only *KRAS* WT and EQ-5D responses for these were used from trials looking at subsequent lines of treatment. The EQ-5D responses were converted to utilities using the Dolan algorithm[107], which was valued using UK responses.

Costs and benefits were discounted at 4% per annum, the suggested discount rate in France.

In this study PAN+mFOLFOX6 resulted in 3.58 life years (2.68 quality adjusted life years, QALYs), compared to 2.73 life years (2.05 QALYs) when BEV+mFOLFOX6 was used. Costs were also higher for PAN+mFOLFOX6, €97,203 compared to €74,440 for BEV+mFOLFOX6. This was due to the higher drug costs associated with panitumumab. This resulted in an ICER €36,577 per QALY gained for PAN+ mFOLFOX6 versus BEV+mFOLFOX6.

The authors conducted multiple scenario analyses, univariate sensitivity analyses and a probabilistic sensitivity analysis. The most notable scenario analysis where no active subsequent treatments were assumed (all patients received BSC) raised the ICER to over €50,000 per QALY gained. The probabilistic sensitivity analysis showed that PAN+mFOLFOX6 was most likely to cost-effective compared to BEV+mFOLFOX6 at a willingness to pay threshold of €40,000.

Kourlaba et al. (2014)

The only available copy of this study was a conference abstract. In this study the authors based their model population on the *RAS* wild type (WT) subset of patients who were retrospectively identified in the PEAK trial and used a previously existing model consisting of seven health states. The authors used this Markov model to conduct a cost-utility analysis of PAN+mFOLFOX6 versus BEV+mFOLFOX6, from the perspective of the Greek health care

setting. Given the description, we believe this model to be the same as that reported in Graham et al.

PAN+mFOLFOX6 led to an increase in QALYs of 0.65 compared to BEV+mFOLFOX6 and a cost increase of €22,464. This gave ICERs of €34,644 per QALY gained compared BEV+mFOLFOX6.

Ortendahl et al. 2014

This study was published as a poster in 2014. In this study the authors based their model population on the *KRAS* wild type (WT) subset of patients who were retrospectively identified in the FIRE-3 trial of CET+FOLFIRI versus bevacizumab in combination with FOLFIRI (BEV+FOLFIRI). However, as a scenario analysis, the *RAS* WT subset was identified and assessed. The authors used a Markov cohort model with four states to conduct a cost-utility analysis of CET+FOLFIRI versus BEV+FOLFIRI, from the United States (US) perspective.

The model included states such as first line (progression free), second line progressed disease states, post curative resection and death states. Overall survival (OS) was based on FIRE-3 data, using Weibull distributions. Resection transition probabilities and transition probabilities for subsequent treatment were also based FIRE-3 data.

Unit costs were reported in 2013 US$, but sources were not given. Utilities were based on a published literature.

In this study, CET+FOLFIRI resulted in 4.04 life years (3.11 quality adjusted life years, QALYs), compared to 3.17 life years (2.43 QALYs) when BEV+FOLFIRI is used. The costs of CET+FOLFIRI were calculated to be greater than $67,000 more expensive than BEV+FOLFIRI. This led to an ICER of more than $99,000 per QALY gained for CET+FOLFIRI versus BEV+FOLFIRI.

As this was only a scenario analysis, the sensitivity analyses were applied to the base case and therefore the exact results are not applicable. However, overall survival and treatment costs appeared to be the most influential parameters in the base case and this is likely to carry over into the scenario analysis.

4.1.4.2. Quality of identified cost-utility studies

Jarrett et al. (2014) is so far only reported as a poster, with further information available through the SMC report on this assessment. As such, it lacks some details, primarily

justification for modelling techniques, which may have been present in a full paper. It is also funded by Merck Serono, so it is not an independent assessment. The assessment does not include all comparators relevant to our review and this was a criticism raised by the SMC, when they requested an additional comparison be done between CET+FOLFOX4 and XELOX (referred to as CAPOX), as this was believed to be in regular use on the Scottish NHS. However, this is the only study that is conducted in the UK and does include two relevant comparators, FOLFOX and FOLFIRI.

Graham et al. (2014) is the only full paper currently published that assesses the cost-effectiveness of panitumumab. However, the only comparator is bevacizumab in combination with chemotherapy, which has not been recommended by NICE and is no longer available on the Cancer Drugs Fund (CDF) for this indication. Furthermore it is not UK based, making the results less generalisable to the NHS. This means that the cost-effectiveness estimates provide limited information to this appraisal. The study was sponsored by Amgen, so is not an independent assessment. However, the model is generally well-reported and relevant to answering the objective set by the paper. Reporting of methods of validating the model (e.g. sensitivity analyses) was the done least well, as demonstrated by the Evers and Philips checklists in Table 63, p. 184 and Table 64, p.185.

The *RAS* WT analysis of Ortendahl et al. is only conducted as a scenario analysis so the quality assessment is based the reporting of the base case model. As it is only a poster, there were limits to the reporting, including cost sources and justification of modelling methods. Given the limitations of the study being reported only as a poster, and the analysis of interest not the base case, the quality assessment is of limited use.

As Kourlaba et al. was only reported as an abstract and no further details could be found, we did not quality assess this study.

All studies appear to feature contributions from or are funded by manufacturers, so they have the potential for bias.

Table 63. Quality appraisal of cost-utility studies using the checklist developed by Evers and colleagues

	Jarrett et al. 2014	Graham et al. 2014	Ortendahl et al. 2014
1. Is the study population clearly described?	Yes	Yes	Yes
2. Are competing alternatives clearly described?	Yes	Yes	Yes
3. Is a well-defined research question posed in answerable form?	Yes	Yes	Yes
4. Is the economic study design appropriate to the stated objective?	Yes	Yes	Yes
5. Is the chosen time horizon appropriate to include relevant costs and consequences?	Yes	Yes	Yes
6. Is the actual perspective chosen appropriate?	Yes	Yes	Yes
7. Are all important and relevant costs for each alternative identified?	No	Yes	No
8. Are all costs measured appropriately in physical units?	Yes	Yes	Yes
9. Are costs valued appropriately?	Unclear	Yes	Unclear
10. Are all important and relevant outcomes for each alternative identified?	Yes	Yes	Yes
11. Are all outcomes measured appropriately?	Yes	Yes	Yes
12. Are outcomes valued appropriately?	Yes	Yes	Yes
13. Is an incremental analysis of costs and outcomes of alternatives performed?	Yes	Yes	Yes
14. Are all future costs and outcomes discounted appropriately?	NR	Yes	NR
15. Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	No	No	No
16. Do the conclusions follow from the data reported?	Yes	Yes	Yes
17. Does the study discuss the generalizability of the results to other settings and patient/client groups?	No	No	Yes
18. Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	No,	No	No
19. Are ethical and distributional issues discussed appropriately?	Yes	No	No

Source: Evers et al. (2005)[1]

Table 64. Quality appraisal of cost-utility studies using the checklist developed by Philips and colleagues

	Graham et al. 2014	Jarrett et al. 2014	Ortendahl et al. 2014
Structure (S)			
S1: Statement of decision problem/objective	Yes	Yes	Yes
S2: Statement of scope/perspective	Yes	Yes	Yes
S3: Rationale for structure	Yes	No	No
S4: Structural assumptions	No	No	No
S5: Strategies/comparators	Yes	Yes	Yes
S6: Model type	Yes	Yes	Yes
S7: Time horizon	Yes	Yes	Yes
S8: Disease states/pathways	Yes	Yes	Yes
S9: Cycle length	Yes	Yes	Yes
Data (D)			
D1: Data identification	No	No	No
D2: Pre-model data analysis	(No)	No	No
D2a: baseline data	No	No	No
D2b: treatment effects	No	No	No
D2c: quality-of-life weights (utilities)	Yes	No	No
D3: Data incorporation	No	No	No
D4: Assessment of uncertainty	(No)	No	(No)
D4a: methodological	Yes	No	No
D4b: structural	Yes	No	No
D4c: heterogeneity	No	No	NR
D4d: parameter	No	No	NR
Consistency (C)			
C1: Internal consistency	No	No	No
C2: External consistency	Yes	No	No

Source: Philips et al. (2006)[2]

4.1.5. Discussion

There is limited knowledge to be gained from the studies identified in this review. None of the studies include all of the comparators relevant to the NHS and only one is relevant to a UK setting: Jarrett et al. (2014). Further details of this study were identified by accessing the SMC associated documents, but this is still limited in its reporting and does not include panitumumab as a comparator.

The quality of the reporting is mixed, primarily because most studies have only been published in abstract form and presented at conferences. This also suggests the potential for these results to change before a full journal publication. Though posters were sought for those abstracts presented at conference, it is important to remember that the posters themselves are not subject to peer review and so they have not been through a level of quality assessment prior to this review. The only study that has been fully peer-reviewed and published is Graham et al. which is not UK-based and whose main comparator, bevacizumab in combination with chemotherapy, is no longer funded by the CDF and therefore not the focus of our research.

4.1.5.1. Strengths and limitations

This review was conducted by an independent group, using a systematic approach to identify and review studies. Update searching also allowed for the most recent evidence to be identified. Strict review criteria meant that only papers relevant to the decision problem were identified and could give a clear demonstration of the limited evidence currently available.

The review also identified relevant posters associated with the abstracts identified at the title and abstract stage, which aided in informing this review in greater detail.

As only one reviewer reviewed at both the title and abstract stage, there is the potential for studies to be missed that may have been identified by a second reviewer. Furthermore, the full text of one study could not be retrieved and assessed at a full text level.[108] However, given the clear inclusion/exclusion criteria we do not believe any relevant studies were missed at the title and abstract screening and comparison with similar reviews, such as that provided in the Merck Serono submission, do not indicate any missed studies, nor that the irretrievable study would have been included at the full text stage.

4.1.6. Conclusions

The Jarrett et al. study did not state it themselves, but the associated SMC documents report that a patient access scheme was required for cetuximab to be considered a cost-effective treatment in Scotland. However, this may not be indicative of the NHS in England and Wales and given the limited reporting of all studies the evidence is not conclusive enough at this stage to state whether cetuximab and/or panitumumab are cost-effective first line treatments for *RAS* WT mCRC patients. Therefore we believe our development of a *de novo* model is both justified and necessary to answer the decision problem described in this report.

KEY POINTS

- This review considered full cost-effectiveness studies for *RAS* WT metastatic colorectal cancer patients.
- 4 studies were identified and reviewed : 1 full paper, 2 conference abstracts with accompanying posters and 1 conference abstract whose accompanying poster could not be retrieved
- One study was UK based, but only compared cetuximab plus chemotherapy to chemotherapy alone. As this study was related to a SMC appraisal, additional details were identified on the SMC website.
- All studies had at least one author employed by a manufacturer
- No studies completely answered the decision problem and as such highlights the need for a *de novo* model

5. Economic evaluations submitted by manufacturers

Here we present and critique the economic evidence submitted by the manufacturers. No economic evidence was submitted by Amgen, so we present only a critique of the evidence from Merck Serono.

5.1. Economic evaluation submitted by Merck Serono

Merck Serono submitted both a systematic review of economic evidence and an economic model.

5.1.1. Cost-effectiveness review

Merck Serono carried out literature searches for cost-effectiveness evidence in MEDLINE, MEDLINE-in-Process, EMBASE and EconLit, via Ovid, and NHS EED and HEED, via the Cochrane library (Merck Serono Submission, Section 3.2.1, p16). The searches combine free-text and index terms for relevant cancers, free-text terms for Cetuximab, and free-text and index terms for relevant cost-effectiveness measurements and study types (Merck Serono Submission, Appendix F, pp52-63). No language or date limits were applied.

The literature searches use an appropriate range of databases for the topic. The choice of free-text and index terms is also appropriate, and the searches have an appropriate balance of sensitivity and specificity. The search strategies are reproduced in the appendices, including the number of hits retrieved per search (Merck Serono Submission, Appendix F, pp58-63). The dates searched are reported elsewhere in the submission (Merck Serono Submission, Section 3.2.1, p16).

There is a small discrepancy between the list of databases in section 3.2.1 and the search strategies reproduced in Appendix F: Section 3.2.1 reports that the databases HEED and NHS EED were searched, but there is no HEED search strategy in the appendices, although there are two NHS EED searches; this is probably a typing rather than methodological error. There is also an error in the EMBASE search strategy where line 8 reads “6 AND 7” but should read “5 AND 7”. This error means that the search terms for cetuximab on line 5 are not included in the final results. However, the search is not adversely affected as the results comprise of records related to mCRC and cost-effectiveness, and are a broader set of records than would have been retrieved by combining the results with terms for cetuximab using the AND Boolean operator.

Merck Serono also searched for literature containing health related quality of life utility values related to mCRC and Cetuixmab (Merck Serono Submission, Section 3.2.1, pp18-19). These searches were carried out in MEDLINE, MEDLINE-in-Process and EMBASE, via Ovid. The choice of databases and search terms are appropriate for the topic, as is the balance of sensitivity and specificity. The search strategies are reproduced in the appendices with appropriate detail and without errors (Merck Serono Submission, Appendix G, pp64-67).

Merck Serono state that their review had two aims: to identify cost-effectiveness evaluations of cetuximab in *KRAS*/*RAS* WT populations and identify UK based costs and resource use. In general their PICOS inclusion/exclusion criteria were appropriate and corresponded to the scope of the project. Detailed comments are presented in Table 65.

Table 65. PICOS criteria of the Merck Serono cost-effectiveness review

Criteria	Review stage	Inclusion	Exclusion	PenTAG comments
Population	Abstract/ full text	Cost-effectiveness evaluations on cetuximab in (K) RAS wt mCRC in all countries of interest Patients with KRAS wt mCRC receiving first-line therapy for their metastatic disease in the UK. Patients with RAS wt mCRC receiving first-line therapy for their metastatic disease in the UK. Patients with mCRC in the UK	Studies conducted outside the UK (except for CE studies in (K) RAS WT mCRC with cetuximab) Non-metastatic CRC studies	These inclusion criteria does not restrict to 1st line, so cost-effectivemess results and resource idenitification will be of limited use in this scenario. These inclusion criteria also excluded panitumumab studies, where they are not compared to cetuximab. This fits Merck Serono's aims but not those of the NICE scope. It is appropriate to limit studies identified for cost and resource use to UK only
Intervention/ treatments	Abstract/ full text	Cetuximab in combination with FOLFOX or irinotecan-based chemotherapy Panitumumab in combination with FOLFOX*	All other therapies that are not relevant to cetuximab	In line with NICE scope
Comparator	Abstract/ full text	No limitations	No limitations	This could include comparators not relevant to NICE

				scope
Outcomes	Abstract selection	No selection on outcomes		Appropriate
	Full text selection	Utilities/Health states Costs (UK) Resource use (UK) Cost utility, cost-effectiveness, budget impact outcomes Model structure and sources Cost Effectiveness results (cost/LY; cost/QALY) in the target population cetuximab in (K)RAS wt mCRC (not limited to UK)	Costs other than UK costs	Appropriate for aim of review
Study design	Abstract/ full text	Economic evaluations (cost-effectiveness, cost-utility and budget impact analyses) HTA submissions and reports including economic data Cost of illness studies Utility studies	Pharmacokinetic studies Genomic studies Methodology/protocols Case reports/studies Editorials/letters etc. Conference proceedings < 2013 will be excluded Studies lasting <2 weeks	Appropriate for aim of review

Source: Merck Serono submission Appendix C pp. 68-69

Our review had stricter population inclusion criteria, in line with the NICE scope. Of the included studies identified by Merck Serono, we also identified 2 as includes (Jarrett et al., 2014 and Ortendahl et al., 2014)[9, 104]. The remaining studies identified by Merck Serono were excluded from our review on the basis of population (either not first line or not *RAS* WT). Merck Serono's restriction to cetuximab studies also contradicts the NICE scope, which includes panitumumab plus chemotherapy as an intervention of interest.

Though we chose a narrower population for our economic review, we agree with a broader patient population that Merck Serono uses for their health related quality of life (HRQL) search. However, it appears that this wider population was not necessarily implemented in practice as 10 studies were excluded as not being 'not specific to *RAS* WT mCRC type patients' Merck Serono submission Section 3.4.1, p.59. The utilities studies that Merck uses to inform their model seem in general to be appropriate.

5.1.2. De novo economic evaluation

As well as a review of economic studies, Merck provided an executable economic model. We received several iterations of this model, which we have summarised below.

5.1.2.1. History of submission

We received Merck Serono's original submission on 6th May 2015. We requested an explanation of the discrepancies between the model and report, as well as how to implement the liver metastases subgroup.

Merck Serono submitted a new executable model and report on 15th June 2015, which had one significant change. Merck claimed that they had detected another error of their own in the cost of cetuximab, and had adjusted this value accordingly. Some other discrepancies between this model and the previous version were identified, but checks revealed that these were unlikely to have a big impact upon the cost-effectiveness: implementing the changes we could identify into the original model gave very similar results to the new model (ICERs differed by less than £3 per QALY). This also suggested that no major wiring errors had been introduced into this new model. **As such the model methods and results described in this section refer to the version of the model that we received 15th June 2015**.

Merck also submitted an additional executable model for the liver metastases subgroup on 16th June 2015. On request, Merck Serono submitted a list of the parameters that had been altered in the 'overall population model' to create this subgroup analysis on 26th June 2015. The ICERs for this subgroup had again been updated.

Even with the list of parameters, we were unable to reconcile the overall population model and the liver limited disease subgroup model. We also noted that overall survival had been hardcoded into this subgroup model, which we believe was in error, as this meant survival did not alter when different interventions and comparators were selected.

As we could not reconcile this subgroup model with the model for the overall population, and as Merck Serono submitted their independent model for the liver metastates subgroup at a late stage in this HTA, we have not critiqued the liver limited disease subgroup model. We therefore present the results for this subgroup without comment.

5.1.2.2. Description of methods

Comparator treatments

Merck Serono considered the following three independent comparisons in their economic evaluation:

- Cetuximab plus FOLFOX (CET+FOLFOX) vs. FOLFOX
- Cetuximab plus FOLFIRI (CET+FOLFIRI) vs. FOLFIRI
- Cetuximab plus FOLFIRI (CET+FOLFIRI) vs. bevacizumab plus FOLFIRI (BEV+FOLFIRI)

Merck Serono state (Merck Serono submission, Section 2.2.2, p.44): "*As there was significant uncertainty surrounding the results of the NMA, head-to-head trial data was preferred for use in the health economic model*". Whilst we believe it is possible to perform a 3-way comparison between CET+FOLFIRI, FOLFIRI and BEV+FOLFIRI, we believe that Merck Serono's approach of performing the three independent comparisons is reasonable because:

- BEV+FOLFIRI has been delisted from the Cancer Drugs Fund,[60] and hence is no longer a main comparator.
- We agree with Merck Serono, that there is no clinical data that allows the comparison of FOLFOX-based and FOLFIRI-based treatments.

However, we note that Merck have not included PAN+FOLFOX as a comparator, even though the relevant RCT data is publicly available.

XELOX

In their economic model, Merck Serono considered XELOX (also referred to as CAPOX) as a treatment in a scenario analysis, despite the lack of head to head data specific to RAS wild-type mCRC patients. Merck Serono assumed:

- the clinical effectiveness of XELOX, i.e. % patients resected, PFS, mortality from PFS, incidences of adverse events, is all exactly the same as for FOLFOX.
- a higher mean per patient total cost of acquisition of XELOX compared to FOLFOX: £8,093 vs. £6,416,

- a slightly lower mean per patient total cost of administration of XELOX compared to FOLFOX: £2,296 vs. £2,803.

Merck Serono justify the first assumption as follows: "*In a Phase III trial by Cassidy et al. (Cassidy et al., 2006,[109] Cassidy et al., 2007[110] CAPOX was shown to be non-inferior to FOLFOX-4 as a first-line treatment for mCRC. Therefore the two regimens are expected to be equivalent in terms of efficacy and can thus be treated as equal in terms of outcomes. In addition, this assumption was validated by clinical experts (Merck Serono, 2015) who stated that the combinations of different forms of 5FU (differing infusion regimens and oral analogues) along with both FOLFIRI and FOLFOX have equivalent efficacy*." (Merck Serono submission, Section 3.7.3.1, p.66).

We agree with Merck Serono that there are no trials that directly compare cetuximab-based treatment versus XELOX. Our systematic review of the literature (Section 3.2, p.88), also found no such trials comparing panitumumab-based treatment vs. XELOX.

Given time constraints, we have not performed a full systematic search of the literature for clinical effectiveness evidence of XELOX vs. any other treatment in our base case analysis. Instead, we report the findings of a review of XELOX vs. FOLFOX. [111] This study found that several RCTs have compared continuous-infusion 5-FU/oxaliplatin with oral fluoropyrimidine capecitabine plus oxaliplatin. In all these trials, noninferiority was demonstrated for the use of oral fluoropyrimidines on the predefined endpoints such as PFS, OS, response rate. However, the hazard ratios and median TTP / PFS were almost always in favour of FOLFOX (Table 66).

Table 66. PFS/TTP results of RCTs of CAPOX/XELOX vs. FOLFOX reported in Douillard et al. (2008)

		Median TTP/ PFS (months)		
Trial	**Number patients**	**Continuous-infusion 5-FU - based treatment**	**Oral fluoropyrimidines based treatment**	**PFS/TTP hazard ratio**
NO16966 trial	634	FOLFOX4 = 7.7	XELOX = 7.3	0.96; 97.5% CI, 0.8-1.16
TREE-1 trial	106	Modified FOLFOX6 = 6.4	CAPEOX = 4.4	Not reported
Ducreux et al.	306	FOLFOX6 = 9.3	XELOX = 8.8	1.00; 90% CI, 0.82-1.22
Diaz-Rubio et al.	348	FUOX = 9.5	XELOX = 8.9	1.18 (0.9-1.5)
Porschen et al.	Not reported	FUFOX = 8.0	CAPOX = 7.1	1.17; 95% CI, 0.96-1.43)
COFFEE trial	322	OXAFAFU = 6.3	OXXEL= 6.2	1.06 (0.81-1.35)

Key FOLFOX4/FOLFOX6/FUFOX/OXAFAFU = folinic acid + fluorouracil + oxaliplatin; FUOX = fluorouracil + oxaliplatin; CAPOX/CAPEOX/OXXEL/XELOX = capecitabine + oxaliplatin
Source: Douillard et al. (2008).[111]

This data then gives us a suggestion of the likely relative clinical effectiveness of CAPOX/XELOX and FOLFOX. But note that this data does not relate specifically to patients with *RAS* WT mCRC, rather to both *RAS* WT and mutant.

Of course, there are several other parameters that could differ between CAPOX/XELOX and FOLFOX:

- Mean treatment duration.
- Resection rates. However, it seems plausible that resection rates are correlated with PFS.
- Incidences of adverse events. However, given that we find that incidences of adverse events have little impact on cost-effectiveness, we consider this to be a minor issue.

Given all these uncertainties, we believe that it is reasonable for Merck Serono to model XELOX as a comparator treatment in a scenario analysis, assuming differences in treatment acquisition and administration costs, but equal clinical effectiveness as FOLFOX.

Tegafur/uracil

Merck Serono have not included tegafur/uracil as a comparator treatment, even though it is a comparator in the NICE Scope. They say that they withdrew this product from the market in the UK in 2013 and no other equivalent preparations are available in the UK (p19 Merck Serono submission). We agree that tegafur/uracil has been discontinued and our clinical advisor believes it is unlikely to be used in the UK.

Capecitabine monotherapy

Merck Serono have not included capecitabine monotherapy, even though it is a comparator in the NICE Scope, as their expert advice indicated that it is typically used in elderly patients with poor performance status (PS) as these patients would not generally be fit to receive biological agents in combination with chemotherapy (Merck Serono submission, p.19). They also did not identify any studies which compare cetuximab plus chemotherapy to capecitabine in a *RAS* WT population (Merck Serono submission, Section 3.2.3, Table 22, p. 52).

Our clinical advisor agrees that capecitabine monotherapy and fluorouracil plus folinic acid (5FU+FA) are not the preferred first line treatments in mCRC patients. In general single agent fluoropyrimidine regimens (capecitabine or 5FU+FA) would be used for patients unfit for combination therapy or who have overlapping comorbidities that make other agents problematic. We also did not identify any studies which compare cetuximab plus chemotherapy to capecitabine in a *RAS* WT population

Patient population & liver metastases subgroup

Merck Serono consider two patient populations, with a separate model for each group:

- All 1st line patients with *RAS* wild-type mCRC.
- Subgroup of these patients with liver metastases confined to their liver, the “Liver metastases subgroup”.

As discussed in Section 5.1.2.1, p191, we do not critique the liver metastases subgroup model.

Merck Serono claim that the following parameters are unique for the liver metastases subgroup:

- Resection rates,
- PFS for unresected patients.

and that all other parameters are unchanged from the total population analysis.

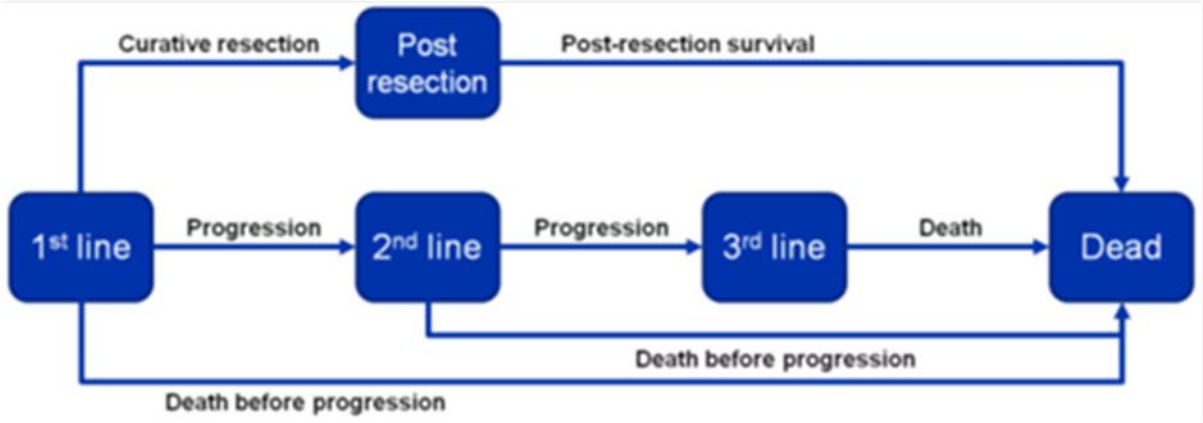
Model structure

In common with us, in the base case, Merck Serono do not use OS from the RCTs of 1st-line drugs. Instead, the RCTs are used to estimate only resection rates and PFS on 1st-line treatment. OS is instead estimated as the sum of times on 1st-, 2nd- and 3rd-line treatments, allowing for mortality from each line.

Merck Serono's model is made of 5 health states: 1st line progression free, 2nd line progressive disease, 3rd line progressive disease, post resection and dead (Figure 11). Patients remain in 1st line until they move to either post resection or to further lines of treatment. Patients can die in any state.

The model uses tunnel states to apply time dependent transition probabilities to move patients between states.

Figure 11. Structure of Merck Serono's model



Source: Merck Serono submission, Figure 12, p.48

Differences in clinical effectiveness between 1st-line drug treatments are represented by the differences between:

- 1st-line PFS,
- Resection rates,
- Incidences of adverse events.

The model cycle length is one month, which is appropriate. A model half-cycle correction is applied.

The model time horizon is 10 years, which we believe is far too short. The model time horizon should be sufficiently long that the vast majority of deaths are modelled. However, 10 years after resection, Merck Serono estimate that 12% of patients are still alive. Merck Serono's model can deal with a time horizon up to 20 years, at which time Merck estimate that 4% of patients are still alive. When we change the time horizon from 10 to 20 years, their ICERs for: CET+FOLFOX vs. FOLFOX and CET+FOLFIRI vs. FOLFIRI both decrease because we now model more QALYs post resection, and more patients receive a resection under CET+FOLFOX than FOLFOX and CET+FOLFIRI than FOLFIRI.

However, as explained below, we believe that their estimates of PFS and OS post-resection are logically impossible after about 11 years, as then they estimate PFS as greater than OS.

In our model, we use a time horizon of 30 years.

Future costs and benefits are discounted at 3.5% per annum, and the perspective is that of the NHS and Personal Social Services, in accordance with the NICE Reference Case.[112]

Overall survival

As in our model, Merck Serono do not take OS from the RCTs. Instead life expectancy for all randomised patients is calculated separately for each treatment arm as:

% patients resected x life expectancy given resected

+ (100% - % patients resected) x life expectancy given unresected.

The last quantity, life expectancy for unresected patients for each treatment arm is calculated as the sum of expected times on 1st, 2nd and 3rd lines of treatment, allowing for mortality from each line.

Model parameters

Resection rates

Resection of liver metastases is an important component of both our model and Merck Serono's model, as cost-effectiveness is sensitive to it.

Merck Serono use the resection rates from the RCTs to estimate the rates for use in their model (Table 60).

Table 67 Liver metastases resection rates assumed in Merck Serono model

Treatment	All *RAS* WT patients
FOLFIRI network	
CET+FOLFIRI	7.3% (Merck Serono data from CRYSTAL).
FOLFIRI	2.1% (Merck Serono data from CRYSTAL).
BEV + FOLFIRI	7.3% No justification given
FOLFOX network	
CET+FOLFOX	7.3% (derivation explained in text)
FOLFOX	2.1% (Tournigand et al. 2004[113])

Key: BEV = bevacizumab; CET = cetuximab; FOLFIRI = folinic acid + flurouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin

Merck Serono do not discuss the derivation of their estimate of the rate of resection for CET+FOLFOX, 7.3%. We assume it was set equal to their rate for CET+FOLFIRI, which we believe is unreasonable. They estimate the rate of resection for FOLFOX as 2.1% from Tournigand et al. 2004[113]. This is substantially lower than our estimate of [redacted] (Section 6.1.4.1, p.251). Tournigand et al. (2004)[113] concerns 2nd-line treatment not restricted to *RAS* WT, whereas our estimate is taken from 1st-line treatment for *RAS* WT patients. Therefore, we prefer our value of [redacted]

Time of liver resection

Merck Serono simulate liver resection at cycle 3 in their model. Notably, the timing of liver resection was not clearly stated in their submission. As detailed in Table 20 (Merck Serono submission, Section 3.2.2, p.49), resection is modelled at cycle/month 4. However, in Table

21 they state that at 3 months in their model some patients can be referred for curative-intent resection of liver metastases.

Merck Serono's assumption on the timing of liver resection surgery is based on Adam et al. (2004)[3] as indicated in Table 20 of their submission (Section 3.2.2, p.49).

This assumption seems reasonable, based on advice from our clinical experts and the values used in TA176.

Post liver resection: PFS & OS

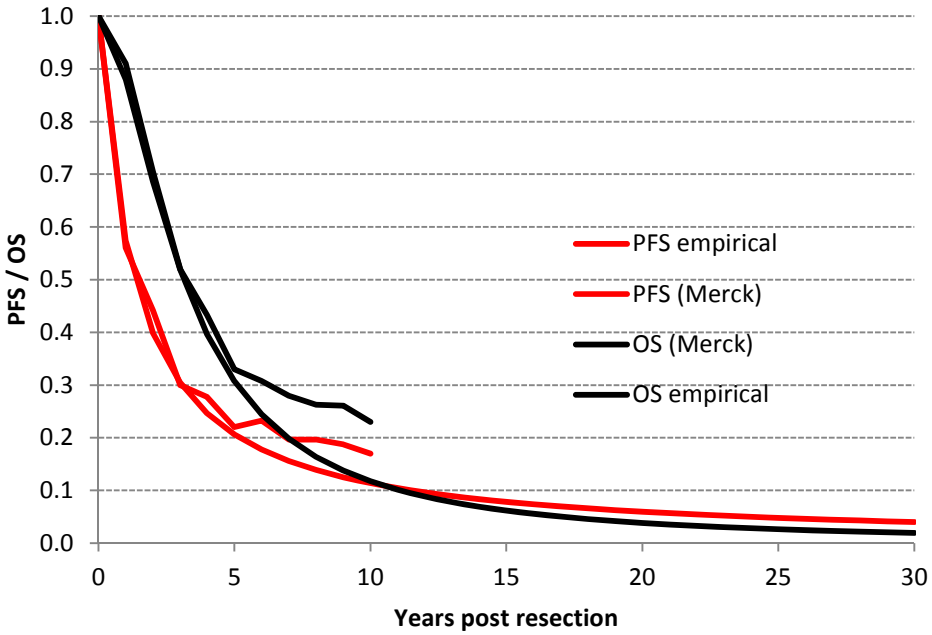
In their submission, Merck Serono state that they assume all patients who undergo curative liver resection for initially unresectable colorectal liver metastases, turned resectable by systematic chemotherapy, and are cured of the disease, "remain in a progression free state until death and do not require second-line treatment" (Merck Serono submission, Section 3.2.2, p.47).

However, elsewhere in the submission and in the executable model there exists a progressive disease state, including treatment, for patients post liver resection.

Merck Serono model PFS and OS after liver resection surgery according to data from Adam et al. (2004).[3] We also use this data, as we understand it to be the most appropriate available. Further discussion of the study can be found in Section 6.1.4.3, p.260.

Merck Serono fitted a log-logistic distribution to both PFS and OS post-resection (Figure 12). Technically, this data is taken from rows 95 and 96 of Merck Serono's worksheet "Survival models". Importantly, they do not explain their choice of distribution, or indeed how they estimated the curve fits.

Figure 12. Merck Serono PFS and OS post-resection fit to empirical data



Key: PFS = progression free survival; OS = overall survival

The fits appear reasonable up to end of study follow up at 10 years. This is also the time horizon of Merck Serono's model. But after about 11 years, Merck Serono model PFS as greater than OS, which is clearly impossible. Therefore, we believe that this renders the results from Merck Serono's model for time horizons greater than 11 years incorrect.

In common with us, for those patients who had a successful resection, Merck Serono assumed PFS and OS were independent of 1st-line treatment.

Based on their 10 year time horizon, which we believe is far too short, we calculate that Merck Serono estimate a mean PFS of 2.8 years and OS of 4.1 years.

1st-line Progression-free survival: unresected patients

Merck estimate 1st-line PFS for unresected patients directly from the pivotal RCTs: CRYSTAL, FIRE-3, OPUS. They compare pairs of treatment independently, and do not perform simultaneous comparisons of multiple treatments. Therefore, unlike us, they do not perform indirect comparison on 1st-line PFS for unresected patients.

Merck Serono estimate PFS for unresected patients from all patients (resected + unresected) in the RCTs. We believe this is an important mistake. Given that they model PFS for

resected patients separately, as described in the previous section, they are effectively double counting PFS for resected patients. They over-estimate PFS for unresected patients, because PFS for resected patients (our estimate 4.5 years) is far greater than for unresected patients (e.g. our estimate for CET+FOLFIRI 1.0 years).

In our analysis, as explained above, we also estimate PFS for resected patients from Adam et al. (2004).[3] However, we estimate PFS for unresected patients from the RCT data for PFS for all patients, and then subtracting off PFS for resected patients (Section 6.1.4.4).

Merck Serono's choices of statistical distributions and estimates of mean PFS for 1st-line unresected patients are given in Table 68.

Table 68. Merck Serono modelled PFS for unresected patients

	Distribution	Mean PFS (months) [1]
CET+FOLFOX	Lognormal	13.4
FOLFOX	Lognormal	9.0
CET+FOLFIRI (vs. FOLFIRI)	Weibull	12.5
CET+FOLFIRI (vs. BEV+FOLFIRI)	Weibull	12.8
FOLFIRI	Weibull	8.9
BEV+FOLFIRI	Weibull	10.8

Notes: 1 We estimate mean PFS from Merck Serono model from the "Results" worksheet, setting the discount rate to 0% and the resection rates in the "Setup" worksheet to 0%.

We believe that their PFS curve fits, and hence the mean PFS above are reasonable. However, we repeat that we believe these are over-estimates of PFS for unresected patients. All other things being equal, their approach makes CET+FOLFOX/FOLFIRI appear better value for money than we believe, given that a greater proportion of patients in the CET+FOLFOX/FOLFIRI arms compared to the FOLFOX/FOLFIRI arms are resected, and that PFS for resected patients is substantially greater than for unresected patients.

Probability of post-operative death

Merck Serono state in Table 21, Section 3.2.2, p.50 of their submission that the postoperative death is set to 0%, based on the CRYSTAL trial. However, in the executable model Merck assume a probability of post-operative death of 1% for all treatment regimens. As Merck Serono use data from the Adam et al. (2004)[3] to model the cohort post-resection,

we think it would be more appropriate to use the value of 0.7% reported in Adam et al. (2004)[3] for operative mortality within 2 months.

Time on 1st-line drug treatment

The mean times on 1st-line drug treatment are extremely important quantities because, in Merck Serono's model, they affect the total mean cost of drug acquisition and administration per person. In Merck Serono's model, the former in particular is a critical driver of cost-effectiveness. Therefore, treatment duration is worthy of close scrutiny.

Despite its importance, Merck Serono mention treatment duration only very briefly.

Merck Serono Merck Serono estimate the mean duration of cetuximab use in England as 24-25 weeks "depending on chemotherapy backbone and disease progression", citing the source as "Data on file" (Merck Serono submission, Table 3, p17). They state (Merck Serono submission, Section 3.7.2, p.64): "The period of treatment with cetuximab plus chemotherapy used in the model were obtained from the relevant clinical trials. As stated in the clinical evidence section, the period of treatment in the clinical trial represents clinical practice as Merck Serono research indicates that the period of cetuximab treatment is 25 weeks on average".

In their model, Merck Serono assume that all patients take 1st-line drug treatment whilst in PFS, up to a certain cut-off time, which varies slightly by treatment arm. After the cut-off time, patients take no 1st-line drug. The cut-off times are:

- CET+FOLFOX: 5.5 months
- FOLFOX: 5.5 months
- CET+FOLFIRI (vs. FOLFIRI): 5.8 months
- CET+FOLFIRI (vs. BEV+FOLFIRI): 4.8 months
- FOLFIRI: 5.9 months
- BEV+FOLFIRI: 5.3 months

Under their method of modelling treatment duration, we calculate that Merck Serono estimate the following mean durations:

- CET+FOLFOX: 4.9 months
- FOLFOX: 4.6 months
- CET+FOLFIRI (vs. FOLFIRI): 5.3 months
- CET+FOLFIRI (vs. BEV+FOLFIRI): 4.5 months

- FOLFIRI: 5.2 months
- BEV+FOLFIRI: 5.1 months

Below, we argue that these are underestimates.

2nd-line PFS: unresected patients

Both we and Merck Serono assume that all patients have 2nd-line FOLFIRI after 1st-line FOLFOX-based treatment and all patients have 2nd-line FOLFOX after 1st-line FOLFIRI-based treatment.

Merck Serono model 2nd-line PFS using data from the study by Tournigand et al. (2004).[113] Inspection of their model reveals that they assume a log-logistic distribution, and we calculate a mean of 0.31 years in 2nd-line PFS for patients that start on 2nd-line treatment. Merck Serono assume this value independent of 1st-line treatment (whether FOLFOX or FOLFIRI based).

Given lack of data to the contrary, both we and Merck assume that PFS on 2nd-line FOLFOX or FOLFIRI is independent of 1st-line treatment.

Although not stated in their report, and in common with us, inspection of their model reveals that Merck Serono assume that patients take FOLFOX or FOLFIRI for the entire duration of 2nd-line PFS.

3rd-line survival: unresected patients

In common with us (Section 6.1.4.9, p.306), Merck Serono model 3rd-line survival using data from Jonker et al. (2009)[114]. Inspection of their model reveals that they assume a Weibull distribution, and we calculate a mean of 0.74 years survival for patients that start on 3rd-line treatment. Merck Serono also assume this value independent of 1st- or 2nd-line treatment.

Merck Serono assume most patients receive BSC in 3rd-line, with 17% getting capecitabine or cetuximab. They further assumed that patients would not be re-treated with cetuximab.

Utilities

The utilities used in Merck Serono's model are reported in Table 69. We note that there are differences between the utilities in the main report and those in Appendix B. The values in the appendix correspond to those in the model.

No *RAS* WT utility data was identified by Merck Serono or reported by their included trials. Merck Serono used Bennett et al. (2011) for estimates of utilities in first and second line treatment. Bennett et al. reports utilities for first and second line *KRAS* WT mCRC populations.[5] Further discussion of this source can be found in Section 6.1.4.11, p.309. Merck Serono used the estimate of utility reported at baseline for the PAN+FOLFOX population: 0.778. For second line utility, Merck Serono used the second line baseline results for PAN+FOLFIRI: 0.769.

Merck Serono used an estimate of 0.663 from Wang et al. (2011) for third line treatment.[6] This source is for a previously treated *KRAS* WT mCRC population who are receiving best supportive care. This source is also discussed further in Section 6.1.4.11, p.310.

Table 69. Health state utilities reported by Merck Serono

Health state utility	Merck Serono main report	Merck Serono in model (and report Appendix B)	Source
1st line	0.77	0.778	Bennet t et al. 2011[5]
2nd line	0.73	0.769	Bennet t et al. 2011[5]
3rd line	0.68	0.663	Wang et al. 2011[6]
PFS Post resection	NR	0.789	Petrou and Hockley 2005[105]
PD post resection	NR	0.682	Average of 2nd and 3rd line utilities , weighted by time spent in 2nd and 3rd line

Source: Merck Serono submission, Table 20 pp.50-51, Appendix B Table 1, p.1

Merck use a general population estimate for utility PFS post resection. The source of this value is Petrou and Hockley (2005) which uses Health Survey for England data from 1996.[105] More recent data and approaches for using this data are available.[7, 8]

For post-resection PD states, the utility is assumed to be a weighted avarge of second line and third line health states, adjusted for time in state.

Costs

RAS mutation testing

Merck Serono report a cost of £200 for *RAS* mutation testing from the All Wales Genetic Laboratory (Merck Serono submission, Appendix B, Table 2), which is applied to all arms of the model, regardless of treatment.

Drug acquisition

Merck Serono assumed costs for drug acquisition per month as shown in Table 70.

Table 70: Drug acquisition costs per month in Merck Serono's model

Regimen	Cost per month of drug acquisition
CET+FOLFOX4	£5,083
FOLFOX4	£1,546
FOLFOX6 (2nd line only)	£1,616
XELOX	£1,950
CET+FOLFIRI	£4,876
BEV+FOLFIRI	£3,345
FOLFIRI	£1,339

Key: BEV = bevacizumab; CET = cetuximab; FOLFOX(4/6) = folinic acid + fluorouracil + oxaliplatin; XELOX = capecitabine + oxaliplatin; FOLFIRI = folinic acid + fluorouracil + irinotecan

These monthly costs were calculated based on pharmaceutical costs shown in Table 71, all of which are list prices and do not include any discounts which may be obtained by the NHS.

Table 71: Costs of pharmaceuticals in Merck Serono's model

Agent	Cost	Source
Cetuximab	20 ml vial (5 mg/ml): £178.10	Merck Serono
	100 ml vial (5 mg/ml): £890.50	
Bevacizumab	4 ml vial (25 mg/ml): £242.66	BNF (March 2014)
	16 ml vial (25 mg/ml): £924.40	
Oxaliplatin	10 ml vial (5 mg/ml): £155.00	BNF (March 2014)
	40 ml vial (5 mg/ml): £622.38	
Fluorouracil	10 ml vial (50 mg/ml): £6.40	BNF (March 2014)
	50 ml vial (50 mg/ml): £32.00	

Agent	Cost	Source
Leucovorin	10 tablet (15 mg) pack: £19.41	BNF (March 2014)
Irinotecan	2 ml vial: £46.50	BNF (March 2014)
	5 ml vial: £114.00	
	25 ml vial: £601.25	
Capecitabine	60 tablet (150 mg) pack: £40.00	BNF (March 2014)
	120 tablet (500 mg) pack: £295.65	
Doxycycline	8 tablet (100 mg) pack: £1.11	BNF
Ondansetrone	30 tablet (4 mg) pack: £5.37	BNF
Dexamethasone	50 tablet (2 mg) pack: £7.05	BNF

Key: BNF = British National Formulary
Source: Merck Serono executable model

For each agent in each regimen, the target dosage was calculated based on an assumed constant body surface area or body mass (Table 72), and then wastage was considered by using the minimum number of vials to achieve the minimum wastage, e.g., for a target cetuximab dose of 895 mg, two 500 mg vials would lead to wastage of 105 mg, while one 500 mg vial and four 100 mg vials would lead to wastage of 5 mg (in which case the latter was assumed). Wastage was not minimised based on cost, but if the average cost per mg is the same across vial sizes (or very similar) this method will minimise cost. It was assumed that for all regimens there would be 2.17 cycles per month, which is accurate for 14 day cycles.

Merck Serono's model allowed for both weekly and fortnightly administration of cetuximab, but we present only the parameter values for fortnightly administration because we believe this is a more appropriate base case since it closer reflects current clinical practice.

Table 72: Methodology used by Merck Serono to calculate monthly costs of regimens

Regimen	Agent	Cycles per month	Dosage per cycle	Cost per cycle	Monthly cost
CET+FOLFOX4	Cetuximab	2.17	500 mg/m²	£1,602.90	£3,478.29
	FOLFOX4	(see below)			£1,546.45
	Doxycycline	2.17	200 mg	£1.11	£2.41
	Ondansetrone	2.17	8 mg	£7.05	£15.30
	Dexamethasone	2.17	8 mg	£5.37	£11.65
	Total				**£5,083.33**
FOLFOX4	Oxaliplatin	2.17	85 mg/m²	£622.38	£1,350.56
	Leucovorin	2.17	200 mg/m²	£58.23	£126.36
	Fluorouracil	2.17	1,600 mg/m²	£32.04	£69.53
	Total				**£1,546.45**
FOLFOX6	Oxaliplatin	2.17	100 mg/m²	£622.38	£1,350.56
	Leucovorin	2.17	200 mg/m²	£58.23	£126.36
	Fluorouracil	2.17	2,800 mg/m²	£64.02	£138.92
	Total				**£1,615.85**
XELOX	Capecitabine	2.17	28,000 mg/m²	£245.94	£533.69
	Oxaliplatin	2.17	130 mg/m²	£652.90	£1,416.79
	Total				**£1,950.50**
CET+FOLFIRI	Cetuximab	2.17	500 mg/m²	£1,602.90	£3,478.29
	FOLFIRI	(see below)			£1,339.04
	Doxycycline	2.17	200 mg	£1.11	£2.41
	Ondansetrone	2.17	8 mg	£7.05	£15.30
	Dexamethasone	2.17	8 mg	£5.37	£11.65
	Total				**£4,875.92**
BEV+FOLFIRI	Bevacizumab	2.17	5 mg/kg	£924.40	£2,005.95
	FOLFIRI	(see below)			£1,339.04
	Total				**£3,344.99**
FOLFIRI	Irinotecan	2.17	180 mg/m²	£456.00	£989.52
	Leucovorin	2.17	400 mg/m²	£97.05	£210.60
	Fluorouracil	2.17	2,800 mg/m²	£64.02	£138.92
	Total				**£1,339.04**

Key: CET = cetuximab; FOLFOX(4/6) = folinic acid + fluorouracil + oxaliplatin; XELOX = capecitabine + oxaliplatin; FOLFIRI = folinic acid + fluorouracil + irinotecan; BEV = bevacizumab

Merck Serono assumed premedication with doxycycline, ondansetrone and dexamethasone prior to cetuximab administration, but these did not significantly contribute to costs.

Merck Serono did not include any adjustments for mean dose intensity – in practice some patients would likely require reductions in their target dose (often due to side effects).

Drug administration

Analysis of Merck Serono's economic model revealed that their drug administration costs were as shown in Table 73. The report differed from the model in that Appendix B appears to report inpatient and outpatient costs the other way around.

Table 73: Merck Serono drug administration unit costs

Administration setting	Visit number	Unit cost	Source
Inpatient chemotherapy administration	First visit	£287	NHS Reference costs 2012–13: SB14Z [OP]
	Subsequent visits	£255	NHS Reference costs 2012–13: SB15Z [OP]
Outpatient chemotherapy administration	First visit	£226	NHS Reference costs 2013–14: SB14Z [OP]
	Subsequent visits	£314	NHS Reference costs 2013–14: SB15Z [OP]

Key: OP = Outpatients

It was not stated in Merck Serono's report how these unit costs were used, so it was necessary to check in the executable model.

Merck Serono assumed that the "first visit" cost applied to the whole of the first cycle and that the "subsequent visits" cost applied to all subsequent cycles, i.e., even if a patient would have multiple attendances per cycle, only one attendance was costed. Drug administration costs were consistent across all regimens per cycle and all regimens were assumed to have 2.17 treatment cycles per month (including XELOX).

Merck Serono also assumed that drug administration was 100% in the outpatients setting in first-line and 100% in the inpatients/day case setting in second-line.

In summary, total drug administration costs per month in Merck Serono's model were £633.38 (first month) or £681.38 (subsequent months) for first-line treatments and £585.35 (first month, except XELOX) or £553.35 (subsequent months, all months for XELOX) for second-line treatments.

Medical management

The executable model submitted by Merck Serono uses resource use and unit costs for medical management as shown in Table 74. As can be seen, Merck Serono assumed no medical management costs in three health states (1st line progression-free, 2nd line, and post-resection progression-free), a cost of £315 per month for post-resection progressive disease and a cost of £1,040 per month for 3rd line treatment (mainly best supportive care).

Table 74: Medical management costs in the model submitted by Merck Serono

Health state	Item	Unit cost	Resource use (per month)	Monthly cost
1st line progression-free				£0
2nd line				£0
3rd line	Best supportive care costs			£997
	Capecitabine monotherapy	£246 per month per patient receiving	17.5% of patients	£43
	Total			£1,040
Post-resection progression-free				£0
Post-resection progressive disease	Evaluation of tumour markers: CEA	£60	1 [a]	£60
	Evaluation of tumour markers: CA 19-9	£60	1 [a]	£60
	Liver function tests	£28	1 [a]	£28
	Hepatic ultrasonography	£51	1 [a]	£51
	Oncology outpatient attendance	£333	0.25 [a]	£83
	Abdominal CT scan	£90	0.125 [a]	£11
	Lung CT scan	£90	0.125 [a]	£11
	Large bowel CT scan	£90	0.125 [a]	£11
	Total			£315

Key: CEA = carcinoembryonic antigen; CA 19-9 = carbohydrate antigen 19-9; CT = computed tomography
Notes: a Merck Serono state that these were intended only to be the resource use values for the first month, but were applied throughout in the executable model submitted by Merck Serono

Resection cost

Merck Serono specify in Table 2, Appendix B of their submission that the average cost of liver resection surgery assumed in their model is £2,707. This cost is derived from NHS HRG's for Hepatobiliary & Pancreatic Surgery in Malignant gastro-intestinal disorders (NHS Reference Costs 2013/2014). It represents the average of the HRGs weighted by the number of finished consulting episodes (Merck Serono submission, Table 2, Appendix B). The relevant HRGs are detailed in Table 3 of Appendix B of their submission.

Notably, national average unit costs for the HRGs, used to estimate the average cost of liver resection in the manufacturer's model (Merck Serono submission, Table 3, Appendix B) are not consistent with the NHS Reference Costs 2013/2014. The average cost of liver resection based on the actual average unit costs reported for these HRG codes is £2,467.

Costs post-resection

Follow-up consultations

Merck Serono assumed a cost of £333 per oncological outpatient attendance. In their executable model they reported the source as National Reference Costs 2012/13 but we could not confirm this cost.

The frequency of follow-up consultations in the manufacturer's model is one visit per four months as in Adam et al.[3] We agree that this is appropriate.

Blood tests

Merck Serono detail in Table 2, Appendix B of their submission that they model the following blood tests in patients post-resection: liver function test and the tests for the tumour markers CEA (Carcinoembryonic antigen) and CA19-9 (Carbohydrate antigen 19-9).

The cost of liver function test, stated in the submission, is £28.76 (in £ 2013). However, in their executable model they use the cost of £27.60 per test (in £ 2013). This cost is based on the NICE submission TA176 (Table 2, Appendix B of the manufacturer's submission) and we believe that this source is appropriate.

Merck Serono assume that each tumour marker test costs £59.87 based on information from ISD Scotland. We were unable to identify this source, so cannot comment on its relevance.

In the manufacturer's model, the blood tests are conducted during the first month after resection and then every 4 months, based on Adam et al. (2004).[3] On advice of our clinical experts, we believe that this cost should occur every 3 months.

Despite the differences between our estimates and those by Merck Serono, altering the cost and frequency of blood tests has very little impact on the cost-effectiveness results.

Imaging tests

Merck Serono model hepatic ultrasonography and CT scans in patients post-resection. The cost of hepatic ultrasonography test is £51 (Merck Serono submission, Table 2, Appendix B). It is assumed to be conducted during the first month after the surgery and then every 8 months. Merck Serono model abdominal, lung and large bowel CT scans separately, at a cost of £90 per test (Merck Serono submission, Table 2, Appendix B). The tests are assumed to be performed every 8 months.

Merck Serono state that the above estimates are based on the National Reference Costs 2012/13. However, we could not confirm these estimates.

We note that the despite calculating different costs for the first month after resection to the subsequent months, based on changes to the resource use, Merck Serono do not implement these correctly in the model and instead use the first month costs throughout.

Adverse events

Merck Serono modelled costs and disutilities of Grade 3/4 adverse events. The probability of an adverse event is taken directly from each of the relevant trials and for some these come from a *KRAS* WT rather than *RAS* WT population. They assume that all adverse events last for one month.

The costs and disutilities associated with each adverse event are reported in Table 75. Periphery sensory neuropathy and vomiting have disutilities, but no costs.

The reporting of the cost sources is poorly done. We were unable to confirm the source of costs for: hypertension, arterial thromboembolism, venous thromboembolism, neutropenia or neurological toxicities.

The disutility estimates for adverse events were better reported and come from a range of published literature.[115-118] All of these sources are UK based studies, using EQ-5D vignettes,

but none were conducted on a CRC population and there was a mixture of studies reporting on the EQ-5D VAS scale and some on the EQ-5D TTO scale.

Table 75. Adverse event utilities and unit costs used in Merck Serono model

Adverse Event	Cost (£)	Source	Utility decrement	Source
Hypertension	622	National Reference Costs Non-elective inpatient stay - EB04Z - hypertension	-0.069	Doyle et al. (2008)
GI perforation	2,693	National Reference Costs FZ38K - Gastrointestinal Bleed with single intervention with CC score 5-7	-0.195	Tolley et al. (2013)
Arterial thromboembolism	777	National Reference Costs Deep Vein Thrombosis with CC Score 3-5 - QZ20D	-0.195	Tolley et al. (2013)
Venous thromboembolism	777	National Reference Costs Deep Vein Thrombosis with CC Score 3-5 - QZ20D	-0.195	Tolley et al. (2013)
Skin reactions	13.09	BNF 2014	-0.03248	Nafees et al. (2008)
Neutropenia	877	National Reference Costs Non-elective inpatient stay - PA45Z - medical oncology	-0.09	Nafees et al. (2008)
Diarrhoea	153	National Reference Costs General Medicine outpatient visit - Service Code 300	-0.103	Lloyd et al. (2006)
Leukopenia	153	National Reference Costs General Medicine outpatient visit - Service Code 300	-0.03248	Assumption: equal to disutility for neutropenia
Periphery sensory neuropathy			-0.116	Lloyd et al. (2006)
Fatigue	153	National Reference Costs General Medicine outpatient visit - Service Code 300	-0.115	Lloyd et al. (2006)
Vomiting			-0.103	Lloyd et al. (2006)
Neurological toxicities	1400	National Reference Costs WA17A Medical Oncology Neoplasm related admission with CC Score 3+	-0.116	Assumption: equal to disutility for peripheral sensory neuropathy
Hypokalemia	153	National Reference Costs General Medicine outpatient visit - Service Code 300	-0.115	Assumption: equal to disutility for fatigue

Source: Merck Serono submission, Appendix B, Table 1, p.1, Table 4, p. 5

5.1.2.3. Merck Serono results

Base case

Merck report six base cases, three pairwise comparisons based on cetuximab given on a weekly dose and three pairwise comparisons where cetuximab is given fortnightly. The three pairwise comparisons are:

- Cetuximab plus FOLFOX (CET+FOLFOX) versus FOLFOX alone
- Cetuximab plus FOLFIRI (CET+FOLFIRI) versus FOLFIRI alone
- Cetuximab plus FOLFIRI (CET+FOLFIRI) versus bevacizumab plus FOLFIRI (BEV+FOLFIRI)

It is unclear whether weekly or fortnightly administration is Merck Serono's preferred base case (Merck submission Section 3.5, p. 59 versus Section 3.9, p.68). However we agree that the results of fortnightly dosing are most relevant and these are the results we focus on here. We also focus on the results for the pairwise comparison of CET+FOLFOX versus FOLFOX and CET+FOLFIRI versus FOLFIRI, and only present summary results of the CET+FOLFIRI versus BEV+FOLFIRI comparison. These base case deterministic results are presented in Table 76-Table 80.

Table 76. Deterministic base case results CET+FOLFOX versus FOLFOX, fortnightly cetuximab dose

	Costs	LYs	QALYs	ICER (£/LY)	ICER (£/QALY)
CET+FOLFOX	41,301	2.22	1.64		
FOLFOX	26,408	1.81	1.32		
Increment (CET+FOLFOX vs. FOLFOX)	14,894	0.41	0.32	36,048	46,503

Key: CET = cetuximab; FOLFOX = folinic acid + fluorouracil + oxaliplatin; ICER = incremental cost-effectiveness ratio LY = life year; QALY = quality adjusted life year
Source: Merck submission, Table 28, Section 3.6.1.1, p.61

Table 77. Disaggregated results for CET+FOLFOX versus FOLFOX, fortnightly cetuximab dose

	CET+FOLFOX	FOLFOX	Increment CET+FOLFOX versus FOLFOX
Costs (£)			
PF (1st line)	25,741	9,888	15,853
Post resection (PD)	364	153	211
Post resection (PF)	0.00	0.00	0.00
PD (2nd line)	7,289	7,968	-679
PD (3rd line)	7,907	8,398	-491
TOTAL	**41,302**	**26,408**	**14,894**
LYs			
PF (1st line)	1.02	0.73	0.29
Post resection (PD)	0.08	0.02	0.06
Post resection (PF)	0.19	0.05	0.13
PD (2nd line)	0.30	0.33	-0.03
PD (3rd line)	0.63	0.67	-0.04
TOTAL	**2.22**	**1.81**	**0.41**
QALYs			
PF (1st line)	0.79	0.56	0.22
Post resection (PD)	0.06	0.02	0.04
Post resection (PF)	0.15	0.04	0.10
PD (2nd line)	0.23	0.25	-0.02
PD (3rd line)	0.42	0.45	-0.03
TOTAL	**1.64**	**1.32**	**0.32**

Key: CET = cetuximab; FOLFOX = folinic acid + fluorouracil + oxaliplatin; ICER = incremental cost-effectiveness ratio LY = life year; PF = progression free; PD = progressive disease; QALY = quality adjusted life year
Source Merck Serono submission, executable model

CET+FOLFOX has an ICER of £46,503 per QALY gained versus FOLFOX alone and CET+FOLFIRI an ICER of £55,971 per QALY gained.

For all comparisons the health state with the highest costs and QALYs is first line progression free survival. This is due to the length of time in this state, the cost of treatment and the higher utilities of the state.

Table 78. Deterministic base case results CET+FOLFIRI versus FOLFIRI, fortnightly cetuximab dose

	Costs	LYs	QALYs	ICER (£/LY)	ICER (£/QALY)
CET+ FOLFIRI	43,592	2.19	1.61		
FOLFIRI	27,139	1.81	1.32		
Increment (CET+ FOLFIRI vs. FOLFIRI)	**16,453**	**0.38**	**0.29**	**42,990**	**55,971**

Key: CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality adjusted life year
Source: Merck submission, Table 28, Section 3.6.1.1, p.61

Table 79. Disaggregated results for CET+FOLFIRI versus FOLFIRI, fortnightly cetuximab dose

	CET+FOLFIRI	FOLFIRI	Increment CET+FOLFIRI versus FOLFIRI
Costs (£)			
PF (1st line)	27,193	10,000	17,193
Post resection (PD)	385	160	224
Post resection (PF)	0.00	0.00	0.00
PD (2nd line)	7,927	8,492	-565
PD (3rd line)	8,087	8,487	-400
TOTAL	**43,592**	**27,139**	**16,453**
LYs			
PF (1st line)	0.97	0.73	0.25
Post resection (PD)	0.08	0.02	0.06
Post resection (PF)	0.19	0.05	0.13
PD (2nd line)	0.30	0.33	-0.02
PD (3rd line)	0.65	0.68	-0.03
TOTAL	**2.19**	**1.81**	**0.38**
QALYs			
PF (1st line)	0.75	0.56	0.19
Post resection (PD)	0.06	0.02	0.04
Post resection (PF)	0.15	0.04	0.10
PD (2nd line)	0.23	0.25	-0.02
PD (3rd line)	0.43	0.45	-0.02
TOTAL	**1.61**	**1.32**	**0.29**

Key: CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; ICER = incremental cost-effectiveness ratio; LY = life year, PF = progression free, PD = progressive disease, QALY = quality adjusted life year
Source Merck Serono submission, executable model

The CET+FOLFIRI results differ for the two different pairwise comparisons (versus FOLFIRI or versus BEV+FOLFIRI) because they are based on different trials (CRYSTAL for the FOLFIRI comparison, FIRE-3 for the BEV+FOLFIRI comparison). The difference between these results seems to be primarily driven by the costs: the CET+FOLFIRI arm has similar QALYs for both CRYSTAL and FIRE-3 results (1.61 for CRYSTAL and 1.60 for FIRE-3).

Table 80. Deterministic base case results CET+FOLFIRI versus BEV+FOLFIRI, fortnightly cetuximab dose

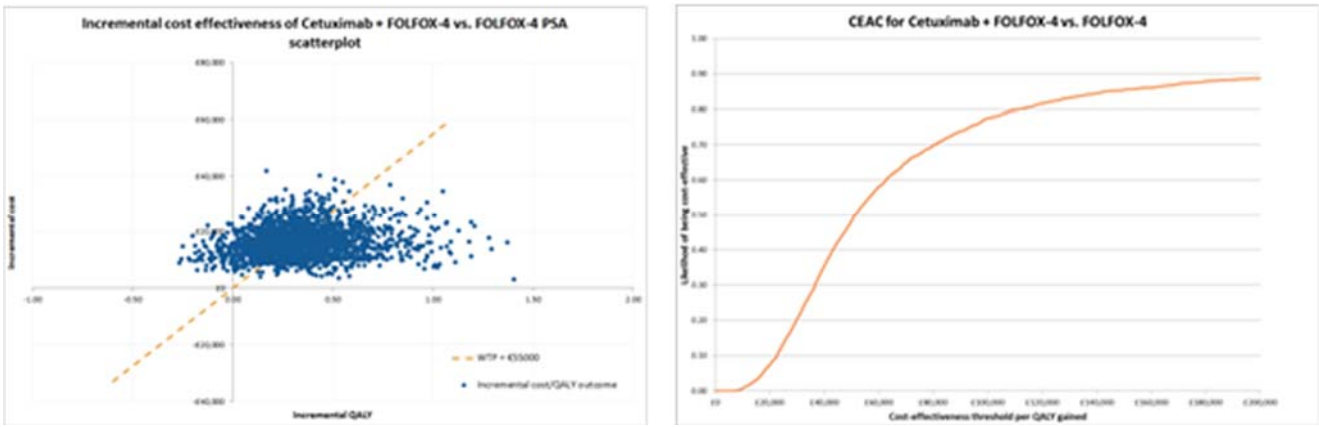
	Costs (£)	LYs	QALYs	ICER (£/LY)	ICER (£/QALY)
CET FOLFIRI	37,978	2.16	1.60		
BEV+ FOLFIRI	34,605	2.03	1.49		
Increment CET+FOLFIRI vs. BEV+FOLFIRI	**3,373**	**0.14**	**0.10**	**24,191**	**32,726**

Key: BEV = bevacizumab, CET = cetuximab, FOLFIRI = , ICER = incremental cost-effectiveness ratio LY = life year, QALY = quality adjusted life year
Source: Merck submission, Table 28, Section 3.6.1.1, p.61

Probabilistic sensitivity analysis

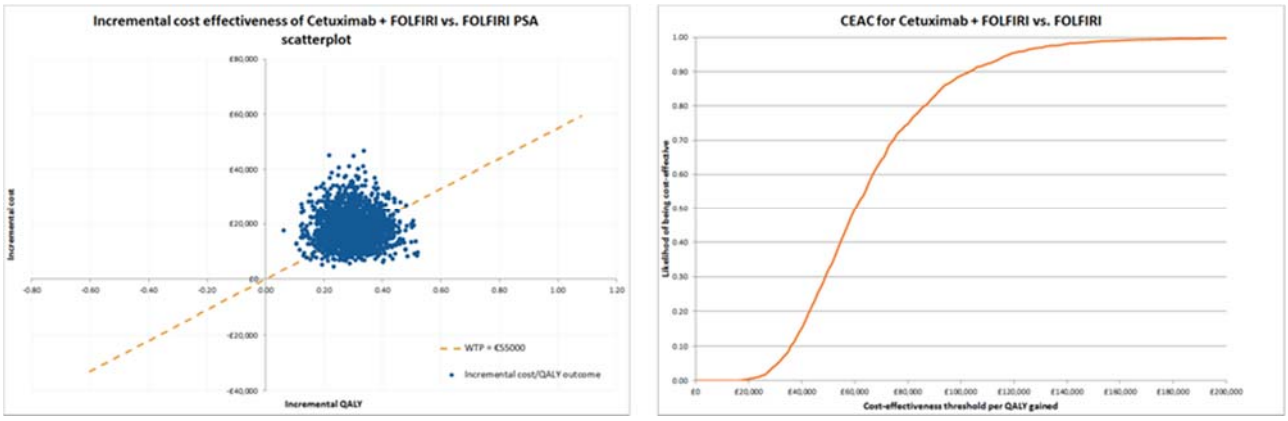
Merck Serono performed a probabilistic sensitivity analysis (PSA) for all of their base case comparisons. These were not all available in the model and so have been reproduced from the report in Figure 13 and Figure 14. CET+FOLFOX is the most likely cost-effective treatment compared to FOLFOX at a willingness to pay threshold >£50,000 per QALY and CET+FOLFIRI is the most likely cost-effective treatment compared to FOLFIRI at a willingness to pay threshold ~£60,000 per QALY. The results of the CET+FOLFOX versus FOLFOX PSA demonstrate the highest uncertainty in terms of QALYs and in a small proportion of simulations, CET+FOLFOX was dominated by FOLFOX, having larger costs and fewer QALYs. In neither PSA did cetuximab plus chemotherapy dominate chemotherapy alone.

Figure 13. ICER scatterplot and CEAC for CET+FOLFOX versus FOLFOX, fortnightly cetuximab dose



Source: Merck Serono submission, Figure 18, Section 3.7.1, page 63

Figure 14. ICER scatterplot and CEAC for CET+FOLFIRI versus FOLFIRI, fortnightly cetuximab dose

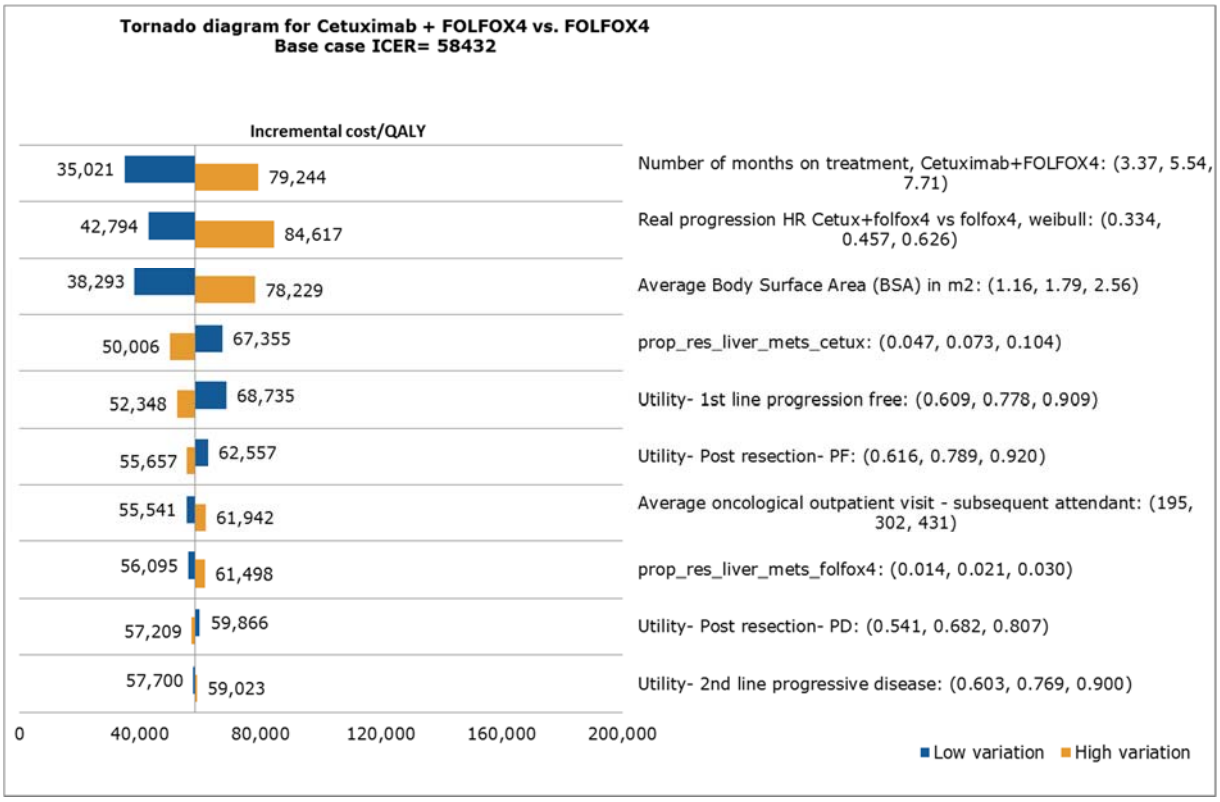


Key: CEAC = cost-effectiveness acceptability curve; ICER = incremental cost-effectiveness ratio
Source: Merck Serono submission, Figure 20, Section 3.7.1 page 63

Univariate sensitivity analysis

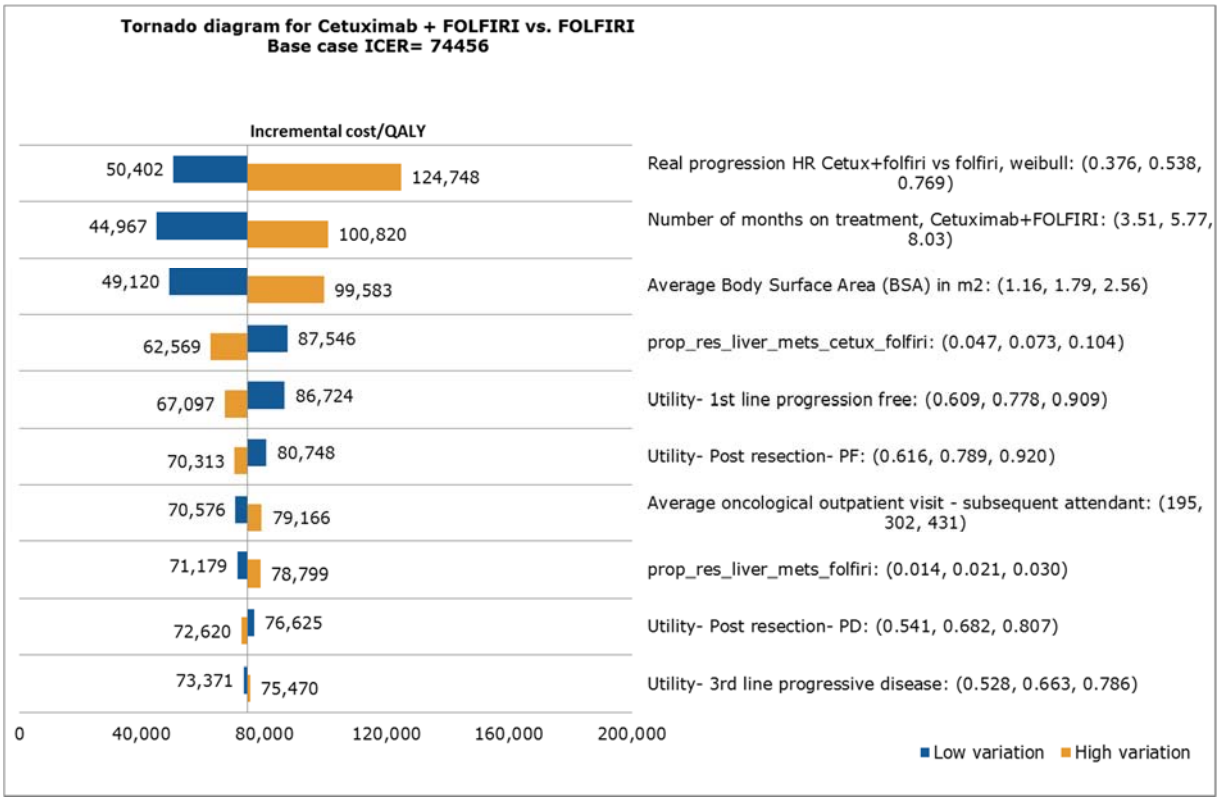
Merck Serono also conducted univariate sensitivity analyses to find the most influential parameters in the model. For both FOLFOX and FOLFIRI comparisons, parameters used to estimate the costs of treatment (number of months of treatment, average body surface area), time in progression free survival (PFS), utility in PFS, and proportion of patients who underwent liver resection were the 5 parameters that have the largest effect on the ICERs.

Figure 15. Univariate sensitivity analysis, CET+FOLFOX versus FOLFOX



Source: Merck Serono submission, Figure 23, Section 3.7.2. page 65

Figure 16. Univariate sensitivity analysis, CET+FOLFIRI versus FOLFIRI



Source: Merck Serono submission, Figure 25, Section 3.7.2. page 65

Scenario analysis

Merck Serono conducted a scenario analysis where CET+FOLFOX was compared to an alternative chemotherapy strategy: XELOX (also referred to as CAPOX). They assumed the same effectiveness of XELOX as FOLFOX and therefore only adjusted XELOX on the basis of cost. As the cost of XELOX was calculated to be higher than FOLFOX, the ICER for CET+FOLFOX versus XELOX was slightly lower than the ICER versus FOLFOX, £42,853 per QALY gained versus £46,503 per QALY gained. Results are presented in Table 81.

Table 81. Deterministic results for CET+FOLFOX versus XELOX

	Costs	LYs	QALYs	ICER (£/LY)	ICER (£/QALY)
CET+FOLFOX	41,302	2.22	1.64		
XELOX	27,577	1.81	1.32		
Increment (CET+FOLFOX vs. XELOX)	13,725	0.41	0.32	33,219	42,853

Key: CET = cetuximab; FOLFOX = folinic acid + fluorouracil + oxaliplatin; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality adjusted life year
Source: Merck submission, Table 31, Section 3.7.3.1, p. 67

Subgroup analysis

Merck conducted a subgroup analysis for a population with metastases confined to the liver. As we are unable to reconcile this analysis against the overall population model, we present the table of results here without comment (Table 82).

Table 82. Deterministic results for the liver metastases subgroup

	Costs	LYs	QALYs	ICER (£/LY)	ICER (£/QALY)
CET+ FOLFIRI versus FOLFIRI					
CET+ FOLFIRI	£45,422	2.76	2.04		
FOLFIRI	£27,790	2.18	1.60		
Increment (CET+FOLFIRI vs. FOLFIRI)	£17,632	0.59	0.45	£29,955	£39,545
CET+ FOLFOX versus FOLFOX					
CET+ FOLFOX	£43,692	2.30	1.69		
FOLFOX	£26,199	1.49	1.07		
Increment (CET+FOLFOX vs. FOLFOX)	£17,494	0.81	0.62	£21,465	£28,230

Key: CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality adjusted life year
Source: Merck submission 'list of changes' document, received 26th June

5.1.2.4. Critique of the Merck Serono model

Here we use our critique of the executable model provided by Merck Serono to assess the impact of parameters that we believe to be inappropriate on the cost-effectiveness results. These help form the basis of the comparison between Merck Serono's results and our cost-effectiveness results.

Model structure

No major wiring errors were discovered in the Merck Serono model. Several small errors and inconsistencies were discovered in the Markov trace sheets, but these had minimal impact on the ICERs. For example, CET+FOLFOX versus FOLFOX changed from £46,503 per QALY gained to £47,185 per QALY gained once these were resolved.

Model parameters

Time on treatment

As stated above, Merck Serono assume that no 1st-line drugs are given after a certain cut-off time, which varies slightly by treatment arm. Strangely, they provide no justification for the cut-off. Further, we note that Merck Serono assumed a similar cut-off time in their model for cetuximab and cetuximab+irinotecan for subsequent lines of treatment for mCRC, NICE TA242, in 2011: "active treatment stops at set cut-off time points, that is, 13 weeks for cetuximab plus best supportive care and 24 weeks for cetuximab plus irinotecan plus best supportive care, even if a patient's disease has not progressed" (NICE FAD Section 4.3.6: http://www.nice.org.uk/guidance/ta242/chapter/4-Evidence-and-interpretation). As the Assessment Group, we, PenTAG, disagreed with the use of a cut-off time, and argued for far longer treatment durations. We estimated mean treatment duration for:

- Cetuximab of 4.8 months, vs. Merck Serono 2.6 months (NICE FAD Section 4.3.13).
- Cetuximab+irinotecan of 8.8 months, vs. Merck Serono 4.4 months (NICE FAD Section 4.3.14).

The NICE committee preferred our estimates of treatment duration, as follows:

- "*The Committee therefore concluded that it did not accept the assumption in the manufacturer's model that a fixed treatment period for cetuximab represented UK clinical practice*" (NICE FAD Section 4.4.11).

- "*The Committee also noted that because the manufacturer did not provide an estimate of the average length of cetuximab treatment in the CO.17 trial, the Assessment Group contacted Dr Mittman to obtain this estimate after the assessment report had been submitted to the Committee. This estimate was provided to the Committee as an addendum, and is not given in this document because it is considered academic-in-confidence. The Committee agreed that this estimate of time on treatment was more appropriate because it was derived from trial data rather than from an assumption*." (NICE FAD Section 4.4.14).

As we state later, on request, Merck Serono gave us the following data on **median** (not mean) treatment durations from the pivotal RCTs:

- CET+FOLFOX: 5.6 months (OPUS)

- FOLFOX: 4.6 months (OPUS)

- CET+FOLFIRI: 7.4 months (CRYSTAL), 4.8 (FIRE-3)
- FOLFIRI: 5.8 months (CRYSTAL)
- BEV+FOLFIRI: 5.3 months (FIRE-3)

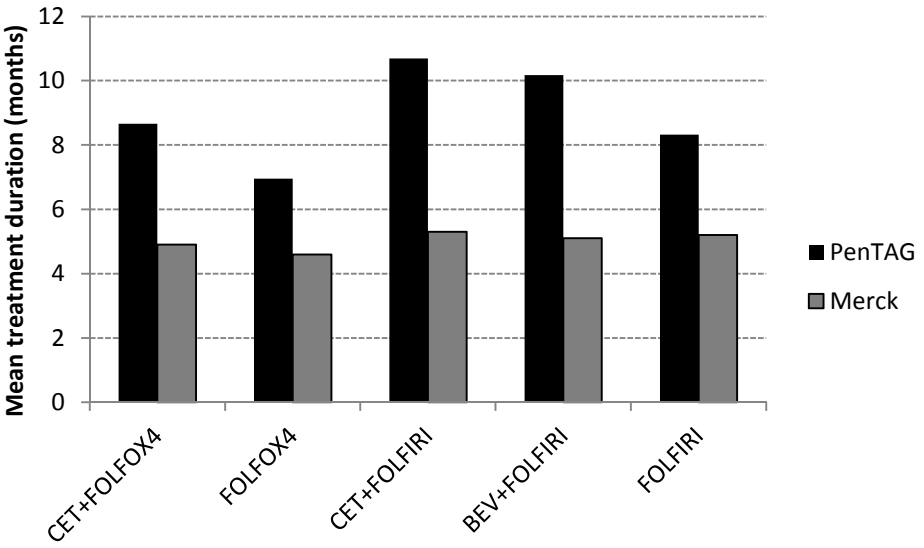
We show in Section 6.1.4.5, p.284, that there is good evidence treatment durations are approximately exponentially distributed, which leads to the followings estimates of **mean** treatment durations from the pivotal RCTs

- CET+FOLFOX: 8.1 months (OPUS)
- FOLFOX: 6.7 months (OPUS)
- CET+FOLFIRI: 10.7 months (CRYSTAL), 6.9 months (FIRE-3)
- FOLFIRI: 8.3 months (CRYSTAL)
- BEV+FOLFIRI: 7.6 months (FIRE-3)

Importantly, these estimates are substantially greater than those of Merck Serono. We model treatment duration using these estimates. We adjust these values to ensure that we do not model 1st-line drug treatment after progression, as both we and Merck Serono assume no clinical benefit of any 1st-line treatment after progression (as our models use only PFS, not OS from the 1st-line RCTs) (Section 6.1.3.2, p243).

The result is that we assume far longer treatment duration than Merck Serono.(Figure 17). This has the important effect that we estimate far higher drug acquisition and drug administration costs, as explained below.

Figure 17. Mean durations of 1st-line line drugs: PenTAG vs. Merck Serono



Key: BEV = bevacizumab; CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin

Utilities

In general we agree with the sources and approach Merck Serono used to identify and implement their utilities.

Merck Serono use Bennett et al. (2011) for estimates of utilities in first and second line treatment. As no *RAS* WT utility data has been identified, we agree that this is the most relevant source currently available. We also agree that there is no significant evidence of a difference between treatment arms (or over time) based on published results of quality of life of first and second line *KRAS* WT mCRC populations.

Merck Serono use an estimate from Wang et al. (2011) for third line treatment.[6] Again, this source is appropriate as it is for a previously treated *KRAS* WT mCRC population who are receiving best supportive care.

Though we agree with these sources, the PenTAG base case uses alternative values based on these sources. Further information on the values and the sources themselves can be found in Section 6.1.4.11, p.313.

Merck Serono use the higher estimates of utilty reported at baseline for the panitumumab plus chemotherapy populations.[5] We believe a better estimate for first line would be to take a weighted average of the treatment arms, 0.767, under the assumption that any difference in

utility between them is the result of random chance. This is discussed in detail in Section 6.1.4.11, p.308. Applying this value results in only a slight increase in ICERs.

In second line, as patients are only expected to receive chemotherapy alone in practice, we believe it would be more appropriate to use the estimate of the FOLFIRI only population, 0.762. Again Merck Serono's ICERs change only very slightly when this value is applied.

Merck Serono's estimate of utility in third line best supportive care is for patients without symptoms of disease or toxicity. We believe it would be more appropriate to use those in the progressive disease state, with a reduced utility of 0.641. This leads to a marginal increase in ICERs from Merck Serono's base case.

As the utilities for Merck Serono's base case, and our base case are quite similar, the impact of altering these values is minimal. Even altering first, second and third line utilities to be in line with the PenTAG model results in ICER changes of <£1,000.

Table 83. Comparison of base case health state utilities in the Merck Serono and PenTAG models

Health state utility	Merck Serono	PenTAG
1st line	0.778	0.767
2nd line	0.769	0.762
3rd line	0.663	0.641
PFS Post resection	0.789	<0.831 (age related)
Disutility PD post resection	0.107	0.142

Key: PD = progressive disease, PFS = progression free survival

Merck use general population estimates for utility PFS post resection, which is the same approach as the PenTAG model. However we would recommend using the approach to calculate this utility produced by Ara and Brazier (2011)[8] adjusted for more recent Health Survey for England data[7]. The value used in the PenTAG submission is also adjusted for age throughout the model and therefore has a maximum of 0.831 for the starting age of 63 years old in the base case.For post-resection PD states, the utility is assumed to be a weighted average of second line and third line health states, adjusted for time in state. Again this seems a reasonable assumption and is an approach we also use, but as our post-resection

progression free survival utility alters according to age, we instead calculate a disutility to apply in this state: 0.142

Once again, adjusting for these parameters results in very little change to the ICERs in Merck Serono's model.

Costs

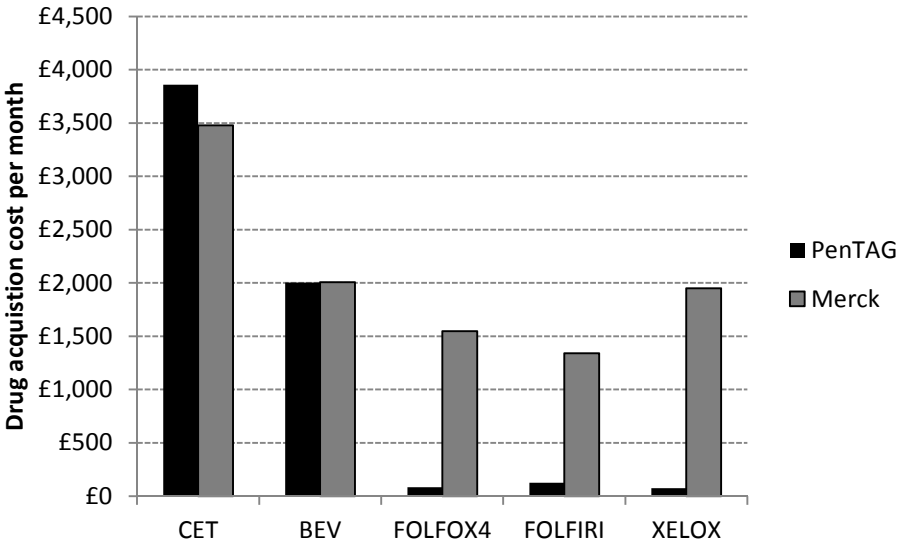
RAS mutation testing

The cost of *RAS* mutation testing used in Merck Serono's model (£200), seems appropriate and information from other genetics laboratories in the UK (discussed in Section 6.1.4.10,) have reinforced the suitability of this cost. However, in the model, this cost is applied to both arms with cetuximab and arms without cetuximab. If all patients were treated with FOLFOX or FOLFIRI, not in combination with cetuximab, a test for *RAS* mutation status would not occur. *RAS* mutation testing can be used as a prognostic tool, but this does not occur in UK practice and for some hospitals *RAS* mutation testing is only available through the Cancer Drugs Fund as a prerequisite for cetuximab or panitumumab (expert opinion, Dr mark Napier). Removing this cost from the FOLFOX and FOLFIRI arms has minimal impact on the cost-effectiveness.

Drug acquisition

After allowing for drug wastage, but not dose intensity, Merck Serono and we estimate similar acquisition costs per month for cetuximab and bevacizumab. However, Merck Serono estimate far lower costs for FOLFOX and FOLFIRI (Figure 18). This is because they use list prices, whereas we use eMit, discounted prices in our base case. Merck Serono do not consider panitumumab.

Figure 18. Mean 1st-line drug acquisition costs: PenTAG vs. Merck Serono

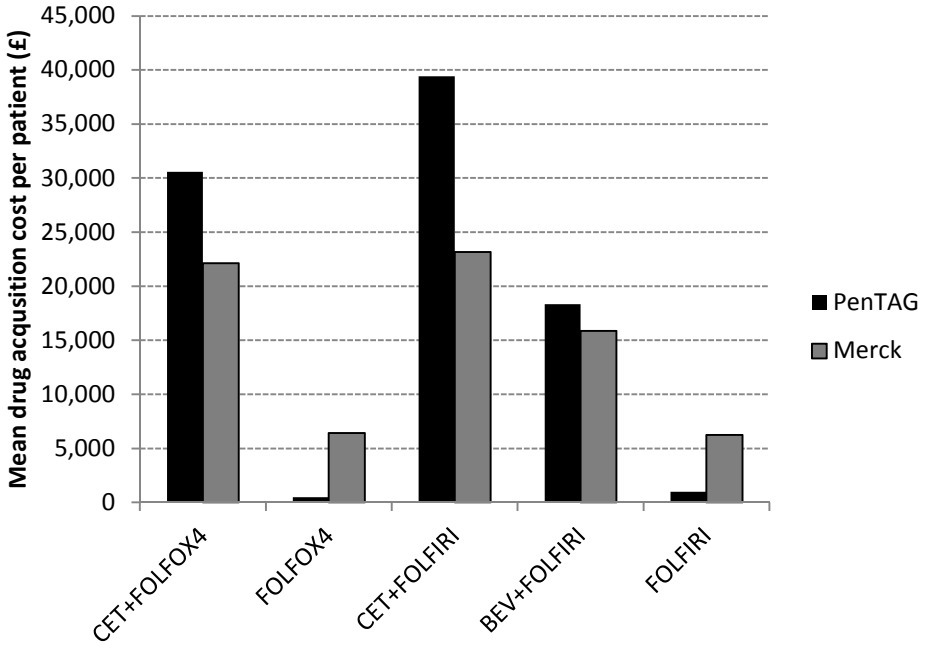


Key: BEV = bevacizumab; CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; XELOX = capecitabine + oxaliplatin

Merck Serono estimate the mean total cost of drug acquisition as the product of the mean time on 1st-line treatment and the cost of treatment per unit time, with no allowance for dose intensity. We also estimate the mean total cost of drug acquisition as the product of the mean time on 1st-line treatment and the cost of treatment per unit time, but we also allow for dose intensity.

Although we use a similar method of calculation, and although our estimate of the mean cost per unit time for cetuximab is similar, Merck Serono's estimates of mean total cost of drug acquisition are far lower than ours for CET+FOLFOX and CET+FOLFIRI (Figure 19). This is because we assume a far greater time on treatment than Merck Serono, as discussed above.

Figure 19. Mean cost of 1st-line drug acquisition all patients combined: PenTAG vs. Merck Serono



Key: BEV = bevacizumab; CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin

Although we estimate longer treatment durations for FOLFOX and FOLFIRI than Merck Serono, we estimate far lower mean total costs for these treatments (Figure 19). This is because we estimate far lower costs per unit time for FOLFOX and FOLFIRI than Merck Serono. This in turn is because we use lower generic prices, from the eMiT database, whereas Merck Serono use higher list prices.

However, this large difference in mean total cost of acquisition of FOLFOX and FOLFIRI between us and Merck Serono has little impact on cost-effectiveness, as FOLFOX and FOLFIRI are used in both treatment arms in any comparison.

Our estimates of the total cost of acquisition of BEV+FOLFIRI are coincidentally similar to those of Merck (Figure 19). One the one hand, we estimate a far greater treatment duration. One the other hand, estimate a far lower cost per unit time (due to difference in cost of FOLFIRI). These two effects cancel to a large extent.

We now critique Merck Serono's estimates of drug prices.

We believe that some of the drug acquisition costs used by Merck Serono were not appropriate for the following reasons:

- The costs of certain agents, and particularly those for oxaliplatin, irinotecan and capecitabine, did not include very significant discounts which are reliably obtained by the NHS;
- The drug acquisition costs for XELOX were overestimated because a 14 day cycle was assumed instead of the actual 21 day cycle;
- The dosages for some agents in some regimens appear to be incorrect;
- Leucovorin tablets were assumed instead of leucovorin vials for infusion;
- The premedication assumed for cetuximab does not appear to match the premedication recommended in the summary of product characteristics.

The combined effect of replacing the drug acquisition costs used by Merck Serono by values preferred by PenTAG is to reduce the total discounted costs of all regimens, but most significantly XELOX. Cetuximab becomes slightly less cost-effective versus comparators.

The NICE guide to the methods of technology appraisal[112] states that "When there are nationally available price reductions […], the reduced price should be used in the reference-case analysis to best reflect the price relevant to the NHS" and makes reference to the Commercial Medicines Unit eMIT database for medicines in the National Generics Programme Framework for England. The eMIT database[119] includes average acquisition costs for oxaliplatin, irinotecan, capecitabine, fluorouracil, leucovorin, and for suitable premedications for cetuximab. Table 84 indicates that substantial price reductions are achieved on average, of 87–98% from the list price.

Table 84: Nationally available price reductions for drugs used in chemotherapy regimens

Agent	Unit cost based on list price (BNF)	Unit cost based on average acquisition cost (eMIT)	Average discount
Oxaliplatin	£3.10 per mg	£0.0630 per mg	98%
Irinotecan	£1.14 per mg	£0.0742 per mg	93%
Fluorouracil	£0.0128 per mg	£0.0012 per mg	91%
Leucovorin	£0.2249 per mg	£0.0276 per mg	88%
Capecitabine	£0.0047 per mg	£0.0006 per mg	87%

Key: BNF = British National Formulary; eMIT = Electronic market information tool

The drug acquisition costs for XELOX were further overestimated because the model submitted by Merck Serono assumed a 14 day cycle whereas XELOX is administered on a 21 day cycle (with seven rest days).

Merck Serono assume that for FOLFOX4, the dosages for each cycle are: oxaliplatin 85 mg/m², leucovorin 200 mg/m², and fluorouracil 1,600 mg/m². We believe that the correct dosage for leucovorin is 400 mg/m² (200 mg/m² infusions on days 1 and 2), and for fluorouracil is 2,000 mg/m² (400 mg/m² bolus and 600 mg/m² prolonged infusion on days 1 and 2).[32, 36] Merck Serono assume that for FOLFOX6, the dosages for each cycle are: oxaliplatin 100 mg/m², leucovorin 200 mg/m², and fluorouracil 2,800 mg/m². We believe that the correct dosage for leucovorin is 400 mg/m² (or 200 mg/m² levoleucovorin, which is equivalent).[33, 37] When the price for leucovorin is estimated based on average acquisition cost in the NHS (Table 84) this does not have a significant impact on overall costs or cost-effectiveness.

Leucovorin tablets were assumed instead of vials for infusion. Leucovorin is administered intravenously over one hour in all regimens (except XELOX), so tablets are not appropriate. The NHS on average acquires leucovorin tablets at a cost of £0.083 per mg, compared to £0.0276 per mg for vials.[119]

The summary of product characteristics for cetuximab states that premedication with an antihistamine and a corticosteroid is mandatory prior to first cetuximab infusion and recommended prior to subsequent infusions.[44] Merck Serono have assumed that doxycycline (an antibiotic), ondansetrone (an antiemetic) and methadexasone (a corticosteroid) would be used as premedication, and therefore seem to have included an antibiotic and antiemetic which are not indicated in the SmPC (although they may be used in practice, they may also

be used in practice across regimens), and have not included an antihistamine. PenTAG estimates that the overall impact of this is small since all of these premedication drugs are inexpensive, particularly considering the reliably obtained discounts.

Finally, Merck Serono have calculated wastage based on average patient characteristics, including an average patient body surface area of 1.79 m² and body mass of 80 kg. We believe more appropriate values are 1.84 m² and 74.7 kg, which in the absence of drug wastage would increase the acquisition costs of all drugs except bevacizumab, which has weight-based dosing, but these are unlikely to have a significant impact given wastage. We are also satisfied that calculating wastage based on mean patient characteristics (rather than calculating average wastage based on a distribution of patient characteristics) is unlikely to significantly impact on cost-effectiveness in this case. This is because, as the Assessment Group, we found this to be the case for the NICE HTA of cetuximab, panitumumab and bevacizumab for subsequent lines of treatment for mCRC in 2011[120] . We note that accounting for the distribution of patient characteristics can in general impact on cost-effectiveness in other situations.[121]

The combined effect of replacing the drug acquisition costs used by Merck Serono with values preferred by PenTAG is that the total discounted costs of all regimens are reduced, but the costs of XELOX are most reduced. The ICER for CET+FOLFOX vs. FOLFOX increases slightly, from approx. £46,500 to £51,900 per QALY, and for CET+FOLFIRI vs. FOLFIRI from £56,000 to £62,900 per QALY, which is likely due to the reduced costs of second-line treatment (meaning that extending time before second-line treatment has less of a beneficial impact on cost-effectiveness).

Drug administration

We believe that the drug administration costs used by Merck Serono were not appropriate for the following reasons:

- NHS Reference costs were used inappropriately in all regimens;
- The drug administration costs for XELOX were particularly poorly estimated;
- Drug administration activity on the second day each cycle in FOLFOX4 was not costed;
- The setting was assumed to be outpatients for all patients in first-line;
- Other cost items were not included.

The combined effect of replacing the drug administration costs in Merck Serono's model with values preferred by PenTAG is to increase total discounted costs in all regimens, most for those containing FOLFOX4 and least for XELOX. The cost-effectiveness of cetuximab versus FOLFOX4 or XELOX is worsens slightly as XELOX becomes better value for money (Section 0, p.376)

NHS Reference costs were used inappropriately in the following ways:

1. Inpatient drug administration costs were estimated using outpatient administration reference costs from 2012/13 (with no justification). The NHS Reference costs do not include costs for chemotherapy delivery in an inpatient setting, but given that inpatient and "day case" seem to have been used interchangeably, the more appropriate costs to use are those in the "Daycase and Regular Day/Night" setting, and from the most recent reference costs (2013/14).

2. The HRG SB15Z (Deliver subsequent elements of a chemotherapy cycle) was inappropriately used for the administration costs for complete cycles after the first cycle, rather than for activity not on the first day of a chemotherapy cycle. The correct usage is for the first attendance in every cycle to use SB14Z (or another delivery code except SB15Z), and then to use SB15Z for any subsequent attendances within each cycle.

The drug administration costs for XELOX were poorly estimated because Merck Serono did not account for the longer duration of XELOX cycles (three weeks rather than two weeks), which result in a 33% reduction in administration costs, and because Merck Serono continued to use SB14Z (Deliver complex chemotherapy, including prolonged infusional treatment, at first attendance) for XELOX although the duration of infusion is significantly shorter. We believe that SB13Z (Deliver more complex parenteral chemotherapy at first attendance) is more appropriate and also results in a cost reduction.

The drug administration costs for FOLFOX4 were poorly estimated because no account was taken of the necessity for an attendance or healthcare professional visit to deliver the bolus and prolonged infusion on the second day of each cycle. We believe this should generate an additional cost estimated by SB15Z each cycle.

Merck Serono also assume that first-line chemotherapy is always delivered in the outpatient setting, while second-line chemotherapy is always delivered in an inpatient/day case setting. The NHS Reference costs and clinical expert opinion suggest that in fact the day case setting is the most common overall. This has a significant impact, since the costs in the day case setting are often more expensive.

Finally, there are a number of cost items relating to drug administration which have been included in previous assessment group models but have not been included by Merck Serono. Most significant of these is "pharmacy costs", which we estimate (see Section "Pharmacy costs", p.327) adds around £200–250 per chemotherapy cycle to overall costs. Other cost items not included by Merck are "infusion pumps" (see Section "Infusion pump", p.328) and "line maintenance" (see Section "Line maintenance", p.329).

When we use our unit costs of drug administration in place of Merck Serono's costs, Merck Serono's base case ICER for

- CET+FOLFOX vs. FOLFOX increases slightly, from £47,000 to £49,000 per QALY
- CET+FOLFIRI vs. FOLFIR increases slightly, from £56,000 to £58,000 per QALY

Medical management

We believe that some of the medical management costs used by Merck Serono are inappropriate for the following reasons:

- No medical management is assumed in the progression-free health states or in the 2nd line progressive disease state;
- The cost of oncology outpatient attendances has been estimated from an inappropriate NHS reference cost and should be roughly half the price.

Merck Serono have assumed no medical management in the progression-free health states or in the second-line progressive disease state. This is not appropriate because patients in these states will receive medical management in the form of regular consultant outpatient appointments and imaging (CT) to monitor response to treatment.

The cost of oncology outpatient attendances was estimated from SB01Z (Procure chemotherapy drugs for regimens in Band 1) in the outpatient setting, which is unrelated. Instead the cost of outpatient attendances should have been estimated from service code 370 (medical oncology), which would have resulted in a cost of £144 (consultant led; 2012/13 prices) as opposed to £333 (2012/13 prices).

The executable model submitted by Merck Serono does not allow for medical management costs to be added to the states in which it is not currently modelled, but it is not considered likely that incorporating values preferred by PenTAG would significantly affect cost-effectiveness since medical management costs are significantly smaller than costs

associated with chemotherapy and do not vary between regimens. Indeed, using our model, we find that cost-effectiveness is insensitive to these costs.

However, we estimate a higher cost per unit time for treatment post-progression for resected patients. We assume £1,254 per month compared to Merck Serono £315 per month. When we use our estimate, Merck's base case ICERs increases slightly (Section 6.3, p394):

- CET+FOLFOX vs. FOLFOX: from £47,000 to £49,000 per QALY.
- CET+FOLFIRI vs. FOLFIRI: from £56,000 to £59,000 per QALY.

Liver resection

We believe that Merck Serono's estimate of the cost of liver resection, £2,707, is too low. In TA176, the NICE Committee agreed that an average cost of £8,900 for liver resection was an accurate reflection of current UK clinical practice.[11] Furthermore, the HRG codes selected by Merck Serono refer to malignant gastrointestinal tract disorder, which though relevant to colorectal cancer, do not appear to be entirely relevant for liver surgery. More appropriate codes are those associated with very complex liver resection surgery, which we use in our base case.

Given our estimate of that the cost of liver surgery, after allowing for repeat operations, and the chance of operation failure, is £17,582

Merck's base case ICERs increases slightly (Section 6.3, p394):

- CET+FOLFOX vs. FOLFOX: from £47,000 to £49,000 per QALY.
- CET+FOLFIRI vs. FOLFIRI: from £56,000 to £59,000 per QALY.

Adverse events

In Merck Serono's executable model, the disutilty for leukopenia is reported to be the same as neutropenia, but the value used refers to the disutility for skin reactions. However, correcting this does not alter the ICERs.

The length of time the adverse events correspond to in Merck Serono's model seem quite long,a s they are applied for the length of a one month cycle. Previous estimates of length of adverse events suggest that this should be much shorter, as described in the Diagnostic Assessment Report by Freeman et al. (2014).[122] Reducing this time primarily reduces the

disutility of these adverse events, but also affects some costs. Reducing the length of the adverse events to 7 days, as in the PenTAG model, changes the ICERs only marginally.

The main driver for the costs and QALYs associated with the adverse events is the type and incidence of each adverse event. The Merck Serono model appears to use adverse event data for the *KRAS* WT population rather than the *RAS* WT population, as the incidences reported for CRYSTAL are different in Merck Serono's model than what is reported in the our clinical effectiveness results. As the PenTAG and Merck Serono models have very different sets of adverse events and PenTAG has comparisons of more than two technologies, it is difficult to adjust Merck Serono's model to the individual parameters we believe are more accurate. Instead we present the total costs and QALYs associated with adverse events for the PenTAG and Merck Serono base cases (Table 85). Despite these being different, the adverse event costs and QALYs have little impact on the overall results, increasing the ICERs by less than £1,500 when the PenTAG values are used.

Table 85. Total adverse event costs and QALYs for Merck Serono and PenTAG models

Arm of model	Total AE costs		Total AE QALYs	
	Merck	PenTAG	Merck	PenTAG
CET+FOLFOX	£458	£1,472	-0.0075	-0.0018
FOLFOX	£469	£1,039	-0.0058	-0.0012
CET+FOLFIRI	£567	£803	-0.0111	-0.0009
FOLFIRI	£418	£780	-0.0077	-0.0005

Key: AE = adverse event; CET = cetuximab; FOLFIRI = folinic acid + flurouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; QALY = quality-adjusted life year
Source: Merck submission, executable model.

5.2. Conclusions

As no economic evaluation was submitted by Amgen and Merck Serono did not report results for panitumumab, we are unable to draw conclusions for panitumumab based on the industry submissions.

The cost-effectiveness review submitted by Merck Serono did not raise any additional analyses relevant to the decision problem. Their model structure seems generally appropriate and fit for purpose. Merck Serono concluded that their de novo analysis demonstrated that cetuximab was cost-effective, but we believe important parameter estimates such as treatment duration, have been underestimated. This is discussed further in our comparison with Merck Serono's model: Section 6.3, p.394.

KEY POINTS

- Amgen did not submit cost-effectiveness evidence
- Merck Serono submitted a cost-effectiveness review that was generally appropriate for this project, but limited to cetuximab studies so missed evidence on panitumumab. The separate review for utilities appeared to give appropriate includes.
- Merck Serono submitted two versions of an overall population model. We have critiqued the most recent version, which was received 16th June 2015.
- Merck produced a Markov cohort model, with time dependent transition probabilities which produced pairwise comparisons based on data from the OPUS (CET+FOLFOX versus FOLFOX), CRYSTAL (CET+FOLFIRI versus FOLFIRI) and FIRE-3 (CET +FOLFIRI versus BEV+FOLFIRI) trials.
- There were multiple inconsistencies between the report and the executable model submitted by Merck Serono.
- We disagreed with several parameters in the model, which are discussed further in Section 6.3, p.394. The most important of these affect the costs of first line treatment: treatment duration, drug acquisition and drug administration.
- Merck Serono submitted a separate executable model for the liver limited disease subgroup on 16th June, over a month after the original submission deadline of 6th May. We were unable to reconcile this executable model with the overall population model and as such have not critiqued the results of this subgroup.

6. Independent economic assessment

6.1. Methods

6.1.1. Comparator treatments

In our base case analysis, we simultaneously compare the treatments separately within the following two groups. All treatments are in the NICE Scope:

"FOLFOX network"

- Cetuximab plus FOLFOX (CET+FOLFOX),
- Panitumumab plus FOLFOX (PAN+FOLFOX)
- FOLFOX.

"FOLFIRI network"

- Cetuximab plus FOLFIRI (CET+FOLFIRI),
- FOLFIRI.

Two networks are considered as we find no randomised evidence that connects the networks (Section 3.2).

These treatments are all widely used on the NHS (Table 86).

Table 86. Current use of comparator treatments in England & Wales

Scope comparator[1]	Merck Serono	PenTAG[2]
Cetuximab/Panitumumab in combination with Oxaliplatin- or irinotecan based chemotherapy	Important	30% of all patients
Bevacizumab + oxaliplatin or irinotecan-based drugs	Not reflect clinical practice as bevacizumab is no longer funded by NHS England or the National Cancer Drugs Fund for the treatment of colorectal cancer. Therefore these comparisons are not meaningful (p69 Merck Serono submission)	10% of all patients
FOLFOX / XELOX	Important	30% of all patients
FOLFIRI / XELIRI	Important	10% of all patients
Capecitabine Tegafur, folinic acid and fluorouracil	Not comparators	20% of all patients

Key: FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; XELIRI = capecitabine + irinotecan; XELOX = capecitabine + oxaliplatin
Notes: 1. Including those on the Cancer Drugs Fund, 2. Estimated by our clinical advisor (Dr Mark Napier), based on correspondence at Exeter and South West Regional Gastro Oncology Meeting

Bevacizumab-based treatments

Bevacizumab plus FOLFOX (BEV+FOLFOX) and bevacizumab plus FOLFIRI (BEV+FOLFIRI) are both listed as treatments in the NICE Scope. NICE have not recommended these treatments for 1st-line mCRC. Furthermore, as discussed in Section 1.2, p. 67, since the NICE Scope was issued, bevacizumab containing treatment for 1st-line mCRC has been delisted from the Cancer Drugs Fund.[60] For this reason, we do not consider this as a comparator in our base case analysis.

However, in a sensitivity analysis, we consider BEV+FOLFOX in the FOLFOX network, and BEV+FOLFIRI in the FOLFIRI network, as these treatments have recently accounted for approximately 10% of all eligible patients (Table 86)

XELOX

In common with Merck Serono we model CAPOX/XELOX as a comparator treatment in a scenario analysis, assuming equal clinical effectiveness as FOLFOX. As Merck Serono, we assume the only difference is in the treatment acquisition and administration costs. See Section 5.1.2.2.

Capecitabine monotherapy and tegafur, folinic acid and fluorouracil

Though our estimates suggest that they account for 20% of all first line treatments in patients with metastatic cancer treated on the NHS, capecitabine monotherapy and fluorouracil plus folinic acid are not included as comparators in our model. On advice from our clinical advisor, we believe that these single fluoropyrimidine regimens are only used in patients for whom combination therapies are not suitable, for example when patients have comorbidities such as diabetes or liver dysfunction for which oxaliplatin or irinotecan would not be appropriate. Merck Serono state that capecitabine is 'typically used in elderly patients with poor performance status' (Merck Serono submission, Table 4, p.20), which broadly agrees with our clinical advisor.

If these patients for whom combination chemotherapies were to be modelled, they should be modelled as a separate subgroup of the treatment arms. As such this subgroup would apply to all arms equally they therefore would have no impact on the cost-effectiveness results.

To model these treatments as a separate arm seems clinically implausible (our estimates suggest that 80% of patients receive combination chemotherapy in clinical practice and that single fluoropyrimidine regimens are not the preferred first line treatment). Furthermore, no evidence of single fluoropyrimidine regimens in comparison to cetuximab or panitumumab was identified in our clinical effectiveness review. The trials which inform treatment effect of panitumumab and cetuximab restrict to patients who can receive combination chemotherapies and therefore the patients who receive single fluoropyrimidine regimens are not accounted for in these effectiveness estimates.

We also do not model tegafur, because as well as being used in single fluoropyrimidine regimens, tegafur/uracil (the combination most appropriate to this assessment) has been discontinued in the UK and no relevant alternatives are available (Merck Serono submission, Table 4, p.20).

6.1.2. Patient population & liver metastases subgroup

In common with Merck Serono and the NICE Scope, we consider two patient populations:

- All 1st line patients with *RAS* wild-type mCRC.
- Subgroup of these patients with liver metastases confined to their liver, the "Liver metastases subgroup".

We estimate that the Liver metastases subgroup comprises approximately 26% of all patients, based on the patients in the five pivotal RCTs.

The following parameters are unique for the Liver metastases subgroup:

- Resection rates,
- PFS for unresected patients.
- Treatment duration

All other parameters are unchanged from the total population analysis.

Merck Serono claim that they change only the resection rates and PFS for unresected patients for the liver metastases population. In addition, we change the treatment duration.

6.1.3. Model structure

6.1.3.1. Structure of relevant published models

Key aspects of the structure of relevant published models of the cost-effectiveness of drugs for 1st-line mCRC are given in Table 87. This table includes all models that we have included in our systematic review, plus the Merck Serono model from TA176. Although the Merck Serono TA176 model is not an included study, as it was for *KRAS* WT patients, we have included this model below, as the current HTA is a review of TA176.

For comparison, we also include our current model in the far right hand column.

The model for the cost-effectiveness of *KRAS* testing by Westwood et al. (2014)[4] is based on the Merck Serono model for TA176. Indeed, the key model structures are identical (Table 87).

Table 87. Structure of relevant published cost-effectiveness models compared to current PenTAG model

	TA176 Merck model ERG report[123] and Westwood et al (2014)[4]	Graham et al (2014)[102]	Jarrett et al (2014)[9] / SMC 2014 submission[106]	Ortendahl et al (2014) [104]	PenTAG: this HTA
Patients	1st-line mCRC *KRAS* WT	1st-line mCRC *RAS* WT	1st-line mCRC *RAS* WT	1st-line mCRC *RAS* WT	1st-line mCRC *RAS* WT
Treatments	CET+FOLFIRI vs. FOLFIRI CET+FOLFOX vs. FOLFOX	PAN+FOLFOX vs. BEV+FOLFOX	CET+FOLFIRI vs. FOLFIRI CET+FOLFOX vs. FOLFOX	CET+FOLFIRI vs. BEV+FOLFIRI	CET+FOLFIRI vs. BEV+FOLFIRI vs. FOLFIRI, CET+FOLFOX vs. PAN+FOLFOX vs. BEV+FOLFOX vs. FOLFOX
Health states					
PFS & drug costs	1st-line treatment assumed up to progression or until curative resection.	Number of cycles of treatment from PEAK RCT.	Not stated	Not stated	1st-line treatment assumed up to progression
PD Treatments 2nd-line	FOLFOX or FOLFIRI (FAD Section 3.18[11]). Split between patients with no resection and unsuccessful resection. Progression-free survival in 2nd line is derived from the PFS curves published in Tournigand et al [2004],[113] regardless of the time of progression from the first line	Distribution of treatments from PEAK RCT: anti-EGFR + FOLFIRI, or BEV + FOLFIRI, or BSC Treatment duration estimated by published PFS in 2nd-line treatment (Peeters et al 2010[124] and Giantonio et al.[125], *see Table 1 in Graha*m), as not collected in PEAK. Transition probabilities to 3rd-line calculated from weighted PFS of each 2nd-line treatment.	FOLFOX or FOLFIRI. Progression-free survival in 2nd line is derived from the PFS curves published in Tournigand et al [2004],[113] regardless of the time of progression from the first line	Based on treatments in FIRE-3 RCT	FOLFOX or FOLFIRI, independent of treatment arm
Treatments 3rd-line	BSC (FAD Section 3.18[11]). The probability of death is	BSC.	BSC. The probability of death is	Not stated	BSC. The probability of death is

	TA176 Merck model ERG report[123] and Westwood et al (2014)[4]	Graham et al (2014)[102]	Jarrett et al (2014)[9] / SMC 2014 submission[106]	Ortendahl et al (2014)[104]	PenTAG: this HTA
	derived from Jonker et al. (2009)[114] comparing treatment with CET + BSC to BSC alone. Similar to 2nd line therapy, the risk of death is independent of treatment arm.		derived from Jonker et al. (2009)[114] comparing treatment with CET + BSC to BSC alone.		derived from Jonker et al. , independent of treatment arm
After successful curative resection	1 health state only. CET not given.	2 health states: PFS and PD.	1 health state only.	1 health state only.	2 health states: PFS and PD.
After unsuccessful curative resection	As if no resection attempted	As if no resection attempted	Not stated.	Not stated	As if no resection attempted
Method of estimating overall survival					
	Not clear, but appears to be combination of survival in 1st, 2nd and 3rd line trials and survival post-resection. It appears that survival from the 1st-line trials was not extrapolated due to immaturity of data.	From extrapolation of OS data from PEAK RCT.	Not clear, but stated that "the PFS benefit translates into a direct overall survival benefit"	Not stated	Base case: combination of survival in 1st, 2nd and 3rd line trials and survival post-resection Sensitivity analysis: As Graham (2014), i.e. extrapolation of OS from RCTs.
Model basic variables					
Patient age at model entry (years)	60	Not stated	Not stated		63
Cycle length	1 week	2 weeks	4.3 weeks (1 month)	2 weeks	4.3 weeks (1 month)
Time horizon	23 years	20 years	10 years		30 years

Key: BEV = bevacizumab; BSC = best supportive care; CET = cetuximab; FAD = Final Appraisal Determination; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; mCRC = metastatic colorectal cancer; OS = overall survival; PAN = panitumumab; PFS = progression free survival; PD = progressive disease; RCT = randomised control trial; WT = wild type

6.1.3.2. Structure of PenTAG model

We have identified two candidate model structures: Structures 1 and 2 (Table 87, Table 88). Ordinarily, we would choose Structure 2 because of the consistency between the costs and health outcomes. However, this is arguably inappropriate because the RCTs of the 1st-line drugs included 2nd-line drugs that are not commonly used in the NHS (Table 89).Also, subsequent lines, e.g. 2nd-line treatment may have a very strong effect on overall survival. For example, in the FIRE-3 RCT, there was no significant difference in PFS, but there was a significant difference in OS (Section 3.2.2, p91), and very different subsequent treatments between treatment arms (Table 89).

Structure 1 assumes that the PFS benefits of the 1st-line drugs translate into OS benefits if the subsequent lines of treatment are balanced between treatment arms. Expressed differently, we assume that survival after 1st-line progression is independent of 1st-line treatment, which seems plausible, given evidence to the contrary. We use Structure 1 in our base case analysis.

Conversely, Structure 2 assumes OS is a product of responses to both 1st and subsequent lines of treatment, as experienced in the RCTs. We consider Structure 2 in a scenario analysis. Given limited data on subsequent treatments, we are forced to make approximations for the costs of these.

In our experience, both structures have been used in many previous NICE appraisals. For example, Structure 1 was used in the recent NICE assessment TA343: obinutuzumab in combination with chlorambucil for previously untreated chronic lymphocytic leukaemia,[126] and endorsed by the NICE committee

We use Structure 1 in our base case analysis, and Structure 2 in a scenario analysis

We note that Merck Serono also use Structure 1 in their analysis (Section 5.1.2.2, p192).

Table 88. Candidate cost-effectiveness model structures

	Structure 1: PenTAG base case	Structure 2: Scenario analysis
Summary of clinical data	Based on RCTs of 1st-line drugs up to 1st-line progression, time on 2nd-line treatment based on 2nd-line trials of FOLFOX and FOLFIRI. Time in 3rd-line BSC based on published data (Jonker et al).	Based completely on RCTs of 1st-line drugs. .
Similarity to previous included economic evaluations	Appears to be similar to Merck Serono TA176	Graham et al (2014)[102]
Overall survival	For unresected patients, the sum of times on 1st, 2nd and 3rd lines of treatment, allowing for mortality from each line, and affected by survival for resected patients. See end of this section for details.	Estimated by extrapolation from RCTs of 1st-line drugs.
Subsequent treatments	2nd-line FOLFOX for patients on 1st-line FOLFIRI based treatments, 2nd-line FOLFIRI for patients on 1st-line FOLFOX based treatments.	% patients taking each subsequent treatment as in the 1st-line RCTs.
Advantages and disadvantages of methods		
Simplicity	Less complex	More complex
Consistency between costs and outcomes in RCTs	Mostly, except with do not have access to IPD for mortality on 1st-line treatment only in 1st-line RCTs. Also, assume that progression and survival on 2nd-line treatment does not depend on 1st-line treatment.	Consistent
Use of 1st-line RCT data	Uses data up to progression only.	Uses all relevant data , including overall survival
Effect of 1st-line treatment post-progression	Assumed either no effect, or assumed equal for all treatment arms	Captured (but confounded with effect of subsequent lines of treatment)
Consistency with subsequent line treatments on NHS	Consistent, as FOLFOX and FOLFIRI are most likely 2nd-line treatments on NHS.	Less consistent, as not all treatments (e.g. cetuximab, panitumumab, bevacizumab) after progression available on NHS.
Suitability for indirect comparisons between multiple treatment arms	Suitable	Less suitable because the relative numbers of patients taking the various 2nd-line treatments varies between treatments in the evidence networks.

Key: FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; IPD = individual patient data; RCT = randomised control trial; TA = technology assessment

Table 89. 2nd-line treatments in 1st-line mCRC RCTs

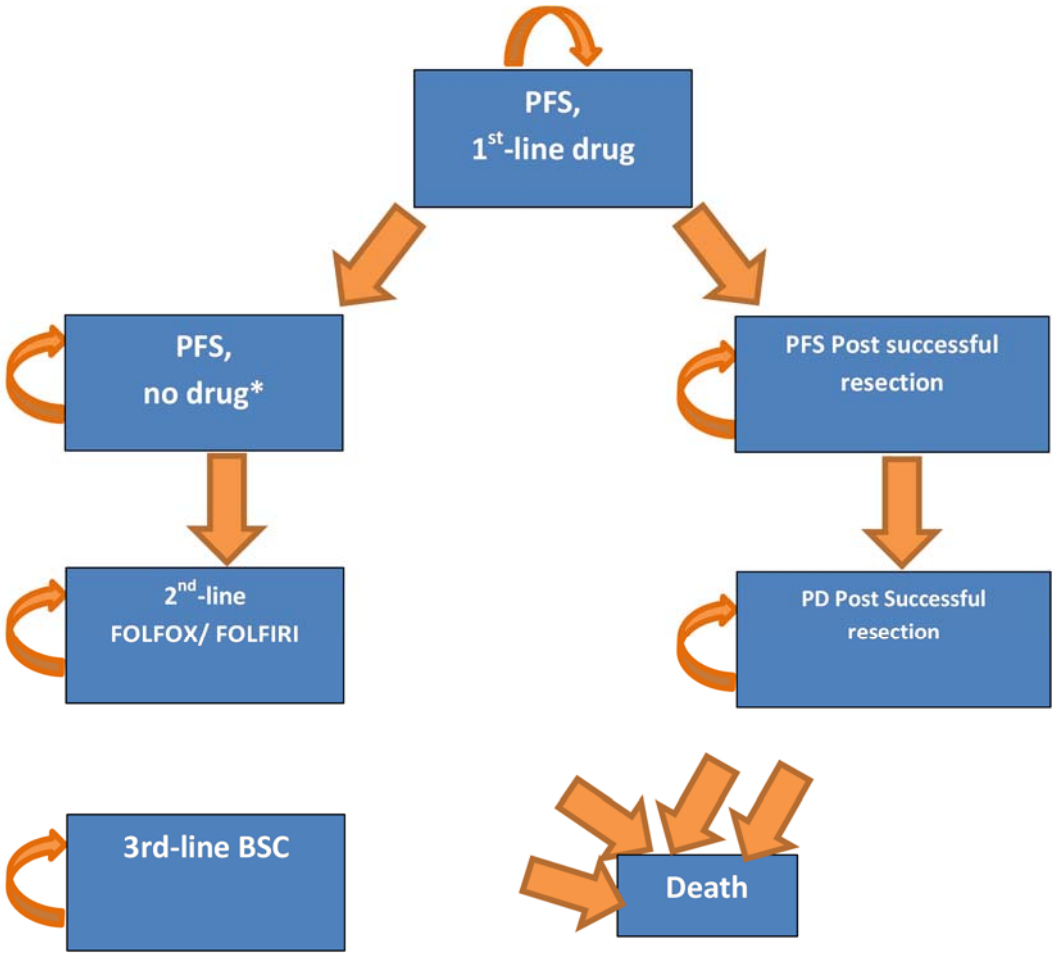
		Population	N	Anti-EGFR (Cetux/Pan)	Anti-VEGF (bevacizumab)	Oxaliplatin or irinotecan	Reference
FOLFOX network							
PRIME	PAN+FOLFOX	KRAS WT	325	13%	NR	59% chemo	Douillard, (2014)[35] (p1350)
	FOLFOX		331	25%	NR	65% chemo	
PEAK	PAN+FOLFOX	*RAS* WT	88	22% (presumably CET)	40%	Irinotecan-based 50%, oxaliplatin-based 13%	Schwarzberg, (2014)[38] (Table 3 & Appendix A2)
	BEV+FOLFOX		82	37% (presumably mix CET/PAN)	33%	Irinotecan-based 51%, oxaliplatin-based 23%	
OPUS	FOLFOX	KRAS WT	97	18%	19%	Irinotecan-based 48%, oxaliplatin-based 9%	Bokemeyer (2011)[31] Table 2
	CET+FOLFOX		82	10%	16%	Irinotecan-based 45%, oxaliplatin-based 18%	
FOLFIRI network							
FIRE-3	CET+FOLFIRI	KRAS WT	260	13%	46%	oxaliplatin-based 34.3% [a]	Ortendahl (2014)[104] CEA
	BEV+FOLFIRI		250	39%	17%	oxaliplatin-based 38.3% [a]	
CRYSTAL	CET+FOLFIRI	KRAS WT	316	NR	NR	NR	Van Custem (2011)
	FOLFIRI		350	NR	NR	NR	

Key: CET = Cetuximab; EGFR= epidermal growth factor receptor ; anti-VEGF = vascular endothelial growth factor; FOLFOX = folinic acid + fluorouracil + oxaliplatin; FOLFIRI = folinic acid + fluorouracil + irinotecan *KRAS* = kirsten rat sarcoma; PAN = panitumumab; WT = wild type

Notes: a Numbers of living patients receiving second line therapy extracted from Heinemann et al. 2014 pg. 1069, proportions for treatment type extracted from Ortendahl (2014)

The PenTAG cost-effectiveness model, implemented in Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA), simulates a cohort of people with *RAS* WT mCRC starting on 1st-line line treatment. The structure of the model was informed by a review of the literature (Section 6.1.3.1, p240) and the opinions of our clinical expert, Dr Mark Napier (Figure 20). The structure of our model is very similar to that of Merck Serono's model (Section 5.1.2.2, p196).

Figure 20 Structure of PenTAG cost-effectiveness model



Key: BSC = best supportive care FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; PD = progressive disease; PFS = progression free survival
Notes: * For CET+FOLFIRI and FOLFIRI only

In Figure 20, arrows represent the possible transitions between health states. Circular arrows denote that patients can remain in a state at the end of each model cycle. During each cycle, a patient is assumed to be in one of the states. Patients are assumed to move between states once at the end of each cycle.

Patients can die whilst in any state.

As with Merck Serono's model, differences in clinical effectiveness between 1st-line drug treatments are represented by the differences between:

- 1st-line PFS,
- Resection rates,
- Incidences of adverse events.

Estimates of cost and utility per cycle are assigned to each health state. These are aggregated over the modelled time horizon to estimate the total per patient costs and QALY for each treatment. The main economic outcome is the ICER, the incremental cost per QALY gained.

The model cycle length is one month, and the model time horizon is 30 years, after which time virtually all people in all cohorts have died. This is substantially longer than the 10 years horizon assumed by Merck Serono, and we have criticized their assumption in Section 5.1.2.2, p192. A model half-cycle correction is applied.

Future costs and benefits are discounted at 3.5% per annum, and the perspective is that of the NHS and Personal Social Services, in accordance with the NICE Reference Case.[112]

We assume all patients are aged 63 at start of 1st-line treatment, and that 66% are male, to be consistent with the clinical effectiveness data from the RCTs. In the model, this affects only the age-related utilities and the background mortality.

Baseline RCTs

For the FOLFIRI network, the CRYSTAL RCT was chosen as the baseline trial, because this contains the only two treatments in our base case analysis, CET+FOLFIRI and FOLFIRI. The other RCT, FIRE-3 includes BEV+FOLFIRI, which we consider in a sensitivity analysis only.

For the FOLFOX network, the PRIME RCT was selected as the baseline trial, as it containes two of the three treatments, PAN+FOLFOX and FOLFOX in our base case analysis. PEAK was not selected, as it contains one treatment, BEV+FOLFOX, not in our base case. Although OPUS also contains two of the three treatments, CET+FOLFOX and FOLFOX, in our base case analysis, we did not select this trial, as it is far smaller than PRIME (87 vs. 512 *RAS* WT patients).

However, we use OPUS as the baseline RCT for the FOLFOX network in a scenario analysis (Section 6.2.3.3, p379). In this case, the following parameters change in the FOLFOX network:

- Resection rates (Section 6.1.4.1, p251),
- PFS unresected patients (Section 6.1.4.4, p267) ,
- Treatment durations (Section 6.1.4.5, p284).

Modelled patients resected

Drug treatment can reduce the sizes of tumours to allow resection surgery to remove metastases. Our clinical advisor, Dr Napier, suggests that generally resection is offered only to patients with metastases confined to the liver.

As Merck Serono, and as all previous models of treatments in this indication, we assume that a proportion of patients randomised to each treatment arm have liver metastases resected (Figure 20, p246). This proportion varies by treatment arm, and according to whether the cohort represents all patients, or only patients with liver metastases confined to their liver, the "Liver metastases subgroup".

Life expectancy after successful resection is substantially greater than for patients without successful resection. Survival after resection is split in to PFS and PD, and patients can die from PFS and PD (Figure 20, p246).

Modelled 1st-line PFS: unresected patients

In the RCTs relevant to this HTA, the mean time on 1st-line treatment was less than the mean time in PFS for the CET+FOLFIRI and FOLFIRI treatments. Given also that we assume that patients start 2nd-line treatment at the time of progression, for these two treatments, there is therefore a period in 1st-line PFS during which patients are on no active drug treatment (Figure 20 "PFS, no drug" state). In this way, for unresected patients, 1st-line PFS is split in to two states: on drug, and not on drug. Merck Serono also made this assumption, although it was not stated in their report. For all other treatments, patients were assumed to receive 1st-line treatment for the complete duration of 1st-line PFS.

Time in the "PFS no drug" state is calculated as the difference between time in PFS 1st-line and 1st-line treatment duration, using the simple "area under the curve" method, i.e. transition probabilities from "PFS 1st-line drug" to "PFS no drug" are not calculated explicitly.

As explained in Section 6.1.4.4, p267 below, 1st-line PFS for unresected patients is calculated using PFS from the 5 pivotal RCTs, with adjustment for indirect comparison, and with an adjustment to subtract off PFS for resected patients.

1st-line PFS for unresected patients is calculated separately for all patients and for the Liver metastases subgroup.

Patients can die from 1st-line PFS, i.e. before progressing (Figure 20).

Modelled 2nd-line treatments: unresected patients

We assume that all unresected patients have 2nd-line FOLFIRI after 1st-line FOLFOX-based treatment and all patients have 2nd-line FOLFOX after 1st-line FOLFIRI-based treatment (Figure 20, p246).

Merck Serono also made these assumptions (Section 5.1.2.2, p192).

Our clinical expert, Dr Napier, advises us that this is the standard treatment for UK patients. In addition, our assumptions are consistent with NICE clinical guideline number 131; Colorectal cancer: the diagnosis and management of colorectal cancer, December,[13] which recommends that after 1st-line FOLFOX, then 2nd-line FOLFIRI or irinotecan is recommended. After 1st-line FOLFIRI, there is no recommendation for 2nd-line treatment.

Even though 2nd-line panitumumab, cetuximab and bevacizumab were used extensively in the relevant RCTs (Table 89, p245) we do not model these because:

- NICE have recommended none of these treatments (Table 90).
- The CDF have recommended only 2nd-line bevacizumab + FOLFOX. They have recommended neither panitumumab nor cetuximab.
- Our clinical expert, Dr Napier, advises us that these treatments are used little in UK practice.

Table 90. Recommendations of NICE and Cancer Drugs Fund on possible 2nd-line drugs

	Panitumumab	Cetuximab	Bevacizumab
NICE recommendations	Monotherapy not recommended http://www.nice.org.uk/guidance/ta242	Monotherapy or with chemotherapy not recommended http://www.nice.org.uk/guidance/ta242	Bevacizumab in combination with fluoropyrimidine-based chemotherapy not recommended http://www.nice.org.uk/guidance/ta242
Cancer Drugs Fund[58]	Not recommended	Not recommended	BEV+FOLFIRI not recommended . BEV+FOLFOX is recommended

Key: BEV = bevacizumab; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin

Patients can die from 2st-line PFS (Figure 20).

Modelled 3rd-line treatment: unresected patients

Based on clinical advice, we assume that all unresected patients have 3rd-line best supportive care after progression on 2nd-line treatment. This consists of palliative care, with no active drug treatment.

Merck Serono assume similarly that most patients, 83%, receive 3rd-line BSC, with just 17% getting capecitabine or cetuximab (Section 5.1.2.2, p192).

Overall survival

In our base case analysis, we model only PFS from the RCTs. Life expectancy for all randomised patients is calculated separately for each treatment arm as:

% patients resected x life expectancy given resected

+ (100% - % patients resected) x life expectancy given unresected.

The last quantity, life expectancy for unresected patients for each treatment arm is calculated as the sum of expected times on 1st, 2nd and 3rd lines of treatment, allowing for mortality from each line, see Section 1.1.1.1, p.297 for details.

6.1.4. Model parameters

6.1.4.1. Resection rates

Resection of liver metastases is an important component of both our model and Merck Serono's model (Figure 20), as we find that cost-effectiveness is sensitive to the rates of resection.

In TA176, Merck Serono judged rates of resection from the RCTs to be low compared with clinical practice (p12 NICE FAD[11]). Therefore, they considered resection rates for the KRAS WT population for cetuximab+FOLFIRI and cetuximab +FOLFOX of 43%, taken from the CELIM trial, which is substantially greater than in the RCTs. The NICE clinical experts and the committee instead preferred a lower value of 35% (p20, p22 NICE FAD[11]), still greater than in the RCTs.

Conversely, our clinical expert, Dr Napier, believes that the rates of liver resection in normal practice will be similar to or lower thanthose rates seen in PEAK and CRYSTAL (2-12% for all patients, Table 91). He believes that the CELIM data is not comparable as these represented carefully selected patients with liver only low volume mets and 'nearly' operable patients.

Given this, and in common with Merck Serono, we use the resection rates from the RCTs (Table 91) to estimate the rates for use in our model (Table 92).

Table 91. Liver metastases resection rates in RCTs

	Type of resection	Treatment	Liver-limited subgroup		All patients	
			RAS WT	*KRAS* WT	*RAS* WT	*KRAS* WT
FOLFIRI network						
CRYSTAL	Surgical resection - attempted resection	CET+FOLFIRI	16.3% = 7/43 (Merck Serono)	Not reported	7.3% = 13/178	Not reported
		FOLFIRI	6.5% = 3/46 (Merck Serono)		2.1% = 4/189	
FIRE-3	Secondary resection of liver mets with curative intent	CET+FOLFIRI	Not reported	Not reported	Not reported	12.1% = 36/297 (Heinemann, 2014).[37]
		BEV+FOLFIRI				13.6% (40/295) (Heinemann, 2014) [37]
FOLFOX network						
OPUS	R0 Rate of curative metastatic surgery	CET+FOLFOX	13.3 % = 2/15	Not reported	Not reported	9.8%= 6/61 (Bokemeyer, 2009)[32]
		FOLFOX	0 % = 0/12			4.1% = 3/73 (Bokemeyer, 2009)
PEAK	R0 Rate of curative metastatic surgery	PAN+FOLFOX	[redacted] (Amgen)	Not reported	12.5% = 11/88 (Amgen)	10% = 14/142 (Schwartzberg, 2014) [38]
		BEV+FOLFOX	[redacted] (Amgen)		11.0%= 9/82 (Amgen)	8.4% = 12/143 (Schwartzberg, 2014) [38]
PRIME	Results reported in the KRAS trials as R0 but endpoint definition is "reported as complete or partial [status of surgical margins not required to be captured]"	PAN+FOLFOX	31 % = 15/48 (Amgen)	27.9% = 17/61 (Douillard 2014) [35]	[redacted] (Amgen)	9.5% = 31/325 (Douillard 2014)[35]
		FOLFOX	17 % = 7/41 (Amgen)	17.5% = 10/57 (Douillard 2014) [35]	[redacted] (Amgen)	7.6% = 25/331 (Douillard 2014) [35]

Key: BEV = bevacizumab; CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; *KRAS* = Kirsten rat sarcoma; PAN = panitumumab; *RAS* = rat sarcoma; WT = wild type

Table 92. Resection rates assumed in PenTAG and Merck Serono models

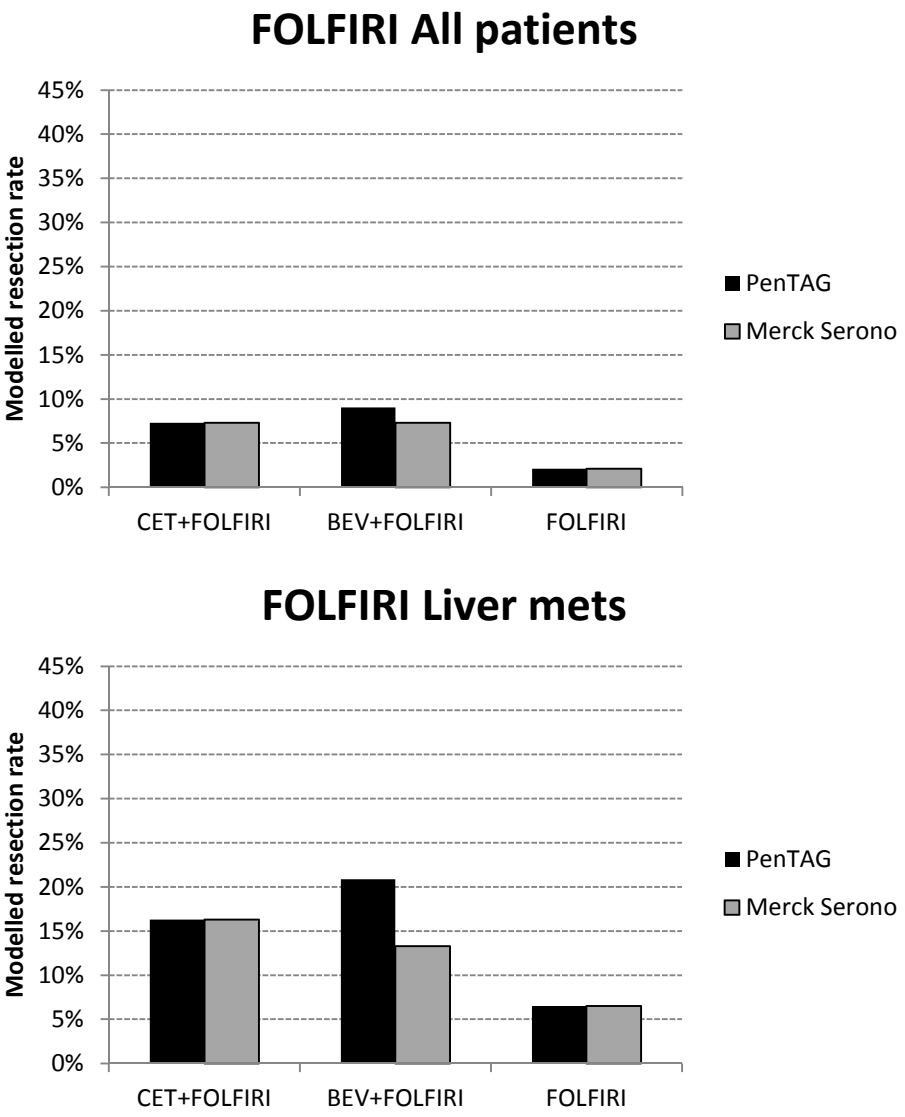
Treatment	Liver-limited mets subgroup *RAS* WT		All *RAS* WT patients	
	PenTAG	**Merck Serono**	**PenTAG**	**Merck Serono**
FOLFIRI network				
CET+FOLFIRI	16.3% (Merck Serono data).	16.3% (Merck Serono data).	7.3% (Merck Serono data).	7.3% (Merck Serono data).
FOLFIRI	6.5% (Merck Serono data).	6.5% (Merck Serono data).	2.1% (Merck Serono data).	2.1% (Merck Serono data).
BEV+FOLFIRI	20.9% (derivation explained in text)		9.0% (derivation explained in text)	7.3% No justification given
FOLFOX network				
CET+FOLFOX	[redacted] (derivation explained in text)	13.3% (OPUS)	[redacted] (derivation explained in text)	7.3% (derivation explained in text)
FOLFOX	17.1% (PRIME)	*0%* (OPUS)	[redacted] (PRIME)	2.1% (Tournigand et al. 2004[113])
PAN+FOLFOX	31.3% (PRIME)	n/a, as not modelled	[redacted] (PRIME)	n/a, as not modelled
BEV+FOLFOX	[redacted] (derivation explained in text)	n/a, as not modelled	[redacted] (derivation explained in text)	n/a, as not modelled

Key: BEV = bevacizumab; CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; ; *KRAS* = Kirsten rat sarcoma; PAN = panitumumab; *RAS* = rat sarcoma; WT = wild type

FOLFIRI network

In the FOLFIRI network, resection rates for cetuximab plus FOLFIRI and FOLFIRI were taken directly from CRYSTAL (Table 92) (Figure 21). This is also Merck Serono's approach.

Figure 21 PenTAG vs. Merck Serono modelled resection rates: FOLFIRI network



Key: BEV = bevacizumab; CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan;

For BEV+FOLFIRI, some assumptions were necessary. The "all patients" value for BEV+FOLFIRI in FIRE-3 for the *RAS* WT patients was estimated as 17.7% = 13.6% * (11.0% / 8.4%), where the value for *KRAS* WT patients was 13.6% (Table 91), and we adjust from KRAS WT to RAS WT by the ratio of 11.0% / 8.4% as in PEAK for BEV+ FOLFOX.

Next, the “all patients” value in CRYSTAL for the *RAS* WT patients for CET+FOLFIRI was estimated as 14.6% = 12.1% / 83%, where the value for *KRAS* WT patients was 12.1% (Table 91), and we assume that 83% of *KRAS* WT patients are also *RAS* WT. It was also assumed that only participants with RAS WT tumours were resected given that CET+FOLFIRI has been shown to be more effective, and is licensed, for this population

Finally, the logit of the value of 9.0% for bevacizumab plus FOLFIRI (Table 92) was calculated on the logit scale as logit(7.3%) + (logit(17.7%) - logit(14.6%)), in the manner of an adjusted indirect comparison, where the 7.3% is the chosen value for CET+FOLFIRI, and 17.7% and 14.6% are explained above. We worked on the logist transformation, as this ensured that the resulting resection rates would lie between 0% and 100%.

This is slightly different to the value of 7.3% estimated by Merck Serono. They do not justify their value, but we assume they estimated this as the value for CET+FOLFIRI

Now we turn to the derivation of the resection rate for BEV+FOLFIRI for the liver mets subgroup. The resection rates for CET+FOLFIRI and FOLFIRI were taken directly from CRYSTAL (Table 92) (Figure 21). This is also Merck Serono’s approach.

Next, we estimate the rate for BEV+FOLFIRI.

First, we estimate the rate for *RAS* WT in FIRE-3 for CET+FOLFIRI as 32.6% = 14.6% * (16.3% / 7.3%), where 14.6% is the estimated value for all patients, and 16.3% and 7.3% are the values reported for the *RAS* WT populations for CET+FOLFIRI in the subgroup and all patients populations respectively (Table 91).

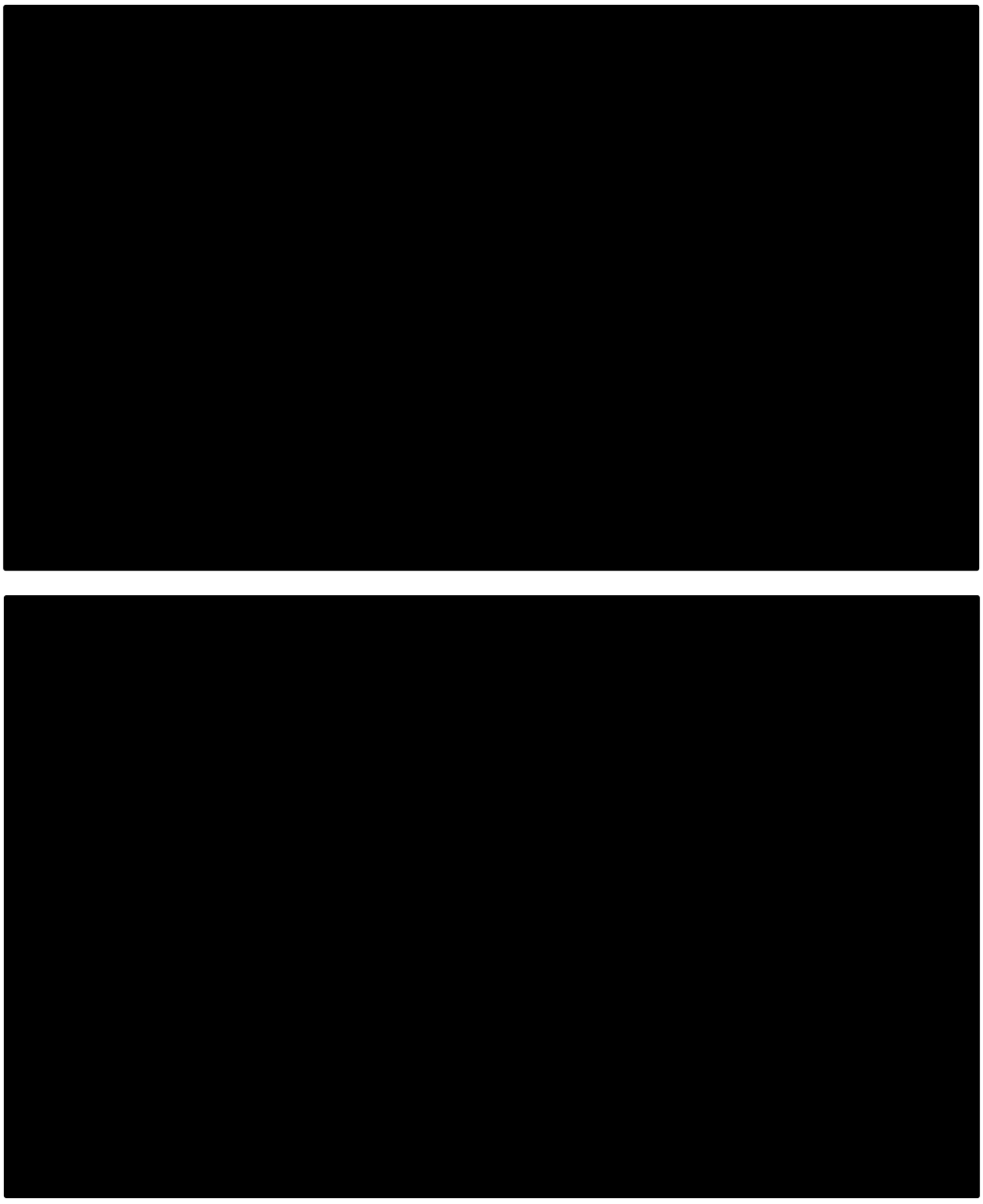
Next, we estimate the rate for *RAS* WT in FIRE-3 for BEV+FOLFIRI similarly, as 39.6% = 17.7% * (16.3% / 7.3%), where 17.7% is the estimated value for all patients, and 16.3% and 7.3% are as before.

Finally, the value of 19.8% for BEV+FOLFIRI (Table 92) was calculated as 16.3% * (39.6% / 32.6%), in the manner of an adjusted indirect comparison, where the 16.3% is the chosen value for CET+FOLFIRI, and 39.6% and 32.6% are explained above.

Finally, the value of logit of 20.9% for BEV+FOLFIRI (Table 92) was calculated as logit(16.3%) + (logit(39.6%) - logit (32.6%)), in the manner of an adjusted indirect comparison, where the 16.3% is the chosen value for CET+FOLFIRI, and 39.6% and 32.6% are explained above.

FOLFOX network

Figure 22 PenTAG vs. Merck Serono modelled resection rates: FOLFOX network



Key: BEV = bevacizumab; CET = cetuximab; FOLFOX = folinic acid + fluorouracil + oxaliplatin; PAN = panitumumab

In the FOLFOX network, resection rates for all patients for PAN+FOLFOX, [redacted], and FOLFOX, [redacted] were taken directly from PRIME (Table 92), as this is the baseline RCT in our model for the FOLFOX network (Figure 22). Merck Serono do not consider PAN+FOLFOX. They estimate the rate for FOLFOX as 2.1%, which they say is taken from Tournigand et al. (2004).[113] This is substantially lower than our estimate of [redacted].

Tournigand et al. (2004)[113] concerns 2nd-line treatment not restricted to RAS WT, whereas our estimate is taken from 1st-line treatment for RAS WT patients. Therefore, we prefer our value of [redacted].

The value of logit of the value of [redacted] for BEV+FOLFOX (Table 92) was calculated as logit([redacted]) + (logit(11.0%) - logit(12.5%)), as an adjusted indirect comparison, where the [redacted] is the chosen value for PAN+FOLFOX, and 11.0% and 12.5% are the resection rates for BEV+FOLFOX and PAN+FOLFOX from PEAK (Table 91). Merck do not model this treatment.

The value logit of the value of [redacted] for CET+FOLFOX (Table 92) was calculated by first estimating the values for CET+FOLFOX and for FOLFOX for *RAS* WT patients from OPUS. Unfortunately, we are not aware of this value being reported. Therefore, we were forced to estimate them from the corresponding values for *KRAS* WT patients from OPUS, which are reported. Specifically, the estimated rate for *RAS* patients for CET+FOLFOX = 9.8% / 83% = 11.9%, and, as above, we assume that 83% of *KRAS* WT patients are also RAS WT. The estimated rate for RAS patients for FOLFOX was estimated as 4.1% * ([redacted] / 7.6%) = [redacted], where the [redacted] / 7.6% are the rates for FOLFOX from OPUS for RAS and KRAS WT patients respectively.

Finally, the logit of the value of [redacted] for cetuximab+FOLFOX was calculated as logit(11.9%) + (logit([redacted]) - logit ([redacted])), as an adjusted indirect comparison, where 11.9% is the rate for *RAS* patients for CET+FOLFOX in OPUS and [redacted] is the rate for FOLFOX in PRIME, and [redacted] the estimate rate for FOLFOX just calculated.

By comparison, Merck Serono estimate the rate for CET+FOLFOX as 7.3%, substantially lower than our value of [redacted]. Merck Serono do not discuss the derivation of their estimate. However, we assume it was set equal to their rate for CET+FOLFIRI. If so, we believe that our estimate, whilst apparently high, is methodologically more sound, as Merck Serono's assumption seems unreasonable.

Now we turn to the derivation of the resection rates for the liver mets subgroup.

The rates of 17.1% and 31.3% for FOLFOX and PAN+FOLFOX were taken directly from PRIME, the base case RCT in the FOLFOX network.

The rate of [redacted] for BEV+FOLFOX was estimated via an indirect comparison as 31.3% * ([redacted]% / [redacted]%), where the 31.3% is the chosen rate for PAN+FOLFOX, and the [redacted]% and [redacted]% are the rates for BEV+FOLFOX and PAN+FOLFOX from PEAK.

Finally, the rate of [redacted] for CET+FOLFOX was estimated as follows. Ordinarily, we would estimate the rate as logit(17.1%) * (logit(13.3%) / logit(0%)), where 17.1% is the chosen rate for FOLFOX and 13.3% and 0% are the rates for CET+FOLFOX and FOLFOX in OPUS. However, we do not estimate the rate in this way, as it gives an estimate of infinity, which is clearly impossible. The extreme value of 0% in OPUS is partly due to the fact that this is estimated from a very small sample size of 12 patients (Table 91), which in turn is because we consider a small subgroup in a small RCT.

Instead, we estimate the rate of [redacted] for CET+FOLFOX as logit(17.1%) + (logit(11.9%) / logit([redacted] where 17.1% is as before, and 11.9% and [redacted] are the estimated rates for all patients in OPUS.

For the probabilistic sensitivity analysis, the resection rates were assumed to follow gamma distributions, with means from the RCTs, and variances of the mean calculated by p(1-p)/n, where p = deterministic resection rate, and n= number patients (Table 91).

In a scenario analysis, we consider OPUS, not PRIME as the baseline RCT for the FOLFOX network (Section 6.1.3.2, p243).

In this case, we estimate the following resection rates for all patients:

- CET+FOLFOX = 11.9% (OPUS).
- PAN+FOLFOX = [redacted]. Estimated as [redacted] (FOLFOX) x [redacted] PAN+FOLFOX PRIME / [redacted] FOLFOX, PRIME)
- BEV+FOLFOX = [redacted] Estimated as [redacted] (est. PAN+FOLFOX) * (11.0% (BEV+FOLFOX PEAK - 12.5% PAN+FOLFOX, PEAK).
- FOLFOX = 5.8% (OPUS).

and the following resection rates for the liver mets subgroup:

- CET+FOLFOX = 13.3% (OPUS).
- PAN+FOLFOX = 14.2%. Estimated as 0.0% (CET+FOLFOX) + 31.3% (PAN+FOLFOX PRIME - 17.1% FOLFOX, PRIME)
- BEV+FOLFOX = [redacted] Estimated as 14.2% (PAN+FOLFOX) * ([redacted]% (BEV+FOLFOX PEAK / [redacted] PAN+FOLFOX, PEAK).
- FOLFOX = 0.0% (OPUS).

6.1.4.2. Time of resection

In the previous assessment TA176, Merck Serono assumed in their revised analysis that the point at which patients were assessed for curative resection was 16 weeks after the start of treatment (Table 93).

Merck Serono's assumption on the timing of liver resection surgery is based on Adam et al. (2004).[3] as indicated in Table 20 (Section 3.2.2, p.49) of their submission, and is 3 months after the start of treatment.

Table 93. Time of liver resection surgery

Time to resection	Source
Normally assess after 8 weeks, but others might assess at 16 weeks.	Mark Napier, clinical advisor to PenTAG
Of people whose disease responds sufficiently to cetuximab to enable resection of liver metastases, approximately 90% would do so within 12 weeks of treatment with cetuximab.	NICE TA176,[11] clinical specialists' opinion
All patients would normally stop receiving treatment with cetuximab at the time of the assessment for possible liver resection (that is, after approximately 12–16 weeks).	NICE TA176,[11] clinical specialists' opinion
16 weeks after the start of treatment	Manufacturer's revised analysis in TA176 (section 3.31, NICE TA176,[11])
NR patients were routinely reassessed every 4 courses of chemo. Surgery was reconsidered every time a documented response to chemotherapy was observed.	Adam et al. (2004)[3]
At cycle/month 4 based upon Adam et al. (2004) which found that most resections occur before 4 months.	Merck Serono submission current HTA (Table 20, section 3.2.2, p.49).
At 3 months in the model some patients can be referred for curative-intent resection of liver metastases.	Merck Serono submission current HTA (Table 21, section 3.2.2, p.50).

We believe that it is reasonable to assume that liver resection is performed approximately 12 weeks after the start of treatment. This is based on expert opinion (Dr Mark Napier) and TA176, and also agrees with the value of 3 months used in the submission from Merck Serono. Given that this is so soon after randomisation, in our model, in common with Merck Serono, and for simplicity, we assume that resection occurs at time zero. The only loss of accuracy is due to omission of discounting of costs and QALYs for resected patients of just 1%.

6.1.4.3. Post liver resection: PFS & OS

We find that the cost-effectiveness of cetuximab+FOLFOX/FOLFIRI and panitumumab+FOLFOX/FOLFIRI is sensitive to mean PFS and OS post-resection. Therefore, estimation of these quantities is worthy of close scrutiny.

In the previous assessment TA176, overall survival after liver resection with curative intent was based on Adam et al. (2004)[3]. This is also the source used by Merck Serono in their submission.

Given sufficient time, we would have performed a systematic review of the literature for PFS and OS after resection. However, due to time constraints, we searched the literature as follows. We performed a forward reference search on Adam et al. (2004)[3] in PubMed to identify all relevant studies relating to the survival after liver resection for colorectal metastases. This yielded two other candidate studies:

- Adam et al. 2009[127]
- Adam et al. 2012[128]

A comparative analysis of these publications is shown in Table 94.

Table 94. Comparison of the study populations, types and frequencies of liver resections, and outcomes reported in Adam et al. (2004), Adam et al. (2009) and Adam et al. (2012)

	Adam et al. (2004)[3]	Adam et al. (2009)[127]	Adam et al. (2012)[128]
		Patient characteristics and treatment	
Patients from	Centre He´pato-Biliaire and Inserm E0354 "Cancer Chronotherapeutics,"Hopital Paul Brousse, Assistance Publique–Hopitaux de Paris Universite´ Paris, Sud Villejuif, France.	The AP-HP Hopital Paul Brousse, Centre Hepato-Biliaire and Department of Medical Oncology; L'Institut National de la Sante´ et de la Recherche Me´ dicale (INSERM), Unite´ 785; INSERM, Laboratoire 'Rythmes biologiques et cancers' Unite´ 776; Universite´ Paris-Sud, Villejuif, France; and Department of Surgery, University Medical Center Utrecht, Utrecht, the Netherlands.	330 centres in 58 countries, including the UK, with the majority from Western Europe. Data from LiverMetSurvey, accessed in November 23, 2011.
Patient population	Patients whose metastases were significantly downstaged by chemotherapy	Patients with unresectable CLM at the time of diagnosis who underwent rescue surgery after downsizing chemotherapy and had a minimum follow-up of 5 years from surgery	Patients who underwent conversion chemotherapy and resection for colorectal liver metastases
Number of patients initially unresectable	138	184	1,999
Lines of treatment	77% 1 line, 14% 2 lines, 9% 3 lines	74% 1 line, 26% more lines	Not reported
Stage of disease	Patients with initially unresectable colorectal liver metastases	Patients with initially unresectable liver metastases	Patients with initially unresectable liver metastases
Site of metastases	62% of patients with metastases confined to liver	73% of patients with metastases confined to liver	No reported
RAS status	Not determined	Not determined	Not determined
Year	1988-1999	1988-2002	2004-2011
Mean age (years)	57	56.9	Not reported
Gender	56% male: 44% female	58% male:42% female	Not reported

	Adam et al. (2004)[3]	Adam et al. (2009)[127]	Adam et al. (2012)[128]	
Total number of resections, including repeat resections	223, i.e. 223/138 = 1.6 per patient (p.650)	Not reported	Not reported	
Treatment after resection	Systemic chemotherapy continued for 6-8 course after resection, due to high risk of recurrence (p.646)	Postoperative chemotherapy in 93% of patients for 6 to 8 cycles.		
Type of resection	93% first hepatectomies. 75% major, 25% limited hepatectomies (p.647)	major resections in 48% patients; 26% anatomical, 25% nonanatomical, 49% both.		
Outcomes				
Post-operative Mortality	0.7%	0%	Not reported	
Post-operative morbidity	28%	25%	Not reported	
5 years disease-free survival, % (number of patients exposed)	22%(28)	19%(31)	Not reported	
10 years disease-free survival, % (number of patients exposed)	17%(12)	15%(12)	Not reported	
5 years survival, % (number of patients exposed)	33% (37)	33% (41)		33% (131)
10 years survival, % (number of patients exposed)	23% (12)	27% (14)		20% (23)

Key information concerning the patient population (such as age and gender composition) was reported in Adam et al. (2004),[3] but not in Adam et al. (2009)[127] and Adam et al. (2012).[128] Overall survival (OS) and progression-free survival (PFS) were both detailed in Adam et al. (2004),[3] and Adam et al. (2009)[127] but not in Adam (2012).[128] Frequencies of surgeries were published only in Adam et al. (2004).[3]. Therefore, for all these reasons, in common with Merck Serono, we estimate PFS and OS post-resection from Adam (2004).[3]

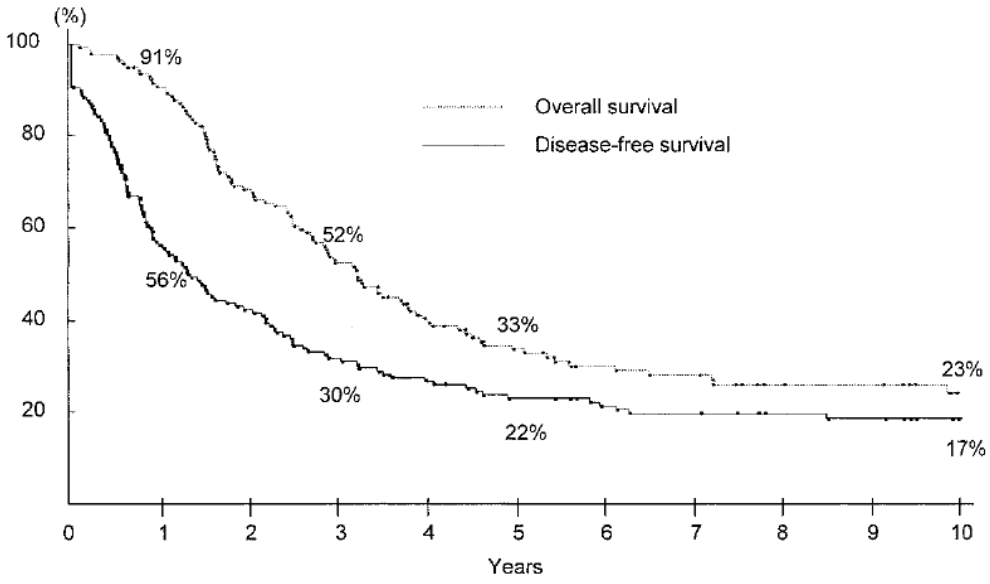
However, the choice of study has little impact on cost-effectiveness, as OS is similar across the three studies , and PFS is similar for Adam et al. (2004)[3] and Adam et al. (2009)[127] (Table 94).

Modelled PFS post-resection

Given lack of data to the contrary, and in common with Merck Serono, for those patients who had a successful resection, we assumed PFS and OS were independent of 1st-line treatment.

PFS was modelled as follows. A progression event is assumed to occur if either a patient dies due to general background non-CRC mortality, or there is a progression due to any other cause. General background non-CRC mortality was modelled explicitly because the PFS tail in Adam et al. (2004)[3] is long (Figure 23). Two functional forms were chosen for progression due to any other cause: Weibull and log-logistic. Choice of parameters of these distributions was assessed pragmatically by minimising the sums of squares of differences between Kaplan-Meier PFS and modelled PFS. Under this method, AIC and BIC are not obtained. We acknowledge that it would have been preferable to estimate the underlying individual patient data by using the method of Hoyle & Henley (2011)[129] (as we did for 1st-line PFS (Section 6.1.4.4, p267), or Guyot et al. (2012)[130]. However, given time constraints, we did not do this, in part because the adjustment for background mortality would have required additional analysis.

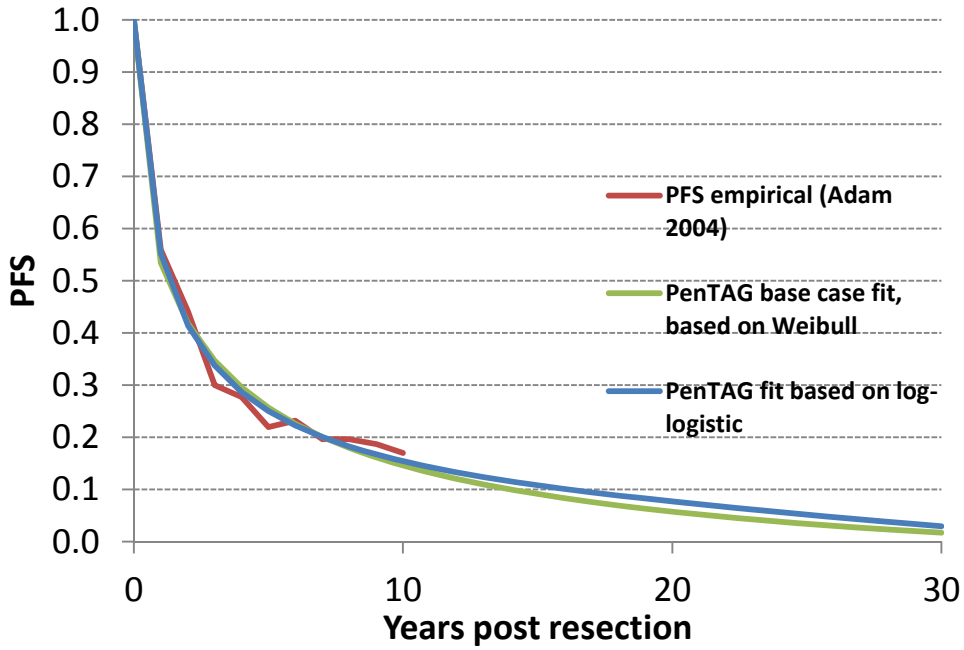
Figure 23. PFS & OS post-resection: Adam et al. (2004)



No Pts at risk	0 Yr	1 Yr	3 Yrs	5 Yrs	8 Yrs	10 Yrs
Overall	138	124	69	37	18	12
Disease-free	138	77	42	28	17	12

Source: Adam et al. (2004), Figure 5.[3]

Figure 24 PenTAG modelled PFS post-resection



Key: PFS = progression free survival

Given a 30-year time horizon, mean PFS was estimated as 4.5 years assuming the Weibull, and 4.8 years assuming the log-logistic, substantially greater than mean PFS for non resected patients (Section 6.1.4.4, p267).

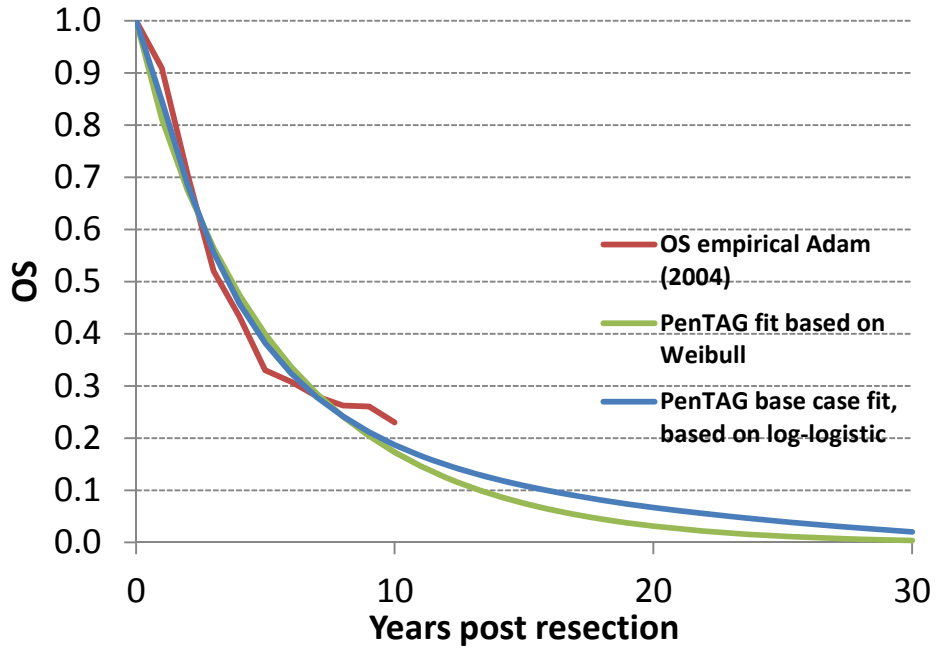
For our base case analysis, we chose the Weibull, as it is possible that the long tail in Adam et al. (2004)[3] is heavily influenced by the small numbers of patients at risk in the tail (e.g. 17 patients at 8 years, Figure 23), and the tail of the log-logistic is longer than the Weibull.

For the probabilistic sensitivity analysis, parameter gamma (shape) of the Weibull was held constant, and parameter lambda (scale) was varied in such a way to give the required mean PFS. Mean PFS was modelled as a gamma distribution with mean equal to the deterministic mean, and standard error of the mean given by the standard deviation of the Weibull distribution, divided by the square root of the number of patients, 138, in Adam et al (2004).

Modelled OS post-resection

OS post-resection was modelled as for PFS (Figure 25).

Figure 25 PenTAG modelled OS post-resection

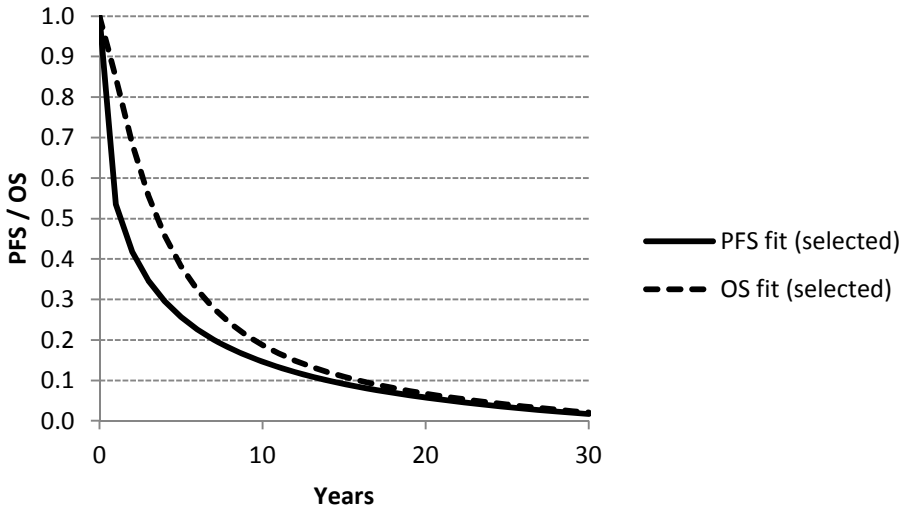


Key: OS = overall survival

Given a 30-year time horizon, mean OS was estimated as 5.6 years assuming the Weibull, and 6.2 years assuming the log-logistic.

We rejected the Weibull, as, for time over 13 years, OS was predicted to be lower than PFS. For our base case analysis, we chose the log-logistic as OS was predicted always to be greater than PFS (Figure 26).

Figure 26 PenTAG modelled PFS and OS post-resection



Key: PFS = progression free survival; OS = overall survival

Based on their overly short time horizon of 10 years, Merck Serono predict substantially shorter mean PFS and OS than us:

- PFS: 4.5 years us vs. 2.8 years Merck.
- OS: 6.2 years us vs. 4.1 years Merck.

This difference in itself acts to improve the cost-effectiveness of cetuximab plus FOLFOX/FOLFIRI and panitumumab plus FOLFOX/FOLFIRI in our model compared to Merck Serono's model, given that these treatments have relatively high resection rates.

For the probabilistic sensitivity analysis, similar to the calculations for PFS, one parameter of the log-logistic distribution was held constant, and the other parameter was varied in such a way to give the required mean OS. Mean OS was modelled as a gamma distribution with mean equal to the deterministic mean, and standard error of the mean given by the standard deviation of the log-logistic distribution, divided by the square root of the number of patients, 138, in Adam et al. (2004).

6.1.4.4. 1st-line Progression-free survival: unresected patients

In common with Merck Serono, we based our estimates of 1st-line PFS for unresected patients on the data from the pivotal RCTs.

However, Merck Serono (Section 5.1.2.2, p192), and, as far as we are aware, all previous economic analyses of 1st-line treatments for mCRC, estimate PFS for non-resected patients directly from the RCTs of all patients (resected and non-resected). We believe that this over-estimates PFS for non-resected patients, given that some patients in the RCTs are resected and that PFS for these patients is substantially longer than for non-resected patients (Section 6.1.4.3, p.263).

In summary, we estimate PFS for non-resected patients in the following steps:

A. Extrapolate PFS for all patients (resected + non-resected) separately for each treatment arm from the 5 RCTs relevant to the current HTA. We found that the Weibull distribution was most appropriate in all cases.

B. Calculate mean PFS and standard error of the mean from each extrapolated PFS curve.

C. Perform a mixed treatment comparison on the mean PFS.

D. Estimate the mean PFS for patients post-resection based on data from Adam et al. (2004)[3] which is likely to be available at the time of maximum follow-up time of 3 years in the RCTs. This is assumed to apply in all modelled treatment arms.

E. Estimate PFS for non-resected patients. The mean PFS for non-resected patients is estimated from the mean PFS for all patients (point C), mean PFS for resected patients (Step D), and proportion of patients in each treatment arm that have resection (Section 1.1.4, p67). Assume PFS for non-resected patients follows the same type of distribution as for all patients (Step A), Weibull in all cases. The shape parameter for the Weibull was estimated from Step A, and scale parameter estimated from the mean PFS for non-resected patients (Step A) and shape parameter.

The details are as follows:

A. Extrapolate PFS for all patients (resected and non-resected)

First, the Kaplan-Meieir data was extracted from the publications of the RCTs using DigitizeIt software (http://www.digitizeit.de/). The published numbers of patients at risk at each of several time points was recorded. Next, the underlying individual patients data was

estimated using this data and the method of Hoyle & Henley (2011)[129], using the online spreadsheet.[131] This method has been shown to be accurate (Wan et al. 2015).[132]

The fits of the following distributions: exponential, Weibull, log-logistic, lognormal, logistic were estimated by maximum likelihood, using the R code in the spreadsheet of Hoyle & Henley (2011). In every case, we chose the Weibull because:

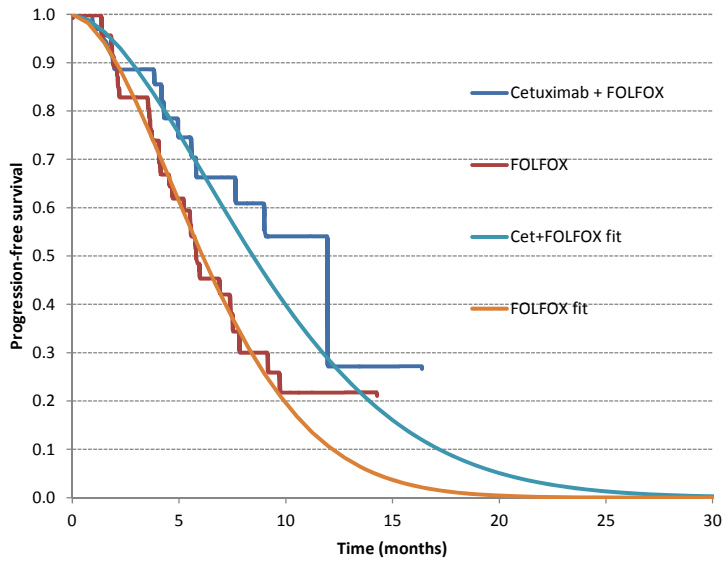
- The Weibull usually gave the lowest AIC and BIC values. If it did not, the values were nearly the lowest of all distributions.
- It seemed desirable to choose the same type of distribution for each treatment within the FOLFOX network, and separately for each treatment within the FOLFIR network, because the choice of distribution affects mean PFS, and we believe that substantial evidence would be required to choose different distributions.

We note that Merck Serono choose the Weibull distribution for all treatments in the FOLFIRI network, and the log-logistic for both treatments in the FOLFOX network.

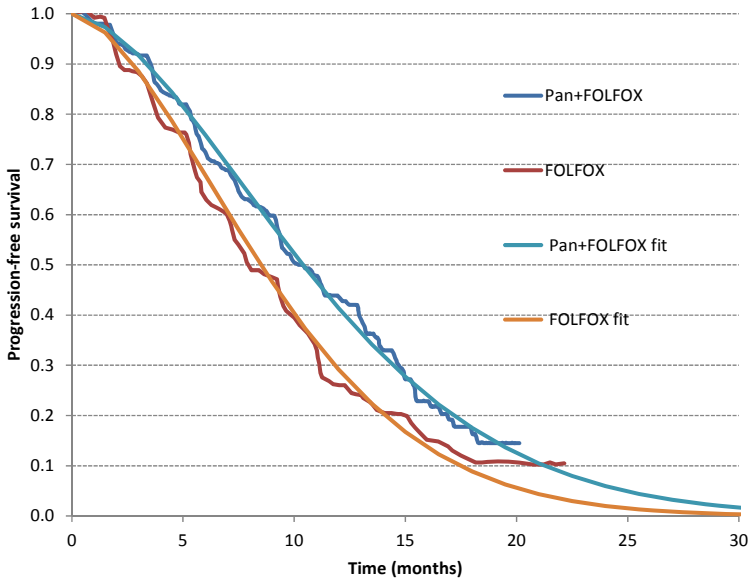
Our chosen curve fits are given in Figure 27 below. In each case, the mean and variance-covariance matrix of the parameters of the Weibull were recorded.

Figure 27 1st-line PFS (unresected patients) in PenTAG model

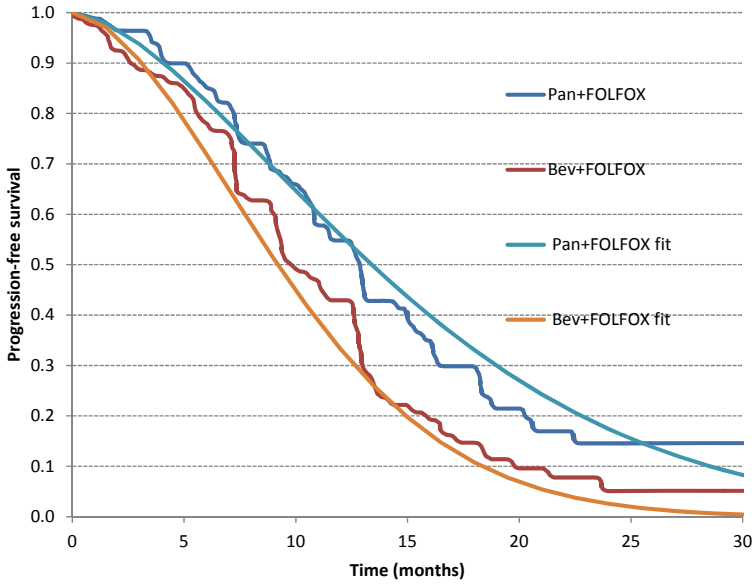
(a) CET+FOLFOX vs. FOLFOX from OPUS



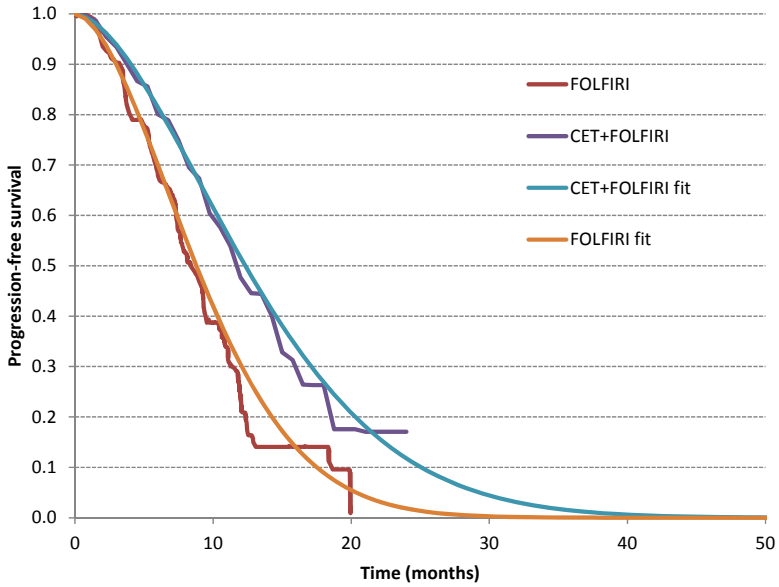
(b) PAN+FOLFOX vs. FOLFOX from PRIME



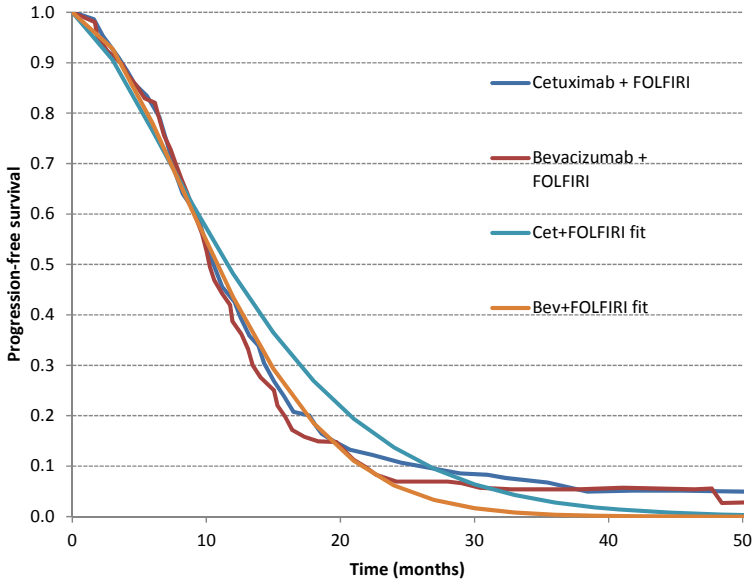
(c) PAN+FOLFOX vs. BEV+FOLFOX from PEAK



(d) CET+FOLFIRI vs. FOLFIRI from CRYSTAL



(e) CET+FOLFIRI vs. BEV+FOLFIRI from FIRE-3



Key: BEV = bevacizumab; CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; PAN = panitumumab

B. Calculate mean PFS and standard error of the mean

The means and standard errors of the mean were then calculated from the mean and variance-covariance matrices of the Weibull parameters (Table 95).

Table 95. Estimated mean PFS and standard errors for all patients (resected+unresected) from RCTs

(a) FOLFIRI network

		CET+FOLFIRI	FOLFIRI	BEV+FOLFIRI
CRYSTAL (baseline)	Mean	13.68	9.67	
	Standard error	1.09	0.59	
	Gamma of Weibull	1.69	1.74	
FIRE-3	Mean	13.53		11.88
	Standard error	0.8		0.58
	Gamma of Weibull	1.45		1.74

Key: BEV = bevacizumab; CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan

(b) FOLFOX network

		CET+FOLFOX	FOLFOX	PAN+FOLFOX
PRIME (baseline)	Mean		9.46	11.55
	Standard error		0.45	0.57
	Gamma of Weibull		1.67	1.68
OPUS	Mean	9.38	6.72	
	Standard error	1.63	0.64	
	Gamma of Weibull	1.7	1.74	
PEAK	Mean			15.14
	Standard error			1.28
	Gamma of Weibull			1.59

Key: CET = cetuximab; FOLFOX = folinic acid + fluorouracil + oxaliplatin; PAN = panitumumab

C. Mixed treatment comparison on mean PFS

For the FOLFIRI network, the CRYSTAL RCT was chosen as the baseline trial, and for the FOLFOX network, PRIME was chosen (Section 6.1.3.2, p243).

For the purposes of the economic model, we performed a mixed treatment comparisons for PFS on mean survival, not the hazard ratio. Indeed, this was our approach in our role as the Assessment Group in 2011 for the NICE MTA of cetuximab, panitumumab and bevacizumab for subsequent lines of treatment for colorectal cancer.[120] Our approach was endorsed by the NICE appraisal committee.

Furthermore, there is growing awareness that the hazard ratio cannot be recommended as a general measure of the treatment effect in RCTs.[133] It has recently been argued that for a hazard ratio to make scientific sense, we must assume that proportional hazards of the treatment effect holds, at least approximately, and that when the proportional hazards assumption fails, it is misleading to report the treatment effect through the estimated hazard ratio, since it depends on follow-up time.[133] Instead, the "restricted mean" has recently been advocated as a superior method of assessment the treatment effect in trials, where the restricted mean for a trial arm is defined as survival up to some agreed time point.[133] For our purposes, as in the previous assessment of cetuximab, panitumumab and bevacizumab for subsequent lines of treatment for colorectal cancer,[120] we perform a mixed treatment comparisons on mean survival, which is in the spirit of the "restricted mean", but with the time point set to infinity, and survival extrapolated to infinity. We argue that the full, not restricted, life expectancy is a preferable clinical outcome, as (1) cost-effectiveness is driven by the overall mean and (2) for the purposes of the mixed treatment comparison, it would be difficult to choose a time point relevant to all trials.

The network meta-analyses were undertaken within a Bayesian framework using WinBUGS. Prior distributions, when used, were defined as vague as possible.

The FOLFOX and FOLFIRI networks were analysed independently. FOLFOX was the baseline treatment in the FOLFOX network, and FOLFIRI in the FOLFIRI network. The absolute treatment effects were obtained from the network meta-analysis models where the FOLFOX analysis was based on the PRIME study and the FOLFIRI analysis was based on CRYSTAL.

Models with a normal likelihood and identity link were used.[74] Analyses were run with 3 chains, an initial burn-in of 50,000 iterations, followed by an additional 20,000 iterations on

which the results were based. Due to the small number of RCTs contributing to each network, only fixed effects models were used.

D. Estimate mean PFS for patients post-resection

Here, we estimate mean PFS for patients post-resection based on data from Adam et al. (2004)[3] which is likely to be available at the time of maximum follow-up time in the RCTs. Expressed differently, we estimate the likely PFS from resected patients in the data from the RCTs.

We judge that it is reasonable to assume that PFS from Adam et al. (2004) up to 3 years is likely to affect PFS from the RCTs, as this appears to be the latest time at which there are few censorships in the OS data from the RCTs in our base case analysis: CRYSTAL, PRIME and OPUS.

Specifically, in CRYSTAL, inspection of Figure 3B of Van Cutsem et al. (2015)[52] , reveals that there were very few censorships for OS for follow-up to 3 years. In detail, in the CT arm, at 3 years, OS is approx. 0.23, which given 189 patients randomised to this arm, gives estimated 43 patients at risk at 3 years if no censorships. Given that this is close to the 38 patients at risk, this implies that follow-up is largely complete up to 3 years. By 4 years, at 3 years, OS is approx. 0.18, which given 189 patients randomised to this arm, gives estimated 34 patients at risk at 3 years if no censorships. Given that this is substantially greater than the actual 10 patients at risk, follow-up is incomplete to 4 years.

Similarly, inspection of the OS Kaplan-Meier graphs from PRIME and OPUS reveals a similar follow-up time.

Given that PFS for resected patients at 3 years is 0.30 from Adam et al. (2004), we estimate the mean PFS for resected patients *given data up to 3 years* as 2.5 years, assuming constant hazard.

E. Estimate PFS for non-resected patients

Next, we estimate mean PFS for non-resected patients using the following equation:

mean PFS (resected + non-resected) =

% patients resected x mean PFS (resected)

+ % patients non-resected x mean PFS (non-resected)

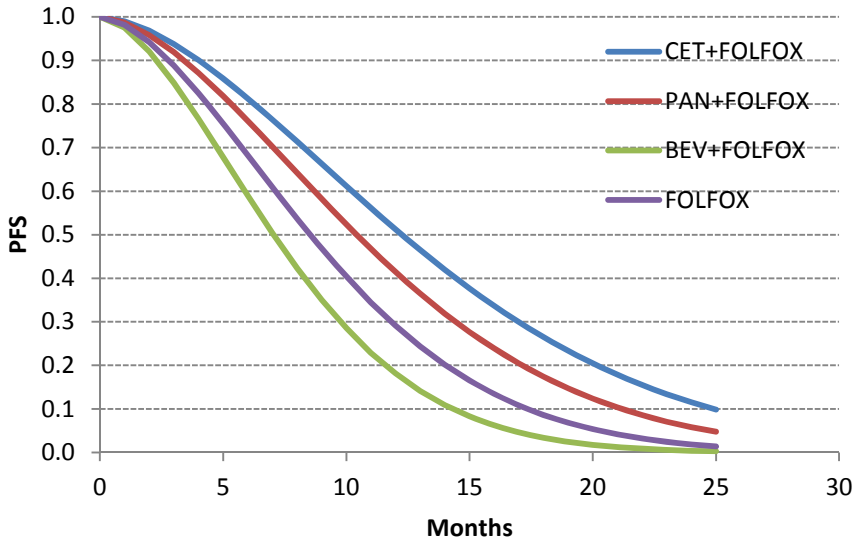
We assume PFS for non-resected patients follows same distribution as for all patients, the Weibull in all cases. The shape parameter for the Weibull was estimated from Step point A, and scale parameter estimated from the mean PFS for non-resected patients and shape parameter.

For the FOLFOX network, modelled PFS for all patients from the RCTs, resected patients and unresected patients is given in Figure 28, andsimilarly for the FOLFIRI network in Figure 29.

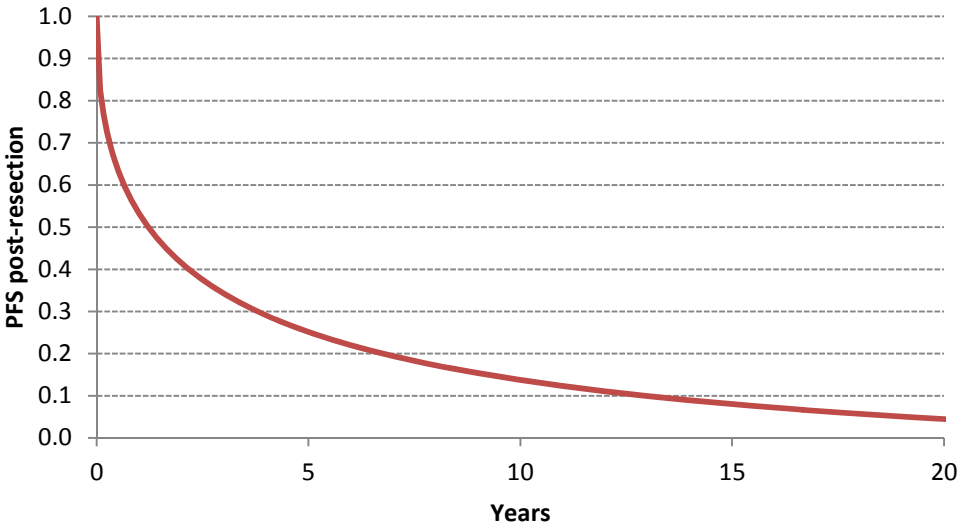
Notice that PFS for unresected patients is shorter than for all patients, as PFS for resected patients is substantially greater than for unresected patients (noting difference in scale of time axis).

Figure 28. 1st-line PFS for the FOLFOX network in PenTAG model

(a) all patients



(b) resected patients



(c) unresected patients

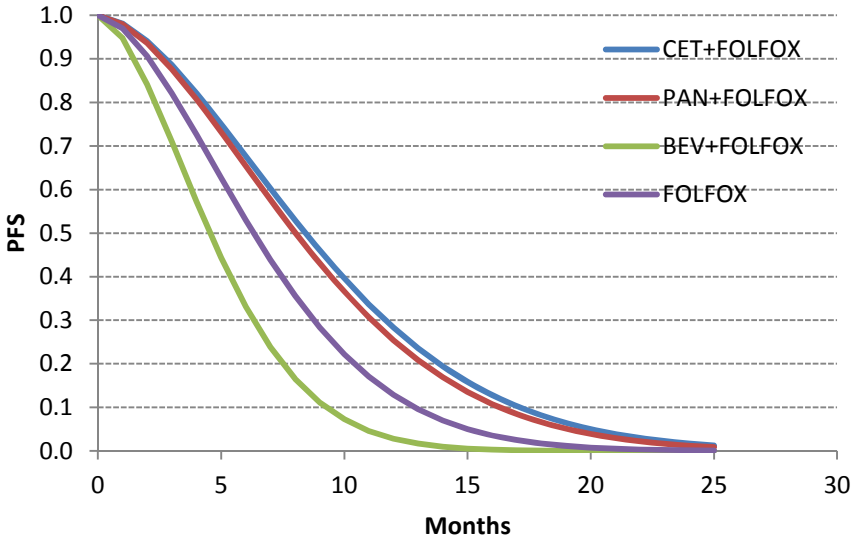
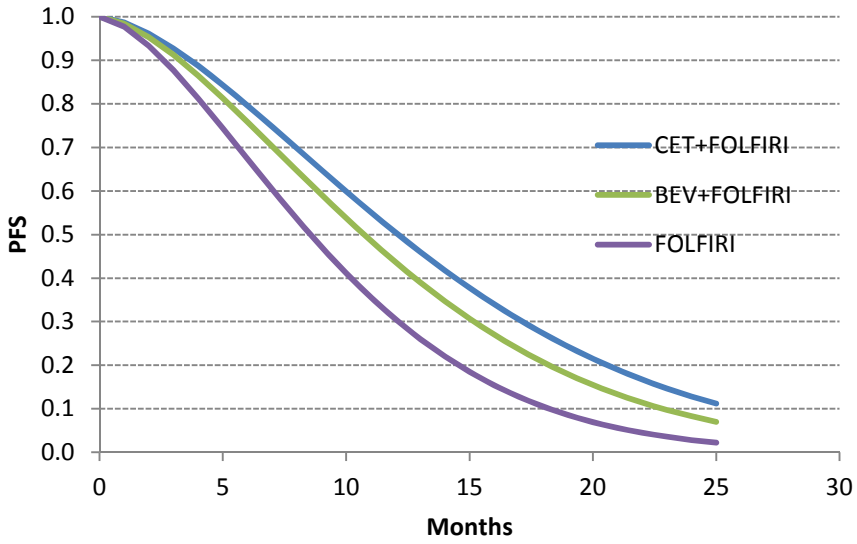
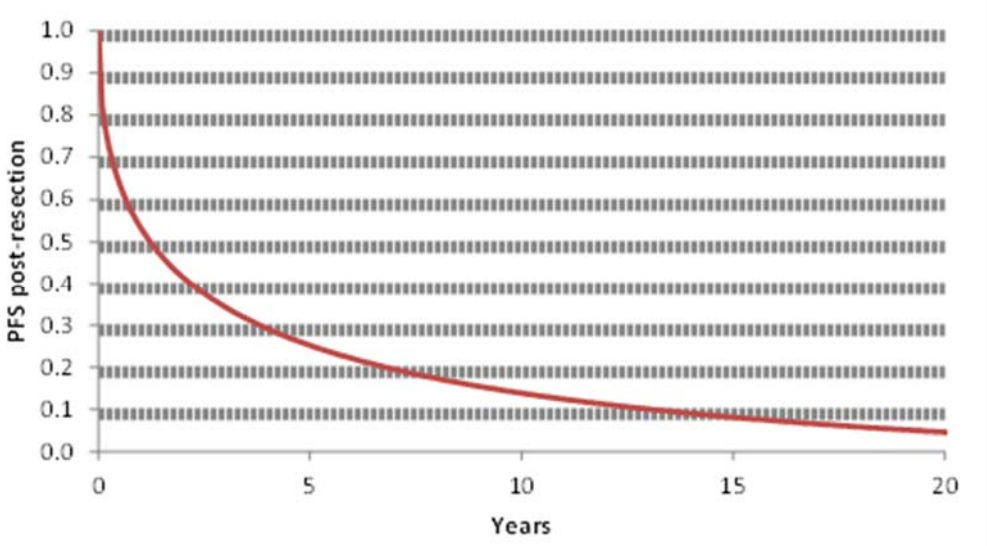


Figure 29. 1st-line PFS for the FOLFIRI network in PenTAG model

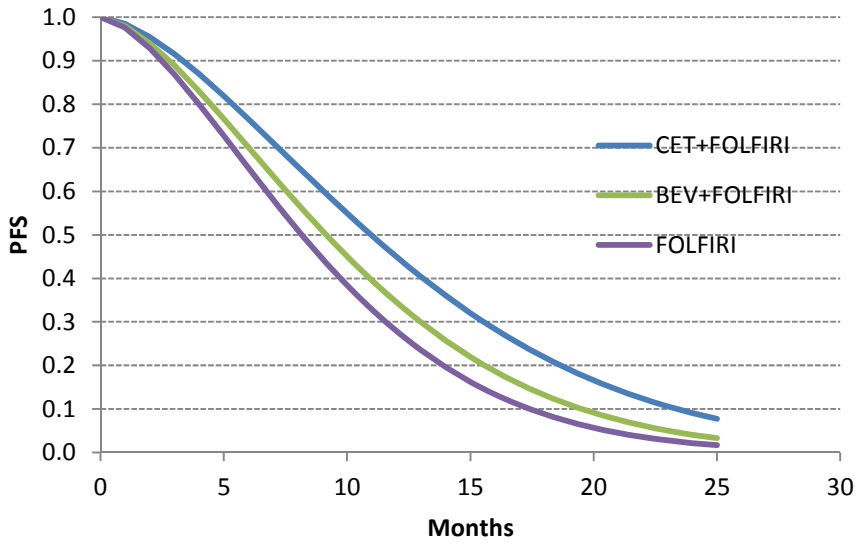
(a) all patients



(b) resected patients



(c) unresected patients



Key: BEV = bevacizumab; CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; PAN = panitumumab; PFS = progression free survival

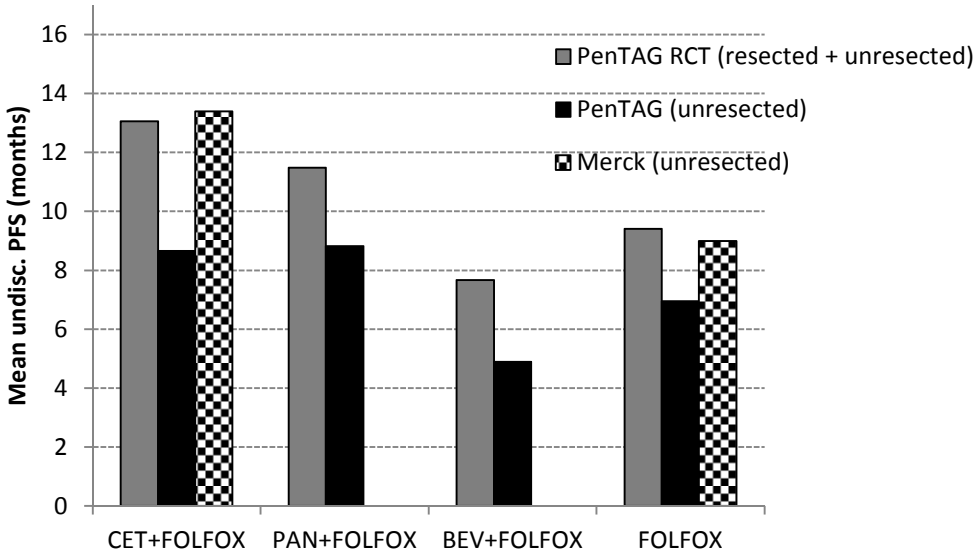
Comparison with Merck Serono

For the FOLFOX network, our estimates of mean PFS for resected + unresected patients are very similar to those of Merck Serono (Section 5.1.2.2, p192) for unresected patients only (Figure 30a). However, our estimates of mean PFS for unresected patients are substantially lower, as we have subtracted off PFS for resected patients, as described above.

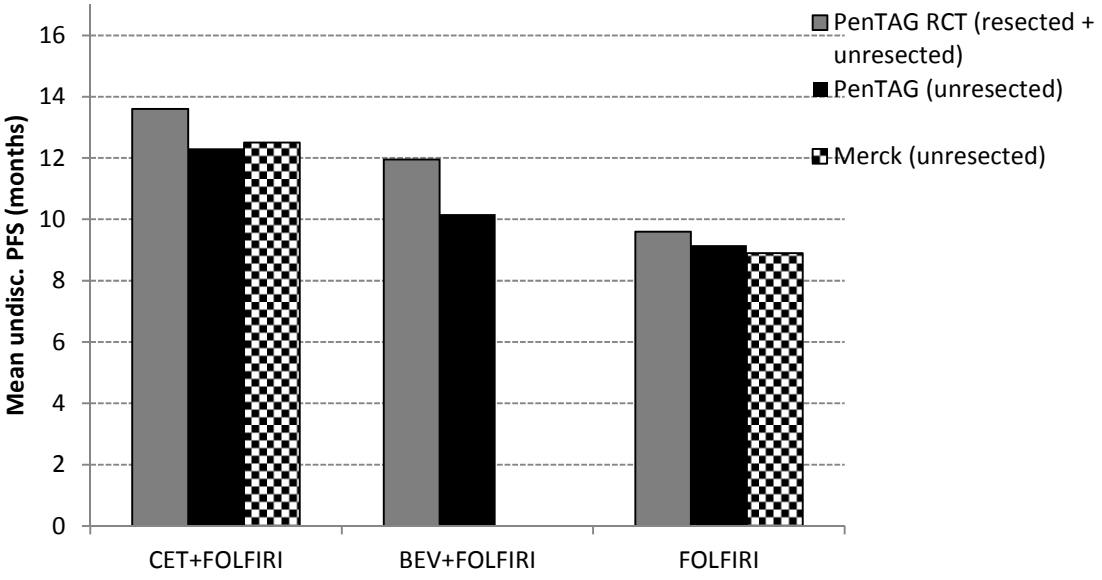
For the FOLFIRI network, our estimates of mean PFS for resected + unresected patients are slightly higher than those of Merck Serono for unresected patients only (Figure 30b). Coincidently, even though we have subtracted off PFS for resected patients, our estimates of mean PFS for unresected patients are very similar to those of Merck Serono.

Figure 30. 1st-line mean PFS PenTAG vs. Merck Serono

(a) FOLFOX network



(b) FOLFIRI network



Key: BEV = bevacizumab; CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; PAN = panitumumab; PFS = progression free survival; RCT = randomised control trial

OPUS Baseline RCT

In a scenario analysis, we consider OPUS, not PRIME as the baseline RCT for the FOLFOX network (Section 6.1.3.2, p243).

In this case, we estimate the following mean PFS for unresected patients for all patients:

- CET+FOLFOX = 9.4 months (OPUS, Table 95, p271).
- PAN+FOLFOX = 8.2 months. Estimated as 6.7 (FOLFOX) x (11.55 PAN+FOLFOX PRIME / 9.46 FOLFOX, PRIME)
- BEV+FOLFOX = 5.5* Estimated as 8.2 (est. PAN+FOLFOX) * (10.12 (BEV+FOLFOX PEAK / 15.14 PAN+FOLFOX, PEAK).
- FOLFOX = 6.7 months (OPUS, Table 95, p271).

1st-line PFS liver metastases subgroup: unresected patients

Data on 1st-line PFS for the liver metastases subgroup for *RAS* WT patients is rather limited (Table 96).

Table 96. 1st-line PFS for liver metastases subgroup for *RAS* WT patients from RCTs

	Treatment	Hazard ratio (95% CI)	Median PFS (months) (95% CI)
FOLFIRI network			
CRYSTAL	CET+FOLFIRI	0.21 (0.09 – 0.49)	14 (NR – NR)
	FOLFIRI		8.1 (NR – NR)
FIRE-3	CET+FOLFIRI	NR (Merck Serono)	NR (Merck Serono)
	BEV+FOLFIRI		
FOLFOX network			
OPUS	CET+FOLFOX	0.35 (0.06 – 1.91)	NR
	FOLFOX		7.4 (NR – NR)
PEAK	PAN+FOLFOX	[redacted]	[redacted]
	BEV+FOLFOX		[redacted]
PRIME	PAN+FOLFOX	0.75 (95% CI 0.48-1.19) (Amgen March data).	
	FOLFOX		

Key: BEV = bevacizumab; CET = cetuximab; CI = confidence interval; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; NR = not reported; PAN = panitumumab; PFS = progression free survival

PFS for the liver metastases subgroup for resected + unresected patients combined was estimated as follows:

When the median PFS for a particular treatment A for the subgroup was available, the mean PFS for the subgroup was estimated as:

Mean PFS treatment A (all patients) * { median PFS treatment A (subgroup) / median PFS treatment A (all patients) }

The assumption is that, for each treatment, the shape of PFS for the subgroup is the same as the shape for all patients.

For cetuximab+FOLFOX, we have been given no estimate of median PFS for the liver mets subgroup. Instead, we estimated the ratio above in the curly brackets as the ratio for cetuximab+FOLFIRI.

Similarly, for bevacizumab+FOLFIRI, we have been given no estimate of median PFS for the liver mets subgroup. Instead, we estimated the ratio above in the curly brackets as the ratio for bevacizumab+FOLFOX.

This approach yielded the estimates of mean PFS for all patients (resected + unresected) for the liver mets subgroup in Figure 31.

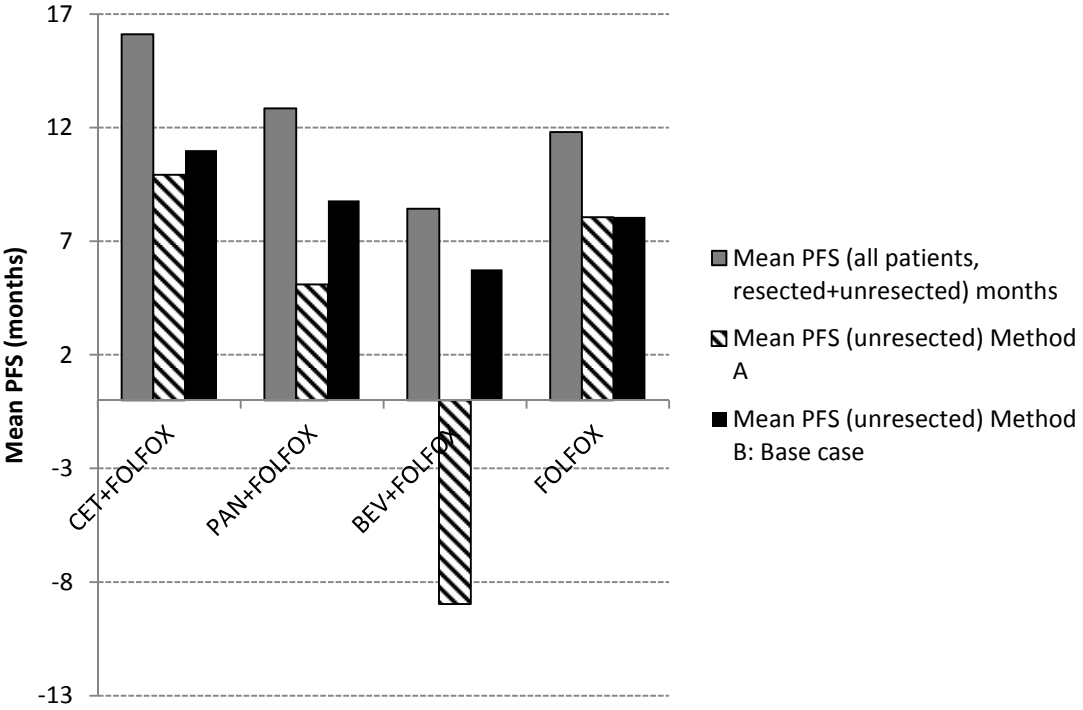
Next, estimated mean PFS for the unresected patients in the liver mets subgroup were first estimated by “Method A”, as above for all patients, by subtracting off mean PFS for resected patients, and using the resection rates specific to the subgroup. This yielded estimates of mean PFS for unresected patients in the liver mets subgroup in Figure 31.

However, the method is clearly inappropriate, because it yields a negative estimated mean PFS for unresected patients for BEV+FOLFOX (Figure 31)

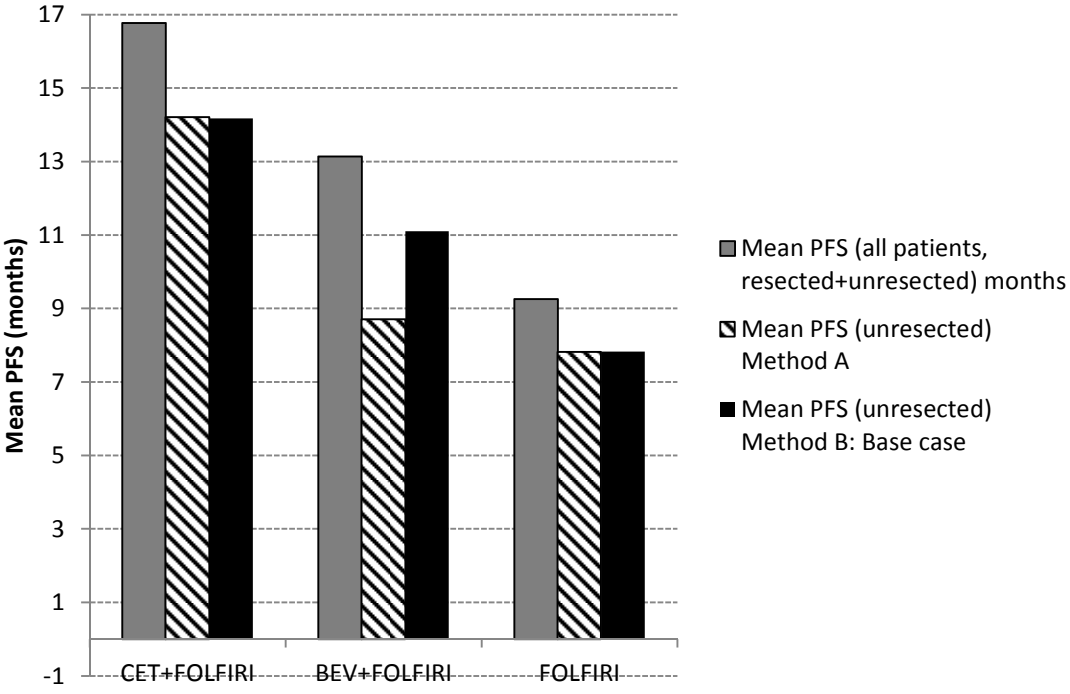
We stress that mean PFS for unresected patients for the liver metastases subgroup are highly uncertain for all treatments given the number of assumptions. Given that cost-effectivess is sensitive to this, then cost-effectivess is also highly uncertain for all treatments for the liver metastases subgroup.

Figure 31 1st-line mean PFS PenTAG liver mets subgroup

(a) FOLFOX network



(b) FOLFIRI network



Key: BEV = bevacizumab; CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; PAN = panitumumab; PFS = progression free survival

For the probabilistic sensitivity analysis, PFS for unresected patients was calculated as for the deterministic analysis, but in addition, we allow for uncertainty in:

- PFS (resected+unresected patients), discussed below.
- Resection rates (Section 6.1.4.1, p251).
- Post-resection PFS (Section 6.1.4.3, p260).

As these variables are all used to calculate PFS for unresected patients.

Mean PFS for resected+unresected patients was calculated by a mixed treatment comparison, as described Step C above. For the FOLFOX network, this yielded the following covariance matrix on the log scale, with columns and rows corresponding to FOLFOX, CET+FOLFOX and PAN+FOLFOX, in that order:

$$\begin{pmatrix} 0.005 & & \\ 0.005 & 0.038 & \\ 0.005 & 0.005 & 0.015 \end{pmatrix}$$

Log of the mean PFS for resected+unresected patients was then estimated as a multivariate normal distribution with deterministic means and covariance matrix given above.

The covariance matrix for the FOLFIRI network, with columns and rows corresponding to FOLFIRI and CET+FOLFIRI, in that order is:

$$\begin{pmatrix} 0.0063 & \\ 0 & 0.0058 \end{pmatrix}$$

Similarly, the log of the mean PFS for resected+unresected patients was then estimated as a multivariate normal distribution with deterministic means and covariance matrix given above.

Mortality from 1st-line PFS

Some of the progression events will be due to deaths. Unfortunately, we could find no information on the number of deaths from the PFS 1st-line health state in either the RAS or KRAS populations in the 5 pivotal RCTs. However, Merck Serono provide some useful data in their model. We estimate mortality from 1st-line PFS as follows.

Merck Serono provide the survival curve for progressions not related to death for the following treatment arms. We calculate the mean as in Table 97.

Table 97. Estimation of proportion of progression dues to death

	CET+FOLFOX	FOLFOX	CET+FOLFIRI	FOLFIRI
Mean progression (years) not related to death	1.15	0.77	1.07	0.76
Mean PFS unresected patients (years) (Merck Serono model)	1.04	0.74	0.98	0.73
Estimated # deaths as % of all progressions	10%	4%	8%	4%

Key: CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin

First,

Mean progression not related to death was set equal to 1/(rate progression not related to death)

Mean progression all causes was set equal to 1/(rate progression not related to death + rate progression related to death)

From these simultaneous equations, we can calculate each component rate.

Then the proportion of all progressions due to death is estimated as:

Rate progression related to death / (Rate progression related to death + Rate progression not related to death) (Table 97).

Due to the paucity of data, we pragmatically estimated the proportion related to death as the average of the proportions in the table above, at 6%.

This figure was used for all seven treatment arms of our model to calculate the number of deaths at each model cycle from the PFS 1st-line health state.

Further, given lack of alternative data, the same proportion was used to calculate the number of deaths at each model cycle from the 2nd-line health state.

In the Results, we show that cost-effectiveness is very insensitive to this proportion.

6.1.4.5. 1st-line Time on treatment

The mean times on 1st-line drug treatment are extremely important quantities because they affect the total mean cost of drug acquisition and administration per person, which are critical drivers of cost-effectiveness.

We estimate the mean treatment duration for each 1st-line treatment in the following Steps:

A. Estimate the mean treatment duration for each 1st-line treatment in each of the pivotal RCTs, based on median treatment duration from each RCT, and 25% and 75% percentile of the treatment duration when available (Table 98).

B. Estimate mean treatment duration for each 1st-line treatment by simple indirect comparison, using CRYSTAL and PRIME as baseline RCTs (Table 98).

Table 98 Steps A and B in estimation of mean treatment durations

	From RCTs	Step A	Step B
	Median treatment duration (months)	**Estimated mean treatment duration (months)**	**Modelled mean treatment duration (months)**
FOLFOX network			
CET+FOLFOX	5.6 (OPUS)	8.0 (OPUS)	14.4 (indirect comparison)
FOLFOX	4.6 (OPUS), 6.2 (PRIME)	5.0 (OPUS), 9.0 (PRIME)	9.0 (PRIME)
PAN+FOLFOX	6.5 (PRIME), 7.5 (PEAK),	9.3 (PRIME), 10.7 (PEAK),	9.3 (PRIME)
BEV+FOLFOX	5.9 (PEAK),	8.5 (PEAK),	7.3 (indirect comparison)
FOLFIRI network			
CET+FOLFIRI	7.4 (CRYSTAL),, 4.8 (FIRE-3),	10.7 (CRYSTAL), 6.9 (FIRE-3),	10.7 (CRYSTAL)
FOLFIRI	5.8 (CRYSTAL),	8.3 (CRYSTAL),	8.3 (CRYSTAL)
BEV+FOLFIRI	5.3 (FIRE-3),	7.6 (FIRE-3),	11.8 (indirect comparison),

Key: BEV = bevacizumab; CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; PAN = panitumumab

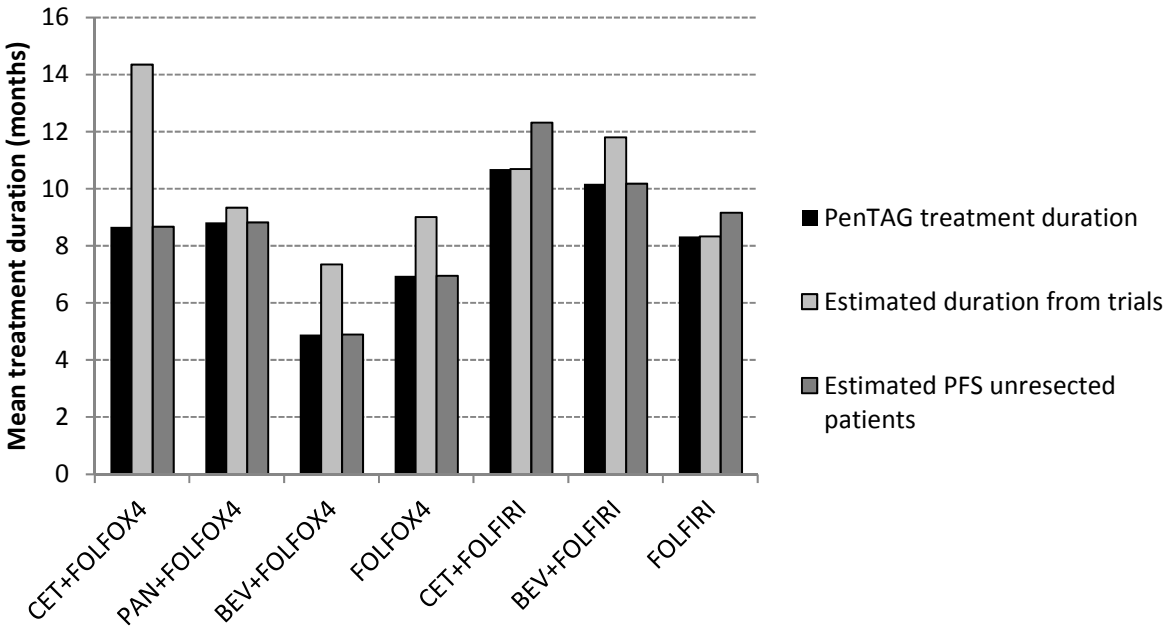
C. For each treatment, compare the estimated mean treatment duration with the estimated mean 1st-line PFS for unresected patients (Section 6.1.4.4, p267). We would expect the mean treatment duration to be lower, because in all RCTs, treatment was supposed to stop on progression. However, we show below that this was generally not the case – usually, mean treatment duration was greater than mean 1st-line PFS for unresected patients.

Given that we use only PFS, not OS from the RCTs, we assume no, or equal treatment effects across treatment arms post-progression. Therefore, we should not model 1st-line treatment after 1st-line PFS for unresected patients. If we did, we would incur the costs of 1st-line drug treatment after progression, but gain no clinical benefit from this, which is clearly inappropriate. Therefore:

- If mean treatment duration was estimated less than mean 1st-line PFS for unresected patients, our estimate of mean treatment duration was left unaltered.
- Otherwise, mean treatment duration was capped at mean 1st-line PFS for unresected patients.

The resulting mean durations of 1st-line treatment for all patients combined in the PenTAG model, the estimated mean treatment durations from the RCTs and the estimated mean 1st-line PFS are given in Figure 32.

Figure 32 Mean durations of 1st-line treatment for all patients combined in the PenTAG model



Key: BEV = bevacizumab; CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; PAN = panitumumab; PFS = progression free survival

In our base case, we use the resulting mean treatment durations for the calculation of drug administration and drug acquisition costs. In particular, the mean total cost of drug

acquisition per patient is estimated as the product of the drug price per unit time, the mean treatment duration and the mean dose intensity (Section “Drug acquisition costs”, p316).

For the purposes of discounting of costs only, we assume treatment duration follows an exponential distribution. Cost-effectiveness is almost complete independent of this assumption.

In a sensitivity analysis, we use OS, in addition to PFS, from the RCTs. In this case, we use the mean treatment duration in Step C, but without the cap for mean 1st-line PFS, because any 1st-line treatment after progression could affect OS.

In another sensitivity analysis, we use a different, more complex, method to estimate the cost of 1st-line drug acquisition. This method is based on the mean cumulative doses (mg/m2 or mg/kg) of all constituent drugs from the RCTs. We do not use this in our base case analysis, as it gives very similar estimates as using our base case method, and it is more complex.

In this sensitivity analysis, we estimate the mean drug acquisition cost per patients in the following Steps:

AA. Calculate the mean total cumulative dose of each drug within each 1st-line treatment in each of the pivotal RCTs, based on median total cumulative dose from each RCT, and 25% and 75% percentiles when available. The total cost of drug acquisition for each treatment is then summed over the costs of each constituent drug within a treatment.

BB. Estimate mean total cumulative dose for each drug within each 1st-line treatment by simple indirect comparison, using CRYSTAL and PRIME as baseline RCTs.

CC. Estimate the mean treatment duration of each of the monoclonal antibody drugs (CET, PAN and BEV) and of OXAL in FOLFOX arm and IRIN in FOLFIRI arm as the mean total cumulative dose of each of these drugs in Step BB divided by the dose per infusion, divided by the number of doses per month divided by the dose intensity.

DD. The estimated mean total cumulative dose for each drug within each 1st-line treatment in Step BB is then multiplied by a factor, between 0 and 1, to cap mean treatment duration to mean 1st-line PFS for unresected patients. This factor is calculated as the minimum of mean 1st-line PFS for unresected patients and the estimated mean treatment duration, based on the cumulative dose and dose intensity from Step CC.

EE. The costs of each of the constituent drugs in each 1st-line treatment are then calculated as adjusted total cumulative doses in Step DD, multiplied by body surface area or body

weight multiplied by the cost of the drug per mg, multiplied by a factor for drug wastage, which varies between 1.07 and 1.21.

We now turn to Step A, our estimation of the mean treatment duration for each 1st-line treatment in each of the pivotal RCTs, based on median treatment duration from each RCT, and 25% and 75% percentile of the treatment duration when available.

We have data on treatment durations for the 5 RCTs for all patients only. We have no data for the liver metastases subgroup. We explain our estimation of mean treatment durations for the liver mets subgroup below.

OPUS 1st-line treatment duration

We asked Merck Serono and Amgen for data on treatment duration information for the *RAS* WT population. We have information on treatment duration for the *KRAS* WT population from OPUS (Bokemeyer, 2011)[31] (Table 99).

Table 99: Treatment durations and cumulative doses from OPUS for *KRAS* WT patients

	CET+FOLFOX (n=82)	FOLFOX (n=97)
Duration of treatment (weeks)		
CET median (Q1-Q3 range)	25 (19-45)	NA
OX median (Q1-Q3 range)	24 (16-32)	24 (16-29)
5FU median (Q1-Q3 range)	24 (17-41)	24 (16-32)
Cumulative dose		
CET mg/m2 median (Q1-Q3 range)	6123 (4165-9181)	NA
OX mg/m2 median (Q1-Q3 range)	850 (596-1104)	879 (564-1095)
5FU mg/m2 median (Q1-Q3 range)	21104 (13936-32715)	20779 (13606-27932)

Key: 5FU = fluorouracil; CET = cetuximab; FOLFOX = folinic acid + fluorouracil + oxaliplatin; OX = oxaliplatin
Source: Bokemeyer (2011)[31]

In addition, in response to our question, Merck Serono provided us with data for *RAS* WT patients (Table 100).

Table 100: Treatment durations and cumulative doses from OPUS for *RAS* WT patients

	CET+FOLFOX (n=38)	FOLFOX (n=49)
Duration of treatment (weeks)	24.3	20.0
Cumulative dose		
CET mg/m2 median	5,502	NA
OX mg/m2 median	840	779
5FU mg/m2 median	19,968	18,004

Key: 5FU = fluorouracil; CET = cetuximab; FOLFOX = folinic acid + fluorouracil + oxaliplatin; OX = oxaliplatin

For OPUS, we estimated the treatment durations and cumulative doses for the RAS WT population by setting them equal to those of the KRAS WT population, but multiplied by the ratio of median RAS WT value to the median KRAS WT value (Table 101).

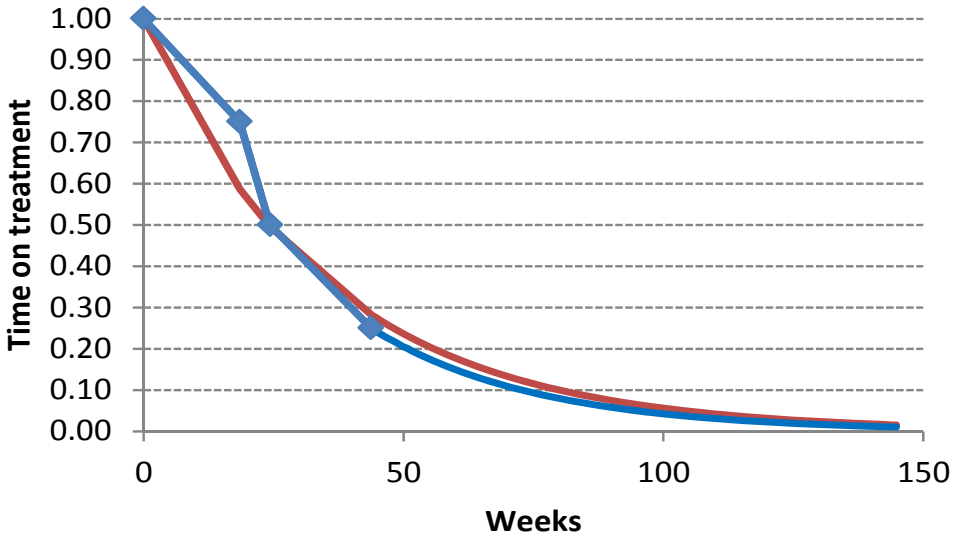
Table 101: Estimated treatment durations and cumulative doses from OPUS for RAS WT patients

	CET+ FOLFOX	FOLFOX
Duration of treatment (weeks)		
CET median (Q1-Q3 range)	24.3 (18.5 – 43.7)	20 (13.3 – 24.2)
OX median (Q1-Q3 range)	24.3 (18.5 – 43.7)	20 (13.3 – 24.2)
5FU median (Q1-Q3 range)	24.3 (18.5 – 43.7)	20 (13.3 – 24.2)
Cumulative dose		
CET mg/m2 median (Q1-Q3 range)	5,502 (3,743 – 8,250)	n/a
OX mg/m2 median (Q1-Q3 range)	840 (589 – 1,091)	779 (500 – 971)
5FU mg/m2 median (Q1-Q3 range)	19,968 (13,186 – 30,954)	18,004 (11,789 – 24,202)

Key: 5FU = fluorouracil; CET = cetuximab; FOLFOX = folinic acid + fluorouracil + oxaliplatin; OX = oxaliplatin

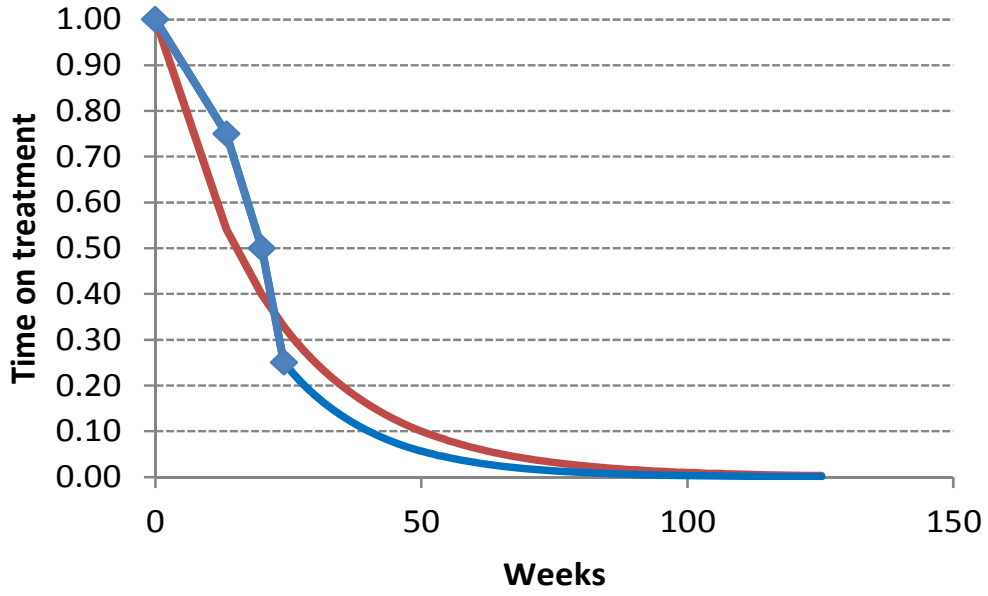
First, this data was used to estimate the mean time on cetuximab+FOLFOX for RAS WT patients. An exponential tail was fit to the 25% percentile (Figure 33), with hazard set equal to that at the 25% percentile. The mean was then estimated as 34.7 weeks, being the area under the empirical data and fitted tail.

Figure 33 Estimated time on CET+FOLFOX treatment for *RAS* WT patients in OPUS



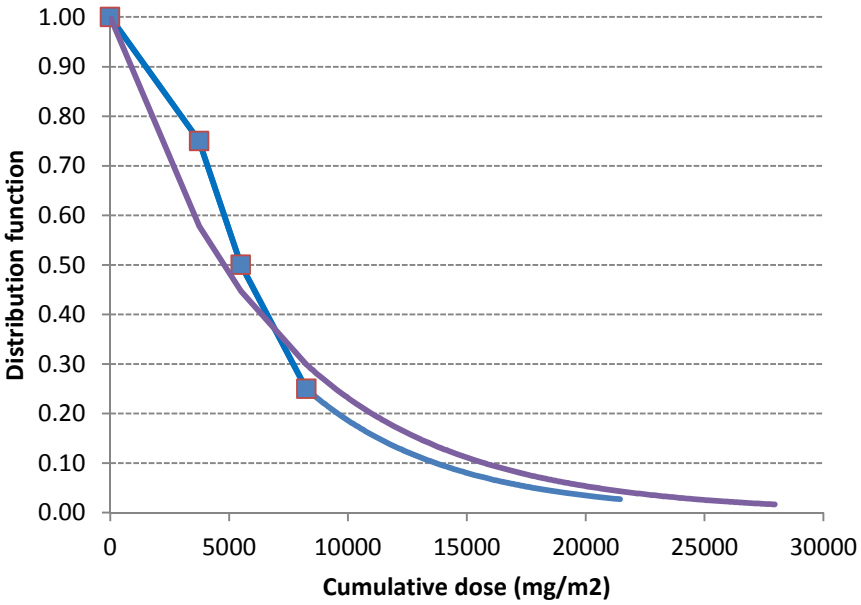
The same process was followed to estimate the mean time on FOLFOX in the FOLFOX arm as 21.7 weeks (Figure 34).

Figure 34 Estimated time on FOLFOX treatment in FOLFOX arm for *RAS* WT patients in OPUS



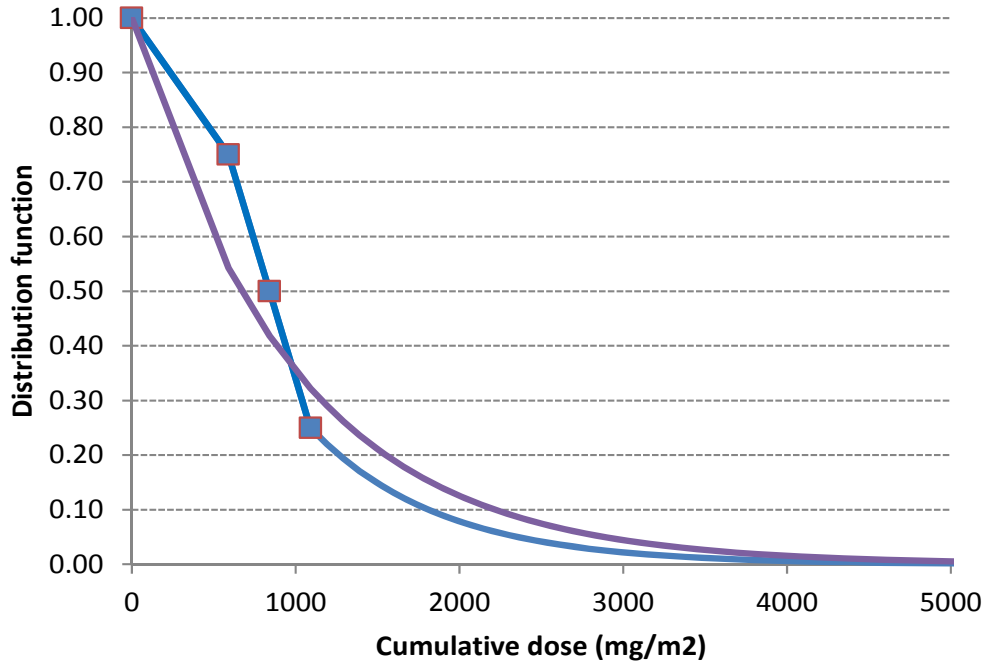
In a sensitivity analysis, we estimate treatment duration from cumulative drug doses. The total cumulative doses were calculated in a similar way. First, for cetuximab in OPUS (Figure 35). This yielded an estimated total dose of cetuximab of 6,838mg/m2.

Figure 35 Estimated cumulative total dose for cetuximab in CET+FOLFOX arm for *RAS* WT patients in OPUS



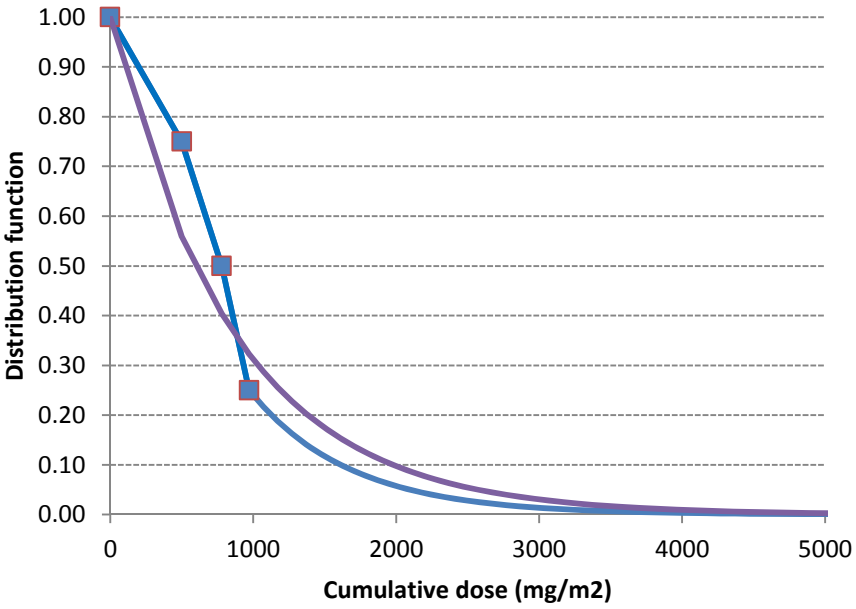
Similarly, the estimated mean total dose of oxaliplatin in the CET+FOLFOX arm in OPUS is 963mg/m2 (Figure 36).

Figure 36 Estimated cumulative total dose for oxaliplatin in cetuximab+FOLFOX arm for RAS WT patients in OPUS



Similarly, the estimated mean total dose of oxaliplatin in the FOLFOX arm in OPUS is 859mg/m2 (Figure 37).

Figure 37 Estimated cumulative total dose for oxaliplatin in FOLFOX arm for RAS WT patients in OPUS



We do not consider the distribution function of fluorouracil (5FU), as it is very cheap. Instead, we estimate the mean time on 5FU simply from the median time. In the cetuximab+FOLFOX arm, this is 19,968 / ln(2) = 28,808mg/m2, and in the FOLFOX arm, 18,004 / ln(2) = 25,975mg/m2.

CRYSTAL

Merck Serono provided us with the following information on treatment durations and cumulative doses (Table 102).

Table 102: Estimated treatment durations and cumulative doses from CRYSTAL for RAS WT patients

	CET+ FOLFIRI (n=178)	FOLFIRI (n=189)
Duration of treatment (median) (months)	7.41	5.77
Cumulative dose		
CET mg/m2 median	7,128	NA
Irinotecan mg/m2 median	2,501	2,106
FU bolus & continuous infusion combined mg/m2 median	38,228	33,034

We estimated the corresponding mean values in the simplest way possible, by assuming all distributions are exponential. Indeed, inspection of the distributions from OPUS, PEAK and PRIME show that this is reasonable. Therefore, the mean values were estimated as the median (Table 102) divided by ln(2) (Table 103).

Table 103: Estimated mean treatment durations and mean cumulative doses from CRYSTAL for RAS WT patients

	CET FOLFIRI (n=178)	FOLFIRI (n=189)
Duration of treatment (mean) (months)	10.7	8.3
Mean cumulative dose (mg/m2)		
CET	10,284	NA
Irinotecan	3,608	3,039
5FU bolus & continuous infusion combined	55,151	47,657

Key: 5FU = fluorouracil; CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; NA = not applicable

FIRE-3

Merck provided no data for the RAS WT population. However, some data is published for the KRAS WT population (Table 104).

Table 104: Treatment durations from FIRE-3 for KRAS WT patients

	CET + FOLFIRI (n=297)	FOLFIRI (n=295)
Mean duration of treatment (months)	4.8 (IQR 2.6, 7.7)	5.3 (IQR 2.8, 8.3)

Key: CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan

-

Given that the *RAS* patient population is only 17% smaller than the *KRAS* population, we assumed that the *RAS* data is the same as the *KRAS*.

We therefore estimate:

- Mean treatment duration CET+FOLFIRI = 4.8 / ln(2) = 6.9 months.
- Mean treatment duration FOLFIRI = 5.3 / ln(2) = 7.6 months.

In our sensitivity analysis whereby we estimate treatment duration from cumulative dose, given lack of data, we estimate total cumulative dose as equal to that for CET+FOLFIRI in CRYSTAL. However, our base case method is clearly superior, as it uses data from FIRE-3.

PRIME

Amgen provided us with the following information on treatment durations and cumulative doses in PRIME (Table 105).

Table 105: Median treatment durations and cumulative doses from PRIME for *RAS* WT patients

	PAN + FOLFOX (n=250)	FOLFOX (n=249)
Median duration of treatment (months) (Q1-Q3 range)	6.47 (3.68, 11.40)	6.24 (3.98, 9.50)
Median cumulative dose (mg/m2)		
PAN	63	NA
OX	855	872
5FU bolus	9,028	8,632
5FU continuous infusion	13,699	13,309

Key: 5FU = fluorouracil; FOLFOX = folinic acid + fluorouracil + oxaliplatin; OX = oxaliplatin; NA = not applicable; PAN = panitumumab

As for CRYSTAL, we estimated the corresponding mean values in the simplest way possible, by assuming all distributions are exponential (Table 106)

Table 106: Estimated mean treatment durations and cumulative doses from PRIME for *RAS* WT patients

	PAN+ FOLFOX	FOLFOX
Mean duration of treatment (months)	9.3	9.0
Mean cumulative dose (mg/m2)		
PAN	91	NA
OX	1,234	1,258
5FU bolus	13,025	12,453
5FU continuous infusion	19,764	19,202

Key: 5FU = fluorouracil; FOLFOX = folinic acid + fluorouracil + oxaliplatin; OX = oxaliplatin; NA = not applicable; PAN = panitumumab

We estimated mean treatment durations from the median alone, as this gives very similar estimates based on the median and the 25% and 75% centiles (Figure 38, Figure 39)

Figure 38 Duration of treatment in PAN+FOLFOX arm in PRIME

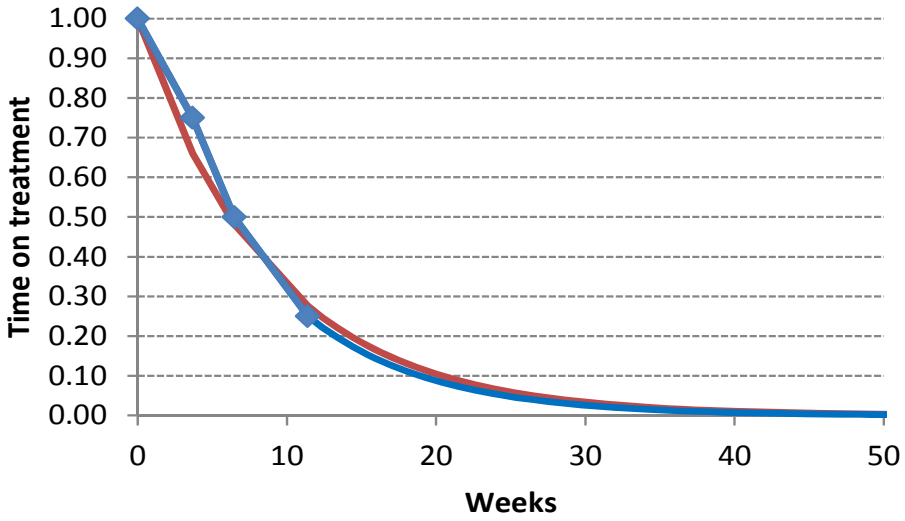
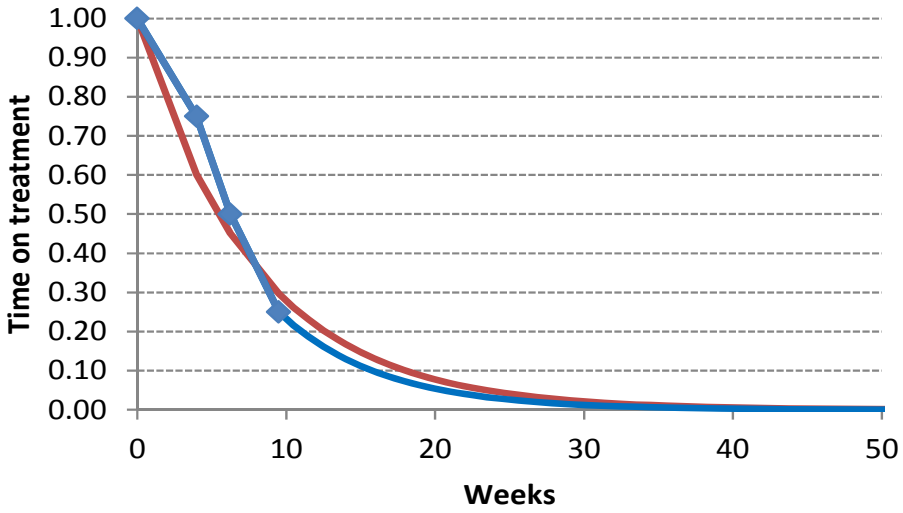


Figure 39 Duration of treatment in FOLFOX arm in PRIME



PEAK

Amgen provided us with the following information on treatment durations and cumulative doses in PRIME (Table 107).

Table 107: Treatment durations and cumulative doses from PEAK for RAS WT patients

	Panitumumab + FOLFOX	Bevacizumab+FOLFOX
Mean duration of treatment (months)	7.45 (3.91, 11.66)	5.86 (3.13, 9.57)
Mean cumulative dose (mg/m2)		
PAN	74	NA
BEV	NA	59
OX	846	793
5FU bolus	4,648	4,921
5FU continuous infusion	27,963	29,525

Key: 5FU = fluorouracil; BEV = bevacizumab; FOLFOX = folinic acid + fluorouracil + oxaliplatin; OX = oxaliplatin; PAN = panitumumab

Once again, we estimated the corresponding mean values in the simplest way possible, by assuming all distributions are exponential (Table 108).

Table 108: Estimated mean treatment durations and cumulative doses from PEAK for *RAS* WT patients

	PAN+FOLFOX	BEV+FOLFOX
Mean duration of treatment (months)	10.7	8.5
Mean cumulative dose (mg/m2)		
PAN	107	N/A
BEV	N/A	85
OX	1,220	1,144
5FU bolus	6,705	7,099
5FU continuous infusion	40,342	42,596

Key: 5FU = fluorouracil; BEV = bevacizumab; FOLFOX = folinic acid + fluorouracil + oxaliplatin; OX = oxaliplatin; PAN = panitumumab

We estimated the mean treatment duration based on the median alone, as this gave very similar estimates based on the median and the 25% and 75% centiles.

Figure 40 Duration of treatment in PAN+FOLFOX arm in PEAK

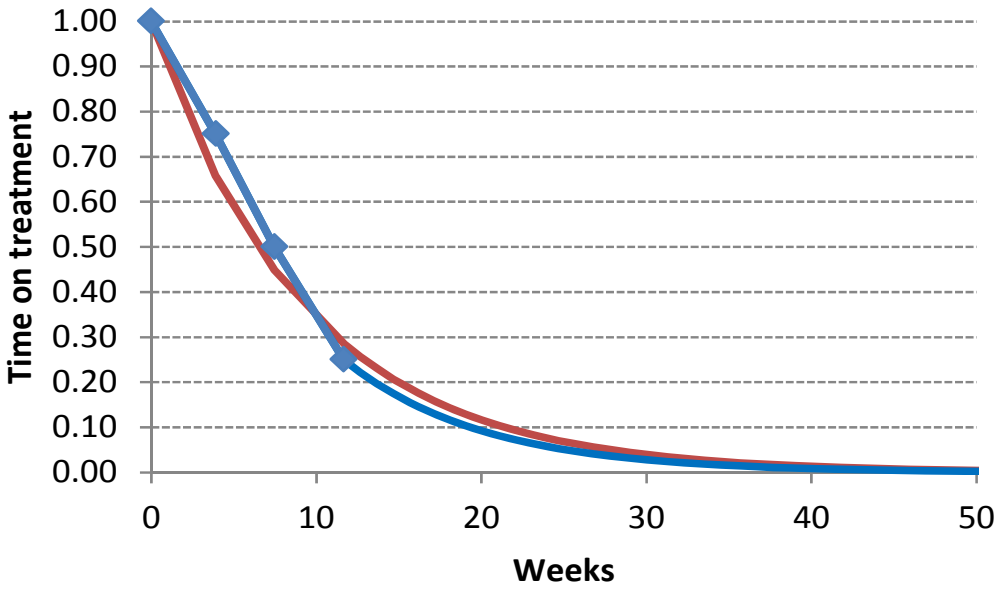
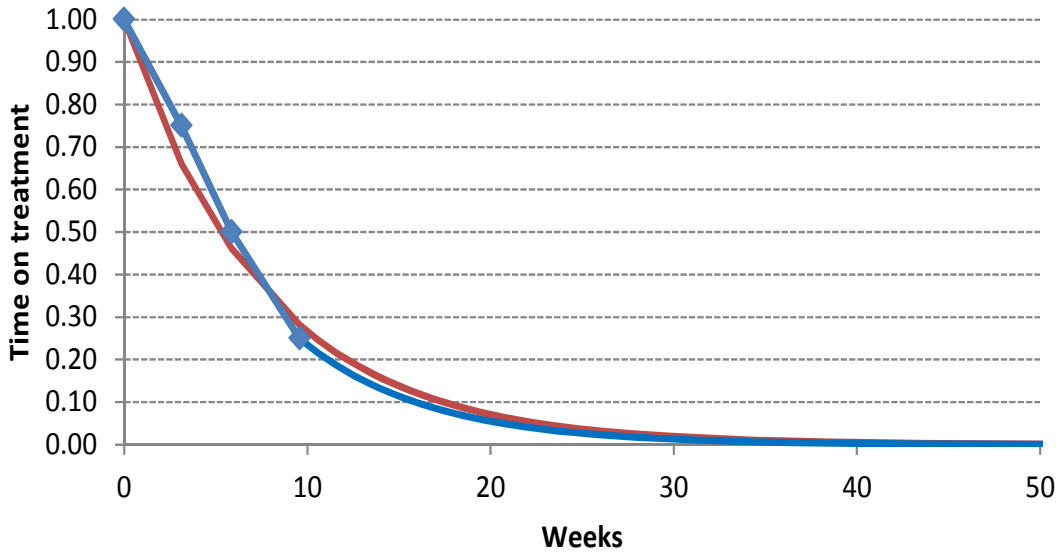


Figure 41. Duration of treatment in BEV+FOLFOX arm in PEAK



Mean treatment durations for patients in liver metastases subgroup

Merck Serono and Amgen provided us with no information on treatment duration for the liver metastases subgroup from the RCTs. We estimated this as the mean treatment duration from the RCTs for all patients, multiplied by the ratio:

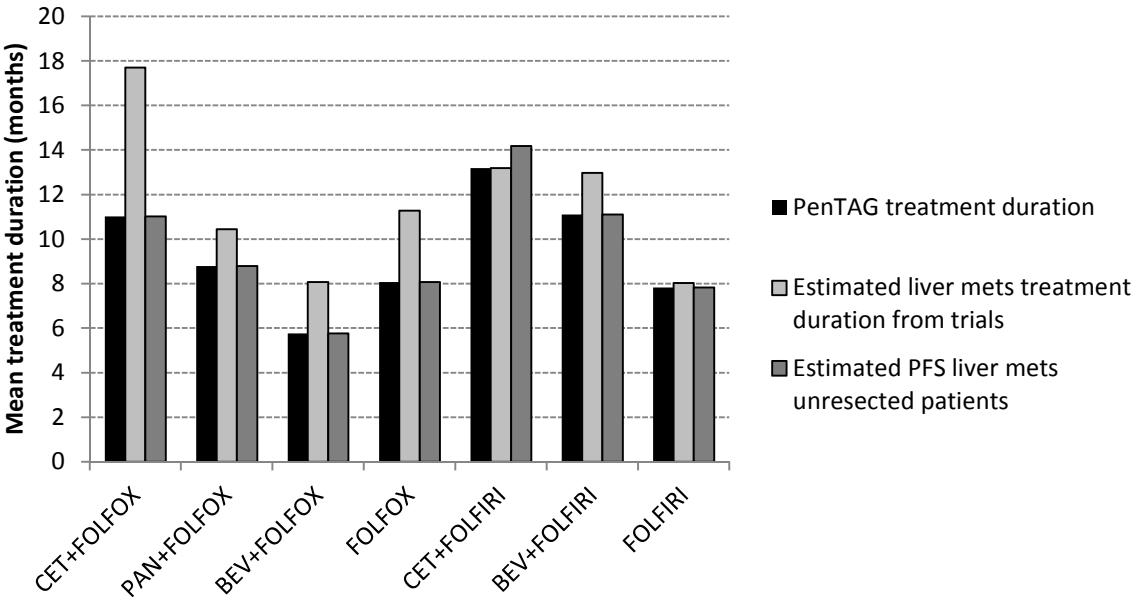
Mean PFS (resected + unresected) liver mets / Mean PFS (resected + unresected) all patients

This seems reasonable given that progression is a reason for treatment cessation.

The mean treatment duration for the model for the liver mets subgroup was calculated as for all patients, using our estimates of the mean treatment durations for the liver metastases subgroup from the RCTs. Also, we capped the modelled mean treatment durations as our estimates of the mean 1st-line PFS for unresected patients for the liver mets subgroup (Figure 42).

For the probabilistic sensitivity analysis, uncertainty in treatment duration was reflected in the uncertainty in PFS for unresected patients, and the uncertainty in treatment duration from the RCTs. The treatment durations from the trials were estimated as gamma distributions (hence, minimum value 0), with the same deterministic mean, and standard error given by the standard deviation from the trial, divided by the square root of the number of patients.

Figure 42 Estimated treatment durations for liver mets group in PenTAG model



Key: BEV = bevacizumab, CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; PAN = panitumumab; PFS = progression free survival

OPUS Baseline RCT

In a scenario analysis, we consider OPUS, not PRIME as the baseline RCT for the FOLFOX network (Section 6.1.3.2, p243).

In this case, we estimate the following mean treatment durations for unresected patients for all patients, using the same methodology as discussed as for the base case, when we use PRIME as the baseline RCT:

- CET+FOLFOX = 6.6 months.
- PAN+FOLFOX = 5.2 months.
- BEV+FOLFOX = 3.9 months.
- FOLFOX = 5.0 months.

6.1.4.6. Overall survival: unresected patients

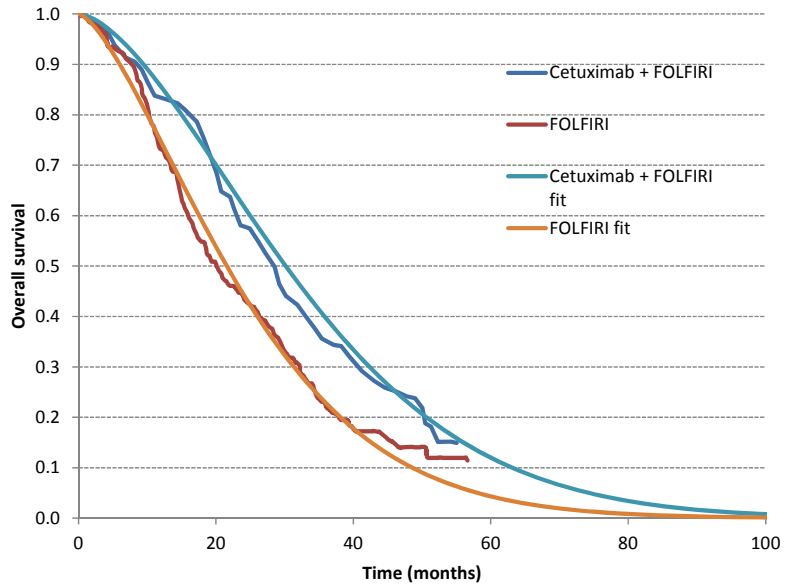
In our base case analysis, we model only PFS from the RCTs. As mentioned in Section 6.1.3.2, p243, in a sensitivity analysis, we model OS for unresected patients, in addition to PFS for unresected patients, from the RCTs. In particular, our method of estimating OS for unresected patients is the same as for PFS for unresected patients, using all Steps A – E (Section 6.1.4.4, p267).

For the same reasons as for PFS, we found the Weibull distribution to be most appropriate.

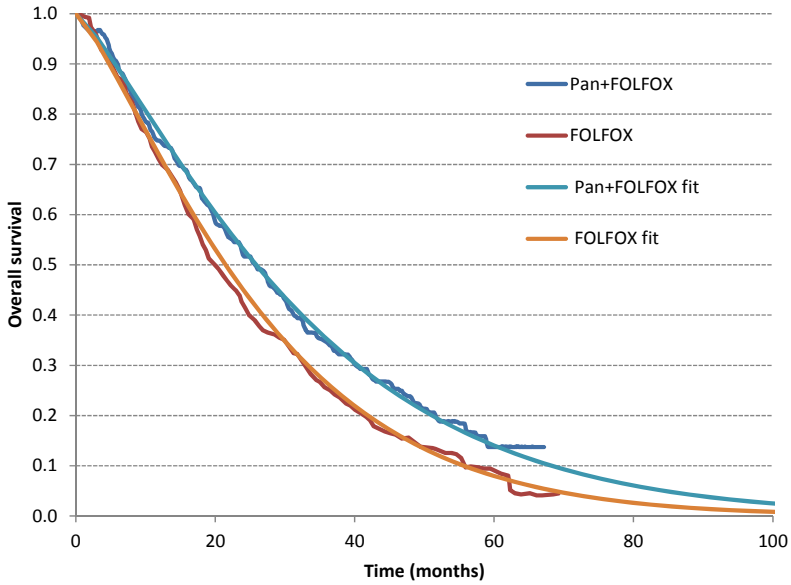
Our chosen curve fits are given in Figure 43 below.

Figure 43. 1st-line OS (unresected patients) in PenTAG model

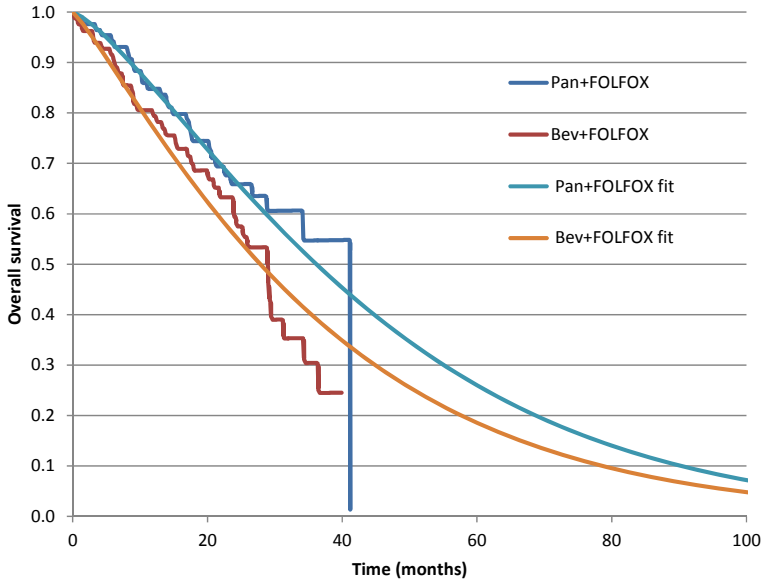
(a) CET+FOLFOX vs. FOLFOX from OPUS



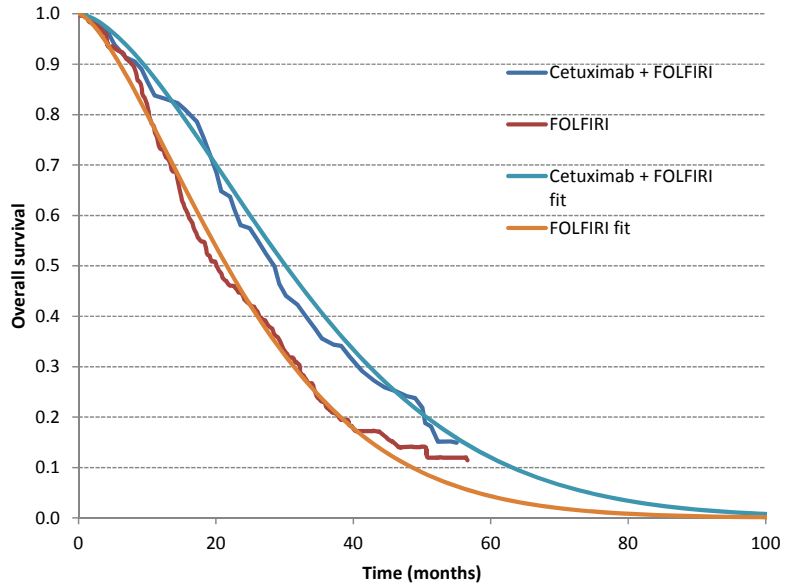
(b) PAN+FOLFOX vs. FOLFOX from PRIME



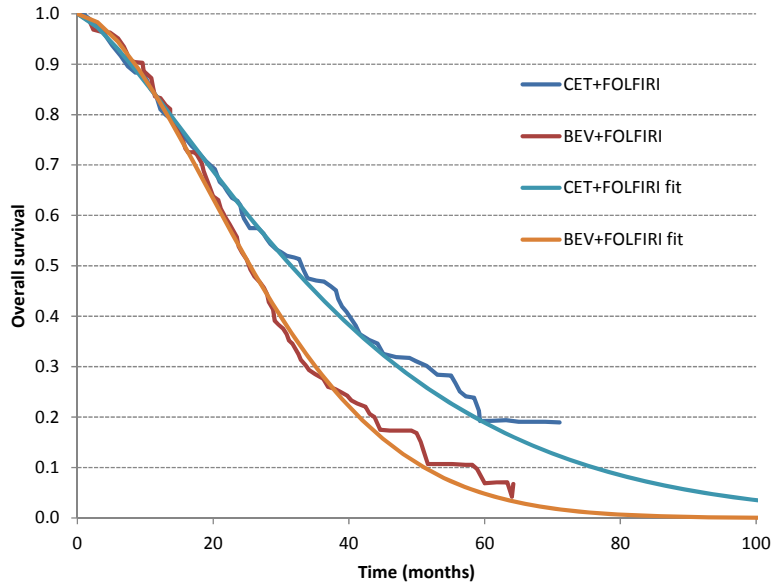
(c) PAN+FOLFOX vs. BEV+FOLFOX from PEAK



(d) CET+FOLFIRI vs. FOLFIRI from CRYSTAL



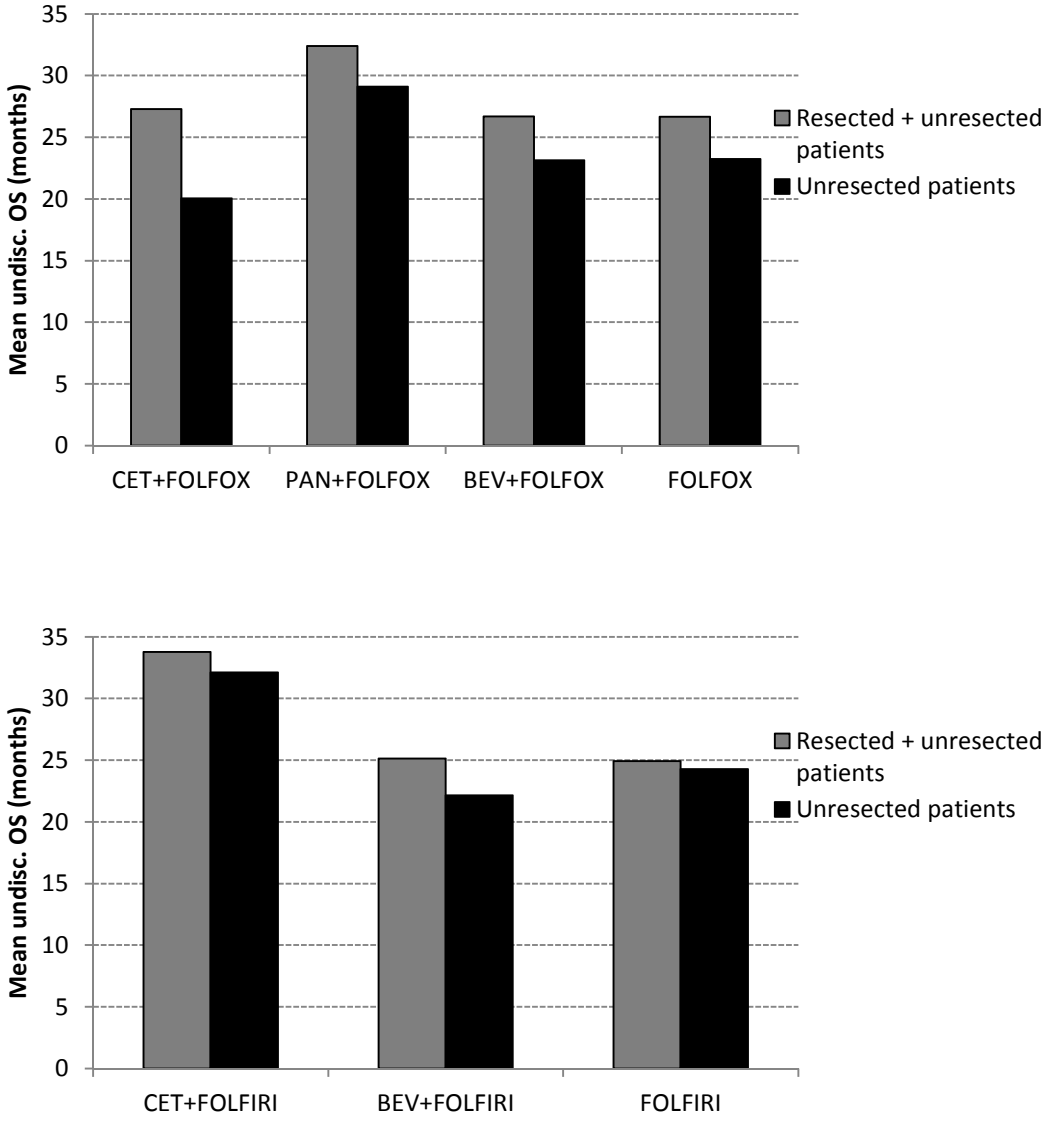
(e) CET+FOLFIRI vs. BEV+FOLFIRI from FIRE-3



Key: BEV = bevacizumab; CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; PAN = panitumumab

As for PFS, OS from the RCTs was adjusted using data from Adam et al. (2004) to allow for the fact that this data reflected some patients after resection (Figure 44).

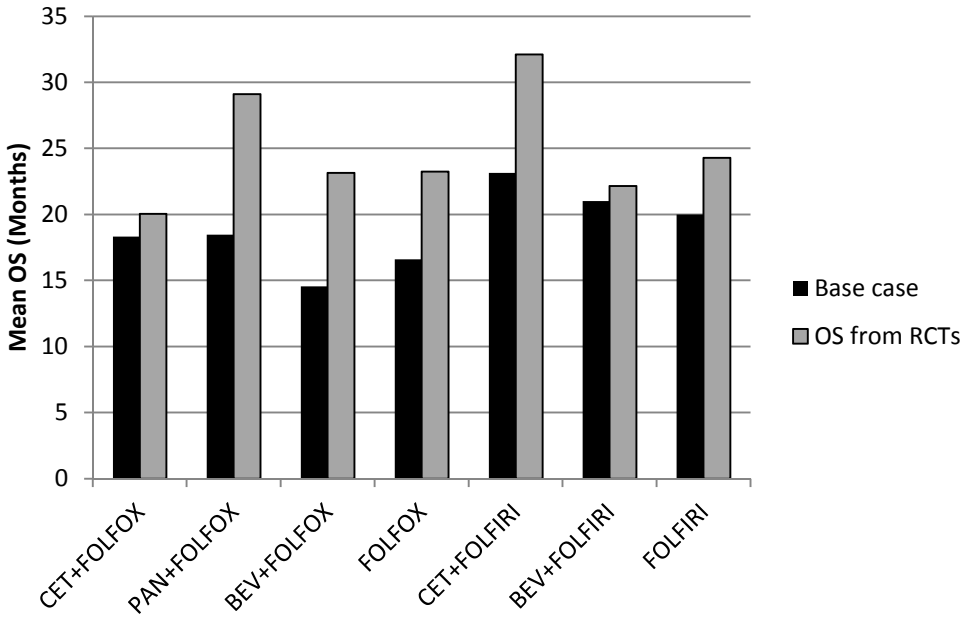
Figure 44. PenTAG mean OS from 1st-line RCTs



Key: BEV = bevacizumab; CET = cetuxiamb; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; OS = overall survival; PAN = panitumumab

Estimated mean OS for unresected patients when estimated directly from the RCTs of 1st-line drugs is substantially greater than as estimated in our base case (Figure 45). Differences are to be expected, as the subsequent treatments in the RCTs (Table 89) were different to those assumed in our model. Indeed, this is the key reason chose our model structure (Section 6.1.3.2, p243).

Figure 45 Mean OS for unresected patients: from PenTAG base case vs. 1st-line RCTs



Key: BEV = bevacizumab; CET = cetuxiamb; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; OS = overall survival; PAN = panitumumab; RCT = randomised control trial

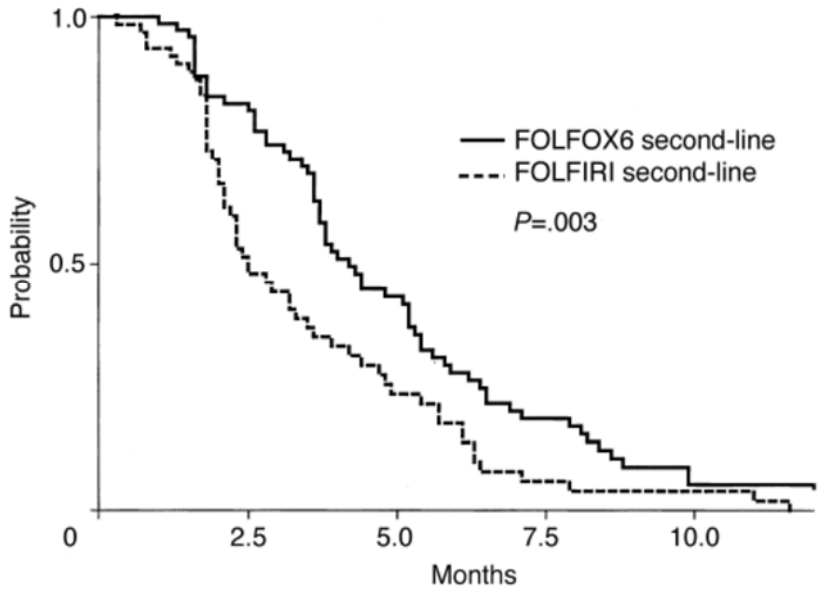
6.1.4.7. 2nd-line Progression-free survival: unresected patients

Both we and Merck Serono assume that all patients have 2nd-line FOLFIRI after 1st-line FOLFOX-based treatment and all patients have 2nd-line FOLFOX after 1st-line FOLFIRI-based treatment (Section 6.1.3.2, p.243; Section 5.1.2.2, p.203).

We find that the cost-effectiveness of CET and PAN is insensitive to our assumption for 2nd-line PFS, because we also assume that this is equal in all treatment arms. Therefore, this parameter does not merit close scrutiny.

In common with Merck Serono, we also model 2nd-line PFS from Tournigand et al. (2004) (Figure 46). In particular, we model separately PFS on 2nd-line FOLFOX and PFS on 2nd-line FOLFIRI.

Figure 46 2nd-line PFS on FOLFOX or FOLFIRI from Tournigand et al. (2004)

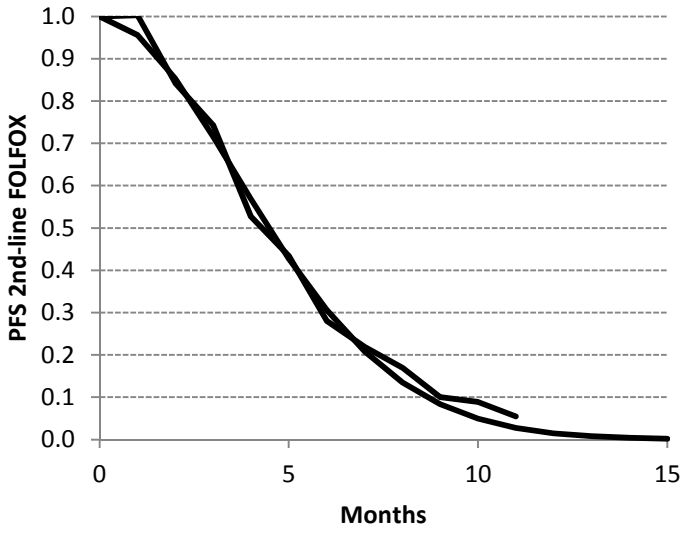


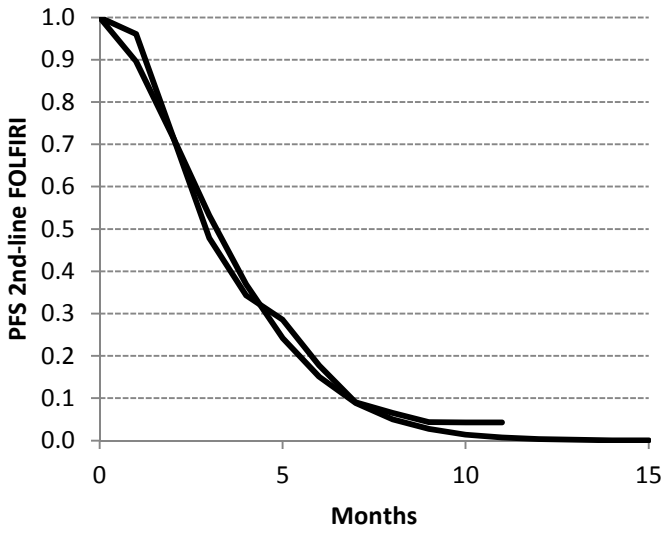
Source:Figure 2B, Tournigand et al. (2004).[113]

Given lack of data to the contrary, both we and Merck assume that PFS on 2nd-line FOLFOX or FOLFIRI is independent of 1st-line treatment.

First, we digitised the Kaplan-Meier data in Figure 46. We then fitted Weibull distributions to each of the two curves (Figure 47 Given that cost-effectiveness is only weakly affected by 2nd-line PFS, we used a simple pragmatic fitting method: by minimising the weighted sums of squares of differences between empirical and fitted PFS at each month up to 11 months. The weights pragmatically decreased linearly over time, from 1 at 0 months to 0 at 11 months to reflect the reduction in the numbers of patients at risk over time.

Figure 47 Weibull curves fit to PFS from Tournigand et al. (2004)





Key: FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; PFS = progression free survival
Source: Tournigand et al. (2004).[113]

This yields an estimated mean PFS for FOLFOX of 0.41 years and for FOLFIRI of 0.30 years.

Ideally, we would then model 2nd-line PFS corresponding to the fitted Weibull distributions. However, this would substantially complicate the model, as it would demand time-in-state specific transition probabilities. Therefore, we pragmatically assumed 2nd-line PFS follows an exponential distribution, with lambda parameter set to 0.186 and 0.242 (time measured in months) for FOLFOX and FOLFIRI respectively, giving means equal to those above. This

then renders the 2nd-line transition probabilities independent of time. This assumption will affect cost-effectiveness only incrementally.

Mortality from 2nd-line PFS

Given lack of data to the contrary, we estimated the proportion of progression from 2nd-line treatment that are due to death as 6%, the corresponding value for 1st-line (Section 6.1.4.4, p.267). Cost-effectiveness is almost completely unaffected by this estimate.

6.1.4.8. 2nd-line time on treatment: unresected patients

It is appropriate to base time on 2nd-line treatment on data from Tournigand et al. (2004)[113] as this study informs 2nd-line PFS.

In this study, there was a median of 8 cycles of 2nd-line FOLFOX and 6 cycles of 2nd-line FOLFIRI.[113] Given that 1 cycle lasted 2 weeks in this study, this equates to a median time on treatment of 16 and 12 weeks on FOLFOX and FOLFIRI respectively. Given no data to the contrary, we assume that treatment duration follows an exponential distribution. Then the mean time on treatment is 0.44 and 0.33 years on FOLFOX and FOLFIRI respectively. These values are very similar to the estimated mean PFS in the previous section, 0.41 and 0.30 years respectively. Therefore, we pragmatically assume that 2nd-line treatments are taken for the entire duration of PFS.

Although not stated in their report, inspection of their model reveals that Merck Serono also assume that patients take FOLFOX or FOLFIRI for the entire duration of 2nd-line PFS.

6.1.4.9. 3rd-line survival: unresected patients

We find that the cost-effectiveness of CET and PAN is insensitive to our assumption for 3rd-line PFS, because we also assume that this is equal in all treatment arms. Therefore, this parameter does not merit close scrutiny.

We estimate the mean time in 3rd-line treatment as 0.51 years, which was our estimated value for *KRAS* WT people from our model for 3rd-line treatments for mCRC from TA242 in 2011, and which was endorsed by the NICE committee.[134] This estimate itself was derived from the study Jonker et al. (2009)[114] comparing treatment with cetuximab plus BSC to BSC alone.

Merck Serono model 3rd-line survival also using data from Jonker et al. (2009)[114]. Inspection of their model reveals that they assume a Weibull distribution, and we calculate a mean of 0.74 years survival for patients that start on 3rd-line treatment. Merck Serono also assume this value independent of 1st- or 2nd-line treatment.

6.1.4.10. Test accuracy

The ERG report for TA176 raised concerns that the model did not account for patients who were incorrectly diagnosed.[123] Some time was spent determining the relative accuracy of *RAS* testing in clinical practice, compared to how it was conducted in the trials described in the clinical effectiveness section. This is described in detail in Appendix I. This was necessary to assess whether some adjustment was necessary to account for differences in patients incorrectly diagnosed in the trials compared to in clinical practice.

However, the relationship between a test ability to diagnose mutation status and the test's ability to predict the outcome of this diagnosis (which treatment patients receive and how effective this is) is a complex one. In their assessment of diagnostic tests for detecting *KRAS* mutations, Westwood et al. (2014) adjusted the meaning of accuracy from 'test accuracy' (as discussed in our previous sections) to include 'accuracy for predicting response to treatment with cetuximab in combination with standard chemotherapy, or variation in clinical outcomes following treatment with cetuximab in combination with standard chemotherapy depending on which method is used to classify patients as having KRAS wild-type tumours'.[4]

The report explains that due to the nature of companion diagnostics, the only conclusions that could reasonably be drawn regarding the diagnostic tests used in trials were that they appeared to result in a benefit for patients, and that there is no evidence to show that different tests used in practice would lead to significantly different outcomes. Unfortunately, this was difficult to assess, as not all tests used in practice have been used in trials of this nature.

Given the paucity of significant accuracy data to say otherwise and the apparent similarity in test accuracy between *KRAS* and *RAS* WT testing, we agree with the conclusions provided in Westwood et al.'s assessment; that there is no evidence of a difference between testing techniques. As such, the true proportion of incorrect diagnoses in trials or clinical practice is not considered in our model and we do not adjust the accuracy in the trials to reflect what is done in practice.

Similarly, our clinical advisors (Dr Mark Napier and Christopher Bowles, based at the Royal Devon and Exeter hospital), advise that testing for EGFR expression is rarely, if ever, done

in practice, as it is believed to not be indicative of the effectiveness of treatment. Therefore we do not include EGFR testing in the model in either a cost or effectiveness capacity.

6.1.4.11. Utilities

In this section, we follow the principles for the identification, review and synthesis of health state utility values from the literature, as recommended by the NICE Decision Support Unit in the UK.[135] There are no agreed reporting standards for studies of utilities, but the following information is key to understanding the nature and the quantity and quality of evidence[135]:

- the population describing the health state (e.g. age, sex, disease severity)
- the approach used to describe the health state
- utility value elicitation technique, for example time trade-off, standard gamble, visual analogue score
- sample size
- respondent selection and recruitment, inclusion and exclusion criteria
- survey response rates, numbers lost to follow-up (and reasons), methods of handling missing data.

Clearly, the relevance of the data to the decision model, and to the agency to which the model will be submitted, is important. In the current project, the NICE reference case is used.[112] Modification of utility values from the literature for use in economic models, and sensitivity analyses using less relevant utility values, should be considered.[135] A systematic search for studies reporting utilities should be undertaken.[135] For the current project, the search method is given in Appendix B. The results of this search were combined with the cost-effectiveness search results and screened simultaneously. We expanded the population to all mCRC, rather than just *RAS* WT, as we believed little evidence would be available for the utility of *RAS* WT population. In addition, sources of utility values were obtained from published models on the cost-effectiveness of panitumumab and cetuximab in combination with chemotherapy. We also considered any sources presented in the manufacturers' submissions.

We also compared the results of our utility review to the studies reported by a recent diagnostic appraisal report, which included a complete mCRC population (both *KRAS* mutant and WT).

We report the findings of the quality of life search in Table 109 and the utilities from the cost-effectiveness papers in Table 110. Only sources of *KRAS* WT utilities were identified, but we believe that the *KRAS* WT population would not differ greatly from the *RAS* WT population.

As well as our included cost-effectiveness studies, we identified Lawrence et al. (2013)[136] and Ewara et al. (2014)[137] as potential utility sources, as these were cost-effectiveness studies of *KRAS* WT mCRC populations. Ewara et al. did not highlight any sources of utilities we had not already found through other sources and the main utility study used in Lawrence et al.: Petrou and Campbell (1997), was irretrievable. However this study is nearly 20 years old and was conducted on UK oncology nursesso we do not believe it to be relevant.

Sources of progression free utilities

From the search we identified two full papers reporting utilities in *KRAS* WT population. These reported outcomes from the PRIME and CRYSTAL studies.[5, 138]

The utilities from the CRYSTAL trial are valued from the EORTC-QLQ30, a cancer specific quality of life questionnaire and reported in Lang et al. (2011).[138] The difference in utilities between CET+FOLFIRI and FOLFIRI alone did not appear to be significant and neither was the change in utility over time. This supports the conclusions of other utility sources. EQ-5D based utilities are preferred in the NICE reference case.[112] There are methods to convert these values to the EQ-5D, including those given in Kim et al. 2012.[139] This transformation was calculated for a population that included multiple cancers, but was validated on a CRC population and therefore is the most relevant transformation to our results. It includes several covariates, but can be used as a simple linear transformation using the global health score reported by the EORTC-QLQ30. We manually extracted data points from Lang et al. and used the Kim et al. transformation, to calculate utility values between 0.62 and 0.63 for the *KRAS* WT population receiving CET+FOLFIRI, across the follow up time reported in Lang et al. This seems quite low compared to other utilities reported for the *KRAS* WT population, which are preferred as they do not require transformation to the EQ-5D..

Graham et al. (2014),[102] Siena et al. (2015)[76] and Bennett et al. (2011)[5] all report utilities from the PRIME trial for either *KRAS* WT or *RAS* WT populations. However the estimates are quite different across these studies. Bennett et al. is the only full paper that reports utility data collected for the *KRAS* WT population from the PRIME trial, and also includes utility results for a second line panitumumab trial. It includes the results of the EQ-5D questionnaires valued on the UK value set calculated by Dolan (1997).[107] Bennett et al. also report that the utility change from baseline across until disease progression for both arms is not clinically significant and find that the difference between arms not statistically or clinically significant. This group includes both patients who completed treatment and those that had to withdraw early. The weighted average of baseline utility from Bennett et al. is 0.767 (to 3 significant

figures).This is similar to the utility used in Ortendahl et al. (2014), 0.77, also for a *KRAS* WT mCRC population.[104]

Siena et al. (2015) is an abstract reporting utility values for the *RAS* WT subpopulation of the PRIME trial. The abstract does not specify at what time point the reported utilities are from, but it does state that the difference from baseline utility and the difference between arms were not found to be statistically significant for this subgroup. In this abstract, the weighted average of the PAN+FOLFOX and FOLFOX arms is 0.750, which is below, but not dissimilar to the utility of the *KRAS* WT population reported in Bennett et al.[76]

The utility estimate reported by Graham et al. is noticeably higher than either the baseline or endpoint utilities reported in Bennett et al. or Siena et al., 0.821.[102] It is unclear why this is the case, as the authors report that it is EQ-5D utility data for the *RAS* WT population, valued from the UK valuation set, similar to Siena et al. and Bennett et al. Both Graham et al. and Siena et al. report the utilities for a *RAS* WT population, rather than *KRAS* WT, but are still markedly different, suggesting that the difference in population between Graham et al and Bennett et al. is not responsible for this higher utility. It is possible that an increase in utility at an earlier time point in the follow up could result in a higher overall utility. However, this was not described in any of the PRIME trial studies and the results from CRYSTAL Lang et al. suggest a fairly linear relationship between utility and time, so this is unlikely.

Sources of post first line utilities

The study by Bennett et al. (2011) also contains information on utilities for a second line *KRAS* WT mCRC population, comparing PAN+FOLFIRI to FOLFIRI. Though again there is no significant difference between arms reported by Bennett et al., the most relevant of the reported utilities to a UK setting is FOLFIRI as only chemotherapy alone is recommended as second line treatment. Keeping this consistent with the first line utility and using the baseline utility for FOLFIRI gives a utility of 0.762. This is not significantly different to first line utility (0.767), but does indicate that progression to second line treatment is associated with a reduction in quality of life, which seems clinically plausible.

Graham et al. (2014) reports a higher utility (0.782), but quotes the source as the same trial reported in Bennett et al. (NCT00339183). As with the first line utility it is unclear why this value is higher. Merck Serono also uses Bennett et al. as the source for second line utility, but uses the value for the PAN+FOLFIRI arm, which is marginally higher at 0.769.

Ortendahl et al. (2014) reports a figure from Meads et al (2010) and Mittmann et al (2009) of 0.75. We could not confirm the source of this value nor how this value was elicited.

Table 109. Utility studies identified by quality of life search.

Study	Study population	Preference elicitation	Results	Criticisms of study
1st line				
Bennett et al. 2011[5]	PRIME trial- 576 previously untreated KRAS-WT mCRC pts receiving either PAN+FOLFOX or FOLFOX alone	EQ-5D questionnaire, UK value set	Baseline EQ-5D: PAN+FOLFOX 0.778 (s.d. 0.247), FOLFOX 0.756 (s.d. 0.244) LSM change from baseline: PAN+FOLFOX 0.022 (95% CI 0.003 - 0.041), FOLFOX 0.027 (95% CI 0.008 - 0.046), difference -0.005 (95% CI -0.032 - 0.022)	*RAS* WT results not currently published Only reports PAN+FOLFOX and FOLFOX
Lang et al. 2013[138]	CRYSTAL trial- 627 previously untreated KRAS WT mCRC pts receiving either CET+FOLFIRI or FOLFIRI alone	EORTC QLQ-C30 questionnaire	Values on EORTC QLQ-C30 global health scale: Baseline: ~60 both CET+FOLFIRI and FOLFIRI End of follow up: ~65 CET +FOLFIRI, ~63 FOLFIRI Range of values converted to EQ-5D all lie with 0.62-0.63	*RAS* WT results not currently published, EQ-5D preferred
Post 1st line				
Bennett et al. 2011	NCT00339183 597 trial- previously treated *KRAS* WT mCRC patients receiving either PAN+FOLFIRI or FOLFIRI alone	EQ-5D questionnaire, UK value set	Baseline EQ-5D: PAN+FOLFIRI 0.769 (s.d. 0.230), FOLFOX 0.762 (s.d. 0.252) LSM change from baseline: PAN+FOLFIRI -0.024 (95% CI -0.045 – -0.003), FOLFIRI 0.000 (95% CI -0.021 – 0.022), difference -0.0.024 (95% CI -0.054 - 0.006)	*RAS* WT results not currently published Only reports PAN+FOLFOX and FOLFIRI
Wang et al. 2011	Previously treated *KRAS* WT mCRC patients PAN+BSC or BSC alone	EQ-5D	BSC only: Toxicity 0.4409; without disease or toxicity (PF) 0.6630; relapse/disease prog 0.6407	*KRAS* WT, not *RAS* WT Small population size (13 informed toxicity utility),

Key: BSC = best supportive care, CET = cetuximab, FOLFOX = folinic acid + fluourouracil + oxaliplatin, FOLFIRI = folinic acid + fluourouracil + irinotecan, mCRC = metastatic colorectal cancer, PAN = panitumumab, WT = wild type.

Utilities in progressive disease on best supportive care are reported in Graham et al. (2014) as 0.681. This is based on the trial reported by Odom et al. (2011), where the *KRAS* WT population were in a progressive disease state receiving either panitumumab plus best supportive care (PAN+BSC) or best supportive care alone (BSC). This trial also forms the basis for the analyses conducted by Wang et al. (2011), which aimed to estimate utilities for patients in a post-first line health state based on their disease progression or adverse event status. Merck Serono use Wang et al. to inform the third line utility in their submitted model, choosing a utility for BSC without symptoms or adverse events.

Table 110. Utility values reported in cost-effectiveness studies

	Utility	Stated source	Notes
Graham et al. 2014[102]	Progression free 0.821	PRIME trial *RAS* WT results	Not reported elsewhere: Most recent values from Siena et al. 2015 appear much lower ~0.75
	Subsequent treatment 0.782	2nd line panitumumab trial, *KRAS* WT	This trial is also reported in Bennett et al. 2011, where second line utility is given as 0.762-0.769 dependign on arm
	BSC 0.681	*KRAS* WT third line trial	This trial is also reported in Odom et al. 2011, where post first line utility is given as 0.68
	Post resection 0.821	Assumed same as PF	
Ortendahl et al. 2014 (*KRAS* WT)	1st line 0.77	Meads et al. 2010	Source not confirmed, but Ewara et al. (2014) report the same value. Their source is also unconfirmed.
	2nd line 0.75	Meads et al. 2010 Mittman et al. 2009	Source not confirmed
	Post successful resection 0.84	Fryback et al. 1993	Study is 22 years old

Post-resection progression free utilities are generally high in the models. Both Graham et al. and Ortendahl et al. report utilities above 0.8 (0.821 and 0.84 respectively). However, the value for Graham et al. corresponds to 1st line progression free state and Ortendahl et al. refers to a study by Fryback et al. (1993), neither of which sources have been confirmed. Furthermore, the Fryback et al. study is over 20 years old.

Merck Serono suggest that the utility of this progression free post-resection population should be equal to population utility for the mean age of the cohort. Though this is likely to be an upper limit for this utility this is also a reasonable approach to take due to the curative intent of the resection.

Progressive disease post-resection utility was assumed to be an average of second and third line utility weights in both Graham et al. (2014) and the Merck Serono submission. These are the only studies we have found that report this progressive disease post resection utility and the approach seems to be a reasonable compromise to include second and third line information whilst keeping progressive disease post-resection as one health state.

One additional utility source that was identified was Farkkila et al. (2013), which assessed 508 colorectal cancer patients in Finland, with EQ-5D data valued on the UK valuation set.[140] 151 patients had metastatic disease of whom the average age was 66 and 58% of the cohort were men. For metastatic disease with treatment (n = 108) the utility was 0.820 (95% CI 0.783 – 0.858) and for those with metastatic disease receiving palliative care (n = 41) the utility was 0.643 (0.546 – 0.747). The mean time since diagnosis was 18 months. The utility for metastatic disease with treatment is higher than those reported in Bennett et al. and indeed seem high compared to estimates of general population utility for this cohort: ~0.0821 using the PenTAG model methods. The utility for people receiving palliative care is similar to those reported in Wang et al. This study included patients who underwent resection as well as those who were unresectable and may also reflect differences between different countries' values of health related quality of life. However, in general this study supports the findings of Bennett et al. and Wang et al. and does not supersede their relevance to this analysis.

Utilities in the PenTAG model

The health state utilities used in the PenTAG base case are presented in Table 111, p.314.

We conclude that utility in first line progression free survival will be the same for all treatments and that the most relevant results are those reported in Bennett et al. Therefore these form the basis of the PenTAG base case. We use the value of 0.767, the average of the PAN+FOLFOX and FOLFOX arms of the trial, weighted by number of patients.

For consistency, and because it is a recent study in a relevant population, we also use Bennett et al. for the second line utility estimate, as this is within the relevant population and is EQ-5D data valued on a UK data set.

Based on the Wang et al. study, we believe the most sensible value to use is the utility for people receiving BSC who are in disease progression, which gives a value of 0.641.

Post resection progression free utility uses the same approach as Merck Serono. However, instead of the Petrou and Hockley (2005)[105] study, which uses Health Survey for England

data from 1996, we use the well-established methodology published by Ara and Brazier (2010), updated to use Health Survey for England 2012 data:

$$U_{\text{HSE (2012)}} = 0.967981 - 0.00181 \times \text{age} - 0.00001 \times \text{age}^2 + 0.02329 \times \text{male}$$

Source: Ara and Brazier (2010)[8], Health Survey for England (2012)[7]

As with Graham et al. (2014) and the Merck Serono submission, we also estimate the utility in disease progression post successful resection by averaging the second and third line utilities. We use the same approach as Merck Serono and weight the average by the time spent in each line of treatment, which gives us a disutility value in this health state of 0.142.

Table 111. PenTAG base case utility parameters

Parameter	Base case	Standard error	Distribution	Source
1st line (PFS)	0.767	0.0110	Beta	Bennett et al. (2011)[5]
2nd line	0.762	0.0155	Beta	Bennett et al. (2011)[5]
3rd line (PD)	0.6407	0.0155	Beta	Wang et al. (2011)[6]
PFS post successful resection	0.831 at age 63	NA		Age related general population utility
PD post successful resection disutility	0.142	NA		Average of 2nd and 3rd line utilities, weighted by time spent in 2nd or 3rd line.

Key: NA = not applicable; PFS = progression free survival, PD = progressive disease
Notes: Post resection utilities are calculated as required in the model and it is the uncertainty of their input parameters that drive the uncertainty for these utilities. As such we do not calculate standard errors for these parameters

In the probabilistic sensitivity analysis, utilities for unresected patients are varied with beta distributions based on their means and standard errors.

The utilities post-resection are driven by other parameters (for example PFS post resection is driven by mean age of cohort). Though strictly these parameters should have additional uncertainty assigned to them, the lack of information on this uncertainty would lead to estiamtes of standard errors that would overshadow the influence of the primary drivers of these parameters. Therefore to ensure that the impact of these parameters is recognised in our results, we do not assign additional uncertainty to the post-resection utilities.

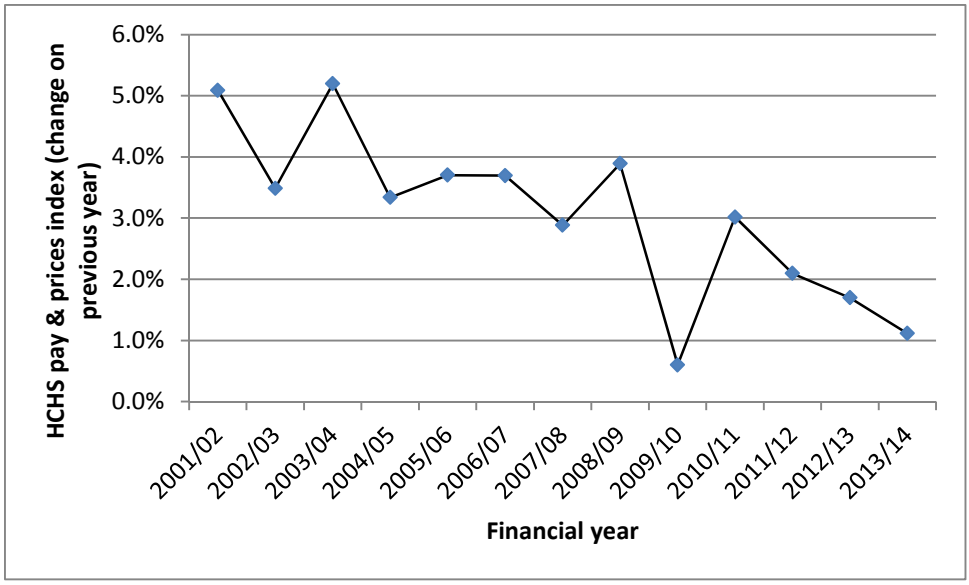
6.1.4.12. Costs

Inflation to 2015/16 prices

Unit costs were inflated to 2015/16 prices by inflating to 2013/14 prices using the Hospital and Community Health Services Pay & Prices Index[141] and then to 2015/16 prices at a rate of 1.64% per annum.

The rate at which the pay and prices index has grown appears to have slowed in recent years (Figure 48), so the inclusion of historical values could lead to an overestimate of the likely inflation between 2013/14 and 2015/16. We therefore adopted the approach of taking the average increase in the index for the previous three years (i.e., from 2010/11 to 2013/14), i.e., a rate of 1.64% per annum.

Figure 48: HCHS Pay & Prices index (change on previous year)



Sources: [2003/04 onwards] PSSRU. Unit Costs of Health & Social Care 2014. Compiled by Lesley Curtis.
[2001/02 and 2002/03] PSSRU. Unit Costs of Health & Social Care 2010.

Table 112 gives the inflation factor used in the model

Table 112: Inflation factor to 2015/16 prices

From calendar year	From financial year	Inflation factor to 2015/16 prices
2000	2000/01	1.527
2001	2001/02	1.453
2002	2002/03	1.404
2003	2003/04	1.335

From calendar year	From financial year	Inflation factor to 2015/16 prices
2004	2004/05	1.292
2005	2005/06	1.246
2006	2006/07	1.201
2007	2007/08	1.168
2008	2008/09	1.124
2009	2009/10	1.117
2010	2010/11	1.084
2011	2011/12	1.062
2012	2012/13	1.044
2013	2013/14	1.033
2014	2014/15	1.016
2015	2015/16	1

Source: PSSRU. Unit Costs of Health & Social Care 2014;[141] PSSRU. Unit Costs of Health & Social Care 2010[142]

Conversion to GBP

Where conversion from other currencies to GBP was required, IMF purchasing power parity was used to convert within year (e.g., from 2010 EUR to 2010 GBP), after which inflation was applied. The CCEMG – EPPI-Centre Cost Converter [http://eppi.ioe.ac.uk/costconversion/default.aspx] was used for the PPP conversion.

Cost of RAS testing

As detailed in Appendix I, personal communication with All Wales Medical Genetics Service and the Genetics Laboratory at Royal Devon and Exeter Hospital suggest a cost of £200 for joint *KRAS* and *NRAS* mutation testing. This was despite differences in the number of codons assessed and possible differences in the type of test used.

As such, we assume a unit cost of £200 from *RAS* mutation testing in our model. We also allow for the cost for patients who were tested as *RAS* mutant. We do this by setting cost as £200 / 50% = £400, where 50% of patients are assumed *RAS* wild type

Drug acquisition costs

We estimate the mean drug acquisition cost per patient as:

Mean 1st-line treatment duration (Section 6.1.4.5, p.284),

x drug acquisition cost per unit time (discussed below)

x dose intensity (discussed below).

We repeat that, in our base case, we use the mean treatment duration from the RCTs, capped by the mean time in 1st-line PFS for unresected patients (Section 6.1.4.5, p.284).

We now discuss our estimates of drug acquisition cost per unit time, the first item in the product above.

Table 113 summarises the cost per month of the chemotherapy regimens in the PenTAG model.

Table 113: Summary of monthly costs of chemotherapy regimens

Regimen	Cost per month of drug acquisition
CET+FOLFOX4	£3,955
CET+FOLFOX6	£3,961
PAN+FOLFOX4	£4,195
PAN+FOLFOX6	£4,200
BEV+FOLFOX4	£2,089
BEV+FOLFOX6	£2,094
FOLFOX4	£86
FOLFOX6	£91
XELOX	£76
CET+FOLFIRI	£3,987
BEV+FOLFIRI	£2,131
FOLFIRI	£128

Key: CET = cetuximab, PAN = panitumumab, BEV = bevacizumab, FOLFOX(4/6) = folinic acid + fluorouracil + oxaliplatin, XELOX = capecitabine + oxaliplatin, FOLFIRI = folinic acid + fluorouracil + irinotecan

Unit costs for each agent were drawn from the CMU eMIT database[119] where possible, or from the BNF[26] when an agent was not present in eMIT. When eMIT prices were used, the average unit cost was derived with a weighted average (weighted by the market share in mg sold of each preparation). The unit cost for bevacizumab was calculated assuming 16 mg vial usage, since this resulted in slightly lower costs and did not increase wastage, thereby slightly lowering total costs. The company submissions from Merck Serono and Amgen included details of an alternative pricing strategy for cetuximab and a PAS for panitumumab; we were advised by NICE to use the list prices in the base case and the PAS prices in scenario analyses. These can be found in Appendix J.

Table 114: Unit costs for individual agents

Agent	Cost	Source
Cetuximab	20 ml vial (5 mg/ml): £178.10	BNF (June 2015)
	100 ml vial (5 mg/ml): £890.50	
Panitumumab	5 ml vial (20 mg/ml): £379.29	BNF (June 2015)
	20 ml vial (20 mg/ml): £1,517.16	
Bevacizumab	4 ml vial (25 mg/ml): £242.66	BNF (June 2015)
	16 ml vial (25 mg/ml): £924.40	
Oxaliplatin	20 ml vial (5 mg/ml): £6.14	CMU eMIT
	10 ml vial (5 mg/ml): £3.65	
Fluorouracil	20 ml vial (50 mg/ml): £1.33	CMU eMIT
	100 ml vial (25 mg/ml): £6.14	
	50 ml vial (50 mg/ml): £2.04	
	5 × 10 ml vial (25 mg/ml): £17.63	
	10 ml vial (50 mg/ml): £0.87	
	10 × 20 ml vial (25 mg/ml): £47.50	
	100 ml vial (50 mg/ml): £3.71	
Leucovorin	10 ml vial (10 mg/ml): £2.41	CMU eMIT
	5 × 2 ml vial (7.5 mg/ml): £32.39	
	30 ml vial (10 mg/ml): £3.98	
	5 × 10 ml vial (3 mg/ml): £23.42	
	5 × 1 ml vial (3 mg/ml): £25.33	
	5 ml vial (10 mg/ml): £1.86	
Irinotecan	5 ml vial (20 mg/ml): £7.38	CMU eMIT
	15 ml vial (20 mg/ml): £20.11	
	2 ml vial (20 mg/ml): £5.43	
	25 mg vial (20 mg/ml): £48.53	
Capecitabine	60 tablet (150 mg) pack: £5.63	CMU eMIT
	120 tablet (500 mg) pack: £39.04	
Chlorphenamine	5 × 1 ml vial (10 mg/ml): £14.47	CMU eMIT
Dexamethasone	28 tablet (0.5 mg) pack: £45.10	CMU eMIT
	50 tablet (2 mg) pack: £21.50	
	100 tablet (2 mg) pack: £33.96	
	150 ml oral solution (60 mg): £19.13	
	75 ml oral solution (30 mg): £17.00	

Key: BNF = British National Formulary, CMU = Commercial Medicines Unit, eMIT = Electronic market information tool

Target dosages per cycle were drawn from the literature (i.e., from RCTs). Cetuximab was assumed to be administered on a biweekly schedule to coincide with FOLFOX/FOLFIRI administration, as this is common clinical practice within the NHS, and Merck Serono argued on the basis of an open-label RCT by Brodowicz et al.[143] and a literature review[144] that 500 mg/m² biweekly administration is equivalent to induction 400 mg/m² followed by weekly 250 mg/m² administration. Biweekly administration is not included in the summary of product characteristics of cetuximab. [redacted] We consider the RCT by Brodowicz et al. to be of sufficient quality to make this claim and believe the claim of equivalence to be reasonable.

The cost-effectiveness of weekly dosing of cetuximab was evaluated in a scenario analysis. In this analysis the cost per month of drug acquisition for cetuximab (alone) was £4,393 for the first month and £3,859 thereafter.

Target dosages and unit costs were not varied in the probabilistic sensitivity analysis.

Target dosage and wastage were calculated based on assumed body surface area of 1.85 m² and body weight of 74.7 kg.

Table 115: Dosages in each regimen and resulting cost per month

Regimen	Agent	Cycles per month	Dosage per cycle	Cost per cycle	Monthly cost
CET+FOLFOX4	Cetuximab	2.17	500 mg/m²	£1,781	£3,859
	FOLFOX4	(see below)			£86
	Chlorphenamine	2.17	10 mg	£2.89	£6
	Dexamethasone	2.17	8 mg	£2.08	£5
	Total				**£3,955**
CET+FOLFOX6	Cetuximab	2.17	500 mg/m²	£1,781	£3,859
	FOLFOX6	(see below)			£91
	Chlorphenamine	2.17	10 mg	£2.89	£6
	Dexamethasone	2.17	8 mg	£2.08	£5
	Total				**£3,961**
PAN+FOLFOX4	Panitumumab	2.17	6 mg/kg	£1,896.45	£4,109
	FOLFOX4	(see below)			£86
	Total				**£4,195**
PAN+FOLFOX6	Panitumumab	2.17	6 mg/kg	£1,896.45	£4,109
	FOLFOX6	(see below)			£91

Regimen	Agent	Cycles per month	Dosage per cycle	Cost per cycle	Monthly cost
	Total				**£4,200**
BEV+FOLFOX4	Bevacizumab	2.17	5 mg/kg	£924.40	£2,003
	FOLFOX4	(see below)			£86
	Total				**£2,089**
BEV+FOLFOX6	Bevacizumab	2.17	5 mg/kg	£924.40	£2,003
	FOLFOX6	(see below)			£91
	Total				**£2,089**
FOLFOX4	Oxaliplatin	2.17	85 mg/m²	£12.59	£27
	Leucovorin	2.17	400 mg/m²	£22.07	£48
	Fluorouracil	2.17	2,000 mg/m²	£4.92	£11
	Total				**£86**
FOLFOX6	Oxaliplatin	2.17	100 mg/m²	£12.59	£27
	Leucovorin	2.17	400 mg/m²	£11.03	£48
	Fluorouracil	2.17	2,800 mg/m²	£7.38	£16
	Total				**£91**
XELOX	Capecitabine	1.45	28,000 mg/m²	£33.55	£49
	Oxaliplatin	1.45	130 mg/m²	£18.89	£27
	Total				**£76**
CET+FOLFIRI	Cetuximab	2.17	500 mg/m²	£1,781	£3,859
	FOLFIRI	(see below)			£128
	Chlorphenamine	2.17	10 mg	£2.89	£6
	Dexamethasone	2.17	8 mg	£2.08	£5
	Total				**£3,987**
BEV+FOLFIRI	Bevacizumab	2.17	5 mg/kg	£924.40	£2,003
	FOLFIRI	(see below)			£128
	Total				**£2,131**
FOLFIRI	Irinotecan	2.17	180 mg/m²	£29.68	£64
	Leucovorin	2.17	400 mg/m²	£11.03	£48
	Fluorouracil	2.17	2,800 mg/m²	£7.38	£16
	Total				**£128**

Key: CET = cetuximab, PAN = panitumumab, BEV = bevacizumab, FOLFOX(4/6) = folinic acid + fluorouracil + oxaliplatin, XELOX = capecitabine + oxaliplatin, FOLFIRI = folinic acid + fluorouracil + irinotecan

Next, we discuss our estimates of mean dose intensity, the last term in the calculation of the mean drug acquisition cost at the start of the current section. Mean dose intensities were

assumed equal to the following median dose intensities from the RCTs that were given to us by Merck Serono and Amgen:

CET+FOLFOX: 89% (OPUS)

FOLFOX: 79% (OPUS)

PAN+FOLFOX: 80% (PRIME)

BEV+FOLFOX: 85% (PEAK)

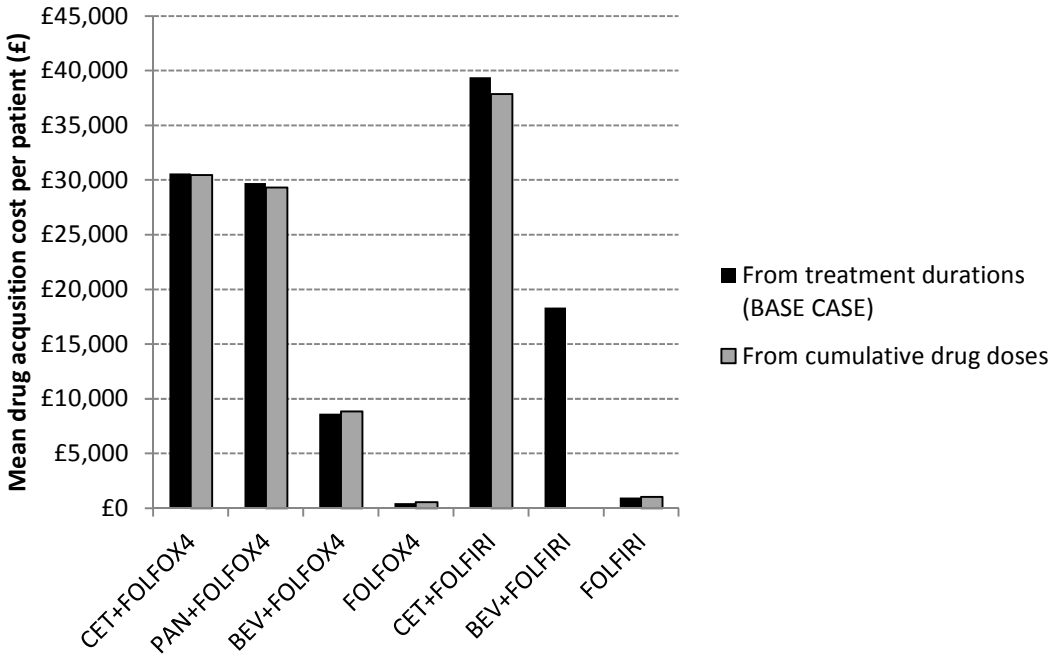
CET+FOLFIRI: 92% (CRYSTAL)

BEV+FOLFIRI: 85% (From PEAK, as not given in FIRE-3)

FOLFIRI: 91% (CRYSTAL)

The resulting mean drug acquisition costs per patient are given in Figure 49. As mentioned in Section 6.1.4.5, p284, in a sensitivity analysis, we also estimated the mean drug acquisition cost per patient based on cumulative doses of drugs from the RCTs. These are similar to our base case estimates (Figure 49). The only difference of any note is that for CET+FOLFIRI. However, we prefer our estimate from our base case, as this used data from FIRE-3, whereas the sensitivity analysis method did not.

Figure 49. Mean drug acquisition costs per patient for all patients combined in PenTAG model



Key: BEV = bevacizumab; CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; PAN = panitumumab

For the Scenario analysis in which we model OS from the RCTs, we assume that some patients in the FOLFOX network take cetuximab or panitumumab-based treatments (Section 6.2.3.3, p379).

Drug administration costs

Drug administration costs are all costs borne by the NHS and personal social services of administering chemotherapy to a patient, excluding the direct cost of drug acquisition (i.e., payments to drug manufacturers or distributors).

Following a similar approach to previous NICE appraisals relating to metastatic colorectal cancer,[122, 145] we include the following cost components in drug administration:

- Delivery
- Pharmacy costs
- Infusion pump
- Line maintenance

The greatest of these cost components is delivery, followed by pharmacy costs.

According to the NHS reference costs collection guidance, [146] chemotherapy "patients receive a core HRG [relating to the purpose of their attendance (which is SB97Z if no other significant procedure takes place besides chemotherapy delivery),] and one or more unbundled chemotherapy HRGs split into two categories". The first category is procurement HRGs, one of which is generated per chemotherapy cycle and includes the cost of the entire procurement service, including pharmacy costs. The procurement HRGs are divided according to setting and cost bands. The second category is delivery HRGs, which are generated for each attendance (not just at the start of each cycle). The delivery HRGs are divided according to setting and complexity (for the first day only, subsequent elements have a single unit cost per day in each setting).

It was not possible to use the procurement HRGs to estimate non-delivery administration costs because they would include the cost of drug acquisition and because the mapping from chemotherapy regimens to cost bands is not publicly available.

Although it is considered possible that infusion pump and line maintenance costs could be already included in the delivery HRGs, it was judged more likely that this would not be the case, and that infusion pumps would be included under procurement and line maintenance would be costed as a separate item. In any case, these two items are small compared to the delivery and pharmacy costs.

Drug delivery

The drug administration costs for each chemotherapy regimen are given in Table 116.

Table 116: Unit costs of drug delivery in PenTAG model

Regimen	Drug administration costs per cycle
CET+FOLFOX4	£721
PAN+FOLFOX4	£721
BEV+FOLFOX4	£721
CET+FOLFOX6	£392
PAN+FOLFOX6	£392
BEV+FOLFOX6	£392
FOLFOX4	£713
FOLFOX6	£383
CET+FOLFIRI	£392
BEV+FOLFIRI	£392
FOLFIRI	£383
XELOX	£303

Key: BEV = bevacizumab; CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; PAN = panitumumab; XELOX = capecitabine + oxaliplatin

The interventions (cetuximab and panitumumab) are delivered as intravenous infusions prior to initiation of the other component of chemotherapy (FOLFOX or FOLFIRI).[44, 45] The comparator bevacizumab is administered similarly. FOLFOX6 and FOLFIRI consist of two hour infusions (leucovorin plus oxaliplatin or irinotecan), followed by bolus 5-FU and then prolonged infusional 5-FU (46 hours). FOLFOX4 consists of a two hour infusion (leucovorin plus oxaliplatin), followed by bolus 5-FU and prolonged infusional 5-FU (22 hours), which is all repeated the subsequent day of the cycle.

Based on guidance for NHS Reference Costs 2013 to 2014[146] (Table 117), we believe the appropriate unit cost for one cycle of FOLFOX4 will comprise the unit costs of SB14Z (Deliver complex chemotherapy, including prolonged infusional treatment) for day 1 and SB15Z (Deliver subsequent elements of a chemotherapy cycle) for day 2 of the cycle. FOLFOX6 and FOLFIRI will incur only SB14Z. This results in significantly increased costs for FOLFOX4 versus FOLFOX6 and FOLFIRI, but these are justified by the necessity to remove the infusion pump, flush the line, deliver a two-hour infusion, and initiate the next 22-hour infusion, which must either be done in hospital with a patient attendance, or by a nurse visitor.

Table 117: Chemotherapy delivery definitions

Definition	Explanation
Deliver simple parenteral chemotherapy	Overall time of 30 minutes nurse time and 30 to 60 minutes chair time for the delivery of a complete cycle.
Deliver more complex parenteral chemotherapy	Overall time of 60 minutes nurse time and up to 120 minutes chair time for the delivery of a complete cycle.
Deliver complex chemotherapy, including prolonged infusional treatment	Overall time of 60 minutes nurse time and over two hours chair time for the delivery of a complete cycle.
Deliver subsequent elements of a chemotherapy cycle	Delivery of any pattern of outpatient chemotherapy regimen, other than the first attendance, i.e. day 8 of a day 1 and 8 regimen or days 8 and 15 of a day 1, 8 and 15 regimen.

Source: Table 10 (p41) of "Department of Health. Reference costs guidance 2013-14. February 2014 © Crown copyright", re-used under the terms of the Open Government Licence [http://www.nationalarchives.gov.uk/doc/open-government-licence/]

The setting of chemotherapy delivery is also important, since the unit costs vary considerably according to setting (Table 118). It can be seen that while daycase and regular day/night are the majority of activity, they also produce the highest unit costs. Delivery in an outpatient or "other" setting significantly reduces the unit cost of the first attendance in a cycle, while delivery in the "other" setting significantly reduces the unit cost of delivery of subsequent elements of a chemotherapy cycle. The "other" setting refers to community chemotherapy, where patients receive their chemotherapy treatment in facilities nearer to home than their cancer centre (e.g., GP surgery) or in their own homes.

Table 118: Variation in unit costs relating to chemotherapy delivery according to setting

Setting	SB14Z: Deliver complex chemotherapy, including prolonged infusional treatment		SB15Z: Deliver subsequent elements of a chemotherapy cycle	
	Activity	***Unit cost***	***Activity***	***Unit cost***
Daycase and regular day/night	151,689	£401	167,850	£328
Outpatient	37,146	£266	40,880	£314
Other	8,577	£284	7,313	£187

The estimated standard error for each unit cost was calculated from the underlying reference cost data, which provides the unit cost and activity supplied by each submitting organisation.

First the weighted standard deviation was calculated for each unit cost, with the weight for each organisation equal to its activity. Then the standard error was estimated by dividing by the square root of the number of organisations (Table 119).

Table 119: Estimated unit costs and standard errors for chemotherapy delivery

HRG	Setting	Nb. of organisations	Total activity	Unit cost	Std. dev.	Std. err.
SB13Z	DCRDN	128	132,260	316.95	248.46	21.96
	OP	49	25,223	218.60	96.55	13.79
	Oth	10	5,468	189.91	107.72	34.06
SB14Z	DCRDN	127	151,689	401.48	307.37	27.27
	OP	41	37,146	265.85	113.46	17.72
	Oth	11	8,577	283.81	175.79	53.00
SB15Z	DCRDN	117	167,850	327.75	258.29	23.88
	OP	36	40,880	313.80	156.91	26.15
	Oth	11	7,313	187.00	106.79	32.20

Key: HRG = healthcare resource group; DCRDN = day case and regular day/night; OP = outpatients; Oth = other

A gamma distribution was used for each unit cost, with parameters derived using the method of moments.[147]

The drug delivery cost per cycle of FOLFOX6 and FOLFIRI was therefore £383, while the cost per cycle of FOLFOX4 was £713.

It was further deemed important to reflect the additional nursing time required to deliver monoclonal antibody therapy (cetuximab, panitumumab or bevacizumab) at the start of each cycle, even though this would not result in a different HRG currency being generated for the attendance. It is acknowledged (e.g., paragraph 5.5.6 of the NICE methods guide[112]) that in such circumstances other sources of evidence may be appropriate. As such it was considered appropriate to estimate the additional resource use of nursing time and cost for this. Our clinical expert advised that 15 minutes additional nursing time would be required for administering monoclonal antibodies, which was costed at £34 [£35.12] per hour in 2013/14 prices,[141] resulting in an additional cost per cycle of £8.78 for chemotherapy regimens including monoclonal antibodies. A gamma distribution was used for the duration of nursing time (independently drawn for each monoclonal antibody) with standard error 20% of the

mean. Likewise a gamma distribution was used for the cost per hour of nursing time, with standard error 20% of the mean.

Finally the drug delivery cost per cycle of XELOX was estimated using HRG SB13Z (Deliver more complex parenteral chemotherapy at first attendance), at a cost of £303 per cycle. It was assumed that there would be no additional cost for delivery of oral capecitabine.

In the scenario analysis of weekly cetuximab administration (Section 1.1.1.1, p385), the delivery cost per cycle for cetuximab regimens increased by £303 to reflect the extra attendance for drug delivery.

Pharmacy costs

A significant variation in pharmacy costs for chemotherapy for metastatic colorectal cancer has been observed in the literature.

We considered pharmacy costs from recent NICE technology appraisals:

- DG16: Freeman et al. 2014[122] estimate a pharmacy cost per cycle for FOLFOX/FOLFIRI of £189.06 [£197.47] by uprating the relevant parameter from TA93 to 2012/13 prices.
- TA242: Hoyle et al. (2011)[120] estimate a pharmacy cost of £15 [£16.86] per cycle in 2008/09 prices.
- TA212: £42 [£47.20] for complex infusion, £25 [£28.10] for simple infusion (price year not stated so assumed to be 2008/09).[148]
- TA176: No pharmacy costs were explicitly included.[149]
- TA118: Tappenden et al. 2007[145] estimate a pharmacy cost of £152 [£196.35] per cycle (2004 prices) for FOLFOX6, as well as estimating costs per cycle of other regimens from £46 [£59.42] to £251 [£324.24].

DG16 and TA118 appear to have assumed the highest costs, while TA242 and TA212 have assumed lower costs and for TA176 no pharmacy costs were explicitly included.

Merck Serono in their submission for this appraisal did not explicitly include pharmacy costs.

We believe it is very likely that there will be increased pharmacy costs for regimens including monoclonal antibodies versus regimens without monoclonal antibodies. For TA118 the

addition of bevacizumab to FOLFIRI or 5-FU/FA incurred an additional £38 [£49.09] in pharmacy cost, and we assumed this would apply (once inflated to 2015/16 prices) to all regimens containing cetuximab, panitumumab or bevacizumab.

For the basic pharmacy cost of FOLFOX and FOLFIRI we considered the inflated costs from DG16 and TA118 and noted that they were very consistent despite being apparently independent estimates. We also noted that the total unit cost for procuring a cycle of the cheapest chemotherapy regimen in the NHS reference costs 2013–14[150] was £240.01 [£247.93], suggesting that there are significant non-acquisition costs associated with procurement and that these could be well reflected by using a pharmacy unit cost per cycle of £197, plus £49 for regimens including cetuximab, panitumumab and bevacizumab.

XELOX includes an infusion of oxaliplatin plus oral chemotherapy to be taken by the patient at home. It was assumed that an appropriate pharmacy cost for XELOX would be £47 (the cost of a complex infusion in TA212 inflated to 2015/16 prices).

In the PSA a gamma distribution was used for pharmacy costs, with standard error 20% of the mean.

Infusion pump

We considered costs for infusion pumps from previous NICE technology appraisals:

- DG16: Freeman et al. 2014[122] estimate a cost of £39 [£40.73] per disposable pump, based on a consideration of existing evidence
- TA242: No cost for infusion pumps was explicitly included.[120]
- TA212: A cost of £35 [£39.34] per pump (price year not stated so assumed to be 2008/09).[148]
- TA176: No cost for infusion pumps was explicitly included.[149]
- TA118: A cost of £62 [£80.09] per pump (2004 prices) was assumed.[145]

We believe the cost assumed for DG16 is most appropriate, since it is a recent estimate based on consideration of a number of alternative evidence sources. A cost of £40.73 per pump was therefore assumed, which applied to each cycle (one pump per cycle) in every regimen except XELOX.

In the PSA a gamma distribution was used for the infusion pump cost, with standard error 20% of the mean.

Line maintenance

PICC and Hickman lines require maintenance to reduce the risk of infection, which involves changing the dressing, replacing the cap and flushing the line. It was assumed that this maintenance would be carried out by a nurse or health visitor and would take place at the end of 5-FU infusion (i.e., on day 3) and once more in the fortnight cycle. For XELOX it was also assumed that there would be two visits per cycle (although the cycles are three weeks long rather than fortnightly), based on the assumption that maintenance would be required at the end of the first and second weeks of the cycle but would be carried out in hospital with the oxaliplatin administration at the end of the third week/start of first week.

We assumed a cost per visit of £67 based on NHS reference costs 2013–14[150] HRG Community Health Services N10AF Specialist nursing, cancer related, adult, face to face.

This is somewhat greater than the cost of £40.67 [£42.48] assumed by Freeman et al. 2014,[122] although they appear to have used the cost per hour of "patient-related work" rather than face to face time.

In the PSA a gamma distribution was assumed for the cost per visit, with standard error of £6.94 in 2013/14 prices, estimated using the same methodology as in the section "Drug delivery" above.

Cost of liver resection

Resection of liver metastases failure rate

We find the following sources of data for the failure rate of liver metastases resection (Table 120).

Table 120 Liver surgery failure rate

Rate, %	Source
<10	Mark Napier, clinical advisor to PenTAG
27.8	NICE TA176, manufacturer's initial submission
5	NICE TA176, clinical specialists' opinion, section 4.7
5	NICE TA176, manufacturer's revised economic analysis
0	Merck submission, current HTA
33.3	PAN+FOLFOX, PEAK trial (used in Graham et al. (2014)[102], p.2795)
22.2	BEV+FOLFOX, PEAK trial (uses in Graham et al. (2014)[102], p.2795)

In Merck Serono's revised analysis in TA176, the failure rate was assumed to be 5%.

Higher liver surgery failure rates, 33% for panitumumab plus FOLFOX and 22% for bevacizumab plus FOLFOX, were observed in PEAK trial (Table 120).

In our model we assume liver resection failure rate at 5% (NICE TA176 and Dr. Napier).

Cost of liver surgery

We note that, in their current submission, Merck Serono model a cost of £2,707 per liver resection operation.

In Graham et al. (2014),[102] liver resection surgery and hospitalisation cost was assumed to be 14,428 euro (£10,241 as of 21.05.15), see Table 121.

Table 121 Average liver resection surgery and hospitalisation cost reported in Graham et al (2014)

Cost, £ (2015)	Source
11,356	HEVA. HEOR analysis of PMSI database; 2012.

Source: Graham et al. (2014).[102] The conversion from € (2012) to GBP (2015) was done using CCEMG EPPI-Centre Cost Converter.[151]

In TA176, in their original submission to NICE, Merck Serono estimated a cost of £2,271 for liver resection. This was later revised to £8,929, and approved by the NICE committee. (NICE FAD,[11])

In the revised submission in the previous appraisal TA176, Merck Serono used a weighted average cost per liver resection surgery calculated from two liver healthcare resource

groups: G02 (liver – complex procedures) and G03 (liver – very major procedures), see HRG v3.5 codes, Table 121.

We could not identify a mapping from HRG v3.5 to HRG4+ so instead we identified which OPCS codes mapped to HRG v3.5 codes G02 and G03. Of these, the codes shown in Table 122 seem potentially relevant to resection of liver metastases.

Table 122 Mapping between OPCS, HRG v3.5 and HRG4+ codes

OPCS	HRG v3.5	Description	HRG4+ codes
J021	G02	Right hemihepatectomy NEC	GA03, GA04
J022	G02	Left hemihepatectomy NEC	GA03, GA04
J023	G02	Resection of segment of liver	GA03, GA04, GA05
J028	G02	Other specified partial excision of liver	GA03, GA04, GA05
J029	G02	Unspecified partial excision of liver	GA05, GA06, GA07
J024	G03	Wedge excision of liver	GA03, GA04, GA05
J031	G03	Excision of lesion of liver NEC	GA05, GA06, GA07
J032	G03	Destruction of lesion of liver NEC	GA06, GA07, GA13

Based on clinical advice we understand that all liver resection surgeries for mCRC are very complex; 80% of them are open operations and the remaining 20% are laparoscopic surgeries. Based on this assumption, GA03 (Very complex) is likely to be a suitable candidate.

Open liver resection

We estimated the unit cost of very complex open liver resection surgery as a weighted average of the costs for the HRGs GA03C, GA03D and GA03E (Table 123). They were derived including:

- elective inpatients
- elective inpatients excess bed days
- non-elective inpatient (long stay)
- non-elective inpatient (long stay) excess bed days
- non-elective inpatient (short stay)

Table 123 Average cost per liver resection surgery

Currency	Currency Description	Activity	Unit Cost, £	Total Cost, £
GA03C	Very Complex Open, Hepatobiliary or Pancreatic Procedures, with CC Score 4+	627	13,433	8,422,455
GA03D	Very Complex Open, Hepatobiliary or Pancreatic Procedures, with CC Score 2-3	596	10,258	6,113,911
GA03E	Very Complex Open, Hepatobiliary or Pancreatic Procedures, with CC Score 0-1	940	8,659	8,139,070
Weighted average		2163	10,483	22,675,436

Source: National Schedule of Reference Costs - Year 2013-14.[146]

Laparoscopic liver resection

In the section above, “Open liver resection”, we estimated the cost of open liver resection to be £10,483 in 2013/14 prices (£10,829 in 2015/16 prices). We were not able to identify appropriate HRGs in the NHS Reference costs for laparoscopic liver resection, but we identified a cost study reported by Polignano et al. (2008),[152] in which the costs of elective laparoscopic and open liver segmentectomy, performed with an intention to treat the disease, were compared (Table 124). Twenty-five laparoscopic liver resections carried out at Ninewells Hospital and Medical School between 2005 and 2007 were compared to 25 matching open resections conducted at the same institution between 2004 and 2007. The two groups were homogeneous by age, sex, coexistent morbidity and magnitude of resection. Hospital costs were obtained from the Scottish Health Service Costs Book (ISD Scotland) and average costs were calculated. Laparoscopic surgery was associated with a reduction in total costs of 18.0%, from which we estimate the cost of laparoscopic liver resection to be £8,598 in 2013/14 prices.

Table 124 Overall cost of liver segmentectomy reported by Polignano et al (2008)

	Laparoscopic, £	Open, £
Total (mean ± SD)	11,727 ± 3288	14,298 ± 3817

Source: Polignano et al. (2014).[152] Hospital costs in this study were obtained from the Scottish Health Service Costs Book (ISD Scotland).

Based on expert opinion that 80% of liver resections for metastases are open and 20% laparoscopic, we estimate an average cost for liver resection (weighted for proportion which are open and laparoscopic) of £10,106 in 2013/14 prices, which is inflated to £10,440 in 2015/16 prices.

Frequency of liver resection

In the TA176, the cost of liver resection was assumed to occur only once (NICE TA176,[11] p.13).

This was despite the fact that the NICE Appraisal Committee believed that some patients may undergo more than one operation to achieve complete resection of metastases (NICE FAD,[11] p.22).

In their current submission, Merck Serono also assume one liver resection operation per patient.

Adam et al.(2004)[3] reported 223 hepatectomies (out of 342 surgical procedures) performed on 138 patients, i.e. 1.6 per patient.

Frequencies of repeat hepatectomies for recurring colorectal cancer in patients with initially unresectable metastases, observed between January 1990 and January 2010 in a French hospital, were reported in Wicherts et al. (2013)[153] (Table 125).

Table 125 Number of repeat hepatectomies in patients with initially unresectable colorectal metastases, reported in Wicherts et al. (2013)

Number of hepatectomies	Number of patients out of 114
2	42
3	8

Source: Wicherts et al. (2013).[153]

This gives a mean of 1.4 operations per patient.

In conclusion, we assume the mean of 1.6 operations per patient, based on Adam et al. (2004)[3], since our estimate for overall and progression-free survival post resection are based on this source.

Medical management costs

Resource use

Below we describe medical management not covered by other cost categories, including:

- Oncology outpatient attendances
- Blood tests
- Imaging tests (MRI, CT)
- Colonoscopy
- Palliative care

Resource use is different pre- and post-progression as well as depending whether liver metastases have been successfully resected.

Resource use parameters are presented per month unless otherwise stated.

First- and second-line pre-progression

Individuals receiving 1st or 2nd line chemotherapy who have not had successful liver resection are estimated to have consultant outpatient appointments every two weeks regardless of their chemotherapy regimen, according to expert opinion (Mark Napier). This assumption was also made in TA242.[120] One appointment every two weeks corresponds to 2.17 appointments on average per month.

Simple blood tests are performed every two weeks, but are low cost and therefore not included. More involved blood tests (tumour markers and liver function tests) are estimated to be performed at 1 month and then every four months.[3, 154] For simplicity it was assumed that these tests would be performed on average 0.25 times per month.

During staging, all patients are offered (and are very likely to receive) contrast-enhanced CT of the chest, abdomen and pelvis.[13] This is not included as it is common to all regimens and occurs before chemotherapy commences.

Rectal cancer patients are also offered MRI to assess the risk of local recurrence during staging,[13] this is likewise not included.

Other investigations with MRI, contrast-enhanced CT and PET-CT may be offered to patients with metastatic disease to determine locations of disease and inform MDTs.[13] These are not included since they are common to all regimens and are likely to occur before chemotherapy commences.

CT scans are estimated to be conducted every three months to monitor response to chemotherapy.[155] Ultrasound and MRI are not believed to be conducted routinely to monitor response, but it was considered plausible that patients may receive one or two MRI per course (expert opinion, Mark Napier). Based on mean time on FOLFOX 1st line in non-resected patients of 0.58 years, and assuming two MRI over this period, we estimated 0.288 MRI per month.

It was assumed that these patients would not have routine surveillance for local recurrence (i.e., colonoscopy) on the basis of expert opinion.

Resource use parameters were assumed to follow a gamma distribution in the PSA with standard error 20% of the mean.

Third-line post-progression

Post-progression patients are expected to receive best supportive care, with their management largely being transferred from secondary care to a palliative care team and/or the patient's GP.

Rather than estimate resource use across a large number of cost components we instead estimated the cost of best supportive care per month (Section "Best supportive care", p.337).

Post-successful resection pre-progression

Given these patients have a good prognosis (versus patients unsuitable for liver resection or in whom liver resection is incomplete) there is expected to be less intensive medical management required.

Oncology outpatient attendances are expected every four months, i.e., 0.25 appointments per month on average.[3]

Blood tests (tumour markers and liver function) are conducted every three months (expert opinion).

CT scans are assumed to be conducted every three months (expert opinion). MRI scans may be conducted but given the limited size of this population and the low number of tests which would be expected to be conducted, these were not included.

Colonoscopy may be recommended as surveillance for local recurrence in these patients. It is recommended that the first surveillance colonoscopy be offered at one year after initial treatment,[13] with subsequent surveillance dictated by the risk of further malignancy, which may be 1–3 yearly if adenomas are found (expert opinion) or at five years if there are no abnormal findings. We assumed that there would be one colonoscopy at 12 months, plus one colonoscopy every three years thereafter (using an average 0.028 colonoscopies per month).

Resource use parameters were assumed to follow a gamma distribution in the PSA with standard error 20% of the mean.

Post-successful resection post-progression

These patients were assumed to receive the same as third-line post-progression patients who were not resected, i.e., to receive best supportive care.

Unit costs

Unless otherwise stated, unit costs for medical management were drawn from gamma distributions in the PSA with standard error 20% of the mean.

Oncology outpatient attendance

A cost of £155 was assumed per oncology outpatient attendance, based on consultant-led outpatient attendances in medical oncology (service code 370) in the NHS Reference costs 2013–14,[150] inflated from £150.

Blood tests

We use the same unit cost of blood tests for medical management as we do post-resection, namely, £13 per a tumour marker test and £27 per a liver function test (in £ 2015/16) (NICE[156]).

Imaging

Costs of imaging tests were estimated from the NHS Reference costs 2013–14, assumed to be in the outpatient setting.

CT scans were assumed to be three areas, with contrast, with an estimated cost of £132 [£137] (2013/14 prices).[150]

MRI scans were assumed to be two to three areas, with contrast, with an estimated cost of £193 [£200] (2013/14 prices).[150]

Colonoscopy

The cost of colonoscopy was estimated from the NHS Reference costs 2013–14,[150] assumed to be either as day case or outpatient procedure (and weighted according to the activity recorded for each setting). This resulted in a cost of £519 in 2015/16 values.

Best supportive care

In previous assessments the cost of supportive care has been estimated based on a cost-of-illness study in Stage IV breast cancer by Remák and Brazil.[157] The cost per month of supportive care was estimated as £675 [£1,031] in 2000 prices, while the total cost of end-of-life care was estimated as £1,316 [£2,010].

We performed a pragmatic literature search for cost-of-illness studies in metastatic colorectal cancer and identified the following two studies of interest:

- In a Finnish study, Färkkilä et al. (2015)[158] estimate direct health care costs per month of €1,667 [£1,254] (2010 EUR) in the “palliative state”, with over half of this being “primary/hospice care”.

- In a US study, Song et al. (2011)[159] estimate average medical expenditure per month of $26,649 [£17,402] (2008 USD) in the “death phase” (which covered up to three months prior to death) based on commercial and Medicare claims data, although this might include time on active treatment.

Given the significant differences between the US and UK health care systems it was decided that the estimate from Song et al. (2011)[159] was not generalizable to the NHS.

It was judged that the estimate from Färkkilä et al. 2015[158] was more recent than the estimate from Remák and Brazil[157] and was in the correct patient population, although it is in

a different country, albeit one with “fairly comprehensive provision of public health care”. On this basis we use a cost per month of supportive care of £1,254. This is substantially greater than Merck Serono’s estimate of £315 per month (Section 5.1.2.2, p192).

No separate cost for end-of-life care was included, as these costs should be included in the palliative state in the analysis by Färkkilä et al.

The 95% confidence interval for direct medical costs ranged from 54.5% to 145.5% of the mean cost. This suggests a standard error of approximately 23.2% of the mean. To further acknowledge uncertainty resulting from the generalisation from another country a standard error of 40% of the mean was used in the PSA.

6.1.4.13. Adverse events

The network meta-analyses for adverse events reported in Section 3.2.7 have limited results for types of Grade 3 or 4 adverse events. The FOLFOX network reports results for all comparators for neutropenia, paresthesia, rash and skin conditions and the FOLFIRI network skin conditions and diarrhoea.

On advice from our clinical experts we believe that not all clinically important adverse events are likely to have been picked up by these NMAs.

As such we have used an alternative approach to estimate costs and QALYs associated with adverse event that is not reliant on incidences of all types from every trial. Instead we have chosen two trials as the bases for our two cost-effectiveness networks, calculated total adverse event costs and QALYs for FOLFOX and FOLFIRI for those trials, then calculated costs and QALYs for the other arms of those trials by adjusting for relative risk of any Grade 3/4 adverse event.

The two trials chosen as our bases are PRIME for the FOLFOX network and CRYSTAL for the FOLFIRI network. These were chosen for consistency to the rest of the model, because they are the largest trials with the most relevant comparators.

The relative risk of any Grade 3/4 is calculated by adjusting the odds ratios reported in Section 3.3, using the formula:

$$\mathrm{RR} = \frac{\mathrm{OR}}{(1 - p(\mathrm{AE\ in\ base})) + (p(\mathrm{AE\ in\ base}) \times \mathrm{OR})}$$

Source: Zhang and Kai (1998)[160]

For the purposes of our analysis, we grouped together adverse events which were thought to have similar costs and utilities.

Disutilities for adverse events

The only cost effectiveness study to report adverse event (AE) disutility was Ortendahl et al. (2014), which used a value of -0.07 from Jonker et al. (2007). This is a simplistic approach as it assumes the same disutility for all AEs. No studies on disutilities for adverse events were identified from our literature review of quality of life, however we have identified a recent NICE Diagnostic Appraisal Report (Freeman et al. 2014[122]). This report included a review on adverse events in CRC, including UK data. We also consulted the sources provided by Merck Serono in their submission as potential sources for our model.

Freeman et al. were able to identify the SCOT trial, which reported UK based, EQ-5D data for colorectal cancer patients. They also received a personal communication related to this trial, which included additional information.[122] Though the Freeman et al. study has not yet been published, it has been reviewed as part of the NICE process and as such we believe it to be of relevance to our report. However, the EQ-5D data is limited to a few adverse events and as such, we were required to use the studies identified by Freeman et al., the Merck Serono submission and some additional searching to find disutility estimates for all adverse events reported in our identified trials.

Many of the utility studies identified by Freeman et al. and the Merck Serono submission were not specific to colorectal cancer patients. Neither of these studies report disutility associated with anaemia or thromboembolic events. We used a recent NICE Technology Assessment into cancer treatment induced anaemia, TA323 (Crathorne et al., in press)[120] to estimate the utility difference for anaemia. This used estimates from Harrow et al. (2011), scaled from SF-6D to the EQ-5D and was based on a cancer population.[161]

We did not identify any UK based studies that report disutility for thrombosis, nor any specific to a colorectal cancer population. Instead we use the value reported by Hogg et al. (2013): -0.190. This was a study conducted with 215 people who underwent treatment for thromboembolic events at the Ottawa Hospital Thrombosis Clinic in Canada. 23% of patients had cancer related thrombosis. A standard gamble approach was used to elicit quality of life data from patients, but the measure used is not reported. This value of -0.190 is similar to the value of -0.195 used by Merck Serono (Merck Serono submission, Appendix B, Table 1) though Merck Serono base their value on the disutility associated with infection.

Table 126. PenTAG base case utilities for adverse events

Disutilities	Base case	Standard error	Source
Anaemia	-0.08500	0.17	Harrow et al. (2011), scaled to EQ-5D, as reported in Crathorne et al. (in press)
Asthenia	-0.08000	0.0615	Assumed same as fatigue
Diarrhoea	-0.09000	0.0379	Freeman et al. (2014), SCOT trial data[122]
Fatigue	-0.08000	0.0615	Freeman et al. (2014), SCOT trial data[122]
Hypokalemia	-0.08000	0.0615	Same as fatigue
Infection	-0.19500	0.012	Tolley et al. 2013[116]
Leukopenia	-0.06070	0.0457	Assumed same as neutropenia
Mucosal inflammation	-0.03750	0.1438	Assumed same as mucostitis
Mucositis/Stomatitis	-0.03750	0.1438	Freeman et al. (2014), SCOT trial data[122]
Neuropathy	-0.19700	0.091	Freeman et al. (2014), SCOT trial data[122]
Neutropenia	-0.06070	0.0457	Freeman et al. (2014), SCOT trial data[122]
Pain	-0.06900	0.012	Doyle et al. (2008), chest pain[115]
Paresthesia	-0.06900	0.012	Assume equal to pain
Thrombosis	-0.19000	0.038	Hogg et al. (2013)
Skin conditions	-0.03248	0.01171	Nafees et al. (2008)[117]

A length of 1 week was applied to disutilities, in line with the approach used in Freeman et al. (2014), where expert opinion indicated durations of a maximum of 7 days for Grade 3/4.adverse events. They state that this was broadly similar to the length of stay associated with adverse events as reported in Twelves et al. (2001). Some adverse events may persist longer than 7 days, but with reduced severity and in this analysis, Grade 1/2 adverse events are assumed to have no disutility.

It is probable that some of the disutility of adverse events is already captured in the first line utility reported by Bennett et al., as the PRIME trial also recorded adverse events and utilities. However, it is unclear what crossover there is between the cohort who reported utility estimates and those that reported adverse event data. To arbitrarily reduce the disutility of adverse events related to the PRIME trial would likely underestimate the impact of these events. As such, we calculate the disutilities independently from the utility estimates in the base case and set equal to 0 in a sensitivity analysis. As the values are small for all arms (-0.0018 - -0.0005) and the PRIME halth state utilities are applied for all treatment arms any double counting is also applied in all arms and therefore does not impact greatly on the results.

Unit costs for adverse events

Unit costs were again based on the submission by Merck Serono and Freeman et al. (2014). These are detailed in Table 127. and most are NHS reference costs refering to specific events. As these are event costs, the duration of the adverse event is not applied to these values.

Table 127. PenTAG base case costs for adverse events

Costs	Base case cost	Standard error	Source
Anaemia	£799	£159.80	Crathorne et al. (in press)
Asthenia	£157	£31.40	Same as fatigue
Diarrhoea	£157	£31.40	NHS Reference costs General Medicine 2013-14 outpatient visit service code 300[150]
Fatigue	£157	£31.40	NHS Reference costs General Medicine 2013-14 outpatient visit service code 300[150]
Hypokalemia	£157	£31.40	Same as fatigue
Infection	£2,160	£432.00	NHS Reference costs 2013-14, spell based average inpatient stay[150]
Leukopenia	£157	£31.40	NHS Ref costs General Medicine 2013-14 outpatient visit service code 300[150]
Mucosal inflammation	£941	£188.20	Assumed same as mucostitis
Mucositis/Stomatitis	£941	£188.20	Based on Freeman et al. (2014): NHS Ref costs 2013-14 Non-malignant, ear, nose, mouth, throat or neck disorders (CB02A, CB02B, CB02C, CB02D, CB02E, CB02F)[150]
Neuropathy	£1,736	£347.20	Based on Merck submission: NHS Reference cost 2013-14, Neoplasm related admission (WA17A, WA17B, WA17C, WA17D)[150]
Neutropenia	£2,160	£432.00	NHS Reference costs 2013-14, spell based average inpatient stay[150]
Pain	£135	£27.00	NHS Reference costs 2013-14, outpatient pain management code 191[150]
Paresthesia	£0	-	Assumed no cost
Thrombosis	£712	£142.40	NHS Reference costs 2013-14, Deep Vein Thrombosis (YQ51A, YQ51B, YQ51C, YQ51D)[150]
Skin conditions	£6	£1.20	Diprobase 500mg pump (as used in Freeman et al., 2014).[26]

6.1.4.14. Checking the Peninsula Technology Assessment Group model for wiring errors

The PenTAG model was checked for wiring errors in the following ways:

- All model formulae written were checked by memebers of the team who did not build the model (NH, IT, TS).
- The reasonableness of outputs given extreme input values was checked. For example, LYs equal to QALYs when utility estimates were set to 1.
- A simplified model was built that did not rely on model cycles, to compare results with the full model to quickly identify errors.
- Base-case model results were checked for reasonableness using numerous graphs.
- Model results were checked for reasonableness through numerous univariate sensitivity analyses and a probabilistic sensitivity analysis.

6.2. PenTAG Results

Here, we present our cost-effectiveness results. We first present and discuss the base-case results, and then the results of the sensitivity analyses.

6.2.1. Base case results

6.2.1.1. All patients: Base case results

Our base case results for the FOLFOX and FOLFIRI networks are given in Table 128, Table 129, Table 130 and Table 131 below.

Table 128. PenTAG base case summary cost-effectiveness results: All patients, FOLFOX network

				CET+FOLFOX vs.	PAN+FOLFOX vs.
	CET+FOLFOX	**PAN+FOLFOX**	**FOLFOX**	**FOLFOX**	**FOLFOX**
Life years (mean, undiscounted)	2.41	2.08	1.86	0.55	0.22
QALYs (mean, discounted)	1.61	1.41	1.26	0.35	0.15
Total costs (mean, discounted)	£77,262	£74,705	£38,825	£38,437	£35,880
ICER (Cost / QALY) vs. FOLFOX				**£109,820**	**£239,007**
ICER (Cost / QALY) on efficieny frontier	**£109,820**	Extended dominated	Reference		

Key: CET = cetuximab; FOLFOX = folinic acid + fluorouracil + oxaliplatin; ICER, incremental cost-effectiveness ratio; PAN = panitumumab; QALYs, quality-adjusted life years
Notes: PAN+FOLFOX is extended dominated as it has lower QALY gains and a higher ICER vs. FOLFOX in comparison to CET+FOLFOX

Table 129. PenTAG base case detailed results: All patients, FOLFOX network

				CET+FOLFOX vs.		PAN+FOLFOX vs.
	CET+FOLFOX	PAN+FOLFOX	FOLFOX	PAN+FOLFOX	FOLFOX	FOLFOX
Life years (mean, undiscounted)						
1st-line drug (resected+unresected)	0.72	0.74	0.58	-0.01	0.14	0.16
PFS non-resected	0.57	0.64	0.52	-0.07	0.06	0.12
PFS post-resection	0.85	0.52	0.44	0.33	0.41	0.08
PFS 1st-line	1.42	1.16	0.96	0.26	0.46	0.2
2nd-line FOLFOX or FOLFIRI (non-resected)	0.26	0.28	0.29	-0.03	-0.03	-0.01
3rd-line BSC (non-resected)	0.38	0.42	0.43	-0.04	-0.05	-0.01
PD post-resection	0.35	0.21	0.18	0.14	0.17	0.03
Overall survival (mean)	**2.41**	**2.08**	**1.86**	**0.33**	**0.55**	**0.22**
Cohort split						
% non-resected	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% start 2nd-line FOLFOX/FOLFIRI (non-resect)	93.50%	93.50%	93.50%	0.00%	0.00%	0.00%
% start 3rd-line BSC (non-resected)	87.50%	87.50%	87.50%	0.00%	0.00%	0.00%
% resected	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Life years (mean) (undisc eligible cohort)						
PFS non-resected	0.72	0.73	0.58	-0.01	0.14	0.16
PFS post-resection	4.09	4.09	4.09	0	0	0
PFS 1st-line	4.81	4.82	4.67	-0.01	0.14	0.16
2nd-line FOLFOX or FOLFIRI (non-resected)	0.34	0.34	0.34	0	0	0
3rd-line BSC (non-resected)	0.55	0.55	0.55	0	0	0
PD post-resection	1.69	1.69	1.69	0	0	0

				CET+FOLFOX vs.		PAN+FOLFOX vs.
	CET+FOLFOX	**PAN+FOLFOX**	**FOLFOX**	**PAN+FOLFOX**	**FOLFOX**	**FOLFOX**
OS unresected	1.53	1.54	1.38	-0.01	0.14	0.16
QALYs (discounted)						
PFS non-resected	0.43	0.48	0.39	-0.05	0.04	0.09
PFS post-resection	0.56	0.34	0.29	0.22	0.27	0.05
AEs 1st line	0.00	0.00	0.00	0.00	0.00	0.00
PFS 1st-line	0.99	0.82	0.68	0.16	0.31	0.14
2nd-line FOLFOX or FOLFIRI (non-resected)	0.19	0.21	0.21	-0.02	-0.02	-0.01
3rd-line BSC (non-resected)	0.23	0.26	0.26	-0.02	-0.03	-0.01
PD post-resection	0.20	0.12	0.10	0.08	0.10	0.02
Total	**1.61**	**1.41**	**1.26**	**0.2**	**0.35**	**0.15**
Costs (discounted)						
RAS test	£400	£400	£0	£0	£400	£400
1st-line drug acqusition	£29,850	£28,986	£461	£864	£29,389	£28,525
1st-line drug administration	£20,906	£21,272	£16,008	-£367	£4,898	£5,264
1st-line AEs	£1,512	£1,582	£1,068	-£70	£444	£514
1st-line medical management (unresected)	£3,029	£3,394	£2,746	-£365	£283	£648
2nd-line FOLFOX or FOLFIRI acquisition (non-resected)	£379	£417	£429	-£38	-£50	-£12
2nd-line FOLFOX or FOLFIRI admin (non-resected)	£4,836	£5,322	£5,469	-£487	-£634	-£147
2nd-line FOLFOX or FOLFIRI medical management (non-resected)	£1,325	£1,458	£1,499	-£133	-£174	-£40
3rd-line BSC (non-resected)	£5,481	£6,033	£6,199	-£552	-£718	-£166
Resection operation	£3,635	£2,224	£1,884	£1,411	£1,751	£340
PFS post-resection	£1,014	£620	£526	£394	£488	£95

				CET+FOLFOX vs.		PAN+FOLFOX vs.
	CET+FOLFOX	PAN+FOLFOX	FOLFOX	PAN+FOLFOX	FOLFOX	FOLFOX
PD post-resection	£4,895	£2,995	£2,537	£1,900	£2,358	£458
Total	**£77,262**	**£74,705**	**£38,825**	**£2,557**	**£38,437**	**£35,880**
ICER (Cost / QALY)				**£12,792**	**£109,820**	**£239,007**

Key: AE = adverse event; BSC = best supportive care; CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; ICER, incremental cost-effectiveness ratio; PAN = panitumumab; PD = progressive disease; PFS = progression free survival; QALYs, quality-adjusted life years

Table 130. PenTAG base case summary cost-effectiveness results: All patients, FOLFIRI network

			CET+FOLFIRI vs.
	CET+FOLFIRI	FOLFIRI	FOLFIRI
Life years (mean, undiscounted)	2.21	1.75	0.46
QALYs (mean, discounted)	1.53	1.23	0.30
Total costs (mean, discounted)	£85,197	£40,027	£45,170
ICER (Cost / QALY)			£149,091

Key: CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; ICER, incremental cost-effectiveness ratio; PD = progressive disease; PFS = progression free survival; QALYs, quality-adjusted life years

Table 131. PenTAG base case detailed results: All patients, FOLFIRI network

			CET+FOLFIRI vs.
	CET+FOLFIRI	FOLFIRI	FOLFIRI
Life years (mean, undiscounted)			
1st-line drug (resected+unresected)	0.89	0.69	0.20
PFS non-resected	0.95	0.75	0.20
PFS post-resection	0.30	0.09	0.21
PFS 1st-line	1.25	0.83	0.42
2nd-line FOLFOX or FOLFIRI (non-resected)	0.39	0.41	-0.02
3rd-line BSC (non-resected)	0.45	0.47	-0.03
PD post-resection	0.12	0.04	0.09
Overall survival (mean)	**2.21**	**1.75**	**0.46**
Cohort split			
% non-resected	92.7%	97.9%	-5.2%
% start 2nd-line FOLFOX/FOLFIRI (non-resect)	93.5%	93.5%	0.0%
% start 3rd-line BSC (non-resected)	87.5%	87.5%	0.0%
% resected	7.3%	2.1%	5.2%
Life years (mean) (undisc eligible cohort)			
PFS non-resected	1.03	0.76	0.26
PFS post-resection	4.09	4.09	0.00
PFS 1st-line	5.12	4.85	0.26

			CET+FOLFIRI vs.
	CET+FOLFIRI	FOLFIRI	FOLFIRI
2nd-line FOLFOX or FOLFIRI (non-resected)	0.45	0.45	0.00
3rd-line BSC (non-resected)	0.55	0.55	0.00
PD post-resection	1.69	1.69	0.00
OS unresected	1.93	1.67	0.26
QALYs (discounted)			
PFS non-resected	0.71	0.56	0.15
PFS post-resection	0.20	0.06	0.14
AEs 1st line	-0.00	-0.00	-0.00
PFS 1st-line	0.91	0.62	0.29
2nd-line FOLFOX or FOLFIRI (non-resected)	0.28	0.30	-0.02
3rd-line BSC (non-resected)	0.27	0.29	-0.02
PD post-resection	0.07	0.02	0.05
Total	**1.53**	**1.23**	**0.30**
Costs (discounted)			
RAS test	£400	£0	£400
1st-line drug acqusition	£38,230	£952	£37,279
1st-line drug administration	£18,249	£13,285	£4,964
1st-line AEs	£821	£482	£339
1st-line medical management (unresected)	£4,993	£3,948	£1,045
2nd-line FOLFOX or FOLFIRI acquisition (non-resected)	£382	£407	-£25
2nd-line FOLFOX or FOLFIRI admin (non-resected)	£10,443	£11,126	-£683
2nd-line FOLFOX or FOLFIRI medical management (non-resected)	£1,991	£2,122	-£130
3rd-line BSC (non-resected)	£6,316	£6,730	-£413
Resection operation	£1,284	£372	£912
PFS post-resection	£358	£104	£254
PD post-resection	£1,729	£501	£1,228
Total	**£85,197**	**£40,027**	**£45,170**
ICER (Cost / QALY)			**£149,091**

Key: AE = adverse event; BSC = best supportive care; CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; ICER, incremental cost-effectiveness ratio; PAN = panitumumab; PD = progressive disease; PFS = progression free survival; QALYs, quality-adjusted life years

Survival results

The relative proportions of patients in each health state for each treatment throughout the time horizon of the model is displayed in Figure 50. The mean duration in each health state for each treatment (Table 129 and Table 131) is represented in these graphs by the area under each curve. Virtually all patients are predicted to have died 20 years from start of treatment, which is less than the model time horizon of 30 years.

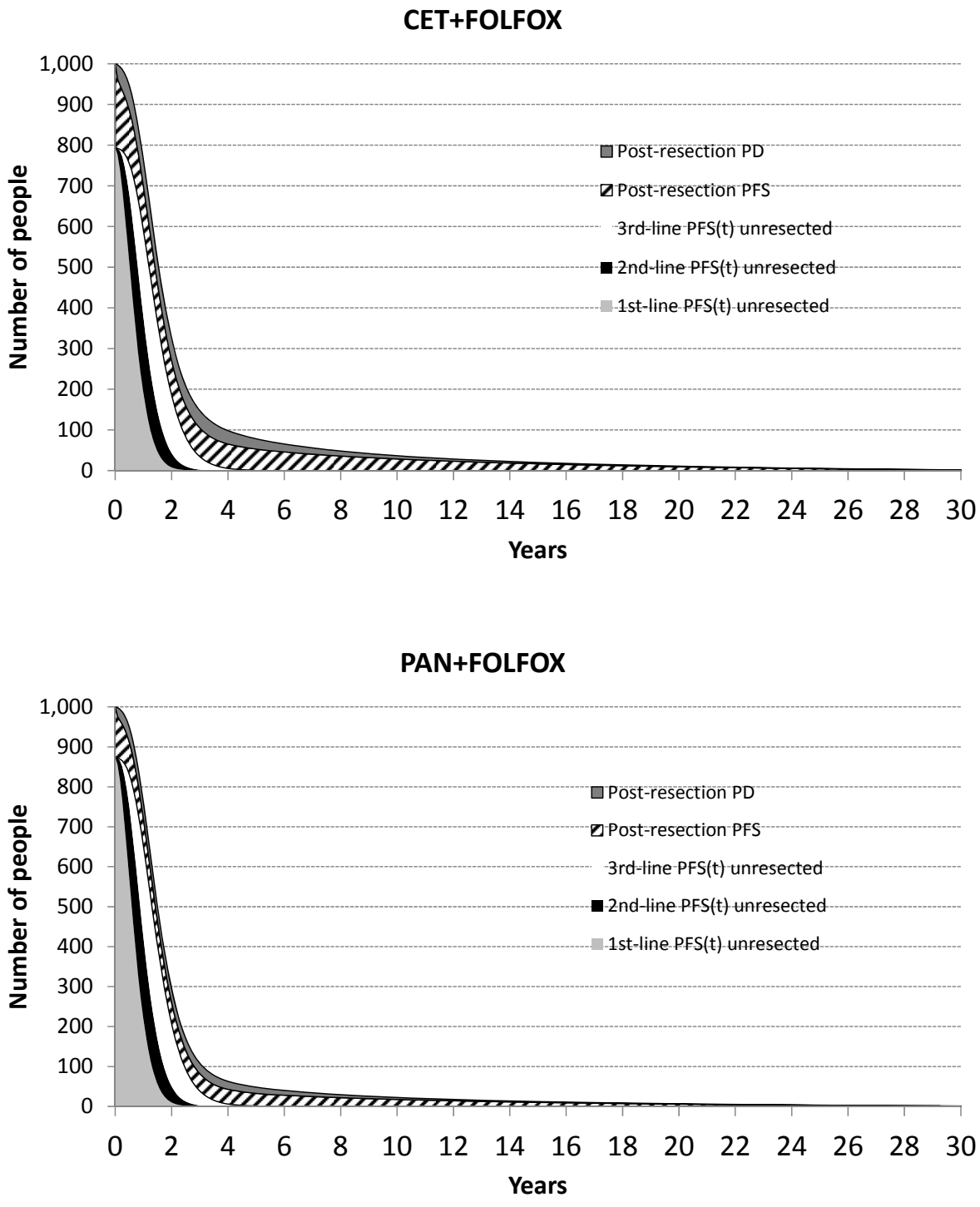
Notice that all graphs show two distinct features. The times on 1st-, 2nd- and 3rd-line for unresected patients are short, and last in total up to about 4 years. The time on PFS and PD post-resection are much longer. This reflects the substantial improvement in survival that we predict for patients post-resection.

We can clearly see that we predict higher rates of resection in the FOLFOX network compared to the FOLFIRI network. However, we should note that comparisons between the two networks need to be made with caution, as they represent different cohorts of patients, as the data is not randomised between networks.

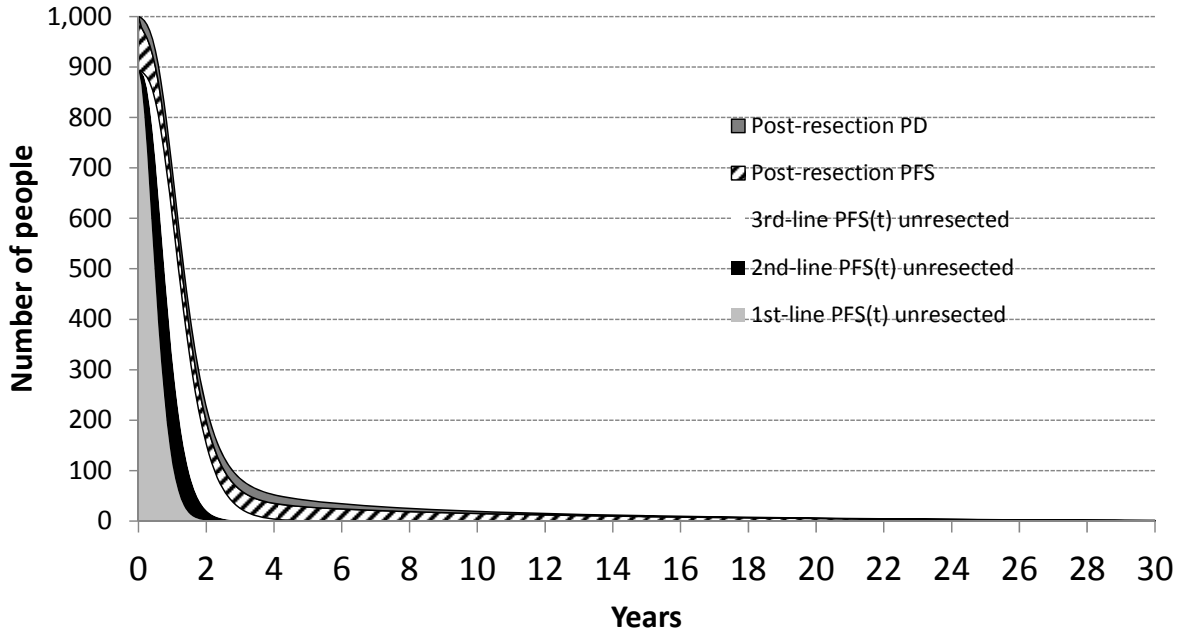
See see further than we expect slightly longer times in 1st-line PFS for unresected patients for CET+FOLFOX and PAN+FOLFOX compared to FOLFOX and for CET+FOLFIRI compared to FOLFIRI.

We predict similar mean times across the treatment arms in 2nd-line PFS and 3rd-line for unresected patients. Any differences are due to slightly different expected proportions of patients that reach these lines of treatment (Table 129 and Table 131: “Cohort split”).

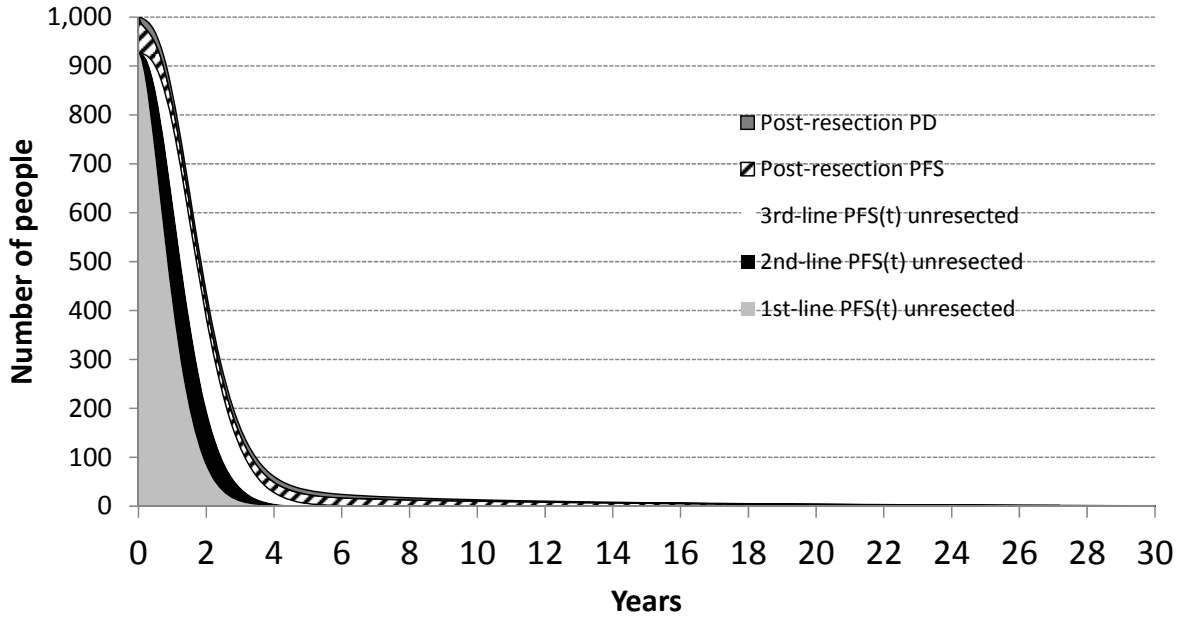
Figure 50. Cohort composition over time by treatment.

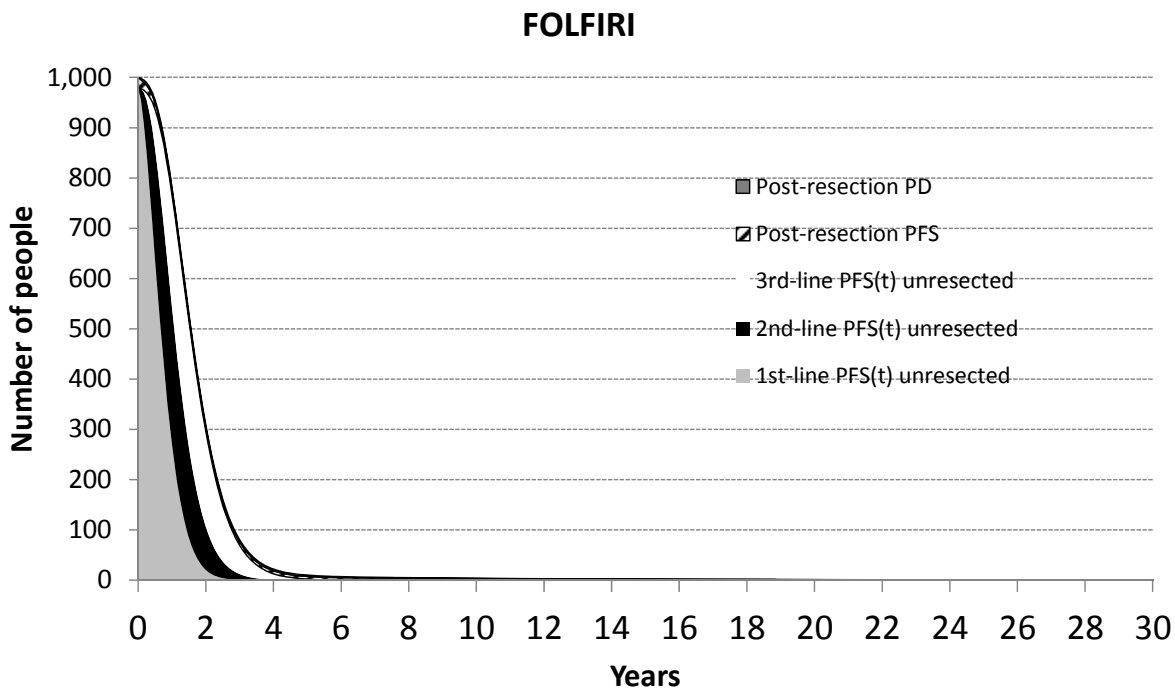


FOLFOX



CET+FOLFIRI





Key: PD = progressive disease, PFS = progression free survival

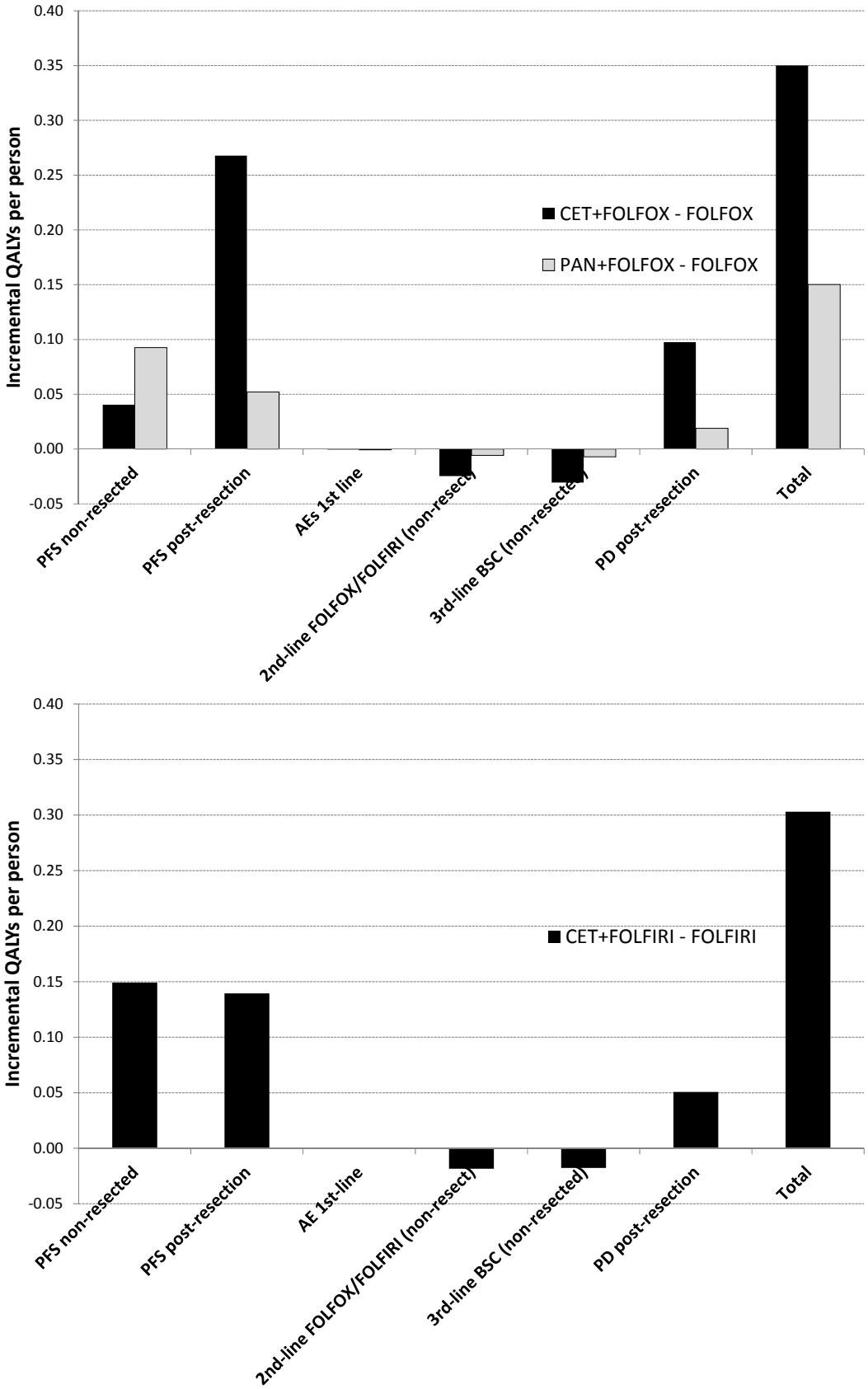
The relative magnitudes of the QALYs are similar to the relative magnitudes of the life years, as the QALYs are simply the life years, discounted and then multiplied by the utilities appropriate for each health state.

Reductions in QALYs due to adverse events are very small in all cases. Incremental QALYs in respect of times in 2nd- and 3rd-line for unresected patients are small in all cases, because patients are expected to spend similar times in 2nd-line for all comparator arms, and similarly for 3rd-line.

We predict that for the comparison CET+FOLFOX versus FOLFOX, most incremental QALYs come from PFS post-resection (Figure 51). This is largely due to the high expected resection rate for CET+FOLFOX ([redacted]) compared to FOLFOX ([redacted]). Total incremental QALYs for PAN+FOLFOX versus FOLFOX are far lower than for CET+FOLFOX vs. FOLFOX. This is mostly because we predict a lower resection rate for PAN+FOLFOX ([redacted]), compared to CET+FOLFOX.

For the comparison CET+FOLFIRI versus FOLFIRI, most incremental QALYs come from PFS non-resected and PFS post-resection (Figure 51). Post-resection QALYs are less important than for CET+FOLFOX versus FOLFOX, as we predict low rates of resection for CET+FOLFIRI (7.3%) and FOLFIRI (2.1%).

Figure 51. Incremental QALYs: PenTAG base case, all patients.



Key: AE = adverse event; BSC = best supportive care; CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; ICER, incremental cost-effectiveness ratio; PAN = panitumumab; PD = progressive disease; PFS = progression free survival; QALYs, quality-adjusted life years

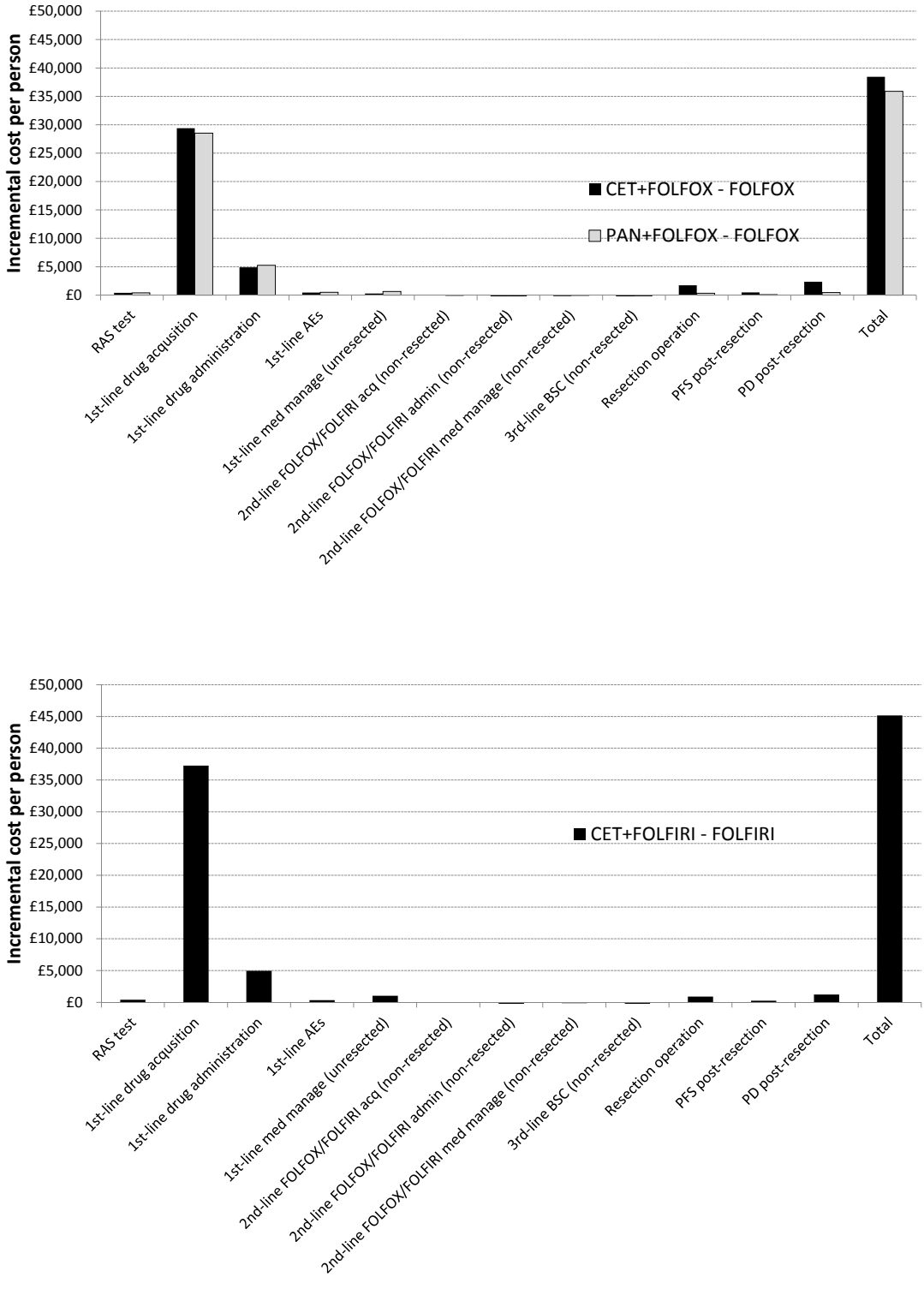
Costs results

We now turn to the expected costs per person. The expected absolute 1st-line drug acquisition costs and 1st-line drug administration costs are by far the largest cost items in the FOLFOX network (Table 129). In the FOLFIRI network, the largest cost items are again the 1st-line drug acquisition costs and 1st-line drug administration costs, but also the 2nd-line drug administration costs. The 2nd-line drug administration costs are also large because we predict a larger proportion of patients in the FOLFIRI network are unresected and because we predict patients spend longer on 2nd-line FOLFOX than 2nd-line FOLFIRI (Table 129, Table 131).

Now turning to incremental costs, we predict that 1st-line drug acquisition costs dominate (Figure 52). Incremental costs of drug acquisition for CET+FOLFOX and PAN+FOLFOX are similar because CET and PAN cost similar amount per month, and because we predict that these two treatments are taken for similar times (8.7 and 8.8 months respectively). 1st-line drug administration costs also make an important contribution to total incremental costs.

Incremental costs of *RAS* testing and treating adverse events are very small. As for incremental QALYs, incremental costs in respect of 2nd and 3rd-line are also very small, as we predict that patients spend very similar times in these states between treatment arms.

Figure 52. Incremental costs: PenTAG base case: all patients.



Key: AE = adverse event; BSC = best supportive care; CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; ICER, incremental cost-effectiveness ratio; PAN = panitumumab; PD = progressive disease; PFS = progression free survival; QALYs, quality-adjusted life years

Cost-effectiveness results and associated uncertainty

Combining all the information on expected costs and QALYs per person, we estimate the following ICERs:

- CET+FOLFOX vs FOLFOX as £110,000 per QALY
- PAN+FOLFOX vs FOLFOX as £239,000 per QALY (extended dominated by CET+FOLFOX and FOLFOX)
- CET+FOLFIRI vs FOLFIRI as £149,000 per QALY

We present all ICERs here and henceforth rounded to the nearest £thousand as we have no confidence in the accuracy of any further significant figures.

We now discuss the degree of certainty of these ICERs. Overall, we believe that these estimates are subject to substantial uncertainty, only some of which is captured in the PSA (Section 6.2.2, p370).

In favour of our approach, the PFS data for 1st-line treatment is of high quality, as it comes directly from RCTs. However, we note that the evidence for CET+FOLFOX is not as strong as for PAN+FOLFOX, as the OPUS trial for CET+FOLFOX vs. FOLFOX had far fewer *RAS* WT patients (87) than the PRIME RCT for PAN+FOLFOX vs. FOLFOX (512).

Furthermore, we adjusted the PFS from the RCTs of 1st-line drugs by subtracting off patients who are resected (Section 6.1.4.4, p267). Without access to the underlying individual patient data from the RCTs, we acknowledge that our method is only approximate.

We estimated survival post-resection from a study that is now several years old. Also, none of the patients in this study (Adam et al. 2004) took either cetuximab or panitumumab. It is therefore possible that survival post-resection for patients initially treated with these drugs could differ from Adam et al. (2004).

We assumed that any treatment effect from 1st-line drugs stops on progression. This is because we do not model OS from the RCTs, but instead only PFS. We explore the use of OS from the RCTs in a scenario analysis later (Section 6.2.3.3 p379).

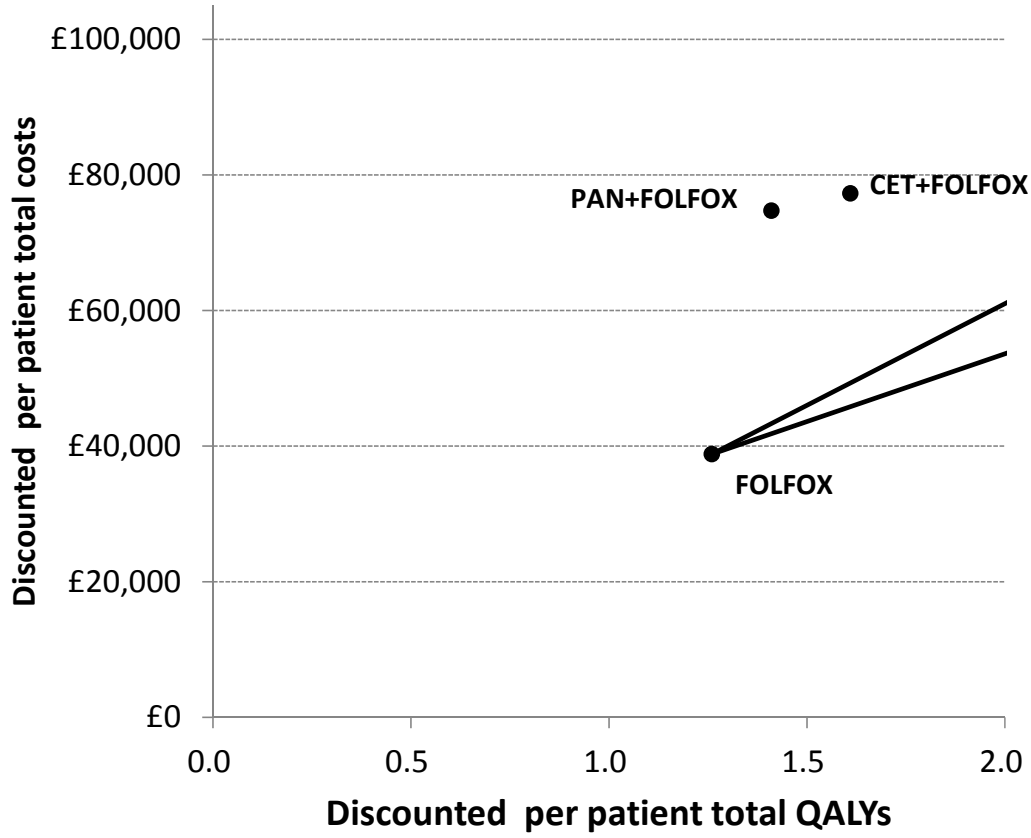
Given lack of data to suggest otherwise, we assume the same accuracy of the *RAS* test in clinical practice as in the 1st-line RCTs (Section 6.1.4.10, p307). Any differences are likely to render worse estimates of cost-effectiveness for cetuximab and panitumumab.

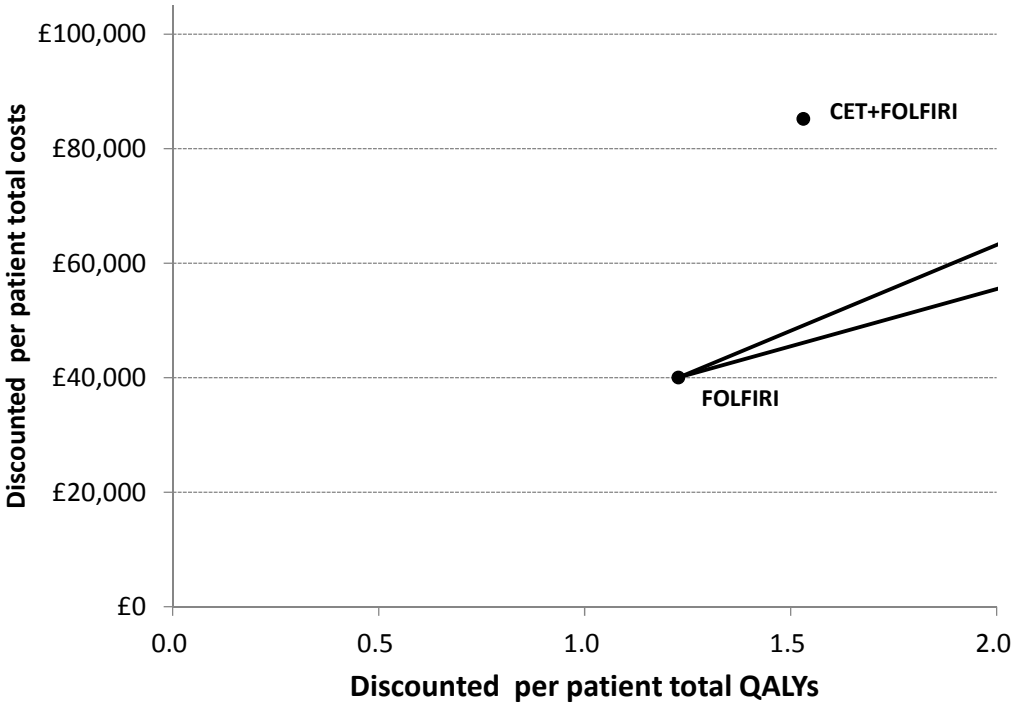
For FOLFOX, our clinical effectiveness is based on the PRIME RCT. Instead, we use the OPUS RCT in a scenario analysis (Section,1.1.1.1, p383).

Also, we assume cetuximab is given fortnightly, whilst it was given weekly in the RCTs of cetuximab: OPUS and CRYSTAL. We therefore assume that the frequency of administration does not affect the effectiveness of cetuximab. We model weekly administration in a scenario analysis later (Section 1.1.1.1, p385).

We have confidence in our estimated rates of resection for the FOLFIRI network (CET+FOLFIRI = 7.3%, FOLFIRI = 2.1%). Also, our estimates for the FOLFOX network of PAN+FOLFOX = [redacted], FOLFOX = [redacted] are reliable, as they are taken directly from PRIME. However, our estimate for CET+FOLFOX = [redacted] is subject to a good deal of uncertainty because this is estimated by an indirect comparison (Section 6.1.4.1, p251).

Figure 53. PenTAG base case results on cost-effectiveness plane: all patients





Straight lines represent the £20,000 and £30,000 per QALY willingness to pay thresholds

6.2.1.2. Liver mets subgroup: Base case results

Our base case results for the FOLFOX and FOLFIRI networks are given in Table 132, Table 134 and Table 135 below.

Table 132. PenTAG base case summary cost-effectiveness results: Liver mets subgroup, FOLFOX network

				CET+FOLFOX vs.	PAN+FOLFOX vs.
	CET+FOLFOX	PAN+FOLFOX	FOLFOX	FOLFOX	FOLFOX
Life years (mean, undiscounted)	2.98	2.86	2.21	0.76	0.65
QALYs (mean, discounted)	1.97	1.89	1.49	0.49	0.40
Total costs (mean, discounted)	£94,008	£79,579	£43,537	£50,471	£36,042
ICER (Cost / QALY) vs. FOLFOX				**£104,045**	**£89,673**
ICER (Cost / QALY) on efficieny frontier	**£173,505 (vs. PAN+FOLFOX)**	**£89,673 (vs. FOLFOX)**	**Reference**		

Key: BEV = bevacizumab; CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; PAN = panitumumab;ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year

Table 133. PenTAG base case detailed results: Liver metastases subgroup, FOLFOX network

				CET+FOLFOX vs.		PAN+FOLFOX vs.
	CET+FOLFOX	PAN+FOLFOX	FOLFOX	PAN+FOLFOX	FOLFOX	FOLFOX
Life years (mean, undiscounted)						
1st-line drug (resected+unresected)	0.92	0.73	0.67	0.18	0.25	0.06
PFS non-resected	0.63	0.50	0.56	0.13	0.08	-0.05
PFS post-resection	1.26	1.28	0.70	-0.01	0.57	0.58
PFS 1st-line	1.90	1.78	1.26	0.12	0.64	0.53
2nd-line FOLFOX or FOLFIRI (non-resected)	0.22	0.22	0.27	0	-0.04	-0.05
3rd-line BSC (non-resected)	0.33	0.33	0.40	0	-0.07	-0.07
PD post-resection	0.52	0.53	0.29	-0.01	0.23	0.24
Overall survival (mean)	2.98	2.86	2.21	0.11	0.76	0.65
Cohort split						
% non-resected	[redacted]	68.8%	82.9%	0.4%	[redacted]	-14.2%
% start 2nd-line FOLFOX/FOLFIRI (non-resect)	93.5%	93.5%	93.5%	0.0%	0.0%	0.0%
% start 3rd-line BSC (non-resected)	87.5%	87.5%	87.5%	0.0%	0.0%	0.0%
% resected	[redacted]	31.3%	17.1%	-0.4%	[redacted]	14.2%
Life years (mean) (undisc eligible cohort)						
PFS non-resected	0.92	0.73	0.67	0.19	0.25	0.06
PFS post-resection	4.09	4.09	4.09	0	0	0
PFS 1st-line	5.01	4.82	4.76	0.19	0.25	0.06
2nd-line FOLFOX or FOLFIRI (non-resected)	0.34	0.34	0.34	0	0	0
3rd-line BSC (non-resected)	0.55	0.55	0.55	0	0	0
PD post-resection	1.69	1.69	1.69	0	0	0
OS unresected	1.72	1.54	1.48	0.19	0.25	0.06
QALYs (discounted)						
PFS non-resected	0.48	0.38	0.42	0.10	0.06	-0.04
PFS post-resection	0.83	0.84	0.46	-0.01	0.37	0.38

				CET+FOLFOX vs.		PAN+FOLFOX vs.
	CET+FOLFOX	**PAN+FOLFOX**	**FOLFOX**	**PAN+FOLFOX**	**FOLFOX**	**FOLFOX**
AEs 1st line	0	0	0	0	0	0
PFS 1st-line	1.31	1.22	0.88	0.09	0.43	0.34
2nd-line FOLFOX or FOLFIRI (non-resected)	0.16	0.16	0.2	0	-0.03	-0.03
3rd-line BSC (non-resected)	0.20	0.20	0.24	0	-0.04	-0.04
PD post-resection	0.30	0.31	0.17	0	0.14	0.14
Total	1.97	1.89	1.49	0.08	0.49	0.40
Costs (discounted)						
RAS test	£400	£400	£0	£0	£400	£400
1st-line drug acqusition	£37,693	£28,891	£533	£8,802	£37,160	£28,357
1st-line drug administration	£26,399	£21,202	£18,514	£5,196	£7,885	£2,689
1st-line AEs	£1,512	£1,582	£1,068	-£70	£444	£514
1st-line medical management (unresected)	£3,339	£2,663	£2,952	£676	£386	-£290
2nd-line FOLFOX or FOLFIRI acquisition (non-resected)	£328	£329	£397	£0	-£69	-£69
2nd-line FOLFOX or FOLFIRI admin (non-resected)	£4,184	£4,189	£5,063	-£5	-£879	-£874
2nd-line FOLFOX or FOLFIRI medical management (non-resected)	£1,147	£1,148	£1,387	-£1	-£241	-£240
3rd-line BSC (non-resected)	£4,743	£4,748	£5,739	-£6	-£996	-£991
Resection operation	£5,432	£5,495	£3,002	-£62	£2,430	£2,493
PFS post-resection	£1,515	£1,533	£837	-£17	£678	£695
PD post-resection	£7,316	£7,400	£4,043	-£84	£3,273	£3,357
Total	£94,008	£79,579	£43,537	£14,429	£50,471	£36,042
ICER (Cost / QALY)				**£173,505**	**£104,045**	**£89,673**

Key: AE = adverse event; BSC = best supportive care; CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; ICER = incremental cost-effectiveness ratio; PAN = panitumumab; PD = progressive disease; PFS = progression free survival; QALYs = quality-adjusted life years

Table 134. PenTAG base case summary cost-effectiveness results: Liver mets subgroup, FOLFIRI network

			CET+FOLFIRI vs.
	CET+FOLFIRI	FOLFIRI	FOLFIRI
Life years (mean, undiscounted)	2.69	1.83	0.86
QALYs (mean, discounted)	1.83	1.26	0.57
Total costs (mean, discounted)	£100,274	£39,654	£60,620
ICER (Cost / QALY)			**£106,707**

Key: BEV = bevacizumab; CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; PAN = panitumumab; ICER = incremental cost-effectiveness ratio; QALYs = quality-adjusted life years

Table 135. PenTAG base case detailed results: Liver metastases subgroup, FOLFIRI network

			CET+FOLFIRI vs.
	CET+FOLFIRI	FOLFIRI	FOLFIRI
Life years (mean, undiscounted)			
1st-line drug (resected+unresected)	1.10	0.65	0.45
PFS non-resected	0.99	0.61	0.38
PFS post-resection	0.67	0.27	0.40
PFS 1st-line	1.66	0.88	0.78
2nd-line FOLFOX or FOLFIRI (non-resected)	0.35	0.39	-0.04
3rd-line BSC (non-resected)	0.40	0.45	-0.05
PD post-resection	0.28	0.11	0.17
Overall survival (mean)	2.69	1.83	0.86
Cohort split			
% non-resected	83.7%	93.5%	-9.8%
% start 2nd-line FOLFOX/FOLFIRI (non-resect)	93.5%	93.5%	0.0%
% start 3rd-line BSC (non-resected)	87.5%	87.5%	0.0%
% resected	16.3%	6.5%	9.8%
Life years (mean) (undisc eligible cohort)			
PFS non-resected	1.18	0.65	0.53

			CET+FOLFIRI vs.
PFS post-resection	4.09	4.09	0.00
PFS 1st-line	5.27	4.74	0.53
2nd-line FOLFOX or FOLFIRI (non-resected)	0.45	0.45	0.00
3rd-line BSC (non-resected)	0.55	0.55	0.00
PD post-resection	1.69	1.69	0.00
OS unresected	2.08	1.56	0.53
QALYs (discounted)			
PFS non-resected	0.74	0.46	0.28
PFS post-resection	0.44	0.17	0.26
AEs 1st line	-0.00	-0.00	-0.00
PFS 1st-line	1.18	0.64	0.54
2nd-line FOLFOX or FOLFIRI (non-resected)	0.25	0.29	-0.03
3rd-line BSC (non-resected)	0.24	0.27	-0.03
PD post-resection	0.16	0.06	0.10
Total	**1.83**	**1.26**	**0.57**
Costs (discounted)			
RAS test	£400	£0	£400
1st-line drug acqusition	£46,823	£896	£45,928
1st-line drug administration	£22,350	£12,502	£9,848
1st-line AEs	£821	£482	£339
1st-line medical management (unresected)	£5,169	£3,228	£1,941
2nd-line FOLFOX or FOLFIRI acquisition (non-resected)	£343	£390	-£47
2nd-line FOLFOX or FOLFIRI admin (non-resected)	£9,379	£10,669	-£1,289
2nd-line FOLFOX or FOLFIRI medical management (non-resected)	£1,788	£2,034	-£246
3rd-line BSC (non-resected)	£5,673	£6,453	-£780
Resection operation	£2,866	£1,143	£1,723
PFS post-resection	£799	£319	£481
PD post-resection	£3,860	£1,539	£2,321
Total	£100,274	£39,654	£60,620
ICER (Cost / QALY)			**£106,707**

Key: AE = adverse event; BEV = bevacizumab; BSC = best supportive care; CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; ICER = incremental cost-effectiveness ratio; PAN = panitumumab; PD = progressive disease; PFS = progression free survival QALY = quality adjusted life year

Survival results

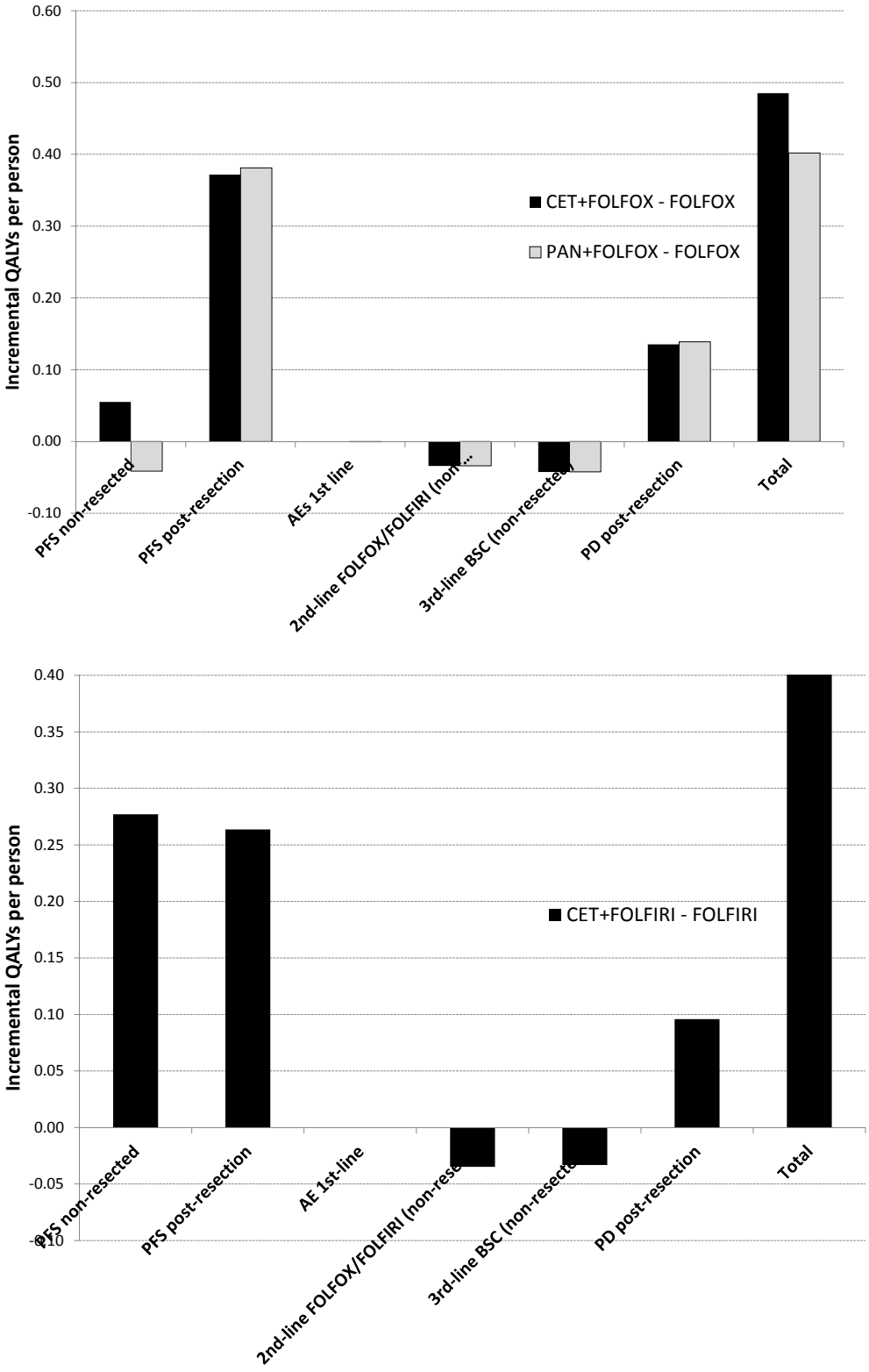
Many of the comments for all patients carry over to the liver mets subgroup. Here, we explain features unique to the liver mets subgroup.

We predict slightly longer life expectancy for the liver mets subgroup (1.8 – 3.0 years) compared to all patients (1.7 – 2.4 years). This is because we also predict greater resection rates for the liver mets subgroup ([redacted]) than for all patients ([redacted]), and life expectancy is substantially greater for patients after resection compared to without resection.

We predict that for both comparisons CET+FOLFOX vs. FOLFOX and PAN+FOLFOX vs. FOLFOX, most incremental QALYs come from PFS and PD post-resection (Figure 54). This is largely due to the high expected resection rates for CET+FOLFOX ([redacted]) and PAN+FOLFOX (31.3%) compared to FOLFOX (17.1%).

For the comparison CET+FOLFIRI vs. FOLFIRI, most incremental QALYs come from PFS non-resected and PFS post-resection (Figure 54). Post-resection QALYs are less important than for CET+FOLFOX vs. FOLFOX, as we predict low rates of resection for CET+FOLFIRI (16.3%) and FOLFIRI (6.5%).

Figure 54. Incremental QALYs: PenTAG base case liver mets subgroup.



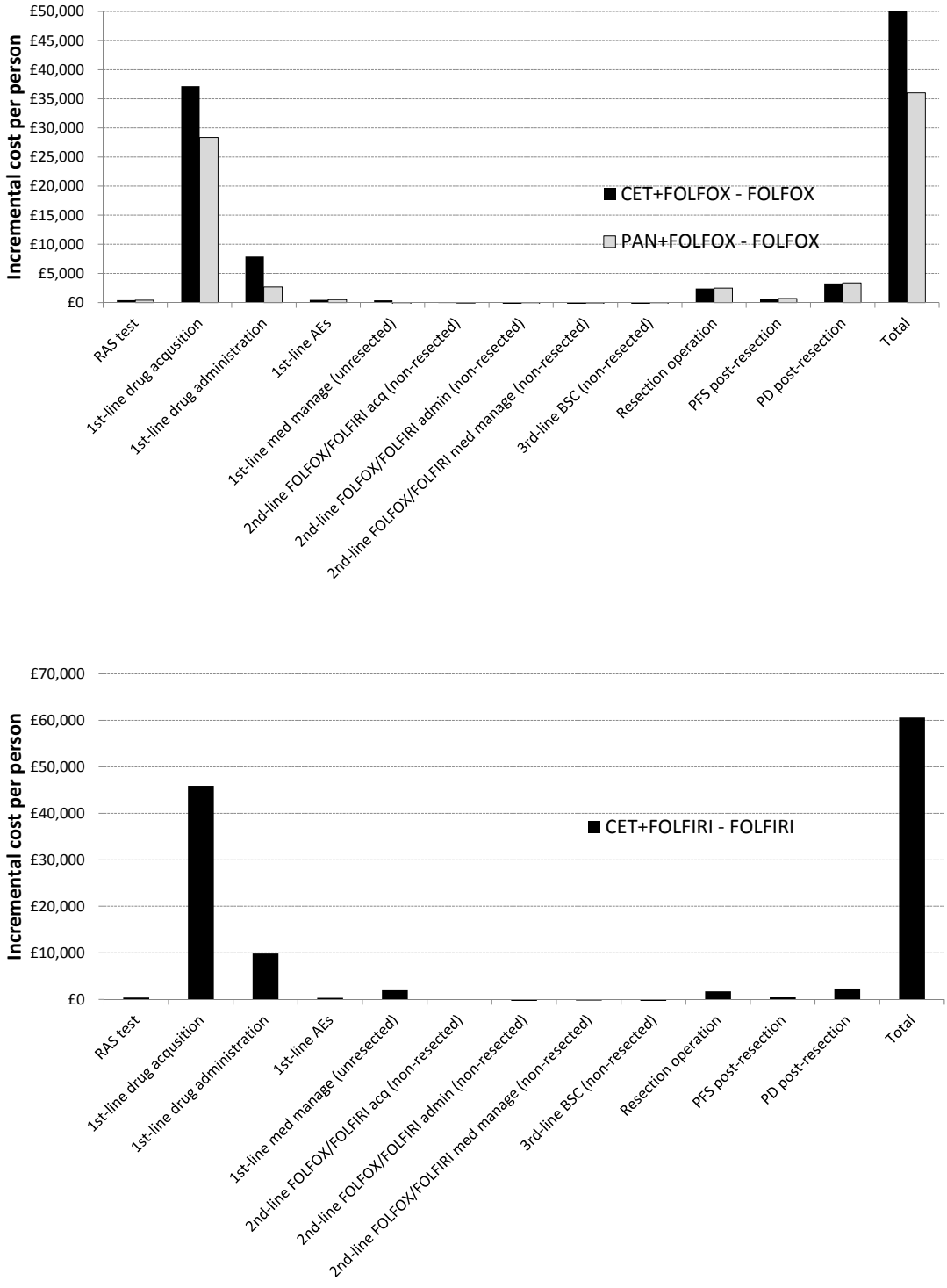
Key: AE = adverse event; BEV = bevacizumab; BSC = best supportive care; CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; PAN = panitumumab; PD = progressive disease; PFS = progression free survival QALY = quality adjusted life year

Costs results

We now turn to the expected costs per person. The expected incremental 1st-line drug acquisition costs and to a lesser extent, 1st-line drug administration costs are the largest items in both networks (Figure 55).

Incremental costs of drug acquisition for CET+FOLFOX vs. FOLFOX is greater than for PAN+FOLFOX vs. FOLFOX even though the monthly acquisition costs of CET+FOLFOX and PAN+FOLFOX are similar. This is because we predict that patients take CET+FOLFOX for longer than PAN+FOLFOX (11.0 vs. 8.8 months).

Figure 55. Incremental costs: PenTAG base case: liver mets subgroup



Key: AE = adverse event; BEV = bevacizumab; BSC = best supportive care; CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; PAN = panitumumab; PD = progressive disease; PFS = progression free survival

Cost-effectiveness results and associated uncertainty

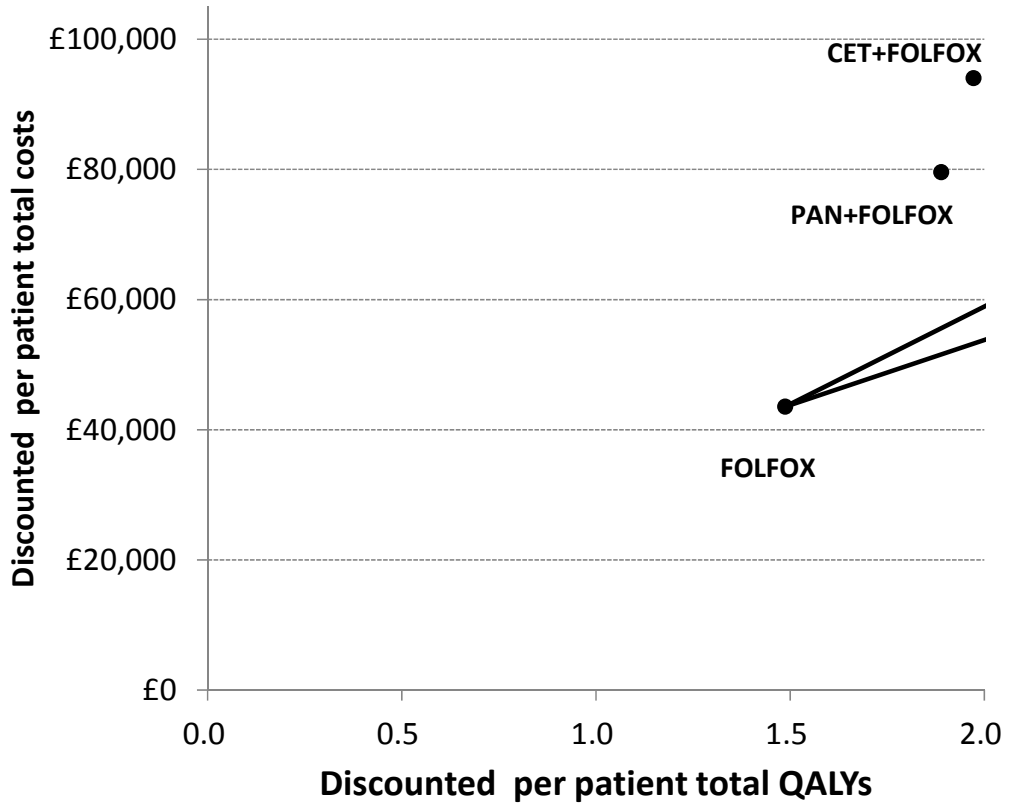
Combining all the information on expected costs and QALYs per person, we estimate the following ICERs for the liver mets subgroup:

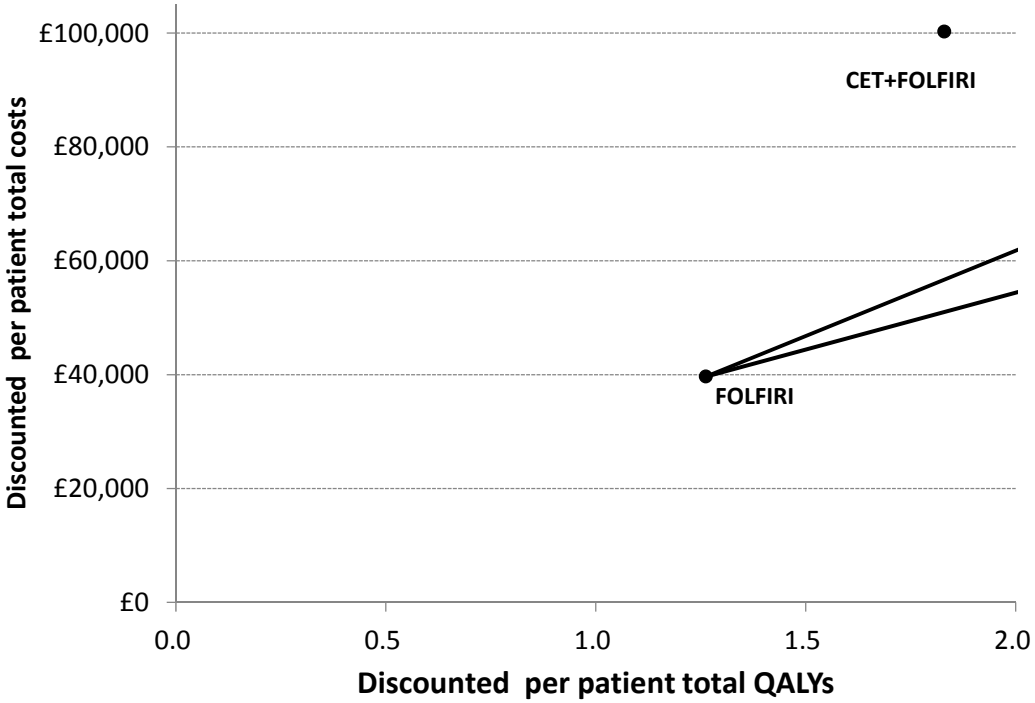
- CET+FOLFOX vs FOLFOX as £104,000 per QALY
- PAN+FOLFOX vs FOLFOX as £90,000 per QALY.
- CET+FOLFIRI vs FOLFIRI as £107,000 per QALY

We believe that these estimates are highly uncertain, indeed more uncertain than for all patients combined, for the reasons give below. Only some of the uncertainty is captured in the PSA (Section 6.2.2, p.370).

- All the uncertainties given for all patients in the previous section still apply.
- PFS for unresected patients is more uncertain than for all patients for the following two reasons:
  - PFS for resected + unresected patients, which is used to estimate PFS for unresected patients, is more uncertain than for all patients because for the liver mets subgroup, this is estimated from the corresponding PFS for all patients, adjusted for the ratio of the median PFS for liver mets / median PFS for all patients (Section 6.1.4.4, p267). Furthermore, given that the median PFS for CET+FOLFOX is not reported from OPUS, we based our estimate for this treatment on the ratio corresponding to CET+FOLFIRI (6.1.4.4, p267), thus adding further uncertainty.
  - we are forced to estimate PFS for unresected patients from PFS for resected + unresected patients for the liver mets subgroup using a different, and arguably less rigorous, method compared to all patients (Section 6.1.4.4, p267).

Figure 56. PenTAG base case results on cost-effectiveness plane: liver mets subgroup





Key: CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; PAN = panitumumab; QALY = quality adjusted life year
Notes: Straight lines represent the £20,000 and £30,000 per QALY willingness to pay thresholds

6.2.2. Probabilistic sensitivity analyses

The scatter-plots shown in Figure 57, Figure 58 and Figure 59 depict the results for all patients of the 1,000 simulations of the PSA, in terms of the incremental cost–utility of CET+FOLFOX vs. FOLFOX, PAN+FOLFOX vs. FOLFOX and CET+FOLFIRI vs. FOLFIRI. This shows that there is substantial uncertainty in the cost-effectiveness of CET+FOLFOX vs. FOLFOX, but less for the other two comparisons. This is not surprising, as there were relatively few patients in the OPUS RCT of CET+FOLFOX vs. FOLFOX.

Figure 60 and Figure 61 show the cost-effectiveness acceptability curves for the treatments in the FOLFOX and FOLFIRI networks respectively, showing the probability that each provides best value for money given a range of willingness-to-pay thresholds.

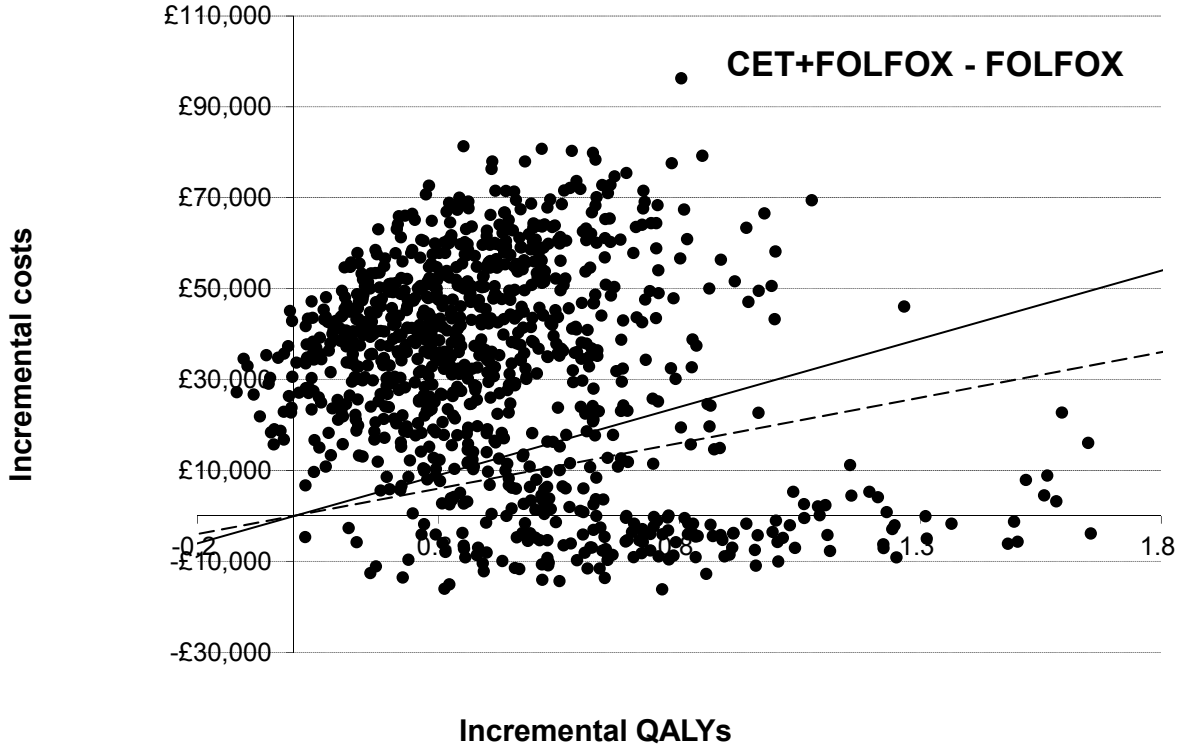
In the FOLFOX network, we predict that the probability is zero that PAN+FOLFOX provides the best value at any willingness to pay threshold investigated (£0 to £150,000 per QALY). The probability that CET+FOLFOX provides the best value exceeds 50% only at a willingness to pay of about £105,000 per QALY, which is consistent with the deterministic ICER for CET+FOLFOX vs. FOLFOX of £110,000 per QALY.

We predict that the probability that CET+FOLFIRI provides the best value exceeds 50% only at a willingness to pay of about £150,000 per QALY, which is consistent with the deterministic ICER for CET+FOLFIRI vs. FOLFIRI of £149,000 per QALY.

The probability that the following treatments are most cost-effective at a willingness to pay threshold of £30,000 per QALY are:

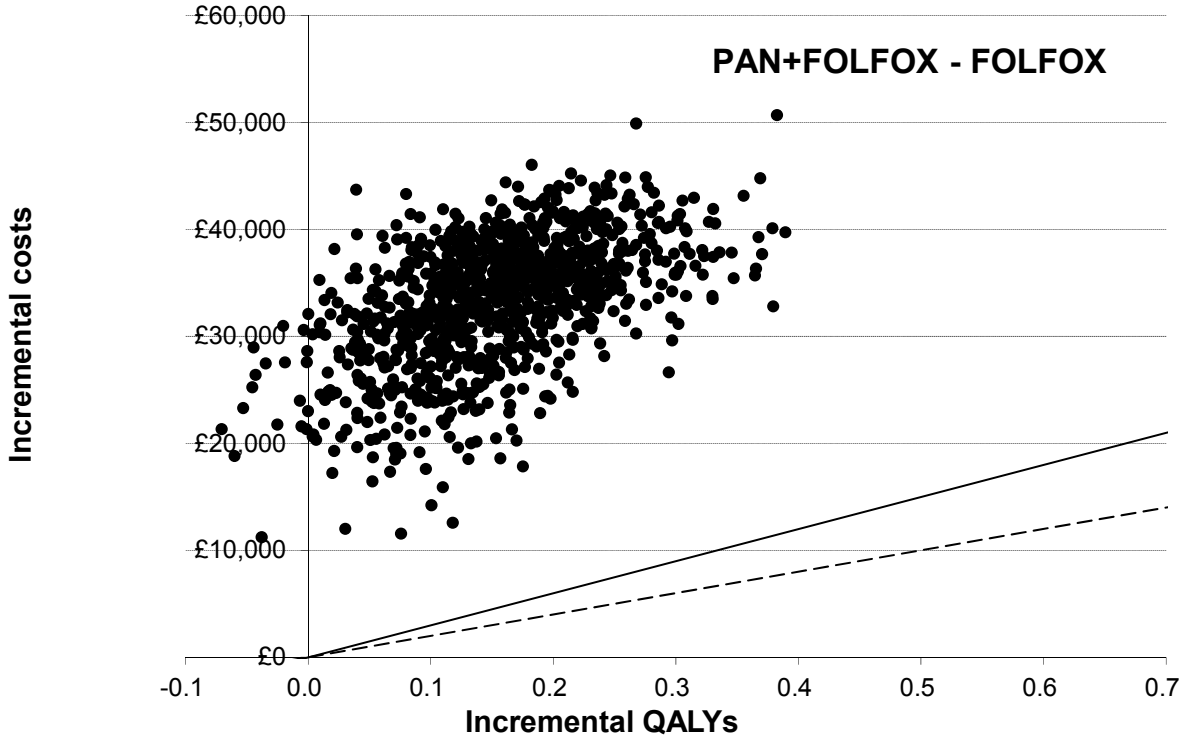
- CET+FOLFOX: 22%.
- PAN+FOLFOX: 0%.
- CET+FOLFIRI: 0%

Figure 57. PenTAG PSA results: incremental cost–utility per person of CET+FOLFOX vs. FOLFOX, all patients



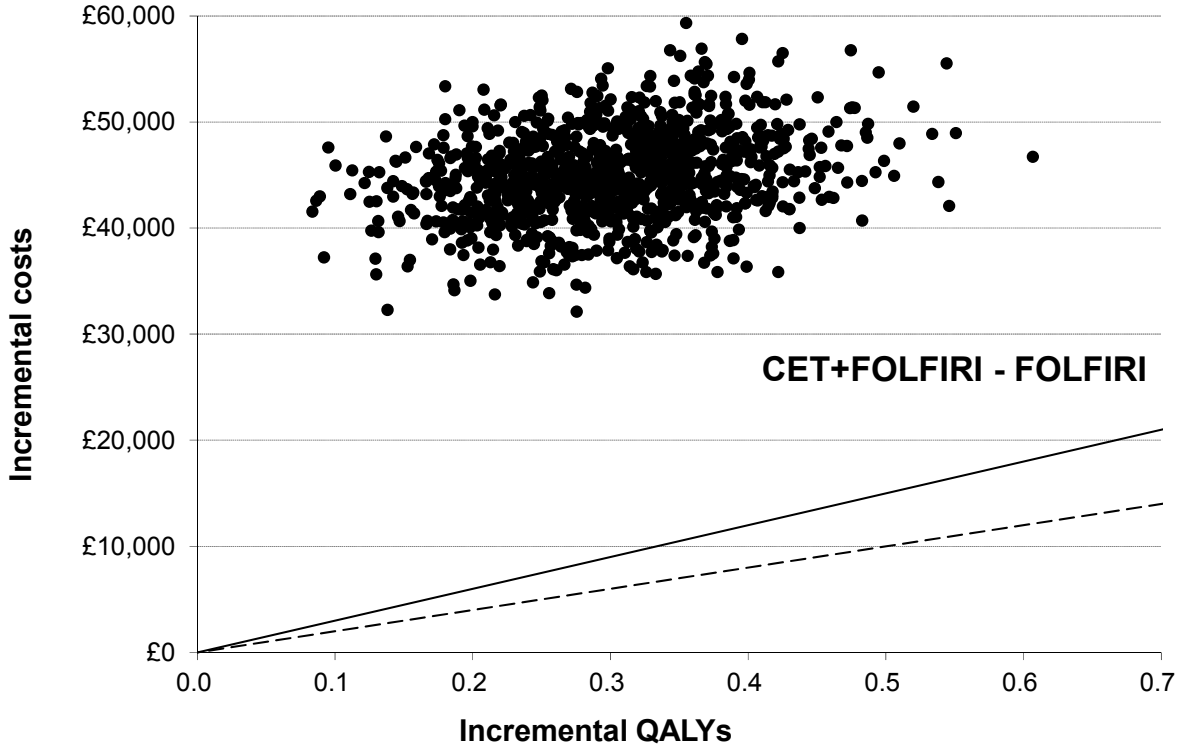
Key: CET = cetuximab; FOLFOX = folinic acid + fluorouracil + oxaliplatin; QALY = quality adjusted life year
Notes: - - - - = willingness to pay threshold £20,000 per QALY gained; ____ = willingness to pay threshold £30,000 per QALY

Figure 58. PenTAG PSA results: incremental cost–utility per person of PAN+FOLFOX vs. FOLFOX, all patients



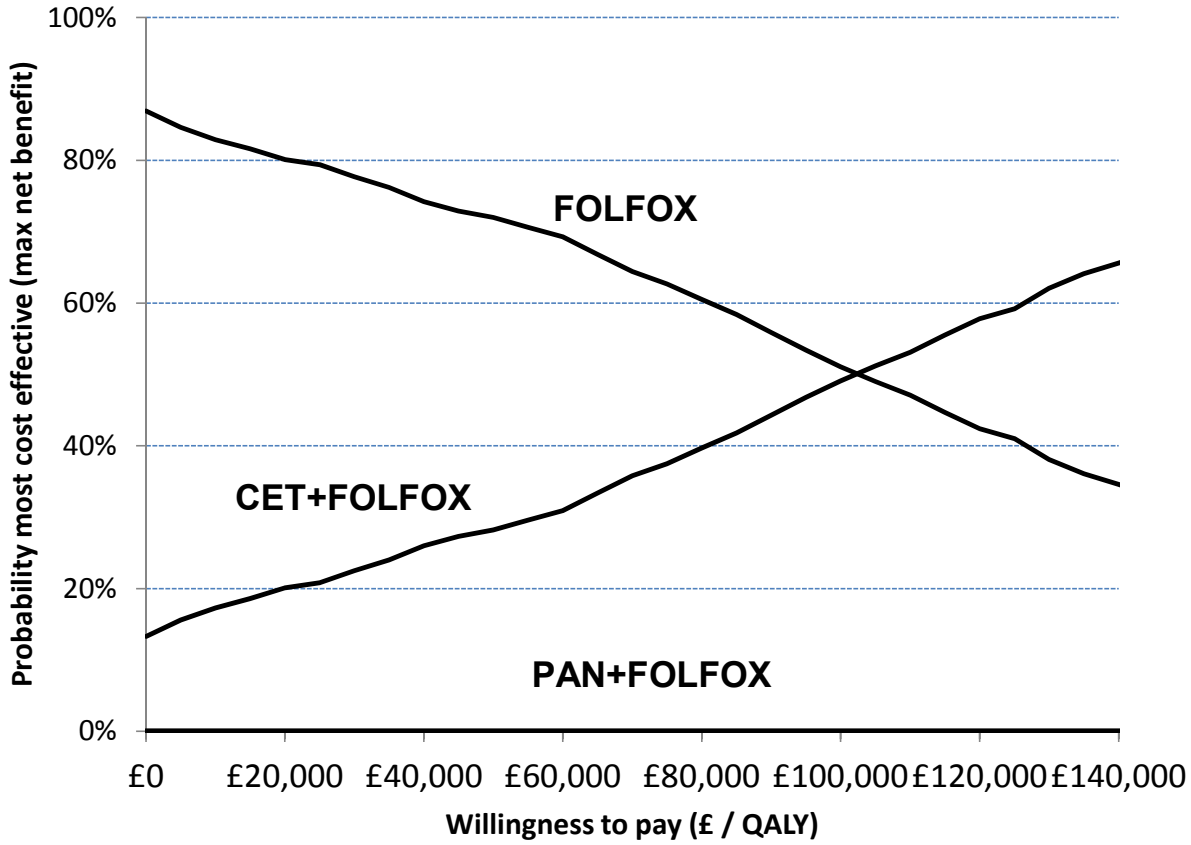
Key: FOLFOX = folinic acid + fluorouracil + oxaliplatin; PAN = panitumumab; QALY = quality adjusted life year
Notes: - - - - = willingness to pay threshold £20,000 per QALY gained; ____ = willingness to pay threshold £30,000 per QALY

Figure 59. PenTAG PSA results: incremental cost–utility per person of CET+FOLFIRI vs. FOLFIRI, all patients



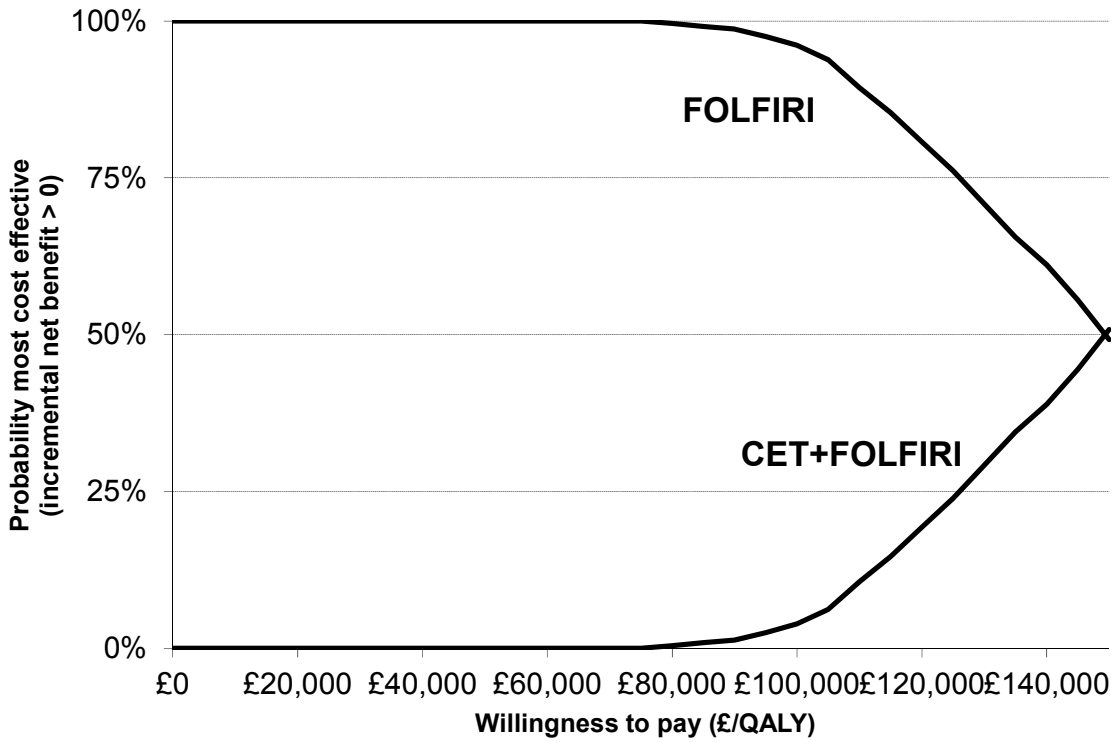
Key: CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irintoecan; QALY = quality adjusted life year
Notes: - - - - = willingness to pay threshold £20,000 per QALY gained; ____ = willingness to pay threshold £30,000 per QALY

Figure 60. PenTAG PSA results: cost-effectiveness acceptability curves: FOLFOX network, all patients



Key: CET = cetuximab; FOLFOX = folinic acid + fluorouracil + oxaliplatin; PAN = panitumumab; QALY = quality adjusted life year

Figure 61. PenTAG PSA results: cost-effectiveness acceptability curves: FOLFIRI network, all patients



Key: CET = cetuximab; FOLFOX = folinic acid + fluorouracil + oxaliplatin; QALY = quality adjusted life year

We now discuss the liver mets subgroup.

In the FOLFOX network, we again predict that the probability is zero that PAN+FOLFOX provides the best value at any willingness to pay threshold investigated (£0 to £150,000 per QALY). The probability that CET+FOLFOX provides the best value tends to about 40% above willingness to pay thresholds of £100,000 per QALY, which is consistent with the deterministic ICER for CET+FOLFOX vs. FOLFOX of £104,000 per QALY.

We predict that the probability that CET+FOLFIRI provides the best value exceeds 50% only at a willingness to pay of about £105,000 per QALY, which is consistent with the deterministic ICER for CET+FOLFIRI vs. FOLFIRI of £107,000 per QALY.

The probability that the following treatments are most cost-effective at a willingness to pay threshold of £30,000 per QALY are:

- CET+FOLFOX: 2%.
- PAN+FOLFOX: 0%.
- CET+FOLFIRI: 0%.

6.2.3. Scenario analyses

In this section, we give the cost-effectiveness results given each of several important scenario analyses.

6.2.3.1. BEV+FOLFOX and BEV+FOLFIRI as comparators

For all patients, in the FOLFOX network, we predict that BEV+FOLFOX is dominated by FOLFOX (Table 136), partly because the resection rate for BEV+FOLFOX is similar to that for FOLFOX (Section 6.1.4.1, p251), and because estimated PFS is rather low (Section 6.1.4.4, p267). Therefore, it does not affect the conclusions of the cost-effectiveness of CET+FOLFOX and PAN+FOLFOX from our base case, in which BEV+FOLFOX is not a comparator (Section 6.2.1.1, p343).

In the FOLFIRI network, under our base case, in which we did not include BEV+FOLFIRI, the ICER for CET+FOLFIRI vs. FOLFIRI was approximately £149,000 (Section 6.2.1.1, p343). When we now include BEV+FOLFIRI, the ICER for CET+FOLFIRI vs. BEV+FOLFIRI is £290,000 (Table 137), i.e. CET+FOLFIRI becomes even worse value versus the most cost-effective comparator.

For the liver mets subgroup, in the FOLFOX network, we predict an ICER for BEV+FOLFOX vs. FOLFOX of £18,000, and that BEV+FOLFOX dominates both CET+FOLFOX and PAN+FOLFOX (Table 138). Although PFS for BEV+FOLFOX is the lowest of the four treatments, it is the most cost-effective because it has the highest estimated resection rate of *** (Section 6.1.4.1, p251).

In the FOLFIRI network, under our base case, in which we did not include BEV+FOLFIRI, the ICER for CET+FOLFIRI vs. FOLFIRI was approximately £107,000 (Section 6.2.1.1, p343). When we now include BEV+FOLFIRI, the ICER for CET+FOLFIRI vs. BEV+FOLFIRI is £724,000 (Table 139), i.e. CET+FOLFIRI becomes even worse value versus the most cost-effective comparator.

Table 136. PenTAG summary cost-effectiveness results including BEV+FOLFOX: All patients, FOLFOX network

					CET+FOLFOX vs.	CET+FOLFOX vs.	PAN+FOLFOX vs.	PAN+FOLFOX vs.
	CET+FOLFOX	PAN+FOLFOX	BEV+FOLFOX	FOLFOX	BEV+FOLFOX	FOLFOX	BEV+FOLFOX	FOLFOX
Life years (mean, undiscounted)	2.41	2.08	1.72	1.86	0.69	0.55	0.36	0.22
QALYs (mean, discounted)	1.61	1.41	1.16	1.26	0.45	0.35	0.25	0.15
Total costs (mean, discounted)	£77,262	£74,705	£42,071	£38,825	£35,191	£38,437	£32,634	£35,880
ICER (Cost / QALY) vs. BEV + FOLFOX or FOLFOX					**£78,000**	**£109,820**	**£129,867**	**£239,007**
ICER (Cost / QALY) on efficieny frontier	**£109,820**	**Extended dominated by FOLFOX and CET+FOLFOX**	**Dominated by FOLFOX**	**Reference**				

Key: BEV = bevacizumab; CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; PAN = panitumumab; ICER = incremental cost-effectiveness ratio; QALYs = quality-adjusted life years

Notes: BEV+FOLFOX is dominated by FOLFOX as is has lower QALY gains and higher costs than FOLFOX;PAN+FOLFOX is extended dominated as it has lower QALY gains and a higher ICER vs. FOLFOX in comparison to CET+FOLFOX

Table 137. PenTAG summary cost-effectiveness results including BEV+FOLFIRI: All patients, FOLFIRI network

				CET+FOLFIRI vs.	CET+FOLFIRI vs.
	CET+FOLFIRI	BEV+FOLFIRI	FOLFIRI	BEV+FOLFIRI	FOLFIRI
Life years (mean, undiscounted)	2.21	2.11	1.75	0.10	0.46
QALYs (mean, discounted)	1.53	1.45	1.23	0.08	0.30
Total costs (mean, discounted)	£85,197	£63,126	£40,027	£22,071	£45,170
ICER (Cost / QALY) vs. FOLFOX				**£290,202**	**£149,091**
ICER (Cost / QALY) on efficieny frontier	**£290,202 vs. BEV+FOLFIRI**	**£101,796 vs. FOLFIRI**	**Reference**		

Key: BEV = bevacizumab; CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; PAN = panitumumab; ICER = incremental cost-effectiveness ratio; QALYs = quality-adjusted life years

Table 138. PenTAG summary cost-effectiveness results including BEV+FOLFOX: Liver metastases subgroup, FOLFOX network

					CET+FOLFOX vs.	CET+FOLFOX vs.	PAN+FOLFOX vs.	PAN+FOLFOX vs.
	CET+FOLFOX	PAN+FOLFOX	BEV+FOLFOX	FOLFOX	BEV+FOLFOX	FOLFOX	BEV+FOLFOX	FOLFOX
Life years (mean, undiscounted)	2.98	2.86	3.30	2.21	-0.32	0.76	-0.43	0.65
QALYs (mean, discounted)	1.97	1.89	2.14	1.49	-0.16	0.49	-0.25	0.40
Total costs (mean, discounted)	£94,008	£79,579	£55,504	£43,537	£38,505	£50,471	£24,075	£36,042
ICER (Cost / QALY) vs. BEV+FOLFOX or FOLFOX					**-£233,589**	**£104,045**	**-£97,078**	**£89,673**
ICER (Cost / QALY) on efficieny frontier	**Dominated by BEV+FOLFOX**	**Dominated by BEV+FOLFOX**	**£18,412 (vs. FOLFOX)**	**Reference**				

Key: BEV = bevacizumab; CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; PAN = panitumumab; ICER = incremental cost-effectiveness ratio; QALYs = quality-adjusted life years
Notes: CET+FOLFOX and PAN+FOLFOX are dominated by BEV+FOLFOX as they have lower QALY gains and higher costs than BEV+FOLFOX;

Table 139. PenTAG summary cost-effectiveness results including BEV+FOLFIRI: Liver metastases subgroup, FOLFIRI network

				CET+FOLFIRI vs.	CET+FOLFIRI vs.
	CET+FOLFIRI	BEV+FOLFIRI	FOLFIRI	BEV+FOLFIRI	FOLFIRI
Life years (mean, undiscounted)	2.69	2.65	1.83	0.03	0.86
QALYs (mean, discounted)	1.83	1.79	1.26	0.04	0.57
Total costs (mean, discounted)	£100,274	£68,997	£39,654	£31,277	£60,620
ICER (Cost / QALY) vs. FOLFOX				**£723,508**	**£106,707**
ICER (Cost / QALY) on efficieny frontier	**£723,508**	**£55,905**	**Reference**		

Key: BEV = bevacizumab; CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; PAN = panitumumab; ICER = incremental cost-effectiveness ratio; QALYs = quality-adjusted life years

6.2.3.2. XELOX as comparator

In this scenario analysis, we use XELOX in place of FOLFOX as a comparator in the FOLFOX network. Only the drug acquisition and administration costs are changed from FOLFOX, all effectiveness parameters are unchanged. In particular, we assume that the drug acqusiton costs of both XELOX and FOLFOX are similar and very low, and that administration cost of XELOX is clearly lower than for FOLFOX (Section 0, p314). This explains why following the ICERs vs. XELOX are higher than vs. FOLFOX:

- The ICER for all patients for CET+FOLFOX vs. FOLFOX is £110,000 per QALY. The ICER for CET+FOLFOX vs. XELOX is higher, at £142,000 per QALY.
- The ICER for all patients for PAN+FOLFOX vs. FOLFOX is £239,000 per QALY. The ICER for PAN+FOLFOX vs. XELOX is higher, at £314,000 per QALY.
-
- The ICER for liver mets patients for CET+FOLFOX vs. FOLFOX is £104,000 per QALY. The ICER for CET+FOLFOX vs. XELOX is higher, at £131,000 per QALY.
- The ICER for liver mets patients for PAN+FOLFOX vs. FOLFOX is £90,000 per QALY. The ICER for PAN+FOLFOX vs. XELOX is higher, at £122,000 per QALY.

6.2.3.3. Overall survival from RCTs

In our base case analysis, we model only PFS from the RCTs. OS is estimated from the times on 1st-, 2nd and 3rd-line of treatment for unresected patients, and for OS for resected patients. In a sensitivity analysis, we model OS, in addition to PFS, from the RCTs (Section 6.1.3.2, p243). The two differences in the model are:

- The modelled mean treatment duration for each treatment arm is set equal to the treatment duration from the RCTs. Unlike in the base case, we do not cap treatment duration as the mean time in 1st-line PFS for unresected patients. The rationale for removing the cap is that OS from the RCTs is likely to be affected (probably lengthened), by 1st-line drugs taken post-progression.
- The time on 3rd-line BSC for unresected patients is changed in such a way as to yield the OS curves from the RCTs (after subtracting patients post-resection, and after the indirect comparisons). The times in all other health states are unaltered.
- We estimated the proportions of patients taking cetuximab- and panitumumab-based treatments 2nd-line from the limited data from the RCTs (Table 89, p245) and we estimate the mean treatment durations of the 2nd-line treatments, as the averages of the durations

on 1st line (from current model) and 3rd-line treatment (from our 2011 mCRC model for the relevant NICE HTA) (Table 140). From this, and the estimated monthly costs of drug acquisition and administration for the current model, we estimate the total costs of drug acquisition and administration of 2nd-line CET+FOLFIRI and PAN+FOLFIRI in the table below.

Table 140. Estimated costs of 2nd-line CET+FOLFIRI and PAN+FOLFIRI

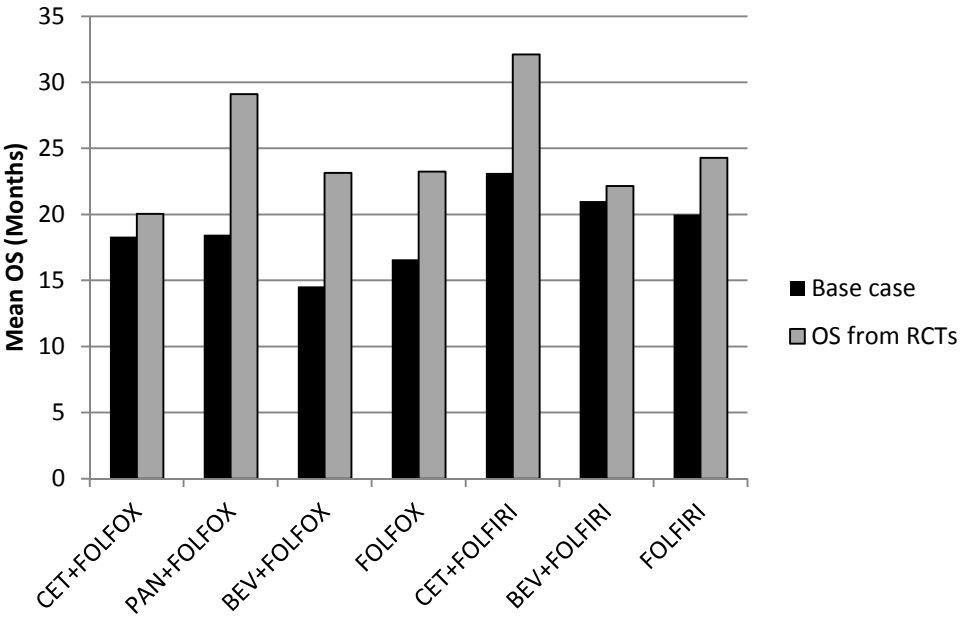
	Estimated treatment duration (months)			1st-line treatment: Estimated % patients on 2nd-line treatment		
2nd-line treatment	**1st-line**	**3rd-line**	**2nd-line**	**CET+FOLFOX**	**PAN+FOLFOX**	**FOLFOX**
CET+FOLFIRI	10.7	8.8	9.7	0%	12.9%	12.7%
PAN+FOLFIRI	8.8	8.8	8.8	14.1%	0%	12.7%
Estimated total cost of 2nd-line treatment				£7,642	£7,209	£13,975

Key: BEV = bevacizumab; CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; PAN = panitumumab

OS for unresected patients is greater in this sensitivity analysis for all treatment arms (Figure 62). This may be because a large proportion of patients in the RCTs took monoclonal antibodies after progression (Table 89, p245), whereas we assumed no such treatment in the base case analysis.

Due to time constraints, we present only the results for all patients, not the results for the liver mets subgroup.

Figure 62 OS estimated via base case method or from RCTs



The cost-effectiveness of CET+FOLFOX vs. FOLFOX now worsens substantially so that CET+FOLFOX is now dominated by FOLFOX (Table 141). This is because OS increases vs baseline OS less for CET+FOLFOX than for FOLFOX (Figure 62), and because mean treatment duration increases far more for CET+FOLFOX than for FOLFOX (Figure 33, p289).

The cost-effectiveness of PAN+FOLFOX vs. FOLFOX now improves substantially from £239,000 to £100,409 per QALY because OS increases vs baseline OS more for PAN+FOLFOX than for FOLFOX (Figure 62), and because mean treatment duration increases less for PAN+FOLFOX than for FOLFOX (Figure 33, p289).

The ICER for CET+FOLFIRI vs. FOLFIRI now improves from £149,000 to £101,000 per QALY because OS increases vs baseline OS more for CET+FOLFIRI than for FOLFIRI (Table 142), and mean treatment durations for both treatments are unchanged (Figure 33, p289).

Merck Serono also present a scenario analysis whereby they take OS directly from the RCTs. In this case, their base case ICERs change as follows:

- CET+FOLFOX vs. FOLFOX: from £47,000 to £133,000 per QALY, a substantial increase.
- CET+FOLFIRI vs. FOLFIRI: from £56,000 to £55,000 per QALY, virtually unchanged.

Table 141. PenTAG cost-effectiveness results OS from RCTs: All patients, FOLFOX network

				CET+FOLFOX vs.	PAN+FOLFOX vs.
	CET+FOLFOX	PAN+FOLFOX	FOLFOX	FOLFOX	FOLFOX
Life years (mean, undiscounted)	2.52	2.85	2.35	-0.33	0.17
QALYs (mean, discounted)	1.67	1.86	1.55	-0.19	0.12
Total costs (mean, discounted)	£118,466	£95,354	£64,368	£54,098	£30,986
ICER (Cost / QALY) vs. FOLFOX				£444,301	£100,409
ICER (Cost / QALY) on efficieny frontier	**Dominated by PAN+FOLFOX**	**£100,409**	**Reference**		

Key: BEV = bevacizumab; CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; PAN = panitumumab; ICER = incremental cost-effectiveness ratio; QALYs = quality-adjusted life years

Table 142. PenTAG cost-effectiveness results OS from RCTs: All patients, FOLFIRI network

			CET+FOLFIRI vs.
	CET+FOLFIRI	FOLFIRI	FOLFIRI
Life years (mean, undiscounted)	2.90	2.10	0.80
QALYs (mean, discounted)	1.92	1.43	0.49
Total costs (mean, discounted)	£94,404	£44,750	£49,654
ICER (Cost / QALY)			**£100,853**

Key: BEV = bevacizumab; CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; PAN = panitumumab; ICER = incremental cost-effectiveness ratio; QALYs = quality-adjusted life years

6.2.3.4. OPUS as baseline RCT in FOLFOX network

For the FOLFOX network, PRIME was selected as the baseline trial, as it contains two of the three treatments, PAN+FOLFOX and FOLFOX in our base case analysis. Although OPUS also contains two of the three treatments, CET+FOLFOX and FOLFOX, in our base case analysis, we did not select this trial, as it is far smaller than PRIME (87 vs. 512 *RAS* WT patients) (Section 6.1.3.2, p243).

However, here, we use OPUS as the baseline RCT for the FOLFOX network in a scenario analysis. In this case, the following parameters change in the FOLFOX network:

- Resection rates (Section 6.1.4.1, p251),
- PFS unresected patients (Section 6.1.4.4, p267).
- Treatment durations (Section 6.1.4.5, p284).

For all patients,

- the ICER for CET+FOLFOX vs. FOLFOX worsens slightly, from £110,000 to £126,000
- the ICER for PAN+FOLFOX vs. FOLFOX improves, from £239,000 to £190,000

For liver mets patients,

- the ICER for CET+FOLFOX vs. FOLFOX improves slightly, from £104,000 to £94,000
- the ICER for PAN+FOLFOX vs. FOLFOX improves, from £90,000 to £58,000.

Table 143. PenTAG cost-effectiveness results OPUS baseline RCT: All patients, FOLFOX network

				CET+FOLFOX vs.	PAN+FOLFOX vs.
	CET+FOLFOX	PAN+FOLFOX	FOLFOX	FOLFOX	FOLFOX
Life years (mean, undiscounted)	1.88	1.66	1.51	0.22	0.37
QALYs (mean, discounted)	1.27	1.14	1.03	0.14	0.24
Total costs (mean, discounted)	£62,422	£52,028	£32,325	£10,394	£30,097
ICER (Cost / QALY) vs. FOLFOX				**£125,539**	**£190,211**
ICER (Cost / QALY) on efficieny frontier	**£76,337 (vs. PAN+FOLFOX)**	**£190,211 (vs. FOLFOX)**	**Reference**		

Key: BEV = bevacizumab; CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; PAN = panitumumab; ICER = incremental cost-effectiveness ratio; QALYs = quality-adjusted life years

Table 144. PenTAG cost-effectiveness results OPUS baseline RCT: Liver mets subgroup, FOLFOX network

				CET+FOLFOX vs.	PAN+FOLFOX vs.
	CET+FOLFOX	PAN+FOLFOX	FOLFOX	FOLFOX	FOLFOX
Life years (mean, undiscounted)	2.30	2.17	1.51	0.14	0.80
QALYs (mean, discounted)	1.57	1.47	1.06	0.10	0.51
Total costs (mean, discounted)	£83,096	£58,438	£34,866	£24,659	£48,230
ICER (Cost / QALY) vs. FOLFOX				**£94,423**	**£57,745**
ICER (Cost / QALY) on efficieny frontier	**£240,365 vs PAN+FOLFOX**	**£57,745 vs. FOLFOX**	**Reference**		

Key: BEV = bevacizumab; CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; PAN = panitumumab; ICER = incremental cost-effectiveness ratio; QALYs = quality-adjusted life years

6.2.3.5. Weekly administration of cetuximab

In all cases, the ICERs for cetuximab increase, because the monthly cost of administration of cetuximab increases substantially:

- CET+FOLFOX increases from £2,473 to £4,714.
- CET+FOLFIRI increases from £1,759 to £4,000.

For all patients, the ICER for:

- CET+FOLFOX vs. FOLFOX increases from £110,000 to £165,000 per QALY.
- CET+FOLFIRI vs. FOLFIRI increases from £149,000 to £227,000 per QALY.

For the liver mets subgroup, the ICER for:

- CET+FOLFOX vs. FOLFOX increases from £104,000 to £154,000 per QALY.
- CET+FOLFIRI vs. FOLFIRI increases from £107,000 to £158,000 per QALY.

6.2.3.6. FOLFOX6

In this scenario analysis, we use FOLFOX 6 in place of FOLFOX 4 as a comparator in the FOLFOX network. Only the drug acquisition and administration costs for CET+FOLFOX, PAN+FOLFOX and FOLFOX are changed - all effectiveness parameters are unchanged. In particular, we assume that the drug acqusiton costs are largely unchanged, and that the administration costs of all treatments fall substantially and by a similar amount, e.g. for FOLFOX, from £2,348 to £1,634 per month (Section 0, p314). This explains why all ICERs change very little:

- The ICER for all patients for CET+FOLFOX vs. FOLFOX decreases from £110,000 to £107,000 per QALY.
- The ICER for all patients for PAN+FOLFOX vs. FOLFOX decreases from £239,000 to £231,000 per QALY.
- The ICER for all patients for CET+FOLFIRI vs. FOLFIRI increases from £149,000 to £150,000 per QALY.

- The ICER for liver mets patients for CET+FOLFOX vs. FOLFOX increases from £104,000 to £100,000 per QALY.
- The ICER for liver mets patients for PAN+FOLFOX vs. FOLFOX increases from £90,000 to £88,000 per QALY.

- The ICER for all patients for CET+FOLFIRI vs. FOLFIRI remains at £107,000 per QALY.

Note that the ICERs for CET+FOLFIRI vs. FOLFIRI change very slightly due to the change in the costs acquisition and administration of 2nd-line FOLFOX and FOLFIRI.

6.2.3.7. List prices for FOLFOX and FOLFIRI

In our base case, we assumed eMit discounted prices for FOLFOX and FOLFIRI.

All ICERs increase when we assume list prices for FOLFOX and FOLFIRI, because the prices of these treatments now increase, and because we assume a longer treatment duration for CET+FOLFOX and PAN+FOLFOX than for FOLFOX and a longer treatment duration for CET+FOLFIRI than for FOLFIRI (Section 6.1.4.5, p284).

For all patients, the ICER:

- for CET+FOLFOX vs. FOLFOX increases from £110,000 to £122,000 per QALY.
- for PAN+FOLFOX vs. FOLFOX increases from £239,000 to £259,000 per QALY.
- for CET+FOLFIRI vs. FOLFIRI increases from £150,000 to £160,000 per QALY.

For liver mets subgroup, the ICER:

- for CET+FOLFOX vs. FOLFOX increases from £104,000 to £117,000 per QALY.
- for PAN+FOLFOX vs. FOLFOX increases from £90,000 to £92,000 per QALY.
- for CET+FOLFIRI vs. FOLFIRI increases from £107,000 to £119,000 per QALY.

6.2.3.8. Cost of drug acquisition based on cumulative dose data

In our base case, we estimated the cost of 1st-line drug acquisition as the product of the dose intensity, the cost per patient per unit time, and the expected treatment duration (Section 6.1.4.5, p284).

Here, we use a different, more complex, method to estimate the cost of 1st-line drug acquisition. This method is based on the mean cumulative doses (mg/m2 or mg/kg) of all constituent drugs from the RCTs (Section 6.1.4.5, p284).

The ICERs change only very slightly, as both method estimate similar drug acquisition costs (Figure 49, p322).

For all patients, the ICER:

- for CET+FOLFOX vs. FOLFOX decreases from £110,000 to £109,000 per QALY.
- for PAN+FOLFOX vs. FOLFOX decreases from £239,000 to £236,000 per QALY.
- for CET+FOLFIRI vs. FOLFIRI decreases from £150,000 to £144,000 per QALY.

For liver mets subgroup, the ICER:

- for CET+FOLFOX vs. FOLFOX remains at £104,000 per QALY.
- for PAN+FOLFOX vs. FOLFOX remains at £90,000 per QALY.
- for CET+FOLFIRI vs. FOLFIRI decreases from £107,000 to £103,000 per QALY.

6.2.4. Deterministic sensitivity analyses

Sensitivity analyses were chosen to demonstrate the drivers of cost-effectiveness by setting parameters to extreme values, e.g. price of cetuximab = price of panitumumab = £0. We do not suggest these parameter values as plausible alternatives to our base case values. We investigate the choice of values for key parameters when we compare our model with Merck Serono's model (Section 6.3, p394).

6.2.4.1. CET+FOLFOX vs. FOLFOX

One-way deterministic sensitivity analyses for CET+FOLFOX vs. FOLFOX are reported in Figure 63, which shows the impact on the deterministic ICER of various alterations in model parameters.

None of these sensitivity analyses brings the ICER below the £20,000 per QALY usual maximum accepted willingness-to-pay threshold for treatments that do not qualify for End of Life.

We see that cost-effectiveness is very sensitive to the resection rates. In particular, if we set the rate for CET+FOLFOX equal to that for FOLFOX, or if we set both rates equal to 0%, the ICER increases substantially.

Cost-effectiveness is sensitive to assumed PFS and OS post-resection. If we set these to zero, CET+FOLFOX is dominated by FOLFOX.

Cost-effectiveness is sensitive to estimate PFS for unresected patients. Setting PFS for CET+FOLFOX equal to that for FOLFOX, whilst holding the treatment duration for

CET+FOLFOX constant (as this is caped at PFS for unresected patients), the ICER increases markedly.

As expected, the ICER falls substantially, to £26,600, when we set the price of cetuximab to £0. However, even then, it lies above the £20,000 per QALY threshold. We discuss this further in Section 6.2.4.4, p392.

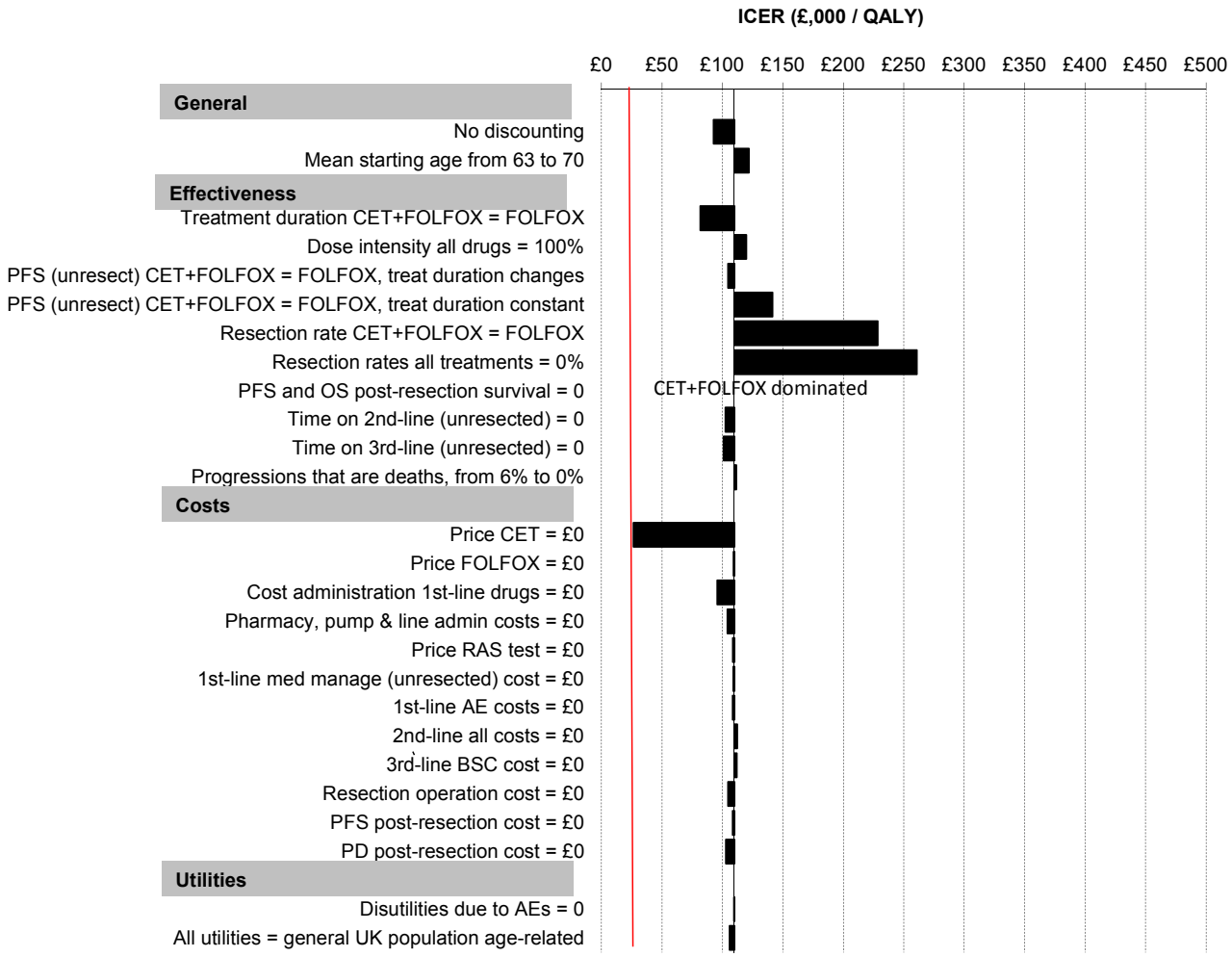
Cost-effectiveness is sensitive to the treatment durations. If we reduce the treatment duration for CET+FOLFOX from 8.7 to 7.0 months, the duration for FOLFOX, the ICER falls substantially.

Cost-effectiveness is quite sensitive to discounting and the cost of administration of 1st-line drugs. If we set these independently to zero, the ICER falls noticeably.

Cost-effectiveness is insensitive to the changes in the remaining parameters:

- Mean starting age (affecting only utilities and general UK mortality, not treatment effectiveness).
- Dose intensity.
- PFS (unresected).
- Time on 2nd-line treatment.
- Time on 3rd-line treatment.
- Proportion of progressions that are deaths, i.e. mortality from PFS, 2nd-line and 3rd-line.
- Price FOLFOX.
- Cost of pharmacy, pump & line admin costs.
- Price *RAS* test.
- 1st-line medical management (unresected) cost.
- 1st-line adverse event costs.
- 2nd-line costs.
- 3rd-line costs.
- Resection operation cost.
- PFS & PD post-resection cost.
- Disutilities due to AEs.
- Utilities: all set to general UK population age-related.

Figure 63 Sensitivity analyses: CET+FOLFOX vs FOLFOX



Key: AE = adverse event; BEV = bevacizumab; BSC = best supportive care; CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; OS = overall survival; PAN = panitumumab; PD = progressive disease; PFS = progression free survival

6.2.4.2. PAN+FOLFOX vs. FOLFOX

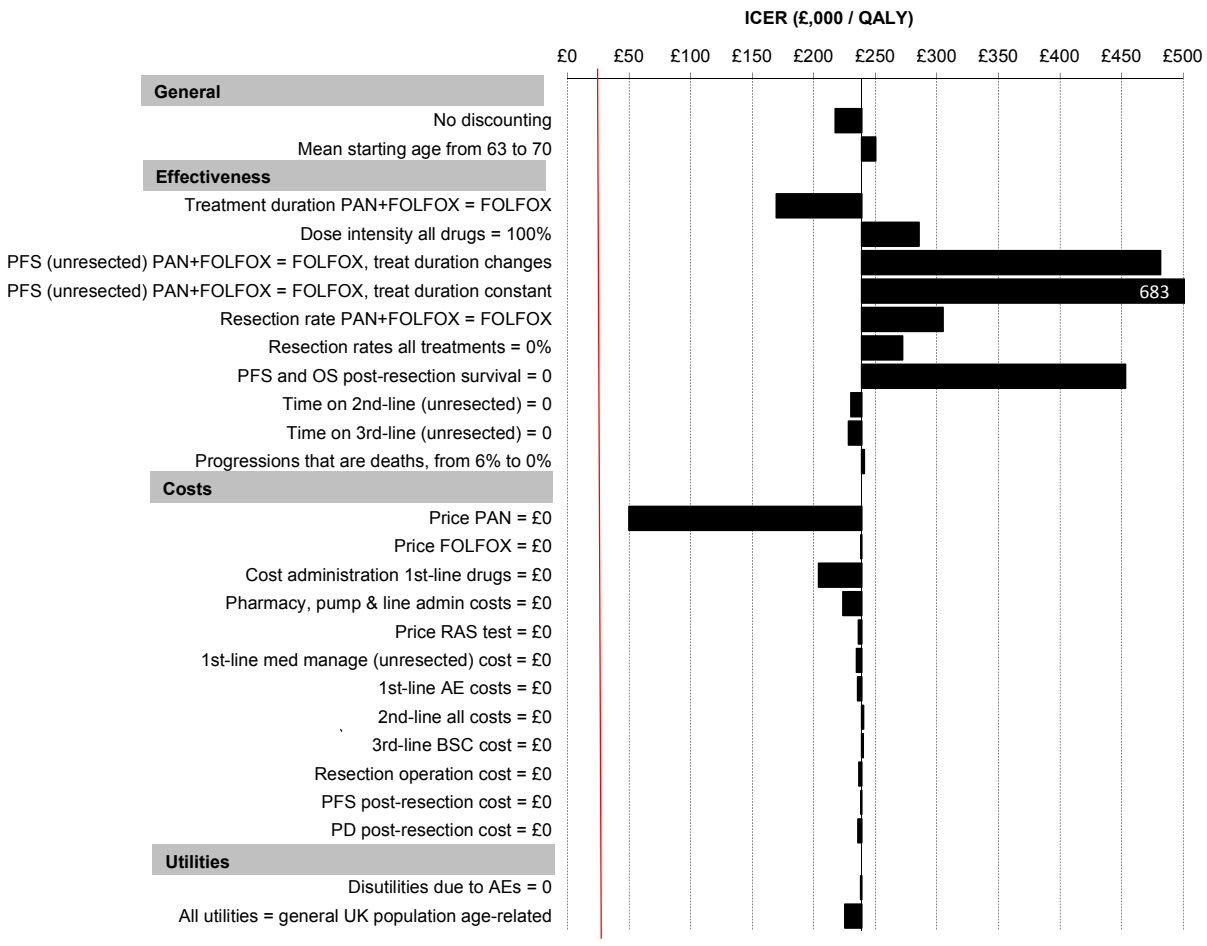
One-way deterministic sensitivity analyses for PAN+FOLFOX vs FOLFOX are reported in Figure 64. Again, none of these sensitivity analyses bring the ICER below usually accepted willingness-to-pay thresholds. There are many similarities with the CET+FOLFOX vs. FOLFOX sensitivity analyses. Here, we discuss the differences.

Cost-effectiveness is less sensitive to changes in resection rates, because the rate for PAN+FOLFOX is only slightly greater than for FOLFOX ([redacted] vs. [redacted]), whereas the estimate for CET+FOLFOX, at [redacted] is far greater.

Cost-effectiveness worsens substantially when PFS for unresected patients for PAN+FOLFOX is set equal to that for FOLFOX, whist holding the treatment duration for PAN+FOLFOX constant. At first sight it appears counterintuitive that the ICER changes proportionally far more than for the CET+FOLFOX vs. comparison above. However, this is explained because incremental QALYs in respect for PFS for unresected patients account for proportionally more of total incremental QALYs for PAN+FOLFOX vs. FOLFOX than for CET+FOLFOX vs. FOLFOX. This in turn is because we assume a far lower resection rate for PAN+FOLFOX than for CET+FOLFOX ([redacted]).

As expected, the ICER falls substantially, to £50,000, when we set the price of panitumumab to £0. However, even then, as CET+FOLFOX vs. FOLFOX, it lies above the £20,000 per QALY threshold. We discuss this further in Section 6.2.4.4, p392.

Figure 64 Sensitivity analyses: PAN+FOLFOX vs FOLFOX



Key: AE = adverse event; BEV = bevacizumab; BSC = best supportive care; CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; OS = overall survival; PAN = panitumumab; PD = progressive disease; PFS = progression free survival

6.2.4.3. CET+FOLFIRI vs. FOLFIRI

One-way deterministic sensitivity analyses for CET+FOLFIRI vs FOLFIRI are reported in Figure 65.

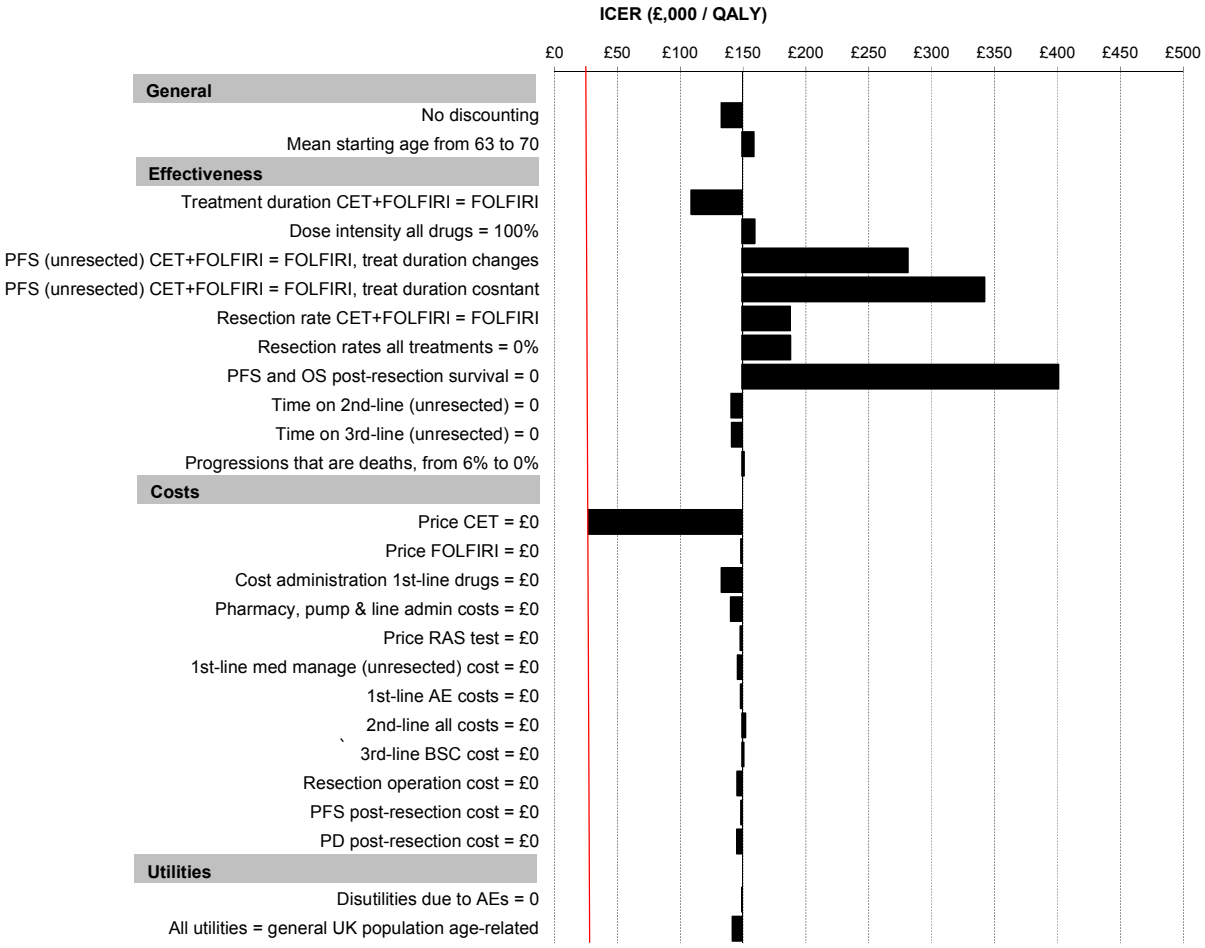
Again, there are many similarities with the CET+FOLFOX vs. FOLFOX sensitivity analyses. Here, we discuss the differences.

Cost-effectiveness is less sensitive to changes in resection rates, because the estimated rate for CET+FOLFIRI is only slightly greater than for FOLFIRI (7.3% vs. 2.1%), whereas the estimate for CET+FOLFOX, at [redacted], is far greater than for FOLFOX (10.7%).

Cost-effectiveness worsens substantially when PFS for unresected patients for CET+FOLFIRI is set equal to that for FOLFIRI, whist holding the treatment duration for CET+FOLFIRI constant. The explanation is the same as for PAN+FOLFOX.

As expected, the ICER falls substantially, to £27,000, when we set the price of cetuximab to £0. However, even then, as for CET+FOLFOX vs. FOLFOX, it lies above the £20,000 per QALY threshold. We discuss this further in Section 6.2.4.4, p392.

Figure 65 Sensitivity analyses: CET+FOLFIRI vs FOLFIRI



Key: AE = adverse event; BEV = bevacizumab; BSC = best supportive care; CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; OS = overall survival; PAN = panitumumab; PD = progressive disease; PFS = progression free survival

6.2.4.4. Not cost-effective at zero price

We find the following ICERs, when the prices of cetuximab and panitumumab are set to £0:

- CET+FOLFOX vs. FOLFOX: £27,000 per QALY.
- PAN+FOLFOX vs. FOLFOX: £50,000 per QALY.
- CET+FOLFIRI vs. FOLFIRI: £27,000 per QALY.

In other words, none of the combination treatments are cost-effective at the £20,000 per QALY threshold.

There are several precedent HTAs in this case.[162] For example, in the NICE assessment of pertuzumab for metastatic breast cancer, the drug was found to be poor value for money even when the price of pertuzumab was set to zero.[163] The reason was that pertuzumab was

given in combination with another drug, which was also the comparator treatment, and the additional PFS for the combination arm was accompanied by the costs of both pertuzumab and the comparator drug. In view of the fact that the technology was associated with substantial benefits in terms of both PFS and OS, the NICE's Guidance Executive decided not to issue the Final Appraisal Documents (FAD) pending further exploration.

The Decision Support Unit (DSU) was asked to explore the circumstances in which clinically effective technologies are not cost-effective even at a zero price.[162]

In the current HTA, we find a similar explanation for why all three combination treatments are not cost-effective. In particular, total costs of administration of the combination treatments far exceed those of either FOLFOX or FOLFIRI. This in turn is because we predict that the combination treatments are taken for longer than FOLFOX or FOLFIRI:

- CET+FOLFOX 8.7 vs. FOLFOX 7.0 months.
- PAN+FOLFOX 8.8 vs. FOLFOX 7.0 months.
- CET+FOLFIRI 10.7 months vs. FOLFIRI 8.3 months.

Setting the costs of administration of all 1st-line drugs to zero and the prices of cetuximab and panitumumab to zero yields the following ICERs:

- CET+FOLFOX vs. FOLFOX: £13,000 per QALY.
- PAN+FOLFOX vs. FOLFOX: £15,000 per QALY.
- CET+FOLFIRI vs. FOLFIRI: £11,000 per QALY.

Alternatively, setting the treatment durations of CET+FOLFOX and PAN+FOLFOX equal to that for FOLFOX and of CET+FOLFIRI equal to that for FOLFIRI and setting the prices of cetuximab and panitumumab to zero yields the following ICERs:

- CET+FOLFOX vs. FOLFOX: £15,000 per QALY.
- PAN+FOLFOX vs. FOLFOX: £20,000 per QALY.
- CET+FOLFIRI vs. FOLFIRI: £13,000 per QALY.

These ICERs are similar to the previous set of ICERs because we assume very similar costs of administration of combination treatments as for FOLFOX or FOLFIRI.

Interestingly, if CET+FOLFOX, PAN+FOLFOX and CET+FOLFIRI were oral treatments, and FOLFOX and FOLFIRI remained as intravenous treatments, then, keeping the list prices of cetuximab and panitumumab, the base case ICERs would fall substantially:

- CET+FOLFOX vs. FOLFOX: £110,000 to £50,000 per QALY.
- PAN+FOLFOX vs. FOLFOX: £239,000 to £97,000 per QALY.
- CET+FOLFIRI vs. FOLFIRI: £149,000 to £89,000 per QALY.

Furthermore, if cetuximab and panitumumab were free, all three combination treatments would then dominate FOLFOX or FOLFIRI.

This demonstrates that there is a strong economic incentive to design an effective treatment for mCRC that can be taken orally, as opposed to intravenously.

We further note that administration costs are "related" (as opposed to "unrelated") medical costs, and therefore should be included in the economic analysis, in accordance with the NICE Method Guide [112].

6.3. Comparison of results with Merck Serono submission

Merck Serono, but not Amgen, have performed a cost-effectiveness analysis. Therefore, in this section, we compare our cost-effectiveness results with those from Merck Serono. We have not critiqued the liver metastases model from Merck Serono, for the reasons given in Section 5.1.2.1, p191. Therefore, we confine the comparison of results to the "All patients" group, see Table 145 and Table 146.

First, there are many similarities between our model and Merck Serono's model. For example, we assume:

- The same overall model structure, Structure 1 (Section 6.1.3.2, p243), that is we both use only resection rates and PFS, but not OS, from the trials of 1st-line drugs. In scenario analyses, we both also model OS from the RCTs (Section 6.1.3.2, p243).
- Similar utilities (Section 6.1.4.11, p308).
- The same source for estimation of PFS and OS after resection (Section 6.1.4.3, p260).
- The same prices of cetuximab, panitumumab and bevacizumab (Section "Drug acquisition costs", p314). We assume far lower prices for FOLFOX and FOLFIRI, but this affects cost-effectiveness little.
- Similar times and treatment duration in 2nd-line FOLFOX and FOLFIRI (Section 6.1.4.8, p306, Section 5.1.2.2, p203, Section 6.1.3.2, p249).

Yet, there are several important differences between our models which act to yield very different estimates of cost-effectiveness of cetuximab.

Table 145. PenTAG vs. Merck Serono base case results: All patients, FOLFOX network

	PenTAG			Merck Serono		
	CET+FOLFOX	FOLFOX	CET+FOLFOX vs. FOLFOX	CET+FOLFOX	FOLFOX	CET+FOLFOX vs. FOLFOX
Life years (mean, undiscounted)						
1st-line drug (resected+unresected)	0.72	0.58	0.14	0.41	0.39	0.02
PFS non-resected	0.57	0.52	0.06	1.04	0.74	0.30
PFS post-resection	0.85	0.44	0.41	0.20	0.06	0.14
PFS 1st-line	1.42	0.96	0.46	1.24	0.80	0.44
2nd-line FOLFOX or FOLFIRI (non-resected)	0.26	0.29	-0.03	0.31	0.33	-0.02
3rd-line BSC (non-resected)	0.38	0.43	-0.05	0.67	0.70	-0.03
PD post-resection	0.35	0.18	0.17	0.09	0.03	0.06
Overall survival (mean)	**2.41**	**1.86**	**0.55**	**2.32**	**1.86**	**0.46**
QALYs (discounted)						
PFS non-resected	0.43	0.39	0.04	0.79	0.57	0.22
PFS post-resection	0.56	0.29	0.27	0.15	0.04	0.11
AEs 1st line	0.00	0.00	0.00	0.00	-0.01	0.01
PFS 1st-line	0.99	0.68	0.31	0.94	0.60	0.34
2nd-line FOLFOX or FOLFIRI (non-resected)	0.19	0.21	-0.02	0.23	0.25	-0.02
3rd-line BSC (non-resected)	0.23	0.26	-0.03	0.42	0.45	-0.03
PD post-resection	0.20	0.10	0.10	0.06	0.02	0.04
Total	**1.61**	**1.26**	**0.35**	**1.65**	**1.32**	**0.33**
Costs (discounted)						
RAS test	£400	£0	£400	£200	£200	£0
1st-line drug acqusition	£29,850	£461	£29,389	£22,113	£6,416	£15,697
1st-line drug administration	£20,906	£16,008	£4,898	£2,971	£2,803	£168
1st-line AEs	£1,512	£1,068	£444	£458	£469	-£11
1st-line medical management (unresected)	£3,029	£2,746	£283	£0	£0	£0
2nd-line (Drug acq, admin, medical management)	£6,540	£7,397	-£857	£7,289	£7,968	-£679

	PenTAG			Merck Serono		
	CET+FOLFOX	FOLFOX	CET+FOLFOX vs. FOLFOX	CET+FOLFOX	FOLFOX	CET+FOLFOX vs. FOLFOX
3rd-line BSC (non-resected)	£5,481	£6,199	-£718	£7,907	£8,398	-£491
Resection operation	£3,635	£1,884	£1,751	£196	£56	£140
PFS post-resection	£1,014	£526	£488	£0	£0	£0
PD post-resection	£4,895	£2,537	£2,358	£169	£97	£72
Total	£77,262	£38,825	£38,437	**£41,303**	**£26,407**	**£14,896**
ICER (Cost / QALY)			**£109,820**			**£46,503**

Key: AE = adverse event; BEV = bevacizumab; BSC = best supportive care; CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; OS = overall survival; PAN = panitumumab; PD = progressive disease; PFS = progression free survival

Table 146. PenTAG vs. Merck Serono base case results: All patients, FOLFIRI network

	PenTAG			Merck Serono		
	CET+FOLFIRI	FOLFIRI	CET+FOLFIRI vs. FOLFIRI	CET+FOLFIRI	FOLFIRI	CET+FOLFIRI vs. FOLFIRI
Life years (mean, undiscounted)						
1st-line drug (resected+unresected)	0.89	0.69	0.20	0.44	0.43	0.01
PFS non-resected	0.95	0.75	0.20	0.98	0.73	0.25
PFS post-resection	0.30	0.09	0.21	0.20	0.06	0.14
PFS 1st-line	1.25	0.83	0.42	1.18	0.79	0.39
2nd-line FOLFOX or FOLFIRI (non-resected)	0.39	0.41	-0.02	0.31	0.33	-0.02
3rd-line BSC (non-resected)	0.45	0.47	-0.03	0.68	0.71	-0.03
PD post-resection	0.12	0.04	0.09	0.09	0.03	0.06
Overall survival (mean)	2.21	1.75	0.46	2.27	1.86	0.41
QALYs (discounted)						
PFS non-resected	0.71	0.56	0.15	0.76	0.57	0.19
PFS post-resection	0.20	0.06	0.14	0.15	0.04	0.11
AEs 1st line	-0.00	-0.00	-0.00	-0.01	-0.01	0.00
PFS 1st-line	0.91	0.62	0.29	0.91	0.61	0.30
2nd-line FOLFOX or FOLFIRI (non-resected)	0.28	0.30	-0.02	0.23	0.25	-0.02
3rd-line BSC (non-resected)	0.27	0.29	-0.02	0.43	0.45	-0.02
PD post-resection	0.07	0.02	0.05	0.06	0.02	0.04
Total	**1.53**	**1.23**	**0.30**	**1.63**	**1.33**	**0.30**

	PenTAG			Merck Serono		
	CET+FOLFIRI	FOLFIRI	CET+FOLFIRI vs. FOLFIRI	CET+FOLFIRI	FOLFIRI	CET+FOLFIRI vs. FOLFIRI
Costs (discounted)						
RAS test	£400	£0	£400	£200	£200	£0
1st-line drug acqusition	£38,230	£952	£37,279	£23,176	£6,234	£16,942
1st-line drug administration	£18,249	£13,285	£4,964	£3,250	£3,148	£102
1st-line AEs	£821	£482	£339	£567	£418	£149
1st-line medical management (unresected)	£4,993	£3,948	£1,045	£0	£0	£0
2nd-line (Drug acq, admin, medical management)	£12,816	£13,655	-£838	£7,927	£8,492	-£565
3rd-line BSC (non-resected)	£6,316	£6,730	-£413	£8,087	£8,487	-£400
Resection operation	£1,284	£372	£912	£196	£56	£140
PFS post-resection	£358	£104	£254	£0	£0	£0
PD post-resection	£1,729	£501	£1,228	£189	£104	£85
Total	£85,197	£40,027	£45,170			
ICER (Cost / QALY)			**£149,091**			**£55,971**

Key: AE = adverse event; BEV = bevacizumab; BSC = best supportive care; CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; OS = overall survival; PAN = panitumumab; PD = progressive disease; PFS = progression free survival

The PenTAG ICERs in the two tables above:

- CET+FOLFOX vs. FOLFOX = £110,000 per QALY,
- CET+FOLFIRI vs. FOLFIRI = £149,000 per QALY.

are much higher than Merck ICERs:

- CET+FOLFOX vs. FOLFOX = £47,000 per QALY,
- CET+FOLFIRI vs. FOLFIRI = £55,000 per QALY.

In total, we have identified 8 items that differ between our model and Merck Serono's model which have an important impact on cost-effectiveness (

Figure 66, Table 147).

For the FOLFOX network, treatment duration and PFS for unresected patients are the most important items. The ICER from Merck Serono's model increases substantially when both are independently changed to our estimate, because we assume substantially greater treatment durations than Merck Serono (Section 6.1.4.5, p284), and because we assume substantially smaller differences between mean PFS for unresected patients for CET+FOLFOX vs. FOLFOX than do Merck Serono. This itself is because we estimate PFS for unresected patients by subtracting off PFS for resected patients from the PFS data for resected+unresected patients from the RCT, whereas Merck Serono do not (Section 6.1.4.4, p267).

For the FOLFIRI network, treatment duration is clearly the most important item. The ICER from Merck Serono's model increases substantially when durations are changed to our estimates. Unlike for the FOLFOX network, the ICER for CET+FOLFIRI vs. FOLFIRI increases only slightly when we use our estimates of PFS for unresected patients, even though we again subtract off PFS for resected patients from PFS for resected+unresected patients from the RCTs. This is because we estimate substantially lower resection rates for the FOLFIRI network compared to the FOLFOX network (Section 6.1.4.4, p267).

Above all, treatment duration is the most critical issue in the current HTA with regards to explaining the difference in cost-effectiveness as produced by our model and Merk Serono's model.

Similarly, in the NICE assessment for cetuximab, panitumumab and bevacizumab for subsequent lines of treatment for mCRC in 2011, in which we were the Assessment Group, the difference between Merck Serono and our assessment of cost-effectiveness of cetuximab was virtually entirely caused by the large difference in total mean costs of acquisition and administration of cetuximab. This itself was mostly due to the fact that we, the Assessment Group, estimated a far higher mean time on CET+BSC treatment than Merck Serono: we assumed 4.8 months, Merck Serono assumed 2.6 months. This led to a large difference between our estimated ICER for CET+BSC vs. BSC of £98,000 per QALY, and Merck Serono's estimate of £48,000 per QALY.[134] Similarly for the comparison of CET+irinotecan vs. BSC, we assumed a far longer treatment duration, 8.8 months than Merck, 4.4 months. The ICER for CET+irinotecan vs BSC from our analysis, £88,000 per QALY, was therefore much higher than Merck Serono's £44,000 per QALY.[134] The NICE committee accepted our estimates of treatment duration in preference to those of Merck Serono.[134]

We now turn to the two important differences under which the cost-effectiveness improves under our assumptions.

We assume a far longer duration in PFS and PD post-resection for than Merck Serono (Section 6.1.4.3, p260). This substantially improves the cost-effectiveness of CET+FOLFOX vs. FOLFOX and CET+FOLFIRI vs. FOLFIRI (Figure 66, Table 147).

For the FOLFOX network, we assume far higher resection rates than Merck Serono (Section 6.1.4.1, p251). This also substantially improves the cost-effectiveness of CET+FOLFOX vs. FOLFOX (Figure 66

Figure 66, Table 147). We assume the same resection rates as Merck Serono for CET+FOLFIRI and FOLFIRI.

We have already discussed that our treatment duration estimates for both the FOLFOX and FOLFIRI networks and our estimates of PFS for unresected patients for the FOLFOX network both substantially worsen cost-effectiveness. There are four other differences under which cost-effectiveness worsens in both networks, although only slightly, under our assumptions.

- We assume far higher unit costs of drug administration than Merck Serono (Section 6.1.4.12, p322). Our values yield slightly worse cost-effectiveness because we assume that patients are on treatment for longer on CET+FOLFOX than FOLFOX and for longer on CET+FOLFIRI than FOLFIRI (Figure 17, p224).
- We assume a far higher cost for resection operation than do Merck Serono (Section 0, p314). This acts to worsen cost-effectiveness, as the resection rate is higher for CET+FOLFOX than FOLFOX and for CET+FOLFIRI than FOLFIRI (6.1.4.1, p251).
- We assume a higher cost per month for treating patients in PD post-resection (Section 0, p314). This acts to worsen cost-effectiveness, again as the resection rate is higher for CET+FOLFOX than FOLFOX and for CET+FOLFIRI than FOLFIRI.
- We assume different costs of drug acqusiton per month (Section 6.1.4.12, p316This acts to worsen cost-effectiveness, as we assume a slightly higher cost of acquisition of cetuximab per month than Merck Serono (£3,859 vs. £3,478). Our estimates of the monthly cost of acquisition of FOLFOX and FOLFIRI are much lower than those of Merck Serono. However, cost-effectiveness is insensitive to these differences because they affect both arms similarly in treatment comparison pairs.
- We assume a higher monthly acquisition cost of cetuximab than Merck Serono because we assume a slightly larger body surface area, 1.85m^2 vs. 1.79m^2, and the dose of cetuximab depends on body surface area. In 2011, Merck Serono also estimated body surface area as 1.79m^2 and we estimated 1.85m^2. [120] Merck Serono do not now give the source of their estimate. Further, as we explained then, we prefer our estimate as it is taken from a database of people receiving palliative chemotherapy for CRC (Sacco and colleagues (2010), Appendix S3, http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0008933), with 66% males, 34% females, the typical sex mix in the RCTs for mCRC.

When we amend Merck Serono's model for all eight changes simultaneously, the resulting ICERs are similar the base case ICERs in our model (Table 147,Figure 66).

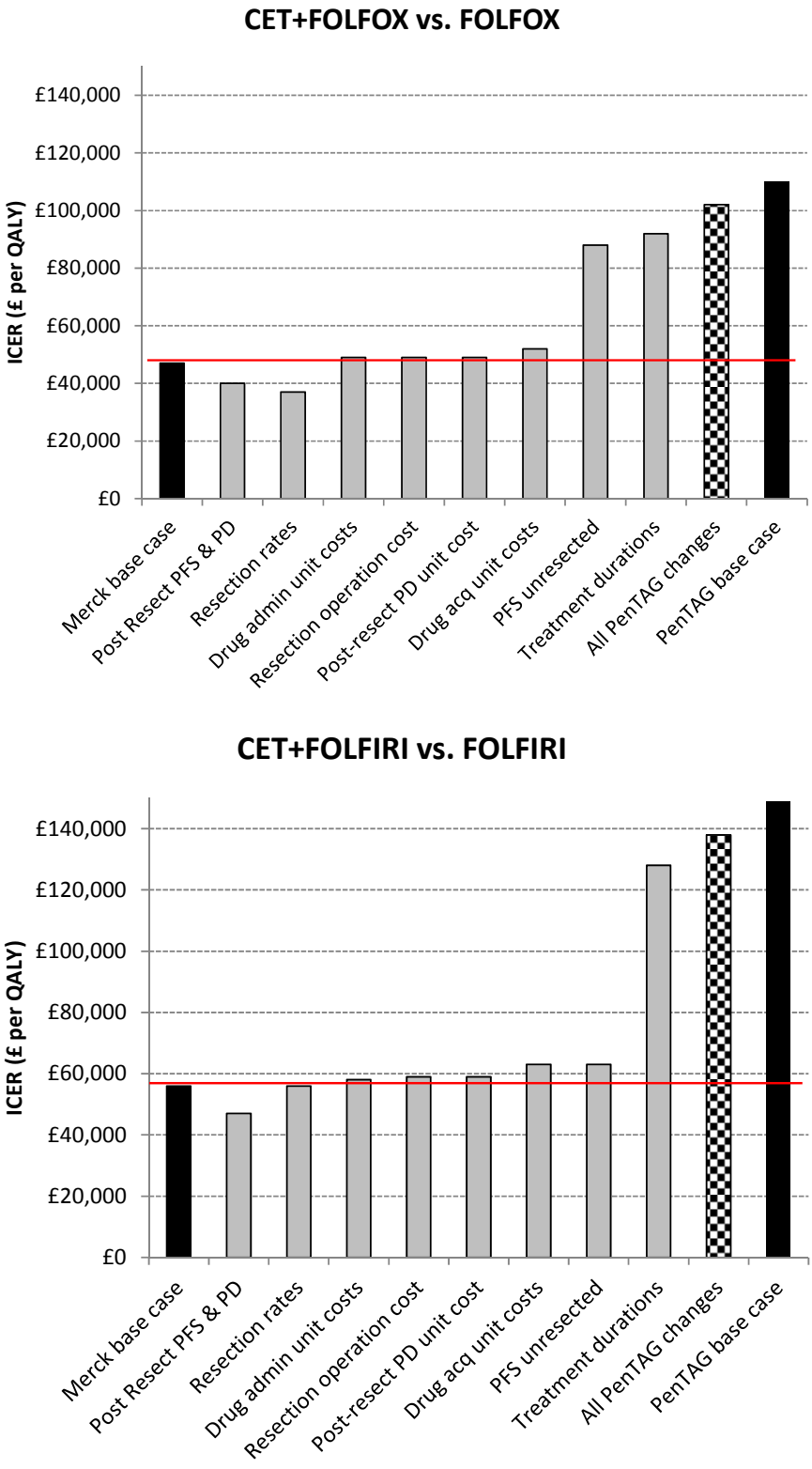
Of course, this does not in itself prove that there are no important differences between Merck's amended model and our model. However, we find no remaining large differences in incremental mean life years, QALYs and costs between Merck's amended model and our model (Figure 67, Figure 68). We conclude that there are no further differences between our model and Merck Serono's model that have a large impact on cost-effectiveness.

Table 147. ICERs from Merck Serono model with PenTAG changes applied independently or in combination

	CET+FOLFOX vs. FOLFOX	CET+FOLFIRI vs. FOLFIRI
Merck base case	£47,000	£56,000
PenTAG post pesection PFS & PD	£40,000	£47,000
PenTAG resection rates	£37,000	£56,000
PenTAG units costs of drug administration	£49,000	£58,000
PenTAG resection operation cost	£49,000	£59,000
PenTAG post-resection PD unit cost	£49,000	£59,000
PenTAG drug acqusition cost per month	£52,000	£63,000
PenTAG PFS unresected patients	£88,000	£63,000
PenTAG treatment durations	£92,000	£128,000
All 8 PenTAG changes	£102,000	£138,000
PenTAG base case	£110,000	£149,000

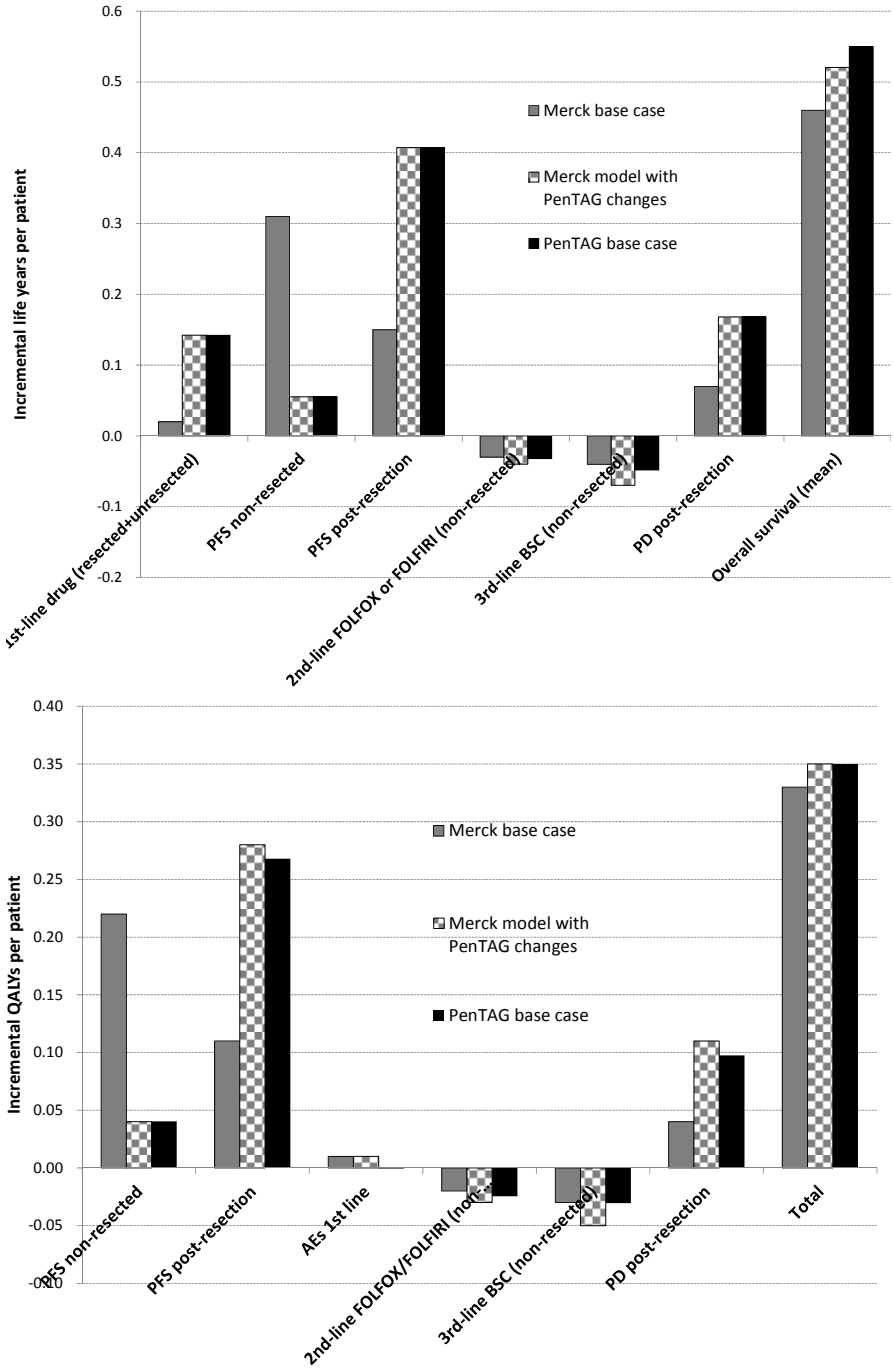
Key: PD = progressive disease; PFS = progression free survival

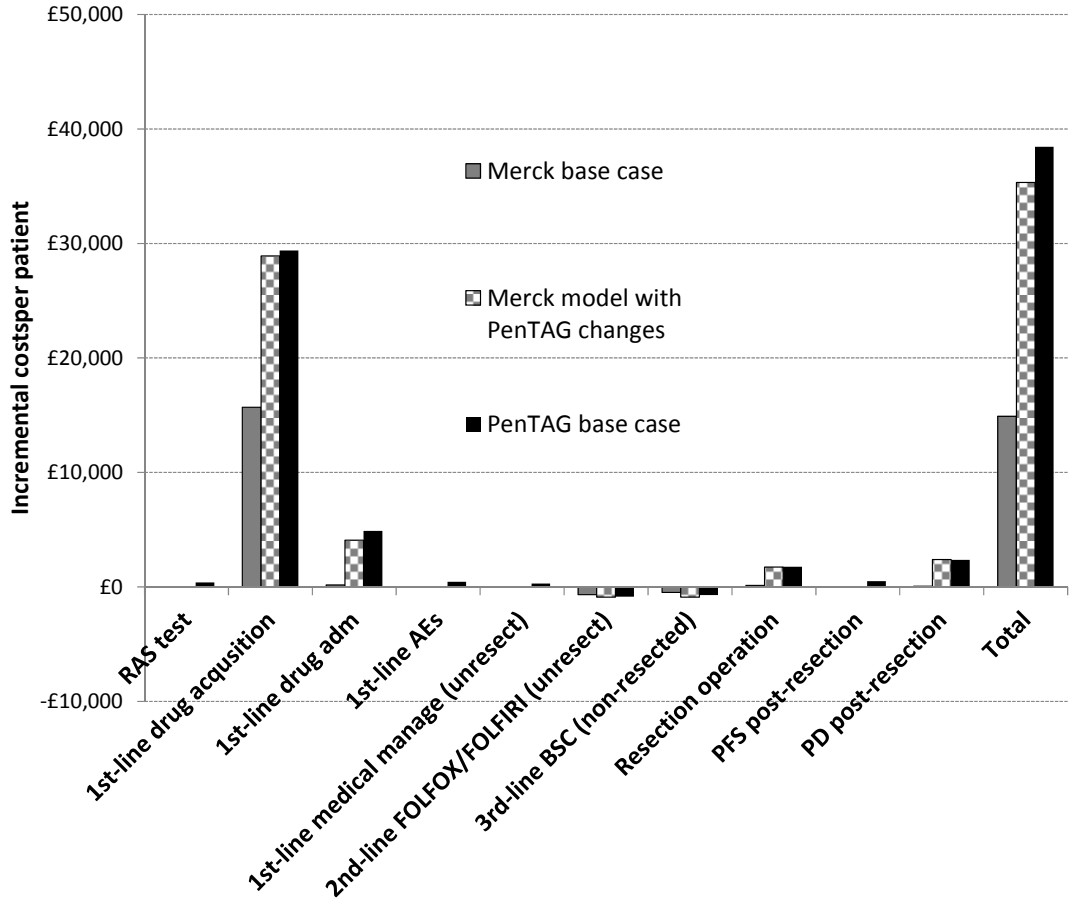
Figure 66. ICERs from Merck Serono model with PenTAG changes applied independently or in combination



Key: CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; PD = progressive disease; PFS = progression free survival

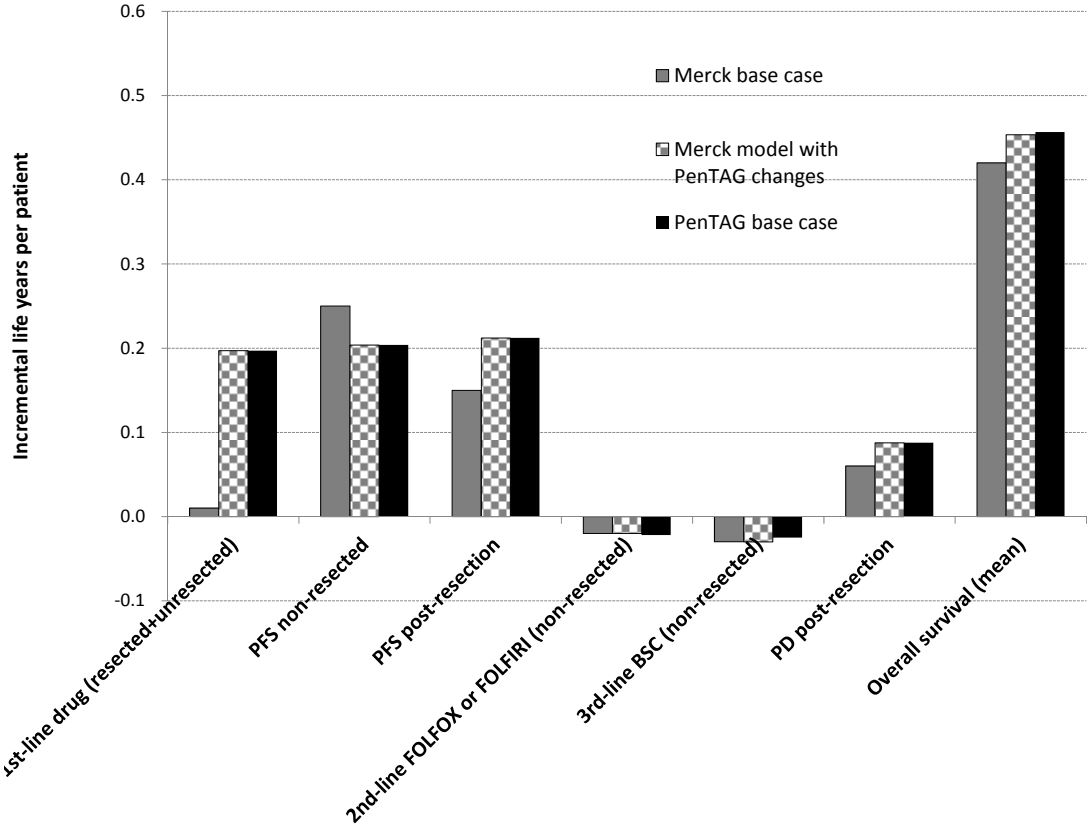
Figure 67 Incremental life years, QALYs and costs from Merck Serono model, Merck Serono model with all 8 PenTAG changes and from PenTAG model: FOLFOX network

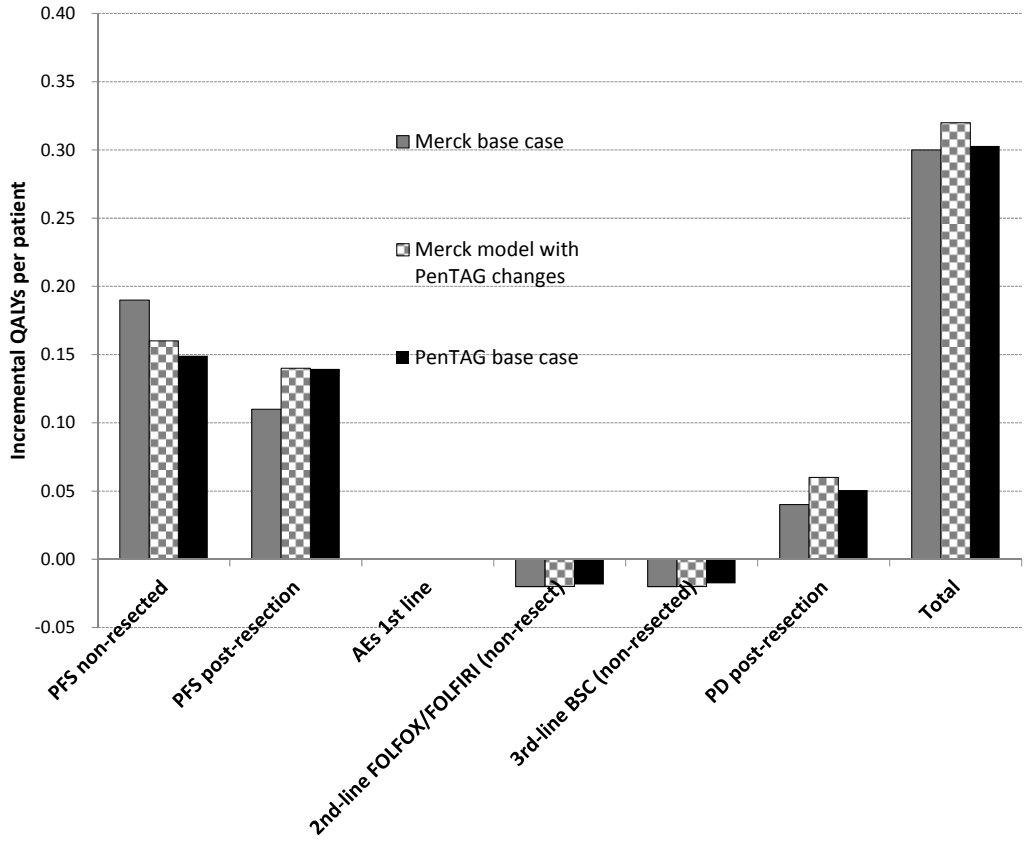


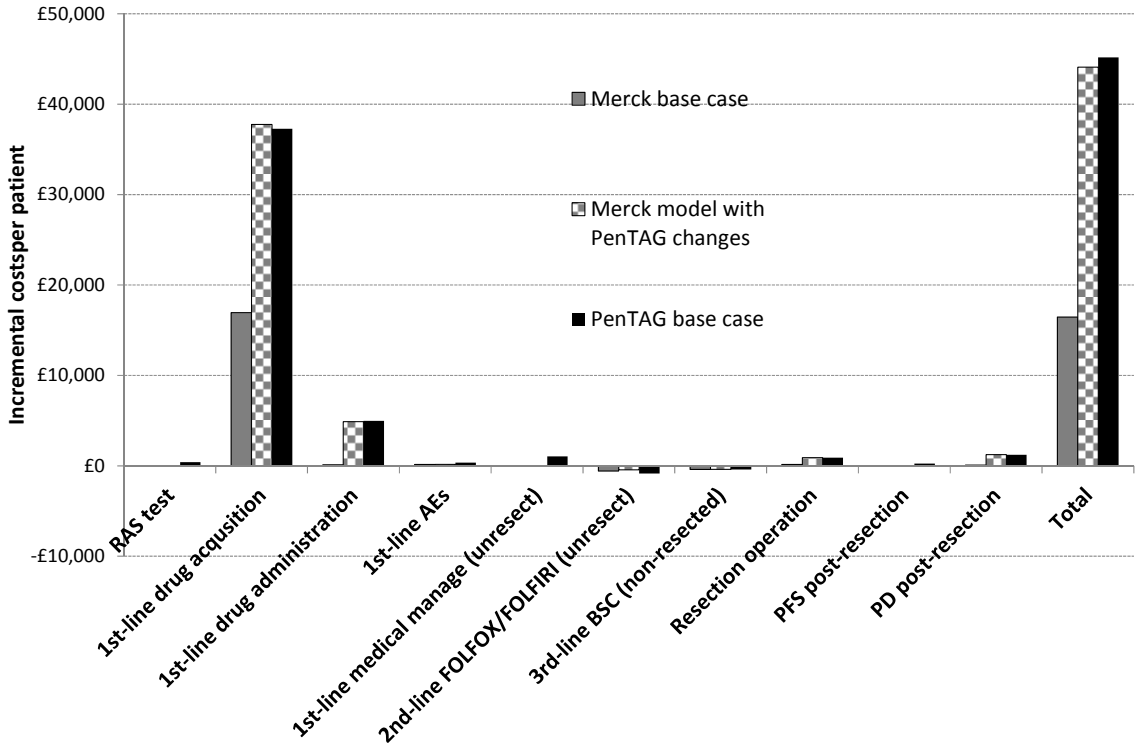


Key: AE = adverse event; BSC = best supportive care; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; PD = progressive disease; PFS = progression free survival

Figure 68 Incremental life years, QALYs and costs from Merck Serono model, Merck Serono model with all 8 PenTAG changes and from PenTAG model: FOLFIRI network







Key: AE = adverse event; BSC = best supportive care; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; PD = progressive disease; PFS = progression free survival

6.4. End of Life criteria

In Table 148 and Table 149 below we assess cetuximab and panitumumab against NICE's End of Life (EoL) criteria. Merck Serono consider that cetuximab qualifies for EoL (Merck Serono submission, p7).

One of the criteria in the tables below is that the total patient population for all licensed indications in England should be less than 7,000. We understand that CRC is the only indication for panitumumab. In NICE TA242 from 2011, for cetuximab, bevacizumab and panitumumab for the treatment of mCRC after first-line chemotherapy, the NICE committee concluded:

"*The Committee was aware from the manufacturer's data that approximately 7600 people have EGFR-positive, KRAS wild-type metastatic colorectal cancer in England and Wales….*

However, the Committee noted that cetuximab has a marketing authorisation for people with any stage of EGFR-positive KRAS wild-type metastatic colorectal cancer, and also for people

with locally advanced and recurrent and/or metastatic head and neck cancer, which has previously been estimated to be a population of about 3000 (NICE technology appraisal guidance 172 [TA172]) ….

The Committee therefore concluded that the true size of the cumulative population covered by the marketing authorisation for cetuximab was likely to be over 10,000 patients and was not small, and that cetuximab does not meet all of the criteria for a life-extending, end-of-life treatment".

Based on these figures, and:

- 83% of KRAS WT patients are also RAS WT (Section 5.1.2.2, p192)
- England comprises 95% of the population of England & Wales[164]

We calculate the total population for cetuximab relevant for End of Life as

7,600 x 83% x 95% + 3,000 x 95% = 8,807.

This exceeds that End of Life criterion of 7,000.

In the current HTA, Merck Serono estimate 5,623 patients have *RAS* WT mCRC in the UK (p18, 70 Merck Serono report). Based on this figure, and that England comprises 84% of the population of the UK,[164] we calculate the total population for cetuximab relevant for End of Life as:

4,728 x 84% + 3,000 x 95% = 7,567.

This again exceeds the End of Life criterion of 7,000.

Next, we find we estimate the size of the patient population relevant for cetuximab for EoL using figures in our report. We find there were 34,044 new cases of colorectal cancer in England in 2011 (Table 2, p.64), and "almost" 50% of people with colorectal cancer develop metastases (Section 1.1.2.1, p63). Given that about 50% of patients are *RAS* WT (Section 1.1.2.1, p63), this gives 8,511 estimated new cases of mCRC in England in 2011. Combining this with our estimated 2,838 head and neck cancer cases, gives 11,349. This again exceeds the End of Life criterion of 7,000.

We now turn to panitumumab. We have three estimates for the relevant population of *RAS* WT mCRC as 5,968, 4,728 and 8,511. The first two estimates are below the 7,000 threshold, but the third estimate exceeds the threshold.

On balance, we believe that cetuximab definitely does not meet the End of Life criteria (Table 148), and that panitumumab probably does not meet the criteria (Table 148, Table 149).

Table 148. Assessment of cetuximab against NICE's EoL criteria

EoL criteria	CET+FOLFOX vs. FOLFOX	CET+FOLFIRI vs. FOLFIRI	Meets criterion ?
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	**22.3 months on FOLFOX based on our model (Section 6.2.1.1, p343). However, 26.7 months based on PRIME RCT**	**21.0 months on FOLFIRI based on our model (Section 6.2.1.1, p343). However, 24.9 months based on CRYSTAL RCT**	**Unsure**
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Mean 6.6 months extension to life expectancy based on our model (Section 6.2.1.1, p343). However, only 0.5 months based on OPUS RCT alone.	Mean 5.5 months extension to life expectancy based on our model (Section 6.2.1.1, p343). However, 8.8 months based on CRYSTAL RCT alone.	Unsure
The technology is licensed or otherwise indicated, for small patient populations normally not exceeding a cumulative total of 7000 for all licensed indications in England.	Estimated as 8,807 or 7,567		Fails, as both estimates > 7,000
The estimates of the extension to life are robust and can be shown or reasonably inferred from either progression-free survival or overall survival (taking account of trials in which crossover has occurred and been accounted for in the effectiveness review)	There is plenty of uncertainty concerning the extensions to life, as noted in this table. For example, based soley on the OPUS RCT, extension to life is expected as only 0.5 months.		On balance, we think that extension to life are not robust
The assumptions used in the reference case economic modelling are plausible, objective and robust.	Life expectancy is subject to many assumptions. However, our model has been carefully constructed using the best available evidence.		Unsure
Overall qualification for End of Life			**Does not meet EoL, as patient population too large, and extension to life are not robust.** **Also unsure of whether life expectancy on FOLFOX and FOLFIRI are less than 24 months, and whether extension to life is greater than 3**

EoL criteria	CET+FOLFOX vs. FOLFOX	CET+FOLFIRI vs. FOLFIRI	Meets criterion ?
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	**22.3 months on FOLFOX based on our model (Section 6.2.1.1, p343). However, 26.7 months based on PRIME RCT**	**21.0 months on FOLFIRI based on our model (Section 6.2.1.1, p343). However, 24.9 months based on CRYSTAL RCT**	**Unsure**
			months.

Key: CET = cetuximab; EoL = end of life; mCRC = metastatic colorectal cancer;

Table 149. Assessment of panitumumab against NICE's EoL criteria

EoL criteria	PAN+FOLFOX vs. FOLFOX	Meets criterion ?
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	**22.3 months on FOLFOX based on our model (Section 6.2.1.1, p343). However, 26.7 months based on PRIME RCT**	**unsure**
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Mean 2.6 months extension to life based on our model (Section 6.2.1.1, p343). However, 5.7 months based on PRIME RCT alone.	unsure
The technology is licensed or otherwise indicated, for small patient populations normally not exceeding a cumulative total of 7000 for all licensed indications in England.	Estimated as 5,968, 4,728 or 8,511	Unsure, as borderline
The estimates of the extension to life are robust and can be shown or reasonably inferred from either progression-free survival or overall survival (taking account of trials in which crossover has occurred and been accounted for in the effectiveness review)	There is plenty of uncertainty concerning the extensions to life, as noted in this table. For example, based on our model, extension to life is expected as only 2.6 months.	On balance, we think that extension to life are not robust
The assumptions used in the reference case economic modelling are plausible, objective and robust.	Life expectancy is subject to many assumptions. However, our model has been carefully constructed using the best available evidence.	Unsure
Overall qualification for End of Life		**Probably does not meet EoL as extension to life is not robust.** **Also unsure of whether patient population is sufficiently small, whether life expectancy on FOLFIRI is less than 24 months, and whether extension to life is greater than 3 months.**

Key: CET = cetuximab; EoL = end of life; mCRC = metastatic colorectal cancer;

7. Comparison of current MTA with previous STAs

Although this MTA seeks to update previous guidance from two single technology appraisals (STAs) (TA 176 and TA 240),[11, 12] there are some important differences between the scope for the previous STA reviews and this current MTA review (ID794). The main difference is in the patient population. The current scope specifies people with *RAS* WT mCRC, whereas previous STA reviews specified EGFR-expressing mCRC (TA 176) [11], and *KRAS* WT mCRC (TA 240)[12]. A summary of all the differences between the scopes for the reviews alongside a summary of how the product licences have changed is provided in Section 1.3.2, p.77.

7.1. STA, TA 176 (2009) (cetuximab) vs MTA, ID794 (2015)

7.1.1. Assessment of clinical effectiveness

The appraisal of cetuximab in combination with chemotherapy for the treatment of mCRC (NICE single technology appraisal 176) included two studies: CRYSTAL (Van Cutsem *et al.*, 2009),[33] and OPUS (Bokemeyer *et al.,* 2009).[32] Comparatively, three studies were included in this MTA review. Although two of the studies were included in the last health technology assessment (HTA) (CRYSTAL and OPUS), only data from the subgroup of people evaluated as *RAS* WT from these trials are relevant to the NICE scope of this review as set out in the final scope from NICE.[52, 75] One additional study was identified by the Assessment Group's searches for this MTA Assessment (FIRE-3 [Heinemann *et al.,* 2014])[37].

Results from the previous STA of cetuximab (TA 176) are summarised and compared with the results for the current MTA in 150. Comparisons can only be made between TA 176 and the current assessment MTA for the OPUS and CRYSTAL trials, since FIRE-3 is new to the current appraisal. In line with research developments, effect estimates (where reported) for OS, PFS and ORR were either similar or point estimates were slightly decreased in the *RAS* WT subgroup compared with the *KRAS* WT population suggesting reduced risk of progression or death in the *RAS* WT population.However, these results should be interpreted with caution, as the analyses are based on subgroup analyses and as sample sizes (for some studies) were small reducing the power of the studies to show statistical significance. No comparison could be made in respect of HRQoL data as the current HTA did not identify any data for HRQoL among the *RAS* WT population. Variability in the reporting of AEs between TA 176 and the current MTA; e.g. summary AEs, AEs in ≥5% of participants; or AEs >5% difference between treatment arms made it difficult to draw comparison where data

were reported. Although, both neutropenia and skin related reactions are stated in both reports. However, all results are subject to uncertainty (see limitations Section 8.3, p.431).

Table 150. Comparison of clinical effectiveness: TA176 (2009) vs Assessment Group MTA (2015)

Trial	Outcome		STA: TA176 (2009) EGFR-expressing mCRC[a]	STA: TA176 (2009) *KRAS* WT mCRC	MTA: ID794 (2009) *RAS* WT mCRC
OPUS	N		336	134	87
CET+ FOLFOX4 vs. FOLFOX4	PFS		NR	HR 0.570 (95% CI: 0.358, 0.907)	HR 0.53 (95% CI: 0.27, 1.04)
	OS		NR	NR	HR 0.94 (95% CI: 0.56, 1.56)
	ORR		45.6 % vs 36.0 %[b]	60.7% (95% CI: 47.3, 72.9) vs 37.0% (95% CI: 26.0, 49.1) * [b]	58% (95% CI: 41, 74) vs 29 % (95%CI: 17, 43)[b]
	Resection Rate		NR	11.5% vs 4.1% [b]	NR
	HRQoL		NR	NR	NR
	Safety	Any Grade 3/4 events	CiC	NR	79% vs 63% [b]
		Most commonly reported Grade 3/4 AE [c]	NR	NR	Leukopenia, neutropenia, paraesthesia, rash, any skin reactions and acne-like rash skin reaction
CRYSTAL	N		1198	348	367
CET+ FOLFIRI vs FOLFIRI	PFS		HR 0.85 (95% CI: 0.726, 0.998)	HR 0.684 (95% CI: 0.501, 0.934)	HR 0.56 (95% CI:0.41, 0.76)
	OS		HR 0.93 (95% CI: 0.81, 1.07)	HR 0.84 (95% CI: 0.64, 1.11)	HR 0.69 (95% CI: 0.54, 0.88)
	ORR		45.6% vs 36.0%[d]	59.3% (95% CI: 51.6, 66.7) vs 43.2% (95% CI: 35.8, 58.9) ** [d]	66% (95% CI: 59, 73) vs 39 % (95%CI: 32, 46)[d]
	Resection Rate		NR	3.5% vs 2.3% [d]	OR 3.11 (95% CI: 2.03, 4.78)
	HRQoL	EORTC QLQ-C30; EQ-5D	NR	Statistically significant differences between the two treatment groups in favour of the FOLFIRI-only group were reported [e]	NR
	Safety	Any Grade 3/4 events	CiC	NR	80.9% vs 58.2% [d]

Trial	Outcome		STA: TA176 (2009) EGFR-expressing mCRC[a]	STA: TA176 (2009) *KRAS* WT mCRC	MTA: ID794 (2009) *RAS* WT mCRC
		Most commonly reported Grade 3/4 AE [c]	NR	Neutropenia, constipation, dyspepsia, dyspnoea, dysgeusia, injection site reaction, erythema, hypotension, hypertrichosis and cheilitis[f]	Deep vein thrombosis, dermatitis acneiform, diarrhoea, fatigue, leukopenia, neutropenia, rash, any skin reactions and acne-like rash skin reaction
FIRE-3	N		NA	NA	342
CET+FOLFIRI vs BEV+ FOLFIRI	PFS		NA	NA	HR 0.93 (95% CI: 0.74, 1.17)
	OS		NA	NA	HR 0.7 (95% CI: 0.53, 0.92)
	ORR		NA	NA	65.5% (95% CI: 58, 73) vs 60 % (95%CI: 52, 67)[g]
	Resection Rate		NA	NA	NR
	HRQoL		NA	NA	NR
	Safety	Any Grade 3/4 events	NA	NA	69% vs 67.3%
		Most commonly reported Grade 3/4 AE [c]	NA	NA	Acneiform/exanthema, desquamation, diarrhoea, haematotoxicity, hepatotoxicity, hypertension, hypokalemia, infection, nail changes/paronychia, nausea, pain, skin reactions, thromboembolic events and thrombosis (any)

Key: AE = adverse events; CET = cetuximab; CI = confidence interval; BEV = bevacizumab; EGFR = epidermal growth factor receptor; EORTC QLQ-C30 = Euopean Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire C30; EQ-5D = measure of health outcome by EuroQol; FAS = full analysis set; FOLFIRI = fluorouracil + folinic acid + irinotecan; FOLFOX = fluorouracil + folinic acid oxaliplatin; HR = hazard ratio; HRQoL = health-related quality of life; KRAS = Kirsten rat sarcoma; mCRC = metastatic colorectal cancer; MTA = multiple technology appraisal; NA = not applicable; NR = not recorded; ORR = overall response rate; OS = overall survival; PFS = progression free survival;; STA = single technology appraisal; TA = technology appraisal; WT = wild type; * p=0.011; ** p=0.0028

Notes: a Full analysis set, people with EGFR-expressing mCRC; b CET + FOLFOX4 vs FOLFOX4; c most commonly reported grade 3/4 adverse events where at least one arm had incidences of ≥5%; d CET +FOLFIRI vs FOLFIRI; e QLQ-C30 measurement reported, EQ-5D measure also used however, only 37 patients completed evaluable baseline ED-5D questionnaires; therefore no formal statistical analyses wer eperformed ; f a difference of 5% or more between the groups; g CET + FOLFIRI vs BEV + FOLFIRI

Sources: NICE, Technology appraisal guidance 176, August 2009; Evidence review group report (TA176) commissioned by the NHS R&D Programme on behalf of NICE: Cetuximab for the first-line treatment of metastatic colorectal cancer

7.1.2. Assessment of cost-effectiveness

As TA176 was a single technology assessment, only economic evidence submitted by the manufacturer (Merck Serono) was available, critiqued by an evidence review group (ERG). In this assessment economic evidence is available both from the manufacturer and from us, the Assessment Group.

No studies were identified in the cost-effectiveness review of TA176. In the recent submission, Merck Serono identified 15 studies which included an economic analysis of cetuximab, two of which were specific to the *RAS* WT population and also identified by the assessment group.[9, 104] Our review excluded the remaining 13 papers on the basis of population and the two includes were both abstracts with associated posters. This indicates that some economic evidence is currently available compared to when TA176 was completed, but still not enough to adequately answer the decision problem.

Both TA176 and this assessment included a *de novo* economic analysis submitted by Merck Serono. As Merck Serono have therefore updated their model from TA176 we do not go into detail over the model from TA176 but present a brief comparison with the Merck Serono submission (2015) and the PenTAG economic analysis. Furthermore, both Merck Serono models appear very similar in structure. In particular the health states remain generally similar: 3 lines of treatment, plus post-resection states. Modelling of first line was based on trial evidence and subsequent lines and post resection informed by literature[3, 113, 114] for both models. In both TA176 and the 2015 submission, Merck Serono presented the cost-effectivness results as head to head comparisons based on trials. The main differences between TA176 and the cost-effectiveness analyses in this assemssent are described in Table 151.

Table 151. Comparison of model characteristics: TA176, Merck Serono submission (2015), PenTAG (2015)

	TA176		Merck Serono 2015		PenTAG	
Programme used to build model	TreeAge Pro 2006/2007 software (TreeAge Software Inc., Williamstown, USA)		Excel		Excel	
Population	EGFR expressing, KRAS WT mCRC. Also require:good performance status, suitable for irinotecan or oxilaplatin chemotherapy, initially unresectable liver metastases		RAS WT mCRC, unresectable metastases at any site		RAS WT mCRC, unresectable metastases at any site	
Intervention(s)	CET+FOLFOX	CET+FOLFIRI	CET+FOLFOX	CET+FOLFIRI	CET+FOLFOX, PAN+FOLFOX	CET+FOLFIRI
Comparators including scenario analysis	FOLFOX	FOLFIRI	FOLFOX, XELOX	FOLFIRI, BEV+FOLFIRI	FOLFOX, BEV+FOLFOX, XELOX	FOLFIRI, BEV+FOLFIRI
Time horizon	Lifetime (mean 23 years in model)		10 years		lifetime (30 years)	
Cycle length	1 week		1 month		1 month	

Key: AE = adverse events; CET = cetuximab; BEV = bevacizumab; FOLFIRI = fluorouracil + folinic acid + irinotecan; FOLFOX = fluorouracil + folinic acid+ oxaliplatin; ICER = incremental cost-effectiveness ratio; LY= life year; QALY = quality adjusted life year; STA = single technology appraisal; TA = technology appraisal; WT = wild type

Given the similarities in the models and the absence of the TA176 executable model, we present only summary results and narratively compare results. We focus on the comparisons with FOLFOX and FOLFIRI as we have done in our comparison with Merck Serono's submission (2015).

Table 152. Base case cost-effectiveness results, comparison of TA176, Merck Serono submission 2015 and PenTAG economic model 2015

	TA176			Merck Serono submission 2015			PenTAG 2015		
	FOLFOX	**CET+FOLFOX**	**CET+FOLFOX vs. FOLFOX**	**FOLFOX**	**CET+FOLFOX**	**CET+FOLFOX vs. FOLFOX**	**FOLFOX**	**CET+FOLFOX**	**CET+FOLFOX vs. FOLFOX**
LYs	1.48	1.89	0.41	1.81	2.22	0.41	1.86	2.41	0.55
Costs (discounted)	£21,842	£42,084	£20,242	£26,408	£41,301	£14,894	£38,825	£77,262	£38,437
QALYs (discoutned)	1.09	1.41	0.32	1.32	1.64	0.32	1.26	1.61	0.35
ICERs £/QALY			**£63,245**			**£46,503**			**£109,820**
	FOLFIRI	**CET+FOLFIRI**	**CET+FOLFIRI vs. FOLFIRI**	**FOLFIRI**	**CET+FOLFIRI**	**CET+FOLFIRI vs. FOLFIRI**	**FOLFIRI**	**CET+FOLFIRI**	**CET+FOLFIRI vs. FOLFIRI**
LYs	1.92	2.28	0.36	1.81	2.19	0.38	1.75	2.21	0.46
Costs (discounted)	£26,103	£45,576	£19,473	£27,139	£43,592	£16,453	£40,027	£85,197	£45,170
QALYs (discounted)	1.43	1.71	0.28	1.32	1.61	0.29	1.23	1.53	0.3
ICERs £/QALY			**£69,287**			**£55,971**			**£149,091**

Key: AE = adverse events; CET = cetuximab; BEV = bevacizumab; FOLFIRI = fluorouracil + folinic acid + irinotecan; FOLFOX = fluorouracil + folinic acid+ oxaliplatin; ICER = incremental cost-effectiveness ratio; LY= life year; QALY = quality adjusted life year; STA = single technology appraisal; TA = technology appraisal; WT = wild type
Notes: Discounted LYs reported for TA176 and Merck Serono 2015, undiscounted LYs reported for PenTAG model (2015).

The LYs and QALYs for FOLFOX network appear to have increased from TA176 to the Merck Serono submission (2015), but the LYs and QALYs have decreased for the FOLFIRI networks. These differences are presumably driven by the changes in population and time horizon. However, the incremental LYs and QALYs of these two analyses have remained virtually identical.

The main differences between the models are the costs. The costs in TA176 and the 2015 Merck Serono submission are broadly similar; however, small changes to the costs are amplified in the cost-effectiveness results to give quite different incremental cost-effectiveness ratios (ICERs), with reductions in the ICERs between £13,000 and £17,000 per QALY depending upon the network. These reductions result from higher costs for the FOLFOX/FOLFIRI arms in the most recent Merck Serono submission compared to TA176 and lower costs for the CET+FOLFOX/FOLFIRI arms. The PenTAG model reports the highest costs of all.

Table 153 gives the disaggregated costs for the three analyses. The reporting of these costs varies across analyses, but overall the results suggest that the differences in costs between PenTAG model and TA176 results are driven by the same differences as those between the PenTAG model and the Merck Serono submission: costs relating to the first line treatment, including cheaper acquisition costs for FOLFOX and FOLFIRI (eMIT rather than BNF), more expensive drug admin costs for FOLFOX and FOLFIRI and longer treatment durations. Neither the original submission for TA176 nor the ERG report give disaggregated life years, so the implication of treatment duration cannot be confirmed, but as this is a driver of the cost of administration (and is a major driver of the differences between the Merck Serono and PenTAG models in this assessemt), this seems plausible. Other discrepancies in costs result from higher costs in 2nd and 3rd line treatment; cost of resection;and the addition of medical management costs to first line.

Table 153. Disaggregated costs from TA176, Merck Serono submission (2015), PenTAG (2015)

	TA176			Merck Serono			PenTAG		
	CET+FOLFOX	**FOLFOX**	**CET+FOLFOX - FOLFOX**	**CET+FOLFOX**	**FOLFOX**	**CET+FOLFOX - FOLFOX**	**CET+FOLFOX**	**FOLFOX**	**CET+FOLFOX - FOLFOX**
Costs (discounted)									
(K)RAS test	462	-	462	200	200	-	400	-	400
1st-line drug acqusition	27,332	9,021	18,311	22,113	6,416	15,697	29,850	461	29,389
1st-line drug administration	3,551	3,202	349	2,971	2,803	168	20,906	16,008	4,898
1st-line AEs	820	467	353	458	469	-11	1,512	1,068	444
1st-line med manage (unresected)							3,029	2,746	283
Total 1st line	**32,165**	**12,690**	**19,475**	**25,741**	**9,888**	**15,853**	**55,697**	**20,283**	**35,414**
2nd-line FOLFOX/FOLFIRI acq (non-resected)							379	429	-50
2nd-line FOLFOX/FOLFIRI admin (non-resected)							4,836	5,469	-634
2nd-line FOLFOX or FOLFIRI medical management (non-resected)							1,325	1,499	-174
Total 2nd line (non-resected)	**4,856**	**5,190**	**-334**	**7,289**	**7,968**	**-679**	**6,540**	**7,397**	**-857**
3rd-line BSC (non-resected)	2,708	2,863	-155	7,907	8,398	-491	5,481	6,199	-718
Resection operation	351	164	187	196	56	139	3,635	1,884	1,751

	TA176			Merck Serono			PenTAG		
PFS post-resection							1,014	526	488
PD post-resection				169	97	71	4,895	2,537	2,358
Total	**42,084**	**21,842**	**20,242**	**41,302**	**26,408**	**14,894**	**77,262**	**38,825**	**38,437**
	CET+FOLFIRI	**FOLFIRI**	**CET+FOLFIRI-FOLFIRI**	**CET+FOLFIRI**	**FOLFIRI**	**CET+FOLFIRI -FOLFIRI**	**CET+FOLFIRI**	**FOLFIRI**	**CET+FOLFIRI -FOLFIRI**
Costs (discounted)									
(K)RAS test	462	0	462	200	200	0	400	-	400
1st-line drug acqusition	27,465	9,887	17,578	23,176	6,234	16,942	38,230	952	37,279
1st-line drug administration	3,467	3,438	29	3,250	3,148	102	18,249	3,285	4,964
1st-line AEs	1,147	491	656	567	418	150	821	482	339
1st-line med manage (unresected)							4,993	3,948	1,045
Total 1st line line	**32,541**	**13,816**	**18,725**	**27,193**	**10,000**	**17,193**	**62,692**	**18,666**	**44,027**
2nd-line FOLFOX/FOLFIRI acq (non-resected)							382	407	-25
2nd-line FOLFOX/FOLFIRI admin (non-resected)							10,443	11,126	-683
2nd-line FOLFOX or FOLFIRI medical management (non-resected)							1,991	2,122	-130
Total 2nd line (non-resected)	**6,088**	**6,833**	**-745**	**7,927**	**8,492**	**-565**	**12,816**	**13,655**	**-838**
3rd-line BSC (non-resected)	2,962	3,288	-326	8,087	8,487	-400	6,316	6,730	-413

	TA176			Merck Serono			PenTAG		
Resection operation	511	278	233	196	56	139	1,284	372	912
PFS post-resection				-	-	-	358	104	254
PD post-resection				189	104	85	1,729	501	1,228
Total	**45,576**	**26,103**	**19,473**	**43,592**	**27,139**	**16,453**	**85,197**	**40,027**	**45,170**

Key: AE = adverse events; CET = cetuximab; BEV = bevacizumab; FOLFIRI = fluorouracil + folinic acid + irinotecan; FOLFOX = fluorouracil + folinic acid+ oxaliplatin; ICER = incremental cost-effectiveness ratio; LY= life year; QALY = quality adjusted life year; STA = single technology appraisal; TA = technology appraisal; WT = wild type

7.2. STA, TA 240 (2013) (panitumumab) vs MTA, ID794 (2015)

The appraisal of panitumumab in combination with chemotherapy for the treatment of mCRC (NICE technology appraisal 240) was ended because no evidence submission was received from the manufacturer or sponsor of the technology.[12] Therefore NICE was unable to make a recommendation about the use in the NHS of panitumumab in combination with chemotherapy for the treatment of mCRC. [12]

Comparatively, two studies of clinical effectiveness were identified in the current MTA review; PEAK [38] and PRIME,[53] both of which contained data from the *RAS* WT population.

Similarly, no economic evidence was submitted in TA240, but two published cost-effectiveness studies[102, 103] have been identified in the current MTA review as well as an independent economic assessment of panitumumab in combination with FOLFOX versus relevant comparators. No *de novo* economic analysi was submitted by Amgen for either assessment.

8. Discussion

8.1. Statement of principle findings

8.1.1. Aim

The remit of this report was to review and update the evidence used to inform the current NICE guidance (TA176 and TA240) on clinical and cost effectiveness of two epidermal growth factor receptors (EGFR) inhibitors: cetuximab and panitumumab for the treatment of first-line metastatic colorectal cancer (mCRC).

In this section we will not re-state the previous evidence, but assume that the discussion will be read in the context of the previous evidence summaries and the decisions which flowed from them. The conclusions will focus on implications of the new effectiveness and cost-effectiveness evidence for service provision.

8.1.2. Clinical effectiveness systematic review

Of 2,811 titles/abstracts screened, five *RAS* WT subgroup analyses from randomised controlled trials (RCTs) met the inclusion criteria for the clinical effectiveness systematic review. Given the differences in the eligible population between this current MTA review and the previous STA reviews, the evidence included in this submission was all identified by the Assessment Group's searches. Three subgroup analyses provided data for the effectiveness of cetuximab and two provided evidence for the effectiveness of panitumumab. Efficacy and safety outcomes were tabulated and discussed in a narrative review. All included studies provided evidence for the NMA where data were available for the outcome of interest. It was not possible to construct a complete network. Two discrete networks were generated, one evaluating FOLFOX-containing chemotherapy regimens and the second comparing FOLFIRI-containing chemotherapy regimens.

The risk of bias was generally similar between studies with respect to randomisation, allocation concealment, blinding, outcome reporting and loss to follow-up. The main consideration with respect to quality is that currently available data for both cetuximab and panitumumab are taken only from a subgroup of the ITT population. To set this in context, the rationale for this is based on tumour biology; research has shown a treatment interaction for *RAS* and EGFR inhibitors. In response to this, the EMA have recently revised the licensed indication for these products based on the subgroup data from the ITT populations of the trials. Currently the only available data demonstrating efficacy in people with *RAS* WT

mCRC is from subgroup analyses; the Assessment Group did not identify any RCT evidence where there was an ITT *RAS* WT population.

Despite this the limitations associated with the interpretation of subgroup data still apply. Given the use of subgroup data all comparisons were made without protection by stratification/randomisation. Instead, allocation to subgroups was based on *RAS* analysis of tumour samples from the *KRAS* WT Exon 2 trial participants; the *RAS* ascertainment rate was 61% minimising the potential for significant ascertainment bias (missing data largely resulted from unavailable tumour samples or inconclusive *RAS* test results). In addition, although imbalances in baseline characteristics between groups were expected, no major differences were observed mimimising the potential for selection bias. Due to the retrospective nature of the *RAS* analysis there were a low number of samples available for analysis reducing the power of the studies to show statistical significance.

8.1.2.1. Summary of benefits and risks

Individuals respond differently to some drugs.[67, 68] Genotype is an important determinant of both the response to treatment and the susceptibility to adverse reactions for a wide range of drugs;[69, 70] for example, response to EGFR inhibitors has been shown to be dependent on gene expression in colon cancer; studies have demonstrated a treatment interaction between *RAS* status and the effectiveness of EGFR inhibitors.[71-73] In line with research developments evaluating the negative impact of *RAS* mutations on the effectiveness of EGFR inhibitors, approval for the use of anti-EGFR antibodies has now been limited to people with mCRC with ***RAS*** WT tumours. Tumour samples from trial populations supporting the original licensed indications were evaluated retrospectively for *RAS* status. Importantly, therefore, data supporting this recent licence change and this NICE assessment not from the ITT trial population for any of the included studies but from a subgroup of people contained within the original RCTs and results are therefore subject to uncertainty. However, no RCTs with an ITT population by *RAS* WT status were identified.

Previously, NICE has appraised cetuximab (TA176) for the treatment of people with EGFR-expressing mCRC; in line with the licensed indication at the time. Although two of the identified cetuximab trials were included in the last appraisal, only data from the subgroup of people evaluated as *RAS* WT from those trials are relevant to the scope of this review as set out in the final scope from NICE (see Section 3.2.1, p88). The appraisal of panitumumab in combination with chemotherapy for the treatment of mCRC (NICE technology appraisal 240) was ended because no evidence submission was received from the manufacturer or sponsor of the technology. As such, NICE was unable to make recommendations relating to the use

of panitumumab in the NHS. All data included in this update review for both cetuximab and panitumumab have been identified by the PenTAG searches.

Cetuximab

Two trials provided evidence for the effectiveness of cetuximab in combination with chemotherapy (FOLFOX or FOLFIRI) compared with chemotherapy alone (FOLFOX or FOLFIRI). Evidence consistently suggests a treatment effect in favour of the addition of cetuximab to chemotherapy (FOLFOX or FOLFIRI) compared with chemotherapy alone (FOLFOX or FOLFIRI) for the outcomes of interest (PFS, OS, ORR, and complete resection rate). Overall, clinical safety was consistent with results for *KRAS* WT population in all the trials. The most common events were diarrhoea, haematotoxiticity, neutropenia and skin reactions.

One trial provided evidence for the effectiveness of cetuximab in combination with chemotherapy (FOLFIRI) compared with bevacizumab with chemotherapy (FOLFIRI). The proportion of people who achieved an objective response was similar between the cetuximab plus FOLFIRI and bevacizumab plus FOLFIRI arms. However, the association with longer overall survival suggests a benefit with cetuximab plus FOLFIRI (HR 0.70, 95% CI 0.53, 0.92).

Panitumumab

One trial provided evidence for the effectiveness of panitumumab in combination with chemotherapy (FOLFOX) compared with chemotherapy alone (FOLFOX). No evidence was identified comparing panitumumab plus FOLFIRI with FOLFIRI. Evidence consistently suggests a treatment effect in favour of the addition of cetuximab to FOLFOX compared with FOLFOX. Overall, clinical safety was consistent with results for *KRAS* WT population in all the trials. The most common events were diarrhoea, haematotoxiticity, neutropenia and skin reactions.

One trial provided evidence for the effectiveness of panitumumab in combination with chemotherapy (mFOLFOX6) compared with bevacizumab with chemotherapy (mFOLFOX6). The proportion of people who achieved an ORR were similar between the cetuximab plus FOLFIRI and bevacizumab plus FOLFIRI. For PFS the addition of panitumumab to mFOLFOX6 was associated with a 35% reduction in risk of progression compared with bevacizumab plus FOLFOX. In addition, a trend towards OS benefit with panitumumab plus FOLFOX was observed (HR 0.63; 95% CI 0.39, 1.02).

Network meta-analysis: FOLFOX network

There is no evidence to suggest that cetuximab plus FOLFOX is any more effective than FOLFOX, bevacizumab plus FOLFOX or panitumumab plus FOLFOX to increase the time to death or the time to progression or death.

Direct evidence suggests that panitumumab plus FOLFOX is more effective at increasing time to progression or death than FOLFOX and bevacizumab plus FOLFOX. Panitumumab plus FOLFOX is also estimated to be more effective at increasing time to death than FOLFOX.

There is limited evidence to suggest that cetuximab plus FOLFOX is more effective at improving overall response rate than panitumumab plus FOLFOX.

There is little evidence than cetuximab plus FOLFOX is associated with fewer AEs than panitumumab plus FOLFOX, however some of these analyses are limited by the small number of events recorded in the treatment arms.

Network meta-analysis: FOLFIRI network

Evidence suggests that cetuximab plus FOLFIRI and bevacizumab plus FOLFIRI are more effective than FOLFIRI at increasing time to progression or death, and objective response rate.

Direct evidence suggests that cetuximab plus FOLFIRI is more effective than FOLFIRI and bevacizumab plus FOLFIRI at increasing the time to death.

8.2. Cost effectiveness

8.2.1. Published economic evaluations

Of 1,979 search results, four studies were identified and reviewed: 1 full paper, 2 conference abstracts with accompanying posters and 1 conference abstract whose accompanying poster could not be retrieved.

One study was UK based, but only compared cetuximab plus chemotherapy to chemotherapy alone. [9] This study was only reported as a conference abstract and poster. As this study was related to a SMC appraisal, additional details were sought from the SMC report.[10]

The full paper compared panitumumab in combination with FOLFOX to bevacizumab in combination with FOLFOX and was conducted in France, so the results were of limited generalizability to the UK. One other conference abstract also looked at this comparison for the Greek healthcare perspective.

The final abstract with accompanying poster looked only at the *RAS* WT population as a scenario analysis and was conducted from a healthcare perspective.

As the majority of includes were not full papers, the quality of reporting was limited. One important note from the quality assessment was that all studies had at least one author employed by a manufacturer.

No studies completely answered the decision problem and as such highlights the need for a *de novo* cost-effectiveness model.

8.2.2. Critique of company submission

Amgen did not submit an economic evaluation.

Merck Serono conducted a cost-effectiveness review and two executable models: one for the overall *RAS* WT population and one for a liver limited disease subgroup. As Merck Serono sent us their liver subgroup model very late in the review period, and as we were unable to reconcile the subgroup analysis with the overall population model, we did not critique this subgroup analysis.

The model was generally poorly reported: there were several discrepancies between the parameters in the report and model and the sources of some parameters could not be identified. A second iteration of the overall population model and report were received to solve discrepancies between the results reported in the first submission.

Merck Serono estimate the ICERs for the two key comparisons:

- CET+FOLFOX vs. FOLFOX: £47,000 per QALY,
- CET+FOLFIRI vs. FOLFIRI: £56,000 per QALY.

The model itself contained some minor errors and inconsistencies, but no major wiring errors were identified.

We are satisfied with the general structure of and the great majority of parameter values in Merck Serono's model. However we disagree with several of their parameters, which are discussed in elsewhere.

8.2.3. Independent economic assessment

The ICERs for anti-EGFR therapy versus chemotherapy alone were all over £100,000 per QALY gained. In the FOLFOX network, PAN+FOLFOX was extended dominated by CET+FOLFOX versus FOLFOX as it had less QALY gains compared to FOLFOX and higher ICERs. In general, there was a survival gain for patients on anti-EGFR therapy, ranging from 0.22-0.55 undiscounted life years gained in the FOLFOX arm and 0.46 in the FOLFIRI arm. This benefit remained in the QALY results: 0.15-0.35 QALYs gained in the FOLFOX network, 0.30 QALYs gained in the FOLFIRI network for anti-EGFR therapies. However the additional costs were substantial: >£35,000 for all anti-EGFR therapies compared to FOLFOX or FOLFIRI.

The probabilistic sensitivity analyses (PSA) suggests that anti-EGFR tharapies are unlikely to be cost-effective at a willingness to pay threshold of £30,000 per QALY gained: in the FOLFOX network, FOLFOX was 78% likely to be most cost-effective, CET+FOLFOX 22% likely to be most cost-effective and PAN+FOLFOX 0% likely to be most cost-effective. Similarly in the FOLOFIRI network FOLFIRI was 100% likely to be most cost-effective at a willingness to pay threshold of £30,000 per QALY gained and CET+FOLFIRI 0% likely to be most cost-effective.

Deterministic sensitivity analyses show that cost-effectiveness is very sensitive to: resection rates; PFS and OS post resction; PFS for unresected patients; and treatment duration. Cost-effectiveness is quite sensitive to discounting and cost of administering 1st-line therapies. Other parameters had little impact on cost effectiveness.

Subgroup analyses show that for patients with liver metastases only, the ICERs for anti-EGFR therapies versus chemotherapy alone do improve: £90,000-£104,000 per QALY gained in the FOLFOX network; £107,000 per QALY gained in the FOLFIRI network. However, due to the higher uncertainty of this subgroup (effectiveness estiamtes based on smaller sample sizes) the PSAs demonstrate that anti-EGFR therapy is unlikely to be cost-effective at a willingness to pay threshold of £30,000 per QALY gained: in the FOLFOX network, FOLFOX was 98% likely to be most cost-effective and in the FOLFIRI network FOLFIRI was100% likely to be most cost-effective.

When bevacizumab is considered as a comparator it is found to be not cost-effective at a willingness to pay threshold of £30,000 per QALY: BEV+FOLFOX is dominated by FOLFOX (fewer QALYS and higher costs) and the ICER for CET+FOLFIRI versus BEV+FOLFIRI is much higher than the ICER for CET+FOLFIRI versus FOLFIRI.

When XELOX is considered as a comparator the ICERs for PAN+FOLFOX and CET+FOLFOX increase, due to the lower cost of XELOX compared to FOLFOX.

8.2.4. Comparison of the PenTAG and Merck Serono cost-effectiveness results

- Merck Serono report ICERs of £47,000 per QALY for CET+FOLFOX vs. FOLFOX and £55,000 per QALY for CET+FOLFIRI vs. FOLFIRI, much lower than our estimates.

We identified eight major differences between the PenTAG and Merck Serono cost-effectiveness models that had significant impact on cost-effectiveness results:

- post pesection PFS & PD
- resection rates
- units costs of drug administration
- resection operation cost
- post-resection PD unit cost
- drug acqusition cost per month
- PFS unresected patients
- treatment durations

Accounting for these differences increased Merck Serono's ICERs to £102,000 per QALY gained for CET+FOLFOX vs. FOLFOX and £138,000 per QALY gained for CET+FOLFIRI vs. FOLFIRI,very similar to our base case ICERs. Therefore we are confident we have identified the most important differences between the two models.

8.3. Strengths and limitations

8.3.1. Systematic review of effectiveness studies

A strength of this report is that a systematic review of RCTs for cetuximab and panitumumab in people with mCRC with *RAS* WT tumours, and an NMA has been conducted to evaluate relative efficacy. In the absence of head-to-head RCTs, an NMA was conducted to assess relative efficacy of panitumumab in combination with chemotherapy and cetuximab in combination with chemotherapy.

However, there are some important sources of uncertainty that may impact on the conclusions:

- Currently available data providing evidence for the effectiveness of cetuximab and panitumumab are taken from subgroups of protocol-defined trial populations.The rationale is based on developments in tumour biology research (i.e. research demonstrating an interaction between *RAS* and EGFR inhibitors [specifically the negative implications of *RAS* mutations on the effectiveness of EGFR inhibitors],. Of note, the recent change to the licensed indication by the EMA is based on these same subgroup data and treatmenteffect estimates for both cetuximab and panitumumab are in the expected direction and consistent across trial populations.
- Given the use of subgroup data all comparisons were made without protection by stratification/randomization. Instead, allocation to subgroups was based on re-evaluating tumour samples from the *KRAS* WT Exon 2 population for *RAS* status. While this minimised the potential for ascertainment bias, there were missing data for some of the trials (either the tumour was not evaluable for *RAS* status or the results were inconclusive). No significant imbalances between the trial populations were observed minimising the potential for selection bias. Of note, none of the included subgroup analyses reported the results a test for treatment interaction. Due to the retrospective nature of the *RAS* analysis, for some studies, there were a low number of samples available for analysis reducing the power of the studies to show statistical significance.
- No evidence was identified to estimate the effectiveness panitumumab plus FOLFIRI (licence approved for panitumumab plus FOLFIRI for the first-line treatment of adults with *RAS* WT metastatic colorectal cancer [mCRC] in Q1 2015).
- The subgroup analyses all contributed to network meta-analyses. However, it was not possible to construct a complete network and two discrete networks were generated, one evaluating FOLFOX-containing chemotherapy regimens and the second comparing FOLFIRI-containing chemotherapy regimens. It was therefore not possible to make comparison between FOLFOX-containing and FOLFIRI-containing regimens.
- Although there were some reporting omissions in the publications of the subgroup analyses were able to confirm estimates via other sources; e.g. European Medicines Agency (EMA) reports or via the companies.
- The timepoint at which ORR was measured was unclear for all of the trials. Objective response rate was measured at either six- or eight-week intervals (according to methods reported in the primary publications). Given this uncertainty results reported for the *RAS* WT population for this outcome should be treated with caution.

- Sample sizes for the subgroup of the *RAS* WT population with liver metastases at baseline were small increasing the level of uncertainty; lack of statistical power and limitations with precision and validity. However, subgroup data provide the only available evidence. In addition, the effect estimates are consistent across all studies. Although one trial – FIRE-3 (which contributed evidence for the effectiveness of cetuximab plus FOLFIRI compared with FOLFIRI) – did not report data for all outcomes for this subgroup.
- None of the included publications reported HRQoL estimates for the *RAS* WT population.
- We are aware of other cetuximab trials; for example, COIN and NORDIC VII for which there is currently no *RAS* WT subgroup data available.
- Data comparing cetuximab plus FOLFOX with panitumumab plus FOLFOX was only available from the network meta-analysis. The limitations regarding the data for the *RAS* WT population (above), also apply to the network meta-analysis, and as such results should also be interpreted with caution.
- The extent to which the results of included trials can provide a reasonable basis for generalization to the UK NHS population of people with mCRC is unclear.

8.3.2. Economic model (PenTAG)

8.3.2.1. Strengths

The PenTAG model is an independent model that is not sponsored by any of the manufacturers producing cetuximab or panitumumab. We have used up to date clinical effectiveness data, which has been acquired through a systemic review of current evidence.

Drug acquisition costs were obtained, where possible, from the Commercial Medicines Unit eMit database, which reflects the true cost to the NHS of acquiring these drugs as it includes discounts obtained by hospital pharmacies. For other drugs the list price from the BNF was used, as in the NICE reference case.

We have explored areas of uncertainty through scenario analyses and sensitivity analyses (deterministic and probabilistic). Though ICERs for anti-EGFR therapies versus chemotherapy alone altered quite substantially in some analyses, none fell below a willingness to pay threshold of £20,000 per QALY gained.

8.3.2.2. Limitations

The model is subject to the same limitations as the clinical effectiveness review as these are carried through into the modelling

Similarly, where data were unavailable directly from trials, assumptions were made to inform the model leading to areas of uncertainty discussed below.

8.3.2.3. Areas of uncertainty

The evidence is poor for the accuracy and effectiveness of companion diagnostic for testing *RAS* mutation status, with no trials presenting effectiveness of treatment following diagnosis for all tests used in clinical practice. We have assumed, due to the the evidence available, that this is the same in practice as it is in the trials, but this may not be true and would likely result in lower effectiveness for cetuximab and panitumumab in practice.

Some drugs (those for which the BNF price was used) may be obtained at lower costs than assumed due to locally procured discounts. There is no indication what these costs might be, and the NICE reference case has been adhered to in this regard.

It has been assumed that fortnightly cetuximab will be used in the NHS as this is believed to be current clinical practice and is less costly and burdensome for patients. It was assumed that clinical effectiveness would be unchanged going from weekly to fortnightly on the basis of a single non-inferiority trial. It remains possible that there is in fact a difference in effectiveness between the schedules, although on the basis of current evidence there is unlikely to be a substantial difference. This also adds complexity to the decision process, since to achieve the ICER reported in the PenTAG base case might require NICE to issue guidance outside the current marketing authorisation

The PFS data for 1st-line treatment is of high quality, as it comes directly from RCTs, but we note that the evidence of CET+FOLFOX is not as strong as for PAN+FOLFOX, as the OPUS trial of CET+FOLFOX vs. FOLFOX had far fewer *RAS* WT patients (87) than the PRIME RCT of PAN+FOLFOX vs. FOLFOX (512). This is demonstrated in the probabilistic sensitivity analysis, where the CET+FOLFOX versus FOLFOX results are much more uncertain than PAN+FOLFOX versus FOLFOX.

As there were two trials to base the effectiveness of FOLFOX on, one had to be chosen for the base case. Due to its larger size, we based our effectiveness estimates for FOLFOX on the PRIME trial. In a scenario analysis where OPUS is chosen to base the effectiveness

estimates the ICERs for PAN+FOLFOX versus FOLFOX do decrease substantially, particularly for the liver metastases subgroup.

We adjusted the PFS from the RCTs of 1st-line drugs by subtracting patients who are resected (Section 6.1.4.4, p267) to calculate PFS for unresected patients. As the underlying individual patient data from the RCTs was not available, this method is only approximate.

We estimated survival post-resection from a study that is now several years old, where no patients received either cetuximab or panitumumab. [3] It is therefore possible that survival post-resection for patients initially treated with these drugs could differ from Adam et al. (2004).

Treatment effect from 1st-line drugs was assumed to stop following disease progression. This is because we do not model overall survival (OS) from the RCTs, only PFS. We explore the use of OS from the RCTs in a scenario analysis where the ICERs for CET+FOLFOX significantly worsened versus FOLFOX; PAN+FOLFOX ICERs significantly improved versus FOLFOX; CET+FOLFIRI versus FOLFIRI ICER improve. These changes are driven by the treatment duration which is now calculated directly from the RCTs.

For the liver metastases subgroup progression free survival is even more uncertain as direct evidence was unavailable so adjustments to PFS for all patients were made. Furthermore, we estimated PFS for unresected patients from PFS for resected + unresected patients for the liver mets subgroup using a different, and arguably less rigorous, method compared to all patients.

9. Conclusions

Clinical effectiveness evidence in this review suggests there is some clinical benefit from anti-EGFR therapies in comparison to standard chemotherapy treatments and mixed clinical benefit in comparison to anti-VEGF therapies: e.g. direct evidence suggests that panitumumab plus FOLFOX is more effective at increasing time to progression or death than FOLFOX and bevacizumab plus FOLFOX. Panitumumab plus FOLFOX is also estimated to be more effective at increasing time to death than FOLFOX., Evidence suggests that cetuximab plus FOLFIRI and bevacizumab plus FOLFIRI are more effective than FOLFIRI at increasing time to progression or death, and objective response rate.

There is limited evidence to draw conclusions over which anti-EGFR therapy has most clinical benefit: There is no evidence to suggest that cetuximab plus FOLFOX is any more effective panitumumab plus FOLFOX to increase the time to death or the time to progression or death and there is limited evidence to suggest that cetuximab plus FOLFOX is more effective at improving overall response rate than panitumumab plus FOLFOX.

Estimates of cost-effectiveness currently suggest poor value for money at willingness to pay thresholds of £30,000. Our results currently indicate that the cost of administering these treatments is what drives this poor value for money, as even when reducing reducing the cost to £0, ICERs remain above a £30,000 per QALY gained willingness to pay threshold. Probabilistic sensitivity analyses further demonstrate that anti-EGFR therapies are unlikely to be cost-effective at a willingness to pay threshold of £30,000 per QALY gained: for the FOLFOX network, FOLFOX has 78% likelihood of being most cost-effective treatment; and for the FOLFIRI network, FOLFIRI has 100% likelihood of being the most cost-effective treatment.

In summary, there is potential for clinical benefit from anti-EGFR therapies, but cost of administering these therapies is substantial.

9.1. Implications for service provision

Both panitumumab and cetuximab are currently available on the Cancer Drugs Fund for first line metastatic colorectal cancer. As *RAS* WT is a prerequisite for using cetuximab and panitumumab in this indication, *RAS* mutation testing is also funded this way for many hospitals (expert opinion, Dr Mark Napier). Therefore currently both *RAS* mutation testing and cetuximab and panitumumab treatment are currently supported by the CDF. Were anti-

EGFR therapies to be approved by NICE guidance, the implications for *RAS* mutation testing would have to be considered.

Bevacizumab, one of the named comparators in this analysis, is no longer available on the Cancer Drugs Fund and is not recommended by NICE for first line treatment of metastatic colorectal cancer patients. As this is a recent change, the proportion of patients who would have previously been considered for bevacizumab will now receive alternative treatment, which may have some impact to the proportion of patients tested for cetuximab and panitumumab.

9.2. Suggested research priorities

Here we highlight suggested research priorities:

- Given the uncertainty associated with drug administration costs for chemotherapy regimens, a study to identify the most appropriate methods for costing drug administration in chemotherapy, considering microcosting and the use of NHS reference costs, could be justified given the significant number of technology appraisals in which parenteral chemotherapy is administered.
- We recommend that the economic analysis should be repeated when the PFS and OS data from the RCTs is more mature. Given sufficiently mature data, we would no longer need to use PFS and OS related to patients post-resection, with all the associated uncertainty, as we do currently.
- The RCTs of 1st-line drugs included subsequent treatments that are not widely used in the UK NHS. Therefore, the economic analysis would benefit from RCTs with subsequent treatments in line with those widely used in the NHS. However, given the substantial costs of conducting trials, we appreciate that this is unlikely to happen.
- Given lack of data to suggest otherwise, we assume the same accuracy of the *RAS* test in clinical practice as in the 1st-line RCTs. Any differences are likely to render worse estimates of cost-effectiveness for cetuximab and panitumumab. Therefore, we would welcome further research in to the relative accuracies of the tests as used in the trials and in clinical practice.
- Our economic analysis is desgined for the NHS in England & Wales. However, it could easily be adapted for the healthcare systems of other countries.
- CET+FOLFOX, CET+FOLFIRI and PAN+FOLFOX are all given intravenously. Our economic analysis suggests that the administration of these treatments is expensive, and it highlights that there is a strong economic incentive to develop oral treatments for mCRC.

- The cost-effective of treatments for the liver metastases subgroup are very uncertain, partly due to the small numbers of patients in the trials. Therefore, if there is further interest in giving these treatments to this subgroup of patients, then we need better quality and quantity of clinical evidence.

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The clinical effectiveness and cost-effectiveness of cetuximab (review of TA176) and panitumumab (partial review of TA240) for previously untreated metastatic colorectal cancer: a systematic review and economic evaluation

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Date completed: 7 August 2015

Declared competing interests of authors: None

Rider on responsibility for this report::	The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.
This report should be referenced as follows:	Huxley N, Crathorne L, Varley-Campbell J, Tikhonova I, Snowsill T, Briscoe S, Peters J, Bond M, Napier M, Hoyle M. The clinical effectiveness and cost-effectiveness of cetuximab (review of TA176) and panitumumab (partial review of TA240) for previously untreated metastatic colorectal cancer: a systematic review and economic evaluation (2015) PenTAG, University of Exeter Medical School (Report for NICE)

Contributions of authors

Nicola Huxley	Provided project management (Feb 2015 to Aug 2015), and led the review of published cost-effectiveness studies and critique of the manufacturer submission of cost-effectiveness. Contributed to the parameterisation and checking of the PenTAG independent economic assessment. Contributed to the writing and editing of the report.
Louise Crathorne	Provided project management (Nov 2014 to Feb 2015), and led the systematic review of clinical effectiveness, including assessment of all abstracts and titles for possible inclusion. Wrote the Background, Decision Problem, and Section 3 (Clinical Effectiveness Review).. Contributed to the writing and editing of the report.
Jo Varley-Campbell	Screened titles, abstracts and papers for inclusion in the systematic review Contributed to the writing of the clinical effectiveness section and corresponding sections within the executive summary, discussion and appendices. Contributed to the editing of the report.
Irina Tikhonova	Contributed to the critique of the submission by Merck Serono, parameterisation and checking of the PenTAG independent economic assessment and writing and editing of the report.
Tristan Snowsill	Contributed to the critique of the submission by Merck Serono, parameterisation and checking of the PenTAG independent economic assessment and writing and editing of the report.
Simon Briscoe	Designed and carried out literature searches for the systematic reviews and identification of model parameters, and contributed to the writing and editing of the report

Jaime Peters	Carried out the network meta-analyses and contributed to the writing of the clinical effectiveness section.
Mary Bond	Screened titles, abstracts and papers for inclusion in the systematic review and commented on the draft report
Mark Napier	Provided clinical input into the design of the model, and advised on clinical matters.
Martin Hoyle	Led the design and parameterisation of the PenTAG economic model and implemented the model in Excel, wrote the sections on the design, parameterisation and results of the economic model (Chapter 6). Contributed to the critique of the submission by Merck Serono. Contributed to the writing and editing of the report. Overall Director and Guarantor of the report.

Acknowledgments: The authors are pleased to acknowledge Mrs Sue Whiffin and Ms Jenny Lowe who provided administrative support.

Mr Christopher Bowles (Royal Devon and Exeter Hospital), Mr Neil Atkey (Sheffield Children's NHS Foundation Trust), Dr Michelle Wood (Institue of Medical Genetics, University Hospital of Wales), Dr Marie Westwood (Kleijnen Systematic Reviews Ltd) who provided information about *RAS* mutation testing

Dr Sandi Deans (UK NEQAS) who contacted UK genetic laboratories on our behalf

Dr Paul Tappenden (University of Sheffield) who commented on the draft report.

Professor Chris Hyde who commented on the draft report and provided senior management support.

All 'commercial in confidence' and 'academic in confidence' data provided by companies, and specified as such, has been redacted, for example: [redacted].

The Peninsula Technology Assessment Group (PenTAG) is part of the Evidence Synthesis and Modelling for Health Improvement (ESMI) group based at the University of Exeter Medical School. PenTAG was established in 2000 and carries out independent Health Technology Assessments (HTAs) for the NIHR HTA Programme, systematic reviews and

economic analyses for other local and national decision-makers. The group is multi-disciplinary and draws on individuals' backgrounds in public health, health services research, computing and decision analysis, systematic reviewing, statistics and health economics. The Institute of Health Research is made up of discrete but methodologically related research groups, among which HTA is a strong and recurring theme.

Health technology assessment projects in 2014/2015 included:

- Immunosuppressive therapy for kidney transplantation in children (review of technology appraisal guidance 99)
- Immunosuppressive therapy for kidney transplantation in adults (review of technology appraisal guidance 85)
- Ofatumumab in combination with chlorambucil or bendamustine for previously untreated chronic lymphocytic leukaemia
- Obinutuzumab for previously untreated chronic lymphocytic leukaemia
- The effectiveness and cost-effectiveness of erythropoiesis-stimulating agents (epoetin and darbepoetin) for treating cancer-treatment induced anaemia (including review of TA142): a systematic review and economic model

For a full list of previous projects please see
http://medicine.exeter.ac.uk/esmi/workstreams/pentaghealthtechnologyassessment/

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Abbreviations

AEs	adverse events
BEV	Bevacizumab
BNF	British National Formulary
CAP	Capecitabine
CDF	Cancer Drugs Fund
CET	Cetuximab
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CRC	colorectal cancer
CR	complete response
CRD	Centre for Reviews and Dissemination
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EQ-5D	EuroQol 5-Dimensions
FOLFIRI	folinic acid + fluorouracil + irinotecan
FOLFOX	folinic acid + fluorouracil + oxaliplatin
HRAS	Harvey rat sarcoma

HRQoL	health-related quality of life
ICER	Incremental cost-effectiveness ratio
IRIN	Irinotecan
KRAS	kirsten rat sarcoma
LLD	liver limited disease
mCRC	metatstatic colorectal cancer
MTA	multiple technology appraisal
MTC	mixed treatment comparison
mths	Months
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NRAS	neuroblastoma rat sarcoma
ORR	objective response rate
OS	overall survival
OX	Oxaliplatin
PAN	Panitumumab
PD	progressive disease
PFS	progression free survival
PR	partial response

PS	performance status
PSSRU	Personal Social Services and Resource Use
QALY	quality-adjusted life year
RAS	rat sarcoma
RCT	randomised controlled trial
SAEs	serious adverse events
sd	standard deviation
SD	stable disease
SE	standard error
SPC	Summary of Product Characteristics
SR	systematic review
STA	single technology appraisal
TA	technology appraisal
wks	Weeks
WT	wild type
XELOX	capecitabine + oxaliplatin
yrs	Years

Glossary

Epidermal growth factor receptor (EGFR)	The protein encoded by this gene is a transmembrane glycoprotein that is a member of the protein kinase superfamily. This protein is a receptor for members of the epidermal growth factor family. EGFR is a cell surface protein that binds to epidermal growth factor. Binding of the protein to a ligand induces receptor dimerization and tyrosine autophosphorylation and leads to cell proliferation. Mutations in this gene are associated with lung cancer. Multiple alternatively spliced transcript variants that encode different protein isoforms have been found for this gene
Kirsten rat sarcoma (*KRAS*)	The *KRAS* gene belongs to a class of genes known as oncogenes. When mutated, oncogenes have the potential to cause normal cells to become cancerous. These proteins play important roles in cell division, cell differentiation, and the self-destruction of cells (apoptosis).
Neuroblastoma rat sarcoma (*NRAS*)	The *NRAS* gene belongs to a class of genes known as oncogenes. When mutated, oncogenes have the potential to cause normal cells to become cancerous. These proteins play important roles in cell division, cell differentiation, and the self-destruction of cells (apoptosis).
Rat sarcoma (*RAS*)	Gene family consisting of *HRAS*, neuroblastoma rat sarcoma (*NRAS*), and kirsten rat sarcoma (*KRAS*)

Wild type (WT)	The normal, non-mutated version of a gene common in nature

Appendices

Appendix A: Protocol

Technology Assessment Report commissioned by the NETSCC HTA Programme on behalf of the National Institute for Health and Care Excellence: HTA 14/65/01

15 January 2014

Title of the project

The clinical effectiveness and cost-effectiveness of cetuximab (review of TA176) and panitumumab (partial review of TA240) for previously untreated metastatic colorectal cancer: a systematic review and economic evaluation.

Name of TAR team and project 'lead'

TAR Team Peninsula Technology Assessment Group (PenTAG), Evidence Synthesis and Modelling for Health Improvement (ESMI), University of Exeter Medical School

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Plain English Summary

The aim of this project is to review the clinical effectiveness and cost effectiveness of cetuximab and panitumumab in a multiple technology appraisal. This will include a review of

TA176 (cetuximab), and a part review of TA240 (panitumumab) for previously untreated metastatic colorectal cancer (mCRC). The medical benefit and risks associated with these treatments will be assessed and compared across the treatments and against available standard drug treatments. The review will also assess whether these drugs are likely to be considered good value for money for the NHS.

Decision problem

Objectives

This assessment will address the question: "What is the clinical effectiveness and cost-effectiveness of cetuximab (review of TA176) and panitumumab (partial review of TA240) for previously untreated metastatic colorectal cancer?"

Background

Colorectal cancer is a malignant tumour arising from the lining of the large intestine (colon and rectum). Metastatic colorectal cancer (mCRC) refers to disease that has spread beyond the large intestine and nearby lymph nodes. This type of cancer most often spreads first to the liver, but metastases may also occur in other parts of the body including the lungs, brain and bones.

Colorectal cancer is the third most common cancer in the UK after breast and lung cancer: in 2012, there were 34,322 people new registrations of colorectal cancer and 12,900 deaths.[13] Occurrence of colorectal cancer is strongly related to age, with almost three-quarters of cases occurring in people aged 65 or over.[13] Colorectal cancer is the second most common cause of cancer death in the UK.[13] Around half of people diagnosed with colorectal cancer survive for at least 5 years after diagnosis.[13]

Treatment of mCRC may involve a combination of surgery, chemotherapy, radiotherapy, and supportive care.[13] When possible, surgical removal (resection) or destruction of the primary tumour and metastases may be considered.[13] For people with metastases only in their livers, complete resection appears to offer the best chance of long-term survival, providing 5 year survival rates ranging from 25% to 44%. Chemotherapy is an option to prolong survival and/or to make the primary tumour or metastases suitable for resection. NICE clinical guideline 131 recommends chemotherapy options including fluorouracil and folinic acid in combination with oxaliplatin (FOLFOX), tegafur in combination with fluorouracil and folinic acid, capecitabine in combination with oxaliplatin (XELOX), and capecitabine alone.[13] In practice, fluorouracil and folinic acid may also be used in combination with irinotecan (FOLFIRI) in some people for whom oxaliplatin is not suitable.[13] Chemotherapy may be

combined with biological agents such as cetuximab (recommended for people satisfying criteria specified in technology appraisal 176),[11] panitumumab,[12] and bevacizumab (not recommended by NICE but funded via the Cancer Drugs Fund).).[60]

The choice and effectiveness of some treatments for mCRC may be influenced by genetic markers.[23] Several studies in CRC have shown that, owing to the convergence of the epidermal growth factor receptor (eGFR) and Kirsten rat sarcoma (*KRAS*) pathways, people with mutations in genes in the rat sarcoma (*RAS*) family (specifically *KRAS* and neuroblastoma rat sarcoma [*NRAS*]) treated with the eGFR specific antibodies cetuximab and panitumumab derive considerably less benefit than people with wild type.[165] Approximately 50% of people with advanced colorectal cancer have mutations in the *KRAS* or *NRAS* genes.[23]

At the time of technology appraisal 176 (2009), *RAS* wild-type status was defined based on a single part ('exon') of the *KRAS* gene, and testing typically focused on *KRAS* codons 12 and 13.[65] However, subsequent evidence suggested that mutations in other *KRAS* codons and other genes downstream of EGFR may also confer drug resistance explaining why some individuals with *KRAS* codon 12 and 13 wild-type tumours did not respond to therapy.[65] The absence of mutations in the *NRAS* gene and in 2 further exons (3 and 4) of *KRAS* was found to improve the effectiveness of cetuximab and panitumumab.[65] These developments led the European Medicines Agency to update the marketing authorisations for cetuximab and panitumumab in 2013 by restricting the indication in colorectal cancer to the treatment of people with *RAS* (i.e. both *KRAS* and *NRAS*) wild-type tumours.[48, 49] It is this change to the licensed indications for these products that provides the rationale for this appraisal.[23]

Interventions

Cetuximab (Erbitux®, Merck Serono) is a recombinant monoclonal antibody that blocks the human epidermal growth factor receptor (EGFR), inhibiting the growth of tumours expressing EGFR.[44] Cetuximab has a UK marketing authorisation for the treatment of people with EGFR-expressing, *RAS* wild-type metastatic colorectal cancer (mCRC), either in combination with FOLFOX (FOL [folinic acid;F [Fluorouracil, 5-FU], OX [Oxaliplatin, Eloxatin]), or irinotecan-based chemotherapy.[44]

Panitumumab (Vectibix®, Amgen) is a recombinant, fully human immunoglobulin (Ig) G2 monoclonal antibody that binds to EGFR, blocking its signalling pathway and inhibiting the growth of tumours.[45] It has a UK marketing authorisation for use in combination with FOLFOX, for treating previously untreated, *RAS* wild-type mCRC.[45] Panitumumab is also licensed for use second-line in combination with FOLFIRI for people who have received first-

line fluoropyrimidine-based chemotherapy (excluding irinotecan), although clinical trials have also measured the effectiveness of panitumumab in combination with FOLFIRI for previously untreated mCRC.[45]

Place of the interventions in the treatment pathway

NICE TA176: Cetuximab for the first-line treatment of mCRC

In the previous assessment (TA176):

- Cetuximab in combination with 5-fluorouracil (5-FU), folinic acid and oxaliplatin (FOLFOX), within its licensed indication, is recommended for the first-line treatment of mCRC only when all of the following criteria are met:

1. the primary colorectal tumour has been resected or is potentially operable;
2. the metastatic disease is confined to the liver and is unresectable;
3. the patient is fit enough to undergo surgery to resect the primary colorectal tumour and to undergo liver surgery if the metastases become resectable after treatment with cetuximab; and
4. the manufacturer rebates 16% of the amount of cetuximab used on a per patient basis.[11]

- Cetuximab in combination with 5-FU, folinic acid and irinotecan (FOLFIRI), within its licensed indication, is recommended for the first-line treatment of mCRC only when all of the following criteria are met:

1. the primary colorectal tumour has been resected or is potentially operable;
2. the metastatic disease is confined to the liver and is unresectable;
3. the patient is fit enough to undergo surgery to resect the primary colorectal tumour and to undergo liver surgery if the metastases become resectable after treatment with cetuximab; and
4. the patient is unable to tolerate or has contraindications to oxaliplatin.[11]

People who meet the criteria above should receive treatment with cetuximab for no more than 16 weeks.[11] At 16 weeks, treatment with cetuximab should stop and the patient should be assessed for resection of liver metastases.[11]

NICE TA240: Panitumumab for the first-line treatment of mCRC

The appraisal of panitumumab in combination with chemotherapy for the treatment of mCRC (NICE technology appraisal 240) was terminated because no evidence submission was received from the manufacturer or sponsor of the technology.[12] Therefore NICE was unable to make a recommendation about the use in the NHS of panitumumab in combination with chemotherapy for the treatment of mCRC.[12]

Comparators

The interventions should be compared with each other, and with:

- FOLFOX
- XELOX
- FOLFIRI
- Capecitabine
- Tegafur, folinic acid and fluorouracil
- Bevacizumab, in combination with oxaliplatin- or irinotecan-based chemotherapy (not recommended by NICE but funded via the Cancer Drugs Fund).[23]

Population and relevant subgroups

The population of interest to the current appraisal is people with previously untreated, *RAS* wild-type mCRC.[23] We note that the interventions are only licensed in adults (aged ≥18 years).[44, 45]

If the evidence allows, the use of the interventions will be considered in subgroups based on the location of metastases (inside and/or outside the liver).[23]

Outcomes

Evidence on the following outcomes will be considered:

- overall survival
- progression-free survival
- response rate

- rate of resection of metastases
- adverse effects of treatment
- health-related quality of life (HRQoL).[23]

Methods for synthesis of evidence of clinical effectiveness

This MTA will include a review of cetuximab and panitumumab for previously untreated mCRC.[23] It will include a review of TA176 and part review of TA240.[11, 12] The systematic review will be undertaken following the general principles published by the NHS Centre for Reviews and Dissemination.[66]

Search strategy

The search strategy for clinical effectiveness studies will include the following search methods:

- Searching of bibliographic and ongoing trials databases.
- Searching of conference proceedings.
- Contact with experts in the field.
- Scrutiny of bibliographies of retrieved papers and company submissions.

The following bibliographic and ongoing trials databases will be searched for clinical effectiveness studies: MEDLINE (Ovid); MEDLINE In-Process and Other Non-Indexed Citations (Ovid); EMBASE (Ovid); The Cochrane Library including the Cochrane Systematic Reviews Database, CENTRAL, DARE and HTA databases; Web of Science (Thomson Reuters); ClinicalTrials.gov; UK Clinical Research Network's (UKCRN) portfolio; ISRCTN registry; WHO International Clinical Trials Registry Platform (ICTRP).

The following websites will be searched for conference proceedings:

- National Cancer Research Institute http://conference.ncri.org.uk/
- American Association for Cancer Research http://aacrmeetingabstracts.org/
- American Society of Clinical Oncology http://meetinglibrary.asco.org/abstracts

In addition to the clinical effectiveness searches, the Health Management Information Consortium (HMIC, Ovid) will be searched for grey literature.

The database searches will be developed by an information specialist. Search filters will be used to limit the searches to randomised controlled trials (excluding Cochrane Library databases and HMIC), and all searches will be limited to English language studies where possible. No date limits will be used.

All bibliographic references retrieved by the searches will be exported to Endnote X7 and de-duplicated (using automatic and manual methods) before screening.

Study selection criteria and procedures

Studies retrieved from the searches will be selected for inclusion through a two-stage process according to the inclusion/exclusion criteria specified in Table 1. First, abstracts and titles returned by the search strategy will be screened for inclusion independently by two researchers. Disagreements will be resolved by discussion, with involvement of a third reviewer when necessary. Full texts of identified studies will be obtained and screened in the same way. At each step studies which do not satisfy those criteria will be excluded; abstract-only studies will be included provided sufficient methodological details are reported to allow critical appraisal of study quality.

Table 1. Inclusion criteria

Population	Adults with previously untreated, *RAS* wild-type mCRC	Interventions only licensed in adults
Intervention	Cetuximab, in combination with FOLFOX or irinotecan-based chemotherapy Panitumumab, in combination with fluorouracil-containing regimens	NOTE: Panitumumab, in combination with FOLFIRI is licensed for use second-line. However, there are studies evaluating its effectiveness in people previously untreated. Therefore, ensure that the trial population is relevant to the review
Comparator	The interventions should be compared with each other, and with: FOLFOX XELOX FOLFIRI Capecitabine Tegafur, folinic acid and fluorouracil Bevacizumab, in combination with oxaliplatin- or irinotecan-based chemotherapy (not recommended by NICE but funded via the Cancer	

	Drugs Fund[a])	
Outcomes	Overall survival	
	Progression-free survival	
	Response rate	
	Rate of resection of metastases	
	Adverse events	
	HRQoL	
Study design	Randomised controlled trials	We will also identify systematic reviews (per definition specified below) of RCTs

Key: FOLFIRI = (folinic acid + fluourouracil + irinotecan); FOLFOX (folinic acid + fluourouracil + oxaliplatin; HRQoL = health-related quality of life; mCRC = metastatic colorectal cancer; RCTs = randomised controlled trials; XELOX = capectiabine + oxaliplatin
Notes: (a) Subject to availability of funding through the Cancer Drugs Fund

Study design

The review of clinical effectiveness will include any RCT reporting at least one of the outcomes of interest. However, if any outcomes of interest are lacking RCT evidence or if the RCTs do not provide an adequate length of follow-up, we will extend our search and inclusion criteria to controlled clinical trials. Furthermore, these criteria would also be relaxed for consideration of adverse events, where non-randomised and observational studies may be included. However, scoping searches indicate sufficient RCT evidence should be available.

Studies published as abstracts or conference presentations will only be included if sufficient details are presented to allow an appraisal of the methodology and the assessment of the results to be undertaken. Systematic reviews and clinical guidelines will be included as sources of references for finding further RCTs and to compare with our systematic review.

For the purpose of this review, a systematic review will be defined as one that has:

- a focused research question
- explicit search criteria that are available to review, either in the document or on application
- explicit inclusion/exclusion criteria, defining the population(s), intervention(s), comparator(s), and outcome(s) of interest
- a critical appraisal of included studies, including consideration of internal and external validity of the research

- a synthesis of the included evidence, whether narrative or quantitative.

Data extraction strategy

Included full papers will be split between two reviewers for the purposes of data extraction using a standardised data specification form, and checked independently by another. Information extracted and tabulated will include details of the study's design and methodology, baseline characteristics of participants and results including any adverse events if reported. Where there is incomplete information on key data, we will attempt to contact the study's authors to gain further details. Discrepancies will be resolved by discussion, with involvement of a third reviewer if necessary. Where multiple publications of the same study are identified, data will be extracted and reported as a single study.

Quality assessment strategy

The methodological quality of each included study will be assessed by one reviewer and checked by a second reviewer, using criteria based on those proposed by the NHS Centre for Reviews and Dissemination for RCTs.[66] The potential generalisability of the study will also be assessed, as well as the judged applicability to the current organisation, clinical pathways and practices of the NHS in England.

Methods of analysis/synthesis

Extracted data and quality assessment for each study of clinical effectiveness will be presented in structured tables and as a narrative summary.

If appropriate (i.e., if a number of studies which report data relating to a given outcome are comparable in terms of key features such as their design, populations, and interventions), meta-analysis will be employed to estimate a summary measure of effect on relevant outcomes based on intention-to-treat analyses. We are aware that there are different definitions of *RAS* WT (Section 4.2) which we will consider when pooling data.

Where appropriate, meta-analysis will be carried out using STATA and/or WinBugs software, with the use of fixed and/or random effects appropriate to the assembled datasets. Heterogeneity will be explored through consideration of the study populations, methods and interventions, by visualisation of results and, in statistical terms, by the $\chi 2$ test for homogeneity and the I2 statistic. If data allows, a network meta-analysis will be considered.

Publication bias

We will investigate the likelihood of publication bias using funnel plots if there are sufficient included studies.

Reporting bias in our systematic review and meta-analyses will be assessed according to the Cochrane Handbook for Reviewers.[166]

In addition, the reported outcomes and methods of analysis in included RCTs will be compared with those described in the registered protocols of those trials, and any discrepancies or uncertainties noted. Where there are potentially includable trials in trial registries for which no reported reports or papers are found, these will be documented and efforts made to find out whether the trial was conducted, completed, and whether the findings are available. Conversely, where a reported RCT is not recorded in a trial registry, this will be clearly noted.

Methods for synthesising evidence of cost-effectiveness

The aims of the review of economic studies are to:

- gain insights into the key drivers of cost-effectiveness in this disease area.
- get an overview of the alternative modelling approaches that have been adopted in this disease and treatment area.
- provide a summary of the findings of previous relevant cost-utility, cost-effectiveness, and cost-benefit studies generalisable to the UK.

Review of economic studies

Search strategy

The search strategy for economic studies will include the following search methods:

- Searching of bibliographic and ongoing trials databases.
- Searching of conference proceedings.
- Scrutiny of bibliographies of retrieved papers and company submissions.

The following databases will be searched for economic studies: MEDLINE (Ovid); MEDLINE In-Process and Other Non-Indexed Citations (Ovid); EMBASE (Ovid); NHS EED (via Cochrane Library); EconLit (EBSCO); Web of Science (Thomson Reuters).

A supplementary search for health utilities will be run in the following databases: MEDLINE (Ovid); MEDLINE In-Process and Other Non-Indexed Citations (Ovid); EMBASE (Ovid); PsycINFO (Ovid); Web of Science (Thomson Reuters); ScHARR Health Utilities Database.

The searches will be developed by an information specialist. Search filters will be used to limit the searches to economic or health utilities studies as appropriate, and searches will be limited to English language studies where possible. No date limits will be used. All references retrieved by the searches will be exported to Endnote X7 and de-duplicated (using automatic and manual methods) before screening.

Relevant studies identified and included in the company's submissions will also be included.

Inclusion and exclusion criteria

The inclusion and exclusion criteria for the systematic review of economic evaluations will be identical to those for the systematic review of clinical effectiveness (specified previously) except:

- Non-randomised studies will be included (e.g. decision model based analyses, or analyses of patient-level cost and effectiveness data alongside observational studies).
- Full cost-effectiveness analyses, cost–utility analyses, cost–benefit analyses and cost–consequences analyses will be included. (Economic evaluations which only report average cost-effectiveness ratios will only be included if the incremental ratios can be easily calculated from the published data.)
- Studies that measure only costs but not health benefits will be excluded except for stand alone cost analyses from the perspective of the UK NHS.

Study selection will be based on the above inclusion/exclusion criteria.

Quality assessment

The quality of identified cost–utility analyses will be assessed using the checklist developed by Evers and colleagues (2005)[1] by one reviewer. Where studies are based on decision models they will be further quality assessed using the checklist developed by Philips and colleagues (2004; 2006).[2, 167]

Synthesis

Economic studies will be summarised and synthesised using tabulated data and narrative synthesis.

Economic modelling

A new cost-effectiveness analysis will be carried out from the perspective of the UK NHS and PSS using a decision analytic model. The aims of the economic modelling are to:

- estimate the base case lifetime incremental QALYs and incremental costs of the defined comparators according to NICE reference case methods (or with only limited deviations from NICE reference case methods due to deficiencies in available data), and assess the cost-effectiveness of the various interventions in the NHS.
- describe and explore the impact of structural and parameter uncertainty on the estimates of cost-effectiveness .
- enable comparison of the cost-utility estimates between the company's economic analyses and those by us, the assessment group.

The evaluation will be constrained by available evidence. The evaluation will produce estimates of incremental cost per QALY gained, unless there is insufficient evidence to estimate utility/HRQoL.

Model structure will be determined on the basis of available research evidence and clinical expert opinion.

The sources of parameter values that determine the effectiveness of the interventions being compared will be obtained from our own systematic review of clinical effectiveness or other relevant research literature. If required parameters are not available from good quality published studies in the relevant patient group, we may use data from sponsor submissions to NICE or from other unpublished data, or where no clinical data is available, from expert opinion.

Resource use (including *RAS* mutation testing) will be specified and valued from the perspective of the NHS and PSS. The resource use associated with different health states or clinical events will be obtained or estimated either from trial data, sponsor submissions, other published sources, or – where published sources are unavailable – relevant expert contacts or NHS Trusts. Unit cost data will be identified from national NHS and PSS reference cost

databases for the most recent year, or, where these are not relevant, extracted from published work and/or sponsor submissions to NICE. If insufficient data are retrieved from published sources, costs may be derived from individual NHS Trusts or groups of Trusts.

Analysis of uncertainty will focus on cost utility, assuming cost per QALY can be estimated. Uncertainty will be explored through one way sensitivity analysis and, if the data and modelling approach permit, probabilistic sensitivity analysis (PSA). The outputs of PSA will be presented using plots on the cost-effectiveness plane and cost-effectiveness acceptability curves.

ICERs estimated from company models will be compared with the respective ICERs from our model, and reasons for large discrepancies in estimated ICERs will be explored and, where possible, explained.

Methods for measuring and valuing health effects

Ideally, health-related quality of life (HRQOL) should be reported directly from patients. The value of changes in patients' HRQOL (that is, utilities) should be based on public preferences using a choice-based method.[112] The EQ-5D will be the preferred measure of HRQOL for the purposes of estimating QALYs.[112] In the absence of reliable EQ-5D utility data from relevant trials or patient groups, the use of alternative sources for utility weights for health states will be informed by the NICE Guide to the methods of technology appraisal (2013).[112]

Time horizon, perspective and discounting

The time horizon of our analysis will be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.

The perspective will be that of the National Health Services and Personal Social Services. Both costs and QALYs will be discounted at 3.5%.[112]

Handling of information from the companies

All data submitted by the companies will be considered if received by NICE no later than 17:00 on 27th April 2015. Data arriving after this date may not be considered.

The industry submissions will be:

- Critically appraised for integrity and quality of evidence

- Used as a source of data, to identify studies not located by the searches and that meet the review inclusion criteria.

- Used to compare any submitted industry model(s) with our independent economic assessment.

Any economic evaluations included in the company submission will be assessed against NICE's guidance on the Methods of Technology Appraisal[112] and will also be assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used. Where we have undertaken further analyses, using models submitted by the companies or via de novo modelling and cost effectiveness analysis, a comparison will be made of the alternative models.

Tabulated summaries and technical commentaries on the economic models used in the company submissions will be provided. This will not be a full critique as for a single technology appraisal but will be used to reflect on the results from the PenTAG de novo model and to discuss any differences.

Any 'commercial in confidence' data provided by companies, and specified as such, will be highlighted in blue and underlined in our assessment report (followed by company name in parentheses). Any 'academic in confidence' data provided by companies, and specified as such, will be highlighted in yellow and underlined in our assessment report. Any confidential data used in the cost-effectiveness models will also be highlighted.

Expertise in this TAR team

Name	Institution	Expertise
Mary Bond	PenTAG, ESMI, University of Exeter Medical School	Project management, systematic review
Simon Briscoe	PenTAG, ESMI, University of Exeter Medical School	Information specialist
Helen Coelho	PenTAG, ESMI, University of Exeter Medical School	Systematic review
Louise Crathorne	PenTAG, ESMI, University of Exeter Medical School	Project management, systematic review and economic evaluation
Martin Hoyle	PenTAG, ESMI, University of Exeter Medical School	Economic modelling, economic evaluation, and Guarantor of the final report
Nicola Huxley	PenTAG, ESMI, University of Exeter Medical School	Project management; economic modelling and economic evaluation
Chris Hyde	PenTAG, ESMI, University of	Systematic review and economic evaluation

	Exeter Medical School	
Mark Napier	Royal Devon and Exeter Hospital, Devon	Consultant oncologist

Key: ESMI = Evidence Synthesis and Modelling for Health Improvement; PenTAG = Peninsula Technology Assessment Group

Other external experts: We will also work in collaboration with other external advisors [[to be advised pre final protocol]].

Other PenTAG resources: Depending on the agreed scope of work we will draw on other researchers from PenTAG as required.

TAR centre

The Peninsula Technology Assessment Group is part of the Evidence Synthesis and Modelling for Health Improvement (ESMI) group at the University of Exeter Medical School. PenTAG was established in 2000 and carries out independent Health Technology Assessments for the UK HTA Programme, as well as for other local and national decision-makers. The group is multi-disciplinary and draws on individuals' backgrounds in public health, health services research, computing and decision analysis, systematic reviewing, statistics and health economics. The Institute of Health Research is made up of discrete but methodologically related research groups, among which Health Technology Assessment is a strong and recurring theme.

Health technology assessment projects include:

- The effectiveness and cost-effectiveness of immunosuppressive therapy for kidney transplantation in adults (review of technology appraisal guidance 85): a systematic review and economic model (in progress)
- The effectiveness and cost-effectiveness of immunosuppressive therapy for kidney transplantation in children (review of technology appraisal guidance 99): a systematic review and economic model (in progress)
- The effectiveness and cost-effectiveness of erythropoiesis-stimulating agents (epoetin and darbepoetin) for treating cancer-treatment induced anaemia (including review of TA142): a systematic review and economic model (2014)
- Bosutinib for previously-treated chronic myeloid leukaemia: a single technology appraisal (2013)

- A systematic review and economic evaluation of intraoperative tests (RD-100i OSNA system and Metasin test) for detecting sentinel lymph node metastases in breast cancer
- Dasatinib and Nilotinib for the 1st line treatment of chronic phase chronic myeloid Leukaemia (CML): a systematic review and economic model
- Bevacizumab, Cetuximab, and Panitumumab for in colorectal cancer (metastatic) after failure of 1st line chemotherapy: a systematic review and economic model
- The psychological consequences of false positive mammograms: a systematic review
- Bendamustine for the first-line treatment of chronic lymphocytic leukaemia (Binet stage B or C) in people for whom fludarabine combination chemotherapy is not appropriate: a critique of the submission from Napp
- The effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review of TA111): a systematic review and economic model
- Ofatumumab (Arzerra®) for the treatment of chronic lymphocytic leukaemia in people who are refractory to fludarabine and alemtuzumab: a critique of the submission from GSK
- Everolimus for the second-line treatment of advanced and/or metastatic renal cell carcinoma: a critique of the submission from Novartis
- The clinical and cost-effectiveness of sunitinib for the treatment of gastrointestinal stromal tumours: a critique of the submission from Pfizer
- The clinical- and cost effectiveness of lenalidomide for multiple myeloma in people who have received at least one prior therapy: an evidence review of the submission from Celgene
- Bevacizumab, sorafenib tosylate, sunitinib and temsirolimus for renal cell carcinoma: a systematic review and economic model
- Machine perfusion systems and cold static storage of kidneys from deceased donors.
- The effectiveness and cost-effectiveness of cochlear implants for severe to profound deafness in children and adults

- The harmful health effects of recreational Ecstasy: A systematic review of observational evidence
- Assessment of surrogate outcomes in model-based cost effectiveness analyses within UK health technology reports: a methodological review
- Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long acting beta2 agonists for the treatment of chronic asthma in adults and children aged 12 years and over.
- Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long acting beta2 agonists for the treatment of chronic asthma in children under the age of 12 years.
- The effectiveness and cost-effectiveness of cardiac resynchronisation (biventricular pacing) for heart failure: a systematic review and economic model.
- The effectiveness and cost-effectiveness of cinacalcet for secondary hyperparathyroidism in end stage renal disease: a systematic review and economic model
- The effectiveness and cost-effectiveness of carmustine implants and temozolomide for the treatment of newly diagnosed high grade glioma: a systematic review and economic evaluation.
- Surveillance of cirrhosis for the development of hepatocellular carcinoma: systematic review and economic analysis.
- Surveillance of Barrett's oesophagus: exploring the uncertainty.
- The cost effectiveness of testing for hepatitis C in former injecting drug users.
- Do the findings of case series vary systematically by methodological characteristics.
- The effectiveness and cost effectiveness of dual chamber pacemakers compared to single chamber pacemakers for bradycardia due to atrioventricular block or sick sinus syndrome: systematic review and economic evaluation.
- The effectiveness and cost-effectiveness of pimecrolimus and tacrolimus for atopic eczema: a systematic review and economic evaluation.

- The effectiveness and cost-effectiveness of microwave and thermal balloon endometrial ablation for heavy menstrual bleeding: a systematic review and economic modelling.
- Effectiveness and cost-effectiveness of imatinib for first-line treatment of chronic myeloid leukaemia in chronic phase: a systematic review and economic analysis.
- Systematic review of endoscopic Sinus Surgery for Nasal Polyps.
- Screening for hepatitis C in GUM clinic attenders and injecting drug users.
- The effectiveness and cost effectiveness of imatinib in chronic myeloid leukaemia: a systematic review.

Competing interests of authors

None

Timetable/milestones

Action	Expected due date
Draft protocol due	29 December 2014
Final protocol due	19 January 2015
Company submissions due to NICE	27 April 2015
Progress report due	13 May 2015
Draft assessment report due to NICE	17 July 2015
Assessment report due	7 August 2015
1st Appraisal Committee meeting	15 October 2015
2nd Appraisal Committee meeting	6 January 2016

Appendix B: Literature search strategies

Clinical effectiveness

Database:	MEDLINE
Host:	Ovid
Data Parameters:	1946 to November Week 3 2014
Date Searched:	5/1/2015
Searcher:	SB
Hits:	447

1. (cetuximab or erbitux or C225 or "IMC C225").tw.
2. (panitumumab or vectibix or "ABX-EGF").tw.
3. 1 or 2
4. (colorectal or colon or colonic or rectal or rectum or bowel or intenstin*).tw.
5. (CRC or mCRC).tw.
6. exp Colorectal Neoplasms/
7. colon/
8. rectum/
9. or/4-8
10. (random* or rct* or "controlled trial*" or "clinical trial*").tw.
11. randomized controlled trial.pt.
12. 10 or 11
13. 3 and 9 and 12
14. limit 13 to english language

Database:	MEDLINE In-Process & Other Non-Indexed Citations
Host:	Ovid
Data Parameters:	December 31, 2014
Date Searched:	5/1/2015
Searcher:	SB
Hits:	66

1. (cetuximab or erbitux or C225 or "IMC C225").tw.
2. (panitumumab or vectibix or " ABX-EGF").tw.
3. 1 or 2
4. (colorectal or colon or colonic or rectal or rectum or bowel or intenstin*).tw.
5. (CRC or mCRC).tw.
6. 4 or 5
7. (random* or rct* or "controlled trial*" or "clinical trial*").tw.
8. 3 and 6 and 7

Database:	EMBASE
Host:	Ovid
Data Parameters:	1974 to 2015 January 05
Date Searched:	6/1/2015
Searcher:	SB

Hits: 1948

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1. (cetuximab or erbitux or C225 or "IMC C225").tw.
2. cetuximab/
3. (panitumumab or vectibix or " ABX-EGF").tw.
4. panitumumab/
5. or/1-4
6. (colorectal or colon or colonic or rectal or rectum or bowel or intenstin*).tw.
7. (CRC or mCRC).tw.
8. exp colon/
9. exp colon tumor/
10. exp rectum/
11. exp rectum tumor/
12. or/6-11
13. (random* or rct* or "controlled trial*" or "clinical trial*").tw.
14. 5 and 12 and 13
15. limit 14 to english language

Database: Web of Science

Host: Thomson Reuters

Data Parameters: SCI-EXPANDED and CPCI-S

Date Searched: 6/1/2015

Searcher: SB

Hits: 1093

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1. TITLE: (cetuximab or erbitux or C225 or "IMC C225") OR TOPIC: (cetuximab or erbitux or C225 or "IMC C225")

2. TITLE: (panitumumab or vectibix or " ABX-EGF") OR TOPIC: (panitumumab or vectibix or " ABX-EGF")

3. #1 OR #2

4. TITLE: (colorectal or colon or colonic or rectal or rectum or bowel or intenstin*) OR TOPIC: (colorectal or colon or colonic or rectal or rectum or bowel or intenstin*)

5. TITLE: (CRC or mCRC) OR TOPIC: (CRC or mCRC)

6. #4 OR #5

7. TITLE: (random* or rct* or "controlled trial*" or "clinical trial*") OR TOPIC: (random* or rct* or "controlled trial*" or "clinical trial*")

8. #7 AND #6 AND #3

Database:	CENTRAL
Host:	Cochrane Collaboration
Data Parameters:	Issue 12 of 12, December 2014
Date Searched:	6/1/2015
Searcher:	SB
Hits:	255

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1. (cetuximab or erbitux or C225 or "IMC C225"):ti or (cetuximab or erbitux or C225 or "IMC C225"):ab

2. (panitumumab or vectibix or " ABX-EGF"):ti or (panitumumab or vectibix or " ABX-EGF"):ab

3. #1 or #2

4. (colorectal or colon or colonic or rectal or rectum or bowel or intenstin*):ti or (colorectal or colon or colonic or rectal or rectum or bowel or intenstin*):ab

5. (CRC or mCRC):ti or (CRC or mCRC):ab

6. MeSH descriptor: [Colorectal Neoplasms] explode all trees

7. MeSH descriptor: [Colon] explode all trees
8. MeSH descriptor: [Rectum] explode all trees
9. #4 or #5 or #6 or #7 or #8
10. #3 and #9 in Technology Assessments

Database:	Cochrane Database of Systematic Reviews (CDSR)
Host:	Cochrane Collaboration
Data Parameters:	Issue 1 of 12, January 2015
Date Searched:	6/1/2015
Searcher:	SB
Hits:	0

Strategy: See CENTRAL strategy

Database:	DARE
Host:	Cochrane Collaboration
Data Parameters:	Issue 4 of 4, October 2014
Date Searched:	6/1/2015
Searcher:	SB
Hits:	14

Strategy: See CENTRAL strategy

Database:	HTA
Host:	Cochrane Collaboration
Data Parameters:	Issue 4 of 4, October 2014
Date Searched:	6/1/2015
Searcher:	SB
Hits:	18

Strategy: See CENTRAL strategy

Clinical effectiveness titles/abstracts identified by searches

Database:	**Hits**
MEDLINE	447
MEDLINE in Process	66
EMBASE	1948
Web of Science	1093
CENTRAL	255
CDSR	0
DARE	14
HTA	18
Total	3841

Duplicate records	1205
Total records to screen	**2636**

Cost effectiveness

Database:	MEDLINE
Host:	Ovid
Data Parameters:	1946 to November Week 3 2014
Date Searched:	8/1/2015
Searcher:	SB
Hits:	126

1. (cetuximab or erbitux or C225 or "IMC C225").tw.
2. (panitumumab or vectibix or " ABX-EGF").tw.
3. 1 or 2
4. (colorectal or colon or colonic or rectal or rectum or bowel or intenstin*).tw.
5. (CRC or mCRC).tw.
6. exp Colorectal Neoplasms/
7. colon/
8. rectum/
9. or/4-8
10. (pharmacoeconomic* or economic* or price* or pricing* or cost* or cba or cea or cua or "health utilit*" or "value for money").tw.
11. (fiscal or funding or financial or finance* or expenditure* or budget*).tw.
12. ("resource* alloca*" or "resource* use").tw.

13. exp Economics/
14. exp models, economic/
15. exp "Costs and Cost Analysis"/
16. Cost of illness/
17. ec.fs.
18. (decision adj2 (model* or tree* or analy*)).tw.
19. markov.tw.
20. decision trees/
21. or/10-20
22. 3 and 9 and 21
23. limit 22 to english language

Database:	MEDLINE In-Process & Other Non-Indexed Citations
Host:	Ovid
Data Parameters:	January 07, 2015
Date Searched:	8/1/2015
Searcher:	SB
Hits:	24

1. (cetuximab or erbitux or C225 or "IMC C225").tw.
2. (panitumumab or vectibix or " ABX-EGF").tw.
3. 1 or 2
4. (colorectal or colon or colonic or rectal or rectum or bowel or intenstin*).tw.
5. (CRC or mCRC).tw.
6. 4 or 5

7. (pharmacoeconomic* or economic* or price* or pricing* or cost* or cba or cea or cua or "health utilit*" or "value for money").tw.

8. (fiscal or funding or financial or finance* or expenditure* or budget*).tw.

9. ("resource* alloca*" or "resource* use").tw.

10. (decision adj2 (model* or tree* or analy*)).tw.

11. markov.tw.

12. or/7-11

13. 3 and 6 and 12

Database:	EMBASE
Host:	Ovid
Data Parameters:	1974 to 2015 January 07
Date Searched:	8/1/2015
Searcher:	SB
Hits:	1314

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1. (cetuximab or erbitux or C225 or "IMC C225").tw.

2. cetuximab/

3. (panitumumab or vectibix or " ABX-EGF").tw.

4. panitumumab/

5. or/1-4

6. (colorectal or colon or colonic or rectal or rectum or bowel or intenstin*).tw.

7. (CRC or mCRC).tw.

8. exp colon/

9. exp colon tumor/

10. exp rectum/

11. exp rectum tumor/

12. or/6-11

13. (pharmacoeconomic* or economic* or price* or pricing* or cost* or cba or cea or cua or "health utilit*" or "value for money").tw.

14. (fiscal or funding or financial or finance* or expenditure* or budget*).tw.

15. ("resource* alloca*" or "resource* use").tw.

16. exp Economics/

17. models, economic/

18. exp health economics/

19. exp "Costs and Cost Analysis"/

20. Cost of illness/

21. resource allocation/

22. pe.fs.

23. (decision adj2 (model* or tree* or analy*)).tw.

24. markov.tw.

25. decision trees/

26. or/13-25

27. 5 and 12 and 26

28. limit 27 to english language

Database:	Web of Science
Host:	Thomson Reuters
Data Parameters:	SCI-EXPANDED and CPCI-S
Date Searched:	8/1/2015
Searcher:	SB

Hits: 231

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1. TITLE: (cetuximab or erbitux or C225 or "IMC C225") OR TOPIC: (cetuximab or erbitux or C225 or "IMC C225")

2. TITLE: (panitumumab or vectibix or " ABX-EGF") OR TOPIC: (panitumumab or vectibix or " ABX-EGF")

3. #2 OR #1

4. TITLE: (colorectal or colon or colonic or rectal or rectum or bowel or intenstin*) OR TOPIC: (colorectal or colon or colonic or rectal or rectum or bowel or intenstin*)

5. TITLE: (CRC or mCRC) OR TOPIC: (CRC or mCRC)

6. #5 OR #4

7. TITLE: (pharmacoeconomic* or economic* or price* or pricing* or cost* or cba or cea or cua or "health utilit*" or "value for money") OR TOPIC: (pharmacoeconomic* or economic* or price* or pricing* or cost* or cba or cea or cua or "health utilit*" or "value for money")

8. TITLE: (fiscal or funding or financial or finance* or expenditure* or budget*) OR TOPIC: (fiscal or funding or financial or finance* or expenditure* or budget*)

9. TITLE: ("resource* alloca*" or "resource* use") OR TOPIC: ("resource* alloca*" or "resource* use")

10. TITLE: (decision near/1 (model* or tree* or analy*)) OR TOPIC: (decision near/1 (model* or tree* or analy*))

11. TITLE: (markov) OR TOPIC: (markov)

12. #11 OR #10 OR #9 OR #8 OR #7

13. #12 AND #6 AND #3

Database: NHS EED

Host: Cochrane Collaboration

Data Parameters: Issue 4 of 4 Oct 2014

Date Searched: 8/1/2015

Searcher: SB

Hits: 10

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1. (cetuximab or erbitux or C225 or "IMC C225"):ti or (cetuximab or erbitux or C225 or "IMC C225"):ab

2. (panitumumab or vectibix or " ABX-EGF"):ti or (panitumumab or vectibix or " ABX-EGF"):ab

3. #1 or #2

4. (colorectal or colon or colonic or rectal or rectum or bowel or intenstin*):ti or (colorectal or colon or colonic or rectal or rectum or bowel or intenstin*):ab

5. (CRC or mCRC):ti or (CRC or mCRC):ab

6. MeSH descriptor: [Colorectal Neoplasms] explode all trees

7. MeSH descriptor: [Colon] explode all trees

8. MeSH descriptor: [Rectum] explode all trees

9. #4 or #5 or #6 or #7 or #8

10. #3 and #9 in Economic Evaluations

Database: EconLit

Host: EBSCO

Data Parameters: n/a

Date Searched: 8/1/2015

Searcher: SB

Hits: 0

1. TI (cetuximab or erbitux or C225 or "IMC C225") OR AB (cetuximab or erbitux or C225 or "IMC C225")

2. TI (panitumumab or vectibix or " ABX-EGF") OR AB (panitumumab or vectibix or " ABX-EGF")

3. S1 OR S2

4. TI (colorectal or colon or colonic or rectal or rectum or bowel or intenstin*) OR AB (colorectal or colon or colonic or rectal or rectum or bowel or intenstin*)

5. TI (CRC or mCRC) OR AB (CRC or mCRC)

6. S4 OR S5

7. (S3 AND S6)

Cost effectiveness titles/abstracts identified by searches

Database:	**Hits**
MEDLINE	126
MEDLINE in Process	24
EMBASE	1314
Web of Science	231
NHS EED	10
EconLit	10
DARE	0
Total	**1705**

Quality of Life

Database:	MEDLINE
Host:	Ovid
Data Parameters:	1946 to January Week 1 2015
Date Searched:	13/1/2015
Searcher:	SB
Hits:	67

1. (cetuximab or erbitux or C225 or "IMC C225").tw.
2. (panitumumab or vectibix or "ABX-EGF").tw.
3. 1 or 2
4. (colorectal or colon or colonic or rectal or rectum or bowel or intenstin*).tw.
5. (CRC or mCRC).tw.
6. exp Colorectal Neoplasms/
7. colon/
8. rectum/
9. or/4-8
10. ("quality of life" or QoL or HRQL or HRQoL or AQoL).tw.
11. quality of life/
12. ("quality adjusted life year*" or QALY*).tw.
13. quality-adjusted life years/
14. ("quality of wellbeing" or QWB).tw.
15. ("health* year* equivalent*" or HYE*).tw.
16. "health status".tw.
17. health status/

18. health status indicators/

19. ("short form 36" or "shortform 36" or "short form thirty six" or "shortform thirty six" or "SF 36" or SF36 or "SF thirty six").tw.

20. ("short form 20" or "shortform 20" or "short form twenty" or "shortform twenty" or "SF 20" or SF20 or "SF twenty").tw.

21. ("short form 16" or "shortform 16" or "short form sixteen" or "shortform sixteen" or "SF 16" or SF16 or "SF sixteen").tw.

22. ("short form 12" or "shortform 12" or "short form twelve" or "shortform twelve" or "SF 12" or "SF12 or “SF twelve").tw.

23. ("short form 10" or "shortform 10" or "short form ten" or "shortform ten" or SF10 or "SF 10" or "SF ten").tw.

24. ("short form 6" or "shortform 6" or "short form six" or "shortform six" or SF6 or "SF 6" or "SF six").tw.

25. (Euroqol or "EQ-5D").tw.

26. Health Surveys/

27. questionnaire*.tw.

28. exp Questionnaires/

29. "willingness to pay".tw.

30. ("time trade off" or "time tradeoff" or tto).tw.

31. ("visual analog* scale" or VAS).tw.

32. (health adj2 (utilit*3 or value* or preference*)).tw.

33. ("health utilities index*" or hui or hui1 or hui2 or hui3 or hui4 or "hui 1" or "hui 2" or "hui 3" or "hui 4").tw.

34. disutil*.tw.

35. "standard gamble*".tw.

36. "discrete choice".tw.

37. or/10-36

38. 3 and 9 and 37

39. limit 38 to english language

Database:	MEDLINE In-Process & Other Non-Indexed Citations
Host:	Ovid
Data Parameters:	January 12, 2015
Date Searched:	13/1/2015
Searcher:	SB
Hits:	13

1. (cetuximab or erbitux or C225 or "IMC C225").tw.
2. (panitumumab or vectibix or "ABX-EGF").tw.
3. 1 or 2
4. (colorectal or colon or colonic or rectal or rectum or bowel or intenstin*).tw.
5. (CRC or mCRC).tw.
6. 4 or 5
7. ("quality of life" or QoL or HRQL or HRQoL or AQoL).tw.
8. ("quality adjusted life year*" or QALY*).tw.
9. ("quality of wellbeing" or QWB).tw.
10. ("health* year* equivalent*" or HYE*).tw.
11. "health status".tw.
12. ("short form 36" or "shortform 36" or "short form thirty six" or "shortform thirty six" or "SF 36" or SF36 or "SF thirty six").tw.
13. ("short form 20" or "shortform 20" or "short form twenty" or "shortform twenty" or "SF 20" or SF20 or "SF twenty").tw.
14. ("short form 16" or "shortform 16" or "short form sixteen" or "shortform sixteen" or "SF 16" or SF16 or "SF sixteen").tw.
15. ("short form 12" or "shortform 12" or "short form twelve" or "shortform twelve" or "SF 12" or "SF12 or “SF twelve").tw.
16. ("short form 10" or "shortform 10" or "short form ten" or "shortform ten" or SF10 or "SF 10" or "SF ten").tw.

17. ("short form 6" or "shortform 6" or "short form six" or "shortform six" or SF6 or "SF 6" or "SF six").tw.

18. (Euroqol or "EQ-5D").tw.

19. questionnaire*.tw.

20. "willingness to pay".tw.

21. ("time trade off" or "time tradeoff" or tto).tw.

22. ("visual analog* scale" or VAS).tw.

23. (health adj2 (utilit*3 or value* or preference*)).tw.

24. ("health utilities index*" or hui or hui1 or hui2 or hui3 or hui4 or "hui 1" or "hui 2" or "hui 3" or "hui 4").tw.

25. disutil*.tw.

26. "standard gamble*".tw.

27. "discrete choice".tw.

28. or/7-27

29. 3 and 6 and 28

Database:	EMBASE
Host:	Ovid
Data Parameters:	1974 to 2015 January 12
Date Searched:	13/1/2015
Searcher:	SB
Hits:	734

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1. (cetuximab or erbitux or C225 or "IMC C225").tw.

2. cetuximab/

3. (panitumumab or vectibix or "ABX-EGF").tw.

4. panitumumab/

5. or/1-4

6. (colorectal or colon or colonic or rectal or rectum or bowel or intenstin*).tw.

7. (CRC or mCRC).tw.

8. exp colon/

9. exp colon tumor/

10. exp rectum/

11. exp rectum tumor/

12. or/6-11

13. ("quality of life" or QoL or HRQL or HRQoL or AQoL).tw.

14. exp quality of life/

15. ("quality adjusted life year*" or QALY*).tw.

16. quality-adjusted life years/

17. ("quality of wellbeing" or QWB).tw.

18. ("health* year* equivalent*" or HYE*).tw.

19. "health status".tw.

20. health status/

21. health status indicators/

22. ("short form 36" or "shortform 36" or "short form thirty six" or "shortform thirty six" or "SF 36" or SF36 or "SF thirty six").tw.

23. ("short form 20" or "shortform 20" or "short form twenty" or "shortform twenty" or "SF 20" or SF20 or "SF twenty").tw.

24. ("short form 16" or "shortform 16" or "short form sixteen" or "shortform sixteen" or "SF 16" or SF16 or "SF sixteen").tw.

25. ("short form 12" or "shortform 12" or "short form twelve" or "shortform twelve" or "SF 12" or "SF12 or “SF twelve").tw.

26. ("short form 10" or "shortform 10" or "short form ten" or "shortform ten" or SF10 or "SF 10" or "SF ten").tw.

27. ("short form 6" or "shortform 6" or "short form six" or "shortform six" or SF6 or "SF 6" or "SF six").tw.

28. (Euroqol or "EQ-5D").tw.

29. health survey/

30. questionnaire*.tw.

31. exp questionnaire/

32. "willingness to pay".tw.

33. ("time trade off" or "time tradeoff" or tto).tw.

34. ("visual analog* scale" or VAS).tw.

35. (health adj2 (utilit*3 or value* or preference*)).tw.

36. ("health utilities index*" or hui or hui1 or hui2 or hui3 or hui4 or "hui 1" or "hui 2" or "hui 3" or "hui 4").tw.

37. disutil*.tw.

38. "standard gamble*".tw.

39. "discrete choice".tw.

40. or/13-39

41. 5 and 12 and 40

42. limit 41 to english language

Database:	PsycINFO
Host:	Ovid
Data Parameters:	1806 to January Week 1 2015
Date Searched:	13/1/2015
Searcher:	SB
Hits:	2

1. (cetuximab or erbitux or C225 or "IMC C225").tw.

2. (panitumumab or vectibix or "ABX-EGF").tw.

3. 1 or 2

4. (colorectal or colon or colonic or rectal or rectum or bowel or intenstin*).tw.

5. (CRC or mCRC).tw.

6. 4 or 5

7. ("quality of life" or QoL or HRQL or HRQoL or AQoL).tw.

8. quality of life/

9. ("quality adjusted life year*" or QALY*).tw.

10. ("quality of wellbeing" or QWB).tw.

11. ("health* year* equivalent*" or HYE*).tw.

12. "health status".tw.

13. ("short form 36" or "shortform 36" or "short form thirty six" or "shortform thirty six" or "SF 36" or SF36 or "SF thirty six").tw.

14. ("short form 20" or "shortform 20" or "short form twenty" or "shortform twenty" or "SF 20" or SF20 or "SF twenty").tw.

15. ("short form 16" or "shortform 16" or "short form sixteen" or "shortform sixteen" or "SF 16" or SF16 or "SF sixteen").tw.

16. ("short form 12" or "shortform 12" or "short form twelve" or "shortform twelve" or "SF 12" or "SF12 or “SF twelve").tw.

17. ("short form 10" or "shortform 10" or "short form ten" or "shortform ten" or SF10 or "SF 10" or "SF ten").tw.

18. ("short form 6" or "shortform 6" or "short form six" or "shortform six" or SF6 or "SF 6" or "SF six").tw.

19. (Euroqol or "EQ-5D").tw.

20. questionnaire*.tw.

21. exp Questionnaires/

22. "willingness to pay".tw.

23. ("time trade off" or "time tradeoff" or tto).tw.

24. ("visual analog* scale" or VAS).tw.

25. (health adj2 (utilit*3 or value* or preference*)).tw.

26. ("health utilities index*" or hui or hui1 or hui2 or hui3 or hui4 or "hui 1" or "hui 2" or "hui 3" or "hui 4").tw.

27. disutil*.tw.

28. "standard gamble*".tw.

29. "discrete choice".tw.

30. or/7-29

31. 3 and 6 and 30

32. limit 31 to english language

Database:	Web of Science
Host:	Thomson Reuters
Data Parameters:	SCI-EXPANDED and CPCI-S
Date Searched:	13/1/2015
Searcher:	SB
Hits:	171

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1. TITLE: (cetuximab or erbitux or C225 or "IMC C225") OR TOPIC: (cetuximab or erbitux or C225 or "IMC C225")

2. TITLE: (panitumumab or vectibix or "ABX-EGF") OR TOPIC: (panitumumab or vectibix or "ABX-EGF")

3. #2 OR #1

4. TITLE: (colorectal or colon or colonic or rectal or rectum or bowel or intenstin*) OR TOPIC: (colorectal or colon or colonic or rectal or rectum or bowel or intenstin*)

5. TITLE: (CRC or mCRC) OR TOPIC: (CRC or mCRC)

6. #5 OR #4

7. TITLE: ("quality of life" or QoL or HRQL or HRQoL or AQoL) OR TOPIC: ("quality of life" or QoL or HRQL or HRQoL or AQoL)

8. TITLE: ("quality adjusted life year*" or QALY*) OR TOPIC: ("quality adjusted life year*" or QALY*)

9. TITLE: ("quality of wellbeing" or QWB) OR TOPIC: ("quality of wellbeing" or QWB)

10. TITLE: ("health* year* equivalent*" or HYE*) OR TOPIC: ("health* year* equivalent*" or HYE*)

11. TITLE: (health status) OR TOPIC: (health status)

12. TITLE: ("short form 36" or "shortform 36" or "short form thirty six" or "shortform thirty six" or "SF 36" or SF36 or "SF thirty six") OR TOPIC: ("short form 36" or "shortform 36" or "short form thirty six" or "shortform thirty six" or "SF 36" or SF36 or "SF thirty six")

13. TITLE: ("short form 20" or "shortform 20" or "short form twenty" or "shortform twenty" or "SF 20" or SF20 or "SF twenty") OR TOPIC: ("short form 20" or "shortform 20" or "short form twenty" or "shortform twenty" or "SF 20" or SF20 or "SF twenty")

14. TITLE: ("short form 16" or "shortform 16" or "short form sixteen" or "shortform sixteen" or "SF 16" or SF16 or "SF sixteen") OR TOPIC: ("short form 16" or "shortform 16" or "short form sixteen" or "shortform sixteen" or "SF 16" or SF16 or "SF sixteen")

15. TITLE: ("short form 12" or "shortform 12" or "short form twelve" or "shortform twelve" or "SF 12" or "SF12 or “SF twelve") OR TOPIC: ("short form 12" or "shortform 12" or "short form twelve" or "shortform twelve" or "SF 12" or "SF12 or “SF twelve")

16. TITLE: ("short form 10" or "shortform 10" or "short form ten" or "shortform ten" or SF10 or "SF 10" or "SF ten") OR TOPIC: ("short form 10" or "shortform 10" or "short form ten" or "shortform ten" or SF10 or "SF 10" or "SF ten")

17. TITLE: ("short form 6" or "shortform 6" or "short form six" or "shortform six" or SF6 or "SF 6" or "SF six") OR TOPIC: ("short form 6" or "shortform 6" or "short form six" or "shortform six" or SF6 or "SF 6" or "SF six")

18. TITLE: (Euroqol or "EQ-5D") OR TOPIC: (Euroqol or "EQ-5D")

19. TITLE: (questionnaire*) OR TOPIC: (questionnaire*)

20. TITLE: ("willingness to pay") OR TOPIC: ("willingness to pay")

21. TITLE: ("visual analog* scale" or VAS) OR TOPIC: ("visual analog* scale" or VAS)

22. TITLE: ("time trade off" or "time tradeoff" or tto) OR TOPIC: ("time trade off" or "time tradeoff" or tto)

23. TITLE: (health near/1 (utilit*3 or value* or preference*)) OR TOPIC: (health near/1 (utilit*3 or value* or preference*))

24. TITLE: ("health utilities index*" or hui or hui1 or hui2 or hui3 or hui4 or "hui 1" or "hui 2" or "hui 3" or "hui 4") OR TOPIC: ("health utilities index*" or hui or hui1 or hui2 or hui3 or hui4 or "hui 1" or "hui 2" or "hui 3" or "hui 4")

25. TITLE: (disutil*) OR TOPIC: (disutil*)

26. TITLE: ("standard gamble*") OR TOPIC: ("standard gamble*")

27. TITLE: ("discrete choice") OR TOPIC: ("discrete choice")

28. #27 OR #26 OR #25 OR #24 OR #23 OR #22 OR #21 OR #20 OR #19 OR #18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7

29. #28 AND #6 AND #3

Database:	ScHARRHUD
Host:	ScHARR
Data Parameters:	n/a
Date Searched:	13/1/2015
Searcher:	SB
Hits:	1

1. (cetuximab or erbitux or C225 or "IMC C225") in Title
2. (cetuximab or erbitux or C225 or "IMC C225") in Abstract
3. (panitumumab or vectibix or "ABX-EGF") in Title
4. (panitumumab or vectibix or "ABX-EGF") in Abstract
5. #1 OR #2 OR #3 OR #4

Quality of life titles/abstracts identified by searches

Database:	**Hits**
MEDLINE	67
MEDLINE in Process	13
EMBASE	734
PsychINFO	2

Web of Science	171
ScHARRHUD	1
Total	**988**

Combined cost-effectiveness and quality of life titles/abstracts identified by searches

Database:	**Hits**
Cost effectiveness	1705
Quality of Life	988
Total	2693
Duplicate records	714
Total records to screen	**1979**

Update searches

Clinical effectiveness

Database: MEDLINE

Host: Ovid

Data Parameters: 1946 to April Week 3 2015

Date Searched: 27/4/2015

Searcher: SB

Hits: 48

Strategy: See main strategy (date limited 2014-current).

Database: MEDLINE In-Process & Other Non-Indexed Citations

Host: Ovid

Data Parameters: April 24, 2015

Date Searched: 27/4/2015

Searcher: SB

Hits: 66

Strategy: See main strategy (no date limit used).

Database: EMBASE

Host: Ovid

Data Parameters: 1974 to 2015 April 24

Date Searched: 27/4/2015

Searcher: SB

Hits: 48

Strategy: See main strategy (date limited 2015-current).

Database: Web of Science

Host: Thomson Reuters

Data Parameters: SCI-EXPANDED and CPCI-S

Date Searched: 27/4/2015

Searcher: SB

Hits: 42

Strategy: See main strategy (date limited 2015-current).

Database: CENTRAL

Host: Cochrane Collaboration

Data Parameters: Issue 3 of 12, March 2015

Date Searched: 27/4/2015

Searcher: SB

Hits: 1

Strategy: See main strategy (date limited 2015-current).

Database: Cochrane Database of Systematic Reviews (CDSR)

Host: Cochrane Collaboration

Data Parameters: Issue 4 of 12, April 2015

Date Searched: 27/4/2015

Searcher: SB

Hits: 0

Strategy: See main strategy (date limited 2015-current).

Database: DARE

Host: Cochrane Collaboration

Data Parameters: Issue 1 of 4, January 2015

Date Searched: 27/4/2015

Searcher: SB

Hits: 0

Strategy: See main strategy (date limited 2015-current).

Notes: Funding for DARE ended in March 2015 and no new records have been added since January 2015.

Database: HTA

Host: Cochrane Collaboration

Data Parameters: Issue 1 of 4, January 2015

Date Searched: 27/4/2015

Searcher: SB

Hits: 0

Strategy: See main strategy (date limited 2015-current).

Numbers of clinical effectiveness references

Clinical effectiveness titles/abstracts identified by update searches

Clinical effectiveness titles/abstracts identified by update searches

Database:	**Hits**
MEDLINE	48
MEDLINE in Process	66
EMBASE	48
Web of Science	42
CENTRAL	1
CDSR	0
DARE	0
HTA	0
Total	**205**
Duplicate records	**30**
Total records to screen	**175**

Cost effectiveness

Database: MEDLINE

Host: Ovid

Data Parameters: 1946 to April Week 3 2015

Date Searched: 27/4/2015

Searcher: SB

Hits: 12

Strategy: See main strategy (date limited 2014-current).

Database: MEDLINE In-Process & Other Non-Indexed Citations

Host: Ovid

Data Parameters: April 24, 2015

Date Searched: 27/4/2015

Searcher: SB

Hits: 20

Strategy: See main strategy (no date limit used).

Database: EMBASE

Host: Ovid

Data Parameters: 1974 to 2015 April 24

Date Searched: 27/4/2015

Searcher: SB

Hits: 26

Strategy: See main strategy (date limited 2015-current).

Database: Web of Science

Host: Thomson Reuters

Data Parameters: SCI-EXPANDED and CPCI-S

Date Searched: 27/4/2015

Searcher: SB

Hits: 9

Strategy: See main strategy (date limited 2015-current).

Database: NHS EED

Host: Cochrane Collaboration

Data Parameters: Issue 4 of 4 Oct 2014

Date Searched: 8/1/2015

Searcher: SB

Hits: 0

Strategy: See main strategy (date limited 2015-current).

Notes: Funding for NHS EED ended in March 2015 and no new records have been added since January 2015.

Database: EconLit

Host: EBSCO

Data Parameters: n/a

Date Searched: 8/1/2015

Searcher: SB

Hits: 0

Strategy: See main strategy (date limited 2015-current).

Numbers of cost effectiveness references

Cost effectiveness titles/abstracts identified by update searches

Database:	**Hits**
MEDLINE	12
MEDLINE in Process	20
EMBASE	26
Web of Science	9
NHS EED	0
EconLit	0
Total	**67**

Quality of Life

Database: MEDLINE

Host: Ovid

Data Parameters: 1946 to April Week 3 2015

Date Searched: 27/4/2015

Searcher: SB

Hits: 0

Strategy: See main strategy (date limited 2015-current).

Database: MEDLINE In-Process & Other Non-Indexed Citations

Host: Ovid

Data Parameters: April 24, 2015

Date Searched: 27/4/2015

Searcher: SB

Hits: 14

Strategy: See main strategy (no date limit used).

Database: EMBASE

Host: Ovid

Data Parameters: 1974 to 2015 April 24

Date Searched: 27/4/2015

Searcher: SB

Hits: 14

Strategy: See main strategy (date limited 2015-current).

Database: PsycINFO

Host: Ovid

Data Parameters: 1806 to April Week 3 2015

Date Searched: 27/4/2015

Searcher: SB

Hits: 0

Strategy: See main strategy (date limited 2015-current).

Database: Web of Science

Host: Thomson Reuters

Data Parameters: SCI-EXPANDED and CPCI-S

Date Searched: 27/4/2015

Searcher: SB

Hits: 3

Strategy: See main strategy (date limited 2015-current).

Database: ScHARRHUD

Host: ScHARR

Data Parameters:

Date Searched: 27/4/2015

Searcher: SB

Hits: 0

Strategy: See main strategy (date limited 2015-current).

Numbers of quality of life references

Quality of life titles/abstracts identified by update searches

Database:	**Hits**
MEDLINE	0
MEDLINE in Process	14
EMBASE	14
PsycINFO	0
Web of Science	3
ScHARRHUD	0
Total	**31**

Combined cost effectiveness and quality of life references

Combined cost effectiveness and quality of life titles/abstracts identified by update searches

Database:	**Hits**
Cost effectiveness	67
Quality of life	31
Total	**98**
Duplicate records	**18**

Total records to screen **80**

Clinical trials registries

The following terms were used to search the **ClinicalTrials.gov register** for condition and interventions:

Condition: colorectal OR colon OR colonic OR rectal OR rectum OR bowel or intenstin* OR CRC OR mCRC

Intervention: cetuximab OR erbitux OR C225 OR "IMC C225" OR panitumumab OR vectibix OR "ABX-EGF"

The following terms were used to search the **WHO (ICTRP) register** for condition and interventions:

Condition: colorectal OR colon OR colonic OR rectal OR rectum OR bowel or intenstin* OR CRC OR mCRC

Intervention: cetuximab OR erbitux OR C225 OR "IMC C225" OR panitumumab OR vectibix OR "ABX-EGF"

The following terms were used to search the **UK Clinical Research Network (UKCRN) portfolio**:

cetuximab erbitux C225 "IMC C225" panitumumab vectibix "ABX-EGF"

The following terms were used to search the **Controlled Trials (ISRCTN) registry**:

cetuximab OR erbitux OR C225 OR "IMC C225" OR panitumumab OR vectibix OR "ABX-EGF"

Appendix C: List of excluded studies

Please find a list of excluded studies by reason for exclusion from the clinical effectiveness review.

Berlin J, Posey J, Tchekmedyian S, Hu E, Chan D, Malik I, et al. Panitumumab with irinotecan/leucovorin/5-fluorouracil for first-line treatment of metastatic colorectal cancer. Clinical Colorectal Cancer. 2007;6:427-32.	Comparator
Douillard JY, Zemelka T, Fountzilas G, Barone C, Schlichting M, Heighway J, et al. FOLFOX4 with cetuximab vs. UFOX with cetuximab as first-line therapy in metastatic colorectal cancer: The randomized phase II FUTURE study. Clinical Colorectal Cancer. 2014;13:14-26.e1.	Comparator
Adams RA, Meade AM, Seymour MT, Wilson RH, Madi A, Fisher D, et al. Intermittent versus continuous oxaliplatin and fluoropyrimidine combination chemotherapy for first-line treatment of advanced colorectal cancer: Results of the randomised phase 3 MRC COIN trial. The Lancet Oncology. 2011;12:642-53.	Population
Alberts SR, Sargent DJ, Nair S, Mahoney MR, Mooney M, Thibodeau SN, et al. Effect of Oxaliplatin, Fluorouracil, and Leucovorin With or Without Cetuximab on Survival Among Patients With Resected Stage III Colon Cancer A Randomized Trial. JAMA-J Am Med Assoc. 2012;307:1383-93.	Population
Blons H, Emile JF, Le Malicot K, Julie C, Zaanan A, Tabernero J, et al. Prognostic value of KRAS mutations in stage III colon cancer: post hoc analysis of the PETACC8 phase III trial dataset. Annals of Oncology. 2014;25:2378-85.	Population
Bokemeyer C, Bondarenko I, Makhson A, Hartmann JT, Aparicio J, Braud F, et al. Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology [Internet]. 2009; 27(5):[663-71 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/493/CN-00667493/frame.html.	Population
Bokemeyer C, Bondarenko I, Hartmann JT, Braud F, Schuch G, Zubel A, et al. Efficacy according to biomarker status of cetuximab plus FOLFOX-4 as first-line treatment for metastatic colorectal cancer: the OPUS study. Annals of oncology [Internet]. 2011; 22(7):[1535-46 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/959/CN-00801959/frame.html.	Population
Bokemeyer C, Cutsem E, Rougier P, Ciardiello F, Heeger S, Schlichting M, et al. Addition of cetuximab to chemotherapy as first-line treatment for KRAS wild-type metastatic colorectal cancer: pooled analysis of the CRYSTAL and OPUS randomised clinical trials. European journal of cancer (Oxford, England : 1990) [Internet]. 2012; 48(10):[1466-75 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/341/CN-00837341/frame.html.	Population
Cervantes-Ruiperez A, Markman B, Siena S, Pericay C, Aprile G, Bridgewater JA, et al. The GAIN-C study (BP25438): Randomized phase II trial of RG7160 (GA201) plus FOLFIRI, compared to cetuximab plus FOLFIRI or FOLFIRI alone in second-line KRAS wild type (WT) or mutant metastatic colorectal cancer (mCRC). Journal of Clinical Oncology. 2012;30:1.	Population
Cutsem E, Köhne CH, Hitre E, Zaluski J, Chang Chien CR, Makhson A, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. New England journal of medicine [Internet]. 2009; 360(14):[1408-17 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/598/CN-00683598/frame.html.	Population
Cutsem E, Köhne CH, Láng I, Folprecht G, Nowacki MP, Cascinu S, et al. Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor KRAS and BRAF mutation status. Journal of clinical oncology [Internet]. 2011; 29(15):[2011-9 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/862/CN-	Population

00788862/frame.html.

Douillard JY, Siena S, Cassidy J, Tabernero J, Burkes R, Barugel M, et al. Final results from PRIME: randomized phase III study of panitumumab with FOLFOX4 for first-line treatment of metastatic colorectal cancer. Annals of Oncology. 2014;25:1346-55. Population

Douillard JY, Siena S, Cassidy J, Tabernero J, Burkes R, Barugel M, et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. Journal of Clinical Oncology. 2010;28:4697-705. Population

Lang I, Kohne CH, Folprecht G, Rougier P, Curran D, Hitre E, et al. Quality of life analysis in patients with KRAS wild-type metastatic colorectal cancer treated first-line with cetuximab plus irinotecan, fluorouracil and leucovorin. European journal of cancer [Internet]. 2013; 49(2):[439-48 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/912/CN-00912912/frame.html. Population

Maughan TS, Adams RA, Smith CG, Meade AM, Seymour MT, Wilson RH, et al. Addition of cetuximab to oxaliplatin-based first-line combination chemotherapy for treatment of advanced colorectal cancer: Results of the randomised phase 3 MRC COIN trial. The Lancet. 2011;377:2103-14. Population

Mitchell EP, Lacouture M, Shearer H, Iannotti N, Piperdi B, Pillai M, et al. Final STEPP results of prophylacatic versus reactive skin toxicity (ST) treatment (tx) for panitumumab (pmab)-related ST in patients (pts) with metastatic colorectal cancer (mCRC). Journal of Clinical OncologyConference: 2009 Annual Meeting of the American Society of Clinical Oncology, ASCO Orlando, FL United StatesConference Start: 20090529 Conference End: 20090602Conference Publication: (varpagings). 2009;27:RA4027. Population

Mitchell EP, Piperdi B, Lacouture ME, Shearer H, Iannotti N, Pillai MV, et al. The efficacy and safety of panitumumab administered concomitantly with FOLFIRI or Irinotecan in second-line therapy for metastatic colorectal cancer: the secondary analysis from STEPP (Skin Toxicity Evaluation Protocol With Panitumumab) by KRAS status. Clinical Colorectal Cancer. 2011;10:333-9. Population

Ocvirk J, Brodowicz T, Wrba F, Ciuleanu TE, Kurteva G, Beslija S, et al. Cetuximab plus FOLFOX6 or FOLFIRI in metastatic colorectal cancer: CECOG trial. World Journal of Gastroenterology. 2010;16:3133-43. Population

Polikoff J, Mitchell EP, Badarinath S, Graham CD, Jennis A, Chen TT, et al. Cetuximab plus FOLFOX for colorectal cancer (EXPLORE): Preliminary efficacy analysis of a randomized phase III trial. Journal of Clinical Oncology. 2005;23:264S-S. Population

Poulin-Costello M, Azoulay L, Van Cutsem E, Peeters M, Siena S, Wolf M. An analysis of the treatment effect of panitumumab on overall survival from a phase 3, randomized, controlled, multicenter trial (20020408) in patients with chemotherapy refractory metastatic colorectal cancer. Targeted Oncology. 2013;8:127-36. Population

Price TJ, Peeters M, Kim TW, Li J, Cascinu S, Ruff P, et al. Panitumumab versus cetuximab in patients with chemotherapy-refractory wild-type KRAS exon 2 metastatic colorectal cancer (ASPECCT): a randomised, multicentre, open-label, non-inferiority phase 3 study. Lancet Oncology. 2014;15:569-79. Population

Primrose J, Falk S, Finch-Jones M, Valle J, O'Reilly D, Siriwardena A, et al. Systemic chemotherapy with or without cetuximab in patients with resectable colorectal liver metastasis: the New EPOC randomised controlled trial.[Erratum appears in Lancet Oncol. 2014 Jun;15(7):e253]. Lancet Oncology. 2014;15:601-11. Population

Seymour MT, Brown SR, Middleton G, Maughan T, Richman S, Gwyther S, et al. Panitumumab and irinotecan versus irinotecan alone for patients with KRAS wild-type, fluorouracil-resistant advanced colorectal cancer (PICCOLO): a prospectively stratified randomised trial. Lancet Oncology. 2013;14:749-59. Population

Siena S, Glynne-Jones R, Adenis A, Thaler J, Preusser P, Aguilar EA, et al. Reduced incidence of infusion-related reactions in metastatic colorectal cancer during treatment with cetuximab plus irinotecan with combined corticosteroid and antihistamine premedication. Cancer. 2010;116:1827-37. Population

Stintzing S, Fischer von Weikersthal L, Decker T, Vehling-Kaiser U, Jager E, Heintges T, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer-subgroup analysis of patients with KRAS: mutated tumours in the randomised German AIO study KRK-0306. Annals of Oncology. 2012;23:1693-9.	Population
Taieb J, Tabernero J, Mini E, Subtil F, Folprecht G, Van Laethem JL, et al. Oxaliplatin, fluorouracil, and leucovorin with or without cetuximab in patients with resected stage III colon cancer (PETACC-8): an open-label, randomised phase 3 trial. Lancet Oncology. 2014;15:862-73.	Population
Tveit KM, Guren T, Glimelius B, Pfeiffer P, Sorbye H, Pyrhonen S, et al. Phase III trial of cetuximab with continuous or intermittent fluorouracil, leucovorin, and oxaliplatin (Nordic FLOX) versus FLOX alone in first-line treatment of metastatic colorectal cancer: the NORDIC-VII study. Journal of Clinical Oncology. 2012;30:1755-62.	Population
Wasan H, Meade AM, Adams R, Wilson R, Pugh C, Fisher D, et al. Intermittent chemotherapy plus either intermittent or continuous cetuximab for first-line treatment of patients with KRAS wild-type advanced colorectal cancer (COIN-B): A randomised phase 2 trial. The Lancet Oncology. 2014;15:631-9.	Population
Ye LC, Liu TS, Ren L, Wei Y, Zhu DX, Zai SY, et al. Randomized controlled trial of cetuximab plus chemotherapy for patients with KRAS wild-type unresectable colorectal liver-limited metastases. Journal of Clinical Oncology. 2013;31:1931-8.	Population
Heinemann V, Fischer Von Weikersthal L, Decker T, Kiani A, Verhling-Kaiser U, Al Batran S, et al. Randomized comparison of FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment of KRAS-wildtype metastatic colorectal cancer: The FIRE- 3 trial (AIO KRK 0307). Jahrestagung der Deutschen, Osterreichischen und Schweizerischen Gesellschaften fur Hamatologie und Onkologie 2013 Wien Austria. 2013;36:105.	Population[a]
Schwartzberg LS, Rivera F, Karthaus M, Fasola G, Canon JL, Yu H, et al. Analysis of KRAS/NRAS mutations in PEAK: A randomized phase II study of FOLFOX6 plus panitumumab (pmab) or bevacizumab (bev) as first-line treatment (tx) for wild-type (WT) KRAS (exon 2) metastatic colorectal cancer (mCRC). Journal of Clinical Oncology. 2013;31:1.	Population[a]
Seymour MT, Brown SR, Richman S, Middleton GW, Maughan TS, Maisey N, et al. Panitumumab in Combination With Irinotecan for Chemoresistant Advanced Colorectal Cancer: Results of PICCOLO, a Large Randomised Trial With Prospective Molecular Stratification. European Journal of Cancer. 2011;47:S393-S.	Population[a]
Siena S, Douillard JY, Tabernero J, Cassidy J, Burkes R, Barugel M, et al. Panitumumab with FOLFOX4 versus FOLFOX4 alone as first-line treatment for metastatic colorectal cancer (mCRC): results from the randomised phase III PRIME study. Onkologie. 2010;33:68-9.	Population[a]
Siena S, Tabernero J, Cunningham D, Koralewski P, Ruff P, Rother M, et al. Randomized phase III study of panitumumab (pmab) with FOLFOX4 compared to FOLFOX4 alone as fist-line treatment (tx) for metastatic colorectal cancer (mCRC): PRIME trial analysis by epidermal growth factor receptor (EGFR) tumor staining. Journal of Clinical Oncology. 2010;28:2.	Population[a]
Siena S, Cassidy J, Tabernero J, Burkes RL, Barugel ME, Humblet Y, et al. Randomized phase III study of panitumumab (pmab) with FOLFOX4 compared with FOLFOX4 alone as first line treatment (tx) for metastatic colorectal cancer (mCRC): Results by Eastern Cooperative Oncology Group (ECOG) performance status (PS). Journal of Clinical Oncology. 2011;29:1.	Population[a]
Stein A, Duex M, Kickuth R, Petrovitch A, Pluntke S, Ricke J, et al. A randomized phase II trial of irinotecan drug-eluting beads administered by hepatic chemoembolization with intravenous cetuximab (DEBIRITUX) versus systemic treatment with intravenous cetuximab and irinotecan in patients with refractory colorectal liver metastases and Kras wild-type tumors. Cardiovascular and Interventional Radiological Society of Europe, CIRSE 2011 Munich Germany. 2011;34:617.	Population[a]
Stintzing S, Neumann J, Jung A, Fischer Von Weikersthal L, Decker T, Vehling-Kaiser U, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment	Population[a]

for patients with metastatic colorectal cancer (mCRC): Analysis of patients with KRAS-mutated tumors in the randomized German AIO study KRK-0306. Journal of clinical oncology [Internet]. 2011; 29(15 suppl. 1). Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/270/CN-01034270/frame.html.	
Wasan H, Adams RA, Wilson RH, Pugh C, Fisher D, Madi A, et al. Intermittent chemotherapy (CT) plus continuous or intermittent cetuximab (C) in the first-line treatment of advanced colorectal cancer (aCRC): Results of the two-arm phase II randomized MRC COIN-B trial. Journal of clinical oncology [Internet]. 2012; 30(4 suppl. 1). Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/069/CN-01028069/frame.html.	Population[a]
Hecht JR, Mitchell E, Chidiac T, Scroggin C, Hagenstad C, Spigel D, et al. A randomized phase IIIB trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer. Journal of Clinical Oncology. 2009;27:672-80.	Intervention
Punt CJ, Tol J, Rodenburg CJ, Cats A, Creemers G, Schrama JG, et al. Randomized phase III study of capecitabine, oxaliplatin, and bevacizumab with or without cetuximab in advanced colorectal cancer (ACC), the CAIRO2 study of the Dutch Colorectal Cancer Group (DCCG). Journal of Clinical Oncology. 2008;26:1.	Intervention
Saif MW, Elfiky A, Salem RR. Gastrointestinal perforation due to bevacizumab in colorectal cancer. Annals of Surgical Oncology. 2007;14:1860-9.	Intervention
Saif MW, Mehra R. Incidence and management of bevacizumab-related toxicities in colorectal cancer. Expert Opinion on Drug Safety. 2006;5:553-66.	Intervention
Tol J, Koopman M, Rodenburg CJ, Cats A, Creemers GJ, Schrama JG, et al. A randomised phase III study on capecitabine, oxaliplatin and bevacizumab with or without cetuximab in first-line advanced colorectal cancer, the CAIRO2 study of the Dutch Colorectal Cancer Group (DCCG). An interim analysis of toxicity. Annals of Oncology. 2008;19:734-8.	Intervention
Pietrantonio F, Garassino MC, Torri V, de Braud F. Reply to FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer-subgroup analysis of patients with KRAS-mutated tumours in the randomised German AIO study KRK-0306. Annals of Oncology. 2012;23:2771-2.	Study design
Saif MW, Kim R. Incidence and management of cutaneous toxicities associated with cetuximab. Expert Opinion on Drug Safety. 2007;6:175-82.	Study design

Notes: a Only published in abstract format

Appendix D: Abstracts

We screened the abstracts identified by the clinical effectiveness searches. A total of 90 were screened, of which four met the eligibility criteria for this review. Authors of the abstracts were contacted which led to the identification of an additional two full papers (**Tejpar *et al.,* 2015** and **Van Cutsem *et al.,* 2015**). A further three abstracts were identified in the update searches conducted on 27 April 2015. Relevant abstracts are summarised below.

Bokemeyer C, Kohne CH, Ciardiello F, Lenz HJ, Heinemann V, Klinkhardt U et al. Treatment outcome according to tumor RAS mutation status in OPUS study patients with metastatic colorectal cancer (mCRC) randomized to FOLFOX4 with/without cetuximab. 2014 Annual Meeting of the American Society of Clinical Oncology, ASCO Chicago, IL United States. 2014; 32 (15 SUPPL. 1.)	OPUS, RAS-WT analysis. Author provided a copy of the full paper submitted to Eur J Cancer as academic in confidence: Tejpar S, C.-H Kohne; F. Ciardiello; H.-J. Lenz; V. Heinemann; U. Klinkhardt et al., FOLFOX4 plus cetuximab treatment and RAS mutations in colorectal cancer. Eur J Cancer, 2015 (under review)
Ciardiello F, Lenz HJ, Kohne CH, Heinemann V, Tejpar S, Melezinek I et al. Treatment outcome according to tumor RAS mutation status in CRYSTAL study patients with metastatic colorectal cancer (mCRC) randomized to FOLFIRI with/without cetuximab. 2014 Annual Meeting of the American Society of Clinical Oncology, ASCO Chicago, IL United States. 2014;32 (15 SUPPL. 1).	CRYSTAL, RAS-WT analysis. Author provided full paper: Van Cutsem E, Lenz HJ, Kohne CH, Heinemann V, Tejpar S, Melezinek I, et al. Fluorouracil, Leucovorin, and Irinotecan Plus Cetuximab Treatment and RAS Mutations in Colorectal Cancer. J Clin Oncol. 2015.
Douillard JY, Tabernero J, Siena S, Peeters M, Koukakis R, Terwey JH et al. Survival outcomes in patients (pts) with KRAS/NRAS (RAS) wild-type (WT) metastatic colorectal cancer (mCRC) and non-liver-limited disease (non-LLD): Data from the PRIME study. 2014 Annual Meeting of the American Society of Clinical Oncology, ASCO Chicago, IL United States. 2014; 32 (15 SUPPL. 1).	PRIME, post-hoc subgroup analysis by liver-limited and non-liver-limited disease [[same as abstract below (Peeters et al., 2013), but reports different outcomes]]. Author approached for more information 13/02/2014; none received
Peeters M, Tabernero J, Douillard JY, Siena S, Davison C, Braun S et al. Resection rates and survival in patients with wild-type KRAS/NRAS metastatic colorectal cancer and liver metastases: Data from the PRIME study. Markers in Cancer: A Joint Meeting by ASCO, EORTC and NCI 2013 Brussels Belgium. 2013; 49: S17-S8.	PRIME, post-hoc subgroup analysis by liver-limited and non-liver-limited disease [[same as abstract below but reports different outcomes]]. Author approached for more information 13/02/2014; none received
Abstracts identified in update searches, 27 April 2015	
Rivera F, Karthaus M, Hecht JR et al. First-line treatment with modified FOLFOX6 (mFOLFOX6) + panitumumab (pmab) or bevacizumab (bev) in wild-type (WT) RAS metastatic colorectal carcinoma (mCRC): Tumor response outcomes beyond RECIST. Gastrointestinal Cancers Symposium, San Francisco (CA) USA. 2015; 33(3): 660	PEAK, post-hoc subgroup analysis reporting tumour response outcomes beyond RECIST (e.g. early tumour shrinkage)
Siena S, Tabernero J, Bodoky G, Cunningham D, Rivera F, Ruff P et al. Quality of life (QoL) during first-line treatment with FOLFOX4 with or without panitumumab (pmab) in RAS wild-type (WT) metastatic colorectal carcinoma (mCRC). Gastrointestinal Cancers Symposium, San Francisco (CA), USA. 2015;	PRIME, post-hoc subgroup analysis of quality of life in the RAS WT population (uses EQ-5D health state index (HIS) and overall health rating (OHR)

33 (3 SUPPL. 1): 693	
Wang J, Dong J, Johnson P, Maglinte GA, Rong, Barber BL *et al*. Quality-adjusted survival in patients with RAS wild-type (WT) metastatic colorectal cancer (mCRC) receiving first-line therapy with panitumumab plus FOLFOX versus FOLFOX alone in the PRIME trial. Gastrointestinal Cancers Symposium San Francisco (CA) USA. 2015; 33 (3 SUPPL. 1):537	PRIME, post-hoc subgroup analysis of quality-adjusted survival in the RAS WT population

Abstracts identified by Amgen (excluded from Assessment Group review)

Abad et al. Panitumumab plus FOLFOX4 or panitumumab plus FOLFIRI in subjects with wild-type KRAS (exon 2) colorectal cancer and multiple or unresectable liver-limited metastases: data from the randomized, phase ii planet study. Annual Meeting of the American Society of Clinical Oncology, ASCO Chicago, IL United States. 2014;32 (15 SUPPL. 1	PLANET, results predominantly reported for KRAS WT population. RAS analysis report data for ORR

Key: ASCO = American Society of Clinical Oncology; CA = California; EORTC = European Organisation for Research and Treatment of Cancer; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluourouracil + oxaliplatin; mCRC = metastatic colorectal cancer; NCI = National Cancer Institute; NRAS = neuroblastoma rat sarcoma; QoL = quality of life; RAS = rat sarcoma; RECIST = Response Criteria in Solid Tumours; WT = wild type

Appendix E: Data extraction forms

Data extraction forms for the included studies in the clinical effectiveness will be provided separately.

Appendix F: KRAS-WT subgroup

Table 2. Baseline characteristics (*KRAS* WT): Cetuximab trials

Author, year Trial Name	Intervention	N	Age, yrs (median (range))	Male n/N (%)	ECOG PS n/N (%)	No. metastatic sites n/N (%)	Primary tumour diagnosis n/N (%)	LLD n/N (%)
Bokemeyer, 2011 OPUS	CET+FOLFOX4	82	62 (24–75)	42/82 (51)	0: 62/82 (39) 1: 44/82 (54) 2: 6/82 (7)	1: 41/82 (50) 2: 26/82 (32) ≥3: 12/82 (18)	NR	25/82 (30)
	FOLFOX4	49	59 (36–82)	55/97 (57)	0: 38/97 (39) 1: 49/97 (51) 2: 10/97 (10)	1: 38/97 (39) 2: 37/97 (38) ≥3: 22/97 (22)	NR	23/97 (24)
Van Cutsem, 2011 CRYSTAL	CET+FOLFIRI	316	61 (24–79)	196/316 (62)	0: 183/316 (57.9) 1: 120/316 (38.0) 2: 13/316 (4.1)	≤2: 277/316 (87.7)	NR	68/316 (21.5)
	FOLFIRI	350	59 (19–84)	211/350 (60.3)	0: 200/350 (57.1) 1: 136/350 (38.9) 2: 14/350 (4.0)	≤2: 295/350 (84.3)	NR	72/350 (20.6)
Heinemann, 2014 FIRE-3	CET+FOLFIRI	297	64 (38-79)	214/297 (72)	0: 154/297 (52) 1: 136/297 (46) 2: 7/297 (2)	1: 119/297 (40) ≥2: 174/297 (59) Unknown: 4/297 (1)	Colon: 168/297 (57) Rectum: 115/297 (39) Colon & rectum: 9/297 (3) Unknown: 5/297 (2)	93/297 (31)
	BEV+FOLFIRI	295	65.0 (27–76)	196/295 (66)	0: 158/295 (54) 1: 133/295 (45) 2: 4/295 (1)	1: 123/295 (42) ≥2: 171/295 (58) Unknown: 1/295 (<1)	Colon: 177/295 (60) Rectum: 106/295 (36) Colon & rectum: 12/295 (4) Unknown: 0/295 (0)	94/295 (32)

Key: BEV = bevacizumab; CET = cetuximab; ECOG = Eastern Cooperative Oncology Group; FOLFIRI = folinic acid + flurouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; LLD = liver limited disease; NA = not applicable; NR = not reported; PS = performance status
Sources: Bokemeyer et al., Ann Oncol, 2011 (OPUS); Van Cutsem et al., J Clin Oncol, 2011 (CRYSTAL); Heinemann et al., Lancet Oncol, 2014 (FIRE-3)

Table 3. Baseline characteristics (*KRAS* WT): Panitumumab trials

Author, year Trial Name	Intervention	N	Age, yrs (median (range))	Male n/N (%)	ECOG PS n/N (%)	No. metastatic sites n/N (%)
Douillard, 2014 PRIME	PAN+FOLFOX4	325	62 (27–85)	217 (67)	0-1: 305/325 (94) ≥2: 20/325 (6)	1: 69/325 (21) 2: 114/325 (35) ≥3: 140/325 (43)
	FOLFOX4	331	61 (24–82)	204 (62)	0-1: 312/331 (94) ≥2: 18/331 (5)	1: 68/331 (21) 2: 118/331 (36) ≥3: 145/331 (44)
Schwartzberg, 2014 PEAK	PAN+ mFOLFOX6	142	63 (23–82)	89/142 (61)	0: 89/142 (63) 1: 53/142 (37) Other[a]: 0/142 (0)	1: 53/142 (37) 2: 50/142 (35) ≥3: 39/142 (27) Other[a]: 0/142 (0)
	BEV+ mFOLFOX6	143	61 (28–82)	96/143 (67)	0: 91/143 (64) 1: 51/143 (36) Other[a]: 1/143 (<1)	1: 56/143 (39) 2: 49/143 (34) ≥3: 37/143 (26) Other[a]: 1/143 (<1)

Key: BEV = bevacizumab; ECOG = Eastern Cooperative Oncology Group; FOLFIRI = folinic acid + flurouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; LLD = liver limited disease; m = modified; NA = not applicable; NR = not reported; PAN = panitumumab; PS = performance status
Notes: a Missing or unknown
Sources: Douillard et al. Ann Oncol, 2014 (PRIME) Schwartzberg et al. J Clin Oncol, 2014 (PEAK)

Table 4. Efficacy results (*KRAS* WT): Cetuximab trials

Author, year, Trial	Experimental (n/N) Median mths/% (95% CI)	Control (n/N) Median mths/% (95% CI)	HR/OR (95% CI)
Progression Free Survival			
OPUS	CET+FOLFOX4 (NR 8.3 (7.2-12.0)	FOLFOX4 (NR) 7.2 (5.6-7.4)	HR: 0.567 (0.375-0.856)
CRYSTAL	CET+FOLFIRI (146/316) 9.9 (9.0-11.3)	FOLFIRI (189/350) 8.4 (7.4-9.2)	HR: 0.696 (0.558-0.867)
FIRE-3	CET+FOLFIRI (250/297) 10.0 (8.8-10.8)	BEV+FOLFIRI (242/295) 10.3 (9.8-11.3)	NR
Overall Survival			
OPUS	CET+FOLFOX4 (NR) 22.8 (19.3-25.9)	FOLFOX4 (NR) 18.5 (16.4-22.6)	HR: 0.855 (0.599-1.219)
CRYSTAL	CET+FOLFIRI (242/316)	FOLFIRI (288/350)	HR: 0.796 (0.670-

	23.5 (21.2-26.3)	20.0 (17.4-21.7)	0.946)
FIRE-3	CET+FOLFIRI (158/297) 28.7 (24.0-36.6)	BEV+FOLFIRI (185/295) 25.0 (22.7-27.6)	NR
Overall Response Rate			
OPUS	CET+FOLFOX4 (43/82) 57% (46-68)	FOLFOX4 (33/97) 34% (25-44)	OR: 2.551 (1.380-4.717)
CRYSTAL	CET+FOLFIRI (181/316) 57.3% (51.6-62.8)	FOLFIRI (139/350) 39.7% (34.6-45.1)	OR: 2.069 (1.515-2.826)
FIRE-3	CET+FOLFIRI (184/297) 62% (56.2-67.5)	BEV+FOLFIRI (171/295) 58% (52.1-63.7)	NR
Complete resection rate (R0)			
OPUS	NR	NR	NR
CRYSTAL	CET+FOLFIRI (16/316) 5.1%	FOLFIRI (7/350) 2.0%	OR: 2.650 (1.083-6.490)
FIRE-3	NR	NR	NR

Key: BEV = bevacizumab; CET = cetuximab; FOLFIRI = folinic acid + flurouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; NR = not reported; OR = Odds Ratio; HR = Hazard Ratio
Sources: Bokemeyer et al., Ann Oncol, 2011 (OPUS); Van Cutsem et al., J Clin Oncol, 2011 (CRYSTAL); Heinemann et al., Lancet Oncol, 2014 (FIRE-3)

Table 5. Efficacy results (*KRAS* WT): Panitumumab trials

Author, year, Trial	Experimental (n/N) Median mths/% (95% CI)	Control (n/N) Median mths/% (95% CI)	HR/OR (95% CI)
Progression Free Survival			
PRIME	PAN+FOLFOX4 (270/325) 10.0 (9.3-11.4)	FOLFOX4 (280/331) 8.6 (7.5-9.5)	HR: 0.80 (0.67-0.95)
PEAK	PAN+mFOLFOX6 (90/142) 10.9 (9.4-13.0)	BEV+mFOLFOX6 (94/143) 10.1 (9.0-12.6)	HR: 0.87 (0.65-1.17)
Overall Survival			
PRIME	PAN+FOLFOX4 (214/325) 23.9 (20.3-27.7)	FOLFOX4 (231/331) 19.4 (17.6-22.7)	HR: 0.88 (0.73-1.06)
PEAK	PAN+mFOLFOX6 (52/142) 34.2 (26.6-NR)	BEV+mFOLFOX6 (78/143) 24.3 (21.0-29.2)	HR:0.62 (0.44-0.89)
Overall Response Rate			
PRIME	PAN+FOLFOX4 (181/317) 57 % (51.5-62.6)	FOLFOX4 (154/324) 48 % (42.0-53.1)	NR
PEAK	PAN+mFOLFOX6 (82/142) 57.8% (49.2-66.0)	BEV+mFOLFOX6 (75/142) 53.5% (45.0-61.9)	NR
Complete resection rate (R0)			
PRIME	PAN+FOLFOX4 (31/325) 10 % (NR)	FOLFOX4 (25/331) 8 % (NR)	NR
PEAK	PAN+mFOLFOX6 (14/142) 10% (NR)	BEV+mFOLFOX6 (12/143) 8%	NR

Key: BEV = bevacizumab; FOLFIRI = folinic acid + flurouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; NR = not reported; PAN = panitumumab; OR = Odds Ratio; HR = Hazard Ratio
Sources: Douillard et al. Ann Oncol, 2014 (PRIME) Schwartzberg et al. J Clin Oncol, 2014 (PEAK)

Table 6. Adverse (*KRAS* WT): Cetuximab trials

	OPUS		CRYSTAL		FIRE-3	
	CET+ FOLFOX4 (n=82)	FOLFOX4 (n=97)	CET+ FOLFIRI (n=317)	FOLFIRI (n=350)	CET+ FOLFIRI (n=297)	BEV+ FOLFIRI (n=295)
Any AE, n/N (%)	NR	NR	NR	NR	NR	NR
Any Grade 1 or 2 event, n/N (%)	NR	NR	NR	NR	NR	NR
Any Grade 3 or Grade 4 event, n/N (%)	67/82 (82)	62/97 (64)	257/317 (81.1)	211/350 (60.3)	211/297 (71)	188/295 (64)
Any serious AE, n/N (%)	NR	NR	NR	NR	NR	NR

Key: AE = adverse event; BEV = bevacizumab; CET = cetuximab; CTC = Common Terminology Criteria; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; NR = not reported

Sources: Bokemeyer et al., Ann Oncol, 2011 (OPUS); Van Cutsem et al., J Clin Oncol, 2011 (CRYSTAL); Heinemann et al., Lancet Oncol, 2014 (FIRE-3)

Table 7. Adverse (*KRAS* WT): Panitumumab trials

	PRIME		PEAK	
	PAN+ FOLFOX4 (n=322)	FOLFOX4 (n=327)	PAN+ mFOLFOX6 (n=139)	BEV+ mFOLFOX6 (n=139)
Any AE, n/N (%)	NR	NR	139/139 (100)	139/139 (100)
Any Grade 1 or 2 event, n/N (%)	NR	NR	NR	NR
Any Grade 3 or Grade 4 event, n/N (%)	270/322 (84)	227/327 (69)	NR	NR
Any serious AE, n/N (%)	NR	NR	61/139 (24)	53/139 (27)

Key: AE = adverse event; BEV = bevacizumab; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX4 = folinic acid + fluorouracil + oxaliplatin; mFOLFOX6 = modified folinic acid + fluorouracil + oxaliplatin; NR = not reported; PAN = panitumumab;

Sources: Sources: Douillard et al. Ann Oncol, 2014 (PRIME) Schwartzberg et al. J Clin Oncol, 2014 (PEAK)

Appendix G: RECIST vs WHO criteria

Response Evaluation Crtieria in Solid Tumours (RECIST)

Evaluation of target lesions	
Complete Response (CR):	Disappearance of all target lesions
Partial Response (PR):	At least a 30 % decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter
Progressive Disease (PD):	At least a 20 % increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum longest diameter since the treatment started
Evaluation of non-target lesions	
Complete Response (CR):	Disappearance of all non-target lesions and normalisation of tumour marker level
Incomplete response/ stable disease (SD):	Persistence of one or more non-target lesion(s) or/and maintenance of tumour marker level above the normal limits
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

Source: Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000;92:205-16

Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started)[168]. In general, an individual's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Table 8. Overall responses for all possible combinations of tumour responses in target and nontarget lesions with or without the appearance of new lesions

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Source: Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000;92:205-16

WHO criteria for response to treatment

Measureable Disease	
Complete Response (CR):	The disappearance of all known disease, determined by 2 observations not less than 4 weeks apart
Partial Response (PR):	50 % or more decrease in total tumour size of the lesions which have been measured to determine the effect of therapy by 2 observations not less than 4 weeks apart. In addition there can be no appearance of new lesions or progression of any lesion
Progressive Disease (PD):	A 25 % or more increase in the size or one or more measurable lesions, or the appearance of new lesions.
No Change (NC):	A 50 % decrease in total tumour size cannot be established nor has a 25 % increase in the size of one or more measurable lesions been demonstrated
Unmeasurable Disease	
Complete Response (CR):	Complete disappearance of all known disease for at least 4 weeks
Partial Response (PR):	Estimated decrease in tumour size of 50% or more for at least 4 weeks
Progressive Disease (PD):	Appearance of any new lesion not previously identified or estimated increase of 25 % or more in existent lesions
No Change (NC):	No significant change for at least 4 weeks. This includes stable disease, estimated decrease of less than 50 % and lesions with estimated increase of less than 25 %

Reference: WHO handbook for reporting results of cancer treatment. WHO, 1979, Geneva: WHO. WHO offset publication No. 48. URI: http://www.who.int/iris/handle/10665/37200

Determination of overall response in solid tumours[168]:

- If both measurable and unmeasurable disease is present in a given patient, the result of each should be recorded separately. Note that an overall assessment of response involves all parameters.
- In people with measurable disease, the poorest response designation shall prevail
- “No change” in unmeasurable lesions will not detract from a partial response in measurable lesions but will reduce a complete response in measurable lesions to partial response overall.
- If in the totals of response by organ site there are equal or greater number of complete plus partial responses than of “ no change “ designations, then the overall response will be partial.
- If progressive disease exists in any lesion or when a new lesion appears, then the overall results will be “progressive disease”

Appendix H: Clinical effectiveness supplementary information

Best available response rate

Best available response rate for the cetuximab trials is reported in Table 9

Table 9. Best available response rate (*RAS* WT [all loci]): Cetuximab trials

Author, year Trial	Experimental	n	N	%	Control	n	N	%
Complete response								
Tejpar, 2015 OPUS[a]	CET+FOLFOX4	[redacted]	[redacted]	[redacted]	FOLFOX4	[redacted]	[redacted]	[redacted]
Van Cutsem, 2015 CRYSTAL[a]	CET+FOLFIRI	2	178	1.1	FOLFIRI	0	189	0
Heinemann, 2014 FIRE-3[b]	CET+FOLFIRI	9	171	5	BEV+FOLFIRI	2	171	1
Partial response								
Tejpar, 2015 OPUS[a]	CET+FOLFOX4	[redacted]	[redacted]	[redacted]	FOLFOX4	[redacted]	[redacted]	[redacted]
Van Cutsem, 2015 CRYSTAL[a]	CET+FOLFIRI	116	178	65.2	FOLFIRI	73	189	38.6
Heinemann, 2014 FIRE-3[b]	CET+FOLFIRI	103	171	60	BEV+FOLFIRI	100	171	58
Stable disease								
Tejpar, 2015 OPUS[a]	CET+FOLFOX4	[redacted]	[redacted]	[redacted]	FOLFOX4	[redacted]	[redacted]	[redacted]
Van Cutsem, 2015 CRYSTAL[a]	CET+FOLFIRI	48	178	27.0	FOLFIRI	90	189	47.6
Heinemann, 2014 FIRE-3[b]	CET+FOLFIRI	26	171	15	BEV+FOLFIRI	50	171	29
Progressive disease								
Tejpar, 2015 OPUS[a]	CET+FOLFOX4	[redacted]	[redacted]	[redacted]	FOLFOX4	[redacted]	[redacted]	[redacted]
Van Cutsem, 2015 CRYSTAL[a]	CET+FOLFIRI	7	178	3.9	FOLFIRI	17	189	9.0
Heinemann, 2014 FIRE-3[b]	CET+FOLFIRI	10	171	6	BEV+FOLFIRI	8	171	5

Author, year Trial	Experimental	n	N	%	Control	n	N	%
Not evaluable								
Tejpar, 2015 OPUS[a]	CET+FOLFOX4	[redacted]	[redacted]	[redacted]	FOLFOX4	[redacted]	[redacted]	[redacted]
Van Cutsem, 2015 CRYSTAL[a]	CET+FOLFIRI	5	178	2.8	FOLFIRI	9	189	4.8
Heinemann, 2014 FIRE-3[b]	CET+FOLFIRI	23	171	13	BEV+FOLFIRI	11	171	6

Key: BEV = bevacizumab; CET = cetuximab; FOLFOX = folinic acid + fluorouracil + oxaliplatin; FOLFIRI = folinic acid + fluorouracil + irinotecan
Notes: a Assessed every eight weeks, median follow-up not reported; c Assessed 28 days from last treatment cycle (tumour evaluations had to be performed at least six weeks after first administration of therapy
Sources: Tejpar et al., Eur J Cancer, 2015 (OPUS); Van Cutsem et al., J Clin Oncol, 2015 (CRYSTAL); Heinemann et al., Lancet Oncol, 2014 (FIRE-3)

Table 10. Best available response rate (*RAS* WT [all loci]): Panitumumab trials

Author, year Trial	Experimental	n	N	%	Control	n	N	%
Complete response								
Douillard, 2014 PRIME[a]	PAN+FOLFOX4	[redacted]	[redacted]	[redacted]	FOLFOX4	[redacted]	[redacted]	[redacted]
Schwarzberg, 2014 PEAK[a]	PAN+mFOLFOX6	2	88	2	BEV+mFOLFOX6	1	82	1
Partial response								
Douillard, 2014 PRIME[a]	PAN+FOLFOX4	[redacted]	[redacted]	[redacted]	FOLFOX4	[redacted]	[redacted]	[redacted]
Schwarzberg, 2014 PEAK[a]	PAN+mFOLFOX6	54	88	61	BEV+mFOLFOX6	48	82	59
Stable disease								
Douillard, 2014 PRIME[a]	PAN+FOLFOX4	[redacted]	[redacted]	[redacted]	FOLFOX4	[redacted]	[redacted]	[redacted]
Schwarzberg, 2014 PEAK[a]	PAN+mFOLFOX6	23	88	26	BEV+mFOLFOX6	22	82	27
Progressive disease								
Douillard, 2014 PRIME[a]	PAN+FOLFOX4	[redacted]	[redacted]	[redacted]	FOLFOX4	[redacted]	[redacted]	[redacted]
Schwarzberg, 2014 PEAK[a]	PAN+mFOLFOX6	1	88	1	BEV+mFOLFOX6	4	82	5
Not evaluable								
Douillard, 2014 PRIME[a]	PAN+FOLFOX4	NR	NR	NR	FOLFOX4	NR	NR	NR

Author, year Trial	Experimental	n	N	%	Control	n	N	%
Schwarzberg, 2014 PEAK[a]	PAN+mFOLFOX6	8	88	9	BEV+mFOLFOX6	6	82	7

Key: BEV = bevacizumab; FOLFOX = folinic acid + fluorouracil + oxaliplatin; FOLFIRI = folinic acid + fluorouracil + irinotecan; mFOLFOX – modified folinic acid + fluorouracil = oxaliplatin; PAN = panitumumab
Notes: a Timepoint measured not reported. Median duration follow-up: 22.31 (10.12, 35.65) months and 17.71 (8.74, 32.20) months for PAN+FOLFOX vs FOLFOX respectively (PRIME), and 14.97 (8.83, 22.81) months vs 14.93 (8.76, 21.39) months for PAN+FOLFOX vs BEV+FOLFOX respectively (PEAK)
Sources: Data on File (PRIME), Amgen UK Ltd; Schwartzberg et al. J Clin Oncol, 2014 (PEAK)

Safety

The incidence of Grade 1 or 2 adverse events for the cetuximab trials is reported in Table 11 and for panitumumab trials in Table 12.

Table 11. Incidence of Grade 1 or 2 adverse events (reported at a frequency of ≥5% in either treatment group) (*RAS* WT [all loci]): Cetuximab

	FIRE-3[a,b,c]	
	CET+FOLFIRI (n=171)	BEV+FOLFIRI (n=171)
Acneiform exenthema / rash	99/171 (58)*	14/171 (8)*
Desquamation	51/171 (30)*	18/171 (11)*
Diarrhoea	85/171 (50)	89/171 (52)
Haemotoxicity	102/171 (60)*	119/171 (70)*
Hepatotoxicity	105/171 (61)	89/171 (52)
Hypertension	32/171 (19)*	46/171 (27)*
Hypokalemia	56/171 (33)*	27/171 (16)
Infection	64/171 (37)	69/171 (40)*
Mucostitis/stomatitis	61/171 (36)	68/171 (40)
Nail changes/paronychia	47/171 (28)*	17/171 (10)*
Nausea	74/171 (43)*	97/171 (57)*
Pain	75/171 (44)*	87/171 (51)*
Skin reaction	98/171 (57)	72/171 (42)
Thromboembolic event	3/171 (2)	2/171 (1)
Thrombosis (any)	3/171 (2)	7/171 (4)

Key: AE = adverse event; BEV = bevacizumab; CET = cetuximab; CTC = Common Terminology Criteria; FOLFIRI = folinic acid + fluorouracil + irinotecan; MedDRA = Medical Dictionary for Regulatory Activities; RAS = rat sarcoma; Vn = Version; WT = wild type

Notes: Grade 1 / 2 AEs not reported/not available for OPUS or CRYSTAL trials; a Participants were observed for safety 30 days after last study drug administration; b Participants were observed for safety approximately 6 months after randomisation; c MedDRA Vn 13.1 preferred terms, with special emphasis on Grade 3 and 4 toxic effects according to the National Cancer Institute – CTC for AEs Vn 3.0

Sources: Merck Serono UK Ltd; Data on File (FIRE-3), Merck Serono UK Ltd

Table 12. Incidence of Grade 1 or 2 adverse events (reported at a frequency of ≥5% in either treatment group) (*RAS* WT [all loci]): Panitumumab

	PRIME[a,b]		PEAK[a,b]	
	PAN+FOLFOX4 (n=250)	FOLFOX4 (n=249)	PAN+mFOLFOX6 (n=86)	BEV+mFOLFOX6 (n=80)
Abdominal pain, n/N (%)				
Abdominal pain (upper), n/N (%)				
Acne, n/N (%)				
Alopecia, n/N (%)				
Anaemia, n/N (%)				
Anorexia, n/N (%)				
Anxiety, n/N (%)				
Arthralgia, n/N (%)				
Ascites, n/N (%)				
Asthenia, n/N (%)				
Back pain, n/N (%)				
Blood creatinine increased, n/N (%)				
Bronchitis, n/N (%)				
Cheilitis, n/N (%)				
Chills, n/N (%)				
Confusional state, n/N (%)				
Conjunctivitis, n/N (%)				
Consitpation, n/N (%)				
Cough, n/N (%)				
Decreased appetite, n/N (%)				
Decreased weight, n/N (%)				

	PRIME[a,b]		PEAK[a,b]	
	PAN+FOLFOX4 (n=250)	FOLFOX4 (n=249)	PAN+mFOLFOX6 (n=86)	BEV+mFOLFOX6 (n=80)
Dehydration, n/N (%)				
Depression, n/N (%)				
Dermatitis acneiform, n/N (%)				
Diarrhoea, n/N (%)				
Dizziness, n/N (%)				
Dry mouth, n/N (%)				
Dry skin, n/N (%)				
Dysaesthesia, n/N (%)				
Dysguesia, n/N (%)				
Dyspepsia, n/N (%)				
Dysphagia, n/N (%)				
Dysphonia, n/N (%)				
Dyspnoea, n/N (%)				
Dyspnoea exertional, n/N (%)				
Epistaxis, n/N (%)				
Erythema, n/N (%)				
Exfoliative rash, n/N (%)				
Fall, n/N (%)				
Fatigue, n/N (%)				
Flatulence, n/N (%)				
Haematoma, n/N (%)				
Haemoglobin decreased, n/N (%)				

	PRIME[a,b]		PEAK[a,b]	
	PAN+FOLFOX4 (n=250)	FOLFOX4 (n=249)	PAN+mFOLFOX6 (n=86)	BEV+mFOLFOX6 (n=80)
Headache, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Hypersensitivity, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Hypertrichosis, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Hypoaesthesia, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Hypoalbuminaemia, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Hypocalcemia, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Hypokalemia, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Hypomagnesemia, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Hypotension, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Influenza, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Infusion-related reaction, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Insomnia, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Lacrimation increased, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Lethargy, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Leukopenia, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Mucosal inflammation, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Muscular weakness, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal chest pain, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal pain, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Nail disorder, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]

	PRIME[a,b]		PEAK[a,b]	
	PAN+FOLFOX4 (n=250)	FOLFOX4 (n=249)	PAN+mFOLFOX6 (n=86)	BEV+mFOLFOX6 (n=80)
Nausea, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Neck pain, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Neuroltoxicity, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Neuropathy peripheral, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Oedema peripheral, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Oropharyngeal pain, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Pain in extremity, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Pain in jaw, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Palmar-plantar erythrodysaesthesia, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Paraesthesia, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Paronychia, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Periperhal sensory neuropathy, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Platelet count decreased, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Pollakiuria, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Polyneuropathy			[redacted]	[redacted]
Productive cough, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Proteinuria, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Pruritus, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Rash, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Rectal haemorrhage, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]

	PRIME[a,b]		PEAK[a,b]	
	PAN+FOLFOX4 (n=250)	FOLFOX4 (n=249)	PAN+mFOLFOX6 (n=86)	BEV+mFOLFOX6 (n=80)
Rhinitis, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Rhinorrhea, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Skin disorders, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Skin fissures, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Skin hyperpigmentation, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Skin toxicity, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Stomatitis, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Temperature intolerance, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Vision blurred, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Weight increased, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]

Key: AE = adverse event; BEV = bevacizumab; CTC = Common Terminology Criteria; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX4 = folinic acid + fluorouracil + oxaliplatin; mFOLFOX6 = modified folinic acid + fluorouracil + oxaliplatin; MedDRA = Medical Dictionary for Regulatory Activities; NR = not reported; PAN = panitumumab; RAS = rat sarcoma; Vn = Version; WT = wild type

Notes: * Of Grade 1 or 2 AEs reported in at ≥5% participants in either treatment arm, * indicates a difference >5% between treatment arms a Participants were observed for safety 30 days after the last study drug administration; b Adverse events were coded using MedDRA Vn 15.0, severity graded according to the National Cancer Institute – CTC for Adverse Events (Vn 3.0) with modifications for specific skin- and nail-related toxicities. Fatal adverse events were classified as Grade 5

Sources: Data on File (PRIME). Amgen UK Ltd; Data on File (PEAK), Amgen UK Ltd.

Network meta-analysis: Additional analyses (safety FOLFOX network)

For the remaining adverse events (AEs), the OPUS study did not provide the required information and so no comparison can be made between cetuximab plus FOLFOX (CET+FOLFOX), and panitumumab plus FOLFOX (PAN+FOLFOX) for diarrhoea, hypokalemia, hypomagnesemia, mucositis/stomatitis, musosal inflammation, fatigue, neuropathy peripheral or asthenia. Instead analyses are reported here to allow the indirect comparison of bevacizumab plus FOLFOX (BEV+FOLFOX) vs FOLFOX (Table 13 to Table 20). Note that due to small numbers of events for hypomagnesemia, mucositis/stomatitis and musosal inflammation, the 95% CrIs are wide.

Table 13. Odds ratio* (and 95% CrI) for Grade 3/4 diarrhoea calculated from a fixed effects network meta-analysis model

	Comparator treatment		Probability ranked		
Intervention treatment	FOLFOX	BEV+FOLFOX	1st	2nd	3rd
FOLFOX			96%	4%	<1%
BEV+FOLFOX	3.04 (0.90, 10.49)		4%	30%	66%
PAN+FOLFOX	[redacted]	[redacted]	<1%	66%	34%

Key: AEs = adverse events; BEV = bevacizumab; CrI = credible interval; FOLFOX = folinic acid + fluorouracil + oxaliplatin; OR = odds ratio; PAN = panitumumab
Note: * OR<1 favours 'Intervention' treatment ** direct evidence from PRIME; *** direct evidence from PEAK

Table 14. Odds ratio* (and 95% CrI) for Grade 3/4 hypokalemia calculated from a fixed effects network meta-analysis model

	Comparator treatment		Probability ranked		
Intervention treatment	FOLFOX	BEV+FOLFOX	1st	2nd	3rd
FOLFOX			84%	15%	<1%
BEV+FOLFOX	2.02 (0.50, 8.03)		16%	41%	43%
PAN+FOLFOX	[redacted]	[redacted]	<1%	44%	56%

Key: AEs = adverse events; BEV = bevacizumab; CrI = credible interval; FOLFOX = folinic acid + fluorouracil + oxaliplatin; OR = odds ratio; PAN = panitumumab
Note: * OR<1 favours 'Intervention' treatment; ** direct evidence from PRIME; *** direct evidence from PEAK

Table 15. Odds ratio* (and 95% CrI) for Grade 3/4 hypomagnesemia calculated from a fixed effects network meta-analysis model

	Comparator treatment		Probability ranked		
Intervention treatment	FOLFOX	BEV+FOLFOX	1st	2nd	3rd
FOLFOX			65%	35%	0%
BEV+FOLFOX	2.80 (0.01, 2176)		35%	65%	<1%
PAN+FOLFOX	[redacted]	[redacted]	0%	<1%	100%

Key: AEs = adverse events; BEV = bevacizumab; CrI = credible interval; FOLFOX = folinic acid + fluorouracil + oxaliplatin; OR = odds ratio; PAN = panitumumab
Note: * OR<1 favours 'Intervention' treatment; ** direct evidence from PRIME; *** direct evidence from PEAK

Table 16. Odds ratio* (and 95% CrI) for Grade 3/4 mucositis/stomatitis calculated from a fixed effects network meta-analysis model

	Comparator treatment		Probability ranked		
Intervention treatment	FOLFOX	BEV+FOLFOX	1st	2nd	3rd
FOLFOX			45%	55%	<1%
BEV+FOLFOX	0.75 (0.01, 44.47)		55%	44%	<1%
PAN+FOLFOX	[redacted]	[redacted]	0%	<1%	100%

Key: AEs = adverse events; BEV = bevacizumab; CrI = credible interval; FOLFOX = folinic acid + fluorouracil + oxaliplatin; OR = odds ratio; PAN = panitumumab
Note: * OR<1 favours 'Intervention' treatment; ** direct evidence from PRIME; *** direct evidence from PEAK

Table 17. Odds ratio* (and 95% CrI) for Grade 3/4 musosal inflammation calculated from a fixed effects network meta-analysis model

	Comparator treatment		Probability ranked		
Intervention treatment	FOLFOX	BEV+FOLFOX	1st	2nd	3rd
FOLFOX			89%	11%	<1%
BEV+FOLFOX	5.77 (0.36, 186.4)		11%	82%	7%
PAN+FOLFOX	[redacted]	[redacted]	<1%	7%	93%

Key: AEs = adverse events; BEV = bevacizumab; CrI = credible interval; FOLFOX = folinic acid + fluorouracil + oxaliplatin; OR = odds ratio; PAN = panitumumab
Note: * OR<1 favours 'Intervention' treatment; ** direct evidence from PRIME; *** direct evidence from PEAK

Table 18. Odds ratio* (and 95% CrI) for Grade 3/4 fatigue calculated from a fixed effects network meta-analysis model

	Comparator treatment		Probability ranked		
Intervention treatment	FOLFOX	BEV+FOLFOX	1st	2nd	3rd
FOLFOX			97%	3%	<1%
BEV+FOLFOX	3.65 (0.98, 14.15)		3%	61%	36%
PAN+FOLFOX	[redacted]	[redacted]	<1%	36%	64%

Key: AEs = adverse events; BEV = bevacizumab; CrI = credible interval; FOLFOX = folinic acid + fluorouracil + oxaliplatin; OR = odds ratio; PAN = panitumumab
Note: * OR<1 favours 'Intervention' treatment; ** direct evidence from PRIME; *** direct evidence from PEAK

Table 19. Odds ratio* (and 95% CrI) for Grade 3/4 neuropathy peropheral calculated from a fixed effects network meta-analysis model

	Comparator treatment		**Probability ranked**		
Intervention treatment	**FOLFOX**	**BEV+FOLFOX**	**1st**	**2nd**	**3rd**
FOLFOX			30%	32%	38%
BEV+FOLFOX	1.00 (0.28, 3.64)		37%	19%	43%
PAN+FOLFOX	[redacted]	[redacted]	32%	49%	19%

Key: AEs = adverse events; BEV = bevacizumab; CrI = credible interval; FOLFOX = folinic acid + fluorouracil + oxaliplatin; OR = odds ratio; PAN = panitumumab
Note: * OR<1 favours 'Intervention' treatment; ** direct evidence from PRIME; *** direct evidence from PEAK

Table 20. Odds ratio* (and 95% CrI) for Grade 3/4 asthenia calculated from a fixed effects network meta-analysis model

	Comparator treatment		Probability ranked		
Intervention treatment	FOLFOX	BEV+FOLFOX	1st	2nd	3rd
FOLFOX			70%	22%	8%
BEV+FOLFOX	2.22 (0.36, 15.22)		17%	16%	67%
PAN+FOLFOX	[redacted]	[redacted]	13%	62%	25%

Key: AEs = adverse events; BEV = bevacizumab; CrI = credible interval; FOLFOX = folinic acid + fluorouracil + oxaliplatin; OR = odds ratio; PAN = panitumumabNote: * OR<1 favours 'Intervention' treatment; ** direct evidence from PRIME; *** direct evidence from PEAK

Appendix I: Ongoing trials

Searches of ClinicalTrials.gov, WHO (ICTRP), UK Clinical Research Network and ISRCTN were conducted (see Appendix B for the search strategy used). All searches were carried out in March 2015. Ten trials were considered as relevant to this review (Table 21)

Table 21. Ongoing trials

Register/ identifier number	Sponsor/ Collaborators	Trial name	Study location	Established or anticipated sample size	Status	Incl in PenTAG Review
NCT00819780	Amgen	PEAK	USA, Canada, Belgium, Germany, Italy, Spain	285	Active, not recruiting[a]	Yes
NCT00125034	Merck KGaA	OPUS	Austria, Belgium, France, Germany, Greece, Israel, Italy, Poland, Portugal, Romania, Russia, Spain, Ukraine	344	Completed	Yes
NCT01228734	Merck KGaA	TAILOR	China	481	Ongoing not recruiting[b]	No
NCT00364013	Amgen	PRIME	Multinational	1183	Completed	Yes
NCT00154102	Merck KGaA	CRYSTAL	Multinational	1221	Completed	Yes
NCT00433927	Merck KGaA	FIRE-3	Germany	568	Ongoing not recruiting[c]	Yes
EUCTR2014-000543-33-BE	Amgen	PANIB	Belgium	NR	Ongoing[d]	No

Key: Incl = included; PenTAG = Peninsular Technology Assessment Group

Notes: a Primary completion date, May 2013; Estimated study completion date March 2015. b Estimated primary completion date, June 2015; Estimated study completion date September 2016. c Estimated primary completion date, April 2014; Estimated study completion date December 2016. d Primary and study completion date information not available

Appendix J: *RAS* mutation testing

Panitumumab and cetuximab are licensed only for EGFR expressing, *RAS* WT populations, as their clinical effectiveness is associated with this. We therefore assessed whether the identification of people as EGFR expressing *RAS* WT was significantly different between the trials and clinical practice, as this could impact the effectiveness of panitumumab and cetuximab in practice.

EGFR expression

The clinical trials included in our review assess patients for EGFR expression, in line with the technologies' licensed indications. Our clinical advisors (Dr Mark Napier and Christopher Bowles, both based at the Royal Devon and Exeter hospital), advise that testing for EGFR expression is rarely, if ever, done in practice, as it is believed to not be indicative of the effectiveness of treatment. They believe that not testing for EGFR expression is unlikely to alter the population such that the treatment effect changes. Therefore, though this is different practice what is conducted in the trials, where EGFR status was confirmed, it is believed that it is unlikely to alter the effectiveness between trials and clinical practice.

As it is not routinely done in practice and is not believed to affect the treatment effect, we do not include EGFR testing in our model.

RAS mutation testing in trials

Here we compare the testing techniques used across our included trials, to see if they are how similar they are to each other. In our included trials, people with metastatic colorectal cancer (mCRC) who are *RAS* WT are identified retrospectively, using a range of techniques for testing. We summarise this information in Table 22, page 97.

In general, the method for preparing tissue samples seemed similar across the trials, with polymerase chain reaction (PCR) methods used. However the actual tests used on these samples seemed to differ. For many studies looking at a *RAS* WT population, the population was already identified as *KRAS* WT, and the reporting of these methods was variable, but indicated that again several testing techniques were used.

All trials looked at exons 2, 3 and 4 for both *NRAS* and *KRAS* testing and nearly all trials looked at the full range of identified codons for both *KRAS* and *NRAS* mutations.

One way we can compare tests across trials and to tests in clinical practice is to compare the failure rates of the tests. This is where the tests are not completed and therefore unable to give a diagnosis, rather than when they give an incorrect diagnosis. We attempted to ascertain the percentage of samples being inadequate for each test and the failure rate of the test on samples that were adequate. The trials were not always specific about why some of the cohort was not tested. PEAK specifies that the intended testing cohort as those patients from whom samples were collected, so that any tests that are not run are explicitly stated to be due to inadequate samples.[38] For the other trials, the number of patient samples collected was not reported, so the failure to run the test becomes a result of both inadequate and unavailable samples. Most trials do not report the reasons people could not be tested, so we cannot adequately estimate the trial failure rate of sample collection. Even for the population where a successful *KRAS* test was conducted, the reasons for the sample being unable to be tested for *RAS* WT are either not reported or unclear.

Similarly, few trials report the failure rate of the actual tests, where tests are unable to give a diagnosis even with an adequate sample. The PEAK and PRIME trials report a failure rate of ~3% for Sanger sequencing, where the test failed on at least one of the codons.[38, 53]

Given the limited reporting of the testing done in the trials, it is difficult to really compare them directly, which in turn makes it difficult to compare them to clinical practice. The one important similarity in trial testing was that the trials generally look for mutations in all identified codons for both *KRAS* and *NRAS* genes.

Table 22. *RAS* mutation testing in included trials

Trial	CRYSTAL	FIRE-3	OPUS	PEAK	PRIME
Initial *KRAS* exon 2 test	Sample type: biopsy Testing technique: LNA-mediated qPCR clamping and melting curve analysis	Pyrosequencing and Qiagen	Melting curve analysis	NR	TheraScreen *KRAS*, Qiagen
Codons	12, 13	12, 13	12, 13	NR	NR
Size of cohort to test	1,198	NR	337	NR	1,183
Size cohort test attempted	540	NR	233	NR	1,096
% cohort tested	45.1%	NR	69.1%	NR	92.6%
Reason for tests not conducted	Sample inadequate or unavailable	NR	NR	NR	NR
Failure rate of test	NR	NR	NR	NR	NR
RAS test	BEAM analysis	Pyrosequencing and Qiagen	[redacted]	Sanger sequencing, WAVE based Surveyor CRC RAScan Kits	Sanger sequencing, WAVE based Surveyor CRC RAScan Kits
Additional *KRAS* codons	59, 61, 117, 146	61, 146	[redacted]	12, 13 , 59 , 61, 117, 146	61, 117, 146
NRAS codons	12, 13 , 59 , 61, 117, 146	12, 13 , 59 , 61, 117, 146	[redacted]	12, 13 , 59 , 61, 117, 146	12, 13 , (59)[a] , 61, 117, 146
Size of cohort to test	666	592	[redacted]	250	656
Size cohort actually tested	430	407	[redacted]	235	641
% cohort tested	64.6%	68.8%	[redacted]	94.0%	97.7%
Reason for tests not conducted	NR	NR	[redacted]	Inadequate samples	NR
Failure rate of test	NR	NR	[redacted]	2.60%	3.28%

Key: NR not reported
Notes: a codon 59 conducted as an exploratory analysis.
Sources: Bokemeyer et al. 2009,[32] Douillard et al. 2010,[36] Douillard et al. 2013,[53] Heinemann et al. 2014,[37] Schwartzberg et al. 2014,[38] Tejpar et al. 2015 (AIC),[75] Van Cutsem et al. 2009,[33] Van Cutsem et al. 2015[52]

RAS mutation testing in the UK

A request was sent out for information on *RAS* mutation tests currently used in the UK via the United Kingdom National External Quality Assessment Service (UK NEQAS). The data we received is summarised in Table 23. For laboratories that reported the cost, this was generally £200 for joint *KRAS* and *NRAS* testing, regardless of technique or codons assessed. There is some variability in tests used, but pyrosequencing appears to be generally well-established. We received little information on the accuracy of the tests available, though personal communication from Dr Michelle Wood of the Cardiff and Vale University Health Board suggested that *NRAS* mutation testing may currently be less sensitive than *KRAS* mutation testing.

When we compare the testing in clinical practice with those done in the trials, we see that in general, less codons are assessed in practice than in the trials. The PRIME trial demonstrated that by adding one additional codon to the tests (codon 59), another 7 people who were *RAS* mutant were discovered. This suggests that in clinical practice there is the potential for people diagnosed as *RAS* WT who would be diagnosed as *RAS* mutant if techniques were more similar to the trials.

Table 23. *RAS* mutation testing in UK

Location	Cardiff	Sheffield	Exeter	Salisbury
Type of test	Pyrosequencing For tumour sample is <10%, COLD-PCR reduces LOD	[redacted]		Next generation sequencing
KRAS codons tested	12, 13, 61, 146	[redacted]	12, 13, 59, 61, 117, 146	12, 13, 61
NRAS codons tested	12, 13, 59, 61	[redacted]	12, 13, 59, 61	12, 13, 61
Reported accuracy	Sensitivity KRAS 99%, NRAS 88%	[redacted]	NR	NR
Cost	£120 KRAS or NRAS, £200 KRAS and NRAS	[redacted]	£200 KRAS and NRAS	Contact
Notes		[redacted]		20% tumour tissue required
Source	Dr Michelle Wood personal communication	Neil Atkey personal communication	Chris Bowles personal communication	Wessex Regional Genetics Laboratory webpage [169] Accessed 26/06/2015

Published evidence of *RAS* mutation testing in practice

As well as contacting the UK genetics laboratories directly, and examining their websites, we searched for literature that compared tests to ascertain the accuracy data available. There is limited published evidence of the accuracy or *RAS* mutation tests. One study by Blons et al. (2013), conducted in France for *KRAS* testing was identified, which compared several testing techniques and the results for tests used in more than one laboratory are reproduced in Table 24. The results show that even high levels of dilution, the sensitivity and specificity remain quite high, in correspondence with the tests' limits of detection.

Table 24. Published evidence of current *RAS* mutation testing

	Labs (n)	Samples (n)	Analytical failures (n)	Analytical failures (%)	TN (%)	TP (%)				
						Dilutions				
						All	100%	50%	25%	5%
Direct sequencing	15	1260	4	0.32	98.90	76.00	99.00	99.00	87.00	38.00
Taqman	8	672	11	1.64	99.00	92.30	95.80	100.00	99.30	76.40
Snapshot	7	588	4	0.68	98.80	89.70	95.20	100.00	93.70	73.80
Pyrosequencing	5	420	6	1.43	95.00	96.60	100.00	100.00	100.00	89.70
HRM and sequencing	5	420	0	0.00	100.00	78.00	100.00	98.90	88.90	40.00

Key: HRM = high resolution melt, PCR = polymerase chain reaction
Source: Table 1, page 3 Blons et al. (2013).[170] Reproduced under terms of the Creative Commons Attribution License.

A further study by Tack et al. (2015) was identified, which reported combined false negative rates of 5.0% (sensitivity 95%) and false positive rates of 1.5% (specificity 98.5%) for *RAS* mutation testing across 131 laboratories (10 samples). This included several testing techniques, including number of exons tested and the types of tests used.[171] This study summarises part of the work conducted by the European Society of Pathology Colon External Quality Assessment scheme, and includes data from the UK. The results are similar to those from Blons et al. suggesting that the accuracy of testing for *RAS* mutations may not differ significantly from testing for *KRAS* mutations. It also suggests that the testing may be fairly consistent, despite the wide range of techniques used.

A recent diagnostic assessment by Westwood et al. (2014) compared diagnostic tests for detecting *KRAS* mutations. They found that the relationship between what the tests predicts (mutation status) and the outcome of this diagnosis (which treatment patients receive) is a complex one. As such they adjusted the meaning of accuracy from 'test accuracy' (as discussed previously) to include 'accuracy for predicting response to treatment with cetuximab in combination with standard chemotherapy, or variation in clinical outcomes following treatment with cetuximab in combination with standard chemotherapy depending on which method is used to classify patients as having KRAS wild-type tumours'.[4]

They concluded that the diagnostic tests used in trials seem to result in a benefit for patients. Unfortunately, as not all tests used in practice have been used trials, there is also little evidence to draw conclusions on the effectiveness of these tests. Westwood et al. concluded that there was no significant evidence to suggest that the tests would result in different outcomes for patients, with the caveat that lack of evidence to show a difference is not equal to proving the effectiveness of the tests are equivalent.

Given the paucity of significant accuracy data to contradict Westwood et al., and because it is outside the scope of this review, we currently agree with Westwood et al.'s assessment. Therefore in our model we assume that the accuracy of the tests in the trials are equal to those used in practice and make now adjustments for this.

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The clinical effectiveness and cost-effectiveness of cetuximab (review of TA176) and panitumumab (partial review of TA240) for previously untreated metastatic colorectal cancer: a systematic review and economic evaluation

Errata

12th October 2015

In this document, we only include the revised pages that replace those in our original report in response to factual errors identified by the appraisal group, NICE and the companies. Amendments to the text are in red font for clarity. Deletion, where no text replacement was made, are shown as a tracked change. Page numbering is as per our ACIC corrected report (24th August 2015)

Confidential information that is academic-in-confidence is redacted: [redacted]

Confidential information that is commercial-in-confidence is redacted: [redacted]

compared with FOLFIRI is £149,091 per QALY gained. All ICERs are sensitive to treatment duration, progression free survival, overall survival (resected patients only) and resection rates.

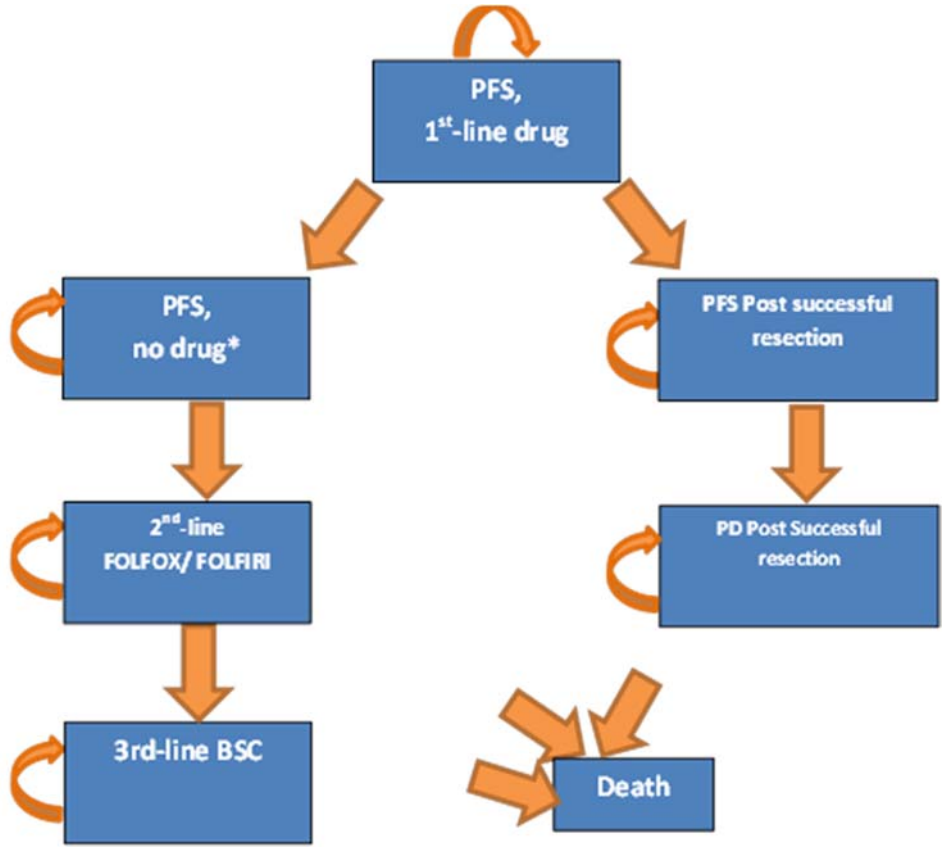
Limitations: The trials only include *RAS* WT populations as subgroups. No evidence was available for panitumumab plus FOLFIRI. Two networks were used for the NMA and the model, based on the different chemotherapies (FOLFOX and FOLFIRI) as no evidence was available to connect these networks.

Conclusions: Although cetuximab and panitumumab in combination with chemotherapy appear to be clinically beneficial for *RAS* WT patients compared with chemotherapy alone, they are likely to represent poor value for money when judged by cost-effectiveness criteria currently used in the UK. It would be useful to conduct a RCT for patients with *RAS* WT.

Funding: The National Institute for Health Research Health Technology Assessment programme

Word count: 497

Figure A. Structure of PenTAG cost-effectiveness model



Key: BSC = best supportive care; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; PD = progressive disease; PFS = progression free survival
Notes: * For CET+FOLFIRI and FOLFIRI only

We have identified two candidate model structures: Structures 1 and 2.

Structure 1 assumes that the PFS benefits of the 1st-line drugs translate into OS benefits if the subsequent lines of treatment are balanced between treatment arms. Expressed differently, we assume that survival after 1st-line progression is independent of 1st-line treatment, which seems plausible, given lack of evidence to the contrary. As Merck Serono, we use Structure 1 in our base case analysis.

Conversely, Structure 2 assumes OS is a product of responses to both 1st and subsequent lines of treatment, as experienced in the RCTs. We consider Structure 2 in a scenario analysis in which we model OS as well as PFS from the RCTs. ~~We make the implicit assumption that the costs of the subsequent lines of treatment from the RCTs are equal between treatment arms.~~

Both Structures have been used in many previous NICE appraisals.

discrete networks were generated, one evaluating FOLFOX-containing chemotherapy regimens and the second comparing FOLFIRI-containing chemotherapy regimens.

Cetuximab

Two trials (OPUS and CRYSTAL), provided evidence for the effectiveness of cetuximab in combination with chemotherapy (FOLFOX4 [FOLFOX may be administered in different regimens, most commonly FOLFOX4 and FOLFOX6, the main difference is in the administration of these regimens] or FOLFIRI) compared with chemotherapy alone (FOLFOX4 or FOLFIRI). These trials included a total of 1,535 participants in the ITT population. Of these, 548 were evaluable for RAS status and 82.8% had *RAS* WT tumours. The median age of participants in these trials was >59.0 years (24–79 years in OPUS and 19–82 years in CRYSTAL), and the majority were male 61% . In both trials, the majority of participants (96%) had Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–1. Twenty-six percent of the *RAS* WT sub-population had liver metastases at baseline.

Evidence consistently suggests a treatment effect in favour of the addition of cetuximab to chemotherapy (FOLFOX4 or FOLFIRI) compared with chemotherapy alone (FOLFOX4 or FOLFIRI) for the outcomes of interest. The addition of cetuximab to FOLFOX4 (**Tejpar *et al.* (2015)** (OPUS)) was associated with a 47% reduction in the risk of progression in people with *RAS* WT tumours (HR 0.53 [95% CI 0.27, 1.04]), similarly, the addition of cetuximab to FOLFIRI (**Van Cutsem *et al.* (2015)** (CRYSTAL)) was associated with a 44% reduction (HR 0.56 [95% CI 0.41, 0.76]). For OS the addition of cetuximab to FOLFOX4 showed no significant evidence of improvement compared to FOLFOX4 alone (HR 0.94 [95% CI 0.56, 1.56]) however, the addition of cetuximab to FOLFIRI resulted in a 31 % reduction in mortality (HR 0.69 [95% CI 0.54, 0.88]). Tumour response rates in the experimental arm ranged from 58% in the **Tejpar *et al.* (2015)** (OPUS) study to 66% in the **Van Cutsem *et al.* (2015)** (CRYSTAL) study vs 29% to 60% in the same respective studies for the control arms. In people with liver metastases at baseline, results in terms of improvement in OS and PFS were consistent with results for overall *RAS* WT population. Of these people 13.3% in the **Tejpar *et al.* (2015)** (OPUS) study to 16.3 % in the **Van Cutsem *et al.* (2015)** (CRYSTAL) study had complete resection in the experimental arms. Overall, clinical safety was consistent with results for *KRAS* WT population in all the trials. The most common events were diarrhoea, haematotoxiticity, neutropenia and skin reactions.

One trial (FIRE-3 trial [**Heinemann *et al.*, 2014**]), provided evidence for the effectiveness of cetuximab in combination with chemotherapy (FOLFIRI) compared with bevacizumab with

- We estimate the proportions of patients taking cetuximab- and panitumumab-based treatments 2nd-line from the limited data from the RCTs. From this, we estimate the total costs of drug acquisition and administration of these 2nd-line treatments.
- The time on 3rd-line best supportive care (BSC) for unresected patients is changed in such a way as to yield the OS curves from the RCTs (after subtracting patients post-resection, and after the indirect comparisons). The times in all other health states are unaltered.

- The cost-effectiveness of CET+FOLFOX vs. FOLFOX decreases substantially so that CET+FOLFOX is now dominated by PAN+FOLFOX.
- The ICER for PAN+FOLFOX vs. FOLFOX decreases substantially from £239,000 to £100,000 per QALY.
- The ICER for CET+FOLFIRI vs. FOLFIRI decreases from £149,000 to £101,000 per QALY.

When we assume that cetuximab is given weekly, as opposed to fortnightly in our base case, the monthly administration cost of cetuximab increases greatly and the ICERs increase substantially:

- CET+FOLFOX vs. FOLFOX: from £110,000 to £165,000 per QALY.
- CET+FOLFIRI vs. FOLFIRI: from £149,000 to £227,000 per QALY.

We now discuss the deterministic sensitivity analyses. Cost-effectiveness is very sensitive to:

- Resection rates.
- PFS and OS post-resection.
- PFS for unresected patients.
- Treatment duration.

Cost-effectiveness is quite sensitive to:

- discounting
- cost of administration of 1st-line drugs.

We find the following ICERs, when the prices of cetuximab and panitumumab are set to £0:

- CET+FOLFOX vs. FOLFOX: £27,000 per QALY.
- PAN+FOLFOX vs. FOLFOX: £50,000 per QALY.
- CET+FOLFIRI vs. FOLFIRI: £27,000 per QALY.

In other words, none of the combination treatments are cost-effective at the £20,000 per QALY threshold. This is largely because the total costs of administration of the combination treatments far exceed those of either FOLFOX or FOLFIRI. This in turn is because we predict that the combination treatments are taken for longer than FOLFOX or FOLFIRI, and because the monthly costs of administration are high.

Now turning to NICE's End of Life (EoL) criteria. Merck Serono claim that cetuximab satisfies these criteria. However, we disagree, as we believe that:

- The eligible patient population is too large,
- ~~The estimated extension to life is not robust.~~
- We are not sure whether life expectancy on FOLFOX and FOLFIRI is less than the required 24 months
- We believe that the extension to life is less than the required 3 months.

We believe that panitumumab probably just fails to meet EoL as:

- ~~The extension to life is not robust.~~
- We are unsure whether the patient population is sufficiently small,
- We believe that life expectancy on FOLFOX is close to, but probably slightly greater than 24 months,
- ~~We are unsure whether the extension to life is greater than the required 3 months~~.

Results of pricing under the Patient Access Schemes for panitumumab and cetuximab can be found in Appendix K.

Comparison of the PenTAG and Merck Serono cost-effectiveness results

There are many similarities between our model and Merck Serono's model. For example, we assume:

- The same overall model structure, that is we both use only resection rates and PFS, but not OS, from the trials of 1st-line drugs. In scenario analyses, we both also model OS from the RCTs.

There is limited evidence to draw conclusions over which anti-EGFR therapy has most clinical benefit. There is no evidence to suggest that cetuximab plus FOLFOX is any more effective than panitumumab plus FOLFOX to increase the time to death or the time to progression or death and there is little evidence to suggest that cetuximab plus FOLFOX is more effective at improving ORR than panitumumab plus FOLFOX.

Estimates of cost-effectiveness currently suggest poor value for money at willingness to pay thresholds of £20,000. Our results indicate that the cost of drug acquisition, and to a lesser extent, cost of drug administration, drives this poor value for money. Probabilistic sensitivity analyses further demonstrate that anti-EGFR therapies are unlikely to be cost-effective at a willingness to pay threshold of £20,000 per QALY gained: for the FOLFOX network, FOLFOX has 78% likelihood of being most cost-effective treatment; and for the FOLFIRI network, FOLFIRI has 100% likelihood of being the most cost-effective treatment.

In summary, there is potential for clinical benefit from anti-EGFR therapies, but cost of administering these therapies is substantial.

Suggested research priorities

- We recommend that the economic analysis should be repeated when the PFS and OS data from the RCTs is more mature. Given sufficiently mature data, we would no longer need to use PFS and OS related to patients post-resection, with all the associated uncertainty, as we do currently.

- The RCTs of 1st-line drugs included subsequent treatments that are not widely used in the UK NHS. Therefore, the economic analysis would benefit from RCTs with subsequent treatments in line with those widely used in the NHS. However, given the substantial costs of conducting trials, we appreciate that this is unlikely to happen.

- Given lack of data to suggest otherwise, we assume the same accuracy of the *RAS* test in clinical practice as in the 1st-line RCTs. Any differences are likely to render higher ICERs for cetuximab and panitumumab. Therefore, we would welcome further research in to the relative accuracies of the tests as used in the trials and in clinical practice.

- Our economic analysis is designed for the NHS in England & Wales. However, it could easily be adapted for the healthcare systems of other countries.

CET+FOLFOX, CET+FOLFIRI and PAN+FOLFOX are all given intravenously. Our economic analysis suggests that the administration of these treatments is expensive, and

Table 54. Results summary (direct and indirect evidence): Efficacy outcomes (*RAS* WT population and *RAS* WT with liver metastases at baseline)

	***RAS* WT**				***RAS* WT with liver metastases at baseline**			
	PFS HR (95%CrI)	**OS** HR (95% CrI)	**ORR** OR (95% CrI)	**Complete resection rate** OR (95% CrI)	**PFS** HR (95%CrI)	**OS** HR (95% CrI)	**ORR** OR (95% CrI)	**Complete resection rate[h]** OR (95% CrI)
Intervention: CET+FOLFOX vs.								
FOLFOX	0.53 (0.27, 1.04)[a]	0.94 (0.56, 1.57)[a]	3.33 (1.36, 8.12)[a]	NE	0.35 (0.06, 1.96)[a]	0.90 (0.33, 2.43)[a]	3.30 (0.63, 17.10)[a]	4.63 (0.20, 104.60)[a]
PAN+FOLFOX	0.74 (0.36, 1.49)	1.22 (0.71, 2.11)	1.90 (0.72, 5.02)	NE	0.44 (0.07, 2.66)	1.29 (0.42 3.94)	1.51 (0.21, 10.80)	2.09 (0.08, 56.28)
BEV+FOLFOX	0.48 (0.21, 1.07)	0.77 (0.37, 1.59)	2.05 (0.63, 6.70)	NE	0.34 (0.05, 2.37)	0.46 (0.06, 3.39)	3.35 (0.30, 38.24)	1.09 (0.03, 44.34)
Intervention: PAN+FOLFOX vs.								
FOLFOX	0.72 (0.58, 0.90)[b]	0.77 (0.64, 0.93)[b]	[redacted]	[redacted]	0.79 (0.49, 1.27)[b]	0.69 (0.42, 1.15)[b]	2.18 (0.74, 6.36)[b]	2.20 (0.80, 6.07)[b]
BEV+FOLFOX	0.65 (0.44, 0.96)[c]	0.63 (0.39, 1.02)[c]	1.08 (0.55, 2.12)[c]	1.16 (0.45, 2.96)[c]	[redacted]	[redacted]	[redacted]	[redacted]
Intervention: CET+FOLFIRI vs.								
FOLFIRI	0.56 (0.41, 0.76)[d]	0.69 (0.54, 0.88)[d]	3.11 (2.03, 4.77)[e]	NE	NE	NE	NE	NE
PAN+FOLFIRI	NE	NE	NE	NE	NE	NE	NE	NE
BEV+FOLFIRI	0.93 (0.74, 1.17)[e,f]	0.70 (0.53, 0.92)[e,g]	1.28 (0.83, 1.99)[f]	NE	NE	NE	NE	NE
Intervention: PAN+FOLFIRI vs.								
FOLFIRI	NE	NE	NE	NE	NE	NE	NE	NE
BEV+FOLFIRI	NE	NE	NE	NE	NE	NE	NE	NE

Key: BEV = bevacizumab; CET = cetuximab; CrI = credible interval; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; HR = hazard ratio; NE = not evaluable; OR = odds ratio; ORR = objective response rate; OS = overall survival; PAN = panitumumab; PFS = progression free survival; *RAS* = rat sarcoma; SAEs = serious adverse events; vs. = versus; WT = wild type

Notes: Fixed effects model; NE = indicates no data available; **Bold** text indicates direct evidence; HR <1 favours intervention; OR >1 favours intervention; a direct evidence from OPUS; b direct evidence from PRIME; c direct evidence from PEAK; d direct evidence from CRYSTAL; e direct evidence from FIRE-3; f Estimate for HR for progression or death using unpublished data HE 0.97 (95% CrI 0.78, 1.20); g Estimate for HR for death using unpublished data HR 0.70 (95% CrI 0.54, 0.90); h Note that surgical resection rate is also reported for PRIME and PEAK studies for the subgroup of *RAS* WT participants with liver metastases at baseline, see Section 3.3.1.6, Table 43, p.141)

progression free survival utility alters according to age, we instead calculate a disutility to apply in this state: 0.142

Once again, adjusting for these parameters results in very little change to the ICERs in Merck Serono's model.

Costs

RAS mutation testing

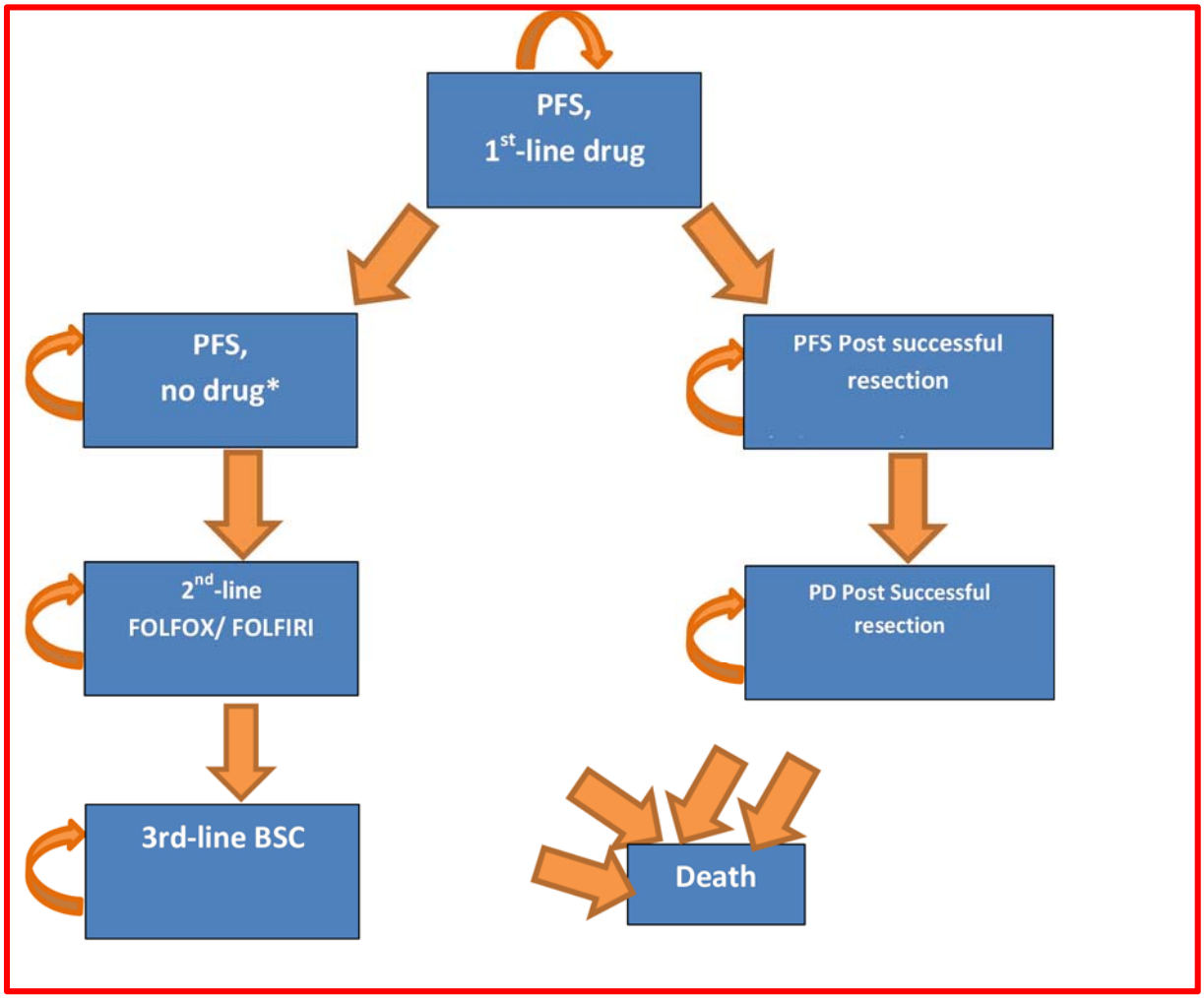
The cost of *RAS* mutation testing used in Merck Serono's model (£200), seems appropriate and information from other genetics laboratories in the UK (discussed in Section 6.1.4.10,) have reinforced the suitability of this cost. However, in the model, this cost is applied to both arms with cetuximab and arms without cetuximab. If all patients were treated with FOLFOX or FOLFIRI, not in combination with cetuximab, a test for *RAS* mutation status would not occur. *RAS* mutation testing can be used as a prognostic tool, but this does not occur in UK practice and for some hospitals *RAS* mutation testing is only available through the Cancer Drugs Fund as a prerequisite for cetuximab or panitumumab (expert opinion, Dr Mark Napier). Removing this cost from the FOLFOX and FOLFIRI arms has minimal impact on the cost-effectiveness.

Drug acquisition

After allowing for drug wastage, but not dose intensity, Merck Serono and we estimate similar acquisition costs per month for cetuximab and bevacizumab. However, Merck Serono estimate far higher costs for FOLFOX and FOLFIRI (Figure 18). This is because they use list prices, whereas we use eMit, discounted prices in our base case. Merck Serono do not consider panitumumab.

The PenTAG cost-effectiveness model, implemented in Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA), simulates a cohort of people with *RAS* WT mCRC starting on 1st-line line treatment. The structure of the model was informed by a review of the literature (Section 6.1.3.1, p240) and the opinions of our clinical expert, Dr Mark Napier (Figure 20). The structure of our model is very similar to that of Merck Serono's model (Section 5.1.2.2, p196).

Figure 20 Structure of PenTAG cost-effectiveness model



Key: BSC = best supportive care FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; PD = progressive disease; PFS = progression free survival
Notes: * For CET+FOLFIRI and FOLFIRI only

In **Error! Reference source not found.**, arrows represent the possible transitions between health states. Circular arrows denote that patients can remain in a state at the end of each model cycle. During each cycle, a patient is assumed to be in one of the states. Patients are assumed to move between states once at the end of each cycle.

Patients can die whilst in any state.

Next, the “all patients” value in FIRE-3 for the *RAS* WT patients for CET+FOLFIRI was estimated as 14.6% = 12.1% / 83%, where the value for *KRAS* WT patients was 12.1% (**Error! Reference source not found.**), and we assume that 83% of *KRAS* WT patients are also *RAS* WT. It was also assumed that only participants with RAS WT tumours were resected given that CET+FOLFIRI has been shown to be more effective, and is licensed, for this population

Finally, the logit of the value of 9.0% for bevacizumab plus FOLFIRI (**Error! Reference source not found.**) was calculated on the logit scale as logit(7.3%) + (logit(17.7%) - logit(14.6%)), in the manner of an adjusted indirect comparison, where the 7.3% is the chosen value for CET+FOLFIRI, and 17.7% and 14.6% are explained above. We worked on the logist transformation, as this ensured that the resulting resection rates would lie between 0% and 100%.

This is slightly different to the value of 7.3% estimated by Merck Serono. They do not justify their value, but we assume they estimated this as the value for CET+FOLFIRI

Now we turn to the derivation of the resection rate for BEV+FOLFIRI for the liver mets subgroup. The resection rates for CET+FOLFIRI and FOLFIRI were taken directly from CRYSTAL (Table 92) (Figure 21). This is also Merck Serono’s approach.

Next, we estimate the rate for BEV+FOLFIRI.

First, we estimate the rate for *RAS* WT in FIRE-3 for CET+FOLFIRI as 32.6% = 14.6% * (16.3% / 7.3%), where 14.6% is the estimated value for all patients, and 16.3% and 7.3% are the values reported for the *RAS* WT populations for CET+FOLFIRI in the subgroup and all patients populations respectively (Table 91).

Next, we estimate the rate for *RAS* WT in FIRE-3 for BEV+FOLFIRI similarly, as 39.6% = 17.7% * (16.3% / 7.3%), where 17.7% is the estimated value for all patients, and 16.3% and 7.3% are as before.

Finally, the value of 19.8% for BEV+FOLFIRI (Table 92) was calculated as 16.3% * (39.6% / 32.6%), in the manner of an adjusted indirect comparison, where the 16.3% is the chosen value for CET+FOLFIRI, and 39.6% and 32.6% are explained above.

Finally, the value of logit of 20.9% for BEV+FOLFIRI (Table 92) was calculated as logit(16.3%) + (logit(39.6%) - logit (32.6%)), in the manner of an adjusted indirect comparison, where the 16.3% is the chosen value for CET+FOLFIRI, and 39.6% and 32.6% are explained above.

Tournigand et al. (2004)[113] concerns 2nd-line treatment not restricted to RAS WT, whereas our estimate is taken from 1st-line treatment for RAS WT patients. Therefore, we prefer our value of [redacted].

The value of logit of the value of [redacted] for BEV+FOLFOX (Table 92) was calculated as logit([redacted] + (logit(11.0%) - logit(12.5%)), as an adjusted indirect comparison, where the [redacted] is the chosen value for PAN+FOLFOX, and 11.0% and 12.5% are the resection rates for BEV+FOLFOX and PAN+FOLFOX from PEAK (Table 91). Merck do not model this treatment.

The value logit of the value of 20.7% for CET+FOLFOX (Table 92) was calculated by first estimating the values for CET+FOLFOX and for FOLFOX for *RAS* WT patients from OPUS. Unfortunately, we are not aware of this value being reported. Therefore, we were forced to estimate them from the corresponding values for *KRAS* WT patients from OPUS, which are reported. Specifically, the estimated rate for *RAS* patients for CET+FOLFOX = 9.8% / 83% = 11.9%, and, as above, we assume that 83% of *KRAS* WT patients are also RAS WT. The estimated rate for RAS patients for FOLFOX was estimated as 4.1% * ([redacted] / 7.6%) = [redacted], where the [redacted] / 7.6% are the rates for FOLFOX from PRIME for *RAS* and *KRAS* WT patients respectively.

Finally, the logit of the value of 20.7% for cetuximab+FOLFOX was calculated as logit(11.9%) + (logit([redacted]) - logit ([redacted])), as an adjusted indirect comparison, where 11.9% is the rate for *RAS* patients for CET+FOLFOX in OPUS and [redacted] is the rate for FOLFOX in PRIME, and [redacted] the estimate rate for FOLFOX just calculated.

By comparison, Merck Serono estimate the rate for CET+FOLFOX as 7.3%, substantially lower than our value of 20.7%. Merck Serono do not discuss the derivation of their estimate. However, we assume it was set equal to their rate for CET+FOLFIRI. If so, we believe that our estimate, whilst apparently high, is methodologically more sound, as Merck Serono's assumption seems unreasonable.

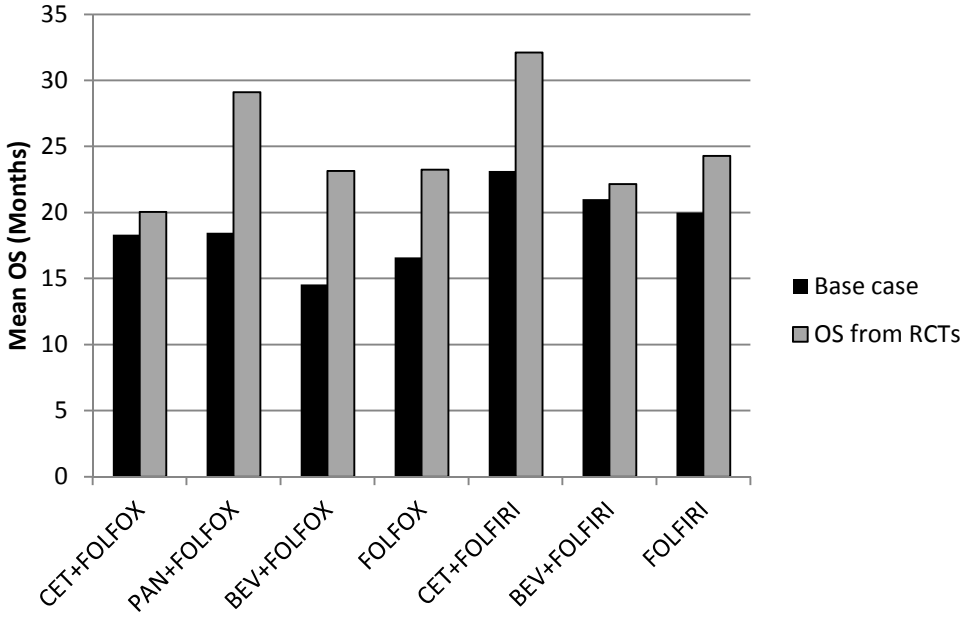
Now we turn to the derivation of the resection rates for the liver mets subgroup.

The rates of 17.1% and 31.3% for FOLFOX and PAN+FOLFOX were taken directly from PRIME, the base case RCT in the FOLFOX network.

The rate of ***** for BEV+FOLFOX was estimated as follows. Logit ([redacted]) was estimated via an indirect comparison as logit (31.3%) + logit ([redacted]) – logit ([redacted]) where the 31.3% is the

chosen rate for PAN+FOLFOX, and the ******and ***** are the rates for BEV+FOLFOX and PAN+FOLFOX from PEAK.

Figure 62 OS estimated via base case method or from RCTs



The cost-effectiveness of CET+FOLFOX vs. FOLFOX now worsens substantially so that CET+FOLFOX is now dominated by PAN+FOLFOX (Table 141). This is because OS increases vs baseline OS less for CET+FOLFOX than for FOLFOX (Figure 62), and because mean treatment duration increases far more for CET+FOLFOX than for FOLFOX (Figure 33, p289).

The cost-effectiveness of PAN+FOLFOX vs. FOLFOX now improves substantially from £239,000 to £100,409 per QALY because OS increases vs baseline OS more for PAN+FOLFOX than for FOLFOX (Figure 62), and because mean treatment duration increases less for PAN+FOLFOX than for FOLFOX (Figure 33, p289).

The ICER for CET+FOLFIRI vs. FOLFIRI now improves from £149,000 to £101,000 per QALY because OS increases vs baseline OS more for CET+FOLFIRI than for FOLFIRI (Table 142), and mean treatment durations for both treatments are unchanged (Figure 33, p289).

Merck Serono also present a scenario analysis whereby they take OS directly from the RCTs. In this case, their base case ICERs change as follows:

- CET+FOLFOX vs. FOLFOX: from £47,000 to £133,000 per QALY, a substantial increase.

CET+FOLFIRI vs. FOLFIRI: from £56,000 to £55,000 per QALY, virtually unchanged.

with locally advanced and recurrent and/or metastatic head and neck cancer, which has previously been estimated to be a population of about 3000 (NICE technology appraisal guidance 172 [TA172]) ….

The Committee therefore concluded that the true size of the cumulative population covered by the marketing authorisation for cetuximab was likely to be over 10,000 patients and was not small, and that cetuximab does not meet all of the criteria for a life-extending, end-of-life treatment".

Based on these figures, and:

- 83% of KRAS WT patients are also RAS WT (Section 5.1.2.2, p192)
- England comprises 95% of the population of England & Wales[164]

We calculate the total population for cetuximab relevant for End of Life as

7,600 x 83% x 94.6% + 3,000 x 94.6% = 8,807.

This exceeds that End of Life criterion of 7,000.

In the current HTA, Merck Serono estimate 5,623 patients have *RAS* WT mCRC in the UK (p18, 70 Merck Serono report). Based on this figure, and that England comprises 84% of the population of the UK,[164] we calculate the total population for cetuximab relevant for End of Life as:

5,623 x 84.1% + 3,000 x 94.6% = 7,567.

This again exceeds the End of Life criterion of 7,000.

Next, we find we estimate the size of the patient population relevant for cetuximab for EoL using figures in our report. We find there were 34,044 new cases of colorectal cancer in England in 2011 (Table 2, p.64), and "almost" 50% of people with colorectal cancer develop metastases (Section 1.1.2.1, p63). Given that about 50% of patients are RAS WT (Section 1.1.2.1, p63), this gives 8,511 estimated new cases of mCRC in England in 2011. Combining this with our estimated 2,838 head and neck cancer cases, gives 11,349. This again exceeds the End of Life criterion of 7,000.

We now turn to panitumumab. We have three estimates for the relevant population of *RAS* WT mCRC as 5,968, 4,728 and 8,511. The first two estimates are below the 7,000 threshold, but the third estimate exceeds the threshold.

On balance, we believe that cetuximab definitely does not meet the End of Life criteria (Table 148), and that panitumumab probably does not meet the criteria (Table 148, Table 149).

Table 148. Assessment of cetuximab against NICE's EoL criteria

EoL criteria	CET+FOLFOX vs. FOLFOX	CET+FOLFIRI vs. FOLFIRI	Meets criterion ?
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	22.3 months on FOLFOX based on our model (Section 6.2.1.1, p343). However, 26.7 months based on PRIME RCT	21.0 months on FOLFIRI based on our model (Section 6.2.1.1, p343).	Unsure
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Mean 6.6 months extension to life expectancy based on our model (Section 6.2.1.1, p343). However, only 0.5 months based on OPUS RCT alone.	Mean 5.5 months extension to life expectancy based on our model (Section 6.2.1.1, p343). However, 8.8 months based on CRYSTAL RCT alone.	Fails, as only 0.5 months based on OPUS RCT.
The technology is licensed or otherwise indicated, for small patient populations normally not exceeding a cumulative total of 7000 for all licensed indications in England.	Estimated as 8,807 or 7,567		Fails, as both estimates > 7,000
The estimates of the extension to life are robust and can be shown or reasonably inferred from either progression-free survival or overall survival (taking account of trials in which crossover has occurred and been accounted for in the effectiveness review)	~~There is plenty of uncertainty concerning the extensions to life, as noted in this table. For example, based solely on the OPUS RCT, extension to life is expected as only 0.5 months.~~		Passes, as we think that estimated extension to life is robust, as from RCT.
The assumptions used in the reference case economic modelling are plausible, objective and robust.	~~Life expectancy is subject to many assumptions.~~ However, our model has been carefully constructed using the best available evidence.		Unsure
Overall qualification for End of Life			Does not meet EoL, as patient population too large, and extension to life too small. Also unsure of whether life expectancy on FOLFOX and FOLFIRI are less than 24 months~~, and whether extension to life is greater than 3~~

EoL criteria	CET+FOLFOX vs. FOLFOX	CET+FOLFIRI vs. FOLFIRI	Meets criterion ?
Overall qualification for End of Life			~~months.~~

Key: CET = cetuximab; EoL = end of life; mCRC = metastatic colorectal cancer;

Table 1. Assessment of panitumumab against NICE's EoL criteria

EoL criteria	PAN+FOLFOX vs. FOLFOX	Meets criterion ?
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Estimated mean OS from FOLFOX studies is <24 months in only a minority of studies.	Probably just fails, as we believe that life expectancy for *RAS* wild-type mCRC patients starting on FOLFOX in the NHS is close to, but probably slightly greater than 24 months.
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Mean 2.6 months extension to life based on our model (Section 6.2.1.1, p343). However, 5.7 months based on PRIME RCT alone.	Passes, as based on PRIME RCT, there is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment
The technology is licensed or otherwise indicated, for small patient populations normally not exceeding a cumulative total of 7000 for all licensed indications in England.	Estimated as 5,968, 4,728 or 8,511	Unsure, as borderline
The estimates of the extension to life are robust and can be shown or reasonably inferred from either progression-free survival or overall survival (taking account of trials in which crossover has occurred and been accounted for in the effectiveness review)	Extension to life is robust	Extension to life is robust, as from RCT
The assumptions used in the reference case economic modelling are plausible, objective and robust.	~~Life expectancy is subject to many assumptions.~~ ~~However,~~ Our model has been carefully constructed using the best available evidence.	Unsure
Overall qualification for End of Life		Probably does not meet EoL as ~~extension to life is not robust.~~ ~~Also~~ unsure of whether patient population is sufficiently small and life expectancy on FOLFIRI probably slightly greater than 24 months~~, and whether extension to life is greater than 3 months~~.

Key: CET = cetuximab; EoL = end of life; mCRC = metastatic colorectal cancer;

Table 150. Comparison of clinical effectiveness: TA176 (2009) vs Assessment Group MTA (2015)

Trial	Outcome		STA: TA176 (2009) EGFR-expressing mCRC[a]	STA: TA176 (2009) *KRAS* WT mCRC	MTA: ID794 (2015) *RAS* WT mCRC
OPUS	N		336	134	87
CET+ FOLFOX4 vs. FOLFOX4	PFS		NR	HR 0.570 (95% CI: 0.358, 0.907)	HR 0.53 (95% CI: 0.27, 1.04)
	OS		NR	NR	HR 0.94 (95% CI: 0.56, 1.56)
	ORR		45.6 % vs 36.0 %[b]	60.7% (95% CI: 47.3, 72.9) vs 37.0% (95% CI: 26.0, 49.1) * [b]	58% (95% CI: 41, 74) vs 29 % (95%CI: 17, 43)[b]
	Resection Rate		NR	11.5% vs 4.1% [b]	NR
	HRQoL		NR	NR	NR
	Safety	Any Grade 3/4 events	CiC	NR	79% vs 63% [b]
		Most commonly reported Grade 3/4 AE [c]	NR	NR	Leukopenia, neutropenia, paraesthesia, rash, any skin reactions and acne-like rash skin reaction
CRYSTAL	N		1198	348	367
CET+ FOLFIRI vs FOLFIRI	PFS		HR 0.85 (95% CI: 0.726, 0.998)	HR 0.684 (95% CI: 0.501, 0.934)	HR 0.56 (95% CI:0.41, 0.76)
	OS		HR 0.93 (95% CI: 0.81, 1.07)	HR 0.84 (95% CI: 0.64, 1.11)	HR 0.69 (95% CI: 0.54, 0.88)
	ORR		45.6% vs 36.0%[d]	59.3% (95% CI: 51.6, 66.7) vs 43.2% (95% CI: 35.8, 58.9) ** [d]	66% (95% CI: 59, 73) vs 39 % (95%CI: 32, 46)[d]
	Resection Rate		NR	3.5% vs 2.3% [d]	OR 3.11 (95% CI: 2.03, 4.78)
	HRQoL	EORTC QLQ-C30; EQ-5D	NR	Statistically significant differences between the two treatment groups in favour of the FOLFIRI-only group were reported [e]	NR
	Safety	Any Grade 3/4 events	CiC	NR	80.9% vs 58.2% [d]

Trial	Outcome		STA: TA176 (2009) EGFR-expressing mCRC[a]	STA: TA176 (2009) *KRAS* WT mCRC	MTA: ID794 (2015) *RAS* WT mCRC
		Most commonly reported Grade 3/4 AE [c]	NR	Neutropenia, constipation, dyspepsia, dyspnoea, dysgeusia, injection site reaction, erythema, hypotension, hypertrichosis and cheilitis[f]	Deep vein thrombosis, dermatitis acneiform, diarrhoea, fatigue, leukopenia, neutropenia, rash, any skin reactions and acne-like rash skin reaction
FIRE-3	N		NA	NA	342
CET+FOLFIRI vs BEV+ FOLFIRI	PFS		NA	NA	HR 0.93 (95% CI: 0.74, 1.17)
	OS		NA	NA	HR 0.7 (95% CI: 0.53, 0.92)
	ORR		NA	NA	65.5% (95% CI: 58, 73) vs 60 % (95%CI: 52, 67)[g]
	Resection Rate		NA	NA	NR
	HRQoL		NA	NA	NR
	Safety	Any Grade 3/4 events	NA	NA	69% vs 67.3%
		Most commonly reported Grade 3/4 AE [c]	NA	NA	Acneiform/exanthema, desquamation, diarrhoea, haematotoxicity, hepatotoxicity, hypertension, hypokalemia, infection, nail changes/paronychia, nausea, pain, skin reactions, thromboembolic events and thrombosis (any)

Key: AE = adverse events; CET = cetuximab; CI = confidence interval; BEV = bevacizumab; EGFR = epidermal growth factor receptor; EORTC QLQ-C30 = Euopean Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire C30; EQ-5D = measure of health outcome by EuroQol; FAS = full analysis set; FOLFIRI = fluorouracil + folinic acid + irinotecan; FOLFOX = fluorouracil + folinic acid oxaliplatin; HR = hazard ratio; HRQoL = health-related quality of life; KRAS = Kirsten rat sarcoma; mCRC = metastatic colorectal cancer; MTA = multiple technology appraisal; NA = not applicable; NR = not recorded; ORR = overall response rate; OS = overall survival; PFS = progression free survival;; STA = single technology appraisal; TA = technology appraisal; WT = wild type; * p=0.011; ** p=0.0028

Notes: a Full analysis set, people with EGFR-expressing mCRC; b CET + FOLFOX4 vs FOLFOX4; c most commonly reported grade 3/4 adverse events where at least one arm had incidences of ≥5%; d CET +FOLFIRI vs FOLFIRI; e QLQ-C30 measurement reported, EQ-5D measure also used however, only 37 patients completed evaluable baseline ED-5D questionnaires; therefore no formal statistical analyses were performed ; f a difference of 5% or more between the groups; g CET + FOLFIRI vs BEV + FOLFIRI

Sources: NICE, Technology appraisal guidance 176, August 2009; Evidence review group report (TA176) commissioned by the NHS R&D Programme on behalf of NICE: Cetuximab for the first-line treatment of metastatic colorectal cancer

9. Conclusions

Clinical effectiveness evidence in this review suggests there is some clinical benefit from anti-EGFR therapies in comparison to standard chemotherapy treatments and mixed clinical benefit in comparison to anti-VEGF therapies: e.g. direct evidence suggests that panitumumab plus FOLFOX is more effective at increasing time to progression or death than FOLFOX and bevacizumab plus FOLFOX. Panitumumab plus FOLFOX is also estimated to be more effective at increasing time to death than FOLFOX., Evidence suggests that cetuximab plus FOLFIRI and bevacizumab plus FOLFIRI are more effective than FOLFIRI at increasing time to progression or death, and objective response rate.

There is limited evidence to draw conclusions over which anti-EGFR therapy has most clinical benefit: There is no evidence to suggest that cetuximab plus FOLFOX is any more effective than panitumumab plus FOLFOX to increase the time to death or the time to progression or death and there is little evidence to suggest that cetuximab plus FOLFOX is more effective at improving overall response rate than panitumumab plus FOLFOX.

Estimates of cost-effectiveness currently suggest poor value for money at willingness to pay thresholds of £20,000. Our results indicate that the cost of drug acquisition, and to a lesser extent, cost of drug administration, drives this poor value for money. Probabilistic sensitivity analyses further demonstrate that anti-EGFR therapies are unlikely to be cost-effective at a willingness to pay threshold of £20,000 per QALY gained: for the FOLFOX network, FOLFOX has 78% likelihood of being most cost-effective treatment; and for the FOLFIRI network, FOLFIRI has 100% likelihood of being the most cost-effective treatment.

In summary, there is potential for clinical benefit from anti-EGFR therapies, but cost of administering these therapies is substantial.

9.1. Implications for service provision

Both panitumumab and cetuximab are currently available on the Cancer Drugs Fund for first line metastatic colorectal cancer (correct as of CDF update September 2015). As *RAS* WT is a prerequisite for using cetuximab and panitumumab in this indication, *RAS* mutation testing is also funded this way for many hospitals (expert opinion, Dr Mark Napier). Therefore currently both *RAS* mutation testing and cetuximab and panitumumab treatment are currently supported by the CDF. Were anti-

Comments on Technology Assessment Report

Cetuximab (review of TA176) and panitumumab (partial review of TA240) for the first line treatment of metastatic colorectal cancer [ID794]

Amgen Limited

Date 29/09/2015

Confidential information that is academic-in-confidence is highlighted and underlined

Confidential information that is commercial-in-confidence is highlighted and underlined

Table of Contents

Executive Summary

We have carefully reviewed and assessed the Assessment Group's (AG) consideration of the evidence on panitumumab combination therapy for the treatment of adults with previously untreated, RAS wild-type (WT) metastatic colorectal cancer (mCRC). We welcome the opportunity to respond to the Assessment Report (AR) and in our response, we address key issues highlighted in the AR.

1. We note that the AG considered in its conclusions around the network meta analyses that there is no evidence to suggest any difference in progression-free survival (PFS) or overall survival (OS) between the two anti-EGFR agents, panitumumab and cetuximab. We also note that the significantly higher incremental cost-effectiveness ratio (ICER) for panitumumab plus FOLFOX versus FOLFOX compared to cetuximab plus FOLFOX versus FOLFOX in the base case is due to the assumption that panitumumab offers patients a much lower chance of benefitting from liver resection compared to cetuximab even though clinical evidence demonstrates that the two agents are similar and that panitumumab combination therapy offers a statistically significant and clinically compelling survival gain. We provide a robust case for using equivalent resection rates for both cetuximab and panitumumab (at least equal to the rates assumed for cetuximab).
2. The AG identified two candidate model structures, a model based on PFS and a model based on OS, but chose the PFS-based model citing the inappropriateness of the OS data. Given the robustness and maturity of the OS data (82% of patients had died when the analysis of OS was conducted), we strongly recommend that the AG considers the use of the OS data in their base case. OS is widely recognised as the most important and reliable endpoint in oncology trials from a clinical and patient perspective.
3. The AG also concludes that panitumumab combination therapy probably does not meet the End of Life (EoL) considerations as the extension to life is not robust. This is despite robust clinical evidence that demonstrates that panitumumab plus FOLFOX increases median OS in patients by 5.6 months. We demonstrate in our response below that panitumumab in combination with FOLFOX is precisely the type of treatment that would qualify for EoL considerations.
4. We would like to underscore that policy level discussions around not being cost-effective at zero price are pertinent to this appraisal. In this case, the high cost of administration for both panitumumab and cetuximab becomes a key factor driving up the ICERs. We urge the Appraisal Committee to take this into account and to consider scenarios such as those presented in the AR (whereby costs of administration of all first-line drugs were set to zero) as plausible.

We address these key issues in detail in our response and strongly recommend that the AG consider a more plausible as well as reasonable base case that is highly likely to yield ICERs for panitumumab in combination with FOLFOX [redacted] We therefore urge the AG to consider all the factors below to arrive at a more plausible and reasonable base case:

- Assume the same resection rates for panitumumab plus FOLFOX and cetuximab plus FOLFOX of at least 20.7%
- Use a model structure based on OS
- Assume, based on clinical evidence, that the EoL considerations apply to panitumumab combination therapy
- Take into account the policy discussion and issues around the high cost of administering anti-EGFR treatments in the first-line setting
- Apply the confidential discount of [redacted] to the drug cost of panitumumab

Colorectal cancer is the third most common cancer in England and prognosis is poor in patients with metastatic disease. It is for these patients with a clear unmet need for whom there are no NICE-approved targeted therapies for the first-line treatment of metastatic colorectal cancer. Panitumumab in combination therapy in the first-line treatment setting offers a chance of providing significant patient benefit and would be a valuable option for these patients (with RAS WT disease).

Clinical Effectiveness

Robust evidence demonstrating efficacy of panitumumab in previously untreated WT RAS mCRC

- The AR acknowledges that clinical evidence consistently demonstrates a treatment effect in favour of the addition of panitumumab to FOLFOX compared with FOLFOX alone. It is noteworthy that the addition of panitumumab to FOLFOX increases median OS by 5.6 months in RAS WT patients (HR 0.77 [95% CI 0.64 to 0.94]; p=0.009) (Douillard et al, 2013). This survival difference is both highly statistically significant and clinically compelling, and therefore the addition of panitumumab to FOLFOX offers a chance of providing significant patient benefit.

Limitations of the cetuximab evidence base

- There are a number of uncertainties in the cetuximab evidence base, due to low sample size and ascertainment rate of RAS status. The AR explains that the evidence evaluating the combination therapy of cetuximab with FOLFOX is not as strong as for panitumumab with FOLFOX; the OPUS trial of cetuximab plus FOLFOX versus FOLFOX had far fewer RAS WT patients (n=87) than the PRIME RCT of panitumumab plus FOLFOX versus FOLFOX (n=512). The probabilistic sensitivity analysis reported in the AR confirms this, with the cetuximab plus FOLFOX versus FOLFOX results much more uncertain than those obtained for panitumumab plus FOLFOX versus FOLFOX. In addition, the RAS ascertainment rate in the OPUS study was 66% compared with 90% in PRIME (Bokemeyer et al, 2015; Douillard et al, 2013).

Clinical benefit from anti-EGFR therapy: equivalence of panitumumab and cetuximab

- Despite the limitations of the cetuximab evidence base, it is notable that the European Medicines Agency (EMA) stated that although *"cetuximab data by RAS status are only derived from the randomised phase II study OPUS, the biological rationale supporting the efficacy in patients with RAS wild type tumours only is strong and the conclusions are supported by data related to panitumumab"* (European Medicines Agency, 2013). This not only lends support to the premise of equivalence between the two anti-EGFR agents but importantly underscores the strength of panitumumab data as it was used to augment the evidence base in patients with RAS WT tumours for cetuximab.
- The CDF similarly, in their assessment of panitumumab and cetuximab in combination with FOLFOX, note that "*there was no known biological difference between panitumumab and cetuximab in terms of efficacy and that side-effect profiles were also very similar"* (Cancer Drugs Fund, 2014).
- The network meta analyses (NMA) performed by Amgen and the AG did not suggest any difference in the clinical effectiveness of panitumumab and cetuximab.
- In addition, panitumumab has been shown to be non-inferior to cetuximab in a phase 3 head-to-head RCT in chemotherapy refractory mCRC (ASPECCT). This study was designed to assess the OS benefit of panitumumab compared with cetuximab in KRAS WT patients. Median OS was 10.4 months with panitumumab and 10.0 months with

cetuximab (HR 0.97; 95% CI 0.84‑1.11) (Price et al, 2014), providing further evidence that these agents offer a similar survival benefit.

- The AG's base case ICER in RAS WT patients for cetuximab plus FOLFOX compared with FOLFOX is £109,820 per quality adjusted life year (QALY) gained and £239,007 for panitumumab plus FOLFOX compared with FOLFOX, the difference driven by larger QALY gains in PFS post resection for cetuximab plus FOLFOX compared with panitumumab plus FOLFOX. Given that the evidence for the combination therapy of panitumumab with FOLFOX is the most robust (with a clinically proven difference in survival) among the anti-EGFR agents and that there is a strong clinical justification to believe that there is no known biological difference between panitumumab and cetuximab, we believe that the AG's estimate of cost-effectiveness of panitumumab is erroneous and inconsistent with clinical evidence.

The liver metastases resection rates assigned to panitumumab plus FOLFOX and cetuximab plus FOLFOX in the AG model are not consistent with clinical evidence

- Despite substantial evidence to suggest clinical equivalence for the two anti-EGFR agents, resection rates assigned to cetuximab plus FOLFOX in the AG base case model were much higher (20.7%) than those assigned to panitumumab plus FOLFOX ([redacted]). These differences resulted in larger incremental QALYs for cetuximab (0.35) versus panitumumab (0.15), coming from PFS post resection, which in turn generated large differences in the ICERs between the two anti-EGFR agents.
- Resection rates assigned to panitumumab plus FOLFOX and FOLFOX alone in the AG model were based on the RAS WT population in the PRIME trial. It is noteworthy that PRIME did not aim, and was not powered, to detect differences in rates of resection, and consequently, the baseline resectability status of patients was not assessed (Amgen, 2013).
- It is also important to note that the resection rate assigned to panitumumab plus FOLFOX was much lower than the rate advised for cetuximab plus FOLFOX by experts during the appraisal of TA176 (35%). However, this estimate of 35% has been criticised because it was obtained from a clinical expert in a non-systematic manner and in the TA176 appraisal proceedings, the Delphi method was recommended as a way to elicit expert opinion (National Institute for Health and Care Excellence, 2009). We therefore undertook a Delphi panel survey to elicit plausible rates of liver resection for anti-EGFR agents and the surgical resection rate from our study is in line with previous clinical expert opinion (Amgen, 2015; National Institute for Health and Care Excellence, 2009). The Delphi panel study elicited expert opinion from 6 surgeons in England on resection rates in patients treated with EGFR inhibitors in clinical practice and shows that resection rates are likely to lie between 25 and 40% (mean 30 to 32%) (Amgen, 2015).
- Consequently, we strongly believe that the resection rate of [redacted] for panitumumab plus FOLFOX used in the AG's model is a gross underestimate of the resection rate expected in clinical practice. In practice we would expect the resection rates for anti-EGFR agents to be higher at around 30% based on the results of the Delphi panel study which is very much in line with the resection rate of 35% for cetuximab plus FOLFOX that was accepted by the committee in TA176. Given overwhelming evidence on the

strength of the efficacy data for panitumumab plus FOLFOX as well as the premise of equivalence between the two anti-EGFR agents, panitumumab and cetuximab, and the results from the Delphi panel survey, we suggest that the true resection rate for panitumumab plus FOLFOX is at least 20.7% (in line with the resection rate assigned to cetuximab plus FOLFOX in the AG base case model).

- In summary, given the strength of evidence showing that panitumumab in combination with FOLFOX provides both statistically significant and clinically relevant gains in survival compared to FOLFOX, the use of this evidence to support the efficacy discussions at the regulatory level for cetuximab in combination with FOLFOX, and the additional head to head study, ASPECCT, which validates the hypothesis that both agents provide similar survival benefit, we urge the Appraisal Committee to consider using equivalent resection rates for both cetuximab and panitumumab of at least 20.7%.

Cost-Effectiveness Analysis

Model structure should be based on overall survival

- OS is widely recognised as the most important and reliable endpoint in oncology trials from a clinical and patient perspective (Driscoll et al, 2009).
- The AG identified two candidate model structures, a model based on PFS and a model based on OS, and commented that ordinarily the latter would be preferable because of the consistency between the costs and health outcomes. The AG however chose the PFS-based model citing the inappropriateness of the OS data due to subsequent lines of treatment used in the trials: i) that the 2nd-line drugs used were not now commonly used in the NHS and ii) that the subsequent lines of treatment may have had a very strong effect on OS. They cite the FIRE-3 RCT as an example where no significant difference in PFS was observed, yet there was a significant OS benefit and very different subsequent treatments in the two treatment arms.
- Unlike the FIRE-3 RCT, the PRIME RCT demonstrated statistically significant differences in both PFS and OS. The proportion of patients receiving any subsequent anti-tumour therapy was slightly higher in the FOLFOX arm compared with the panitumumab arm ([redacted]). Use of traditional chemotherapy agents including irinotecan-, oxaliplatin-, or fluoropyrimidine-containing chemotherapy was slightly higher in the FOLFOX arm ([redacted]) as was use of anti EGFR therapy (19% vs 7%). Use of bevacizumab was broadly similar in both arms (13% vs 16%) (Appendix 4, Amgen submission). It is noteworthy that anti-EGFR agents and bevacizumab were previously approved under the CDF and have been used in the NHS until the recent delisting of bevacizumab (Cancer Drugs Fund, 2015).
- The impact of subsequent anti-EGFR therapy on OS in PRIME has been explored in a sensitivity analysis using statistical methods recognised by NICE including rank preserving structural failure time (RPSTM) models and inverse probability of censoring weighted (IPCW) analysis. This analysis was performed in KRAS WT patients for the final PRIME analysis. Results are presented in Table 1 and consistently show more favourable OS HRs for panitumumab plus FOLFOX versus FOLFOX when subsequent anti EGFR therapy is taken into account. Anti-EGFR therapy was received by 25% of

patients in the FOLFOX arm and 13% of patients in the panitumumab plus FOLFOX arm in this analysis (Douillard et al, 2012).

Table 1. Impact of subsequent anti-EGFR therapy on OS in KRAS WT patients in PRIME

	OS HR (95% CI) Panitumumab plus FOLFOX vs FOLFOX
Intent to treat analysis	0.88 (0.73, 1.06)
Statistical model for influence of subsequent anti-EGFR therapy	
Branson & Whitehead, 2002	0.84 (0.68, 1.05)
Robins & Tsiatis, 1992	0.83 (0.66, 1.04)
Allison, 1995	0.68 (0.55, 0.83)
Inverse probability of censoring weighted (IPCW)	0.74 (0.56, 0.97)

CI, confidence interval; OS, overall survival.
Based on final analysis (data cut-off 02 August 2010).
(Douillard et al, 2012).

Although these analyses are in KRAS WT patients and are based on the final PRIME analysis (as opposed to the later 'OS update' analysis), it is likely that the OS gain for panitumumab plus FOLFOX in WT RAS patients (HR 0.77) will also have been attenuated by the higher use of anti-EGFR therapy in the FOLFOX arm. The results of these sensitivity analyses together with the higher overall use of subsequent therapies in the FOLFOX arm suggest that the PRIME OS estimate for panitumumab plus FOLFOX is potentially an underestimate of the true OS.

- The AR notes that the economic analysis should be repeated when the PFS and OS data from the RCTs is more mature. We would like to underscore that the updated analysis of OS in the PRIME was conducted when 82% of patients had died. This provides mature data on which to build the economic model.
- The use of OS obviates the need to estimate survival after disease progression which in turn reduces the uncertainty around the ICERs. In summary, given the robustness and maturity of the OS data, we strongly recommend that the AG consider the use of the OS data in their base case.

End of Life (EoL) Considerations

- The AR notes that it is unlikely that panitumumab in combination with FOLFOX will qualify for EoL considerations. We are of the view that panitumumab in combination with FOLFOX is precisely the type of treatment that would qualify for EoL considerations.
- **Indicated for patients with a short life expectancy (< 24 months)**

  The AR notes that it is unclear if panitumumab plus FOLFOX therapy would qualify on the basis that it is used for patients with a short life expectancy, normally less than 24 months. The updated analysis of the PRIME RCT, which was conducted when 82% of patients had died, yielded a median OS of 20.2 months (95% CI 17.6 to 23.6) for the FOLFOX arm. As already discussed, subsequent treatments in the FOLFOX arm are likely to have influenced survival gains positively. The studies identified through a systematic search and used in the Amgen NMA (presented in Appendix 8 of Amgen

submission) support the short life expectancy of these patients. From all studies which included a FOLFOX arm, the median OS in the FOLFOX arm ranged from 10.7 months to 20.5 months (Appendix 8, Amgen submission). Indeed, one study in which almost 90% of the patients had died at evaluation, yielded a median OS of 15.4 months for FOLFOX (Seymour et al, 2007). There is therefore considerable evidence to show that panitumumab plus FOLFOX therapy is indicated for patients with a short life expectancy of less than 24 months.

- **Licensed for patient population not exceeding 7000 patients**

  The AR reports three estimates for the total population eligible for panitumumab treatment: 4,728, 5,968 and 8,511 patients. Based on the upper bound of this range, it states that it is unclear whether panitumumab plus FOLFOX would qualify for the criteria that it is licensed for a small patient population. We believe that this is not a balanced conclusion, as two of the three estimates of total population fall well within the 7,000 threshold. We also understand that policy discussions are ongoing and likely to include revisions to the current EoL Criteria (NHS England, 2015). As such, we would urge the Appraisal Committee to take a pragmatic view on this and accept that panitumumab is more than likely to meet this consideration.

- **Offers extension to life (of at least an additional 3 months)**

  The AR explains that it is unlikely that there is sufficient evidence to indicate that panitumumab in combination with FOLFOX offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment. The AG states that based on their model, panitumumab provides a mean 2.6 months extension to life and that the model has been carefully constructed using the best available evidence (even though they chose a PFS-based model). We disagree with this approach and would like to point out that the best available evidence, which is OS for panitumumab in combination with FOLFOX, was not used by the AG to inform this consideration. The median OS gain of 5.6 months has been accepted by the EMA as providing credible evidence to support its license indication. Further, 82% of patients had died when this assessment was conducted and given that the impact of subsequent treatments would likely attenuate OS gains, all provide strong reasons why panitumumab in combination with FOLFOX provides sufficient evidence that it offers at least an additional 3 months of life, compared with FOLFOX, the current NHS treatment.

Not Cost-Effective at Zero Price

- The AR notes that even when the prices of panitumumab and cetuximab are set to zero, none of the combination treatments (panitumumab plus FOLFOX, cetuximab plus FOLFOX/FOLFIRI) are cost-effective at the £20,000 QALY threshold. The AG remarks that *"In the current HTA, we find a similar explanation for why all three combination treatments are not cost-effective. In particular, total costs of administration of the combination treatments far exceed those of either FOLFOX or FOLFIRI. This in turn is because we predict that the combination treatments are taken for longer than FOLFOX or FOLFIRI."* In addition to setting the prices to zero, the AG explored two scenarios, one in which the costs of administration of all first-line drugs (as well as the prices of cetuximab and panitumumab) were set to zero, and another in which the treatment duration of cetuximab plus FOLFOX and panitumumab plus FOLFOX were set equal to

that of FOLFOX (and the prices of cetuximab and panitumumab were set to zero). The ICERs for both these scenarios fell substantially (to ≤ £20,000 per QALY) compared with the scenario where only drug costs were set to zero demonstrating the high cost of administering anti-EGFR combination treatments.

- The NICE policy discussion, currently ongoing around treatments that are not cost-effective at zero price, is very relevant to the technologies appraised in this appraisal. Both panitumumab and cetuximab are given on top of FOLFOX/FOLFIRI and the cost of administering the combination treatment is very similar to FOLFOX or FOLFIRI alone. This implies that any increase in PFS also increases the cost of administering panitumumab or cetuximab plus FOLFOX. Indeed the Decision Support Unit (DSU) paper on this topic concludes that *"the main factor driving the ICER above commonly accepted thresholds, when assuming a zero price, is the cost of administering the technology being appraised rather than the cost of treatments given alongside that technology"* (National Institute for Health and Care Excellence, 2014).
- In light of the DSU paper and the ongoing NICE policy discussion, we urge the Appraisal Committee to take into account the issues around the high cost of administering both panitumumab and cetuximab combination therapy and to consider scenarios such as those presented (whereby costs of administration of all first-line drugs were set to zero) as plausible.

Revised Base Case

- The NICE final scope highlights that colorectal cancer is the third most common cancer in England (National Institute for Health and Care Excellence, 2015). Patients with metastatic colorectal cancer are faced with a poor prognosis and at the same time are also faced with the prospect of having no NICE-approved targeted therapies (monoclonal antibodies such as anti-EGFR agents) for the first-line treatment of metastatic colorectal cancer. Panitumumab in combination therapy in the first-line treatment setting offers a chance of providing significant patient benefit and would be a valuable option for these patients (with RAS WT disease).
- We would strongly recommend that the AG consider and present a more plausible revised base case analysis which we believe would demonstrate that panitumumab in combination with FOLFOX including the confidential patient access discount is highly likely to [redacted].
- Based on the discussions in this response around the lack of biological plausibility that the two anti-EGFR agents would be expected to be different, the use of more mature and robust OS data, the EoL considerations and the policy considerations around drugs that are not cost-effective at zero price, we urge the AG to consider all the factors below to arrive at a more plausible and reasonable base case:
    - Assume the same resection rates for panitumumab plus FOLFOX and cetuximab plus FOLFOX of at least 20.7%
    - Use a model structure based on OS

- Assume, based on clinical evidence, that the EoL considerations apply to panitumumab combination therapy
- Take into account the policy discussion and issues around the high cost of administering anti-EGFR treatments in the first-line setting
- Apply the confidential discount of [redacted] to the drug cost of panitumumab

Additional Comments

Survival data post resection

- It is plausible that patients who undergo successful resection are "cured" and thus should not follow the OS fitted curves after a certain number of years but instead follow life table data. We would recommend that the AG explores the scenario using life table data in the long-term instead of curve fits for successfully resected patients.

Weekly versus fortnightly drug administration schedule for cetuximab

- The marketing authorisation for cetuximab is for weekly dosing, however the base case model assumes fortnightly dosing as this is believed to be current clinical practice. The ICER for cetuximab plus FOLFOX versus FOLFOX becomes much higher when weekly dosing is assumed. The AG assumes no change in effectiveness between weekly and fortnightly cetuximab dosing, but acknowledges that it remains possible that there is a difference. In common with the AG, we note that it would be unusual for NICE to issue guidance outside the current marketing authorisation.

No evidence to suggest any difference in Objective Response Rate (ORR) for panitumumab plus FOLFOX versus cetuximab plus FOLFOX

- The AR states that there was *limited* evidence to suggest that cetuximab plus FOLFOX is more effective at improving ORR than panitumumab plus FOLFOX (Executive Summary). Elsewhere in the dossier it states that there is *little* evidence to support this (section 3.3.1.3). These statements are based on their NMA which estimates the ORR odds ratio for cetuximab plus FOLFOX versus panitumumab plus FOLFOX as 1.90, 95% credible interval 0.72 to 5.02. Given that the 95% credible interval for ORR includes the value 1 (no difference) we would argue that there is no evidence to support a difference between agents for ORR, in line with the clinical similarity evidence discussed earlier. Although the point estimate for ORR is in favour of cetuximab plus FOLFOX, this would appear to be due to a lower than expected ORR in the FOLFOX arm of OPUS (29%); this rate is lower than that reported for FOLFOX in other similar studies (Table 29, Appendix 8 of Amgen submission) and considerably lower than that seen in the FOLFOX arm of PRIME (46%). In contrast, the ORR was similar for cetuximab plus FOLFOX and panitumumab plus FOLFOX in OPUS and PRIME (58% vs 59% respectively). Finally, it is noteworthy that the AR states that ORR results should be interpreted with caution given potential differences in the timing of when ORR was reported.

Factual Inaccuracies

We wish to highlight a few minor factual inaccuracies within the AR and propose the recommended corrections as described in Table 2 below.

Table 2. Factual inaccuracies in the AR

Assessment Report Section	Factual Inaccuracy	Recommended Correction
3.2.6.2	Upper limit of 95% CI for median OS for PEAK is reported in the text as 13.1	The correct value is 31.3 (per Table 21).
3.2.6.2	PRIME WT RAS data is frequently reported to come from Douillard 2014	The year is wrong. Should be corrected to Douillard, 2013

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Multiple Technology Appraisal (MTA)

Cetuximab (review of TA176) and panitumumab (partial review of TA240) for the first line treatment of metastatic colorectal cancer [ID794]

Merck Serono's comments on Technology Assessment Group Report

On behalf of Merck Serono, please find our comments on the Technology Assessment Group's (TAG) Report, dated 7th August 2015, for cetuximab and panitumumab in the first line treatment of RAS wild type metastatic colorectal cancer (mCRC).

Summary

Merck Serono reviewed the TAG Report with particular attention to the differences in methods and calculations involved in the cost effectiveness analyses and the impact these have on the cost effectiveness of cetuximab in combination with chemotherapy against chemotherapy alone.

We note that, on the whole our report and the report from the TAG have similar estimates of efficacy but that the TAG has considerably higher estimates of costs. That is due to the TAG utilising higher estimates of unit costs and of longer durations of treatment.

Although Merck Serono agrees with some of the methods and estimations the TAG have used in estimating the Incremental Cost Effectiveness Ratio (ICER) of cetuximab, we believe that some of the parameters used are neither appropriate nor realistic for the reasons provided in the sections below.

In particular, Merck Serono disagree with the following:

- The estimate of the mean duration time (which is simple based on assumption)
- The estimate of the mean dosage (the TAG assumes that all patients are treated at the highest dosages of medication)
- The acquisition cost of cetuximab (The TAG uses NHS prices for FOLFOX and FOLFIRI, but do not use the NHS prices for cetuximab and utilise the higher list price.)
- The administration cost of all regimen (The TAG have made assumptions using the highest costs and not considered a double counting effect)
- The assumption that resected patients use the same dose of cetuximab as unresected patients
- The method (even though outcomes are similar between models) to estimate of life years gained and QALY's gained
- Considering cetuximab not to meet the End of Life criteria

The TAG outlined 8 main differences in the cost effectiveness model that was developed by them, compared to the model developed by Merck Serono. These differences are discussed in more detail below. A summary of these differences and comparisons of the

estimates/method used by the TAG and the estimates Merck Serono are outlined below in table 5.

A detailed study of the report has indicated that the estimates from Merck Serono can be improved and we agree with the TAG in a number of places. We appreciate parts of their critique and have updated a selection of estimates. We will indicate, in a similar fashion (page 53 of the TAG report), how the updated estimates change our ICERs.

Merck Serono also agrees with the TAG that there were still some errors in our model although we contest that these do not have the same significant impact on the ICER as reported by the TAG. Merck Serono corrected the calculation of the costs of post resection progressive disease where an inappropriate so called "mid-point correction" was carried out. This increases the base case costs-effectiveness ICER of cetuximab in combination with FOLFIRI to £56,614 instead of £55,971 and cetuximab in combination with FOLFOX at £47,030 instead of £46,503.

Cetuximab/FOLFIRI:

Starting with the comparison with FOLFIRI we subsequently note that:

- Merck Serono agrees with the TAG that the costs of the test should be £400 for the cetuximab arm (when assuming reimbursement of cetuximab) and 0 for the chemotherapy arms. Please note this will be different when there is only assuming reimbursement in the liver limited group. This increases the Cost-Effectiveness (CE) ratio from £56,614 to £57,975.
- Indeed we also accept that we may have under-estimated the costs of the liver resection. When increasing the estimate of less than 3,000 to £9,943, our updated estimate, which is comparable to the TAG costs of £10,483, the CE ratio increases to £57,422.
- Similarly, it is agreed that costs would be likely to be incurred during the progression free period post resection and we accept the TAG's estimate for this of £710. Costs post progression may additionally be higher than was estimated by us. The TAG group found a single Finnish study and based their estimate on this study. Finland and the UK have quite different health care systems and many of the costs included in this study would not fall under the NHS. Hence these costs should be excluded. However, we adapted our estimate of £315 per month to £991 per month being the cost of supportive care. As a single change this increases the CE ratio from £56,614 to £58,583 per QALY.
- The TAG estimates the monthly costs of drug administration at £2,473 for FOLFOX 4 and for £1,759 for FOLFOX6. In the case of drug delivery costs, Merck Serono would accept that that administration takes place in the day-care setting and so these costs would be appropriate. Accepting the PenTAG's own recommendations from previous submissions (Hoyle et al 2013) and the weighted cost would result in a total administration cost of £399.83 per cycle or £799.66 per month for chemotherapy

alone. Even following the TAG's own recommendations in the report and adding a quarter of an hour of nursing time in case of the use of cetuximab. These changes increases the CE ratio to £56,766.

- With respect to the unit costs we have assumed that the Appraisal Committee will want to be consistent. One either uses the list prices, or the "real" prices. Merck Serono has now selected the later for the model, leading to much lower estimates of the costs of FOLFOX and FOLFIRI (as the TAG choses to do), but also of cetuximab for which, in practice, the costs are also much lower than the list-price. The net result is in favour of cetuximab. The estimate of the ICER decreases to £[redacted].
- In the TAG model, the body surface area (BSA) was increased 1.79 to 1.85. The link between body surface and costs of the drug is by a step function (due to dose banding) with steps at 1.60, 1.70 and 1.80. By choosing an average of 1.85, it is implicitly assumed that all patients treated would be in the highest dose banding which does not take into account patients with a lower BSA and does not reflect the actual distribution of patients.
- Merck Serono acknowledges, that we have underestimated the duration of treatment, but again with not as significantly as suggested by the TAG. The TAG used a model derived mean which came from median treatment duration. Actual mean treatment duration in the CRYSTAL study was 9.1 months vs 6.8, which has now been taken into the model. Additionally, it is estimated that patients who are resected are only treated for 4 months. As a single action, this increases the CE ratio to £70,065. It is the biggest single influence on the change in CE ratio.
- Finally, in an attempt to be conservative, it was chosen to only model 10 years. When setting the time horizon at 20 years (as a single action) the CE-ratio decreases to £53,408. A time horizon of 20 years captures all patient events in our model. In TA176, a time horizon of 23 years was accepted by the committee.
- When combining all changes the ICER is estimated at £79,044, which is considerably less than the estimate from the TAG group. Most notably because of their estimate of the average duration of the treatment and the asymmetry between the use of costs for Cetuximab and those for FOLFOX and FOLFIRI. When using the PAS-price, this decreases to £74,139.

Cetuximab/FOLFOX:

The estimate when considering the comparison between Cetuximab and FOLFOX changes more, mainly because it was found that the average duration in the relevant patients in the study were 6.3 and 5.2 months for Cetuximab/FOLFOX and FOLFOX.

When considering the various steps we find:

- An increase from £47,030 to £48,2748 due to the costs of RAS testing
- To £47,879 due to costs of the liver resection

- To £48,544 for the costs post resection
- To £47,269 when using higher costs of administration
- Changing the drug acquisition costs to "real" prices, those paid in practice, decreases the cost effectiveness ratio to £[redacted]
- The TAG group criticised the use of the CRYSTAL trial to estimate resection rates and used new number that were not made available to Merck Serono. As a best alternative one might use the numbers from the KRAS sub-population from the OPUS study: 9.8 vs 4.1%. This element, as a single change, decreases the estimate of the cost effectiveness ratio to £46,178. When calculating this account is taken of the fact that patients who have a resection are only treated for 4 months. It is noted that the TAG group, with higher resection rates assumes that resected patients are treated just as long as non-resected (which in the case of the comparison with FOLFIRI is over nine months).
- Increasing the time horizon to 20 years decreases the ICER to £44,304
- Changing the treatment duration to the mean values in the OPUS trial rather than the modelled means derived from medians in the TAG report, and taking account of the fact that resected patients are only treated for 4 months decreases the CE-ratio to £40,427.
- When combining all changes, the costs per QALY are estimated at £46,701. When using the PAS-price of Cetuximab this is £47,978.

Liver Limited Disease (LLD) Group:

Using those estimates it is then possible to calculate the cost effectiveness of treatment in the group with liver limited disease by simply changing the resection rates. If the resection rates in the LLD group are estimated at 0.30 for with Cetuximab and at 0.15 without, the costs per QALY are estimated at £42,793 for the comparison with FOLFOX and at £66,113 for the comparison with FOLFIRI. When the reimbursement for patients with LLD is restricted to 4 months, as is the case in current clinical practice, and under current NICE TA176 guidance, the costs per QALY are £22,473 and £22,612 respectively for cetuximab with FOLFOX and FOLFIRI.

Differences in effectiveness

It is noted that both Merck Serono and the by – TAG estimate the differences in QALY's are about 0.30. Merck Serono does so by straightforwardly using data from trials which investigated cetuximab. It is noted that the survival post resection is estimated to be lower than that estimated by the TAG group and one might suggest that Merck Serono has underestimated some benefit due to the higher resection rates. Still the gain in QALY's is estimated to be about the same. This is related to other survival estimates, which in the case of the TAG group are based on a network meta-analysis. This analysis appears unnecessarily complicated. We strongly believe that instead of adding strength to the comparison it only weakens it by needing too many untested and potentially biased assumptions.

Summary

Notwithstanding the details of the economic evaluation, the overall increase in QALY in both Merck Serono and TAG models is estimated at about 0.30. Differences in costs can be mainly explained by different assessments of costs of the therapy and its administration, which have been addressed above. When considering a treatment regimen of cetuximab plus FOLFIRI versus FOLFIRI alone, one finds that the difference in total costs is estimated at £23,816, while the difference in the costs of medication and administration is £24,567. Hence, apart from minor savings in the long run, all costs are due to the cost of treatment. Given that the difference in efficacy is estimated at about 0.30, it can be approximated that the cost effectiveness ratio is equal to 3.33 times the difference in drug and administration costs.

In our submission we have outlined the data that support the use of cetuximab in combination with both FOLFOX and FOLFIRI. Based on the cost effectiveness analysis, cetuximab combined with FOLFOX appears to more cost effective and therefore may seem to be the most attractive choice from an economic perspective. However, Merck Serono would like to highlight that much of the clinical data supporting this application (CRYSTAL, FIRE-3, CALGB-80405) is in combination with FOLFIRI rather than FOLFOX. This also reflects current clinical practice as indicated by the CDF usage numbers in table 3. Therefore, while cetuximab in combination with FOLFOX is a valuable and valid combination in this setting, Merck Serono would contend that cetuximab in combination with FOLFIRI is of greatest value to the oncology community.

Merck Serono's comments on TAG statements

Merck Serono would like to offer comments under each of the following statements which are included in the TAG report as shown below in the text boxes:

TAG statement 1

Page 33 – model parameters	Also, in common with Merck Serono, we based our estimates of 1st-line PFS for unresected patients on the data from the pivotal RCTs. However, Merck Serono estimate PFS for nonresected patients directly from the RCTs of all patients (resected and non-resected). We believe that this over-estimates PFS for non-resected patients, given that some patients in the RCTs are resected and that PFS for these patients is substantially longer than for nonresected patients. Instead, we estimated PFS for unresected patients by starting with PFS for resected + unresected patients in the RCTs of 1st-line drugs, and then attempting to subtract off the PFS that we expect in the RCTs in respect of resected patients.

The results of the modelling are a weighted average of patients who are and who are not resected, and differences between the PENTAG model and Merck Serono's model can be

found in the estimates of the resection rates, treatment durations and costs after resection. We address each of these below.

With respect to the resection rates, Merck Serono chose to use the most reliable information that was available to them which was from the CRYSTAL study which showed rates 7.3% for Cetuximab/FOLFIRI and 2.1% for FOLFIRI for the overall population (both palliative and LLD). Motivated by many similarities between FOLFIRI and FOLFOX (most notably in terms of efficacy) and due to the low numbers from the OPUS trial for this analysis, similar figures were assumed for the comparison between Cetuximab/FOLFOX and FOLFOX.

The TAG group appears to include undisclosed information based on PRIME and PEAK to estimate a rate for FOLFOX. The resection rates from PRIME are mentioned in table 24 as being 10/41 patients (24%) in the LLD subgroup having resection for FOLFOX with 7/41 (17%) appearing to have complete resection. It is not clear to Merck Serono how they come to an estimate of Cetuximab vs FOLFOX. Dummy values in the spreadsheet suggest that one might end up with a difference of 11.9% vs 6.3%.

With respect to treatment durations and post-resection PFS, the TAG estimates average survival post resection at 11.5 years and average progression free survival post resection at 6.13 years. These estimates are much higher than those in the Merck Serono model where the corresponding estimates were 4.83 years for OS post-resection and 3.56 years post resection PFS.

Therefore, Merck Serono accepts that our model neglected the longer progression free survival of the resected patients but the net result - by using a much lower post resection survival estimate - is that Merck Serono has actually underestimated the survival benefits.

TAG statement 2

Page 35 – model parameters	In our base case, we used the list prices of cetuximab, panitumumab and bevacizumab. This yielded the following monthly costs of drug acquisition: • Cetuximab: £3,859 • Panitumumab: £4,109 • Bevacizumab: £2,003 In our base case, we used the discounted prices of FOLFOX and FOLFIRI, taken from the Commercial Medicines Unit Electronic market information tool (CMU eMit) to reflect the true cost to the NHS. This yielded the following monthly costs of drug acquisition. • FOLFOX-4: £86 • FOLFIRI: £128

Merck Serono comment:

We noted the use of significantly lower chemotherapy acquisition costs using the CMU eMit tool to reflect true cost to the NHS. We believe that following this approach should allow for the use of actual cost of cetuximab to the NHS for fair comparison. We have indicated in our evidence submission that "Cetuximab has been offered at a guaranteed discounted price to

the NHS in agreement with the Department of Health since 2008. This agreement is not limited to a time period. The NHS acquisition prices are [redacted] (100mg/20ml vial); [redacted] (500mg/100ml vial).

However, we followed the NICE methodology in using List prices for all comparators, including cetuximab to allow for a like-to-like comparison. Therefore, the use of CMU eMit cost for chemotherapy without the use of true NHS cost of cetuximab overestimates the cost difference between cetuximab in combination with chemotherapy and chemotherapy alone. Using the model developed by the TAG, the cost of cetuximab acquisition is reduced to £2,665.85 per month using the actual NHS price.

Therefore, we have updated our model to reflect the CMU eMit prices for both FOLFOX and FOLFIRI as well as cetuximab.

Table 1: List price and eMIT/NHS prices for cetuximab and chemotherapy

Price used in calculating cost	Cetuximab acquisition cost	FOLFIRI acquisition cost	FOLFOX-6 acquisition cost
List price	£3,859	£1,797	£2,120
eMIT/NHS price	[redacted]	£128	£91

TAG statement 3

Page 36 – model parameters	Our estimated total monthly drug administration costs are: • CET/PAN/BEV+FOLFOX: £2,473 • FOLFOX4: £2,348 • CET/BEV+FOLFIRI: £1,759 • FOLFIRI: £1,634

Merck Serono comment:

We noted that the cost of administration for FOLFOX was based on the assumption that the FOLFOX-4 regimen is used in the UK. FOLFOX-4 was the chemotherapy regimen that was utilised when the clinical trials were initiated in 2005. Since then, administration of the chemotherapy regimen has been update so that patients have 2 rather than 3 clinical visits for their FOLFOX regimen.

The FOLFOX-4 regimen requires an infusion of oxaliplatin, folinic acid and a 22 hour infusion of 5-FU on day 1 and a repeat infusion of folinic acid and 5-FU on day 2 of a 14 day cycle. The FOLFOX-6 regimen requires an infusion of oxaliplatin, folinic acid and a 46 hour infusion of 5-FU on day 1 of a 14 day cycle, therefore eliminating the need for a clinic visit and repeat infusions on day 2. This is the most commonly used regimen in the UK and is more cost effective and manageable by the patients. This has been confirmed by expert clinical opinion.

According to the TAG calculation, the cost of FOLFOX-6 is £1,634, which is comparable to the FOLFIRI chemotherapy regimen and is significantly cheaper than the cost of administering FOLFOX-4 (£2,473). Therefore, as the aim is to use true costs to the NHS, as

well as the most cost effective regimen, we believe that the FOLFOX-6 chemotherapy regimen that should be utilised, in place of the FOLFOX-4 regimen that is currently being used in the model.

TAG statement 4

Page 232	The HRG SB15Z (Deliver subsequent elements of a chemotherapy cycle) was inappropriately used for the administration costs for complete cycles after the first cycle, rather than for activity not on the first day of a chemotherapy cycle. The correct usage is for the first attendance in every cycle to use SB14Z (or another delivery code except SB15Z), and then to use SB15Z for any subsequent attendances within each cycle.

Merck Serono comment:

In the case of drug delivery costs, Merck Serono would accept that that administration takes place in the day-care setting and so these costs would be appropriate. Based on guidance for NHS Reference Costs 2013 to 2014. We agree that the appropriate unit cost for one cycle will comprise the unit costs of SB14Z (Deliver complex chemotherapy, including prolonged infusional treatment) for day 1 and SB15Z (Deliver subsequent elements of a chemotherapy cycle). These day case reference costs are: £371 and £320. We would even agree on using the weighted average of 3 reference cost items, to deliver complex chemotherapy in different settings, adding up to £383 pounds per session. This would in general (according to table 117 page 325 in the report) cover "60 minutes nurse time and 120 minutes chair time". It is implicit that these costs include the hospital overheads, (unless these are exceptionally expensive nurses) and by adding in the cost of infusion and line maintenance on top of this, there is an element of double counting involved.

We also note that even though the TAG accepts that there is "A significant variation in pharmacy costs for chemotherapy for metastatic colorectal cancer", they have utilised the higher end costs in their model. They considered the inflated costs from DG16 and TA118, even though in the review of TA118, PenTAG themselves used an estimated pharmacy cost of £15 per cycle (2008/09 prices) (Hoyle et al, 2013). Accepting the TAGs costings would mean that the NHS is presently paying over £800 pounds per patient per treatment cycle, for chemotherapy. We consider this inflated costs unrealistic and misleading. Accepting PenTAGs own pharmacy cost recommendations from previous submissions and the weighted cost above would result in a total administration cost of £399.83 per cycle or £799.66 per month for chemotherapy alone and the addition of a quarter of an hour of nurse time for the addition of cetuximab.

TAG statement 5

Page 36 – model parameters	We estimate the cost of resection surgery as £10,440, substantially higher than Merck Serono's estimate of £2,707. Once we allow for the probability of a successful operation and the mean number of operations per person, we estimate a cost of approximately £17,600 per person who is successfully operated.
Page 234	Given our estimate of that the cost of liver surgery, after allowing for repeat operations, and the chance of operation failure, is £17,582

Merck Serono comment:

We agree that the cost of surgical resection of liver metastasis in our submission was low and the true cost should be closer to the cost adopted by NICE in Technology Appraisal 176 (£8,900). However, the TAG did not sufficiently explain the source and assumptions upon which they based their estimation of £17,582 per patient. Therefore, we believe that the cost of surgical resection should remain closer to the cost adopted in TA176.

We believe that the same cost adopted by NICE in TA176 should be used taking account of inflation since 2009, as this cost was deemed representative of the cost in that year by NICE. This equates to £9,941 with the 2009-15 inflation index of 1.117. In reality NHS inflation tends to be much higher than inflation as measured by either CPI or RPI, so this is almost certainly an under-estimate.

TAG statement 6

Page 42 - Appraisal of Merck Serono's economic analysis	Merck Serono assume that no 1st-line drugs are given after a certain cut-off time, which varies slightly by treatment arm. Strangely, they provide no justification for the cut-off. Further, we note that Merck Serono assumed a similar cut-off time in their model for cetuximab and cetuximab+irinotecan for subsequent lines of treatment for mCRC, NICE TA242, in 2011.
Page 284-285 - 6.1.4.5. 1st-line Time on treatment	We estimate the mean treatment duration for each 1st-line treatment in the following Steps: A. Estimate the mean treatment duration for each 1st-line treatment in each of the pivotal RCTs, based on median treatment duration from each RCT, and 25% and 75% percentile of the treatment duration when available (Table 98). B. Estimate mean treatment duration for each 1st-line treatment by simple indirect comparison, using CRYSTAL and PRIME as baseline RCTs (Table 98).

Table 98 Steps A and B in estimation of mean treatment durations

	From RCTs	Step A	Step B
	Median treatment duration (months)	Estimated mean treatment duration (months)	Modelled mean treatment duration (months)
FOLFOX network			
CET+FOLFOX	5.6 (OPUS)	8.0 (OPUS)	14.4 (indirect comparison)
FOLFOX	4.6 (OPUS), 6.2 (PRIME)	5.0 (OPUS), 9.0 (PRIME)	9.0 (PRIME)
PAN+FOLFOX	6.5 (PRIME), 7.5 (PEAK),	9.3 (PRIME), 10.7 (PEAK),	9.3 (PRIME)
BEV+FOLFOX	5.9 (PEAK),	8.5 (PEAK),	7.3 (indirect comparison)
FOLFIRI network			
CET+FOLFIRI	7.4 (CRYSTAL),, 4.8 (FIRE-3),	10.7 (CRYSTAL), 6.9 (FIRE-3),	10.7 (CRYSTAL)
FOLFIRI	5.8 (CRYSTAL),	8.3 (CRYSTAL),	8.3 (CRYSTAL)
BEV+FOLFIRI	5.3 (FIRE-3),	7.6 (FIRE-3),	11.8 (indirect comparison),

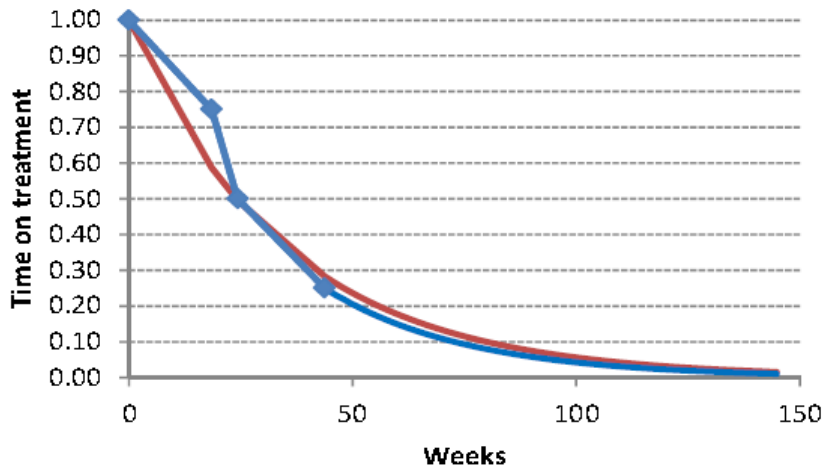
Key: BEV = bevacizumab; CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folini acid + fluorouracil + oxaliplatin; PAN = panitumumab

C. For each treatment, compare the estimated mean treatment duration with the estimated mean 1st-line PFS for unresected patients (Section 6.1.4.4, p267). We would expect the mean treatment duration to be lower, because in all RCTs, treatment was supposed to stop on progression. However, we show below that this was generally not the case – usually, mean treatment duration was greater than mean 1st-line PFS for unresected patients. Given that we use only PFS, not OS from the RCTs, we assume no, or equal treatment effects across treatment arms post-progression. Therefore, we should not model 1st-line treatment after 1st-line PFS for unresected patients. If we did, we would incur the costs of 1st-line drug treatment after progression, but gain no clinical benefit from this, which is clearly inappropriate. Therefore:

- If mean treatment duration was estimated less than mean 1st-line PFS for unresected patients, our estimate of mean treatment duration was left unaltered.
- Otherwise, mean treatment duration was capped at mean 1st-line PFS for unresected patients.

Page 288

First, this data was used to estimate the mean time on cetuximab+FOLFOX for RAS WT patients. An exponential tail was fit to the 25% percentile (Figure 33), with hazard set equal to that at the 25% percentile. The mean was then estimated as 34.7 weeks, being the area under the empirical data and fitted tail.

	Figure 33 Estimated time on CET+FOLFOX treatment for *RAS* WT patients in OPUS 

Merck Serono comment:

The treatment cut off period in the economic mode developed by Merck Serono utilised the median treatment period reported in the relevant clinical trials. No other assumptions were made in this respect.

We note that the TAG have estimated the mean treatment duration using the exponential method. We believe this method is not appropriate. It assumes that the probability to stop treatment at any point in time, given that one has been treated until that time, is always the same. This seems unlikely and an increase in the probability to stop in time, as in a population survival curve or a PFS survival curve, seems far more appropriate.

Moreover, in clinical practice patients do not receive treatment permanently. This observation is evident in figure 33 above where the tail extrapolated extend to a period of treatment close to 150 weeks, which is not practical or possible in clinical practice as patients cannot tolerate treatment toxicity for such a long period of time and are likely to progress in their disease much earlier than this time period.

Upon the review of the TAG methodology in modelling treatment periods, we agree with the TAG that mean treatment periods should be used in the model instead of the median. Therefore, we have revisited our clinical trial data and found that the mean treatment periods for CRYSTAL and OPUS studies are outlined in table 2.

Table 2: Mean treatment durations for CRYSTAL and OPUS

Mean Treatment Duration RAS WT	TAG estimated mean treatment period (months)	Actual mean from trials (months)
Cetuximab/FOLFIRI (CRYSTAL)	10.7	9.1
FOLFIRI (CRYSTAL)	8.3	6.8
Cetuximab/FOLFOX (OPUS)	14.4	6.3
FOLFOX (OPUS)	9.0	5.2

Table 2 demonstrates that the TAG estimates for mean treatment periods were significantly overestimated for the FOLFOX group, which – together with the use of the high list prices - is the main reason for estimating ICERs over £100,000/QALY using TAG-estimated figures.

Therefore, we have updated the model to reflect the actual mean treatment durations from the CRYSTAL and OPUS studies.

TAG statement 7

Page 44 – Appraisal of Merck Serono's economic analysis	For the comparison CET+FOLFIRI vs. FOLFIRI, most incremental QALYs come from PFS non-resected and PFS post-resection (Figure 51). Post-resection QALYs are less important than for CET+FOLFOX vs. FOLFOX, as we predict low rates of resection for CET+FOLFIRI (7.3%) and FOLFIRI (2.1%).

Merck Serono comment:

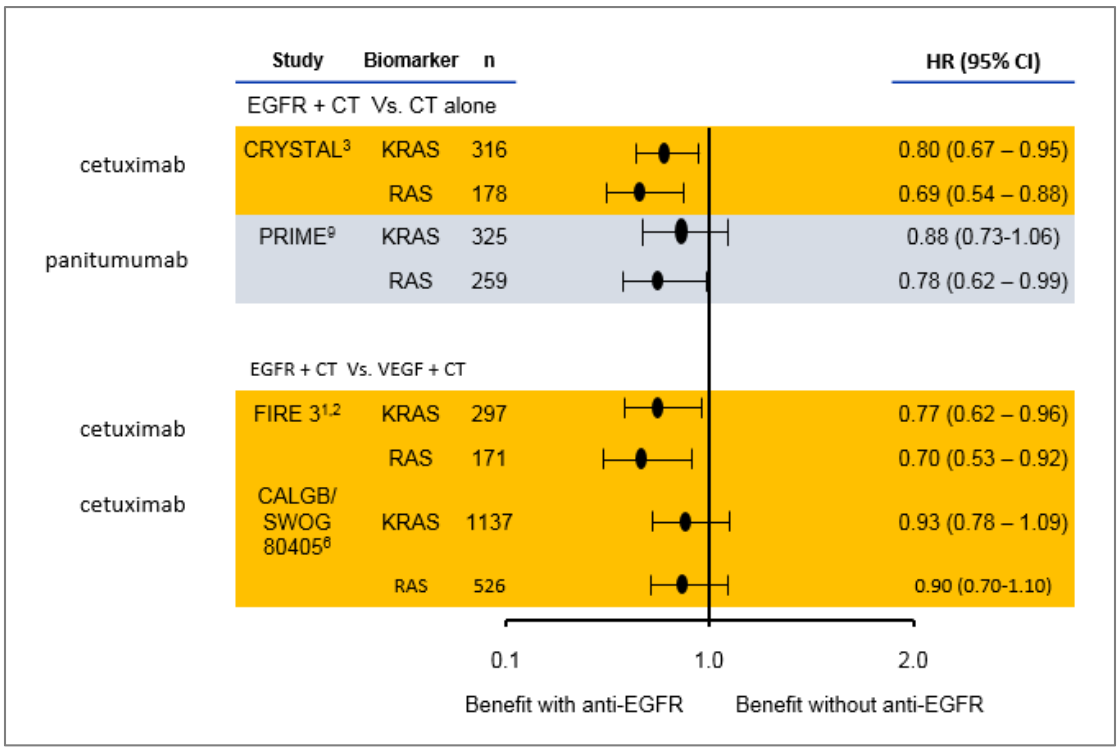
Resection rate was not the primary outcome for OPUS and CRYSTAL studies. Therefore, resection rates for patients in the liver limited disease mCRC population in clinical practice are expected to be higher than those reported in these 2 clinical trials.

There are a number of studies that specifically examine the efficacy of cetuximab/chemo for downsizing liver metastases. In the CELIM trial, an R0 resection rate of 31% was achieved with Cetuximab/chemo (Folprecht et al.) The Ye et al. study resulted in an R0 resection rate of 30% for cetuximab/chemo and in a UK study, real world data from a retrospective observational data collection of patients treated with cetuximab for downsizing of their liver limited mCRC with the goal of resection, cetuximab and chemotherapy resulted in a 28% R0 resection rate.

In the Adam et al. study (2004) chemotherapy alone resulted in a resection rate of 12.5% and the Ye et al. study showed a rate of 9% for chemotherapy alone.

Each of these studies report data in the KRAS wt population and the expectation is that these results would be slightly improved with refinement of the patient population from KRAS to RAS wt as can be seen in figure 1. Therefore, we believe that a conservative resection rate of approximately 30% for cetuximab/chemo in the LLD patient population would reflect clinical reality and 12-15% for chemotherapy alone.

Figure 1. Improved hazard ratios in studies when population refined from KRAS to RAS WT.



These assumptions were confirmed by clinical experts consulted as part of our previous NICE appraisal, TA176 in 2008. Section 4.5 in NICE TA176 states:

"It [the Appraisal Committee] heard from the clinical specialists that the number of patients receiving potentially curative liver resection in the CRYSTAL and OPUS trials was lower than that seen in UK clinical practice, which is based on management by multidisciplinary teams involving highly specialised liver surgical services. The clinical specialists stated that a more realistic rate for potentially curative resection with chemotherapy in general was approximately 12–15%, which could rise to approximately 30–35% with the addition of cetuximab."

With higher resection rates in clinical practice, we expect cetuximab with chemotherapy, compared to chemotherapy alone, to be shown as a more cost effective treatment than estimated by the TAG in their economic modelling.

The patients with LLD, require some slightly different clinical considerations to patients with patients with non-LLD, as the goal of treatment in this setting is to shrink tumours to the point at which a patient is able to undergo surgical liver resection, rather than treatment until progression of disease; this was recognised in TA176. There is a clinical rationale for limiting treatment duration for LLD patients: 1) to maximise the potential for patients receiving

cetuximab with chemotherapy to get an effective response to treatment, with sufficient shrinkage to allow liver resection to proceed, while 2) minimising the duration of treatment with irinotecan or oxaliplatin containing regimens, which both can make surgical liver resection more complicated which could compromise effectiveness of the procedure. Expert opinion still reflects this today and TA176 changed real life clinical practice to this effect after it was published in 2009.

In our current model, it is possible to calculate the cost effectiveness of treatment in the group with liver limited disease by simply changing the resection rates and treatment duration. If the resection rates in the LLD group are estimated at 0.30 for with Cetuximab and at 0.15 without, and the treatment duration is limited to 4 months, the costs per QALY for the addition of cetuximab to chemotherapy are estimated at £22,669 for the comparison with FOLFOX and at £22,527 for the comparison with FOLFIRI.

TAG statement 8

Page 60 - Suggested research priorities	We recommend that the economic analysis should be repeated when the PFS and OS data from the RCTs is more mature. Given sufficiently mature data, we would no longer need to use PFS and OS related to patients post-resection, with all the associated uncertainty, as we do currently.

Merck Serono comment:

PFS and OS data from CRYSTAL and OPUS are mature, no further data is expected from these studies. The data presented to the TAG from these clinical trials is the data available from the post hoc analysis of RAS wild type mCRC patients enrolled in these studies. These post hoc analyses were necessary since the role of RAS biomarkers in predicting treatment benefit was not understood at the time of the studies' initiation. Therefore, using data from the post hoc analyses provided the most robust method for providing accurate data for the RAS wild type subgroup and was accepted by the EMA to update cetuximab license accordingly.

TAG statement 9

Page 49 – Appraisal of Merck Serono's economic analysis	Now turning to NICE's End of Life (EoL) criteria. Merck Serono claim that cetuximab satisfies these criteria. However, we disagree, as we believe that: • The eligible patient population is too large, • The estimated extension to life is not robust. • We are not sure whether life expectancy on FOLFOX and FOLFIRI is less than the required 24 months • We are not sure whether the extension to life is greater than the required 3 months.
Page 410 – End of life criteria	One of the criteria in the tables below is that the total patient population for all licensed indications in England should be less than 7,000. We understand that CRC is the only indication for panitumumab. In NICE TA242 from 2011, for cetuximab, bevacizumab and panitumumab for the treatment of mCRC after first-line chemotherapy, the NICE committee concluded: "*The Committee was aware from the manufacturer's data that approximately 7600 people have EGFR-positive, KRAS wild-type metastatic colorectal cancer in England and Wales…. However, the Committee noted that cetuximab has a marketing authorisation for people with any stage of EGFR-positive KRAS wild-type metastatic colorectal cancer, and also for people with locally advanced and recurrent and/or metastatic head and neck cancer, which has previously been estimated to be a population of about 3000 (NICE technology appraisal guidance 172 [TA172])* Based on these figures, and: • 83% of KRAS WT patients are also RAS WT (Section 5.1.2.2, p192) • England comprises 95% of the population of England & Wales We calculate the total population for cetuximab relevant for End of Life as 7,600 x 83% x 95% + 3,000 x 95% = 8,807. This exceeds that End of Life criterion of 7,000.

Merck Serono comment:

- Criterion 1 – The eligible patient population is too large (population greater than 7,000)

In relation to the size of the population for all licensed indications in England, we noted that the TAG differentiated between cetuximab and panitumumab based on the indications under the license. We believe that to achieve a fair comparison between the two medicines, both should be treated on equal grounds and assessed in accordance with the size of the colorectal cancer population.

It is worth noting that the historical reason for the difference in licensed indications between cetuximab and panitumumab is the fact that cetuximab demonstrated significant clinical effectiveness in the treatment of squamous cell carcinoma of the head and neck in the EXTREME study while panitumumab did not show a significant benefit in the SPECTRUM study for the same indication, resulting in there being a SCCHN indication for cetuximab but not for panitumumab.

Therefore, if the TAG considered that cetuximab does not meet this criterion while panitumumab does, we believe that the TAG are penalising cetuximab for demonstrating clinical benefit in an indication that is not being assessed within the scope of this MTA.

Further to this, cetuximab can only be considered as a treatment option for a small proportion locally advanced SCCHN patients and not at all for recurrent / metastatic head and neck cancer patients. TA145 restricted the funded population to only those locally advanced SCCHN patients with a Karnofsky score of above 90 in whom all forms of platinum based chemotherapy were contraindicated or not tolerated. TA 172 did not recommend the use of cetuximab for SCCHN patients with recurrent or metastatic disease. This restricted SCCHN population, when combined with the RAS WT mCRC eligible patient population which is under discussion in this MTA, does not exceed 7,000. Merck Serono contends that head and neck cancer patients should not be included in this evaluation, for the reasons outlined above. However, even if they are included, and the current patients that are funded within the SCCHN indications are applied, then the addition of these patients to the RAS WT mCRC population described below, still does not exceed 7,000, thus meeting end of life criteria.

Focusing now on the specific mCRC patient population under consideration in this MTA, namely 1st line RAS WT mCRC patients, total is significantly less than 7,000. Restrictions of indication to the RAS WT population since NICE TA242 has further limited the eligible population. This biomarker identified patient population should be further considered in the context of the proportion of patients who are considered appropriate candidates for treatment by physicians based on performance status and co-morbidities.

If we utilise the figures outlined in the TAG report above and calculate the RAS wt mCRC population excluding the SCCHN population, as this MTA is only evaluating the mCRC population and for parity with panitumumab, the eligible population is:

Assuming these figures:

- 83% of KRAS WT patients are also RAS WT (Section 5.1.2.2, p192)
- England comprises 95% of the population of England & Wales

We calculate the total population for cetuximab relevant for End of Life as

7,600 x 83% x 95% = 5,993

This meets the End of Life criterion of 7,000.

Actual usage of cetuximab in the first line setting under the Cancer Drugs Fund, demonstrates that the approximate number of patients treated in 2014, the most recent data available for the UK, can be estimated at 542 for the year, much below the 7,000 cut-off. If all mAb use for mCRC in England based on the CDF is considered, the number of patients that received treatment was just over 3,000 in the first line setting and this population includes patients that are RAS mutant and therefore not eligible for cetuximab. Since cetuximab has been reimbursed through the CDF for several years, a dramatic shift in patient eligibility can be considered unlikely.

1st line only	Total number of notifications received for each indication on:	Apr-14	May-14	Jun-14	Jul-14	Aug-14	Sep-14	Oct-14	Nov-14	Dec-14	3x months average to make up year	Total
Cetuximab	1st Line treatment of metastatic coloreactal cancer in combination with the following regimens: FOLFOX4 or FOLFOX6 or OxMdG Chemotherapy (From 13/02/2014)	3	9	5	5	3	15	7	3	5	18	**73**
	1st line treatment of metastatic colorectal cancer in combination with Irinotecan based chemotherapy (From 13/02/2014)	48	32	56	36	35	36	48	27	34	117	**469**
Bevacizumab	The first line treatment of advanced colorectal cancer with a single agent fluoropyramidine in patients assessed as unfit to receive combination oxaliplatin- or irinotecan-based combination chemotherapy	28	22	22	37	27	30	33	25	26	83	**333**
	1st line treatment of metastatic colorectal cancer. Only to be administered concurrently with chemotherapy, not as single agent maintenance therapy.	161	177	166	189	164	208	199	164	190	539	**2157**
Panitumumab	1st Line treatment of metastatic coloreactal cancer in combination with the following regimens: FOLFOX4 or FOLFOX6 or OxMdG Chemotherapy	1	0	1	1	2	4	3	5	6	8	**31**
											Total	**3064**

Table 3. Monoclonal antibody for first line treatment of mCRC use in England 2014

- Criterion 2 – We are not sure whether life expectancy on FOLFOX and FOLFIRI is less than the required 24 months

Although it appears that in the TAG model, survival for patients that receive chemotherapy alone may be greater than 24 months, there are numerous trials that highlight that the median overall survival on chemotherapy alone is around 20 months as outlined in the table below. In every clinical study, chemotherapy only overall survival was considerably lower than 24 months. This has also been confirmed by expert opinion.

Table 4. Overall survival data for mCRC patients on chemotherapy alone

Data from Clinical Trials on chemo only survival (median Overall Survival)		
RAS WT Data	**1st Line Chemotherapy**	**mOS (months)**
CRYSTAL	FOLFIRI	20.2
OPUS	FOLFOX	17.8
PRIME	FOLFOX	20.2
No biomarker selection		
Tournigand	FOLFOX	20.6
Tournigand	FOLFIRI	21.5
Saltz	FOLFOX/XELOX	19.9
COIN	FOLFOX/XELOX	17.9

- Criterion 3 – The estimated extension to life is not robust. We are not sure whether the extension to life is greater than the required 3 months.

With regards to the increased life expectancy of greater than 3 months, in the CRYSTAL study there was an 8.2 month increase in mOS when cetuximab was added to FOLFIRI. In the OPUS trial in the RAS WT group there was an increase of 2 months, which was actually lower than the benefit seen in the KRAS WT population of 4.3 months in this study when cetuximab was added to FOLFOX.

In general, when the patient population is refined from the KRAS population to the RAS population, due to the exclusion of patients that do not benefit from cetuximab, there is an improvement in outcomes. This has been observed in multiple studies and is the rationale behind the restriction of the cetuximab indication to RAS WT patients. In the KRAS population for the OPUS trial, there was a 4.3 month mOS benefit of cetuximab/FOLFOX compared to FOLFOX alone, which one could assume would improve when refining to the RAS wt population. The 2 month OS difference seen in OPUS is believed to be and artefact due to the lower numbers in the RAS analysis in this study.

In additon, there are a number of other first line trials that show median overall survival rates of 28-33 months (FIRE3 – 33.1 months, CALGB-80405 - 32 months, CECOG/CORE2 – 28.5 months) for cetuximab in combination with chemotherapy. Assuming chemotherapy only provides approximately 20 months OS, these data reinforce the benefit seen with the addtion of cetuximab.

These data support the view that the addition of cetuximab to chemotherapy will increase overall survival by at least 3 months and these additonal study data should allow this to be perceived as robust.

TAG statement 10

Page 49	We find the following ICERs, when the prices of cetuximab and panitumumab are set to £0: • CET+FOLFOX vs. FOLFOX: £27,000 per QALY. • PAN+FOLFOX vs. FOLFOX: £50,000 per QALY. • CET+FOLFIRI vs. FOLFIRI: £27,000 per QALY. In other words, none of the combination treatments are cost-effective at the £20,000 per QALY threshold. This is largely because the total costs of administration of the combination treatments far exceed those of either FOLFOX or FOLFIRI. This in turn is because we predict that the combination treatments are taken for longer than FOLFOX or FOLFIRI, and because the monthly costs of administration are high.

Merck Serono comment:

This statement rests on the TAG derived assumptions of mean treatment lengths. We believe these assumptions are erroneous, based on our analysis outlined in our response TAG statement 6 above.

TAG statement 11

Page 435 – Areas of uncertainty	We estimated survival post-resection from a study that is now several years old, where no patients received either cetuximab or panitumumab. 3 It is therefore possible that survival post-resection for patients initially treated with these drugs could differ from Adam et al. (2004).

Contemporary references exist to resolve this uncertainty as outlined below. Indeed, in the study by Adam et al. only 12.5% of patients with LLD went on to have a resection following chemotherapy alone, whereas treatment with cetuximab/chemo treatment in the CELIM study showed a 31% resection rate, and in the RESECT study, there was an R0 resection rate of 28% in the total population.

Data from the 5 year update from the CELIM trial (cetuximab/chemo for downsizing in LLD mCRC) showed that in KRAS wt patients, those patients with LLD that had R0 resections had a median OS of 53.9 months and a PFS of 15.4 months. The 5 year survival rate for those patients that achieved R0 resection was 46.2% (95% CI 29.5% to 62.9%).

Treatment with chemotherapy alone in the Adam study showed a 5 year survival rate of 33%. In the CELIM study the 5 year survival rate for those patients that achieved R0 resection was 46.2% (95% CI 29.5% to 62.9%). In a UK National Cancer Data Repository study (Morris et al. 2010), the crude 5-year survival rate after liver resection was 44.2% (95% CI 42.4 to 46.1).

Data from the CELIM trial could be considered representative of the UK population that would benefit from cetuximab, as this trial was conducted with cetuximab in the first line setting and at the time it was likely there was only chemotherapy in subsequent lines, which reflects the current treatment landscape in the UK as there will be no other monocolonal antibodies available in the UK post November 2015 and therefore, the treatment choice for an oncologist post first line will be chemotherapy alone.

TAG statement 12

Page 87 – Network Meta analysis	For the analysis of PFS, OS and ORR models with a normal likelihood and identity link were identified

If the preference is to use meta-analysis rather than trial data, this should be based on the data and without too many assumptions. This does not seem to be the case here. It seems that the TAG have constructed their data from published graphs (which is prone to error), after which they seem to use parametric approaches to estimate means (also prone to error) and beyond that they seem to use these means in their meta-analysis. This may introduce smaller uncertainty margins than really needed. Which is on top of the fact that a fixed effects approach is used where one can argue that a random effects approach with a strong prior on the between study variance would have been a better choice and which would also have widened the uncertainty margins.

TAG statement 13

Page 272 – Mixed treatment comparison on mean PFS	We perform a mixed treatment comparison on the mean survival which is in the spirit of the restricted mean but with the time point set to infinity

We think it puzzling that estimates of means based on extrapolations towards infinity using parametric models are equally reliable as using restricted means, which are based on time horizons for which data is available. Use of a network here in not necessary, as our analysis shows.

TAG statement 14

Page 282 – !st line PFS liver metastases sub-group: unresected	Mean PFS for resected and unresected patients was calculated by a mixed treatment comparison, as described

patients	

This approach only addresses the uncertainty in the means which is translated in the sensitivity analysis by only varying one parameter of the Weibull distribution. To express uncertainties it may have been better to reflect on the uncertainties from the heterogeneity of the trials. Varying both parameters (as in the Merck Serono model) reflecting the whole curve from the trial is more respective of the data.

TAG statement 15

Page 30 – Comparator treatments	Two networks are considered as no randomised evidence that connects the networks was identified.

The Merck Serono report includes an analysis where the two treatments FOLFOX and FOLFIRI are pooled. It seems that the submission by Amgen does contain data which links the networks. As such, it comes as a surprise that the TAG simply denies the similarities in the efficacy results from FOLFOX and FOLFIRI (Tournigand). This is important as it doesn't help in the identification of the costs and effects of Cetuximab vs FOLFOX based on the limited trial information.

The trials are chosen with both comparators and in practice clinicians use them for the same types of patients therefore Merck Serono strongly believes that the pooled approach is more appropriate than a network with partly undisclosed information and using a fixed effects approach of a network of clearly heterogeneous trials.

Figure 2 and figure 3 illustrate how the changes to our calculations– based on justified critique from the TAG – has changed our estimates.

Figure 2. ICERs from Merck Serono model with revised data inputs applied independently or in combination for FOLFOX

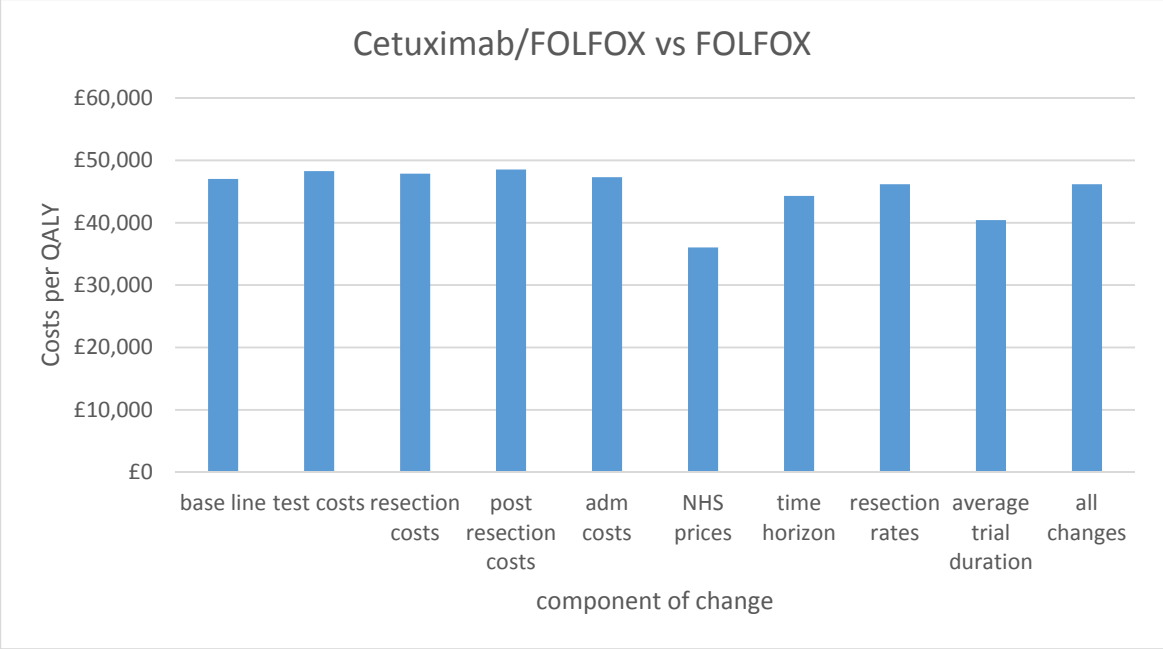
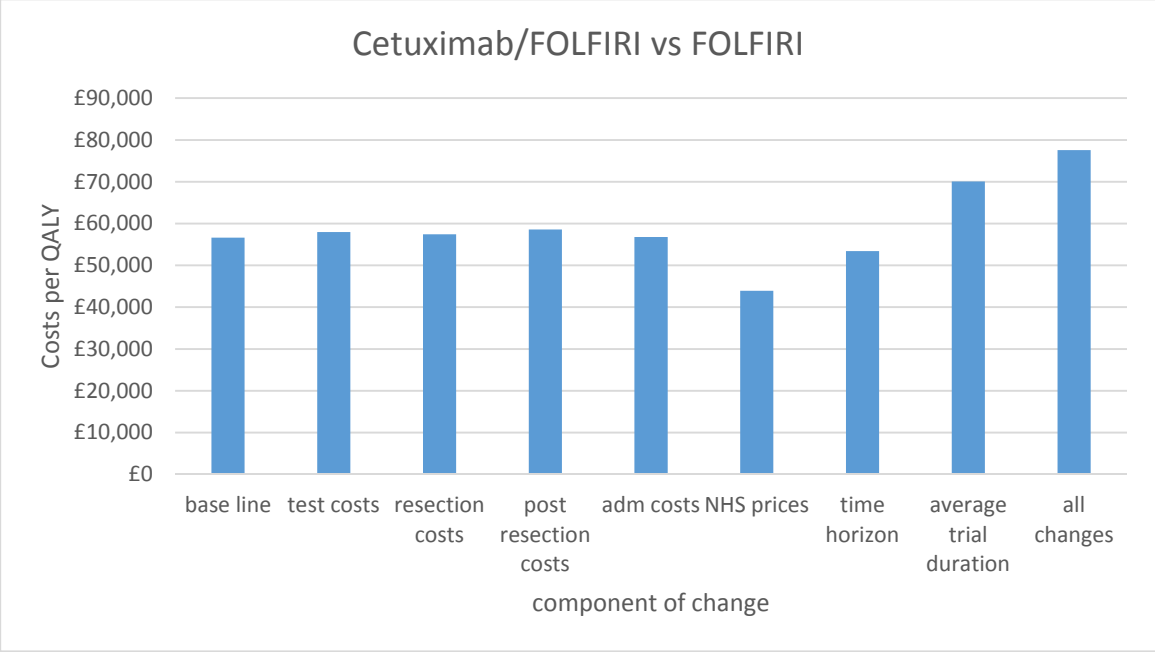


Figure 3. ICERs from Merck Serono model with revised data inputs applied independently or in combination for FOLFIRI



This analysis demonstrates that the ICERs of cetuximab in combination with chemotherapy are significantly lower than those estimated by the TAG. Most parameters did not have a great impact on ICERs. Mean treatment duration and drug acquisition cost had a significant impact on model estimation of the ICER.

Conclusion:

Based on our updated analysis set out above, our ICERs for cetuximab in combination with FOLFOX and FOLFIRI for the entire eligible population and in the LLD population are:

- Cetuximab/FOLFOX with PAS £44,916
- Cetuximab/FOLFIRI with PAS £74,139
- Cetuximab/FOLFOX LLD £42,793
- Cetuximab/FOLFIRI LLD £66,113
- Cetuximab/FOLFOX LLD utilising the TA176 treatment duration £ £22,669
- Cetuximab/FOLFIRI LLD utilising the TA176 treatment duration £ £22,527

As noted previously, both the clinical data and clinician support and preference favour cetuximab use in combination with FOLFIRI. Therefore, although it appears that the FOLFOX combination is more cost effective, Merck Serono contends that it would be counter-productive to recommend cetuximab with FOLFOX in favour of FOLFIRI.

References:

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National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

Executable Model

Cetuximab (review of TA176) and panitumumab (partial review of TA240) for the first line treatment of metastatic colorectal cancer

The economic model enclosed and its contents are confidential and are protected by intellectual property rights, which are owned by Peninsula Technology Assessment Group, University of Exeter. It has been sent to you for information only. It cannot be used for any other purpose than to inform your understanding of the appraisal. Accordingly, neither the model nor its contents should be divulged to anyone other than those individuals within your organisation who need to see to them to enable you to prepare your response. Those to whom you do show the documents must be advised they are bound by the terms of the Confidentiality Agreement Form that has already been signed and returned to the Institute by your organisation.

You may not make copies of the file and you must delete the file from your records when the appraisal process, and any possible appeal, are complete. If asked, you must confirm to us in writing that you have done so. You may not publish it in whole or part, or use it to inform the development of other economic models.

The model must not be re-run for purposes other that the testing of its reliability.

Please set out your comments on reliability in writing providing separate justification, with supporting information, for each specific comment made. Where you have made an alteration to the model details of how this alteration was implemented in the model (e.g. in terms of programme code) must be given in sufficient detail to enable your changes to be replicated from the information provided. Please use the attached pro-forma to present your response.

Please prepare your response carefully. Responses which contain errors or are internally inconsistent (for example where we are unable to replicate the results claimed by implementing the changes said to have been made to the model) will be rejected without further consideration.

Results from amended versions of the model will only be accepted if their purpose is to test robustness and reliability of the economic model. Results calculated purely for the purpose of using alternative inputs will not be accepted.

No electronic versions of the economic model will be accepted with your response.

Responses should be provided in tabular format as suggested below (please add further tables if necessary).

August 2015

The NCRI/RCP/RCR/ACP is grateful for the opportunity to respond to the NICE assessment report - colorectal cancer (metastatic) - cetuximab (review TA176) and panitumumab (part review TA240) (1st line) [ID794].

We would like to make the following comments on the conclusions.

Issue 1

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
In chapter nine, paragraph two, sentence two, the word 'than' appears to be missing	Redraft	N/A

Issue 2

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
In chapter nine, paragraph three, the word 'reducing' is repeated 'even reducing reducing the cost'.	Redraft	N/A

Issue 3

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
In chapter nine, paragraph three, it is unclear how the treatment can remain too	Redraft	N/A

expensive if the cost is reduced to £0.		

Issue 4

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The report may now be out of date as it assumes cetuximab and panitumumab are funded by the Cancer Drugs Fund. We understand this will not be the case from 4 November 2015.	Redraft	N/A

Clinicians Response to Assessment Report

Expert views on NICE Assessment Report

Topic: Cetuximab (review of TA 176) and panitumumab (partial review of TA240) for the first line treatment of metastatic colorectal cancer

Deadline for return of comment to NICE: 21 September 2015

Comments provided to Healthcare Improvement Scotland by*:*

[redacted]

This report provides a very interesting assessment of the use of cetuximab and panitumumab in the treatment of colorectal carcinoma.

Firstly I agree that the main evidence has evolved with time. We now have a much better understanding of the treatment and biology of colorectal carcinoma. This has resulted in a dilution of the power of original studies and what we now have our sub group analyses. However let this in no way take away from the fact that we are presenting OS with greater than 30 months in colorectal cancer.

With regard to the technical content of this report I am alarmed at how many basic assumptions are so fundamentally wrong. There is a complete lack of clinical judgement and basic cancer biology in many of the statements made.

Firstly the thought that progression on first line treatment has no effect on subsequent outcomes is frightening. If I have a 30 metastases in both liver, lung and liver nodes and I treat with chemotherapy; at the end of treatment scan I have say 5 detectable lesions but this has resulted in

a large improvement in my fitness and quality of life. If I then have another scan 3 months later I am found to have 7 lesions,I am deemed to have progressed. To assume that my tumour burden now is comparable to that at presentation is entirely wrong. Not only do I have a dramatic reduction STILL in tumour bulk but I also have an improvement in Quality of life.

This will affect the decision of when to restart treatment and what treatment will be given. If a patient has a very long PFS the decision may well be to re challenge with the same treatment .

Both ASCO and ESMO have developed tools at assessing meaningful clinical benefit ratios . These tools are based on Integration of hazard ratio, prognosis and absolute difference in data interpretation. I think that looking at these tools also will help in our clinical interpretation of the data presented.

For instance when looking at the Prime data the ESMO tool found that the post hoc RAS WT was more robust control OS 20.2 vs 19.4mth. OS gain 5.8 moths vs 4.4 months . Hazard ratio lower confidence limit was < .65 in post hoc and < 7 in WT .

Also assuming that all patients who did well and had a good first line PFS got a resection is again fundamentally wrong. There are a lot of patients alive with multiple areas of metastatic disease who have never had a resection. Also a lot of patients get multiple resections.

To base the outcome of the cost effectiveness of colorectal cancer on the case provided in this report is at best case scenario very lazy.

I think if we try to extract the data " we want " or assume from trials such as Adams et al which is over 11 years old is dangerous and grossly under estimates the clinical picture.

If, as we say, our clinical evidence is based on sub group analysis then perhaps the safest thing to do is to get an audit of what is happening in colorectal cancer. This should be carried out in a trial such as ESTHER in breast cancer. We are now not going to get large numbers of patients in clinical trials to get the answers we desire.

One other very worrying comment: the Assumption that XELOX is necessarily cheaper than FOLFOX. As any clinician will tell you that clinical trial data has very little correlation as to what happens in ' real life'.

XELOX is one of the most toxic chemotherapy combinations I have ever used with extremely low QOL. The number of patients who develop neutropenia sepsis or grade 3 diarrhoea is not insignificant . It is much worse than the trials ever suggested and a significant proportion of patients get switched to FOLFOX. So build in the cost of a hospital admission and extra clinic visits to the cost of XELOX.

We really need a deeper look at what happens in reality compared to clinical trials. Statistical modelling really needs to be more precise and there are way too many assumptions made in this report.

Finally in defence of some of the data presented by Merck. The reason why they give the average first line treatment at about 16 weeks is that if a patient has liver limited disease they are entitled under NICE/SMC to receive 16 weeks of Neoadjuvant treatment to render inoperable liver metastases operable. This is where they are basing the cost. In my practice this is how much cetuximab patients received up until about one year ago when we were allowed to give the drug to all RAS wild type patients first line. So this information should be assessed properly also.

If we are also going to look at liver metastases and surgical resection then the trials looking at Neoadjuvant/ peri operative chemotherapy need to be taken into consideration also.

National Institute for Health and Care Excellence

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Assessment Group response to comments on the Assessment Report provided by companies

Cetuximab (review of TA176) and panitumumab (partial review of TA240) for the first line treatment of metastatic colorectal cancer

9th October 2015

Due to the limited time available to the Assessment Group, written responses have been provided for some but not all of the consultee comments received.

For ease of readability, comments the Assessment Group have conceded to are written in **bold and underlined**

Confidential information that is academic-in-confidence is redacted [redacted]

Confidential information that is commercial-in-confidence is redacted [redacted]

Factual inaccuracies identified by Amgen

Section	Assessment report text	Comment from consultee	Response from assessment group
Section 3.2.6.2	Upper limit of 95% CI for median OS for PEAK is reported in the text as 13.1	The correct value is 31.3 (per Table 21).	Thank you for identifying, we have corrected this in the Errata
Section 3.2.6.2	PRIME WT RAS data is frequently reported to come from Douillard 2014	The year is wrong. Should be corrected to Douillard, 2013	Thank you for identifying, we have corrected this in the Errata

Comments from Amgen

Comment from consultee	Response from assessment group
Executive summary We note that the AG considered in its conclusions around the network meta analyses that there is no evidence to suggest any difference in progression-free survival (PFS) or overall survival (OS) between the two anti-EGFR agents, panitumumab and cetuximab. We also note that the significantly higher incremental cost-effectiveness ratio (ICER) for panitumumab plus FOLFOX versus FOLFOX compared to cetuximab plus FOLFOX versus FOLFOX in the base case is due to the assumption that panitumumab offers patients a much lower chance of benefitting from liver resection compared to cetuximab even though clinical evidence demonstrates that the two agents are similar and that panitumumab combination therapy offers a statistically significant and clinically compelling survival gain. We provide a robust case for using equivalent resection rates for both cetuximab and panitumumab (at least equal to the rates assumed for cetuximab).	We do indeed assume a lower resection rate for PAN+FOLFOX compared to CET+FOLFOX: [redacted] vs. 20.7%. This accounts for some, but not all of the difference in cost-effectiveness between these two treatments. We defend our choice of resection rate below. The other key factor explaining the difference is that we assume that PFS for all patients combined (resected + unresected) is lower for PAN+FOLFOX than for CET+FOLFOX (11.5 vs. 13.1 months).

Comment from consultee	Response from assessment group
The AG identified two candidate model structures, a model based on PFS and a model based on OS, but chose the PFS-based model citing the inappropriateness of the OS data. Given the robustness and maturity of the OS data (82% of patients had died when the analysis of OS was conducted), we strongly recommend that the AG considers the use of the OS data in their base case. OS is widely recognised as the most important and reliable endpoint in oncology trials from a clinical and patient perspective.	This is a very reasonable request. On p243 of our report, we said that we believe there are two candidate model structures: (1) Based on RCTs of 1st-line drugs up to 1st-line progression only, and (2) based completely on RCTs of 1st-line drugs, including OS from these trials. We carefully explained the advantages and disadvantages of both methods in Table 88 (p244). The responses from Amgen have not changed our views on these advantages and disadvantages. The most important reason why we did not chose structure (2) is that a substantial proportion of patients in the RCTs were treated with monoclonal antibodies not in use on the NHS, thus rendering time in progressive disease less relevant to the NHS. We chose structure (1) in our base case, and (2) in a scenario analysis. Amgen now say that it is appropriate to use model structure (2) because: A: OS in the PRIME RCT is mature, and B: OS is widely recognised as the most important and reliable endpoint in oncology trials from a clinical and patient perspective. We agree with Points A and B. We believe that Structure 2 is important. However, as noted, we believe there are also strong arguments for using Structure 1. On balance, we retain Structure 1 in our base case, and stress that Structure 2 is an important scenario analysis.

Comment from consultee	Response from assessment group
The AG also concludes that panitumumab combination therapy probably does not meet the End of Life (EoL) considerations as the extension to life is not robust. This is despite robust clinical evidence that demonstrates that panitumumab plus FOLFOX increases median OS in patients by 5.6 months. We demonstrate in our response below that panitumumab in combination with FOLFOX is precisely the type of treatment that would qualify for EoL considerations	Please see our response on EoL below.
We would like to underscore that policy level discussions around not being cost-effective at zero price are pertinent to this appraisal. In this case, the high cost of administration for both panitumumab and cetuximab becomes a key factor driving up the ICERs. We urge the Appraisal Committee to take this into account and to consider scenarios such as those presented in the AR (whereby costs of administration of all first-line drugs were set to zero) as plausible.	In our base case, the ICER for PAN+FOLFOX vs. FOLFOX is £239,000 per QALY. If we set the price of PAN to zero, this falls to £50,000 per QALY. If we additionally set the cost of administering all 1st-line drugs to zero, the ICER falls further to £15,000 per QALY. This shows that it is true that the cost of administration acts to worsen cost-effectiveness. However, the acquisition cost of PAN is by far the most important quantity accounting for the high ICER.

Comment from consultee	Response from assessment group
We therefore urge the AG to consider all the factors below to arrive at a more plausible and reasonable base case: • Assume the same resection rates for panitumumab plus FOLFOX and cetuximab plus FOLFOX of at least 20.7% • Use a model structure based on OS • Assume, based on clinical evidence, that the EoL considerations apply to panitumumab combination therapy • Take into account the policy discussion and issues around the high cost of administering anti-EGFR treatments in the first-line setting • Apply the confidential discount of [redacted] to the drug cost of panitumumab	The PAS discount was applied in a confidential appendix in line with the latest NICE procedures. This was not circulated as part of the report We address all other bullet points elsewhere in this table.
1.1 Robust evidence demonstrating efficacy of panitumumab in previously untreated WT RAS mCRC	

Comment from consultee	Response from assessment group
1.2 Limitations of the cetuximab evidence base There are a number of uncertainties in the cetuximab evidence base, due to low sample size and ascertainment rate of RAS status. The AR explains that the evidence evaluating the combination therapy of cetuximab with FOLFOX is not as strong as for panitumumab with FOLFOX; the OPUS trial of cetuximab plus FOLFOX versus FOLFOX had far fewer RAS WT patients (n=87) than the PRIME RCT of panitumumab plus FOLFOX versus FOLFOX (n=512). The probabilistic sensitivity analysis reported in the AR confirms this, with the cetuximab plus FOLFOX versus FOLFOX results much more uncertain than those obtained for panitumumab plus FOLFOX versus FOLFOX. In addition, the RAS ascertainment rate in the OPUS study was 66% compared with 90% in PRIME (Bokemeyer et al, 2015; Douillard et al, 2013).	We agree with the statements that the sample size leads to higher uncertainty in the cetuximab evidence base. Given the nature of the *RAS* testing conducted (*KRAS* exon 2 WT subgroup identified first) and the lack of explanations for when test results were not achieved (either failed or not conducted), it is difficult to draw conclusions on what impact this would have other than to reduce sample size.

Comment from consultee	Response from assessment group
1.3 Clinical benefit from anti-EGFR therapy: equivalence of panitumumab and cetuximab • Despite the limitations of the cetuximab evidence base, it is notable that the European Medicines Agency (EMA) stated that although "cetuximab data by RAS status are only derived from the randomised phase II study OPUS, the biological rationale supporting the efficacy in patients with RAS wild type tumours only is strong and the conclusions are supported by data related to panitumumab" (European Medicines Agency, 2013). This not only lends support to the premise of equivalence between the two anti-EGFR agents but importantly underscores the strength of panitumumab data as it was used to augment the evidence base in patients with RAS WT tumours for cetuximab.	The quote from the EMA in 2013 is correct. We agree that the clinical evidence for PAN+FOLFOX is stronger than for CET+FOLFOX. However, the EMA also say in the same paragraph: "*More data by RAS status specifically related to cetuximab are expected from the CRYSTAL and FIRE III studies*". Indeed, in 2015, we now have these data for CET+FOLFIRI. These RCTs had about half the number of RAS WT patients as PRIME, but many more than OPUS. Therefore, we now have strong evidence for the effectiveness of CET+FOLFIRI.
• The CDF similarly, in their assessment of panitumumab and cetuximab in combination with FOLFOX, note that "there was no known biological difference between panitumumab and cetuximab in terms of efficacy and that side-effect profiles were also very similar" (Cancer Drugs Fund, 2014) .	We believe the comparison of clinical effectiveness of CET and PAN in our report should be seen as higher quality evidence than the views of CDF colorectal experts. Nonetheless, our results (p40) are consistent with the statement from these experts, as we found no statistically significant evidence for a difference in PFS or OS between CET+FOLFOX and PAN+FOLFOX.
• The network meta analyses (NMA) performed by Amgen and the AG did not suggest any difference in the clinical effectiveness of panitumumab and cetuximab.	We agree

Comment from consultee	Response from assessment group
• In addition, panitumumab has been shown to be non-inferior to cetuximab in a phase 3 head-to-head RCT in chemotherapy refractory mCRC (ASPECCT). This study was designed to assess the OS benefit of panitumumab compared with cetuximab in KRAS WT patients. Median OS was 10.4 months with panitumumab and 10.0 months with cetuximab (HR 0.97; 95% CI 0.84–1.11) (Price et al, 2014), providing further evidence that these agents offer a similar survival benefit.	We excluded this study both on population, which was previously treated first-line *KRAS* WT patients; and intervention as CET and PAN were given as a monotherapies.
• The AG's base case ICER in RAS WT patients for cetuximab plus FOLFOX compared with FOLFOX is £109,820 per quality adjusted life year (QALY) gained and £239,007 for panitumumab plus FOLFOX compared with FOLFOX, the difference driven by larger QALY gains in PFS post resection for cetuximab plus FOLFOX compared with panitumumab plus FOLFOX. Given that the evidence for the combination therapy of panitumumab with FOLFOX is the most robust (with a clinically proven difference in survival) among the anti-EGFR agents and that there is a strong clinical justification to believe that there is no known biological difference between panitumumab and cetuximab, we believe that the AG's estimate of cost-effectiveness of panitumumab is erroneous and inconsistent with clinical evidence	As stated above in our answer to Point 1 in the Executive Summary, we do indeed assume a lower resection rate for PAN+FOLFOX than CET+FOLFOX: [redacted] vs. 20.7%. We defend our choice of these resection rates in the next section. Above, we agree that the quality of the clinical evidence for PAN+FOLFOX is greater than for CET+FOLFOX. However, we allow for the differences in uncertainty in clinical evidence in our probabilistic sensitivity analysis, as Amgen acknowledge in Point 1.2 above. Resection rates account for some, but not all of the difference in cost-effectiveness between these two treatments. The other key factor explaining the difference is that we assume that PFS for all patients combined (resected + unresected) is lower for PAN+FOLFOX than for CET+FOLFOX (11.5 vs. 13.1 months). This is estimated from the PRIME and OPUS trials. Other factors that differ between PAN+FOLFOX and CET+FOLFOX, but which have much less impact on cost-effectiveness include: The monthly acquisition cost of PAN is slightly (6%) greater than CET. The dose intensity of PAN is lower (80%) than CET (89%).

Comment from consultee	Response from assessment group
1.4 The liver metastases resection rates assigned to panitumumab plus FOLFOX and cetuximab plus FOLFOX in the AG model are not consistent with clinical evidence • Despite substantial evidence to suggest clinical equivalence for the two anti-EGFR agents, resection rates assigned to cetuximab plus FOLFOX in the AG base case model were much higher (20.7%) than those assigned to panitumumab plus FOLFOX ([redacted]). These differences resulted in larger incremental QALYs for cetuximab (0.35) versus panitumumab (0.15), coming from PFS post resection, which in turn generated large differences in the ICERs between the two anti-EGFR agents.	We disagree with the quoted incremental QALY gains from PFS post resection. They should read CET+FOLFOX vs. FOLFOX: 0.27, PAN+FOLFOX vs. FOLFOX: 0.05.
• Resection rates assigned to panitumumab plus FOLFOX and FOLFOX alone in the AG model were based on the RAS WT population in the PRIME trial. It is noteworthy that PRIME did not aim, and was not powered, to detect differences in rates of resection, and consequently, the baseline resectability status of patients was not assessed (Amgen, 2013).	We did indeed estimate resection rates for PAN+FOLFOX and FOLFOX from RAS wild type patients in PRIME. Regardless of whether PRIME was powered to detect a difference in resection rates, it provided a good estimate of the rates, as they were based on a large number of patients. In addition, the scope for bias is minimal as almost all RAS wild type patients were assessed for resection status (253 out of 259 PAN+FOLFOX patients, 252 out of 253 FOLFOX patients). Amgen claim that the baseline resectability status of patients in PRIME was not assessed. This is plausible, because we find no mention to the contrary in the corresponding papers or protocol. If so, then the resection rates from PRIME are an upper bound for the rates from a similar population of initially unresectable patients, as patients who are initially resectable are more likely to be resected than those not initially resectable. Therefore, this does not support Amgen's that the rates from PRIME are a gross underestimate of the rates in clinical practice

Comment from consultee	Response from assessment group
• It is also important to note that the resection rate assigned to panitumumab plus FOLFOX was much lower than the rate advised for cetuximab plus FOLFOX by experts during the appraisal of TA176 (35%). However, this estimate of 35% has been criticised because it was obtained from a clinical expert in a non-systematic manner and in the TA176 appraisal proceedings, the Delphi method was recommended as a way to elicit expert opinion (National Institute for Health and Care Excellence, 2009). We therefore undertook a Delphi panel survey to elicit plausible rates of liver resection for anti-EGFR agents and the surgical resection rate from our study is in line with previous clinical expert opinion (Amgen, 2015; National Institute for Health and Care Excellence, 2009). The Delphi panel study elicited expert opinion from 6 surgeons in England on resection rates in patients treated with EGFR inhibitors in clinical practice and shows that resection rates are likely to lie between 25 and 40% (mean 30 to 32%) (Amgen, 2015).	The NICE FAD from TA176 referenced by Amgen states (p20): "The clinical specialists stated that a more realistic rate for potentially curative resection with chemotherapy in general was approximately 12–15%, which could rise to approximately 30–35% with the addition of cetuximab." However, we see no mention in the FAD of a recommendation to use a Delphi panel. Amgen say they conducted a Delphi panel, which suggested a mean resection rate for CET or PAN in clinical practice of 30-32%. Whilst this is interesting, we have two criticisms with this. First, Amgen provide no information to allow us to assess the quality of the panel. Second, the panel does not give an estimated rate for FOLFOX. This is an important omission, as the cost-effectiveness of PAN+FOLFOX vs. FOLFOX is driven by the difference in resection rates between the treatments. Also, our clinical expert Dr Mark Napier, disagrees with the Delphi panel. Instead, he believes that the rates of resection in normal practice are similar to or lower than those in PEAK (12.5% PAN+FOLFOX, 11% BEV+FOLFOX) and CRYSTAL (7.3% CET+FOLFIRI, 2.1% FOLFIRI).
• Consequently, we strongly believe that the resection rate of [redacted] for panitumumab plus FOLFOX used in the AG's model is a gross underestimate of the resection rate expected in clinical practice. In practice we would expect the resection rates for anti-EGFR agents to be higher at around 30% based on the results of the Delphi panel study which is very much in line with the resection rate of 35% for cetuximab plus FOLFOX that was accepted by the committee in TA176. Given overwhelming evidence on the strength of the efficacy data for panitumumab plus FOLFOX as well as the premise of equivalence between the two anti-EGFR agents, panitumumab and cetuximab, and the results from the Delphi panel survey, we suggest that the true	First, the NICE committee did indeed accept a rate of 35% for CET+FOLFOX for KRAS wild-type patients (p22 FAD). In addition, they accepted a rate of 22% for FOLFOX alone (p22 FAD). However, they did not estimate a rate for PAN+FOLFOX, as this treatment was not subject to this appraisal. Thus we have three possible estimates for resection rates: 1. NICE clinical experts from 2009: 35% for CET+FOLFOX, rate for PAN+FOLFOX not given, 22% for FOLFOX. 2. Amgen Delphi panel for current submission: 30-32% for PAN+FOLFOX or CET+FOLFOX, rate for FOLFOX not given. Patient population not stated (e.g. RAS status not given)

Comment from consultee	Response from assessment group
resection rate for panitumumab plus FOLFOX is at least 20.7% (in line with the resection rate assigned to cetuximab plus FOLFOX in the AG base case model).	3. PRIME RCT of several hundred RAS wild-type patients: [redacted] for PAN+FOLFOX, [redacted] for FOLFOX. We defend our use of resection rates from the RCTs because: A: the quality of evidence from RCTs is considered far greater than of clinical opinion, and B: Neither Amgen nor NICE from TA176 give us evidence that the resection rates from PRIME are atypical of clinical practice. C: Our clinical expert prefers estimates from the RCTs. Next, Amgen argue that we should assume the same rate for PAN+FOLFOX and CET+FOLFOX, as they argue that these treatments are similarly effective. However, our indirect comparison suggests a longer mean PFS time for all patients combined (resected + unresected): 13.1 (estimated from our Table 95b, p271), vs 11.5 months (Table 95b) for CET+FOLFOX vs. PAN+FOLFOX. This is consistent with a higher resection rate for CET+FOLFOX. However, even if we do set the rates equal, we should set them equal to the values from PRIME, not OPUS, because, as Amgen note, the quality of the evidence from PRIME is far stronger than OPUS. This then leaves the ICER of PAN+FOLFOX vs. FOLFOX unchanged at £239,000 per QALY.

Comment from consultee	Response from assessment group
• In summary, given the strength of evidence showing that panitumumab in combination with FOLFOX provides both statistically significant and clinically relevant gains in survival compared to FOLFOX, the use of this evidence to support the efficacy discussions at the regulatory level for cetuximab in combination with FOLFOX, and the additional head to head study, ASPECCT, which validates the hypothesis that both agents provide similar survival benefit, we urge the Appraisal Committee to consider using equivalent resection rates for both cetuximab and panitumumab of at least 20.7%.	No further response required
2.1 Model structure should be based on overall survival • OS is widely recognised as the most important and reliable endpoint in oncology trials from a clinical and patient perspective (Driscoll et al, 2009). • The AG identified two candidate model structures, a model based on PFS and a model based on OS, and commented that ordinarily the latter would be preferable because of the consistency between the costs and health outcomes. The AG however chose the PFS-based model citing the inappropriateness of the OS data due to subsequent lines of treatment used in the trials: i) that the 2nd-line drugs used were not now commonly used in the NHS and ii) that the subsequent lines of treatment may have had a very strong effect on OS. They cite the FIRE-3 RCT as an example where no significant difference in PFS was observed, yet there was a significant OS benefit and very different subsequent treatments in the two treatment arms.	No further response required

Comment from consultee	Response from assessment group
• Unlike the FIRE-3 RCT, the PRIME RCT demonstrated statistically significant differences in both PFS and OS. The proportion of patients receiving any subsequent anti-tumour therapy was slightly higher in the FOLFOX arm compared with the panitumumab arm ([redacted]). Use of traditional chemotherapy agents including irinotecan-, oxaliplatin-, or fluoropyrimidine-containing chemotherapy was slightly higher in the FOLFOX arm ([redacted]) as was use of anti EGFR therapy (19% vs 7%). Use of bevacizumab was broadly similar in both arms (13% vs 16%) (Appendix 4, Amgen submission). It is noteworthy that anti-EGFR agents and bevacizumab were previously approved under the CDF and have been used in the NHS until the recent delisting of bevacizumab (Cancer Drugs Fund, 2015)	As stated in our response to Point 2 of Amgen's Executive Summary above, we consider as plausible Amgen's view that we should model OS from the RCTs of 1st-line treatments. Indeed, this is why we presented a scenario analysis using this method (p379, our report). Our estimates of the proportions of patients receiving subsequent treatments are taken from Douillard (2013) (p1350) and are given in Table 89, p245, of our report. Amgen provide slightly different estimates, which are taken from Appendix 4 of their original report: 32% of patients in the FOLFOX arm and 23% of patients in the PAN+FOLFOX arm of PRIME received either CET, PAN or BEV after first line treatment. None of these subsequent treatments are recommended by NICE. Also, as noted by Amgen, none of these are now funded on the CDF for subsequent treatment of mCRC: second line panitumumab and cetuximab are not funded by the CDF; plus second line bevacizumab and third and fourth line panitumumab and cetuximab are due to be removed from the CDF in November
• The impact of subsequent anti-EGFR therapy on OS in PRIME has been explored in a sensitivity analysis using statistical methods recognised by NICE including rank preserving structural failure time (RPSTM) models and inverse probability of censoring weighted (IPCW) analysis. This analysis was performed in KRAS WT patients for the final PRIME analysis. Results are presented in Table 1 and consistently show more favourable OS HRs for panitumumab plus FOLFOX versus FOLFOX when subsequent anti EGFR therapy is taken into account. Anti-EGFR therapy was received by 25% of patients in the FOLFOX arm and 13% of patients in the panitumumab plus FOLFOX arm in this analysis (Douillard et al, 2012).	We have the following concerns about the statistical techniques to adjust for subsequent treatments. 1. The interpretation of the hazard ratios is not clear. Amgen say they represent the scenario "when subsequent anti EGFR therapy is taken in to account". Does this mean the counterfactual state in which no patients subsequently receive CET or PAN? 2. Amgen do not attempt to adjust for the imbalance in the proportions receiving subsequent BEV, although this is less important than for CET or PAN, as a similar proportion of patients received BEV in the two arms (16% and 13%). 3. Amgen consider the KRAS, not the RAS wild type population. This is also probably not important, as the two populations are similar. 4. As Amgen admit, the underlying data was not based on the latest data cut. 5. We are not convinced that it is appropriate to perform some of the statistical techniques on the data from PRIME. For example, the RPSFT method estimates the

Comment from consultee	Response from assessment group
Table 1. Impact of subsequent anti-EGFR therapy on OS in KRAS WT patients in PRIME CI, confidence interval; OS, overall survival. Based on final analysis (data cut-off 02 August 2010). (Douillard et al, 2012). Although these analyses are in KRAS WT patients and are based on the final PRIME analysis (as opposed to the later 'OS update' analysis), it is likely that the OS gain for panitumumab plus FOLFOX in WT RAS patients (HR 0.77) will also have been attenuated by the higher use of anti-EGFR therapy in the FOLFOX arm. The results of these sensitivity analyses together with the higher overall use of subsequent therapies in the FOLFOX arm suggest that the PRIME OS estimate for panitumumab plus FOLFOX is potentially an underestimate of the true OS.	treatment effect (in terms of an acceleration factor) of subsequent treatments based on its effect first line. However, the subsequent treatment CET was not taken 1st line in PRIME. Also, the impact of subsequent treatments may be largely unknown because only a proportion of patients received each subsequent treatment in both arms, and these may be a biased sample of all patients. Despite these reservations, we agree that it is plausible that the OS benefit of PAN+FOLFOX vs. FOLFOX (e.g. the hazard ratio of 0.77) would have been slightly better if no patients had received either CET, PAN or BEV than that achieved in PRIME. This is because more patients received subsequent CET or PAN in the FOLFOX arm than in the PAN+FOLFOX arm, and a similar proportion received BEV. In our scenario analysis of using OS from the 1st-line RCTs, we estimated the following (p381): - CET+FOLFOX is dominated by PAN+FOLFOX. - ICER £100,000 per QALY for PAN+FOLFOX vs. FOLFOX. - ICER £101,000 per QALY for CET+FOLFIRI vs. FOLFIRI. Using Amgen's estimates of the proportions of patients receiving subsequent treatments in PRIME (slightly different to our estimates), the ICER for PAN+FOLFOX vs. FOLFOX is almost unchanged, and the other ICERs are unchanged. However, on reflection, we believe that if we assume OS from the 1st-line RCTs, it is preferable: - Not to cost for any subsequent treatments, and, - Consider the resulting ICER for PAN+FOLFOX vs. FOLFOX as an upper bound, to reflect our belief that it is plausible that the OS benefit of PAN+FOLFOX vs. FOLFOX would have been slightly greater than that achieved in PRIME if no patients had received either CET, PAN

	OS HR (95% CI) Panitumumab plus FOLFOX vs FOLFO
Intent to treat analysis	0.88 (0.73, 1.06)
Statistical model for influence of subsequent anti-EGFR therapy	
Branson & Whitehead, 2002	0.84 (0.68, 1.05)
Robins & Tsiatis, 1992	0.83 (0.66, 1.04)
Allison, 1995	0.68 (0.55, 0.83)
Inverse probability of censoring weighted (IPCW)	0.74 (0.56, 0.97)

Comment from consultee	Response from assessment group
	or BEV. In this way, we estimate the cost-effectiveness for treatment on the NHS, given that no NHS patients now subsequently received CET, PAN or BEV. In this case, the ICER for PAN+FOLFOX vs. FOLFOX increases to £122,000 per QALY, or [redacted] per QALY with the PAN PAS.
• The AR notes that the economic analysis should be repeated when the PFS and OS data from the RCTs is more mature. We would like to underscore that the updated analysis of OS in the PRIME was conducted when 82% of patients had died. This provides mature data on which to build the economic model.	We agree that the PFS and OS are indeed mature. However, for this HTA, we would like to see PFS and OS that is even more mature. This is because both Merck and we believe that a small proportion of patients (about 10%), those that receive a successful resection, are expected to live substantially longer, and spend substantially longer progression-free, than the remaining patients. We already say words to this effect on p60 of our report. Indeed, Merck have implicitly agreed that the PFS from PRIME does not capture PFS for resected patients, as they instead use PFS for the patients from a different study (Adam 2004). We agree with this.
• The use of OS obviates the need to estimate survival after disease progression which in turn reduces the uncertainty around the ICERs. In summary, given the robustness and maturity of the OS data, we strongly recommend that the AG consider the use of the OS data in their base case.	We repeat that Amgen's suggestion of modelling based on OS from the 1st line RCTs is reasonable. We refer Amgen to our detailed discussion on p243 of our report on the advantages and disadvantages of this method and our base case method.

Comment from consultee	Response from assessment group
3 End of life considerations • The AR notes that it is unlikely that panitumumab in combination with FOLFOX will qualify for EoL considerations. We are of the view that panitumumab in combination with FOLFOX is precisely the type of treatment that would qualify for EoL considerations .	We defend our opinion
• Indicated for patients with a short life expectancy (< 24 months) The AR notes that it is unclear if panitumumab plus FOLFOX therapy would qualify on the basis that it is used for patients with a short life expectancy, normally less than 24 months. The updated analysis of the PRIME RCT, which was conducted when 82% of patients had died, yielded a median OS of 20.2 months (95% CI 17.6 to 23.6) for the FOLFOX arm. As already discussed, subsequent treatments in the FOLFOX arm are likely to have influenced survival gains positively. The studies identified through a systematic search and used in the Amgen NMA (presented in Appendix 8 of Amgen submission) support the short life expectancy of these patients. From all studies which included a FOLFOX arm, the median OS in the FOLFOX arm ranged from 10.7 months to 20.5 months (Appendix 8, Amgen submission). Indeed, one study in which almost 90% of the patients had died at evaluation, yielded a median OS of 15.4 months for FOLFOX (Seymour et al, 2007). There is therefore considerable evidence to show that panitumumab plus FOLFOX therapy is indicated for patients with a short life expectancy of less than 24 months.	We agree that median OS was 20.2 months for patients on FOLFOX in PRIME. However, EoL concerns mean, not median OS. As stated on p410 of our report, we estimate a mean OS of 26.7 months based on PRIME alone, which is greater than the 24 months threshold for End of Life. Furthermore, with greater follow up, we would expect life expectancy in PRIME to be greater than 26.7 months, as the proportion of patients who are resected have a much greater life expectancy than those not resected. Next, Amgen cite several studies (p 67 Amgen Appendix 8) from their systematic literature search which they suggest support the view that life expectancy on FOLFOX is less than 24 months. These studies are all for 1st-line mCRC, which is appropriate. However, only PRIME and OPUS separate out RAS wild-type patients. Further, none of the remaining studies are even restricted to KRAS wild-type patients. Hence, this clearly limits the applicability of these studies to the current HTA. The most relevant studies are the PRIME and OPUS studies, as the populations included are RAS wild-type, as specified in the scope for the current HTA. Although we do accept Amgen's observation that OS would probably have been lower if CET, PAN and BEV had not been taken after 1st-line. We estimate that life expectancy for FOLFOX in these studies is >26.7 months in PRIME and >20.3 months in OPUS. However, assuming an exponential survival distribution, we find that mean OS is less than 24 months in only a minority of studies.

Comment from consultee	Response from assessment group

Study	Median OS FOLFOX (months)	Estimated mean OS (months)	< 24 months ?
Badulescu 2009	17.8	26	No
Comella 2009	17.1	25	No
Seymour 2007	15.4	22	Yes
Seymour 2011	10.7	15	Yes
Ducreux 2011	20.5	30	No
Cassidy 2011	18.9	27	No
Saltz 2008	19.9	29	No
Bokemeyer 2014 (OPUS)	17.8	>20.3	Possibly
Douillard 2013 (PRIME)	20.2	>26.7	No
Porschen 2007	18.8	27	No
Hochster 2008	19.2	28	No

In summary, we believe that life expectancy for RAS wild-type mCRC patients starting on FOLFOX in the NHS is close to, but probably slightly greater than 24 months.
We also believe that life expectancy on FOLFIRI is also relevant, as this is an important comparator. We estimate life expectancy on FOLFIRI from CRYSTAL as >25.0 months, also slightly above the EoL threshold.

Comment from consultee	Response from assessment group
• Licensed for patient population not exceeding 7000 patients The AR reports three estimates for the total population eligible for panitumumab treatment: 4,728, 5,968 and 8,511 patients. Based on the upper bound of this range, it states that it is unclear whether panitumumab plus FOLFOX would qualify for the criteria that it is licensed for a small patient population. We believe that this is not a balanced conclusion, as two of the three estimates of total population fall well within the 7,000 threshold. We also understand that policy discussions are ongoing and likely to include revisions to the current EoL Criteria (NHS England, 2015). As such, we would urge the Appraisal Committee to take a pragmatic view on this and accept that panitumumab is more than likely to meet this consideration.	We base our view on the current End of Life criteria, as given in the NICE Methods guide 2013. We are still unsure whether the patient population is sufficiently small.
• Offers extension to life (of at least an additional 3 months) The AR explains that it is unlikely that there is sufficient evidence to indicate that panitumumab in combination with FOLFOX offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment. The AG states that based on their model, panitumumab provides a mean 2.6 months extension to life and that the model has been carefully constructed using the best available evidence (even though they chose a PFS-based model). We disagree with this approach and would like to point out that the best available evidence, which is OS for panitumumab in combination with FOLFOX, was not used by the AG to inform this consideration. The median OS gain of 5.6 months has been accepted by the EMA as providing	**On reflection, we are sympathetic to Amgen's argument, and we retract the following comments in our report (p49 and p412)** **"*unsure*" related to extension of life expectancy > 3 months and** **"*On balance, we think that extension to life are not robust*".** **" *Life expectancy is subject to many assumptions*".** We agree that in PRIME, the median OS benefit of PAN+FOLFOX vs. FOLFOX was 5.6 months. We estimate a mean OS benefit of 5.8 months after extrapolation. We also agree that if no CET, PAN or BEV had been used as a subsequent line of treatment in PRIME, then the OS benefit of PAN+FOLFOX would probably have been slightly greater than the 5.8 months, because a higher proportion of patients in the FOLFOX arm received these treatments than in the PAN+FOLFOX arm.

Comment from consultee	Response from assessment group
credible evidence to support its license indication. Further, 82% of patients had died when this assessment was conducted and given that the impact of subsequent treatments would likely attenuate OS gains, all provide strong reasons why panitumumab in combination with FOLFOX provides sufficient evidence that it offers at least an additional 3 months of life, compared with FOLFOX, the current NHS treatment.	Therefore, we agree that PAN passes this element of EoL. To summarise, we now rate the following elements of End of Life for PAN: - Life expectancy on comparator: probably slightly greater than 24 months, hence probably fails marginally. - Life expectancy benefit: greater than 3 months, so passes. - Population size: borderline. - Extension to life robustness: Robust, hence passes. - Assumptions in modelling: plausible, hence passes. Overall EoL decision: borderline, probably fails marginally based on life expectancy.

Comment from consultee	Response from assessment group
4 Not Cost-Effective at Zero Price • The AR notes that even when the prices of panitumumab and cetuximab are set to zero, none of the combination treatments (panitumumab plus FOLFOX, cetuximab plus FOLFOX/FOLFIRI) are cost-effective at the £20,000 QALY threshold. The AG remarks that "In the current HTA, we find a similar explanation for why all three combination treatments are not cost-effective. In particular, total costs of administration of the combination treatments far exceed those of either FOLFOX or FOLFIRI. This in turn is because we predict that the combination treatments are taken for longer than FOLFOX or FOLFIRI." In addition to setting the prices to zero, the AG explored two scenarios, one in which the costs of administration of all first-line drugs (as well as the prices of cetuximab and panitumumab) were set to zero, and another in which the treatment duration of cetuximab plus FOLFOX and panitumumab plus FOLFOX were set equal to that of FOLFOX (and the prices of cetuximab and panitumumab were set to zero). The ICERs for both these scenarios fell substantially (to ≤ £20,000 per QALY) compared with the scenario where only drug costs were set to zero demonstrating the high cost of administering anti-EGFR combination treatments.	No comment required

Comment from consultee	Response from assessment group
• The NICE policy discussion, currently ongoing around treatments that are not cost-effective at zero price, is very relevant to the technologies appraised in this appraisal. Both panitumumab and cetuximab are given on top of FOLFOX/FOLFIRI and the cost of administering the combination treatment is very similar to FOLFOX or FOLFIRI alone. This implies that any increase in PFS also increases the cost of administering panitumumab or cetuximab plus FOLFOX. Indeed the Decision Support Unit (DSU) paper on this topic concludes that "the main factor driving the ICER above commonly accepted thresholds, when assuming a zero price, is the cost of administering the technology being appraised rather than the cost of treatments given alongside that technology" (National Institute for Health and Care Excellence, 2014)	The more complete quote is: "*in one example, it appears that the main factor driving the ICER above commonly accepted thresholds, when assuming a zero price, is the cost of administering the technology being appraised rather than the cost of treatments given alongside that technology*,"
• In light of the DSU paper and the ongoing NICE policy discussion, we urge the Appraisal Committee to take into account the issues around the high cost of administering both panitumumab and cetuximab combination therapy and to consider scenarios such as those presented (whereby costs of administration of all first-line drugs were set to zero) as plausible	We do not consider the scenarios mentioned in the first point in this section, such as setting the cost of administration, as plausible. Instead, they merely demonstrate the key drivers of cost-effectiveness. As stated in our report (p60), our analysis highlights that there is a strong economic incentive to develop oral treatments for mCRC.
5 Revised Base Case	No further comments required on the points raised in this section

Comment from consultee	Response from assessment group
6.1 Survival data post resection • It is plausible that patients who undergo successful resection are "cured" and thus should not follow the OS fitted curves after a certain number of years but instead follow life table data. We would recommend that the AG explores the scenario using life table data in the long-term instead of curve fits for successfully resected patients.	We disagree. We estimate OS for resected patients based on what we consider to be the best available evidence, the study by Adam et al (2004), p260 our report. This was also used by Merck for the same purpose. Amgen provide no evidence to suggest that general population life tables would be more appropriate.
6.2 Weekly versus fortnightly drug administration schedule for cetuximab The marketing authorisation for cetuximab is for weekly dosing, however the base case model assumes fortnightly dosing as this is believed to be current clinical practice. The ICER for cetuximab plus FOLFOX versus FOLFOX becomes much higher when weekly dosing is assumed. The AG assumes no change in effectiveness between weekly and fortnightly cetuximab dosing, but acknowledges that it remains possible that there is a difference. In common with the AG, we note that it would be unusual for NICE to issue guidance outside the current marketing authorisation	**We now agree with Amgen**. **We discussed this with NICE at the Pre-meeting briefing teleconference on 30th Sept 2015. They instructed us that we should assume weekly dosing of cetuximab, because NICE must issue guidance in accordance with current marketing authorisation.** However, we note that [redacted] (p36 our report).

Comment from consultee	Response from assessment group
6.3 No evidence to suggest any difference in Objective Response Rate (ORR) for panitumumab plus FOLFOX versus cetuximab plus FOLFOX • The AR states that there was limited evidence to suggest that cetuximab plus FOLFOX is more effective at improving ORR than panitumumab plus FOLFOX (Executive Summary). Elsewhere in the dossier it states that there is little evidence to support this (section 3.3.1.3). These statements are based on their NMA which estimates the ORR odds ratio for cetuximab plus FOLFOX versus panitumumab plus FOLFOX as 1.90, 95% credible interval 0.72 to 5.02. Given that the 95% credible interval for ORR includes the value 1 (no difference) we would argue that there is no evidence to support a difference between agents for ORR, in line with the clinical similarity evidence discussed earlier. Although the point estimate for ORR is in favour of cetuximab plus FOLFOX, this would appear to be due to a lower than expected ORR in the FOLFOX arm of OPUS (29%); this rate is lower than that reported for FOLFOX in other similar studies (Table 29, Appendix 8 of Amgen submission) and considerably lower than that seen in the FOLFOX arm of PRIME (46%). In contrast, the ORR was similar for cetuximab plus FOLFOX and panitumumab plus FOLFOX in OPUS and PRIME (58% vs 59% respectively). Finally, it is noteworthy that the AR states that ORR results should be interpreted with caution given potential differences in the timing of when ORR was reported.	**We have corrected the Executive summary and Conclusions to say 'little' in place of 'limited' to make consistent with the rest of the report. This also reflects the difference in point estimate, but width of the 95% CrI**

Comments from Merck Serono

Section	Assessment report text	Comment from consultee	Response from assessment group
		Cetuximab/FOLFIRI • Merck Serono agrees with the TAG that the costs of the test should be £400 for the cetuximab arm (when assuming reimbursement of cetuximab) and 0 for the chemotherapy arms. Please note this will be different when there is only assuming reimbursement in the liver limited group. This increases the Cost-Effectiveness (CE) ratio from £56,614 to £57,975 • Indeed we also accept that we may have under-estimated the costs of the liver resection. When increasing the estimate of less than 3,000 to £9,943, our updated estimate, which is comparable to the TAG costs of £10,483, the CE ratio increases to £57,422.	Merck's base case ICER, using the list price of CET, for CET+FOLFIRI vs. FOLFIRI was £55,971 per QALY (p61 Merck report). Merck do not explain how they arrived at the figure of £56,614. We find that their base case ICER increases from £56,000 to £57,000 per QALY Please see our comments on this issue below. When we assume a cost of liver resection of £9,943, we find that Merck's base case ICER increases from £56,000 to £57,000 per QALY, in agreement with Merck.

Section	Assessment report text	Comment from consultee	Response from assessment group
		Similarly, it is agreed that costs would be likely to be incurred during the progression free period post resection and we accept the TAG's estimate for this of £710. Costs post progression may additionally be higher than was estimated by us. The TAG group found a single Finnish study and based their estimate on this study. Finland and the UK have quite different health care systems and many of the costs included in this study would not fall under the NHS. Hence these costs should be excluded. However, we adapted our estimate of £315 per month to £991 per month being the cost of supportive care. As a single change this increases the CE ratio from £56,614 to £58,583 per QALY.	We believe that Merck are discussing the cost post progression after resection, not progression free. We estimate the cost in PD as £1,254 per month, not £710 as stated by Merck. In our use of this study we restricted to "direct health care costs", thereby excluding productivity costs and informal care costs. We may have erroneously included "Traveling", which appears to be counted under direct medical costs in the Finnish study but may not be reimbursed in full in the NHS, which account for 4% of costs. Assuming no reimbursement for traveling, an updated cost per month in 2015/16 prices would be £1,203 (down from £1,254). Note that these costs are similar to the £1,031 obtained by uprating from Remák and Brazil (a UK study used for costings in previous appraisals of mCRC) which does not include the end-of-life stage. We note that Merck now accept that their cost was a significant underestimate. However, they do not justify their estimate of £991 per month". If we use Merck's revised value of £991 per month, we find that Merck's base case ICER remains at £56,000 per QALY.

Section	Assessment report text	Comment from consultee	Response from assessment group
		The TAG estimates the monthly costs of drug administration at £2,473 for FOLFOX 4 and for £1,759 for FOLFOX6. In the case of drug delivery costs, Merck Serono would accept that that administration takes place in the day-care setting and so these costs would be appropriate. Accepting the PenTAG's own recommendations from previous submissions (Hoyle et al 2013) and the weighted cost would result in a total administration cost of £399.83 per cycle or £799.66 per month for chemotherapy alone. Even following the TAG's own recommendations in the report and adding a quarter of an hour of nursing time in case of the use of cetuximab. These changes increases the CE ratio to £56,766	Merck's quoted values of drug administration are for CET+FOLFOX4 and CET+FOLFOX6. We find that Merck's base case ICER of £56,000 to per QALY increases to £58,000 per QALY using our estimated administration costs. 1. We believe that in common with a number of other economic evaluations, the previous PenTAG submission incorrectly applied the NHS Reference cost SB15Z "Deliver subsequent elements of a chemotherapy cycle" to the cost of administration in subsequent cycles. Instead, it is appropriate for each chemotherapy cycle to use a code SB12Z–SB14Z for the first visit and code SB15Z for subsequent visits in each cycle. 2. The figure of £2,473 (FOLFOX4) per month additionally includes pharmacy costs, infusion pumps and line maintenance, amounting to £804 (FOLFOX4). The cost of drug delivery per month is £1,544 (FOLFOX4). 3. Given that a patient receiving FOLFOX4 will require on average 4.35 visits per month, a cost of £800 per month (as suggested by Merck) would suggest a cost of £184 per visit, which is significantly lower than the cheapest day case/regular day/night parenteral delivery (£245). We believe the drug delivery and other costs included are appropriate and defensible and reject

Section	Assessment report text	Comment from consultee	Response from assessment group
			Merck's proposed costs.
		With respect to the unit costs we have assumed that the Appraisal Committee will want to be consistent. One either uses the list prices, or the "real" prices. Merck Serono has now selected the later for the model, leading to much lower estimates of the costs of FOLFOX and FOLFIRI (as the TAG choses to do), but also of cetuximab for which, in practice, the costs are also much lower than the list-price. The net result is in favour of cetuximab. The estimate of the ICER decreases to [redacted]	We believe that Merck's "real" cost of CET is the price which they say (p17 Merck report) [redacted] At the Pre-meeting briefing teleconference on 30th Sept 2015, NICE instructed us not to use the "real" cost. As cetuximab is an intervention and not a comparator, we are advised by NICE to use the list price .
		• In the TAG model, the body surface area (BSA) was increased 1.79 to 1.85. The link between body surface and costs of the drug is by a step function (due to dose banding) with steps at 1.60, 1.70 and 1.80. By choosing an average of 1.85, it is implicitly assumed that all patients treated would be in the highest dose banding which does not take into account patients with a lower BSA and does not reflect the actual distribution of patients.	As explained in p401 of our report, our estimated mean BSA of 1.85m2 is based on a database of people receiving palliative chemotherapy for CRC (Sacco and colleagues (2010), Appendix S3, http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0008933), with 66% males, 34% females, the typical sex mix in the RCTs for mCRC. By contrast, Merck Serono do not give the source of their estimate of 1.79m2. Our estimate leads to a slightly higher estimate of mean mg of CET per administration. Assuming 1.85m2, the precise dose of CET is 923mg per patient, or 1,000mg allowing for wastage. Assuming 1.79m2, the precise dose is 895mg, or 900mg allowing for wastage. Both we and Merck assume wastage.

Section	Assessment report text	Comment from consultee	Response from assessment group
			Merck are incorrect to say that we implicitly assume that all patients would be in the highest dose banding. The BSA of some patients may actually be > 2m2. These patients would actually receive more than 1,000mg. We agree that we do not model the actual distribution of patients. We decided not do this, as we found this had little impact on cost-effectiveness in 2011 in TA242. Merck also do not model the actual distribution of patients.
		• Merck Serono acknowledges, that we have underestimated the duration of treatment, but again with not as significantly as suggested by the TAG. The TAG used a model derived mean which came from median treatment duration. Actual mean treatment duration in the CRYSTAL study was 9.1 months vs 6.8, which has now been taken into the model. Additionally, it is estimated that patients who are resected are only treated for 4 months. As a single action, this increases the CE ratio to £70,065. It is the biggest single influence on the change in CE ratio.	Addressed below
		• Finally, in an attempt to be conservative, it was chosen to only model 10 years. When setting the time horizon at 20 years (as a single action) the CE-ratio decreases to £53,408. A time horizon of 20 years captures all patient events in our model. In TA176, a time horizon of 23 years was accepted by the committee.	As stated in our report, we agree that a time horizon of 20 years is appropriate

Section	Assessment report text	Comment from consultee	Response from assessment group
		• When combining all changes the ICER is estimated at £79,044, which is considerably less than the estimate from the TAG group. Most notably because of their estimate of the average duration of the treatment and the asymmetry between the use of costs for Cetuximab and those for FOLFOX and FOLFIRI. When using the PAS-price, this decreases to £74,139	We have not checked these ICERs as we have numerous issues with Merck's revised assumptions. In addition, the revised ICERs do not allow for the key change we made to their model to PFS for unresected patients (p394 our report).
		Cetuximab/FOLFOX The estimate when considering the comparison between Cetuximab and FOLFOX changes more, mainly because it was found that the average duration in the relevant patients in the study were 6.3 and 5.2 months for Cetuximab/FOLFOX and FOLFOX. When considering the various steps we find: • An increase from £47,030 to £48,2748 due to the costs of RAS testing • To £47,879 due to costs of the liver resection • Changing the drug acquisition costs to "real" prices, those paid in practice, decreases the cost effectiveness ratio to [redacted] • The TAG group criticised the use of the CRYSTAL trial to estimate resection rates and used new number that were not made available to Merck	Merck's base case ICER, using the list price of CET, for CET+FOLFOX vs. FOLFOX was £46,503 per QALY (p61 Merck report). Merck do not explain how they arrived at the figure of £47,030. We find that their base case ICER increases from £47,000 to £48,000 per QALY. We also find that their base case ICER increases from £47,000 to £48,000 per QALY See our comments on CET+FOLFIRI above Merck originally assumed resection rates for CET+FOLFOX and FOLFOX of 7.3% and 2.1%, which they took from the rates for CET+FOLFIRI

Section	Assessment report text	Comment from consultee	Response from assessment group
		Serono. As a best alternative one might use the numbers from the KRAS sub-population from the OPUS study: 9.8 vs 4.1%. This element, as a single change, decreases the estimate of the cost effectiveness ratio to £46,178. When calculating this account is taken of the fact that patients who have a resection are only treated for 4 months. It is noted that the TAG group, with higher resection rates assumes that resected patients are treated just as long as non-resected (which in the case of the comparison with FOLFIRI is over nine months).	and FOLFIRI from CRYSTAL. In our report, we disagreed with this, as they are for completely different treatments. We still take this view. PRIME is our baseline trial for the FOLFOX network, as it was far larger than the other candidate trial, OPUS. We therefore estimated the resection rate for FOLFOX of [redacted] directly from PRIME. We then estimated the rate of CET+FOLFOX using the the estimated RAS wild type CET+FOLFOX rate from OPUS, and applying an indirect comparison correction (p257 our report). We estimated the rate for CET+FOLFOX for RAS wild type patients from OPUS from the KRAS wild type rate of 9.8% from OPUS. In a scenario analysis, we instead estimate the rates for FOLFOX and CET+FOLFOX as [redacted] and 11.9% directly from the KRAS wild-type rates of 4.1% and 9.8% from OPUS (p257 & p383 our report). We find that Merck's base case ICER decreases from £47,000 to £45,000 per QALY when we use rates of 4.1% and 9.8%. Next, Merck say we assume that resected patients are treated for the same duration as non-resected patients, and they we should instead assume that resected patients are treated for 4 months. However, Merck cannot say that we assume that resected patients are treated for the same duration as non-resected patients, because neither we nor Merck model 1st-line treatment duration separately

Section	Assessment report text	Comment from consultee	Response from assessment group
			for resected vs. unresected patients. For us, this is because we do not have the data to do so. Instead, for the "all patients" analysis, we take treatment duration for all patients combined from the median and 25% and 75% percentiles given to us by Merck & Amgen. Both we and Merck base treatment durations on the durations in the trials. In the trials, it is likely that 1st-line treatment stopped at about the time of resection, about 4 months, as this appears to be normal clinical practice (as noted by the clinician in TA176). However, we cannot be sure of this, as we do not have the required data from the trials. Therefore, in the absence of data to the contrary, we defend our modelling of treatment duration.
		• Increasing the time horizon to 20 years decreases the ICER to £44,304	We agree
		• Changing the treatment duration to the mean values in the OPUS trial rather than the modelled means derived from medians in the TAG report, and taking account of the fact that resected patients are only treated for 4 months decreases the CE-ratio to £40,427.	Responded to later in table
		• When combining all changes, the costs per QALY are estimated at £46,701. When using the PAS-price of Cetuximab this is £47,978	See our comments on CET+FOLFIRI above.
		Liver Limited Disease (LLD) Group :	On p236 of our report, we explain that Merck submitted a separate model just for LLD patients on

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		Using those estimates it is then possible to calculate the cost effectiveness of treatment in the group with liver limited disease by simply changing the resection rates. If the resection rates in the LLD group are estimated at 0.30 for with Cetuximab and at 0.15 without, the costs per QALY are estimated at £42,793 for the comparison with FOLFOX and at £66,113 for the comparison with FOLFIRI. When the reimbursement for patients with LLD is restricted to 4 months, as is the case in current clinical practice, and under current NICE TA176 guidance, the costs per QALY are £22,473 and £22,612 respectively for cetuximab with FOLFOX and FOLFIRI.	16th June 2015, over a month after the original submission deadline of 6th May 2015. Given that we were unable to reconcile this model with their "all patients" model we did not critique their LLD model. Now Merck seem to suggest that they can model the LLD population simply by changing the resection rates in the "all patients" model. They choose rates of 30% for CET+FOLFOX and CET+FOLFIRI and 15% for FOLFOX and FOLFIRI. We have two criticims of this approach. First, as in our analysis of LLD patients, we suggest that it is necessary to change not just resection rates, but also treatment durations and PFS for unresected patients. Second, Merck provide no evidence for their estimated resection rates for LLD patients. Finally, we have already commented on restricting treatment durations for resected patients.
		Differences in effectiveness It is noted that both Merck Serono and the by – TAG estimate the differences in QALY's are about 0.30. Merck Serono does so by straightforwardly using data from trials which investigated cetuximab. It is noted that the survival post resection is estimated to be lower than that estimated by the TAG group and one might suggest that Merck Serono has underestimated some benefit due to the higher resection rates. Still the gain in QALY's is estimated to be about the same. This is related to other survival estimates, which in the case of the TAG group are	We agree that we and Merck estimate similar incremental QALYs for CET+FOLFOX vs. FOLFOX (0.35 us vs. 0.33 Merck), and for CET+FOLFIRI vs. FOLFIRI (0.30 us vs. 0.30 Merck). However, this is largely coincidental, because, as explained in our report, there were differences in the constituent elements of the QALYs. For example, we estimate greater incremental QALYs post-resection, and lower incremental QALY in PFS for unresected patients. We disagree with Merck's assertion that our indirect

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		based on a network meta-analysis. This analysis appears unnecessarily complicated. We strongly believe that instead of adding strength to the comparison it only weakens it by needing too many untested and potentially biased assumptions.	comparisons of mean PFS and OS are unnecessarily complicated. Indeed, given that we simultaneously compare several treatments in the FOLFOX network, it is necessary to perform such an analysis.
		Summary	No further comment
Page 33 – model parameters	Also, in common with Merck Serono, we based our estimates of 1st-line PFS for unresected patients on the data from the pivotal RCTs. However, Merck Serono estimate PFS for nonresected patients directly from the RCTs of all patients (resected and non-resected). We believe that this over-estimates PFS for non-resected patients, given that some patients in the RCTs are resected and that PFS for these patients is substantially longer than for nonresected patients. Instead, we estimated PFS for unresected patients by starting with PFS for resected + unresected patients in the RCTs of 1st-line drugs, and then attempting to subtract off the PFS that we expect in the RCTs in respect of resected patients.	Statement 1 The results of the modelling are a weighted average of patients who are and who are not resected, and differences between the PENTAG model and Merck Serono's model can be found in the estimates of the resection rates, treatment durations and costs after resection. We address each of these below. With respect to the resection rates, Merck Serono chose to use the most reliable information that was available to them which was from the CRYSTAL study which showed rates 7.3% for Cetuximab/FOLFIRI and 2.1% for FOLFIRI for the overall population (both palliative and LLD). Motivated by many similarities between FOLFIRI and FOLFOX (most notably in terms of efficacy) and due to the low numbers from the OPUS trial for this analysis, similar figures were assumed for the comparison between Cetuximab/FOLFOX and FOLFOX. The TAG group appears to include undisclosed information based on PRIME and PEAK to estimate a rate for FOLFOX. The resection rates from PRIME	In addition to our responses above, we describe our estimation of the resection rate for CET+FOLFOX on p257 of our report. This contains some AiC information. Merck then claim we estimate mean OS after resection of 11.5 years and mean progression free survival post resection of 6.13 years. This is incorrect. These figures should read 5.8 years (cell X4, CET+FOLFOX sheet and similar sheets) and 4.1 years (S4 CET+FOLFOX sheet and similar sheets) respectively. We agree that Merck estimated lower survival after resection.

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		are mentioned in table 24 as being 10/41 patients (24%) in the LLD subgroup having resection for FOLFOX with 7/41 (17%) appearing to have complete resection. It is not clear to Merck Serono how they come to an estimate of Cetuximab vs FOLFOX. Dummy values in the spreadsheet suggest that one might end up with a difference of 11.9% vs 6.3%. With respect to treatment durations and post-resection PFS, the TAG estimates average survival post resection at 11.5 years and average progression free survival post resection at 6.13 years. These estimates are much higher than those in the Merck Serono model where the corresponding estimates were 4.83 years for OS post-resection and 3.56 years post resection PFS. Therefore, Merck Serono accepts that our model neglected the longer progression free survival of the resected patients but the net result - by using a much lower post resection survival estimate - is that Merck Serono has actually underestimated the survival benefits.	

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Page 35 – model parameters	In our base case, we used the list prices of cetuximab, panitumumab and bevacizumab. This yielded the following monthly costs of drug acquisition: Cetuximab: £3,859 Panitumumab: £4,109 Bevacizumab: £2,003 In our base case, we used the discounted prices of FOLFOX and FOLFIRI, taken from the Commercial Medicines Unit Electronic market information tool (CMU eMit) to reflect the true cost to the NHS. This yielded the following monthly costs of drug acquisition. FOLFOX-4: £86 FOLFIRI: £128	Statement 2 We noted the use of significantly lower chemotherapy acquisition costs using the CMU eMit tool to reflect true cost to the NHS. We believe that following this approach should allow for the use of actual cost of cetuximab to the NHS for fair comparison. We have indicated in our evidence submission that "Cetuximab has been offered at a guaranteed discounted price to the NHS in agreement with the Department of Health since 2008. This agreement is not limited to a time period. The NHS acquisition prices are [redacted](100mg/20ml vial); [redacted] (500mg/100ml vial). However, we followed the NICE methodology in using List prices for all comparators, including cetuximab to allow for a like-to-like comparison. Therefore, the use of CMU eMit cost for chemotherapy without the use of true NHS cost of cetuximab overestimates the cost difference between cetuximab in combination with chemotherapy and chemotherapy alone. Using the model developed by the TAG, the cost of cetuximab acquisition is reduced to [redacted] per month using the actual NHS price. Therefore, we have updated our model to reflect the CMU eMit prices for both FOLFOX and FOLFIRI as well as cetuximab.	Please see our response above concerning the discounted price of CET. Merck claim that if we use the discounted price of CET of [redacted](100mg/20ml vial), this gives a mean monthly cost of CET of [redacted]. This is incorrect, it should be [redacted] (allowing for vial wastage). The remaining monthly costs are the same as those we used in our analysis. We also believe the non-confidential PAS analysis, presented in the confidential appendix supersedes the use of the discounted price available on the NHS.

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Page 36 – model parameters	Our estimated total monthly drug administration costs are: CET/PAN/BEV+FOLFOX: £2,473 FOLFOX4: £2,348 CET/BEV+FOLFIRI: £1,759 FOLFIRI: £1,634	Statement 3 We noted that the cost of administration for FOLFOX was based on the assumption that the FOLFOX-4 regimen is used in the UK. FOLFOX-4 was the chemotherapy regimen that was utilised when the clinical trials were initiated in 2005. Since then, administration of the chemotherapy regimen has been update so that patients have 2 rather than 3 clinical visits for their FOLFOX regimen. The FOLFOX-4 regimen requires an infusion of oxaliplatin, folinic acid and a 22 hour infusion of 5-FU on day 1 and a repeat infusion of folinic acid and 5-FU on day 2 of a 14 day cycle. The FOLFOX-6 regimen requires an infusion of oxaliplatin, folinic acid and a 46 hour infusion of 5-FU on day 1 of a 14 day cycle, therefore eliminating the need for a clinic visit and repeat infusions on day 2. This is the most commonly used regimen in the UK and is more cost effective and manageable by the patients. This has been confirmed by expert clinical opinion. According to the TAG calculation, the cost of FOLFOX-6 is £1,634, which is comparable to the FOLFIRI chemotherapy regimen and is significantly cheaper than the cost of administering FOLFOX-4 (£2,473). Therefore, as the aim is to use true costs to the NHS, as well as the most cost effective regimen, we believe that the FOLFOX-6 chemotherapy regimen that should be utilised, in place of the FOLFOX-4 regimen that is currently being used in the model.	In our base case analysis, both we and Merck assume acquisition and administration costs of FOLFOX4. We chose FOLFOX4 rather than FOLFOX6 for consistency with the clinical data from the key RCTs: OPUS and PRIME. We still maintain that it is reasonable to assume FOLFOX4 in our base case. In a scenario analysis, we instead assume FOLFOX6 (p385). We find the ICERs change only slightly. We agree with Merck's quotation of our administration costs of FOLFOX6 and FOLFIRI, but disagree with the value for FOLFOX4, which should be £2,348.

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Page 232	The HRG SB15Z (Deliver subsequent elements of a chemotherapy cycle) was inappropriately used for the administration costs for complete cycles after the first cycle, rather than for activity not on the first day of a chemotherapy cycle. The correct usage is for the first attendance in every cycle to use SB14Z (or another delivery code except SB15Z), and then to use SB15Z for any subsequent attendances within each cycle.	Statement 4 In the case of drug delivery costs, Merck Serono would accept that that administration takes place in the day-care setting and so these costs would be appropriate. Based on guidance for NHS Reference Costs 2013 to 2014. We agree that the appropriate unit cost for one cycle will comprise the unit costs of SB14Z (Deliver complex chemotherapy, including prolonged infusional treatment) for day 1 and SB15Z (Deliver subsequent elements of a chemotherapy cycle). These day case reference costs are: £371 and £320. We would even agree on using the weighted average of 3 reference cost items, to deliver complex chemotherapy in different settings, adding up to £383 pounds per session. This would in general (according to table 117 page 325 in the report) cover “60 minutes nurse time and 120 minutes chair time”. It is implicit that these costs include the hospital overheads, (unless these are exceptionally expensive nurses) and by adding in the cost of infusion and line maintenance on top of this, there is an element of double counting involved. We also note that even though the TAG accepts that there is “A significant variation in pharmacy costs for chemotherapy for metastatic colorectal cancer”, they have utilised the higher end costs in their model. They considered the inflated costs from DG16 and TA118, even though in the review of TA118, PenTAG themselves used an estimated pharmacy cost of £15 per cycle (2008/09 prices) (Hoyle et al, 2013). Accepting the TAGs costings would mean that the	In short, we defend our unit costs of drug administration. We add the cost of infusion pumps, not the cost of infusion. These pumps are taken out of the hospital and are frequently disposed of after each cycle. We considered the possibility of double counting for this (i.e., that it might be counted under administration rather than procurement in NHS reference costs) and considered it was unlikely to be double counted (i.e., we believe it is more likely to be a procurement cost) and in any case it is a small component of total costs. This line maintenance refers to a separate visit to the infusion, which happens mid-way through the cycle. This can be done by a health visitor or nurse. We believe it is unlikely that this is included in the NHS reference cost for drug administration. The meaning of ‘inflated’ here carries connotations given the context. To clarify, these costs were inflation adjusted or uprated. Consideration must be given (as in p328 of the Assessment Report) to the fact that the cheapest chemotherapy procurement cost in the NHS reference costs is £240 in 2013/14 prices. Given the drug acquisition costs are low due to availability of generics (£40-£60 per cycle for FOLFOX/FOLFIRI) there are likely to be significant other costs associated with procurement not counted in the drug

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		NHS is presently paying over £800 pounds per patient per treatment cycle, for chemotherapy. We consider this inflated costs unrealistic and misleading. Accepting PenTAGs own pharmacy cost recommendations from previous submissions and the weighted cost above would result in a total administration cost of £399.83 per cycle or £799.66 per month for chemotherapy alone and the addition of a quarter of an hour of nurse time for the addition of cetuximab.	delivery.
Page 36 – model parameters Page 234	We estimate the cost of resection surgery as £10,440, substantially higher than Merck Serono's estimate of £2,707. Once we allow for the probability of a successful operation and the mean number of operations per person, we estimate a cost of approximately £17,600 per person who is successfully operated. Given our estimate of that the cost of liver surgery, after allowing for repeat operations, and the chance of operation failure, is £17,582	Statement 5 We agree that the cost of surgical resection of liver metastasis in our submission was low and the true cost should be closer to the cost adopted by NICE in Technology Appraisal 176 (£8,900). However, the TAG did not sufficiently explain the source and assumptions upon which they based their estimation of £17,582 per patient. Therefore, we believe that the cost of surgical resection should remain closer to the cost adopted in TA176. We believe that the same cost adopted by NICE in TA176 should be used taking account of inflation since 2009, as this cost was deemed representative of the cost in that year by NICE. This equates to £9,941 with the 2009-15 inflation index of 1.117. In reality NHS inflation tends to be much higher than inflation as measured by either CPI or RPI, so this is almost certainly an under-estimate.	Our assumptions underlying the estimate of the cost of liver resection surgery are based on sources and clinical advice detailed on pp 330-333. We estimate the mean total cost of resection surgery as the product of the mean number of resections per patient (1.6) and the mean cost per resection (£10,440) divided by the probability of a successful resection (95%) Specifically, we assume that all liver resection surgeries for mCRC are very complex operations; 80% of them are open and the remaining 20% are laparoscopic surgeries. We also assume that, on average, mCRC patient undergo more than one liver resection surgery, while in their current submission Merck Serono assume only one liver resection per patient. The source of our assumption on the frequency of liver resection was specified on p 333 of our submission: "Adam et al.(2004)[3] reported 223 hepatectomies (out of 342 surgical procedures)

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			performed on 138 patients, i.e. 1.6 per patient." Notably, this source is used by Merck Serono to parameterise post-resection survival. However, the data on the frequency of liver resection surgery, reported in this source, was overlooked by the manufacturer. If the cost from TA176 was to be used, we should not directly uprate to 2015 costs, but instead used those reported in the latest NHS reference costs. When estimating the cost of liver resection we accounted for recent trends in liver surgery for mCRC, namely, the use of laparoscopic surgery in some mCRC patients. Importantly, the average cost of such a procedure, compared to more traditional open surgery, is lower as reported in the source detailed on p332 of our submission. Hence, the estimate of the average cost of liver resection, used in our model, is lower than the cost of open liver surgery, which the cost in TA176 was based upon.
Page 42 - Appraisal of Merck Serono's economic analysis	Merck Serono assume that no 1st-line drugs are given after a certain cut-off time, which varies slightly by treatment arm. Strangely, they provide no justification for the cut-off. Further, we note that Merck Serono assumed a similar cut-off time in their model for cetuximab and	Statement 6 The treatment cut off period in the economic mode developed by Merck Serono utilised the median treatment period reported in the relevant clinical trials. No other assumptions were made in this respect. We note that the TAG have estimated the mean	As we have stressed throughout our report, we believe that the mean treatment duration are of paramount importance in this HTA, as total drug acquisition costs dominate the incremental costs. Merck's response is therefore important. In summary, we defend our estimates of treatment duration.

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	cetuximab+irinotecan for subsequent lines of treatment for mCRC, NICE TA242, in 2011.	treatment duration using the exponential method. We believe this method is not appropriate. It assumes that the probability to stop treatment at any point in time, given that one has been treated until that time, is always the same. This seems unlikely and an increase in the probability to stop in time, as in a population survival curve or a PFS survival curve, seems far more appropriate.	We disagree with Merck's statement: "*the treatment cut off period in the economic mode developed by Merck Serono utilised the median treatment period reported in the relevant clinical trials. No other assumptions were made in this respect*."
Page 284-285 - 6.1.4.5. 1st-line Time on treatment	We estimate the mean treatment duration for each 1st-line treatment in the following Steps: A. Estimate the mean treatment duration for each 1st-line treatment in each of the pivotal RCTs, based on median treatment duration from each RCT, and 25% and 75% percentile of the treatment duration when available (Table 98). B. Estimate mean treatment duration for each 1st-line treatment by simple indirect comparison, using CRYSTAL and PRIME as baseline RCTs (Table 98).	Moreover, in clinical practice patients do not receive treatment permanently. This observation is evident in figure 33 above where the tail extrapolated extend to a period of treatment close to 150 weeks, which is not practical or possible in clinical practice as patients cannot tolerate treatment toxicity for such a long period of time and are likely to progress in their disease much earlier than this time period. Upon the review of the TAG methodology in modelling treatment periods, we agree with the TAG that mean treatment periods should be used in the model instead of the median. Therefore, we have revisited our clinical trial data and found that the mean treatment periods for CRYSTAL and OPUS studies are outlined in table 2.Table 2: Mean	First, Merck's time of treatment cut-off for CET+FOLFIRI was substantially shorter than the median from CRYSTAL, and longer for FOLFOX and FOLFIRI (table below) in OPUS and CRYSTAL respectively. Second, Merck's estimated mean treatment durations are less than their treatment cut-off times (table below), because additionally, patients were assumed to take 1st-line treatment only whilst progression free. Both these effects act to improve the estimated cost-effectiveness of CET+FOLFIRI and CET+FOLFOX. **Median treatment duration RAS wild-type (data from Merck) (months)** / **Treatment duration cut-off (Merck model) (months)** / **Mean treatment duration (Merck model) (months)** **CET+FOLFOX**: 5.6 / 5.5 / 4.9 **FOLFOX**: 4.6 / 5.5 / 4.6 **CET+FOLFIRI**: 7.4 / 5.8 / 5.3 **FOLFIRI**: 5.8 / 5.9 / 5.2

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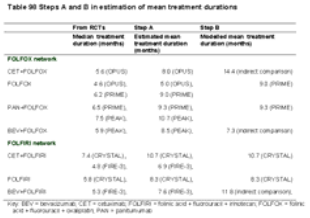
	Table 98 Steps A and B in estimation of mean treatment durations  C. For each treatment, compare the estimated mean treatment duration with the estimated mean 1st-line PFS for unresected patients (Section 6.1.4.4, p267). We would expect the mean treatment duration to be lower, because in all RCTs, treatment was supposed to stop on progression. However, we show below that this was generally not the case – usually, mean treatment duration was greater than mean 1st-line PFS for unresected patients. Given that we use only PFS, not OS from the RCTs, we assume no, or equal treatment effects across treatment arms post-progression. Therefore, we should not model 1st-line treatment after 1st-line PFS for unresected patients. If we did, we would incur the costs of 1st-line drug treatment after	treatment durations for CRYSTAL and OPUS Mean Treatment Duration RAS WT / TAG estimated mean treatment period (months) / Actual mean from trials (months) Cetuximab/FOLFIRI (CRYSTAL): 10.7 / 9.1 FOLFIRI (CRYSTAL): 8.3 / 6.8 Cetuximab/FOLFOX (OPUS): 14.4 / 6.3 FOLFOX (OPUS): 9.0 / 5.2 Table 2 demonstrates that the TAG estimates for mean treatment periods were significantly overestimated for the FOLFOX group, which – together with the use of the high list prices - is the main reason for estimating ICERs over £100,000/QALY using TAG-estimated figures. Therefore, we have updated the model to reflect the actual mean treatment durations from the CRYSTAL and OPUS studies.	Next, Merck say we estimated mean treatment durations using the exponential distribution, and criticise us for doing so. For data from CRYSTAL, we did indeed assume an exponential distribution. For OPUS, we assumed an exponential only for the tail of the distribution, and we used the area under the treatment duration curve up to the 75% percentile. In both cases, we believe that the choice of the exponential is very reasonable, and, given no evidence to the contrary, it should be seen as the default estimate due to parsimony, as it requires just a single parameter. Next, Merck quote mean treatment durations which they say they have taken from CRYSTAL and OPUS. We are skeptical of these estimates for two reasons: - 1: Merck provide neither the method they used to estimate these means nor the underlying treatment duration data. Given that mean treatment durations are critical for this HTA, we believe that it is essential that Merck provide this information. If they provide convincing evidence on both counts, we would happily amend our estimates of mean duration. - 2: The quoted mean of 6.3 months for CET+FOLFOX from OPUS does not seem plausible because we estimate a mean, truncated at the 75th percentile, also of 6.3

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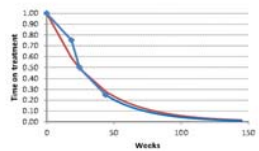
	progression, but gain no clinical benefit from this, which is clearly inappropriate. Therefore: If mean treatment duration was estimated less than mean 1st-line PFS for unresected patients, our estimate of mean treatment duration was left unaltered. Otherwise, mean treatment duration was capped at mean 1st-line PFS for unresected patients.		months (technically, the sum of cells R9:11 in worksheet "1st-line treat duration OPUS" in our model. This implies a mean clearly greater than 6.3 months. Next, Merck suggest that we have significantly overestimated the mean for FOLFOX and CET+FOLFOX. We disagree. The means quoted by Merck are indeed our base case estimates. However, we do not expect them to match the treatment durations from OPUS, because we assume PRIME as the baseline trial. We estimate mean OS from OPUS for CET+FOLFOX of 8.0 months, and for FOLFOX of 5.0 months. In a scenario analysis (p383 our report), we instead assume OPUS as the baseline trial. In this case, we assume mean treatment durations of 6.6 months for CET+FOLFOX and 5.0 months for FOLFOX. For CET+FOLFOX, we did not use the 8.0 months from OPUS, but instead cap treatment duration to mean PFS of 6.6 months, as explained in our report.
Page 288	First, this data was used to estimate the mean time on cetuximab+FOLFOX for RAS WT patients. An exponential tail was fit to the 25% percentile (Figure 33), with hazard set equal to that at the 25% percentile. The mean was then estimated as 34.7 weeks, being the area under the empirical data and fitted tail. Figure 33 Estimated time on CET+FOLFOX treatment for *RAS* WT patients in OPUS  		

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Page 44 – Appraisal of Merck Serono's economic analysis	For the comparison CET+FOLFIRI vs. FOLFIRI, most incremental QALYs come from PFS non-resected and PFS post-resection (Figure 51). Post-resection QALYs are less important than for CET+FOLFOX vs. FOLFOX, as we predict low rates of resection for CET+FOLFIRI (7.3%) and FOLFIRI (2.1%).	Statement 7 Resection rate was not the primary outcome for OPUS and CRYSTAL studies. Therefore, resection rates for patients in the liver limited disease mCRC population in clinical practice are expected to be higher than those reported in these 2 clinical trials. There are a number of studies that specifically examine the efficacy of cetuximab/chemo for downsizing liver metastases. In the CELIM trial, an R0 resection rate of 31% was achieved with Cetuximab/chemo (Folprecht et al.) The Ye et al. study resulted in an R0 resection rate of 30% for cetuximab/chemo and in a UK study, real world data from a retrospective observational data collection of patients treated with cetuximab for downsizing of their liver limited mCRC with the goal of resection, cetuximab and chemotherapy resulted in a 28% R0 resection rate. In the Adam et al. study (2004) chemotherapy alone resulted in a resection rate of 12.5% and the Ye et al. study showed a rate of 9% for chemotherapy alone. Each of these studies report data in the KRAS wt population and the expectation is that these results would be slightly improved with refinement of the patient population from KRAS to RAS wt as can be seen in figure 1. Therefore, we believe that a conservative resection rate of approximately 30% for cetuximab/chemo in the LLD patient population would reflect clinical reality and 12-15% for	We defend our choice of resection rates in our response to Amgen's comments on our report. We do not change our base case rates in response to Merck's comments here. The following statement is a non sequitur: "Therefore, resection rates for patients in the liver limited disease mCRC population in clinical practice are expected to be higher than those reported in these 2 clinical trials" Our clinical expert, Mark Napier, considers the relatively low resection rates in the RCTs as reasonable estimates for clinical practice. He further believes that the data from CELIM is not relevant, as it represents carefully selected patients with liver only low volume metastases and nearly operable patients. We assumed resection rates for all patients combined of 7.3% for CET+FOLFIRI and 2.1% for FOLFIRI, both from CRYSTAL, and 20.7% and [redacted] for CET+FOLFOX and FOLFOX, based on OPUS, adjusted for indirect comparison. Merck now seem to argue for higher rates than these. However, they appear to have changed their thinking, as their base case rates were much lower: 7.3% for CET+FOLFOX and CET+FOLFIRI, and 2.1% for FOLFOX and FOLFIRI, all taken from CRYSTAL. Next, Merck argue for resection rates for the liver

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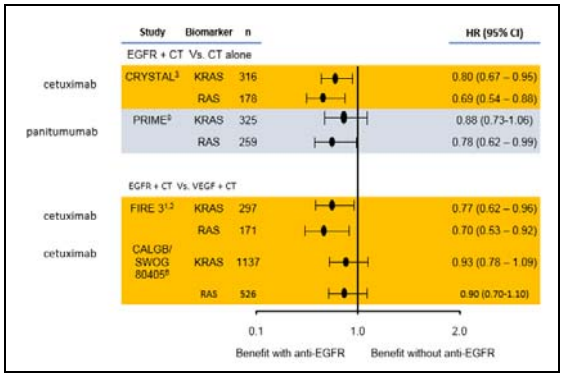
		chemotherapy alone. Figure 1. Improved hazard ratios in studies when population refined from KRAS to RAS WT.  These assumptions were confirmed by clinical experts consulted as part of our previous NICE appraisal, TA176 in 2008. Section 4.5 in NICE TA176 states: ”It [the Appraisal Committee] heard from the clinical specialists that the number of patients receiving potentially curative liver resection in the CRYSTAL and OPUS trials was lower than that seen in UK clinical practice, which is based on management by multidisciplinary teams involving highly specialised liver surgical services. The clinical specialists stated that a more realistic rate for potentially curative resection with chemotherapy in general was approximately 12–15%, which could rise to	limited subgroup of 30% for CET+FOLFOX and CET+FOLFIRI and 12-15% for FOLFOX and FOLFIRI. We see this as an endorsement of our assumed rates of for the liver limited subgroup for CET+FOLFOX of [redacted] and of 17.1% for FOLFOX. Our rates for CET+FOLFIRI and FOLFIRI or 16.3% and 6.5% are lower, and based on the best available evidence from the RCTs.

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		approximately 30–35% with the addition of cetuximab." With higher resection rates in clinical practice, we expect cetuximab with chemotherapy, compared to chemotherapy alone, to be shown as a more cost effective treatment than estimated by the TAG in their economic modelling. The patients with LLD, require some slightly different clinical considerations to patients with patients with non-LLD, as the goal of treatment in this setting is to shrink tumours to the point at which a patient is able to undergo surgical liver resection, rather than treatment until progression of disease; this was recognised in TA176. There is a clinical rationale for limiting treatment duration for LLD patients: 1) to maximise the potential for patients receiving cetuximab with chemotherapy to get an effective response to treatment, with sufficient shrinkage to allow liver resection to proceed, while 2) minimising the duration of treatment with irinotecan or oxaliplatin containing regimens, which both can make surgical liver resection more complicated which could compromise effectiveness of the procedure. Expert opinion still reflects this today and TA176 changed real life clinical practice to this effect after it was published in 2009. In our current model, it is possible to calculate the cost effectiveness of treatment in the group with liver limited disease by simply changing the resection	

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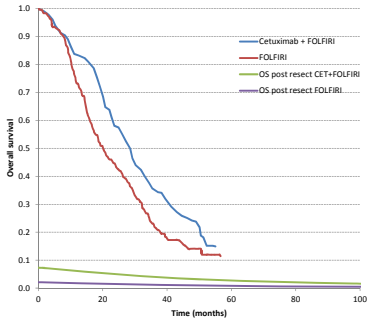
		rates and treatment duration. If the resection rates in the LLD group are estimated at 0.30 for with Cetuximab and at 0.15 without, and the treatment duration is limited to 4 months, the costs per QALY for the addition of cetuximab to chemotherapy are estimated at £22,669 for the comparison with FOLFOX and at £22,527 for the comparison with FOLFIRI.	
Page 60 - Suggested research priorities	We recommend that the economic analysis should be repeated when the PFS and OS data from the RCTs is more mature. Given sufficiently mature data, we would no longer need to use PFS and OS related to patients post-resection, with all the associated uncertainty, as we do currently.	Statement 8 PFS and OS data from CRYSTAL and OPUS are mature, no further data is expected from these studies. The data presented to the TAG from these clinical trials is the data available from the post hoc analysis of RAS wild type mCRC patients enrolled in these studies. These post hoc analyses were necessary since the role of RAS biomarkers in predicting treatment benefit was not understood at the time of the studies' initiation. Therefore, using data from the post hoc analyses provided the most robust method for providing accurate data for the RAS wild type subgroup and was accepted by the EMA to update cetuximab license accordingly.	We agree that PFS and OS are mature. However, for this HTA, we would like to see PFS and OS that is even more mature. This is because both Merck and we believe that a small proportion of patients (about 10%), those that receive a successful resection, are expected to live substantially longer, and spend substantially longer progression-free, than the remaining patients. We already say words to this effect on p60 of our report. Indeed, Merck have implicitly agreed that the PFS from PRIME does not capture PFS for resected patients, as they instead use PFS for the patients from a different study (Adam 2004). We agree with this. The Figure below shows the Kaplan-Meier OS from CRYSTAL together with our estimated OS for resected patients. At time 0, OS for resected patients is 7.3% and 2.1% to reflect the proportion of all patients resected in CRYSTAL. Note the long

Section	Assessment report text	Comment from consultee	Response from assessment group
			tails for resected patients. 
Page 49 – Appraisal of Merck Serono's economic analysis	Now turning to NICE's End of Life (EoL) criteria. Merck Serono claim that cetuximab satisfies these criteria. However, we disagree, as we believe that: The eligible patient population is too large, The estimated extension to life is not robust. We are not sure whether life expectancy on FOLFOX and FOLFIRI is less than the required 24 months We are not sure whether the extension to life is greater than	Statement 9 Criterion 1 – The eligible patient population is too large (population greater than 7,000) In relation to the size of the population for all licensed indications in England, we noted that the TAG differentiated between cetuximab and panitumumab based on the indications under the license. We believe that to achieve a fair comparison between the two medicines, both should be treated on equal grounds and assessed in accordance with the size of the colorectal cancer population. It is worth noting that the historical reason for the difference in licensed indications between cetuximab and panitumumab is the fact that cetuximab demonstrated significant clinical effectiveness in the treatment of squamous cell carcinoma of the head	We disagree, the population criterion for EoL relates to the total eligible population across all indications. This differs between CET and PAN. The historical explanation for the different licensed indications is irrelevant to the current HTA. Merck suggest that the relevant patient population for CET for head & neck cancer that the one for which there exists a positive NICE recommendation. This is not true. Instead, the total licenced population is relevant for EoL. CET is licenced for both locally advanced and for recurrent or metastatic head & neck cancer by the EMA (http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000558/human_me

Section	Assessment report text	Comment from consultee	Response from assessment group
	the required 3 months.	and neck in the EXTREME study while panitumumab did not show a significant benefit in the SPECTRUM study for the same indication, resulting in there being a SCCHN indication for cetuximab but not for panitumumab.	d_000769.jsp&mid=WC0b01ac058001d124).
Page 410 – End of life criteria	One of the criteria in the tables below is that the total patient population for all licensed indications in England should be less than 7,000. We understand that CRC is the only indication for panitumumab. In NICE TA242 from 2011, for cetuximab, bevacizumab and panitumumab for the treatment of mCRC after first-line chemotherapy, the NICE committee concluded: "*The Committee was aware from the manufacturer's data that approximately 7600 people have EGFR-positive, KRAS wild-type metastatic colorectal cancer in England and Wales…. However, the Committee noted that cetuximab has a marketing authorisation for people with any stage of EGFR-positive KRAS wild-type metastatic colorectal cancer, and also for people with locally advanced and recurrent and/or metastatic head and neck cancer, which has previously*	Therefore, if the TAG considered that cetuximab does not meet this criterion while panitumumab does, we believe that the TAG are penalising cetuximab for demonstrating clinical benefit in an indication that is not being assessed within the scope of this MTA. Further to this, cetuximab can only be considered as a treatment option for a small proportion locally advanced SCCHN patients and not at all for recurrent / metastatic head and neck cancer patients. TA145 restricted the funded population to only those locally advanced SCCHN patients with a Karnofsky score of above 90 in whom all forms of platinum based chemotherapy were contraindicated or not tolerated. TA 172 did not recommend the use of cetuximab for SCCHN patients with recurrent or metastatic disease. This restricted SCCHN population, when combined with the RAS WT mCRC eligible patient population which is under discussion in this MTA, does not exceed 7,000. Merck Serono contends that head and neck cancer patients should not be included in this evaluation, for the reasons outlined above. However, even if they are included, and the current patients that are funded within the SCCHN indications are applied, then the addition of these patients to the RAS WT mCRC population described below, still does not exceed 7,000, thus meeting end	Merck Serono report the calculation of one of our 3 estimates of the eligible mCRC patient populations given in our report on p408. The other estimates are 8,511 and 4,728. However, we repeat that the patient population eligible for CET relevant for EoL includes patients with head and neck cancer. The discussion of actual usage of cetuximab on the CDF is irrelevant, as EoL concerns the eligible patient population across all licensed indications, not the population actually taking the drug for one particular indication (Section 6.2.10, NICE 2013 Methods guide).

Section	Assessment report text	Comment from consultee	Response from assessment group
	been estimated to be a population of about 3000 (NICE technology appraisal guidance 172 [TA172]) Based on these figures, and: 83% of KRAS WT patients are also RAS WT (Section 5.1.2.2, p192) England comprises 95% of the population of England & Wales We calculate the total population for cetuximab relevant for End of Life as 7,600 x 83% x 95% + 3,000 x 95% = 8,807. This exceeds that End of Life criterion of 7,000.	of life criteria. Focusing now on the specific mCRC patient population under consideration in this MTA, namely 1st line RAS WT mCRC patients, total is significantly less than 7,000. Restrictions of indication to the RAS WT population since NICE TA242 has further limited the eligible population. This biomarker identified patient population should be further considered in the context of the proportion of patients who are considered appropriate candidates for treatment by physicians based on performance status and co-morbidities. If we utilise the figures outlined in the TAG report above and calculate the RAS wt mCRC population excluding the SCCHN population, as this MTA is only evaluating the mCRC population and for parity with panitumumab, the eligible population is: Assuming these figures: 83% of KRAS WT patients are also RAS WT (Section 5.1.2.2, p192) England comprises 95% of the population of England & Wales We calculate the total population for cetuximab relevant for End of Life as 7,600 x 83% x 95% = 5,993	

Section	Assessment report text	Comment from consultee	Response from assessment group
		This meets the End of Life criterion of 7,000. Actual usage of cetuximab in the first line setting under the Cancer Drugs Fund, demonstrates that the approximate number of patients treated in 2014, the most recent data available for the UK, can be estimated at 542 for the year, much below the 7,000 cut-off. If all mAb use for mCRC in England based on the CDF is considered, the number of patients that received treatment was just over 3,000 in the first line setting and this population includes patients that are RAS mutant and therefore not eligible for cetuximab. Since cetuximab has been reimbursed through the CDF for several years, a dramatic shift in patient eligibility can be considered unlikely.	

Section	Assessment report text	Comment from consultee	Response from assessment group
		Criterion 2 – We are not sure whether life expectancy on FOLFOX and FOLFIRI is less than the required 24 months Although it appears that in the TAG model, survival for patients that receive chemotherapy alone may be greater than 24 months, there are numerous trials that highlight that the median overall survival on chemotherapy alone is around 20 months as outlined in the table below. In every clinical study, chemotherapy only overall survival was considerably lower than 24 months. This has also been confirmed by expert opinion.	We discuss this issue in detail in our response to Amgen. The OS estimates for FOLFOX and FOLFIRI in Merck's Table 4 are medians. However EoL concerns mean, not median survival. To repeat our response to Amgen, we estimate mean OS for FOLFOX from PRIME of >26.7 months, and from OPUS of > 20.3 months, and mean OS for FOLFIRI from CRYSTAL of >24.9 months. This suggests that life expectancy on FOLFOX and FOLFIRI is close to the EoL threshold of 24 months. Next, Merck provide median OS from 4 further trials in Table 4. These are of limited relevance, as they concern all patients, not just RAS wild-type patients. Nonetheless, assuming an exponential distribution, the mean equals the median / ln(2), and we estimate the following mean OS: Tournigand FOLFOX: 30 months Tournigand FOLFIRI: 31 months Saltz: 29 months COIN: 26 months i.e. the mean is greater than 24 months in all trials.

Section	Assessment report text	Comment from consultee	Response from assessment group
		Criterion 3 – The estimated extension to life is not robust. We are not sure whether the extension to life is greater than the required 3 months. With regards to the increased life expectancy of greater than 3 months, in the CRYSTAL study there was an 8.2 month increase in mOS when cetuximab was added to FOLFIRI. In the OPUS trial in the RAS WT group there was an increase of 2 months, which was actually lower than the benefit seen in the KRAS WT population of 4.3 months in this study when cetuximab was added to FOLFOX. In general, when the patient population is refined from the KRAS population to the RAS population, due to the exclusion of patients that do not benefit from cetuximab, there is an improvement in outcomes. This has been observed in multiple studies and is the rationale behind the restriction of the cetuximab indication to RAS WT patients. In the KRAS population for the OPUS trial, there was a 4.3 month mOS benefit of cetuximab/FOLFOX compared to FOLFOX alone, which one could assume would improve when refining to the RAS wt population. The 2 month OS difference seen in OPUS is believed to be and artefact due to the lower numbers in the RAS analysis in this study. In additon, there are a number of other first line trials that show median overall survival rates of 28-33 months (FIRE3 – 33.1 months, CALGB-80405 - 32 months, CECOG/CORE2 – 28.5 months) for cetuximab in combination with chemotherapy.	We agree that the median OS benefit in CRYSTAL for RAS wild-type patients was approx. 8 months, and in OPUS, 2 months. We also agree that the median OS benefit in OPUS for KRAS wild-type patients was 4.3 months. Merck claim that, in OPUS, it is more appropriate to consider the KRAS wild-type median OS benefit of 4.3 months for the current HTA. We disagree. It is clearly more appropriate to use the RAS wild-type population, as this is the population of interest in the current HTA. As stated on p409 of our report, we estimate the mean OS for RAS wild-type patients in OPUS as 0.5 months. This is the most relevant estimate, as EoL concerns the mean, not median survival. Finally, Merck estimate the OS benefit of CET from the median OS for CET from FIRE3, CALGB-80405, and CECOG/CORE2, but with median OS for chemotherapy from a different source. We disagree as (1) it is not appropriate to compare survival from single arms of different trials and (2) Merck do not justify their estimate of 20.0 months for chemotherapy. In our report, p409, we said we are unsure whether there is sufficient evidence to indicate that CET combination therapy offers an extension to life of at least 3 months compared with current NHS treatment.

Section	Assessment report text	Comment from consultee	Response from assessment group
		Assuming chemotherapy only provides approximately 20 months OS, these data reinforce the benefit seen with the addtion of cetuximab. These data support the view that the addition of cetuximab to chemotherapy will increase overall survival by at least 3 months and these additonal study data should allow this to be perceived as robust.	**On reflection, we now change our opinion. We now believe that there is insufficient evidence based on our estimated mean OS benefit for CET+FOLFOX vs. FOLFOX from OPUS of 0.5 months. Therefore, we believe CET fails this EoL criterion.**
Page 49	We find the following ICERs, when the prices of cetuximab and panitumumab are set to £0: CET+FOLFOX vs. FOLFOX: £27,000 per QALY. PAN+FOLFOX vs. FOLFOX: £50,000 per QALY. CET+FOLFIRI vs. FOLFIRI: £27,000 per QALY. In other words, none of the combination treatments are cost-effective at the £20,000 per QALY threshold. This is largely because the total costs of administration of the combination treatments far exceed those of either FOLFOX or FOLFIRI. This in turn is because we predict that the	Statement 10 This statement rests on the TAG derived assumptions of mean treatment lengths. We believe these assumptions are erroneous, based on our analysis outlined in our response TAG statement 6 above.	No further comment required.

Section	Assessment report text	Comment from consultee	Response from assessment group
	combination treatments are taken for longer than FOLFOX or FOLFIRI, and because the monthly costs of administration are high.		
Page 435 – Areas of uncertainty	We estimated survival post-resection from a study that is now several years old, where no patients received either cetuximab or panitumumab. 3 It is therefore possible that survival post-resection for patients initially treated with these drugs could differ from Adam et al. (2004).	Statement 11 Contemporary references exist to resolve this uncertainty as outlined below. Indeed, in the study by Adam et al. only 12.5% of patients with LLD went on to have a resection following chemotherapy alone, whereas treatment with cetuximab/chemo treatment in the CELIM study showed a 31% resection rate, and in the RESECT study, there was an R0 resection rate of 28% in the total population. Data from the 5 year update from the CELIM trial (cetuximab/chemo for downsizing in LLD mCRC) showed that in KRAS wt patients, those patients with LLD that had R0 resections had a median OS of 53.9 months and a PFS of 15.4 months. The 5 year survival rate for those patients that achieved R0 resection was 46.2% (95% CI 29.5% to 62.9%). Treatment with chemotherapy alone in the Adam study showed a 5 year survival rate of 33%. In the CELIM study the 5 year survival rate for those patients that achieved R0 resection was 46.2% (95% CI 29.5% to 62.9%). In a UK National Cancer Data Repository study (Morris et al. 2010), the crude 5-year survival rate after liver resection was 44.2%	We carefully considered the available evidence for PFS and OS after resection (p260 our report). As a result, we used the data from Adam (2004). Merck did the same.

Section	Assessment report text	Comment from consultee	Response from assessment group
		(95% CI 42.4 to 46.1). Data from the CELIM trial could be considered representative of the UK population that would benefit from cetuximab, as this trial was conducted with cetuximab in the first line setting and at the time it was likely there was only chemotherapy in subsequent lines, which reflects the current treatment landscape in the UK as there will be no other monocolonal antibodies available in the UK post November 2015 and therefore, the treatment choice for an oncologist post first line will be chemotherapy alone.	
Page 87 – Network Meta analysis	For the analysis of PFS, OS and ORR models with a normal likelihood and identity link were identified	Statement 12 If the preference is to use meta-analysis rather than trial data, this should be based on the data and without too many assumptions. This does not seem to be the case here. It seems that the TAG have constructed their data from published graphs (which is prone to error), after which they seem to use parametric approaches to estimate means (also prone to error) and beyond that they seem to use these means in their meta-analysis. This may introduce smaller uncertainty margins than really needed. Which is on top of the fact that a fixed effects approach is used where one can argue that a random effects approach with a strong prior on the between study variance would have been a better choice and which would also have widened the uncertainty margins.	For a full description of our method of estimating mean PFS and OS from the RCTs, please see p267 of our report. This methodology is widely recognised. We chose to use a fixed effects model as even in the largest network there were only 3 studies. It would be possible to use a random effects model with a “strong” prior distribution on the between-study heterogeneity, however choice of this prior would dominate the evidence. Instead we have stuck with a fixed effects model. The indirect clinical effectiveness estimates from the network MAs are quite uncertain even with a fixed effects model. Where there is some evidence of an effect, this evidence is from direct evidence.

Section	Assessment report text	Comment from consultee	Response from assessment group
Page 272 – Mixed treatment comparison on mean PFS	We perform a mixed treatment comparison on the mean survival which is in the spirit of the restricted mean but with the time point set to infinity	Statement 13 We think it puzzling that estimates of means based on extrapolations towards infinity using parametric models are equally reliable as using restricted means, which are based on time horizons for which data is available. Use of a network here in not necessary, as our analysis shows.	We disagree - restricted means are completely inappropriate, as they underestimate mean PFS and OS. Instead, our method gives an unbiased estimates. Extrapolation of survival data is ubiquitous and necessary in HTA.
Page 282 – !st line PFS liver metastases sub-group: unresected patients	Mean PFS for resected and unresected patients was calculated by a mixed treatment comparison, as described	Statement 14 This approach only addresses the uncertainty in the means which is translated in the sensitivity analysis by only varying one parameter of the Weibull distribution. To express uncertainties it may have been better to reflect on the uncertainties from the heterogeneity of the trials. Varying both parameters (as in the Merck Serono model) reflecting the whole curve from the trial is more respective of the data.	We agree that uncertainty could have been considered in this way, however we used a fixed effects model which assumed no heterogeneity between trials. Please see our previous response to 12 above as to why we used a fixed effects model We don't follow Merck Serono's line of reasoning for varying both Weibull parameters.

Section	Assessment report text	Comment from consultee	Response from assessment group
Page 30 – Comparator treatments	Two networks are considered as no randomised evidence that connects the networks was identified.	Statement 15 The Merck Serono report includes an analysis where the two treatments FOLFOX and FOLFIRI are pooled. It seems that the submission by Amgen does contain data which links the networks. As such, it comes as a surprise that the TAG simply denies the similarities in the efficacy results from FOLFOX and FOLFIRI (Tournigand). This is important as it doesn't help in the identification of the costs and effects of Cetuximab vs FOLFOX based on the limited trial information. The trials are chosen with both comparators and in practice clinicians use them for the same types of patients therefore Merck Serono strongly believes that the pooled approach is more appropriate than a network with partly undisclosed information and using a fixed effects approach of a network of clearly heterogeneous trials.	In the TAG NMA two networks were analysed: those using FOLFOX regimens and those using FOLFIRI regimens. For the FOLFOX regimens network, the treatment FOLFOX was the baseline treatment, while FOLFIRI was the baseline treatment in the FOLFIRI regimens network. The network was informed only by studies conducted in the *RAS* wild type population. We agree that in the Amgen network these are linked (reference p39 and related tables pp 36-38):(1) link via FOLFOX vs FOLFIRI (FOCUS [Seymour et al.], and Badulescu et al.). Neither of these studies were included in our review as they do not evaluate the population (RAS wild type) or interventions (cetuximab or panitumumab) under review; (2) link via BEV+FOLFOX vs BEV+FOLFIRI and the WJOG4407G trial (Yamazaki et al.). Again, excluded from our analysis as not in RAS wild type population; and , (3) FOLFOX vs XELOX (6 trials); none of these trials conducted in the RAS wild type population. Similarly, Merck Serono had included trials within their network which were excluded from the TAG NMA; e.g. CALGB-80405. In this study participants were only randomised to cetuximab or bevacizumab and not to the background chemotherapy (see reasons for exclusion, p163 TAG report). For the sensitivity analysis, results for FOLFOX and FOLFIRI were pooled as generic chemotherapy ('chemo') based on the assumption that there was little difference between FOLFOX and FOLFIRI in

Section	Assessment report text	Comment from consultee	Response from assessment group
			terms of effectiveness based on evidence reported in the Colucci et al.(2005) trial. Merck Serono do not appear to include Tournigand et al. in their NMA and this study was excluded from our analysis as this was not specific to the RAS wild type population. We would also highlight that Merck Serono did not use the pooled analyses in their cost-effectiveness results. The choice of a fixed effects approach is discussed in Statement 12.

Section	Assessment report text	Comment from consultee	Response from assessment group
		Conclusion Based on our updated analysis set out above, our ICERs for cetuximab in combination with FOLFOX and FOLFIRI for the entire eligible population and in the LLD population are: • Cetuximab/FOLFOX with PAS £44,916 • Cetuximab/FOLFIRI with PAS £74,139 • Cetuximab/FOLFOX LLD £42,793 • Cetuximab/FOLFIRI LLD £66,113 • Cetuximab/FOLFOX LLD utilising the TA176 treatment duration £ £22,669 Cetuximab/FOLFIRI LLD utilising the TA176 treatment duration £ £22,527	Given that we have numerous objections to Merck's comments above, we advise the NICE appraisal committee to consider these ICERs as meaningless.

Other comments

Consultee	Comment from consultee	Response from assessment group
NCRI/RCP/RCR/ACP	In chapter nine, paragraph two, sentence two, the word 'than' appears to be missing- redraft	Many thanks, the 'than' has been added
	In chapter nine, paragraph three, the word 'reducing' is repeated 'even reducing reducing the cost'.- redraft	Many thanks, 'reducing' has been removed
	In chapter nine, paragraph three, it is unclear how the treatment can remain too expensive if the cost is reduced to £0.	Sentence redrafted, many thanks.
	The report may now be out of date as it assumes cetuximab and panitumumab are funded by the Cancer Drugs Fund. We understand this will not be the case from 4 November 2015.	As of September 2015 update, cetuximab and panitumumab will remain on the CDF for 1st line mCRC. On 4th November they will be removed for 3rd and 4th line indications. However, we appreciate that this may change in the future and have added a note that this was correct as of the September update.

The clinical effectiveness and cost-effectiveness of cetuximab (review of TA176) and panitumumab (partial review of TA240) for previously untreated metastatic colorectal cancer: a systematic review and economic evaluation

Addendum

9th October 2015

Confidential information that is commercial-in-confidence is redacted: [redacted]

We submitted our final report for this MTA to NICE on 7th August 2015.

In September 2015, we received responses from Merck and Amgen on our report.

In our base cases, both we and Merck Serono assumed that cetuximab is given fortnightly, as we understand that this is common clinical practice in the NHS, and it appears that fortnightly administration is approximately as effective as weekly administration (p35 our report). [redacted] Our estimated monthly drug administration costs are (p36 our report):

- CET+FOLFOX: £2,473
- CET+FOLFIRI: £1,759

We also presented our cost-effectiveness results assuming that cetuximab is given weekly (p385 our report). Then, the estimated monthly drug administration costs approximately double (p36 our report):

- CET+FOLFOX: £4,714
- CET+FOLFIRI: £4,000

However, Amgen suggested that we should instead assume that cetuximab is given weekly, in accordance with its license. NICE agreed, saying that it must issue guidance within the product license. At a pre-meeting briefing teleconference on 30th September 2015, they instructed us to make this assumption in our base case.

Here, we present our key results under this revision. The results that change from our original base case are highlighted in black below.

We believe that no further changes are required to our base case given the responses from Amgen and Merck Serono.

1. Base case results

Our revised base case results for all patients for the FOLFOX and FOLFIRI networks are given in Table 1 and Table 2 below.

Table 1. PenTAG base case summary cost-effectiveness results: All patients, FOLFOX network

				CET+FOLFOX vs.	PAN+FOLFOX vs.
	CET+FOLFOX	PAN+FOLFOX	FOLFOX	FOLFOX	FOLFOX
Life years (mean, undiscounted)	2.41	2.08	1.86	0.55	0.22
QALYs (mean, discounted)	**1.61**	**1.41**	**1.26**	**0.35**	**0.15**
Total costs (mean, discounted)	**£96,747**	**£74,705**	**£38,825**	**£57,921**	**£35,880**
ICER (Cost / QALY) vs. FOLFOX				**£165,491**	**£239,007**
ICER (Cost / QALY) on efficieny frontier		**Extended dominated**	**Reference**		

Key: CET = cetuximab; FOLFOX = folinic acid + fluorouracil + oxaliplatin; ICER, incremental cost-effectiveness ratio; PAN = panitumumab; QALYs, quality-adjusted life years

Notes: PAN+FOLFOX is extended dominated as it has lower QALY gains and a higher ICER vs. FOLFOX in comparison to CET+FOLFOX

Table 2. PenTAG base case summary cost-effectiveness results: All patients, FOLFIRI network

			CET+FOLFIRI vs.
	CET+FOLFIRI	FOLFIRI	FOLFIRI
Life years (mean, undiscounted)	2.21	1.75	0.46
QALYs (mean, discounted)	**1.53**	**1.23**	**0.30**
Total costs (mean, discounted)	**£108,916**	**£40,027**	**£68,889**
ICER (Cost / QALY)			**£227,381**

Key: CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; ICER, incremental cost-effectiveness ratio; PD = progressive disease; PFS = progression free survival; QALYs, quality-adjusted life years

The probability that the following treatments are most cost-effective for all patients combined at a willingness to pay threshold of £30,000 per QALY are:

- CET+FOLFOX: 18%.
- PAN+FOLFOX: 0%.
- CET+FOLFIRI: 0%

Our revised base case results for the liver metastases subgroup for the FOLFOX and FOLFIRI networks are given in Table 3 and Table 4Table 2 below.

Table 3. PenTAG base case summary cost-effectiveness results: Liver mets subgroup, FOLFOX network

				CET+FOLFOX vs.	PAN+FOLFOX vs.
	CET+FOLFOX	**PAN+FOLFOX**	**FOLFOX**	**FOLFOX**	**FOLFOX**
Life years (mean, undiscounted)	2.98	2.86	2.21	0.11	0.76
QALYs (mean, discounted)	1.97	1.89	1.49	0.08	0.49
Total costs (mean, discounted)	£118,488	£79,579	£43,537	£74,950	£50,471
ICER (Cost / QALY) vs. FOLFOX				**£154,508**	**£89,673**
ICER (Cost / QALY) on efficieny frontier	**£467,857 (vs. PAN+FOLFOX)**	**£89,673 (vs. FOLFOX)**	**Reference**		

Key: BEV = bevacizumab; CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; PAN = panitumumab;ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year

Table 4. PenTAG base case summary cost-effectiveness results: Liver mets subgroup, FOLFIRI network

			CET+FOLFIRI vs.
	CET+FOLFIRI	FOLFIRI	FOLFIRI
Life years (mean, undiscounted)	2.69	1.83	0.86
QALYs (mean, discounted)	1.83	1.26	0.57
Total costs (mean, discounted)	**£129,213**	**£39,654**	**£89,559**
ICER (Cost / QALY)			**£157,649**

Key: BEV = bevacizumab; CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; PAN = panitumumab; ICER = incremental cost-effectiveness ratio; QALYs = quality-adjusted life years

The probability that the following treatments are most cost-effective for the liver mets subgroup at a willingness to pay threshold of £30,000 per QALY are:

- CET+FOLFOX: 0%.
- PAN+FOLFOX: 0%.
- CET+FOLFIRI: 0%

2. PAS prices of CET and PAN

In the tables below, we present our ICERs given the Patient Access scheme (PAS) prices of CET and PAN.

For cetuximab, the list price of a 20 ml vial (5 mg/ml) is £178.10, and of a 100 ml vial (5 mg/ml) is £890.50. Under Merck Serono's PAS, the cost of a 20 ml vial becomes £114.66. This is a 35.6% discount.

For panitumumab, the list price of a 5 ml vial (20 mg/ml) is £379.29, and of a 20 ml vial (20 mg/ml) is £1,517.16. Under Amgen's PAS, these figures become [redacted] and [redacted]. This is a [redacted] discount.

Table 5. ICERs for base case and scenario analyses given PAS pricing for CET and PAN: all patients, weekly CET dosing

	CET+FOLFOX vs. FOLFOX (CET PAS) (changed due to weekly administration of CET)	PAN+FOLFOX vs. FOLFOX (PAN PAS) (unchanged from our report)	CET+FOLFIRI vs. FOLFIRI (CET PAS) (changed due to weekly administration of CET)
Base case (with CET & PAN PAS)	**£135,000**	[redacted]	**£183,000**
Overall survival from RCTs	**£554,000**	[redacted]	**£123,000**
OPUS as baseline RCT in FOLFOX network	**£155,000**	[redacted]	**unchanged**
FOLFOX 6	**£132,000**	[redacted]	**£184,00**
List prices for FOLFOX and FOLFIRI	**£147,000**	[redacted]	**£194,000**

Table 6. ICERs for base case and scenario analyses given PAS pricing for CET and PAN: liver mets patients, weekly CET dosing

	CET+FOLFOX vs. FOLFOX (CET PAS) (changed due to weekly administration of CET)	PAN+FOLFOX vs. FOLFOX (PAN PAS) (unchanged from our report)	CET+FOLFIRI vs. FOLFIRI (CET PAS) (changed due to weekly administration of CET)
Base case (with CET & PAN PAS)	£127,000	[redacted]	£129,000
Overall survival from RCTs	Not calculated	[redacted]	Not calculated
OPUS as baseline RCT in FOLFOX network	£114,000	[redacted]	unchanged
FOLFOX 6	£123,000	[redacted]	£130,000
List prices for FOLFOX and FOLFIRI	£140,000	[redacted]	£142,000

BEV+FOLFOX and BEV+FOLFIRI as comparators

Table 7. ICERs for scenario analysis allowing for bevacizumab as a comparator with PAS pricing for cetuximab and panitumumab, weekly CET dosing

	CET+FOLFOX vs. BEV+FOLFOX (changed due to weekly administration of CET)	PAN+FOLFOX vs. BEV+FOLFOX unchanged from our report)	CET+FOLFIRI vs. BEV+FOLFIRI (changed due to weekly administration of CET)
All patients	£98,000	[redacted]	£427,000
Liver mets subgroup	BEV+FOLFOX dominates CET+FOLFOX	[redacted]	£1,016,000

XELOX as comparator

Table 8. ICERs for scenario analysis allowing for XELOX as a comparator with PAS pricing for cetuximab and panitumumab, weekly CET dosing

	CET+FOLFOX vs. XELOX (changed due to weekly administration of CET)	PAN+FOLFOX vs. XELOX unchanged from our report)
All patients	£168,000	[redacted]
Liver mets subgroup	£154,000	[redacted]

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple technology appraisal

Panitumumab for the first-line treatment of metastatic colorectal cancer [ID794]

Amgen evidence submission

April 2015

File name	Version	Contains confidential information	Date
Panitumumab mCRC 30April2015 redacted	1.0	Yes AIC and CIC information redacted	30 April 2015

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List of abbreviations

CDF	Cancer Drugs Fund
CE	Conformité Européene
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CrI	credible interval
CR	complete response
CRC	colorectal cancer
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EQ-5D	EuroQoL 5-domain
FOLFIRI	5-fluorouracil and leucovorin (folinic acid) in combination with irinotecan
FOLFOX	5-fluorouracil and leucovorin (folinic acid) in combination with oxaliplatin
HR	hazard ratio
HSI	health state index
IC	indirect comparison
Ig	immunoglobulin
KRAS	Kirsten rat sarcoma
LDH	lactate dehydrogenase
LMO	liver metastases only
mCRC	metastatic colorectal cancer
MTC	mixed treatment comparison
NICE	National Institute for Health and Care Excellence
NHS	National Health Service
NMA	network meta-analysis
NRAS	neuroblastoma rat sarcoma
OHR	overall health rating
ORR	objective response rate
OS	overall survival
PFS	progression-free survival
PR	partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
Q-TWiST	quality-adjusted time without symptoms of disease or toxicity
RAS	rat sarcoma;
RCT	randomised controlled trial
RR	relative risk
SPC	Summary of Product Characteristics
XELIRI	irinotecan and capecitabine
XELOX	capecitabine and oxaliplatin

1 Executive summary

1.1 Statement of decision problem

The decision problem is presented in Table 1.

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Intervention(s)	Panitumumab, in combination with fluorouracil-containing regimens Cetuximab, in combination with FOLFOX or irinotecan-based chemotherapy	Panitumumab, in combination with FOLFOX or FOLFIRI	Panitumumab in combination with FOLFIRI received positive CHMP opinion on 27 February 2015, and EMA approval was granted on 30 March 2015
Population(s)	People with previously untreated, RAS wild-type metastatic colorectal cancer	As per scope	
Comparator(s)	The interventions should be compared with each other, and with: • FOLFOX • XELOX • FOLFIRI • Capecitabine • Tegafur, folinic acid and fluorouracil • Bevacizumab, in combination with oxaliplatin- or irinotecan-based chemotherapy	The interventions should be compared with each other, and with: • FOLFOX • XELOX • FOLFIRI • Cetuximab, in combination with oxaliplatin- or irinotecan-based chemotherapy	Capecitabine and tegafur, folinic acid and fluorouracil not assessed as only used in patients unfit for fluoropyrimidine-based combination therapy (ie with oxaliplatin- or irinotecan-based chemotherapy) Bevacizumab not assessed as no longer funded by the Cancer Drugs Fund for first-line treatment of metastatic colorectal cancer
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rate • rate of resection of metastases • adverse effects of treatment • health-related quality of life	As per scope	

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared Costs will be considered from an NHS and Personal Social Services perspective The availability of any patient access schemes for the intervention or comparator technologies should be taken into account Biosimilars are not expected to be in established NHS practice at the time of appraisal and are not included as comparators Where comparator technologies are available through the Cancer Drugs Fund, the cost incurred by the Cancer Drugs Fund should be used in any economic analyses, rather than the list price	Economic analysis not conducted	Analysis to be conducted by Assessment Group for both interventions
Other considerations	If evidence allows, consideration may be given to subgroups based on the location of metastases (inside and/or outside the liver) The appraisal will include consideration of the costs and implications of RAS mutation testing, but will not make recommendations on specific diagnostic tests or devices Guidance will only be issued		

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
	in accordance with the marketing authorisations. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator		

CHMP, Committee for Medicinal Products for Human Use; EMA, European Medicines Agency; FOLFIRI, 5-fluorouracil + leucovorin (folinic acid) + irinotecan; FOLFOX, 5-fluorouracil + leucovorin (folinic acid) + oxaliplatin; NICE, National Institute for Health and Care Excellence; NHS, National Health Service; RAS, rat sarcoma; XELOX, capecitabine + oxaliplatin.

1.2 Description of the technology being appraised

Table 2. Technology being appraised

UK approved name and brand name	**Panitumumab (Vectibix®)**
Marketing authorisation/CE mark status	03 December 2007 – initial EMA marketing authorisation granted as monotherapy for the treatment of adults with epidermal growth factor receptor-expressing mCRC with non-mutated (ie, wild-type) KRAS after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy 10 November 2011 – approval to extend indication to first-line treatment (in combination with FOLFOX) and second-line treatment (in combination with FOLFIRI for patients who have received first-line fluoropyrimidine-based chemotherapy [excluding irinotecan]) of adults with wild-type KRAS mCRC 25 July 2013 – preliminary EMA approval to restrict the above indications to adults with wild-type RAS mCRC; conversion to full approval on 14 January 2015 30 March 2015 – EMA approval for additional first-line indication in combination with FOLFIRI for adults with wild-type RAS mCRC
Indications and any restriction(s) as described in the Summary of Product Characteristics	Panitumumab is indicated for the treatment of adult patients with wild-type RAS mCRC: • in first line in combination with FOLFOX or FOLFIRI • in second line in combination with FOLFIRI for patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan) • as monotherapy after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens Contraindications: • Patients with a history of severe or life-threatening hypersensitivity to the active substance or to any of the excipients listed in section 6.1 of the SPC • Patients with interstitial pneumonitis or pulmonary fibrosis • The combination of panitumumab with oxaliplatin-containing chemotherapy is contraindicated for patients with mutant RAS mCRC or for whom RAS mCRC status is unknown
Method of administration and dosage	Panitumumab must be administered as an intravenous infusion via an infusion pump, using a low protein binding 0.2 or 0.22 µm in-line filter, through a peripheral line or indwelling catheter The recommended infusion time is approximately 60 minutes. If the first infusion is tolerated, then subsequent infusions may be administered over 30 to 60 minutes. Doses higher than 1000 mg should be infused over approximately 90 minutes The recommended dose of panitumumab is 6 mg/kg of bodyweight given once every two weeks. Prior to infusion, panitumumab should be diluted in sodium chloride 9 mg/mL (0.9%) solution for injection to a final concentration not to exceed 10 mg/mL

mCRC, metastatic colorectal cancer; EMA, European Medicines Agency; FOLFIRI, 5-fluorouracil + leucovorin (folinic acid) + irinotecan; FOLFOX, 5-fluorouracil + leucovorin (folinic acid) + oxaliplatin; KRAS, Kirsten rat sarcoma; RAS, rat sarcoma; SPC, Summary of Product Characteristics.

1.3 Summary of the clinical effectiveness analysis

Summary of key clinical evidence

A systematic review was used to identify RCTs in patients with previously untreated mCRC. A total of 46 studies were identified, of which only one was a relevant RCT (PRIME; Study 20050203), which evaluated panitumumab in combination with FOLFOX versus FOLFOX (the primary comparator) in patients with wild-type RAS mCRC. There were no relevant RCTs that compared panitumumab in combination with FOLFOX or FOLFIRI with other relevant comparator treatments (ie, FOLFIRI, XELOX or cetuximab in combination with chemotherapy).

In the absence of head-to-head RCTs, and in order to address the decision problem set out in this appraisal, a NMA was conducted to assess the comparative efficacy of panitumumab in combination with FOLFOX or FOLFIRI versus the other defined relevant comparators in patients with previously untreated mCRC. From the 46 RCTs identified by the systematic review, additional exclusion criteria were applied, in order to identify the NMA evidence base. This comprised a total of 21 RCTs, 17 of which were included in the primary analysis. In addition to the head-to-head RCT comparing panitumumab in combination with FOLFOX versus FOLFOX (PRIME), panitumumab in combination with FOLFOX was linked to XELOX, FOLFIRI and cetuximab in combination with FOLFOX via a single common comparator (FOLFOX) and further linked to cetuximab in combination with FOLFIRI via the network. Due to lack of evidence, an analysis in patients with liver only metastases was not possible.

In addition to the NMA, a further five panitumumab studies, not directly relevant to the decision problem, were identified as supportive evidence. These included the four studies which formed the basis of the recently extended first-line indication of panitumumab in combination with FOLFIRI, (PLANET, Study 20060314, Study 20050181, and ASPECCT) and a study of panitumumab in combination with FOLFOX versus bevacizumab in combination with FOLFOX (PEAK).

Below is a summary of results from the relevant RCTs, NMA and supportive evidence for each of the relevant defined comparisons.

Panitumumab in combination with FOLFOX versus FOLFOX

Results from the relevant panitumumab RCT, PRIME, evaluating efficacy in patients with untreated mCRC, with wild-type RAS, showed a statistically significant and clinically meaningful improvement in median OS of 5.6 months in patients who received panitumumab in combination with FOLFOX compared with FOLFOX alone (25.8 versus 20.2 months; HR 0.77; 95% CI 0.64 to 0.94; P = 0.009). Median PFS was 10.1 months with panitumumab in combination with FOLFOX, compared with 7.9 months with FOLFOX alone (HR 0.72; 95% CI 0.58 to 0.90; P = 0.004). The ORR was higher with panitumumab in combination with FOLFOX than with FOLFOX alone (59% versus 46%; odds ratio 1.63, 95% CI 1.13 to 2.38).

The NMA analysis [redacted]

The safety profile in PRIME among patients with wild-type RAS receiving panitumumab in combination with FOLFOX was similar to that previously reported in patients with wild-type KRAS exon 2 treated with panitumumab in combination with FOLFOX and consistent with the class effects of EGFR inhibition. No new safety concerns were identified.

The results from the supporting study (PEAK) of panitumumab in combination with FOLFOX versus bevacizumab in combination with FOLFOX provide additional evidence to that observed in the PRIME Phase 3 study to support the efficacy of panitumumab in combination with FOLFOX as first-line therapy for mCRC. PFS significantly favoured panitumumab plus FOLFOX over bevacizumab plus FOLFOX and a strong trend towards OS benefit with panitumumab plus FOLFOX was observed.

Panitumumab in combination with FOLFOX versus XELOX

The NMA analysis showed [redacted]

Panitumumab in combination with FOLFOX versus FOLFIRI

The NMA analysis showed [redacted]

Panitumumab in combination with FOLFOX versus cetuximab (in combination with FOLFOX or irinotecan-based chemotherapy)

The NMA analysis showed [redacted]

The NMA also showed [redacted]

Panitumumab in combination with FOLFIRI versus relevant comparators

No head-to-head RCT evidence evaluated first-line use of panitumumab in combination with FOLFIRI versus the defined comparators in the decision problem. There were insufficient data to construct a network to estimate treatment differences for panitumumab in combination with FOLFIRI versus identified comparators.

However, evidence from four supportive studies (PLANET and studies 20060314, 20050181, and ASPECCT), which formed the basis of the recently extended first-line indication of panitumumab in combination with FOLFIRI, show broadly consistent efficacy and safety to that demonstrated in the first-line PRIME study of panitumumab in combination with FOLFOX [redacted]

Panitumumab in combination with FOLFOX versus cetuximab (in combination with FOLFOX or irinotecan-based chemotherapy) in an LMO population

No head-to-head RCT evidence evaluated panitumumab in combination with FOLFOX versus the defined comparators in the decision problem for the liver metastases only (LMO) population. Neither was there sufficient evidence from the RCTs reporting subgroup analyses for the LMO population to form a network to allow comparisons.

Strengths and limitations of evidence

The PRIME trial comparing panitumumab in combination with FOLFOX with FOLFOX alone was a robust, well-controlled RCT. The pre-specified analysis of additional RAS mutations, although exploratory, was conducted under the rigorous statistical standards used for a prospective analysis, enabling robust conclusions on the ability of RAS mutation status to predict response to treatment. The results from the NMA evaluating the relative efficacy of panitumumab in combination with FOLFOX versus other defined comparators should be considered as observational findings across trials, and therefore may suffer the biases of observational studies, with potential bias from heterogeneity of patient populations between wild-type RAS populations treated by EGFR-inhibitors and patients with mixed or unknown RAS status for other treatments. In addition, there is a potential confounding bias in the assessment of OS, since patients in all studies within the NMA had the option to move to a subsequent therapy following disease progression.

1.4 Conclusion

Panitumumab is a proven biological treatment for patients with previously untreated wild-type RAS mCRC. A head-to-head RCT demonstrated that in patients with wild-type RAS tumours, the addition of panitumumab to FOLFOX provided a statistically significant and clinically meaningful 5.6 months OS benefit, and is the first targeted treatment in combination with FOLFOX for mCRC to demonstrate such a gain. An NMA of 21 studies [redacted] With its targeted mechanism of action, improved efficacy and efficient mode of administration, panitumumab provides an important targeted treatment option for patients with previously untreated wild-type RAS mCRC.

2 The technology

2.1 Description of the technology

Approved name: Panitumumab
Brand name: Vectibix®
Therapeutic Class: Antineoplastic agents, monoclonal antibodies

- **Panitumumab is a proven therapeutic for patients with metastatic colorectal cancer (mCRC).**
- **It is the only fully human immunoglobulin (Ig) G2 monoclonal antibody with high affinity for epidermal growth factor receptor (EGFR), and was the first targeted therapy to gain approval from the European Medicines Agency (EMA) for the treatment of patients with wild-type RAS mCRC.**

Panitumumab is a recombinant, fully human IgG2 monoclonal antibody that binds with high affinity and specificity to the human epidermal growth factor receptor (EGFR). The EGFR is a transmembrane glycoprotein that is a member of a subfamily of type 1 receptor tyrosine kinases, including EGFR (HER1/c-ErbB-1), HER2, HER3 and HER4. EGFR promotes cell growth in normal epithelial tissues, including the skin and hair follicle, and is expressed on a variety of tumour cells.

Panitumumab binds to the ligand-binding domain of EGFR and inhibits receptor autophosphorylation induced by all known EGFR ligands. Binding of panitumumab to EGFR results in internalisation of the receptor, inhibition of cell growth, induction of apoptosis, and decreased interleukin 8 and vascular endothelial growth factor production. KRAS (Kirsten rat sarcoma 2 viral oncogene homologue) and NRAS (Neuroblastoma RAS viral oncogene homologue) are highly related members of the rat sarcoma (RAS) oncogene family. KRAS and NRAS genes encode small, GTP-binding proteins involved in signal transduction. A variety of stimuli, including that from the EGFR, activate KRAS and NRAS which, in turn, stimulate other intracellular proteins to promote cell proliferation, cell survival and angiogenesis.

Specifically, activating mutations in KRAS exon 2 occur in approximately 40% of colorectal cancer (CRC) tumours, leading to constitutive activation of KRAS that is independent of EGFR signalling.[1] The most frequently occurring KRAS mutations in CRC are in codons 12 and 13 of exon 2. Tumours with these mutations do not respond to EGFR inhibitors such as panitumumab and cetuximab.[2] Approximately 60% of patients with metastatic colorectal cancer (mCRC) have tumours that are wild-type for KRAS exon 2. Furthermore, approximately 17% of patients from the wild-type KRAS exon 2 mCRC population harbour additional RAS mutations.[3] The identification of biomarkers that predict either response or resistance to targeted biologic agents is important because they provide a way to reduce the risk of exposing patients to treatment-related toxicities when no therapeutic benefit is likely.

2.2 Marketing authorisation/CE marking and health technology assessment

Panitumumab received initial marketing authorisation from the EMA on 03 December 2007 as monotherapy for the treatment of adults with EGFR-expressing mCRC with non-mutated (ie, wild-type) KRAS after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy.[4] The indication was extended on 10 November 2011 to the first- and second-line treatment of adults with wild-type KRAS mCRC.[5,6] Initial KRAS testing focused on mutations in exon 2.

Since the initial EMA approvals, identification of additional RAS mutations beyond KRAS exon 2 (ie, mutations in KRAS exons 3 and 4 and NRAS exons 2, 3 and 4) has been shown to predict lack of response to panitumumab. All these mutations in KRAS exons 2, 3 and 4 and NRAS exons 2, 3 and 4 are collectively referred to as 'RAS mutations'. Analysis of RAS clinical trial data clearly indicates that identification of additional RAS mutations outside those initially investigated in KRAS exon 2 (codons 12/13) leads to further refinement of the patient population and improvement in the efficacy of panitumumab therapy without altering its safety profile and, therefore, improves the benefit–risk balance of panitumumab in the approved indications.

The RAS data were submitted to the EMA on 07 May 2013 as a Type 2 variation to support a change to the product information, restricting the indication to patients with wild-type RAS rather than wild-type KRAS mCRC.[7] Full approval was granted on 14 January 2015.

On 04 November 2014, additional data was submitted to the EMA to add FOLFIRI (5-fluorouracil and folinic acid in combination with irinotecan) as a possible chemotherapy in the first-line combination. The Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion on 27 February 2015 and final approval was granted by the EMA on 30 March 2015.

The rationale for expanding the indication for panitumumab to use in first-line therapy in combination with FOLFIRI included evidence that the efficacy and safety of panitumumab has been demonstrated across lines of therapy and with different chemotherapy backbones and appears to be very similar to that of cetuximab in these settings. Therefore, based on the totality of the data for EGFR monoclonal antibodies (panitumumab and cetuximab) in combination with FOLFIRI and the evidence in the monotherapy setting from ASPECCT (panitumumab versus cetuximab) demonstrating that panitumumab and cetuximab showed similar clinical benefit, panitumumab was granted the indication in combination with FOLFIRI in first-line therapy by the EMA.

In terms of specific evidence, two Phase 2 first-line studies with panitumumab in combination with FOLFIRI support the FOLFIRI indication in the first-line setting: Study 20060314 (single-arm panitumumab in combination with FOLFIRI) and PLANET (panitumumab in combination with FOLFIRI versus panitumumab in combination with FOLFOX (5-fluorouracil and folinic acid in combination with oxaliplatin)). However, the clinical rationale supporting this indication is mainly based on EGFR inhibitor class effects and proven non-inferiority of panitumumab to cetuximab as demonstrated in ASPECCT. The Phase 3, second-line Study 20050181 (panitumumab in combination with FOLFIRI versus FOLFIRI) provides

additional data to further support the efficacy and safety profile for the first-line indication of panitumumab in combination with FOLFIRI.

Panitumumab is therefore indicated for the treatment of patients with wild-type RAS mCRC:

- In first-line therapy in combination with FOLFOX or FOLFIRI.
- In second-line therapy in combination with FOLFIRI for patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan).
- As monotherapy after failure of fluoropyrimidine-, oxaliplatin- and irinotecan-containing chemotherapy regimens.

2.3 Administration and costs of the technology

Table 3. Administration and costs of the technology being appraised

	Information	**Source**
Pharmaceutical formulation	Concentrate for solution for infusion (20 mg/mL) Prior to infusion, panitumumab should be diluted in sodium chloride 9 mg/mL (0.9%) solution for injection to a final concentration not to exceed 10 mg/mL One vial contains 100 mg of panitumumab in 5 mL or 400 mg of panitumumab in 20 mL concentrate for solution for infusion	Summary of Product Characteristics[4]
Acquisition cost (excluding VAT)	NHS list price: 5 mL (100 mg) vial = £379.29 20 mL (400 mg) vial = £1517.16 Patient Access Scheme: 5 mL (100 mg) vial = [redacted] 20 mL (400 mg) vial = [redacted]	British National Formulary, March 2015[8]
Method of administration	Intravenous infusion via an infusion pump, using a low protein binding 0.2 or 0.22 µm in-line filter, through a peripheral line or indwelling catheter. Infusion over 30 to 60 mins The recommended infusion time is approximately 60 minutes. If the first infusion is tolerated, then subsequent infusions may be administered over 30 to 60 minutes. Doses higher than 1000 mg should be infused over approximately 90 minutes.	Summary of Product Characteristics[4]
Doses	6 mg/kg of bodyweight	Summary of Product Characteristics[4]
Dosing frequency	Intravenous infusion (6 mg/kg of bodyweight) given once every two weeks	Summary of Product Characteristics[4]
Dose adjustments	Modification of the dose may be necessary in cases of severe (≥ grade 3)	Summary of Product Characteristics[4]

	Information	Source
	dermatological reactions (see Section 4.4 of the Summary of Product Characteristics)	
Anticipated care setting	Panitumumab treatment should be supervised by a physician experienced in the use of anti-cancer therapy	Summary of Product Characteristics[4]

VAT, value added tax.

2.4 Changes in service provision and management

Patients with wild-type RAS mCRC will already be present at chemotherapy units for administration of FOLFOX or FOLFIRI. First-line treatment with panitumumab in combination with FOLFOX or FOLFIRI will require an incremental 30-60 minutes (depending on infusion tolerability) every visit due to the additional infusion time associated with panitumumab.[4] In addition, consistent with indicated dosing frequency, the additional infusion time would be incurred every two weeks for panitumumab in combination with FOLFOX or FOLFIRI, while it is incurred weekly for cetuximab in combination with oxaliplatin- or irinotecan-based chemotherapy.[4,9] Furthermore, administration of panitumumab does not require premedication or monitoring, while administration of cetuximab requires premedication with an antihistamine and corticosteroid and also requires close monitoring.

Evidence of wild-type RAS (KRAS and NRAS) status is required before initiating treatment with panitumumab. Mutational status should be determined by an experienced laboratory using validated test methods for detection of KRAS (exons 2, 3 and 4) and NRAS (exons 2, 3 and 4) mutations (Summary of Product Characteristics (SPC)).[4] Given the availability of laboratories across the UK that can undertake RAS testing, evidence of wild-type RAS status prior to initiation of treatment with panitumumab can be provided routinely.

3 Health condition and position of the technology in the treatment pathway

3.1 Disease overview and pathogenesis

- **mCRC is a serious, life-threatening disease associated with substantial mortality and morbidity, and represents a significant social and healthcare burden.**

Colorectal cancer (CRC) represents a significant social and healthcare burden. Also known as bowel cancer, CRC includes tumours affecting the large bowel (colon cancer) and cancer of the rectum (rectal cancer). CRC is the third most common cancer in England, with an estimated 34,000 cases diagnosed in 2012 and 12,900 deaths.[10] The biggest risk factors for bowel cancer are age and family history.[11] In 2012, 71% of newly diagnosed cases in men and 73% of those in women were in individuals aged 65 years or older.[10]

mCRC is an advanced stage of disease in which tumour cells have migrated through either the bloodstream or lymphatic system to other organs such as the liver or lung; 20% to 25% of patients have metastatic disease at diagnosis and metastases eventually develop in up to 50% of all patients, most of whom die as a result.[12] Within the UK, the 5-year relative survival rate for patients with mCRC is only 6.6%.[13]

3.2 Clinical pathway of care and how the new technology may change the existing pathway

Goals of therapy

The goals of therapy in mCRC are to extend survival and potentially cure selected patients as well as to prevent disease progression, reduce tumour-related symptoms and maintain health-related quality of life. Advances in systemic combination therapies have improved survival for patients with mCRC. The availability of multiple systemic therapeutic options with differing safety profiles and mechanisms of action allow treatment to be tailored according to the characteristics of an individual patient, using various combinations over multiple lines of therapy.[14]

Patients with mCRC often receive numerous lines of systemic therapy, including: chemotherapy, targeted biologic agents, salvage surgery and maintenance therapy, which are interspersed with treatment-free intervals.[15] Studies examining treatment patterns in mCRC indicate that most patients receive at least one line of systemic therapy.[16]

Description of licensed mCRC treatments

Both conventional chemotherapies and biological agents are licensed and used for the treatment of mCRC in the UK.

Licenced conventional chemotherapies for the treatment of mCRC include:

- oxaliplatin-based chemotherapy regimens (eg, FOLFOX or XELOX (capecitabine in combination with oxaliplatin))
- irinotecan-based chemotherapy regimens (eg, FOLFIRI)
- other chemotherapies (eg, capecitabine alone, tegafur with uracil and folinic acid or raltitrexed monotherapy)

Licenced biological agents for the treatment of mCRC include:

- panitumumab in combination with FOLFOX or FOLFIRI
- bevacizumab in combination with fluoropyrimidine-based therapy
- cetuximab in combination with FOLFOX or irinotecan-based chemotherapy

The development of targeted biologic agents for mCRC has improved outcomes. In contrast to conventional chemotherapy agents that indiscriminately kill rapidly dividing cells, targeted biologic agents act by influencing the processes that control tumour cell proliferation, survival, angiogenesis (the formation of new blood vessels), invasion, and spread. Panitumumab and cetuximab are biologic EGFR inhibitors agents licensed for use in combination with chemotherapies for previously untreated mCRC. Their indications are similar and are summarised in Table 4.

Table 4. Summary of EGFR inhibitors approved for the treatment of mCRC

Medicine	Biomarker	Current label indication
Panitumumab	Wild-type RAS	Adults with wild-type RAS mCRC: • as first-line therapy in combination with FOLFOX or FOLFIRI • as second-line therapy in combination with FOLFIRI for patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan) • as monotherapy after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing regimens
Cetuximab	Wild-type RAS	Treatment of adults with EGFR-expressing, wild-type RAS mCRC: • in combination with irinotecan-based chemotherapy • in combination with FOLFOX in first-line therapy • as monotherapy in patients in whom oxaliplatin- and irinotecan-based therapy has failed or who are intolerant to irinotecan

mCRC, metastatic colorectal cancer; EGFR, epidermal growth factor receptor; FOLFIRI, 5-fluorouracil + leucovorin (folinic acid) + irinotecan; FOLFOX, 5-fluorouracil + leucovorin (folinic acid) + oxaliplatin; RAS, rat sarcoma.

Summary of NICE guidance

The National Institute for Health and Care Excellence (NICE) has issued one clinical guideline of relevance to this appraisal (CG131)[17] and undertaken three relevant technology appraisals in this disease area (TA240,[18] TA212[19] and TA176[20]). A summary of these can be found in Appendix II. From these three technology appraisals there was only one positive recommendation: for cetuximab in combination with FOLFOX or irinotecan-based chemotherapy in patients with metastases confined to the liver (TA176).

Although not currently recommended by NICE in the broad population, cetuximab and panitumumab in combination with chemotherapy, are currently available as first-line treatments for wild-type RAS mCRC patients through the Cancer Drugs Fund (CDF). Prior to March 2015, bevacizumab in combination with chemotherapy was also funded as a first-line treatment for mCRC patients through the CDF; however, following re-review, bevacizumab with chemotherapy for first-line mCRC has been delisted from the CDF.

UK treatment patterns

Treatment pattern data from the UK for patients with previously untreated mCRC are summarised in Table 5. These data support the NICE specified comparators, indicating a relatively larger proportion of patients treated with capecitabine, XELOX, FOLFOX, FOLFIRI and bevacizumab with oxaliplatin- or irinotecan-based chemotherapy. Approximately 63% of patients are treated with chemotherapy alone as first-line therapy, while 37% are treated with a biologic in combination with chemotherapy. However, the treatment pattern data presented represent utilisation in Q3 2014, prior to the delisting of bevacizumab as first-line therapy from the CDF.

Table 5. Summary of treatment patterns for patients with previously untreated mCRC

Treatment		Estimated % of patients receiving first-line treatment[a]
Chemotherapy alone	Capecitabine[b]	18.5
	FOLFOX[c]	**16.1**
	XELOX[c]	**10.9**
	FOLFIRI[c]	**8.7**
	5-FU (infusional)	4.8
	Other chemotherapies	3.0
	XELIRI	0.9
Chemotherapy in combination with biologic	Bevacizumab with oxaliplatin -based chemotherapy	18.4[d]
	Bevacizumab with irinotecan-based chemotherapy	7.8[d]
	Cetuximab with irinotecan-based chemotherapy[c]	**7.3**
	Other biologic and chemotherapy combination	2.8
	Cetuximab with FOLFOX or oxaliplatin-based chemotherapy[c]	**0.8**
Total		100

FOLFIRI, 5-fluorouracil + leucovorin (folinic acid) + irinotecan; FOLFOX, 5-fluorouracil + leucovorin (folinic acid) + oxaliplatin; 5-FU, Fluorouracil; XELIRI, irinotecan + capecitabine; XELOX, capecitabine + oxaliplatin.

[a] Based on IMS data[21] from Q3 2014 (n = 210 patients), independent of RAS status

[b] only used in patients unfit for fluoropyrimidine based combination therapy

[c] Comparators relevant to submission are shown in bold

[d] Indicates market shares for bevacizumab + oxaliplatin- or irinotecan-based chemotherapy prior to delisting from the Cancer Drugs Fund

Of the treatments relevant to this submission, FOLFOX was the most commonly used therapy (16.1%), followed by XELOX (10.9%), FOLFIRI (8.7%) and cetuximab with irinotecan-based chemotherapy (7.3%).

Unmet need of current pathway

Within the UK, the 5-year relative survival rate for patients with mCRC is only 6.6%.[13] Since the majority of mCRC patients are currently treated with chemotherapy alone (63%), there is a clear need for additional therapies that can improve treatment outcomes compared to standard chemotherapy regimens. In addition, there is a need for therapies that can be tailored to individual needs, based on their potential to respond and also safety profiles. Targeted biologic agents have different mechanisms of action and distinct safety profiles that allow physicians to choose the most appropriate option according to comorbidities and likely therapeutic success. In addition, identification of biomarkers that predict either response or resistance to targeted biologic agents is important because they provide a way to reduce the risk of exposing patients to treatment-related toxicities when no therapeutic benefit is likely.

In summary, there is a clear medical need for easier, more consistent access to targeted biologic agents which:

- Improve outcomes versus chemotherapy alone
- Allow therapy to be tailored to individual needs (in terms of potential to respond and safety profile)
- Can be easily/efficiently administered and combined with common chemotherapy regimens.

Position of panitumumab in the treatment pathway

It is recommended that panitumumab should be positioned as a treatment option for the well-defined population of patients with previously untreated, wild-type RAS mCRC.

Selection of comparators

The selection of comparators is based on NICE technology appraisal guidance, NICE clinical guidelines and UK treatment patterns. These indicate that the relevant comparators for patients with previously untreated mCRC include the traditional fluoropyrimidine-based combination chemotherapy regimens (FOLFOX, XELOX and FOLFIRI) and cetuximab in combination with FOLFOX or irinotecan-based chemotherapy.

- **FOLFOX:** is the primary comparator since it is recommended in NICE CG131 as first-line treatment for patients with previously untreated mCRC. FOLFOX is also one of the most commonly used first-line treatments (16.1%) (Table 5).
- **XELOX:** is also recommended as a treatment option in NICE CG131, although treatment patterns show it is a less commonly used chemotherapy combination (10.9%) than FOLFOX.
- **FOLFIRI:** is not recommended in NICE CG131; however it is specified in the NHS England treatment algorithm since it is currently funded nationally by NHS England for this indication. FOLFIRI is used in 8.7% of first-line mCRC patients. Therefore, it is also considered to be a relevant comparator.
- **Cetuximab:** is not recommended by NICE in the broad, previously untreated mCRC population. However, it is considered to be a comparator since it is a specified intervention within this Multiple Technology Appraisal. Cetuximab is also currently funded through the Cancer Drugs Fund for use in first-line treatment in combination with either FOLFOX or irinotecan based combination chemotherapy. Additionally, in the population of previously untreated mCRC with unresectable LMO, cetuximab in combination with chemotherapy is recommended in NICE TA176. Therefore, cetuximab is considered the primary comparator for this subpopulation.

The following comparators listed in the decision problem were not assessed:

- **Capecitabine:** only used in patients unfit for fluoropyrimidine-based combination therapy; therefore, not an appropriate comparator since panitumumab is licenced for use in combination with FOLFOX or FOLFIRI.
- **Tegafur, folinic acid and fluorouracil:** only used in patients unfit for fluoropyrimidine-based combination therapy; therefore, not an appropriate comparator since panitumumab is licenced for use in combination with FOLFOX or FOLFIRI.

- **Bevacizumab in combination with oxaliplatin- or irinotecan-based chemotherapy:** no longer funded by the CDF for first-line treatment of mCRC therefore not considered to be consistently available nationally.

Table 6 summarises the comparators that are assessed in this submission and justification for their selection.

Table 6. List of comparators assessed

Intervention	Recommended in first-line by NICE	Funded via NHS England	Funded via Cancer Drugs Fund	Patient share
Untreated mCRC patients				
FOLFOX	Yes (CG131)[17]	Yes	NA	16.1%
XELOX	Yes (CG131)[17]	Yes	NA	10.9%
FOLFIRI	No (CG131)[17]	Yes	NA	8.7%
Cetuximab, in combination with FOLFOX or irinotecan-based chemotherapy	No (TA176)[20]	No	Yes	8.1%
Untreated mCRC patients with unresectable liver metastases only				
Cetuximab, in combination with FOLFOX or irinotecan-based chemotherapy	Yes (TA176)	Yes	NA	–

FOLFIRI, 5-fluorouracil + leucovorin (folinic acid) + irinotecan; FOLFOX, 5-fluorouracil + leucovorin (folinic acid) + oxaliplatin; mCRC, metastatic colorectal cancer; NA, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; XELOX, capecitabine + oxaliplatin.

4 Clinical effectiveness

4.1 Identification and selection of relevant studies

- **A systematic review was used to identify relevant randomised controlled trial (RCT) evidence.**
- **A total of 46 studies were identified, of which only one was a relevant panitumumab RCT in patients with previously untreated mCRC; this study compared panitumumab plus FOLFOX versus FOLFOX alone in patients with wild-type RAS mCRC.**

To address the information needs of the decision problem as outlined in the final scope for this appraisal, a systematic review was undertaken. The aim was to identify the evidence available from randomised controlled trials (RCTs) evaluating the efficacy and safety of panitumumab and other therapies for the treatment of patients with previously untreated mCRC.

Details of search strategies, study selection, eligibility criteria, search results, Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for study inclusion and lists of studies (included and excluded) are provided in Appendix III.

A total of 327 papers reporting data for 92 RCTs that evaluated treatment of patients with previously untreated mCRC were identified. From the trials, those that reported at least two arms comparing first-line interventions/comparators (licenced and/or used in the UK) were selected for data extraction; in total, 46 trials (229 publications) were extracted in full. These included:

- 2 panitumumab trials
  - PRIME, evaluating panitumumab in combination with FOLFOX versus FOLFOX alone (reported in 35 publications)
  - PEAK, evaluating panitumumab in combination with FOLFOX versus bevacizumab in combination with FOLFOX (reported in 14 publications)
- 22 comparisons of alternative chemotherapy regimens
- 13 comparisons of bevacizumab with/without alternative forms of chemotherapy (13 trials)
- 7 comparisons of cetuximab with/without alternative forms of chemotherapy
- 2 trials of bevacizumab plus chemotherapy versus cetuximab plus chemotherapy.

Details are provided in Appendix III.

All of the trials were parallel RCTs and six were non-inferiority trials. The majority were either Phase 2 or Phase 3 trials funded by the pharmaceutical industry and carried out within Europe. The trials were usually open-label and the duration of follow-up ranged from 9 months to over 2 years, with most trials following up patients for at least 2 years. Overall, the trials showed a good level of homogeneity with respect to their included populations, in terms of their sex, age, Eastern Cooperative Oncology Group (ECOG) performance status

and burden of metastases. Commonly assessed outcomes were overall survival (OS), progression-free survival (PFS), tumour response (objective response rate (ORR), complete response (CR), partial response (PR), stable disease and progressive disease) and adverse events. Some trials assessed health-related quality of life outcomes. In many cases the assessment of bias was difficult due to the inadequate reporting of study methods. The risk of bias within the trials varied with all trials suggestive of at least some level of bias, although in some cases this risk was judged to be low. Further characteristics of the individual trials are reported in Appendix III.

4.2 List of relevant RCTs

Table 7 summarises details of the only relevant RCT identified comparing panitumumab with appropriate comparators in the treatment of mCRC, as defined by the *decision problem addressed in the submission* (Table 1). PRIME (Study 20050203) was a randomised, controlled clinical study which investigated the efficacy and safety of panitumumab plus FOLFOX versus FOLFOX alone in 512 patients with wild-type RAS previously untreated mCRC.

Table 7. List of relevant RCTs

Trial no. (acronym) design	Interventions/ comparators	Population	Primary and secondary endpoints (RAS analysis)	Primary study reference
Study 20050203 (PRIME) – RAS analysis Phase 3, multicentre, open-label, randomised controlled study	Panitumumab in combination with FOLFOX vs. FOLFOX alone	Untreated mCRC patients with RAS status ascertained	Primary • PFS • OS Secondary • 60-day PFS • ORR • Complete resection of metastases in patients with LMO at baseline • Incidence of adverse events	Panitumumab–FOLFOX4 treatment and RAS mutations in colorectal cancer. Douillard et al, N Engl J Med 2013;369: 1023–34.

FOLFOX, 5-fluorouracil + leucovorin (folinic acid) + oxaliplatin; LMO, liver metastases only; mCRC, metastatic colorectal cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RAS, rat sarcoma.

4.3 Summary of methodology of the relevant RCT

- **The key clinical evidence for the efficacy and safety of panitumumab combination therapy as first-line treatment of patients with wild-type RAS mCRC comes from PRIME, a head-to-head, comparator RCT, including 512 wild-type RAS mCRC patients.**
- **PRIME evaluated panitumumab in combination with FOLFOX versus FOLFOX alone, which is the primary comparator for this appraisal.**
- **The primary outcome measures were the standard, clinically relevant endpoints of OS and PFS.**

Appendix IV presents tables summarising details of study design, participants (eligibility criteria), randomisation strata, baseline characteristics, outcomes, statistical analyses, subgroup analyses, extent of exposure, participant flow and critical appraisal of the relevant RCT. Below is a summary description of the relevant RCT methodology.

The PRIME trial was a Phase 3, international, multicentre, open-label, randomised, controlled study designed to compare the efficacy of panitumumab in combination with FOLFOX versus FOLFOX alone in the first-line treatment of mCRC. Patients were randomised in a 1:1 ratio to receive either panitumumab with FOLFOX or FOLFOX alone with randomisation stratified by geographic region and ECOG performance status.[22] The study enrolled mCRC patients with measurable lesions who were aged 18 years or older and had ECOG performance status between 0 and 2. Patients previously treated with anti-EGFR antibodies were not eligible.

The primary endpoint was PFS and the study was designed to have 90% power to detect a difference in PFS between treatment groups within the wild-type KRAS subpopulation. Secondary endpoints included OS, ORR, time to progression and duration of response. Patients were treated until disease progression or unacceptable toxicity, at which point other therapy could be administered including anti-EGFR therapy. The primary analysis prospectively evaluated results according to KRAS status. KRAS testing was initiated after the study population was enrolled and completed 3 months before the primary analysis was conducted.

A subset analysis based on RAS status was pre-specified in a supplemental statistical analysis plan. This analysis forms the basis for the revised indication for wild-type RAS mCRC patients and is therefore the focus of this evidence submission. The efficacy endpoints evaluated in the predefined RAS subset analysis included a subset of those evaluated in the original primary analysis; primary endpoints were PFS and OS and secondary endpoints were 60-day PFS, ORR and complete resection of metastases in patients with LMO at baseline. The same statistical methods were used for all data cut-offs and were consistent with those used in the original primary analysis according to KRAS status (see Appendix IV).

Table 8 summarises analyses performed with their respective data cut-off dates.

Table 8. Analyses and data cut-off dates in PRIME

Analysis	Type of analysis	Data cut-off date(s) [a]
Primary analysis	Event driven OS: pre-specified to occur when at least 50% of patients in each treatment arm within the wild-type KRAS group had an event (death) PFS: pre-specified to occur when 380 patients within the wild-type KRAS group had an event (progression/death)	OS: 28 August 2009 PFS: 30 September 2008
Final analysis	Descriptive; pre-specified to occur 30 months after the last patient was enrolled	OS and PFS: 02 August 2010
OS update analysis	Descriptive; exploratory analysis when at least 80% of patients in the wild-type KRAS and mutant KRAS groups had an event (death)	OS: 24 January 2013

KRAS, Kirsten rat sarcoma; OS, overall survival; PFS, progression-free survival.
[a] The same data cut-off dates were applied in the predefined RAS subset analysis.

A summary of patient disposition, analysis populations and stratification for the relevant RCT, PRIME, is presented in Table 9. Further detail is provided in Appendix IV.

KRAS status was ascertained in 93% of patients (1096 of 1183 patients randomised). The primary KRAS efficacy analysis (PFS, OS) was based on all randomised patients within the wild-type KRAS (n = 656) and mutant KRAS (n = 440) groups. RAS status was ascertained in 90% of patients (1060 of the 1183 patients randomised). The analyses showed that 512 patients had wild-type RAS tumours and 548 had mutated RAS tumours; these patients comprised the main analysis sets for the predefined retrospective efficacy analysis: the wild-type RAS efficacy analysis set and the mutant RAS efficacy analysis set. Patient demographics and baseline disease characteristics are summarised in Appendix IV. In the wild-type RAS subset of interest, patient characteristics were similar to those observed in the primary analysis according to KRAS exon 2 status and were largely consistent between the treatment arms.[3]

After disease progression, anti-EGFR therapy was received by 19% of patients in the FOLFOX arm and 7% of patients in the panitumumab in combination with FOLFOX arm within the wild-type RAS subset (primary analysis).[23] Bevacizumab was received by 13% of patients in the FOLFOX arm and 16% of patients in the panitumumab in combination with FOLFOX arm.[23] Further details are provided in Appendix IV.

Table 9. Summary of patient disposition, analysis sets and stratification in PRIME

	All patients		WT KRAS exon 2		Mutant KRAS exon 2		WT RAS		Mutant RAS	
	Pmab + FOLFOX	**FOLFOX**	**Pmab + FOLFOX**	**FOLFOX**	**Pmab + FOLFOX**	**FOLFOX**	**Pmab + FOLFOX**	**FOLFOX**	**Pmab + FOLFOX**	**FOLFOX**
Randomised	593	590	325	331	221	219	259	253	272	276
Median follow-up time[a] (range), weeks			85 (0 – 150)	74 (0 – 153)	61 (0 – 144)	71 (1 – 142)	89 (0 – 150)	75 (0 – 153)	62 (0 – 144)	73 (1 – 142)
Number ending FOLFOX[b], n (%)			307 (94)	321 (97)	214 (97)	213 (97)	243 (94)	246 (97)	264 (97)	268 (97)
Disease progression			147 (45)	170 (51)	136 (62)	127 (58)	114 (44)	136 (54)	166 (61)	152 (55)
Adverse event			47 (14)	37 (11)	27 (12)	25 (11)	38 (15)	29 (11)	34 (13)	32 (12)
Number ending Pmab[b], n (%)		–	306 (94)	–	214 (97)	–	243 (94)	–	264 (97)	–
Disease progression			158 (49)	–	135 (61)	–	122 (47)	–	165 (61)	–
Adverse event			52 (16)	–	29 (13)	–	43 (17)	–	38 (14)	–
Efficacy analysis set[c]			325	331	221	219	259	253	272	27
Safety analysis set[d]			322	327	217	218	256	250	268	275
Stratification factors	Geographic region (Western Europe, Canada and Australia vs. rest of world) and Eastern Cooperative Oncology Group performance status (0 or 1 vs. 2)									

FOLFOX, 5-fluorouracil + leucovorin (folinic acid) + oxaliplatin; Pmab, panitumumab; RAS, rat sarcoma; WT, wild-type

[a] Time from randomisation to last contact date based on primary overall survival data cut-off (28 August 2009).

[b] Assessed based on primary overall survival data cut-off (28 August 2009).

[c] Defined as all randomised patients.

[d] Defined as patients who received at least one dose of panitumumab or chemotherapy.

Source: Amgen 2010[24] Table 8-2; Amgen 2013[23] Table 6-3, Table 6-5, Table 6-6.

4.4 *Clinical effectiveness results of the relevant RCT*

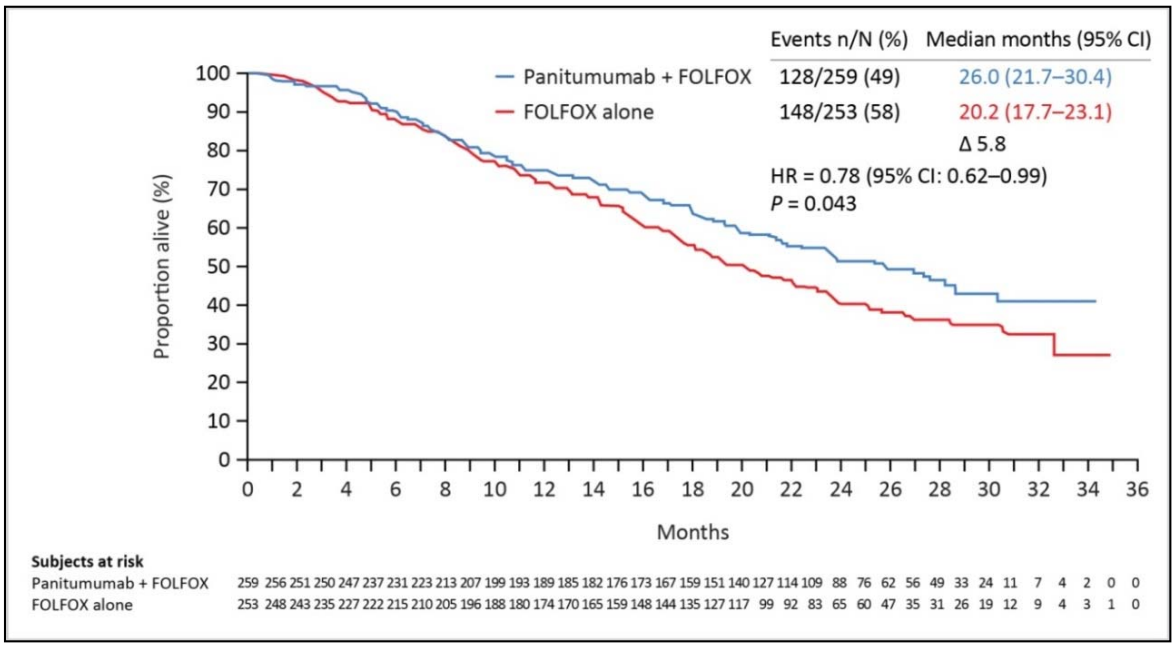
- **In the PRIME study, involving 512 patients with wild-type RAS mCRC, panitumumab + FOLFOX combination therapy resulted in clinically and statistically significant improvements in OS and PFS versus FOLFOX alone.**
- **Median OS was 25.8 months for panitumumab plus FOLFOX compared with 20.2 months for FOLFOX alone (HR 0.77; 95% CI 0.64 to 0.94; P = 0.009).**
- **Median PFS was 10.1 months for panitumumab plus FOLFOX compared with 7.9 months for FOLFOX alone (HR 0.72; 95% CI 0.58 to 0.90; P = 0.004)**

In order to align with the licensed indication for panitumumab as a first-line treatment in patients with wild-type RAS mCRC, data presented in this submission focus on the wild-type RAS subset in the PRIME study.

Overall survival

Overall survival results for the wild-type RAS subset are presented in Figure 1 and Table 10. In the primary analysis, a statistically significant 5.8-month improvement in median OS was seen in patients with wild-type RAS tumours who received panitumumab in combination with FOLFOX compared with FOLFOX alone (26.0 versus 20.2 months; hazard ratio (HR) 0.78; 95% confidence interval (CI), 0.62 to 0.99; P = 0.043).[3] The Kaplan–Meier plot for this analysis is shown in Figure 1. Sensitivity analyses (multivariate analysis, propensity score analysis) supported these results.[23]

Figure 1. Kaplan–Meier plot of overall survival in PRIME (primary analysis, wild-type RAS efficacy analysis set)



CI, confidence interval; FOLFOX, 5-fluorouracil + leucovorin (folinic acid) + oxaliplatin; HR, hazard ratio; RAS, rat sarcoma.

Primary analysis: data cut-off 28 August 2009; Source: Douillard et al, 2013.[3]

Similar results to the primary analysis in wild-type RAS patients were reported for the final analysis (events in 68% of patients) and the most recent OS update analysis (events in 82% of patients) (Table 10). Median survival in the OS update analysis was 25.8 months for the panitumumab plus FOLFOX arm and 20.2 months in the FOLFOX alone arm (5.6 month improvement; HR 0.77, 95% CI 0.64 to 0.94, P = 0.009).

Table 10. Overall survival in PRIME (primary analysis, wild-type RAS efficacy analysis set)

	Panitumumab + FOLFOX (n = 259)	**FOLFOX (n = 253)**
Primary analysis[a]		
Patients with events, n (%)	128 (49)	148 (58)
Median OS, months (95% CI)	26.0 (21.7 – 30.4)	20.2 (17.7 – 23.1)
HR (95% CI)	0.78 (0.62 – 0.99)	
P value	0.043	
Final analysis[b]		
Patients with events, n (%)	[redacted]	[redacted]
Median OS, months (95% CI)	[redacted]	[redacted]
HR (95% CI)	[redacted]	
P value	[redacted]	
OS update analysis[c]		
Patients with events, n (%)	204 (79)	218 (86)
Median OS, months (95% CI)	25.8 (21.7 – 29.7)	20.2 (17.6 – 23.6)
HR (95% CI)	0.77 (0.64 – 0.94)	
P value	0.009	

CI, confidence interval; FOLFOX, 5-fluorouracil + leucovorin (folinic acid) + oxaliplatin; HR, hazard ratio; KRAS, Kirsten rat sarcoma; OS, overall survival; RAS, rat sarcoma.

[a] Data cut-off 28 August 2009; Source: Douillard et al, 2013.[3]

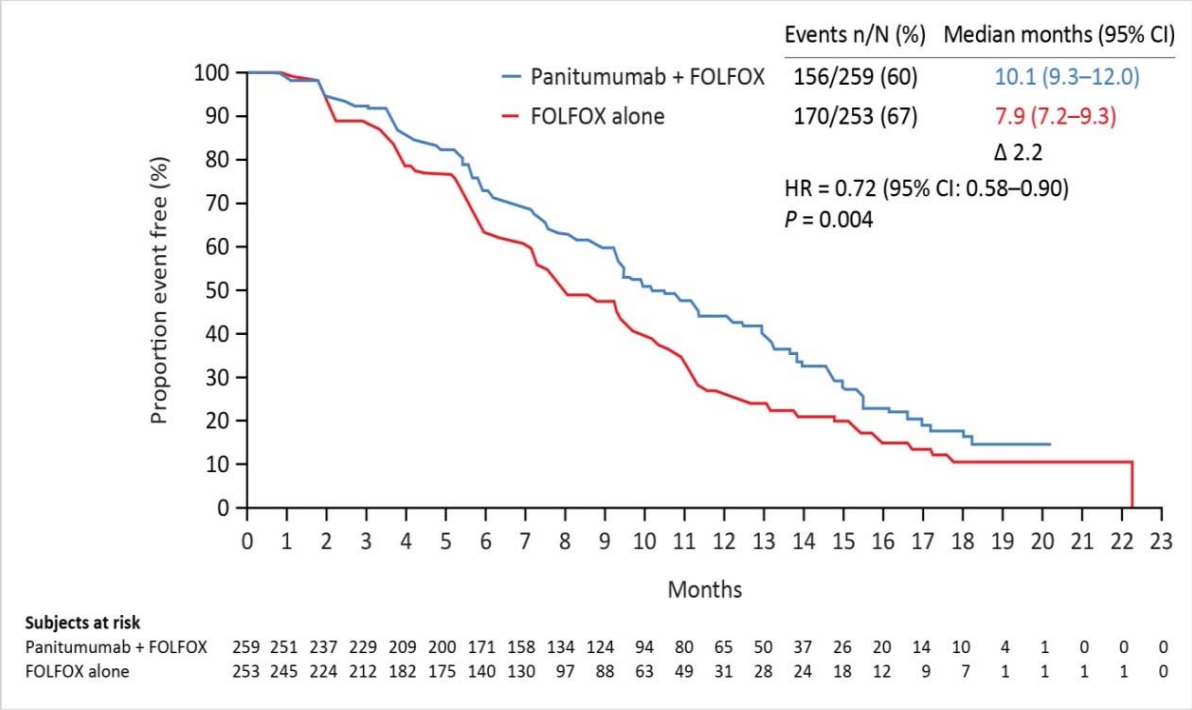
[b] Data cut-off 02 August 2010; Source: Amgen 2013.[23]

[c] Data cut-off 24 January 2013; Source: Douillard et al, 2013.[3]

Progression-free survival

Progression-free survival results for the wild-type RAS subset are presented in Figure 2 and Table 11. In the primary analysis of patients with wild-type RAS tumours, median PFS was 10.1 months with panitumumab in combination with FOLFOX compared with 7.9 months with FOLFOX alone (HR 0.72; 95% CI 0.58 to 0.90; P = 0.004) (Figure 2). These results were supported by sensitivity analyses (multivariate analysis, propensity score analysis).[23] Similar results were observed in the final analysis (patients with events 85%) (Table 11).

Figure 2. Kaplan–Meier plot of progression-free survival in PRIME (primary analysis, wild-type RAS efficacy analysis set)



CI, confidence interval; FOLFOX, 5-fluorouracil + leucovorin (folinic acid) + oxaliplatin; HR, hazard ratio; RAS, rat sarcoma.
Primary analysis: data cut-off 30 September 2008; Source: Douillard et al, 2013.[3]

Table 11. Progression-free survival in PRIME (primary analysis, wild-type RAS efficacy analysis set)

	Panitumumab + FOLFOX (n = 259)	FOLFOX (n = 253)
Primary analysis[a]		
Patients with events, n (%)	156 (60)	170 (67)
Median PFS, months (95% CI)	10.1 (9.3 – 12.0)	7.9 (7.2 – 9.3)
HR (95% CI)	0.72 (0.58 – 0.90)	
P value	0.004	
Final analysis[b]		
Patients with events, n (%)	[redacted]	[redacted]
Median PFS, months (95% CI)	[redacted]	[redacted]
HR (95% CI)	[redacted]	
P value	[redacted]	

CI, confidence interval; FOLFOX, 5-fluorouracil + leucovorin (folinic acid) + oxaliplatin; HR, hazard ratio; KRAS, Kirsten rat sarcoma; PFS, progression-free survival; RAS, rat sarcoma.
[a] Data cut-off 30 September 2008; Source: Douillard et al, 2013.[3]
[b] Data cut-off 2 August 2010; Source: Amgen 2013.[23]

An analysis using an alternative definition of PFS that excluded deaths occurring more than 60 days after the last evaluable tumour assessment or randomisation date (whichever was later) was consistent with the main results (60-day PFS endpoint).[23]

Other endpoints

In patients with wild-type RAS tumours, ORR was higher with panitumumab in combination with FOLFOX than with FOLFOX alone (59% (95% CI 52% to 65%) versus 46% (95% CI 40% to 53%)). The adjusted odds ratio for ORR was 1.63 (95% CI 1.13 to 2.38) in favour of panitumumab in combination with FOLFOX (30 September 2008 data cut-off)[7].

The analysis of complete resection of liver metastases included a relatively small number of patients (n = 90). The frequency of complete resection in patients with wild-type RAS tumours who had liver metastases at baseline suggested some benefit with panitumumab in combination with FOLFOX compared with FOLFOX alone (complete resection in 15 of 49 patients (31%) versus 7 of 41 patients (17%)). The adjusted odds ratio was 2.31 (95% CI 0.74 to 7.66) (28 August 2009 data cut-off).[7] However it should be noted that baseline resectability status was not assessed.

Quality of life, a tertiary endpoint, was assessed every 4 weeks using the EuroQoL 5-domain (EQ-5D) health state index (HSI) and overall health rating (OHR). There were no significant differences in HSI or OHR scores from baseline to disease progression or to discontinuation of first-line treatment between the panitumumab in combination with FOLFOX and FOLFOX arms in patients with wild-type RAS tumours [25]; least-squares mean (95% CI) changes from baseline to disease progression were:

- HSI: 0.74 (0.70 to 0.78) and 0.76 (0.73 to 0.80), respectively
- OHR: 72.5 (69.6 to 75.4) and 74.0 (71.1 to 76.9), respectively.

An analysis of quality-adjusted survival in patients with wild-type RAS tumours using the quality-adjusted time without symptoms of disease or toxicity (Q-TWiST) method showed that mean Q-TWiST was significantly longer for patients in the panitumumab in combination with FOLFOX arm (20.5 months) than for patients in the FOLFOX alone arm (18.2 months); the difference in mean Q-TWiST was 2.3 months in favour of the combination arm ($P < 0.03$).[26]

Subgroup analysis

The OS and PFS treatment effect in favour of panitumumab in combination with FOLFOX in the wild-type RAS efficacy analysis was generally consistent across subpopulations predefined according to baseline covariates (Appendix V).[3] These findings are in line with the original primary analysis in patients with KRAS exon 2 wild-type status.[22] Subpopulations evaluated included region, age, sex, race, ECOG performance status, primary diagnosis (colon/rectal), number of sites of metastatic disease, location of metastatic disease and baseline lactate dehydrogenase (LDH).

4.5 Indirect and mixed treatment comparisons

Introduction

PRIME, the Phase 3 head-to-head RCT comparing panitumumab in combination with FOLFOX versus the defined primary comparator for this appraisal, FOLFOX has been described in section 4.4. There were no head-to-head RCTs evaluating panitumumab in combination with FOLFOX versus other identified comparators and no head-to-head RCTs evaluating panitumumab in combination with FOLFIRI versus any of the identified comparators.

Therefore, in order to address the decision problem set out in this submission, network meta-analysis (NMA) techniques, using direct and indirect evidence, have been used to assess the comparative effectiveness of panitumumab in combination with FOLFOX against the identified comparators used in the UK in first-line therapy for mCRC, as presented in Table 12. The aim of the NMA was to evaluate relative efficacy using the endpoints of OS, PFS, ORR, CR rate and PR rate.

There were insufficient data to perform an NMA comparing panitumumab in combination with FOLFIRI with the comparators of interest. Likewise there were insufficient data to perform an NMA comparing panitumumab in combination with FOLFOX or FOLFIRI with the comparators of interest in the subgroup of patients with LMO.

Table 12. Summary of comparisons evaluated within the NMA

Intervention	Comparator	Evidence
Panitumumab in combination with FOLFOX	FOLFOX	NMA performed with 21 RCTs overall (17 in primary analysis)
	XELOX	
	FOLFIRI	
	Cetuximab, in combination with FOLFOX	
	Cetuximab, in combination with FOLFIRI	

FOLFIRI, 5-fluorouracil + leucovorin (folinic acid) + irinotecan; FOLFOX, 5-fluorouracil + leucovorin (folinic acid) + oxaliplatin; NMA, network meta-analysis; RCT, randomised controlled trial; XELOX, capecitabine + oxaliplatin.

Selection of relevant studies

- **The systematic review identified 46 RCTS in first-line treatment of mCRC.**
- **The NMA was based on 21 RCTs with 17 RCTs included in the primary analysis.**
- **The key endpoints evaluated in the NMA were PFS, OS and ORR, although CR rate and PR rate were also assessed.**

A total of 46 RCTs were identified in the systematic review for first-line treatment of mCRC (section 4.1 and Appendix III). Some of those identified were beyond the scope of the NMA for this appraisal and therefore an additional filter was applied to exclude these studies. Criteria for study inclusion/exclusion in the NMA are described in Table 13. In addition to the comparators of interest (Table 12), the following additional comparators were included in the NMA to increase the body of available evidence and to improve the bridging between treatments: capecitabine, XELIRI (irinotecan and capecitabine) and bevacizumab in combination with FOLFOX, XELOX (capecitabine + oxaliplatin), FOLFIRI or XELIRI.

Table 13. Inclusion/exclusion criteria for the network meta-analysis

PICO criteria	Inclusion criteria	Exclusion criteria
Population	• Patients with previously untreated metastatic colorectal cancer • Patients with RAS wild-type mCRC for studies involving EGFR inhibitors or patients with mixed and unknown wild-type mCRC for studies that did not involve EGFR inhibitors	Did not report on the population of interest
Interventions or comparators	Studies comparing at least two of the following interventions or comparators of interest: • FOLFOX • XELOX • FOLFIRI • Capecitabine • XELIRI • Bevacizumab in combination with FOLFOX, XELOX, FOLFIRI or XELIRI • Cetuximab, in combination with FOLFOX or FOLFIRI • Panitumumab in combination with FOLFOX or FOLFIRI	Did not compare at least two interventions or comparators of interest
Outcomes	Studies reporting at least one of the following outcomes, • HR for overall survival or sufficient data for this to be estimated) • HR for progression-free survival (or	Did not report any relevant efficacy outcomes

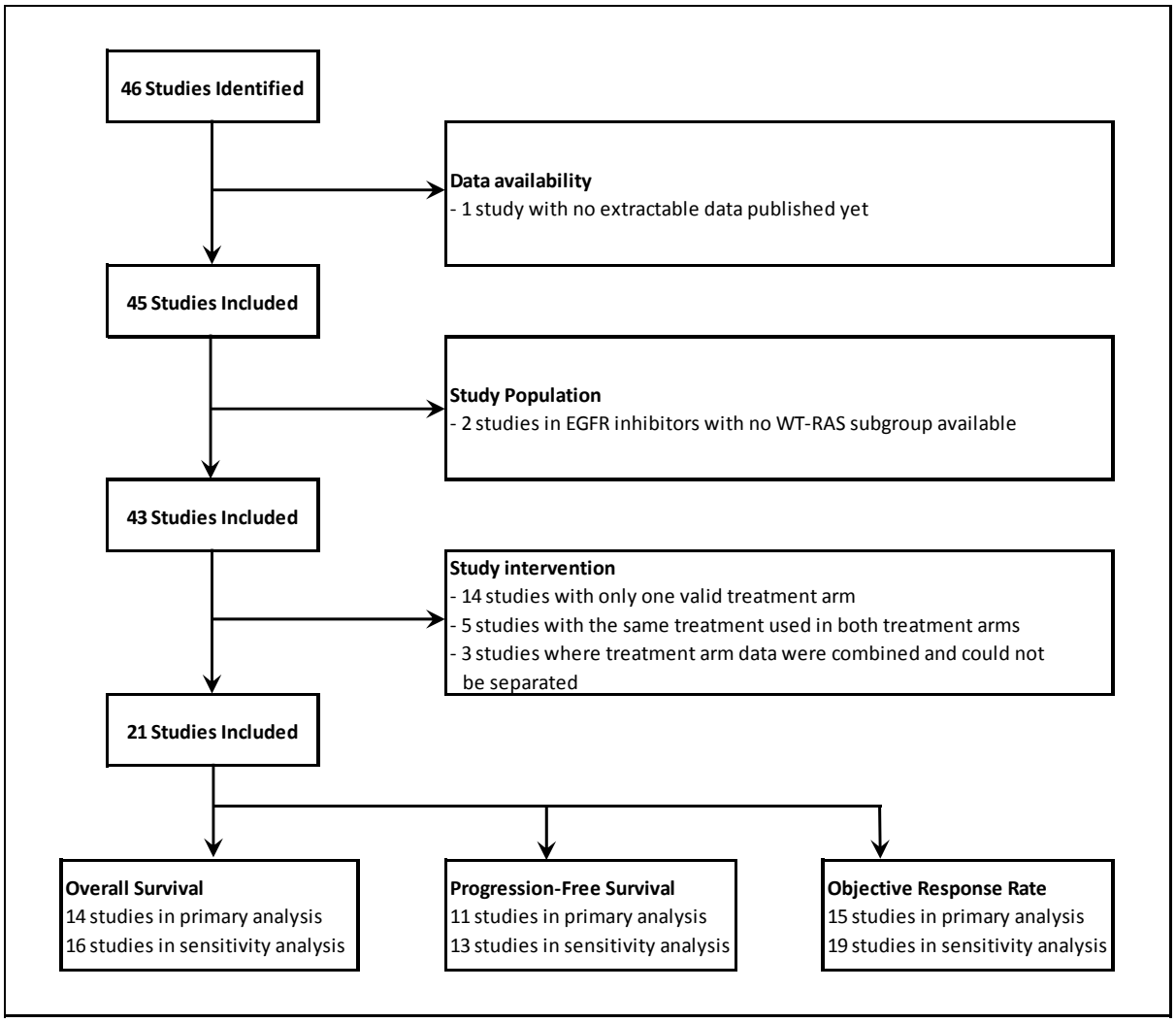
	sufficient data to allow this to be estimated) • Percentage of patients achieving objective response • Percentage of patients achieving complete response • Percentage of patients achieving partial response	

EGFR, epidermal growth factor receptor; FOLFIRI, 5-fluorouracil + leucovorin (folinic acid) + irinotecan; FOLFOX, 5-fluorouracil + leucovorin (folinic acid) + oxaliplatin; HR, hazard ratio; mCRC, metastatic colorectal cancer; PFS, progression-free survival; XELIRI, irinotecan + capecitabine; XELOX, capecitabine + oxaliplatin.

Many studies met more than one criteria for exclusion. To logically provide rationale for exclusion, a hierarchy based on the above categories was used to exclude further studies, ie, population then intervention/comparator then outcome. Details of study exclusion from the NMA are summarised in Figure 3 and Appendix VIII. Note that studies must have had at least one publication including results in order to be evaluated with respect to the further inclusion/exclusion criteria.

A total of 21 RCTs were included in the NMA, evaluating at least one of the five defined endpoints.

Figure 3. Study exclusion for trials analysed in the network meta-analysis



EGFR, epidermal growth factor receptor; WT-RAS, wild-type rat sarcoma.

Summary of available evidence

Table 14 lists the 21 RCTs included in the NMA for the key endpoints (OS, PFS and ORR) and indicates which trials were included in the primary analysis (N = 17). Figure 3 shows how many trials were included in the primary and main sensitivity analyses for each endpoint. A full list of RCTs for all endpoints is presented in Appendix VIII.

Figure 4 summarises the overall network of evidence and shows that panitumumab plus FOLFOX has a direct link to FOLFOX via an RCT and can be linked to XELOX, FOLFIRI and cetuximab plus FOLFOX via a single common comparator (FOLFOX) and further linked to cetuximab plus FOLFIRI via the NMA.

Table 14. List of randomised controlled trials included in the network meta-analysis

Trial name	Interventions	Wild-type RAS population only	Data available for endpoint[a]			Study included in primary analysis	Reference
			OS	PFS	ORR		
ACCORD 13/0503	Bevacizumab + XELIRI (N = 72) Bevacizumab + FOLFIRI (N = 73)	No	No	No	Yes	Yes	Ducreux et al, 2013[27]
Badulescu 2009	FOLFOX (N = 180) FOLFIRI (N =176)	No	Yes	No	No	Yes	Badulescu et al, 2009[28]
CO06-01	Xeloda (N = 40) XELOX (N = 40)	No	Yes	Yes	Yes	No	Hong et al, 2013[29]
COFFE	XELOX (N = 158) FOLFOX (N = 164)	No	Yes	Yes	Yes	Yes	Comella et al, 2009[30]
CRYSTAL	FOLFIRI (N = 189) Cetuximab + FOLFIRI (N = 178)	Yes	Yes	Yes	Yes	Yes	Ciardiello et al, 2014[31]
FOCUS	FOLFOX (N = 357) FOLFIRI (N = 356)	No	Yes	No	Yes	Yes	Seymour et al, 2007[32]
FOCUS2	FOCUS2-1 Xeloda (N = 111) XELOX (N = 111) FOCUS2-2 Xeloda (N = 111) FOLFOX (N = 107) FOCUS2-3 XELOX (N = 111) FOLFOX (N = 107)	No	No	No	Yes	No	Seymour et al, 2011[33]

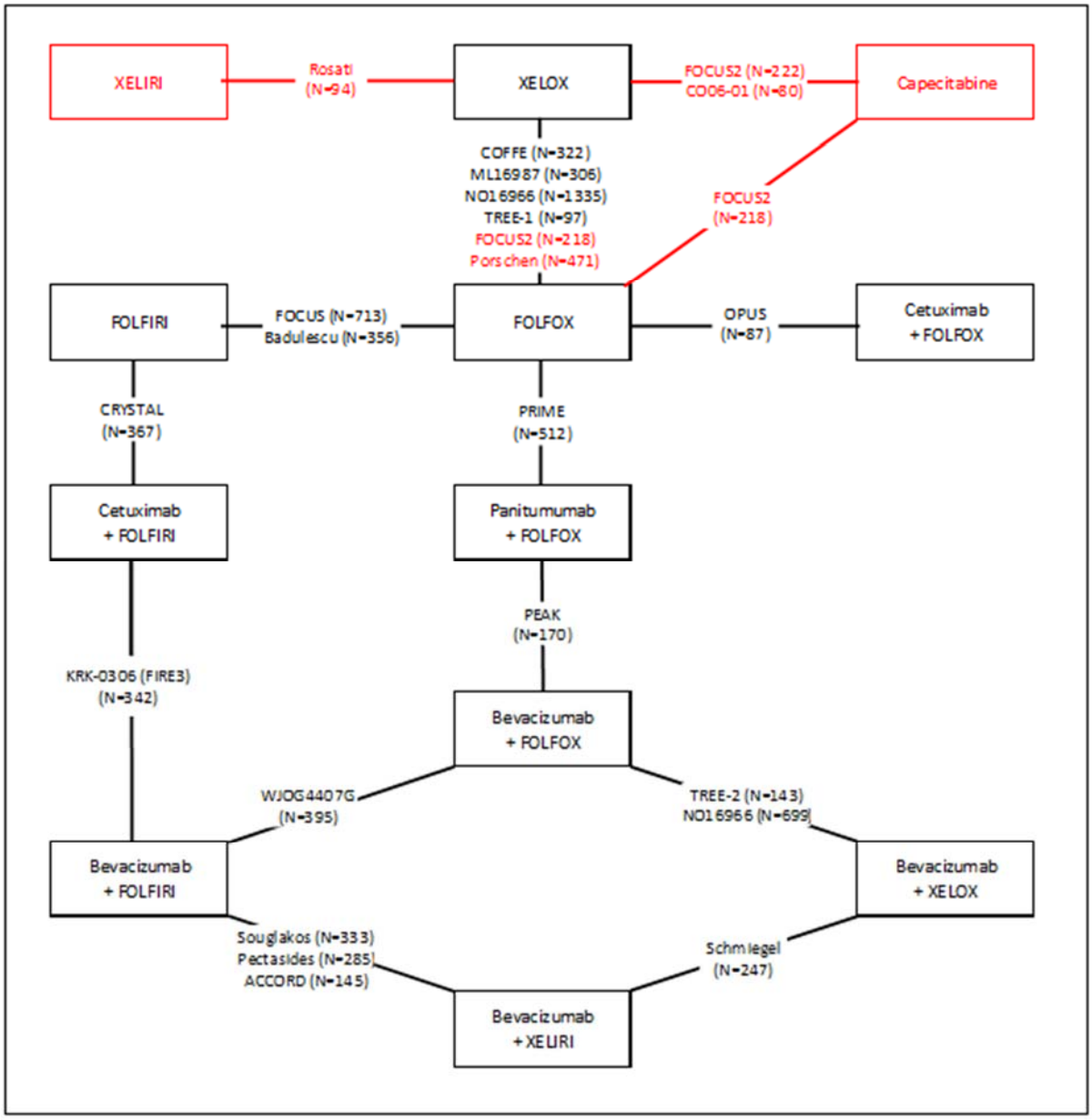
Trial name	Interventions	Wild-type RAS population only	Data available for endpoint[a]			Study included in primary analysis	Reference
			OS	PFS	ORR		
KRK-0306 (FIRE3)	Bevacizumab + FOLFIRI (N = 171) Cetuximab + FOLFIRI (N = 171)	Yes	Yes	Yes	Yes	Yes	Heinemann et al, 2014[34]
ML16987	XELOX (N = 156) FOLFOX (N = 150)	No	Yes	No	Yes	Yes	Ducreux et al, 2011.[35]
NO16966	XELOX (N = 667) FOLFOX (N = 668) Bevacizumab + XELOX (N = 350) Bevacizumab + FOLFOX (N = 349) Bevacizumab + FOLFOX / XELOX (N = 699) FOLFOX / XELOX (N = 1335)	No	Yes	No	No	Yes	Cassidy et al, 2011.[36] Saltz et al, 2008.[37]
OPUS	FOLFOX (N = 49) Cetuximab + FOLFOX (N = 38)	Yes	Yes	Yes	Yes	Yes	Bokemeyer et al, 2014.[38]
PEAK	Bevacizumab + FOLFOX (N = 82) Panitumumab + FOLFOX (N = 88)	Yes	Yes	Yes	Yes	Yes	Schwartzberg et al, 2014.[39] Karthaus et al, 2014.[40]
PRIME	FOLFOX (N = 253) Panitumumab + FOLFOX (N = 259)	Yes	Yes	Yes	Yes	Yes	Douillard et al, 2013.[3] Amgen 2013.[23]
Pectasides et al, 2012	Bevacizumab + XELIRI (N = 143)	No	Yes	Yes	Yes	Yes	Pectasides et al,

Trial name	Interventions	Wild-type RAS population only	Data available for endpoint[a]			Study included in primary analysis	Reference
			OS	PFS	ORR		
	Bevacizumab + FOLFIRI (N = 142)						2012.[41]
Porschen et al, 2007	XELOX (N = 240) FOLFOX (N = 231)	No	Yes	Yes	Yes	No	Porschen et al, 2007.[42]
Rosati et al, 2010	XELOX (N = 47) XELIRI (N = 47)	No	No	No	Yes	No	Rosati et al, 2010.[43]
Schmiegel et al, 2013	Bevacizumab + XELOX (N = 127) Bevacizumab + XELIRI (N = 120)	No	Yes	Yes	Yes	Yes	Schmiegel et al, 2013.[44]
Souglakos et al, 2012	Bevacizumab + XELIRI (N = 166) Bevacizumab + FOLFIRI (N = 167)	No	Yes	Yes	Yes	Yes	Souglakos et al, 2012.[45]
TREE-1	XELOX (N = 48) FOLFOX (N = 49)	No	No	No	Yes	Yes	Hochster et al, 2008.[46]
TREE-2	Bevacizumab + XELOX (N = 72) Bevacizumab + FOLFOX (N = 71)	No	No	No	Yes	Yes	Hochster et al, 2008.[46]
WJOG4407G	Bevacizumab + FOLFOX (N = 198) Bevacizumab + FOLFIRI (N = 197)	No	Yes	Yes	Yes	Yes	Yamazaki et al, 2014.[47]

FOLFIRI, 5-fluorouracil + leucovorin (folinic acid) + irinotecan; FOLFOX, 5-fluorouracil + leucovorin (folinic acid) + oxaliplatin; N, number of patients analysed (where this varies by endpoint the number for OS/PFS is presented); PFS, progression-free survival; ORR, objective response rate; OS, overall survival; RAS, rat sarcoma; XELIRI, irinotecan + capecitabine; XELOX, capecitabine + oxaliplatin.

[a] For OS and PFS, data are considered available if a hazard ratio could be directly extracted or if it could be calculated from other data presented. If only median survival time is available, data are considered not available.

Figure 4. Network diagram of evidence



FOLFIRI, 5-fluorouracil + leucovorin (folinic acid) + irinotecan; FOLFOX, 5-fluorouracil + leucovorin (folinic acid) + oxaliplatin; XELIRI, irinotecan + capecitabine; XELOX, capecitabine + oxaliplatin.
Studies in red were not included in the primary analysis
See Table 14 for the references of included studies

NMA methodology

NMAs include both indirect comparisons (ICs) and mixed-treatment comparisons (MTCs). NMAs have the ability to compare the results from two or more trials that have at least one treatment in common (unlike traditional meta-analysis which summarises the results of trials that have in common just one treatment), see Appendix VIII for details on these analyses.

Network diagrams were constructed to clearly describe the different possible evidence structures. ICs were performed using the methods of Bucher et al (1997)[48] for panitumumab plus FOLFOX compared with XELOX, FOLFIRI and cetuximab plus FOLFIRI using FOLFOX

as the common linking comparator. The IC was preceded by a random effects meta-analysis, which combined similar data for use in the IC. The assumption of homogeneity for the meta-analyses was formally tested. A sensitivity analysis using fixed effects models was also performed.

In the network diagram, there was a mixture of direct and indirect comparisons and therefore an MTC was conducted in a Bayesian Framework. All relevant assumptions, including the consistency assumption, were assessed. For the time to event data, the MTC was based only on the study-level effect of HR as there were insufficient studies that provided arm level data. For the response data, the MTC was performed using treatment arm level data, with a sensitivity analysis performed on the study level relative risk data. Further information on the methods is presented in Appendix VIII.

The primary analysis included RCTs that

- reported endpoints of interest (OS, PFS, ORR, CR or PR)
- used a licensed dose and treatment regimen
- had no major differences in study populations or in their definition of the endpoint being analysed
- were based on the wild-type RAS population for studies including EGFR inhibitors and based on all patients regardless of RAS status for studies including non-EGFR inhibitors
- were without a significant risk of bias.

Four of the 21 studies in the NMA were excluded from the primary analysis due to non-standard treatment or differences in patient populations (CO06-01:[29] elderly population with worse ECOG performance status; FOCUS2:[33] elderly population with worse ECOG performance status and non-standard treatment; Porschen et al, 2007:[42] non-standard treatment; Rosati et al, 2010:[43] elderly population).

Where studies were excluded from the primary analysis, sensitivity analyses were performed, including these studies, to explore the robustness of the results. Additional sensitivity analyses performed included:

- an analysis where clinically similar traditional chemotherapy backbones were pooled (XELOX pooled with FOLFOX, FOLFIRI pooled with XELIRI)
- an analysis including only those comparators deemed relevant in the network (FOLFOX, XELOX, FOLFIRI, cetuximab in combination with FOLFOX/FOLFIRI).

Where multiple publications were identified that reported data from the same study and met the inclusion/exclusion criteria for the NMA, the publication that provided the most complete follow-up for an endpoint was used. For all endpoints, the definitions given in the original trials were used.

Network meta-analysis results

In mCRC patients, panitumumab in combination with FOLFOX as a first-line treatment showed:

The results of the MTC primary analysis for OS, PFS and ORR for panitumumab plus FOLFOX versus the identified comparators are given in Table 15. Results for other endpoints (CR and PR) and sensitivity analyses are presented in Appendix VIII.

A MTC analysis for panitumumab plus FOLFIRI versus the identified comparators could not be performed for any of the endpoints due to insufficient data. Similarly in the LMO population, there were insufficient data to perform a MTC analysis for panitumumab in combination with FOLFOX versus cetuximab (in combination with FOLFOX or irinotecan-based chemotherapy).

Table 15. Mixed-treatment comparison results for panitumumab plus FOLFOX versus identified comparators (primary analysis)

Comparator	PFS HR (95% CrI) [P(HR >1)]	OS RR (95% CrI) [P(HR >1)]	ORR RR (95% CrI) [P(RR <1)]
FOLFOX			
XELOX			
FOLFIRI			
Cetuximab + FOLFOX			
Cetuximab + FOLFIRI			

CrI, credible interval; FOLFIRI, 5-fluorouracil + leucovorin (folinic acid) + irinotecan; FOLFOX, 5-fluorouracil + leucovorin (folinic acid) + oxaliplatin; HR, hazard ratio; ORR, objective response rate; OS, overall survival; P(HR >1), probability that HR is greater than 1; P(RR <1), probability that RR is less than 1; PFS, progression-free survival; RR, relative risk; XELOX, capecitabine + oxaliplatin.
HR <1 favours panitumumab plus FOLFOX; RR >1 favours panitumumab + FOLFOX; statistical significance is indicated by $P < 0.025$ or $P > 0.975$
Source: Appendix VIII.

Panitumumab in combination with FOLFOX versus FOLFOX

[redacted]

Panitumumab in combination with FOLFOX versus XELOX

[redacted]

Panitumumab in combination with FOLFOX versus FOLFIRI

[redacted]

Panitumumab in combination with FOLFOX versus cetuximab in combination with FOLFOX

[redacted]

Panitumumab in combination with FOLFOX versus cetuximab in combination with FOLFIRI

[redacted]

[redacted]

Network meta-analysis limitations

ICs and MTCs are not randomised comparisons, and trials may differ in patient population and design. The results from an NMA should be considered as observational findings across trials and may suffer the biases of observational studies, for example due to confounding.

While results of this NMA should be generalisable to specific populations studied in the trials included in the NMA, generalisation beyond (ie, to adults with mCRC) is problematic. The inclusion and exclusion criteria used may have limited inclusion to patients likely to survive a defined length of time (most commonly 3 months) or who were not previously exposed to specific treatments. The inclusion and exclusion criteria for this NMA were designed to evaluate treatments used in the UK.

Although robust attempts were made to include the grey literature, including conference abstracts and posters, there is still a potential for publication bias if results from negative trials are not published or are less likely to be available in any form. This could also lead to a bias against panitumumab because we were able to obtain results from all clinical trials funded by Amgen, but do not have similar access to all trials with other agents.

Data included in the NMA for panitumumab and cetuximab were restricted to the wild-type RAS mCRC population. However, for non-EGFR inhibitor treatments, where the RAS genotype is not considered to be clinically important to treatment response, data in the wild-type RAS population were not available. Therefore, data included in the NMA for these treatments came from mixed or unspecified RAS status. Consequently, the NMA combines results from study populations with mixed or unknown RAS genotype (for non-EGFR inhibitors) with the results from study populations with wild-type RAS (for panitumumab or cetuximab). This is a potential source of bias as there may be further differences in the prognosis and expected outcomes of patients with wild-type RAS mCRC compared with the general mCRC population that are not yet known or understood. In addition, several studies providing cetuximab data had to be excluded due to the absence of wild-type RAS analyses, leading to a potential source of selection bias. It should also be noted that the subgroup defined by wild-type RAS mCRC was not the protocol-defined population for any of the EGFR inhibitor studies and, therefore was not the intent-to-treat analysis.

For the assessment of OS, there is a high risk of confounding bias in the analyses, since patients in all studies had the option to move to a subsequent therapy following disease progression. Imbalances with respect to the number, type and time to initiation of these subsequent therapies could obscure differences in survival between treatment arms. As a result, caution should be taken in the interpretation of the OS analysis results.

It was not possible to compare panitumumab plus FOLFIRI with any of the comparators due to lack of data within the relevant population. No head-to-head studies met the criteria for inclusion in the systematic review and, as such, it was not possible to link panitumumab plus FOLFIRI to the network.

The results for CR and PR rates have not been presented within this document, although limited results are available within Appendix VIII. For several studies, response data are only presented for the ORR and not for the individual CR and PR. This led to broken networks for these outcomes with no link from panitumumab plus FOLFOX to either cetuximab plus FOLFOX or to cetuximab plus FOLFIRI. In addition, where data were available, complete response was a rare event (<10% incidence in any treatment group in any study where reported) and the studies were not powered to show differences between treatments for such rare events. There were sufficient events for the PR endpoint for

differences to be seen but, due to the low rate of CR events, there was little to no difference in the results between PR and ORR and it was not felt to be worthwhile to present both sets of results.

4.6 Other supportive clinical evidence

A summary of studies that provide supportive evidence of panitumumab use outside the scope of the decision problem, and their rationale for inclusion, are summarised in Table 16. Further details are provided in Appendix VII.

Although bevacizumab is no longer considered a relevant comparator, Study 20070509 (PEAK) is included in this summary for completeness to demonstrate the first-line efficacy and safety of panitumumab in combination with FOLFOX relative to bevacizumab in combination with FOLFOX. Evidence from PLANET, Studies 20060314 and 20050181 and ASPECCT are also summarised, as these studies form the basis of the recently extended first-line indication of panitumumab in combination with FOLFIRI.

Supporting evidence of panitumumab in combination with FOLFOX

In the PEAK study (wild-type RAS analysis), median PFS significantly favoured panitumumab in combination with FOLFOX over bevacizumab in combination with FOLFOX (13.0 months versus 9.5 months; HR 0.65; 95% CI 0.44 to 0.96; P = 0.029), with a strong trend towards median OS benefit with panitumumab in combination with FOLFOX (41.3 months versus 28.9 months; HR 0.63; 95% CI 0.39 to 1.02; P = 0.058).[39] The safety profile in the two treatment arms was similar to that in previously reported studies; no new safety signals were observed.

Supporting evidence of panitumumab in combination with FOLFIRI

In first-line treatment of patients with liver-limited disease (wild-type RAS analysis), PLANET demonstrated similar efficacy for panitumumab in combination with FOLFIRI relative to panitumumab in combination with FOLFOX for ORR (77.8% versus 73.1%), median PFS (12.8 versus 14.8 months; P = 0.621) and median OS (39.0 versus 45.8 months; P = 0.848).[49] The adverse event profile was also similar between groups.

In first-line treatment with panitumumab in combination with FOLFIRI (wild type RAS analysis), Study 20060314 reported an ORR of [redacted] and median PFS of [redacted] months.[50] In second line, study 20050181 demonstrated greater ORR and significant improvement in PFS for panitumumab in combination with FOLFIRI relative to FOLFIRI (ORR of 41% versus 10%, respectively; median PFS of 6.4 versus 4.4 months, respectively; HR 0.70, 95% CI 0.54 to 0.90).[51] The safety profile for panitumumab in combination with FOLFIRI in Studies 20060314 and 20050181 was consistent with that observed in other studies of panitumumab and FOLFIRI chemotherapy in mCRC; the types of events and incidence rates observed are as expected for an EGFR inhibitor in combination with FOLFIRI.

ASPECCT also supported the extended first-line indication of panitumumab in combination with FOLFIRI, demonstrating similar efficacy of panitumumab and cetuximab in chemorefractory patients with wild-type KRAS exon 2 mCRC (median OS of 10.4 versus

10.0 months; HR 0.97, 95% CI 0.84 to 1.11).[52] Overall, the safety profile of panitumumab was similar to that of cetuximab, with the exception that infusion reactions were more frequent with cetuximab and electrolyte disturbances, particularly hypomagnesemia, were more frequent with panitumumab.[52]

Table 16. List of studies providing supporting evidence

Trial No. (Acronym) design	Interventions/ comparators	Population	Primary and secondary endpoints	Rationale for inclusion as supportive evidence	Primary study reference
Study 20070509 (PEAK) Phase 2, open-label, randomised, controlled study	Panitumumab in combination with modified FOLFOX6 vs. bevacizumab in combination with modified FOLFOX6	Previously untreated, non-resectable wild-type KRAS mCRC RAS status ascertained	Primary: PFS Secondary: OS, ORR, resection rate	Bevacizumab is defined as a comparator within the decision problem, although no longer listed on the CDF and therefore not deemed to be a relevant comparator	Schwartzberg et al, *J Clin Oncol* 2014;32:2240-7.[39]
PLANET Phase 2, open-label, randomised, controlled study	Panitumumab in combination with FOLFOX4 vs. panitumumab in combination with FOLFIRI	Previously untreated, wild-type KRAS mCRC with liver metastases only RAS status ascertained	Primary: ORR Secondary: resection rate, time to resection, PFS, OS	Supporting evidence submitted to the regulatory authorities to achieve extended first-line indication of panitumumab in combination with FOLFIRI	Abad et al. Poster presented at World Congress on Gastro-Intestinal Cancer & ESMO 16th World Congress on Gastrointestinal Cancer, Barcelona, Spain 2014.[49]
Study 20060314 Phase 2, single-arm	Panitumumab in combination with FOLFIRI	Previously untreated mCRC RAS status ascertained	Primary: ORR Main secondary: PFS, OS, resection rate	Supporting evidence submitted to the regulatory authorities to achieve extended first-line indication of panitumumab in combination with FOLFIRI	20060314 CSR (RAS analysis), October 2014[50]
Study 20050181 Phase 3, open-label, randomised, controlled study	Panitumumab in combination with FOLFIRI vs. FOLFIRI alone	Previously treated wild-type KRAS mCRC RAS status ascertained	Primary: PFS, OS Secondary: ORR	Supporting evidence submitted to the regulatory authorities to achieve extended first-line indication of panitumumab in combination with FOLFIRI	Peeters et al Poster presented at: Gastrointestinal Cancers Symposium, San Francisco, CA. 2014.[51]
Study 20080763 (ASPECCT) Phase 3,	Panitumumab vs. cetuximab	Previously treated, chemorefractory, wild-type KRAS	Primary: OS Secondary: PFS, ORR, time to	Supportive evidence comparing efficacy of panitumumab monotherapy vs. cetuximab	Price TJ, et al. Lancet Oncol. 2014;15:569-579.[52]

Trial No. (Acronym) design	Interventions/ comparators	Population	Primary and secondary endpoints	Rationale for inclusion as supportive evidence	Primary study reference
open-label non-inferiority, randomised, head-to-head study		mCRC	treatment failure, time to response, duration of response	therapy in third-line treatment. The only head-to-head RCT of panitumumab vs. cetuximab, although not as combination therapy and not in first line. Evidence submitted to the regulatory authorities to achieve extended first-line indication of Panitumumab in combination with FOLFIRI	

CDF, Cancer Drugs Fund; CSR, clinical study report; FOLFIRI, 5-fluorouracil + leucovorin (folinic acid) + irinotecan; FOLFOX, 5-fluorouracil + leucovorin (folinic acid) + oxaliplatin; KRAS, Kirsten rat sarcoma; mCRC, metastatic colorectal cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RAS, rat sarcoma; RCT, randomised controlled trial.

4.7 Adverse reactions

- **Safety data comparing panitumumab plus FOLFOX with FOLFOX alone as first-line therapy in wild-type RAS mCRC were available in 506 patients from the PRIME RCT.**
  - **The safety profile among patients with wild-type RAS receiving panitumumab plus FOLFOX was similar to that previously reported in patients with wild-type KRAS exon 2 treated with panitumumab plus FOLFOX and consistent with the class effects of EGFR inhibition; dermatologic -related reactions were the most commonly reported adverse events.**
  - **No new toxicities or worsening of previously recognised toxicities beyond the expected additive effects were observed with panitumumab in combination with FOLFOX in the subset of patients with wild-type RAS mCRC.**
- **Based on supportive evidence, the safety profile of panitumumab plus FOLFIRI was consistent with that seen in other panitumumab studies with no new safety signals identified.**

Safety data are presented from the RCT relevant to the decision problem, PRIME. Data are shown for the wild-type RAS population of interest and the previously licensed wild-type KRAS population.

Analysis was based on the safety analysis set within each group, which included all randomised patients who received at least one dose of panitumumab or chemotherapy. Adverse event data from PRIME are presented from the final analysis (Table 8) as this represents the most comprehensive dataset. Results were consistent in other analyses (primary OS analysis and OS update analysis).

Overall incidence of adverse events

A summary of adverse events in PRIME is shown in Table 17. In patients with wild-type RAS tumours, serious adverse events, grade 3/4 adverse events and adverse events leading to discontinuation were reported more frequently in the panitumumab plus FOLFOX arm compared with FOLFOX alone, consistent with the known safety profile of panitumumab added to a chemotherapy backbone. Rates of grade 5 (fatal) adverse events were similar in the two treatment arms. The incidences of adverse events in wild-type RAS patients were similar to those observed in wild-type KRAS patients

Table 17. Summary of patient incidence of adverse events in PRIME

	Wild-type RAS (safety analysis set)		Wild-type KRAS (safety analysis set)	
	Pmab + FOLFOX N = 256 n (%)	FOLFOX N = 250 n (%)	Pmab + FOLFOX N = 322 n (%)	FOLFOX N = 327 n (%)
Any AE	256 (100)	248 (99)	322 (100)	323 (99)
Worst grade of 3[a]	145 (57)	125 (50)	181 (56)	162 (50)
Worst grade of 4[a]	72 (28)	50 (20)	90 (28)	65 (20)
Worst grade of 5[a] (death)	14 (5)	16 (6)	16 (5)	20 (6)
Any serious AE	111 (43)	92 (37)	136 (42)	118 (36)
Discontinuation[b]	66 (26)	39 (16)	82 (25)	48 (15)
Any drug-related AE[c]	256 (100)	242 (97)	321 (100)	315 (96)
Worst grade of 3[a]	155 (61)	119 (48)	191 (59)	160 (49)
Worst grade of 4[a]	58 (23)	40 (16)	75 (23)	47 (14)
Worst grade of 5[a] (death)	3 (1)	3 (1)	4 (1)	4 (1)
Any serious AE	71 (28)	41 (16)	83 (26)	52 (16)
Discontinuation[b]	59 (23)	29 (12)	72 (22)	34 (10)

AE, adverse event; FOLFOX, 5-fluorouracil + leucovorin (folinic acid) + oxaliplatin; KRAS, Kirsten rat sarcoma; Pmab, panitumumab; RAS, rat sarcoma.
Final analysis: data cut-off 02 August 2010.
[a] Severity graded using the Common Terminology Criteria for Adverse Events version 3.0 or version 3.0 with modifications.
[b] Leading to permanent discontinuation of any study drug.
[c] The investigator considered there to be a reasonable possibility that the event may have been caused by study drug.
Source: Amgen 2013[23] Table 8-1, Table 8-3.

Appendix VI Table 1 summarises the most commonly reported adverse events in PRIME (occurring in ≥ 10% of patients in either arm). Common adverse events in the wild-type RAS subset were consistent with those expected for patients with mCRC receiving oxaliplatin-containing chemotherapy and included diarrhoea and neutropenia, as well as nausea, fatigue and anorexia (diarrhoea: 65% versus 52% of patients, neutropenia 62% versus 61%, nausea 46% versus 50%, fatigue 39% versus 36% and anorexia 36% versus 26% for the panitumumab plus FOLFOX arm compared with the FOLFOX alone arm). Other commonly occurring adverse events in the panitumumab plus FOLFOX arm included those known to be associated with panitumumab and other EGFR inhibitors, such as rash (55% of patients) and dermatitis acneiform (34% of patients). Results were similar in the wild-type and wild-type KRAS populations.

Appendix VI Table 2 summarises the adverse events with >5% difference in incidence between treatment arms in PRIME. Incidence rates were similar for wild-type RAS and wild-type KRAS patients with hypomagnesaemia and dermatologic toxicities (rash, dermatitis acneiform, pruritus, dry skin, skin fissures and paronychia) and more frequent in patients

treated with panitumumab plus FOLFOX than with FOLFOX alone (hypomagnesaemia 30% versus 7% of patients, rash 55% versus 8%, dermatitis acneiform 34% versus 0%, pruritus 26% versus 4%, dry skin 22% versus 5%, skin fissures 17% versus 0% and paronychia 23% versus 0%).

Overview of pre-specified adverse events of interest

A summary of adverse events of interest for the wild-type RAS and wild-type KRAS populations in PRIME is shown in Table 18.

In patients with wild-type RAS tumours, adverse events associated with EGFR inhibitors, such as integument toxicity (97% versus 44%) and hypomagnesaemia (32% versus 7%) were more common in the panitumumab plus FOLFOX arm compared with the FOLFOX alone arm. Other adverse events that were more common in the panitumumab plus FOLFOX arm were diarrhoea (65% versus 52%) and stomatitis/oral mucositis (49% versus 30%). Hypocalcaemia, which is associated with hypomagnesaemia but is not in and of itself considered a class effect of EGFR treatment, occurred with similar incidences in the two treatment arms (6% versus 3%). The patient incidence of panitumumab infusion reactions was 3% for adverse events reported as infusion reactions and 23% per the Common Terminology Criteria for Adverse Events (CTCAE) definition; grade 3/4 reactions were reported in 1% and 3% of patients, respectively.[23]

Except for haematological toxicities, the majority of adverse events of interest were grade 1 or 2 in severity. Incidences of adverse events of interest were similar in the wild-type RAS and wild-type KRAS populations.

Table 18. Patient incidence of adverse events of interest in PRIME

	Wild-type RAS (Safety analysis set)		Wild-type KRAS (Safety analysis set)	
	Pmab + FOLFOX N = 256 n (%)	FOLFOX N = 250 n (%)	Pmab + FOLFOX N = 322 n (%)	FOLFOX N = 327 n (%)
Any AE of interest	256 (100)	245 (98)	322 (100)	319 (98)
Integument Toxicities	249 (97)	110 (44)	312 (97)	141 (43)
Skin	249 (97)	87 (35)	312 (97)	110 (34)
Nail	93 (36)	5 (2)	108 (34)	6 (2)
Eye	88 (34)	43 (17)	103 (32)	53 (16)
Hair	55 (21)	22 (9)	61 (19)	30 (9)
Cheilitis	11 (4)	3 (1)	13 (4)	5 (2)
Hematological Toxicities	182 (71)	185 (74)	225 (70)	244 (75)
Neutropenias	159 (62)	155 (62)	196 (61)	208 (64)
Thrombocytopenias	54 (21)	65 (26)	63 (20)	88 (27)
Anaemias	37 (14)	33 (13)	49 (15)	43 (13)
Leukopenias	26 (10)	19 (8)	32 (10)	27 (8)
Pancytopenias	0 (0)	1 (0)	0 (0)	1 (0)
Neuro Toxicities	167 (65)	180 (72)	208 (65)	234 (72)
Diarrhea	167 (65)	129 (52)	201 (62)	169 (52)
Stomatitis/Oral Mucositis	126 (49)	76 (30)	157 (49)	94 (29)
Hypomagnesemia	83 (32)	18 (7)	103 (32)	27 (8)
Vascular Toxicity	74 (29)	72 (29)	98 (30)	91 (28)
Pulmonary Toxicity	55 (21)	79 (32)	65 (20)	97 (30)
Cardiac Toxicity	36 (14)	34 (14)	45 (14)	42 (13)
Hypocalcemia	16 (6)	7 (3)	20 (6)	8 (2)
Infusion Reactions				
Infusion Reaction CTCAE		-		-
All grades	59 (23)		78 (24)	
Grade 1/2	52 (20)		69 (21)	
Grade 3/4	7 (3)		9 (3)	
Infusion Reaction USPI		-		-
All grades	21 (8)		25 (8)	
Grade 1/2	14 (5)		17 (5)	
Grade 3/4	7 (3)		8 (2)	
Infusion Reaction Reported AE		-		-
All grades	7 (3)		9 (3)	
Grade 1/2	5 (2)		7 (2)	
Grade 3/4	2 (1)		2 (1)	

Final analysis: data cut-off 2 August 2010; MedDRA V12.0.

AE, adverse event; Beva, bevacizumab; CTCAE, Common Terminology Criteria for Adverse Events (CTCAE); FOLFOX, Folinic acid, fluorouracil (5-FU) and oxaliplatin; n.r., not reported; Pmab, panitumumab; USPI, US package insert.

Source: Amgen 2013 [23]Table 8-21, Table 8-23, Table 11-06.006.013; Amgen 2012[53] Table 14-06.077.003

Overview of the safety of the technology in relation to the decision problem

Safety data for panitumumab in combination with FOLFOX compared with FOLFOX alone as first-line treatment for mCRC are available from the PRIME RCT. The safety profile among patients with wild-type RAS receiving panitumumab in combination with FOLFOX as first-line mCRC therapy was similar to that previously reported in patients with wild-type KRAS exon 2 treated with panitumumab in combination with FOLFOX and consistent with the class effects of EGFR inhibition. No new safety concerns were identified in the further restricted target population and toxicities associated with panitumumab were manageable. Commonly occurring adverse events in the panitumumab arm included those known to be associated with EGFR inhibitors, such as rash and dermatitis acneiform.

Safety data comparing panitumumab in combination with FOLFOX with the other comparators of interest in the first-line setting are not available from RCT evidence and this was not assessed in the NMA. However, supportive evidence was available from the PEAK and ASPECCT studies:

- PEAK (first line): the safety profile in the panitumumab plus FOLFOX arm was similar to that in previously reported studies, and no new safety signals were observed.
- ASPECCT (chemorefractory patients): overall, the safety profile of panitumumab as monotherapy was similar to that of cetuximab as monotherapy, with the exception that infusion reactions were more frequent with cetuximab and electrolyte disturbances, particularly hypomagnesaemia, were more frequent with panitumumab.

Safety data comparing panitumumab in combination with FOLFIRI with the comparators of interest in the first-line setting are not available from RCT evidence and this was not assessed in the NMA. However, safety data on this combination as first-line therapy are available from the PLANET RCT (versus panitumumab plus FOLFOX) and the single-arm Study 20060314. Data from the PLANET study suggest the safety of panitumumab in combination with FOLFIRI in first-line therapy is similar to the safety of panitumumab in combination with FOLFOX in first-line therapy with the exception of known differences based on chemotherapy backbone. The safety profile of panitumumab administered in combination with FOLFIRI in patients with wild-type RAS mCRC in Study 20060314 appears consistent with that observed for cetuximab in combination with FOLFIRI in the CRYSTAL study.[54] In addition, data comparing panitumumab plus FOLFIRI to FOLFIRI alone are available in the second line setting from the Phase 3 RCT Study 20050181; the safety profile of panitumumab in combination with FOLFIRI in patients with wild-type RAS tumours in this study reflects the toxicities expected for an EGFR inhibitor and the background chemotherapy regimen.

The most recent assessment of the risk–benefit of panitumumab did not identify any safety issues that are not reflected in the current panitumumab SPC.[55] The estimated exposure to panitumumab in the marketed setting is 46,104 patient-years up to 31 March 2014.

4.8 Interpretation of clinical effectiveness and safety evidence

Overview of clinical evidence for panitumumab in combination with FOLFOX versus FOLFOX

The key clinical evidence for the efficacy and safety of panitumumab combination therapy as first-line treatment of patients with wild-type RAS mCRC comes from PRIME (Study 20050203): a head-to-head, comparator RCT, including 512 wild-type RAS mCRC patients. PRIME evaluated panitumumab in combination with FOLFOX versus FOLFOX alone, defined as the primary comparator for this appraisal. The primary outcome measures were the standard, clinically relevant endpoints of OS and PFS.

The PRIME study demonstrated that, in patients with wild-type RAS mCRC, panitumumab plus FOLFOX combination therapy resulted in clinically and statistically significant improvements in OS and PFS versus FOLFOX alone. Median OS increased by 5.6 months when panitumumab was added to FOLFOX (median 25.8 versus 20.2 months; HR 0.77; 95% CI 0.64 to 0.94; P = 0.009; OS update analysis). Median PFS was 10.1 months with panitumumab plus FOLFOX, compared with 7.9 months with FOLFOX alone (HR 0.72; 95% CI 0.58 to 0.90; P = 0.004; primary analysis). [redacted]

The safety profile among patients with wild-type RAS receiving panitumumab plus FOLFOX as first-line mCRC therapy in PRIME was similar to that previously reported in patients with wild-type KRAS exon 2 treated with panitumumab plus FOLFOX and consistent with the class effects of EGFR inhibition. No new safety concerns were identified in the further restricted target population.

In addition, the results from the PEAK study of panitumumab plus FOLFOX versus bevacizumab plus FOLFOX provide additional evidence similar to that observed in the PRIME Phase 3 study to support the efficacy and safety of panitumumab plus FOLFOX as first-line therapy for mCRC. PFS significantly favoured panitumumab plus FOLFOX over bevacizumab plus FOLFOX and a strong trend towards OS benefit with panitumumab plus FOLFOX was observed.

Overview of clinical evidence for panitumumab in combination with FOLFOX versus XELOX, FOLFIRI and cetuximab (in combination with oxaliplatin- or irinotecan-based chemotherapy)

In the absence of head-to-head RCT evidence, an NMA was conducted to evaluate the efficacy of panitumumab in combination with FOLFOX versus identified relevant comparators, XELOX, FOLFIRI and cetuximab (in combination with oxaliplatin- or irinotecan-based chemotherapy).

Compared with XELOX, panitumumab in combination with FOLFOX showed [redacted] and, compared with FOLFIRI, panitumumab in combination with FOLFOX showed [redacted]

[redacted]

For panitumumab in combination with FOLFOX versus cetuximab in combination with FOLFOX, the NMA analysis showed [redacted]

The NMA similarly showed [redacted]

In summary results from the NMA [redacted]

Overview of clinical evidence for panitumumab in combination with FOLFIRI versus FOLFOX, XELOX, FOLFIRI and cetuximab (in combination with oxaliplatin- or irinotecan-based chemotherapy)

No head-to-head RCT evidence evaluated panitumumab in combination with FOLFIRI versus the defined comparators in the decision problem. There were insufficient data to construct a network to estimate treatment differences for panitumumab in combination with FOLFIRI versus identified comparators.

Panitumumab plus FOLFIRI as first-line therapy in mCRC received a positive CHMP opinion on 27 February 2015 and EMA approval on 30 March 2015. Although there are no randomised head-to-head studies against the comparators of interest, supportive evidence for the efficacy and safety of the panitumumab plus FOLFIRI combination is available from four studies, which formed the regulatory submission package.

Efficacy data from the LMO study PLANET (panitumumab in combination with FOLFOX, and panitumumab in combination with FOLFIRI) are similar to that of the liver limited disease population of PRIME (panitumumab in combination with FOLFOX).[56] Therefore, it can be extrapolated that in the first-line setting, panitumumab in combination with FOLFIRI has similar clinical benefit to the established regimen of panitumumab in combination with FOLFOX.

In Study 20060314, first-line efficacy of panitumumab in combination with FOLFIRI is similar to that demonstrated for cetuximab in combination with FOLFIRI in CRYSTAL,[54] one of the pivotal studies used to support the approval of cetuximab in combination with FOLFIRI as first-line therapy in patients with mCRC.

In addition to data from the first-line setting, Study 20050181 was a randomised Phase 3 study in the second line setting providing supportive evidence for the clinical benefit of panitumumab in combination with FOLFIRI.

ASPECCT showed that panitumumab and cetuximab provide similar efficacy in the monotherapy setting across subgroups, which is consistent with the data reviewed above for first-line use of EGFR therapy. The consistency of the observed clinical benefit of panitumumab and cetuximab across lines of therapy and with or without chemotherapy suggest that the use of EGFR inhibitor therapy need not be restricted by either line of therapy or chemotherapy backbone.

In regards to safety, results from the first-line studies of panitumumab in combination with FOLFIRI (PLANET and Study 20060314) are consistent with the first-line studies of panitumumab in combination with FOLFOX (PRIME), and cetuximab in combination with FOLFIRI (CRYSTAL). These data, with additional evidence from Study 20050181, support that use of panitumumab for first-line treatment in combination with FOLFIRI has an established safety profile.

Based on the totality of these data in combination with FOLFIRI and the evidence from the ASPECCT study in the monotherapy setting, the EMA granted panitumumab in combination with FOLFIRI with an indication for the first-line treatment of patients with wild-type RAS mCRC.

Strengths and limitations of the clinical evidence base of the intervention

The PRIME study comparing panitumumab in combination with FOLFOX with FOLFOX alone was a robust, well-controlled RCT. The pre-specified subset analysis of additional RAS mutations, although exploratory, was conducted under the rigorous statistical standards used for a prospective analysis, enabling robust conclusions on the ability of RAS mutation status to predict response to treatment. This approach should also be considered appropriate since it would have been unethical to randomly assign patients with RAS mutation into a prospective, confirmatory study once the importance of wild-type RAS as a predictive biomarker for therapy with panitumumab was known. The RAS ascertainment rate was high (90%), minimising the potential for systematic ascertainment bias. It should be noted that the alpha error for hypothesis testing in PRIME was allocated to the primary analysis according to KRAS status and that the wild-type RAS subpopulation may not be representative of the intent-to-treat population from the original randomisation.

The PRIME protocol allowed patients to receive subsequent treatment, including anti-EGFR therapy, post-disease progression, which may have impacted results for the OS endpoint. After disease progression, anti-EGFR therapy was received by 19% of patients in the FOLFOX arm and 7% of patients in the panitumumab in combination with FOLFOX arm within the wild-type RAS subpopulation.

Blinding in the PRIME study was not possible because of expected skin-related toxicities in patients receiving an EGFR inhibitor. Thus, the potential existed for over-reporting and attribution of adverse events to the panitumumab in combination with FOLFOX arm group compared with the FOLFOX alone arm.

In the absence of head-to-head RCTs, an NMA was conducted to assess relative efficacy of panitumumab in combination with FOLFOX versus XELOX, FOLFIRI and cetuximab (in combination with FOLFOX or irinotecan-based chemotherapy). However, the results from the NMA should be considered as observational findings across trials and therefore may suffer the biases of observational studies. A potential source of bias comes from the combination of study populations with mixed or unknown RAS genotype (for non-EGFR inhibitors) with the study populations of wild-type RAS (for panitumumab or cetuximab), since there may be differences in the prognosis and expected outcomes between the two patient populations that are as yet unknown. In addition, within the NMA, there is also a high risk of confounding bias for assessment of OS, since patients in all studies had the option to move to a subsequent therapy following disease progression. As a result, caution should be taken in the interpretation of the OS analysis results.

Relevance of the evidence base to the decision problem

The evidence base for panitumumab in combination with FOLFOX is directly relevant to the specified decision problem: the identified relevant head-to head, comparator RCT (PRIME) investigated panitumumab with FOLFOX as first-line treatment for mCRC, as per the licensed indication and compared this combination with FOLFOX, the primary comparator within the decision problem and considered to be the standard of care in the UK.

PRIME evaluated all outcome measures as specified within the decision problem. The clinical importance of the main outcomes is discussed below.

PFS

PFS was a primary outcome in the PRIME RAS analysis and was centrally assessed in a blinded manner. PFS is a well-accepted and clinically relevant endpoint according to the "*Guideline on the evaluation of anticancer medicinal products in man*" of the CHMP. Prolongation of PFS provides a meaningful clinical benefit to patients by extending the time without disease progression and its associated symptoms.

OS

OS was also a primary outcome in the PRIME RAS analysis; however, treatment cross-over post-disease progression was allowed. This enabled patients receiving FOLFOX initially to receive anti-EGFR antibodies after the protocol treatment phase and vice versa. The proportion of cross-over to anti-EGFR therapy following progression was 19% in the FOLFOX alone arm of PRIME for patients with wild-type RAS tumours (primary analysis).

Summary of the generalisability of trial results of PRIME to the UK population

The efficacy of panitumumab in combination with FOLFOX observed in the PRIME study is expected to be generalizable to effectiveness of panitumumab in combination with FOLFOX in the eligible population in clinical practice within the UK. Treatment of mCRC patients within the study was aligned with current SPCs for both panitumumab and FOLFOX. The eligibility criteria used in PRIME (summarised in Appendix IV) ensured evaluation of an mCRC patient population that is broadly representative for the proposed indications.

Conclusion

In summary, panitumumab is a proven biological treatment for patients with previously untreated wild-type RAS mCRC. A head-to-head RCT demonstrated that in patients with wild-type RAS tumours, the addition of panitumumab to FOLFOX provided a statistically significant and clinically meaningful 5.6 months OS benefit, and is the first targeted treatment in combination with FOLFOX for mCRC to demonstrate such a gain. An NMA of 21 studies [redacted] With its targeted mechanism of action, improved efficacy and efficient mode of administration, panitumumab provides an important targeted treatment option for patients with previously untreated wild-type RAS mCRC.

4.9 Ongoing studies

Table 19. List of ongoing and extension studies expected to report new data in the next 12 months

Trial No. (Acronym) Phase	Interventions	Population	Primary outcome measure	Date expected to report
Study 20070509 (PEAK)	Panitumumab plus mFOLFOX6 Bevacizumab plus mFOLFOX6	Untreated wild-type KRAS mCRC	PFS	Updated OS analysis, CSR Q2 2015
Study 20060314	Panitumumab plus FOLFIRI	Untreated wild-type KRAS mCRC	ORR	Manuscript, Q1 2016 Tumour response data, Q4 2015

FOLFIRI, 5-fluorouracil + leucovorin (folinic acid) + irinotecan; mFOLFOX , modified fluorouracil, leucovorin, and oxaliplatin; IV, intravenous; KRAS, Kirsten rat sarcoma; mCRC, metastatic colorectal cancer; OS, overall survival; ORR, objective response rate; PFS, progression-free survival; Q2, second quarter.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal

Cetuximab (review of TA176) and panitumumab (partial review of TA240) for the first line treatment of metastatic colorectal cancer

Merck Serono evidence submission

May 2015

COMMERCIAL IN CONFIDENCE MATERIAL IS HIGHLIGHTED IN BLUE & UNDERLINED

ACADEMIC IN CONFIDENCE MATERIAL IS HIGHLIGHTED IN YELLOW & UNDERLINED

File name	Version	Contains confidential information	Date
Merck Serono evidence submission-Cetuximab 1st line mCRC-evidence submission document	2.0	Yes	16 June 2015

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Abbreviations

ASCO	American Society of Clinical Oncology
CAPIRI	Capecitabine, Irinotecan
CAPOX	Capecitabine, Oxaliplatin
CCTR	Cochrane Controlled Trials Registry
ECC	European Cancer Congress
EGFR	Epidermal Growth Factor Receptor
ESMO	European Society for Medical Oncology
FOLFIRI	Folinic acid, 5-Fluorouracil, Irinotecan
FOLFOX	Folinic acid, 5-Fluorouracil, Oxaliplatin
HR	Hazard Ratio
HRQoL	Health Related Quality of Life
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
ITT	Intention to Treat population
MTA	Multiple Technology Appraisal
NCDF	National Cancer Drugs Fund
NICE	National Institute for Health and Care Excellence
mCRC	Metastatic Colorectal Cancer
ORR	Overall Response Rate
OS	Overall Survival
PFS	Progression Free Survival
PICOS	Population, Intervention, Comparison, Outcome, Study design
QALY	Quality of Life Year
QoL	Quality of Life
RAS	RAS oncogene (rat sarcoma)
RCT	Randomised Controlled Trial
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
SLR	Systematic Literature Review
UK	United Kingdom
Wt	Wild Type

Executive Summary

Introduction

Colorectal cancer (CRC), also known as bowel cancer, is the fourth most common cancer in the UK and the second most common cause of cancer death (Cancer Research UK 2014). More than 12,000 people annually are diagnosed with advanced or metastatic bowel cancer (mCRC) (Tappenden 2007).

While survival rates in colorectal cancer have been improving globally, the UK continues to lag behind other major economies. The outcomes for adult cancer patients in England have generally been worse than in other high-income countries in Europe (National Audit Office 2015). Survival rates in England remain about 10% lower than the European average, highlighting the opportunity for improved outcomes which may be achieved by increased access to treatments that prolong survival (National Audit Office, 2015).

In metastatic colorectal cancer, the focus of this submission, the tumour has spread beyond the confines of the lymph nodes near the colon to other parts of the body. The tumours which have spread beyond the colorectal region are known as metastases. The cancer is then defined as metastatic and is described as stage IV or Duke's D metastatic colorectal cancer.

Standard treatment for patients with metastatic colorectal cancer in the UK has traditionally been combination chemotherapy, predominantly 5-fluorouracil with irinotecan (FOLFIRI) or oxaliplatin-based chemotherapy (FOLFOX) which gives patients a median overall survival of approximately 20 months (Bokemeyer, 2014, Ciardiello, Douillard et al., 2013, Saltz et al., 2008).

Pathological studies which found a correlation between epidermal growth factor receptor (EGFR) reactivity in colorectal cancer and the reduced survival of patients (Goldstein 2001) led to the development of EGFR inhibitors, including cetuximab.

Activation of the EGFR pathway in tumour cells leads to cell proliferation, cell migration and cell survival. The KRAS and NRAS genes, collectively referred to as RAS, are an important part of the EGFR signalling pathway and lie downstream of the EGFR receptor.

Cetuximab (Erbitux) is a personalised medicine which works by targeting and inhibiting the EGFR. Cetuximab acts as an inhibitor at the start of the EGFR signalling pathway. Mutations in the RAS genes lead to the pathway being "permanently activated", meaning that EGFR inhibition at the start of the pathway has no effect on an EGFR inhibitor's ability to block the pathway and prevent tumour cell proliferation, migration and cell survival. RAS mutation status is therefore used as a biomarker to identify patients that may benefit from treatment with cetuximab.

It is important to consider that when many of the studies in this submission were initiated, the impact of K*RAS* and N*RAS* mutations on the EGFR signalling pathway had not yet been identified.

When scientific understanding of the impact of KRAS and NRAS tumour mutations on the effectiveness of EGFR inhibitors developed, the pivotal studies were re-evaluated and the licensed population for cetuximab was updated accordingly. Cetuximab is indicated for the treatment of patients with epidermal growth factor receptor (EGFR) – expressing, RAS wild-type metastatic colorectal cancer (Electronic medicines compendium).

The key method of identifying those patients who are eligible for treatment with EGFR inhibitor therapies is by using a validated biomarker test. The RAS biomarker test identifies patients whose tumours have the KRAS or NRAS non-mutated (wild-type) oncogene or KRAS/NRAS mutated (exon 2,3 or 4) oncogene. Only those whose tumours have the wild-type oncogene are eligible for EGFR inhibitor treatment e.g. cetuximab. This stratification offers the potential to use NHS resources effectively by identifying patients who are more likely to respond to cetuximab treatment whilst ensuring that those patients with RAS tumour mutations are not inappropriately treated.

In the UK, Merck Serono provided funding for biomarker testing for patients with mCRC between mid-2008 until mid-2014 when funding transitioned back to NHS England. This investment established RAS testing in clinical practice across the UK. Patients newly diagnosed with mCRC should have their tumours routinely RAS tested with a result available in time to inform first-line treatment decision.

Cetuximab is a monoclonal antibody which has shown improvements in response rates (RR), improved progression free survival (PFS) and overall survival (OS) in patients with metastatic colorectal cancer.

The population considered in this submission is the treatment of patients with unresectable metastatic colorectal cancer who have RAS wild-type tumours that are receiving therapy for the first time for their metastatic disease (first-line). There are two potential aims of treatment:

- Prolonging survival through combination therapy with cetuximab and FOLFIRI or FOLFOX;
- Treatment with cetuximab combined with FOLFIRI or FOLFOX may render some metastases, confined to the liver, which were initially unresectable to become resectable after treatment (shrinkage) and these patients may subsequently undergo surgery with the intention of a curative outcome. (This is the population currently recommended for re-imbursement by NICE under TA 176).

At present, it is estimated that there are over 12,000 patients with mCRC in the UK. Approximately 5,400 patients with mCRC have RAS wild-type tumour status in the UK. Not all of these patients will be eligible for cetuximab treatment due to poor performance status and thus unable to tolerate combination chemotherapy. The remaining population, eligible for cetuximab, comprises relatively fitter patients and is small in number which enables cetuximab to be evaluated under the end of life criteria, as defined by NICE.

Clinical Evidence

The key data for cetuximab is comprised of four studies, CRYSTAL, OPUS, FIRE-3 and CALGB-80405 plus the supportive CORE-II study.

Two of the key studies compare cetuximab plus chemotherapy versus chemotherapy alone (CRYSTAL and OPUS). The second two studies compare cetuximab plus chemotherapy to bevacizumab plus chemotherapy (FIRE-3 and CALGB-80405). Both cetuximab and bevacizumab are biological therapies. Bevacizumab is also a monoclonal antibody although it has a different mode of action to cetuximab in that it is a vascular endothelial growth factor (VEGF) inhibitor and inhibits angiogenesis (the formation of new blood vessels).

In the phase III studies CRYSTAL, CALGB-80405 and FIRE-3 the median overall survival (mOS) for cetuximab plus chemotherapy (FOLFOX or FOLFIRI) was 28.4, 32.0 and 33.1 months respectively. The median overall survival for cetuximab/FOLFOX in the phase II CORE-II and OPUS studies was 28.5 and 19.8 months respectively.

Median progression free survival (PFS) ranged from 10.3 months in the CALGB-80405 study to 12.0 months in the OPUS study.

Furthermore, in patients with metastatic disease confined to the liver who have initially unresectable tumours, the improvement in response to chemotherapy with the addition of cetuximab may permit resection of liver metastases. This potentially curative setting for cetuximab is currently recommended by NICE in TA176 (NICE, 2009b).

In an analysis of the CRYSTAL study the overall survival benefit is maintained regardless of whether patients have metastases which are confined to the liver, liver limited disease (LLD) or are more widespread, with a HR for LLD of 0.647 (95% CI 0.380-1.102) and for non-LLD of 0.707 (95% CI 0.539-0.927).

In the group of patients with non-liver limited disease the median overall survival was 27.1 months for the cetuximab plus FOLFIRI group compared with 17.4 months with the FOLFIRI alone group.

As shown in the studies outlined, the addition of cetuximab to chemotherapy in the first-line setting significantly increased overall survival to a median of over 24 months. This meets the criteria set out by NICE for an end of life medicine. Cetuximab has also been accepted to meet the criteria for an end of life medicine by the Scottish Medicines Consortium in its recent appraisal (SMC, 2014).

The side effect profile for cetuximab is well established and listed in the Summary of Product Characteristics (SmPC) and include skin reactions (acne-like rash) and infusion related reactions which are expected adverse events typical of EGFR inhibitors. The most common adverse events are predictable and generally manageable (electronic medicines compendium, emc).

Cetuximab is typically administered intravenously every two weeks in combination with chemotherapy in first line mCRC in England. This treatment schedule, whilst differing from that in the Summary of Product Characteristics (SmPC), has become treatment practice since February 2014 when the National Cancer Drugs Fund in England recommended this dosing regimen as common practice (NHS England website). This decision was based on published clinical evidence on the use of cetuximab every two weeks compared with weekly administration. It also means that cetuximab can be given on the same day as chemotherapy and results in more convenience for the patient and is more economical to the NHS.

[redacted]

Oncologists treating mCRC are familiar with cetuximab since it gained its licence over 10 years ago and its safety and efficacy profile is well known. To date over 600,000 patients have been treated with cetuximab either in interventional clinical trials or in the post-marketing setting (Data on file).

Economic Evidence

A de novo economic model was developed to assess the cost effectiveness of cetuximab in combination with chemotherapy compared to each of the comparators included in the scope of this assessment, where possible. This model was developed for this evidence submission due to the absence of published economic studies which conduct this analysis specifically in the RAS wild type mCRC patient population and the absence of a single clinical trial that contains all the relevant evidence for each comparator included in the scope. Moreover, the benefit of cetuximab treatment extends beyond the clinical trials period, specifically in relation to those patients who receive surgical resection with curative intent. Excluding these patients from the economic analysis significantly underestimates the benefit and cost effectiveness of cetuximab.

Based on head-to-head clinical trial data, the de novo cost effectiveness model results are listed in the tables below. The analysis presented below is based on a fortnightly dose to reflect clinical practice.

Technology (and comparators)	Total costs (£)	Total life years	Total QALYs	Increme-ntal costs	Increme-ntal life years	Increme-ntal QALYs	ICER vs baseline (A)	Increment-al analysis
Cetuximab + FOLFOX versus FOLFOX (based on OPUS study)								
FOLFOX	26,407.55	1.81	1.32					
Cetuximab + FOLFOX	41,301.81	2.22	1.64	14,894	0.41	0.32	36,048.26	46,503.39
Cetuximab + FOLFOX versus FOLFOX (based on CRYSTAL study)								
FOLFIRI	27,138.74	1.81	1.32					
Cetuximab + FOLFIRI	43,591.52	2.19	1.61	16,453	0.38	0.29	42,990.08	55,970.70
Cetuximab + FOLFOX versus bevacizumab + FOLFOX (based on FIRE3 study)								
Bevacizumab + FOLFIRI	34,604.87	2.03	1.49					
Cetuximab + FOLFIRI	37,978.34	2.16	1.60	3,374	0.14	0.10	24,191.18	32,725.95
ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years								

Furthermore, a subgroup analysis was carried out on the use of cetuximab plus chemotherapy in patients whose metastases were confined to the liver. Results from this subgroup analysis indicate that cetuximab remains cost effective. The ICER in this subgroup for the combination of cetuximab with FOLFOX is £28,230 per QALY compared to FOLFOX alone and £39,545 per QALY for cetuximab with FOLFIRI compared to FOLFIRI alone. This demonstrates that cetuximab + chemotherapy remains cost effective in this subgroup.

One Way Sensitivity analyses indicate that the model was sensitive, in all analyses, to the hazard ratio for real progression, the number of months on cetuximab treatment and the average body surface area. These are commonly amongst the parameters that economic models are usually sensitive to as they either have a direct impact on treatment cost or

patients survival estimation in the model. To a lesser extent, the rates of resection also had a significant impact on the model results but not to the extent of the parameters above as it is only relevant to the liver-limited metastatic disease subgroup.

Conclusions

Metastatic colorectal cancer is one of the most common causes of cancer death in the UK with standard current chemotherapy regimens providing an overall survival of less than 24 months. There is currently an unmet need in extending survival and reducing death rates in this population. In patients with RAS wild-type metastatic colorectal cancer, the use of cetuximab in combination with chemotherapy has demonstrated superior efficacy when compared with chemotherapy alone 28.4 months compared with 20.2 months respectively in the CRYSTAL study. In addition cetuximab in combination with chemotherapy has shown survival outcomes of greater than 30 months in two large phase III clinical trials (FIRE-3 and CALGB 80405).

The cost-effectiveness of cetuximab in this setting represents good value to the NHS, utilises NHS resources appropriately through stratification of patients who are most likely to respond to treatment (RAS wild-type) whilst ensuring that those patients with RAS tumour mutations are not inappropriately treated and offers patients a potentially life-extending treatment option.

1. DECISION PROBLEM

1.1. Description of technology under assessment

1.1.1. Approved name, marketing status and mechanism of action

Approved name: **Cetuximab**

Brand name: **Erbitux**

Metastatic Colorectal Cancer:

Colorectal cancer (CRC), also known as bowel cancer, is the fourth most common cancer in the UK and the second most common cause of cancer death (Cancer Research UK, 2014). More than 12,000 people annually are diagnosed with advanced or metastatic bowel cancer (mCRC) (Tappenden et al., 2007).

While survival rates in colorectal cancer have been improving globally, the UK continues to lag behind other major economies. The outcomes for adult cancer patients in England have generally been worse than in other high-income countries in Europe (National Audit Office, 2015). Survival rates in England remain about 10% lower than the European average, highlighting the opportunity for improved outcomes which may be achieved by increased access to treatments that prolong survival (National Audit Office, 2015).

Colorectal cancer can be diagnosed at various degrees of disease progression known as stages (TNM staging, Table 1) or by Duke's classification as detailed in the table below. In metastatic colorectal cancer, the focus of this submission, the tumour has spread beyond the confines of the locoregional lymph nodes to other parts of the body. The tumour is then defined as metastatic and is described as stage IV or Duke's D metastatic colorectal cancer. Cetuximab is used in patients with metastatic colorectal cancer.

Table 1: Colorectal cancer staging

Staging group	**TNM staging & sites involved**	**Modified Duke's System**
Stage 0	Carcinoma in situ (Tis, N0, M0)	
Stage I	No nodal involvement, no distant metastases Tumour invades submucosa (T1, N0, M0) Tumour invades muscularis propria (T2, N0, M0)	A
Stage II	No nodal involvement, no distant metastases Tumour invades muscularis propria into pericolorectal tissues (T3, N0, M0) Tumour penetrates surface of visceral peritoneum or directly invades or is adherent to other organs or structures (T4a/b, N0,M0)	B
Stage III	Nodal involvement, no distant metastases (Any T, Any N, M0)	C
Stage IV	Distant metastases (Any T, Any N, M1a/M1b) Stage IV is the population under consideration in this submission	D

M: Metastases (M0 – M1b); N: Number of nodes (N0 – N2b); T: Tumour size (T0 – T4b)

1.1.1.1. Treatments used in metastatic colorectal cancer

Standard treatment for metastatic colorectal cancer in the UK has traditionally consisted of the chemotherapy regimens of 5-fluorouracil/folinic acid (FA) in combination with oxaliplatin or irinotecan, commonly referred to as FOLFOX (oxaliplatin-based) or FOLFIRI (irinotecan-based). FOLFOX or FOLFIRI are infusional regimens. These regimens are referred to as cytotoxics and target growing and dividing cells, causing cell death. Median overall survival rates for FOLFOX and FOLFIRI regimens are typically 18-21 months (Bokemeyer, 2014, Ciardiello, 2014, Douillard et al., 2013, Saltz et al., 2008).

The oral agent capecitabine is sometimes used as an alternative to 5-fluorouracil/folinic acid, in this case the regimen is referred to as CAPOX or XELOX (oxaliplatin based). In a phase III trial by Cassidy et al (Cassidy et al., 2008) CAPOX was shown to be non-inferior to FOLFOX as a first-line treatment for mCRC. Cassidy et al. found that "the median overall survival was 19.8 months with CAPOX compared with 19.6 months with FOLFOX (HR, 0.99; 97.5% CI, 0.88 to 1.12)" and concluded that CAPOX is non-inferior to FOLFOX as a first-line treatment for mCRC and may be considered as a routine treatment option for appropriate patients. Based on these results for the purposes of this submission FOLFOX and CAPOX are considered to have equivalent efficacy.

In recent years there has been the introduction of biological therapies in mCRC, which are monoclonal antibodies that target specific cellular pathways that are active in cancer cells. Cetuximab is one such monoclonal antibody which targets the epidermal growth factor receptor (EGFR). In the first line treatment of metastatic colorectal cancer, the biological therapies are added to standard chemotherapy regimens, in the case of cetuximab it is usually administered in combination with FOLFOX or FOLFIRI.

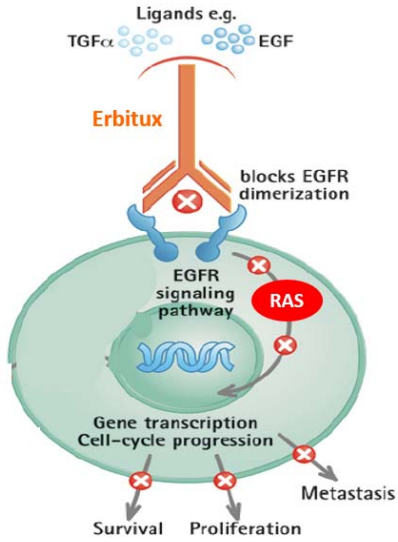
Other monoclonal antibodies used for treatment of first line mCRC include panitumumab which is also an EGFR inhibitor and bevacizumab which is a vascular endothelial growth factor (VEGF) inhibitor that blocks angiogenesis (the formation of new blood vessels).

1.1.1.2. Evolution of Cetuximab licence due to scientific understanding of role of biomarkers

Cetuximab is a monoclonal antibody that is specifically directed against the epidermal growth factor receptor (EGFR). Cetuximab binds to the EGFR with an affinity that is approximately 5- to 10-fold higher than that of endogenous ligands causing receptor inhibition thus blocking the EGFR signalling pathway.

Activation of the EGFR pathway in tumours leads to cell proliferation, cell migration and angiogenesis. The RAS oncogenes (KRAS and NRAS) are located downstream of the EGF receptor in the signalling pathway.

Figure 1: Illustration of cetuximab (Erbitux) mechanism of action



In certain tumours there are mutations in the KRAS and NRAS oncogenes that lead to signalling being “permanently activated”. Consequently blocking the receptor at the start of the pathway prior to the mutated RAS oncogene does not prevent tumour cell proliferation, cell migration and angiogenesis. Therefore cetuximab will not be effective in patients with RAS mutated tumours. The key RAS mutations are in exons 2, 3 or 4 of the KRAS and NRAS genes.

RAS is one of the most frequently activated family of oncogenes in human cancers and is mutated in approximately 55% of patients with mCRC tumours, therefore up to approx. half of patients with mCRC patients may have the opportunity to benefit from cetuximab. Conversely, cetuximab should not be used in the treatment of patients with colorectal cancer whose tumours have RAS mutations or for whom RAS tumour status is unknown.

It is important to consider that when many of the studies in this submission were initiated, the impact of K*RAS* and N*RAS* mutations on the EGFR signalling pathway had not yet been identified. Cetuximab was initially licenced in 2004 for a non-biomarker selected patient population.

When scientific understanding developed on the impact of KRAS tumour mutations on the effectiveness of EGFR inhibitors, the pivotal studies were re-evaluated. Key outcomes e.g. response rate, progression-free survival and overall survival were compared in populations by KRAS mutation or non-mutation (wild-type) tumour status. It was shown that patients with tumours harbouring KRAS mutations did not respond to EGFR inhibitors (cetuximab and panitumumab). This ultimately resulted in a change to the cetuximab licenced indication in 2008 to recommend the use of cetuximab in mCRC in patients with KRAS wild-type (non-mutated) tumours.

Identification of further mutations in the RAS oncogene family (KRAS & NRAS, exons 2, 3 & 4) led to further study re-evaluations and an additional licence indication update in Dec 2013. This is the current cetuximab licenced population i.e. the use of cetuximab in mCRC in patients with RAS (KRAS & NRAS) wild-type tumours.

An example of the re-evaluation of the clinical trials by KRAS/NRAS status can be shown in the pivotal CRYSTAL phase III study. The median overall survival results for the ITT, KRAS and RAS populations are detailed in Table 2 below:

Table 2: Median overall survival (CRYSTAL trial)

Median Overall Survival (months)	FOLFIRI	Cetuximab & FOLFIRI	HR (95% CI) p value
ITT population Non-biomarker selected patient population	18.6 (n=599)	19.9 (n=599)	0.878 (0.774-0.995) P=0.042
KRAS population KRAS exon 2 wt	20.0 (n=350)	23.5 (n=316)	0.796 (0.670-0.946) P=0.0093
RAS population KRAS exons 2, 3 & 4 wt NRAS exons 2, 3 & 4 wt	20.2 (n=189)	28.4 (n=178)	0.69 (0.54-0.88) P=0.0024

This patient stratification by biomarker status offers the potential to use NHS resources more effectively in identifying patients who are most likely to respond to cetuximab treatment whilst ensuring that those patients with the RAS tumour mutations are not inappropriately treated.

1.1.1.3. Tumour response rates, tumour resection and depth of tumour response

Typical measures used to determine response to treatment in patients undergoing treatment for cancer include response rates, progression free survival (PFS) and overall survival (OS). Depth of tumour response is utilised to illustrate why in certain situations there may be a difference in overall survival results but no difference seen in PFS. These are defined below.

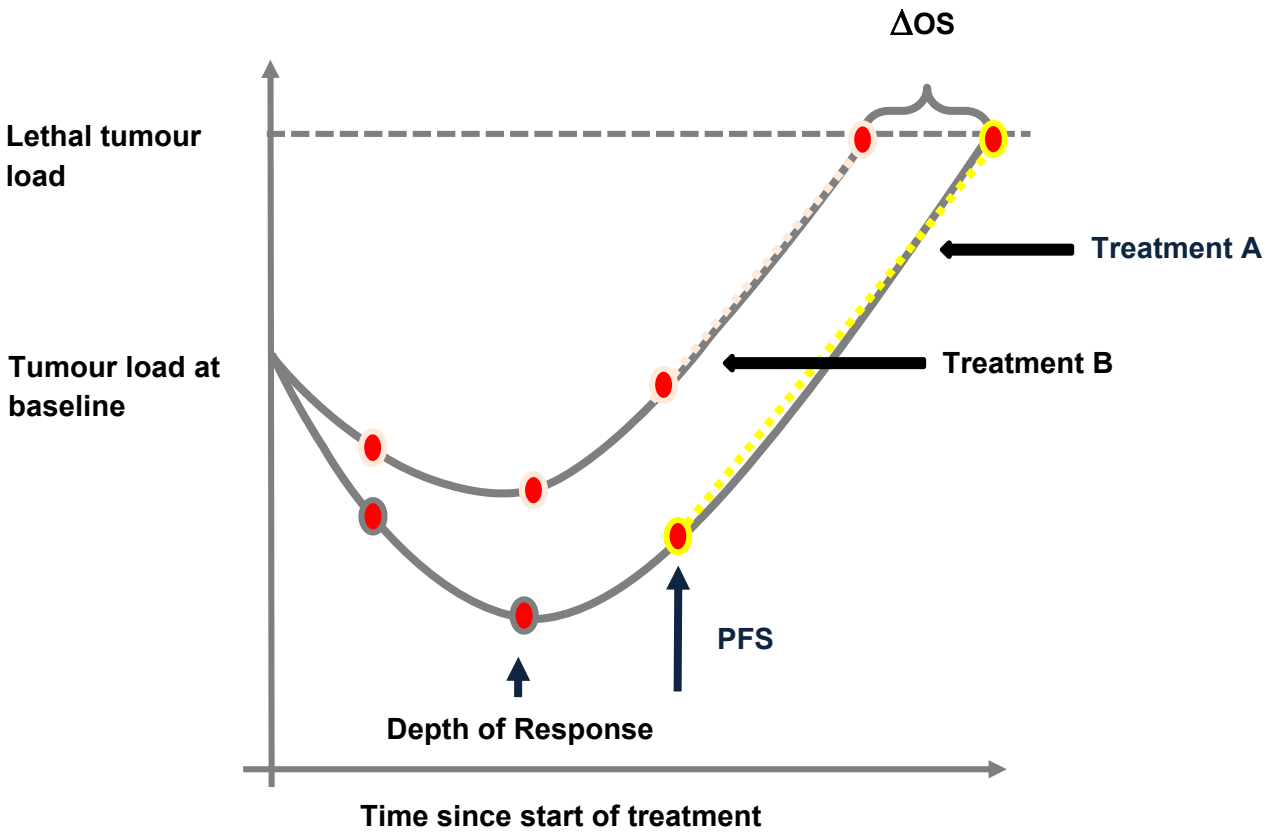
Tumour response rates are measured using the Response Evaluation Criteria In Solid Tumours (RECIST criteria) that define when tumours in cancer patients improve ("respond"), stay the same ("stabilise"), or worsen ("progress") during treatment.

Progression-free survival (PFS) is defined as the time elapsed between treatment initiation and tumour progression or death from any cause, with censoring of patients who are lost to follow-up.

Overall survival (OS) is defined as time from randomisation to death from any cause.

“Depth of response” is defined as the percentage of maximal tumour shrinkage observed at the lowest point of tumour volume compared with baseline, where a greater reduction in tumour volume may lead to longer overall survival even though the time at which patients tumours start to grow (progression) may be the same, as illustrated in Figure 2.

Figure 2: Illustration of depth of response



1.1.1.4. Resection after treatment with cetuximab plus chemotherapy

With advances in surgical technique, it is now possible in some patients to achieve complete resection of metastatic disease, this is referred to as R0 resection. Some patients present with metastatic colorectal cancer with unresectable metastases that are only present in the liver. In these patients there is the possibility to shrink the tumour using cetuximab with chemotherapy in order to make the tumour resectable and allow for potential cure in these patients.

1.1.1.5. Current reimbursement for cetuximab in first line treatment of mCRC in England:

The National Cancer Drugs Fund currently re-imburses cetuximab in combination with FOLFIRI or FOLFOX as a 1st line treatment option for patients with RAS wild-type mCRC.

Treatment with cetuximab combined with FOLFIRI or FOLFOX may render some metastases, confined to the liver, which were initially unresectable to become resectable after treatment (shrinkage) and these patients may subsequently undergo surgery with the intention of a curative outcome. (This is the population currently recommended for re-imbursement by NICE under TA 176).

1.1.1.6. Current Indication (for metastatic colorectal cancer)

Cetuximab is indicated for the treatment of patients with epidermal growth factor receptor (EGFR) – expressing, RAS wild-type metastatic colorectal cancer

- In combination with irinotecan-based chemotherapy;
- In first-line in combination with FOLFOX.
- As a single agent in subjects who have failed oxaliplatin- and irinotecan-based therapy or who are intolerant to irinotecan (European Medicines Agency, 2014)

1.1.1.7. NICE End of Life Criteria

Treatment with standard chemotherapy give a median overall survival of approximately 20 months, which is less than the 24 months defined by NICE and therefore meets this NICE end of life criterion (NICE, 2009a).

1.1.1.8. Population under consideration in this NICE submission

This submission is relevant for all patients with unresectable RAS wild-type metastatic colorectal cancer receiving therapy for the first time for their metastatic disease (first-line). In addition, there is a small subgroup of patients within this population that have metastases which are confined to the liver that may benefit from tumour shrinkage with cetuximab that could allow them to undergo surgery with curative intent. This submission encompasses both of these patient populations.

1.1.2. Product use and HTA assessments

1.1.2.1. Product use in England

(Merck Serono, 2015).

Table 3: provides a summary of how cetuximab is used in England. The product is available in two vial sizes (100mg/20ml and 500mg/100ml) and must be administered under the supervision of a physician with experience in the use of antineoplastic medicinal products. In mCRC patients, cetuximab is administered alongside FOLFOX or irinotecan-containing chemotherapy, usually FOLFIRI.

According to the cetuximab summary of product characteristics, an initial cetuximab loading dose of 400mg/m^2 is given on day one, followed by weekly doses of 250mg/m^2 (European Medicines Agency, 2014) in combination with chemotherapy until disease progression. However, in clinical practice in England and according to the listing of the national Cancer Drugs Fund (NHS England, 2015), cetuximab is given from day 1 as fortnightly (every two weeks) doses of 500mg/m^2 until disease progression.

[redacted]

There are a number of studies where cetuximab has been used on an every two weeks basis. The randomised CECOG-CORE II phase II study evaluated cetuximab/FOLFOX administered weekly or every two weeks in 152 patients (Brodowicz et al., 2013). The authors conclude that cetuximab administered every two weeks has comparable activity and a comparable safety profile as weekly dosing in combination with FOLFOX. In addition, Hubbard and colleagues carried out a review of several studies assessing weekly vs. every two weeks cetuximab dosing and found that the results of dosing cetuximab every 2 weeks were comparable to those obtained from weekly dosing.

In addition, this means that cetuximab can be given on the same day as chemotherapy and results in potentially better quality of life and more convenience for the patient (Hubbard and Alberts, 2013, Brodowicz et al., 2013).

The fortnightly dosing schedule for cetuximab is currently the standard practice in England as well as several other European countries (Merck Serono, 2015).

Table 3: Summary of cetuximab use in England

Pharmaceutical formulation	**Solution for infusion. Colourless solution**
NHS Acquisition cost (excluding VAT)	[redacted]
Method of administration	Cetuximab must be administered under the supervision of a physician experienced in the use of antineoplastic medicinal products. Close monitoring is required during the infusion and for at least 1 hour after the end of the infusion. Availability of resuscitation equipment must be ensured.
Doses	Each mL of solution for infusion contains 5 mg cetuximab. Each vial of 20 mL contains 100 mg cetuximab. Each vial of 100 mL contains 500 mg cetuximab.
Dosing frequency	According the the SmPC (EMA, 2015), cetuximab is administered once a week. The initial dose is 400 mg cetuximab per m^2 body surface area. All subsequent weekly doses are 250 mg cetuximab per m^2 each. In clinical practice, cetuximab is currently routinely dosed at 500 mg/m^2 every two weeks throughout the UK and Europe. In addition the National Cancer Drugs Fund listing states that cetuximab should be given at this dosing schedule; The National Cancer drugs fund is currently the main route for funding for cetuximab treatment in England (NHS England, 2015).
Average length of a course of treatment	24 - 25 weeks depending on chemotherapy backbone and disease progression (Data on file)
Average cost of a course of treatment	[redacted] (based upon an average of 25 weeks of treatment, including cost of pre-medications, excluding cost of chemotherapy and using the NHS discounted price.
Anticipated average interval between courses of treatments	Cetuximab is typically given from day 1, every two weeks until disease progression.
Anticipated number of repeat courses of treatments	None
Dose adjustments	Dose interruption or reductions can be made in the case of grade 3 or higher skin reactions.

Ongoing and completed studies from which additional evidence is expected in the next 12 months include:

- Further overall survival analyses for FIRE-3 study
- Final overall survival in patients with RAS wild-type tumours from CALGB-80405 study
- RAS wild-type data from the COIN study for the cetuximab/FOLFOX and FOLFOX subsets.

1.1.2.2. Health technology assessment in the UK

Cetuximab has a positive recommendation by SMC (SMC, 2010, SMC, 2014) and is under review by AWMSG.

The Scottish medicines consortium has accepted cetuximab for use within NHS Scotland for use in patients with RAS wild-type metastatic colorectal cancer in combination with irinotecan or oxaliplatin-based chemotherapy who have not previously received chemotherapy for their metastatic disease (first-line treatment).

1.1.2.3. End of Life Criteria

The following case is presented to demonstrate that cetuximab meets all of the End of Life Criteria adopted by NICE (NICE, 2009a). The End of life criteria set out by NICE includes the following:

1. The treatment is indicated for patients with a short life expectancy, normally less than 24 months

Cetuximab meets this criterion as clinical evidence outlined in Section 2 demonstrates that patients with mCRC have a survival prognosis of less than 24 months despite treatment with standard treatments available in clinical practice. A panel of experts consulted on this topic confirmed that this survival outcome was also seen in clinical practice (Merck Serono, 2015).

2. There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment

Clinical evidence outlined in Section 2 clearly demonstrates that cetuximab plus chemotherapy treatment results in extension to life by more than 3 months, reaching 8.2 months when combined with FOLFIRI compared with chemotherapy alone in the CRYSTAL study, which highlights the substantial benefit of addition of cetuximab to current NHS treatment.

The mOS in the RAS wild-type group for the phase II OPUS study was 19.8 months, showing a 2 month OS benefit of cetuximab/FOLFOX compared to FOLFOX alone and an outlier compared to the other studies. In the KRAS analysis of the OPUS study cetuximab/FOLFOX showed a 4.3 month OS benefit over FOLFOX alone. But due to the OPUS study originally being a phase 2 trial and the low number of samples remaining for testing to determine RAS status, this benefit is lost in the RAS analysis. Further discussion of the benefits seen when combining cetuximab and FOLFOX are discussed in the clinical section which highlight that the data seen from the RAS analysis of the OPUS study are an outlier. Therefore, cetuximab meets this criterion.

3. The treatment is licensed or otherwise indicated, for small patient populations (up to 7000 patients)

At present, it is estimated that there are over 12,000 patients with mCRC in the UK. However, not all mCRC patients are eligible for cetuximab treatment until they are tested and confirmed as having a RAS wild type tumour status. It is estimated that approximeately half of patients with mCRC have RAS wild-type tumour status in the UK which equates to approximately 5,623 patients.

Of these patients, not all would be fit enough to tolerate first line combination treatment with a monoclonal antibody and a doublet chemotherapy such as cetuximab combined with FOLFOX or FOLFIRI. Therefore approximately 4,049 patients would be deemed to be eligible for cetuximab therefore meeting the small population number needed under the end of life criteria.

1.1.2.4. Service implications of cetuximab use

Treatment with cetuximab requires the use of RAS testing in order to determine the tumour RAS status, i.e. mutated or wild-type (non-mutated). RAS testing is currently standard practice for treatment centres in England. Cetuximab administration requires the use of a chemotherapy suite and is typically given on the same day as infusional chemotherapy. Medications are given to control skin rash and infusion-related reactions (as specified in the SmPC). These medications are inexpensive antihistamines, corticosteroids, hydrocortisone cream and antibiotics. The management of these side-effects are unlikely to give rise to implications on service provision.

1.1.2.5. Additional tests or investigations needed for selection

Evidence of wild-type RAS (KRAS and NRAS) status is required before initiating treatment with Cetuximab. Mutation status should be determined by an experienced laboratory using validated test methods for detection of KRAS and NRAS (exons 2, 3, and 4). Routine testing is carried out for KRAS and NRAS mutation status. EGFR testing is no longer carried out as routine practice in England (Merck Serono, 2015). This is due to the understanding that EGFR over-expression is found in nearly all colorectal tumours and therefore the test for EGFR expression is unwarranted (Chung et al., 2005).

1.2. Statement of the decision problem

The scope of the submission is presented in

Table 4. This submission focuses on cetuximab plus FOLFOX or FOLFIRI for unresectable RAS wt metastatic colorectal cancer in comparison to combination chemotherapy (FOLFOX, FOLFIRI, CAPOX etc.) or the biologic agent bevacizumab in combination with chemotherapy. This includes a small population of patients with metastases confined to the liver who after treatment with cetuximab plus chemotherapy may subsequently be eligible for curative resection.

Tegafur/uracil is not included in this submission as the manufacturer, Merck Serono, withdrew this product from the market in the UK in 2013 and no other equivalent preparations are available in the UK. Capecitabine monotherapy is not considered in this submission after expert advice indicated that capecitabine monotherapy is typically used in elderly patients with poor performance status (PS) as these patients would not generally be fit to receive biological agents in combination with chemotherapy (Merck Serono, 2015)

Table 4: Scope of submission

Criteria	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	People with previously untreated, RAS wild-type metastatic colorectal cancer	• Patients with previously untreated, unresectable RAS wild-type metastatic colorectal cancer • This includes a small population of patients with metastases confined to the liver who after treatment with cetuximab plus chemotherapy may subsequently be eligible for curative resection.	No differences in scope
Intervention	Cetuximab, in combination with FOLFOX or irinotecan-based chemotherapy Panitumumab, in combination with FOLFOX	Cetuximab, in combination with FOLFOX or irinotecan-based chemotherapy	No differences in scope
Comparator(s)	FOLFOX XELOX FOLFIRI Capecitabine Tegafur/uracil, folinic acid and fluorouracil Bevacizumab, in combination with oxaliplatin or irinotecan-based chemotherapy	FOLFOX XELOX/CAPOX FOLFIRI Bevacizumab, in combination with oxaliplatin or irinotecan-based chemotherapy	-This submission does not consider Tegafur/uracil as the manufacturer, Merck Serono, has withdrawn the UK product licence and no longer markets it in the UK. No other equivalent preparations are available. -Capecitabine monotherapy is not considered in this appraisal for reasons previously stated[1]
Outcomes	Overall survival Progression-free survival Response rate Rate of resection of metastases Adverse effects of treatment Health-related quality of life	Overall survival Progression-free survival Response rate Rate of resection of metastases Adverse effects of treatment Health-related quality of life	No differences from scope
Economic analysis	NICE reference case Cancer Drug Fund Price	NICE reference case Cancer Drug Fund Price	No differences from scope
Subgroups to be considered	If evidence allows, consideration may be given to subgroups based on the location of metastases (inside and/or outside the liver)	Subgroup analyses were presented for Patients with unresectable metastatic colorectal cancer whose metastases are confined to the liver and those whose metastasis is not confined to the liver.	No differences from scope

[1] Expert opinion was that capecitabine monotherapy is typically used in elderly patients with poor performance status and is therefore not considered as a comparator in this submission as these patients would not generally be fit to receive biologic therapy with combination chemotherapy.

2. CLINICAL EVIDENCE

2.1. Overview

The clinical evidence presented in this dossier was derived from head-to-head randomised trials. The clinical effectiveness section of this submission presents evidence supporting the use of cetuximab in combination with FOLFIRI based on data from the randomised phase III trials CRYSTAL, FIRE-3 and CALGB-80405, and cetuximab in combination with FOLFOX based on data from the randomised phase II trial OPUS and phase III CALGB-80405 study. CRYSTAL and OPUS were manufacturer-led studies, while FIRE-3 and CALGB-80405 are collaborative study group-led trials.

2.1.1. Systematic Literature Review

A systematic literature review was conducted to identify the relevant efficacy and safety evidence for the interventions of interest in first-line treatment of patients with RAS wild-type mCRC. A single clinical search strategy was performed. The Centre for reviews and dissemination (Centre for Reviews and Dissemination, 2009) recommended electronic databases were searched with no restrictions on time or language, as well as conference proceedings for key clinical conferences from 2011 to 2015 with the assumption that any key study findings prior to this time would now be fully published.

Study selection was performed by two independent researchers in two stages. The first stage involved screening all records by title and abstract against pre-determined eligibility criteria. These criteria were also used to screen the full texts identified from the abstract/title stage. For the records identified as relevant, data extraction was performed by one researcher and reviewed by another. Risk of bias assessment for clinical trials was based on the Cochrane Collaboration's tool for assessing risk of bias (Cochrane Collaboration, 2014). Full details of the study identification, selection process, quality assessment and results are reported in Appendix C.

The numbers of studies included and excluded at each stage of the study selection process are presented in Table 5. A total of 770 records were identified from databases and an additional 379 from congresses. After removal of duplicates and screening, 16 records pertaining to four clinical trials were included.

Seven studies in total were identified that included cetuximab). Four of these studies were considered for inclusion in the analysis (CRYSTAL, OPUS, FIRE-3, and CALGB-80405) as they pertain to the appropriate inclusion criteria and have relevant comparators. The additional 3 studies (New EPOC, COIN and CECOG) were excluded and this is explained below. The methodology of the randomised trials included are summarised in Appendix A (Appendix A, Table 1).

RAS wt data from two panitumumab studies (PRIME and PEAK) was identified and solely utilised in the network meta-analysis to provide robustness to the FOLFOX arm of the network.

While the systematic literature review included CAPOX in the inclusion criteria, the feasibility analysis showed that there was no RAS wild-type data for CAPOX therefore it was not included in the clinical effectiveness section. Previous studies have shown CAPOX and FOLFOX to have similar outcomes (Cassidy et al., 2008). We have assumed that CAPOX clinical data inputs into the economic model model are the same as FOLFOX based on this evidence and the only difference in this scenario analysis was the different cost for CAPOX compared to FOLFOX.

Table 5: Clinical trial (RCT and non-RCT) inclusion and exclusion criteria

Criteria	Review Stage	Inclusion	Exclusion
Population	Abstract (Conference Slides/ Posters)	Adult patients with KRAS wild-type mCRC receiving first-line therapy for their metastatic disease. Adult patients with RAS wild-type mCRC receiving first-line therapy for their metastatic disease.	Any patient not meeting the criteria for inclusion.
	Full-text	Adult patients with RAS wild-type mCRC receiving first-line therapy for their metastatic disease. Studies targeting patients with first-line or ≥ 2nd line therapy can be included if subgroup results of 1st line patients are reported.	Publications only reporting patients with KRAS wild-type mCRC receiving first-line therapy for metastatic disease.
Intervention/ Comparator	Abstract/full text	Cetuximab in combination with FOLFOX Cetuximab in combination with irinotecan-based chemotherapy Panitumumab in combination with FOLFOX Bevacizumab in combination with a fluoropyrimidine-based chemotherapy FOLFOX FOLFIRI FOLFOXIRI FOLFIRINOX Capecitabine Capecitabine in combination with oxaliplatin- or irinotecan-based chemotherapy CAPOX CAPIRI 5-FU	Any other intervention
Outcomes		Reported Hazard Ratio (HR) and/or Kaplan Meier (KM) curves for OS Reported HR and/or KM curves for PFS Overall Response Duration of response Disease control rate Resection rate of metastases Health related quality of life (HRQoL) Safety data	Studies not reporting any of the outcomes of interest

Study design	Abstract / full text	Randomised trials Retrospective analyses of randomised trails Non-randomised clinical trials Conference proceedings from 2011 onwards Ongoing trials	Cost-effectiveness analyses Non-randomised studies Reviews or meta-analyses Methodology studies or protocols Dose-finding studies and other phase 1 studies Letters, editorials, conference summaries Preclinical studies Conference proceedings < 2011 will be excluded

Table 6: Trials identified by the systematic literature review

Trial no. (acronym)	Intervention	Comparator	Primary study ref.	Additional study references
CRYSTAL	Cetuximab + FOLFIRI	FOLFIRI	Van Cutsem 2009 (Van Cutsem et al., 2009)	Van Cutsem 2011 (Van Cutsem et al., 2011), Ciardiello, 2014 (Ciardiello et al., 2014), Van Cutsem 2015 (Van Cutsem et al., 2015), Kohne, 2014 (Kohne, 2014)
OPUS	Cetuximab + FOLFOX	FOLFOX	Bokemeyer 2009 (Bokemeyer et al., 2009)	Tejpar 2014 (Tejpar et al., 2014)
FIRE-3	Cetuximab + FOLFIRI	Bevacizumab + FOLFIRI	Heinemann 2013 (Heinemann et al., 2013)	Stintzing 2014 (Stintzing et al., 2014a) Heinemann 2014 (Heinemann et al., 2014)
CALGB-80405	Cetuximab with FOLFIRI or FOLFOX	Bevacizumab + FOLFIRI or FOLFOX	Lenz 2014 (Lenz et al., 2014)	
COIN	Cetuximab + CAPOX or FOLFOX	CAPOX or FOLFOX alone	Adams 2008 (Adams et al., 2008)	Maughan 2011, Lancet
New EPOC	Cetuximab + FOLFOX or CAPOX or FOLFIRI	FOLFOX or CAPOX or FOLFIRI alone	Primrose 2013 (Primrose et al., 2013)	Primrose 2014 (Primrose et al., 2014)
CECOG/ CORE II	Cetuximab + FOLFOX weekly	Cetuximab + FOLFOX bi-weekly	Brodowicz 2013 (Brodowicz et al., 2013)	
PEAK	Bevacizumab + FOLFOX	Panitumumab + FOLFOX	Schwartzberg, 2014 (Schwartzberg et al., 2014)	
PRIME	Panitumumab + FOLFOX	FOLFOX	Douillard, 2010 (Douillard et al., 2010)	Douillard, 2013 (Douillard et al., 2013)

2.1.1.1. Studies excluded from the economic analysis

COIN

The COIN study was an investigator-sponsored phase III, open label, randomised study which investigated the efficacy of cetuximab when added to FOLFOX or CAPOX versus FOLFOX or CAPOX alone in the KRAS wild-type patient population. There is currently no RAS wild-type data available for this study therefore it was not included in the economic analysis.

New EPOC

The New EPOC trial was an investigator-sponsored phase III, open label, randomised study which investigated the efficacy of cetuximab in combination with FOLFOX, CAPOX or FOLFIRI versus FOLFOX, CAPOX or FOLFIRI alone in the first-line treatment of colorectal cancer in patients with liver metastases which were resectable before treatment initiation (Ciardiello et al., 2013). This trial was excluded from this submission due to the patients having upfront resectable metastatic colorectal cancer who would typically be treated with surgery without biological therapy.

CECOG/CORE II

The CECOG/CORE-II study was an investigator-sponsored, randomised, phase II study comparing weekly to every two weeks dosing regimens of cetuximab plus FOLFOX-4 (Brodowicz, 2013). The original trial protocol was for all patients with mCRC, but was amended shortly after opening to include only patients with RAS wild-type tumours (KRAS plus NRAS).

The primary endpoint of the study was objective tumour response. Secondary endpoints were PFS, OS, and safety. In the RAS wild-type group, the overall response rate was 61.3%. Median OS was 28.5 months, and median PFS was 9.7 months. Analysis of differences between the arms has not been conducted. The trial does not have a relevant comparator and therefore was excluded from the economic analysis. This study is relevant with regards to every two weeks cetuximab dosing.

2.1.1.2. Participants

The randomised RAS wild-type patients for the clinical trials consist of male and female mCRC patients above 18 years of age. The patient inclusion and exclusion criteria for the relevant clinical trials are detailed in Appendix A (Appendix A, Table 2). The study inclusion criteria were consistent across all identified studies, which consisted of adult patients with confirmed mCRC and ECOG status of 2 or less. In CRYSTAL, FIRE-3 and OPUS, patients were excluded if they had previous exposure to anti-EGFR; this was not reported for PRIME, PEAK and CALGB-80405.

Baseline patient characteristics in each trial identified are provided in Appendix A (Appendix A, Table 3). For OPUS, PRIME, PEAK, FIRE-3 and CRYSTAL, the baseline characteristics were balanced between the two treatment arms with respect to age, gender, ethnicity, tumour site, disease duration, disease stage, and the number of metastatic sites.

The populations are comparable to the population of patients in the UK anticipated to be treated with cetuximab in combination with FOLFOX. This combination chemotherapy is only expected to be appropriate for fitter patients and inevitably this will result in the target population having a lower mean age and higher performance status than the average for the whole metastatic colorectal cancer population.

2.1.1.3. Outcomes

The primary and secondary outcomes in each of the clinical trials are presented in Table 7. When these studies were initiated, the significance in terms of response to treatment with respect to KRAS and NRAS (RAS) tumour mutations was yet to be identified and therefore the studies are not powered to differentiate for biomarker selected populations.

Table 7: Primary and secondary outcomes in the RCTs

Trial no. (acronym)	Primary outcome(s) and measures	Secondary outcome(s) and measures
CRYSTAL	Progression free survival (PFS)	• Overall survival (OS) • Overall Response Rate (ORR) • Safety
OPUS	ORR	• OS time • PFS time • Rate of curative metastatic surgery • Duration of response • Disease control rate • Safety
FIRE-3	ORR	• OS time • PFS time • Time to failure of 1st line treatment • Deepness of response (percent of tumor shrinkage compared to baseline) • Secondary resections of liver metastases with potentially curative intention • Safety
CALGB-C80405	OS	• PFS • Time to failure • Duration of tumour response
PEAK	PFS	• OS • Objective response • Resection rates • Safety
PRIME	PFS	• OS • Objective response • Safety
CALGB-80405	OS	• PFS • Time to treatment failure • Duration of tumour response

2.1.1.4. Subgroup analyses

Retrospective subgroup analyses were performed on CRYSTAL and OPUS data to determine the association between PFS, OS and ORR, and the KRAS mutation status of tumours. In the CRYSTAL study, retrospective subgroup analyses were further performed in patients with RAS-wild-type tumours grouped according to whether metastatic lesions were detectable at study entry only in the liver (liver limited disease) or they had additional metastases elsewhere (eg lung) with or without liver metastases (non-liver limited disease); for each of these patient subgroups, OS, PFS, ORR and R0 resection rates were analysed (Kohne, 2014).

There were no planned subgroup analyses in the RAS wild-type population as the data for this population was obtained by retrospective analyses.

2.1.2. Critical appraisal of relevant clinical trials

A critical appraisal was performed for each trial. For the critical appraisal of relevant RCTs, the NICE checklist for RCTs (adapted from Centre for Reviews and Dissemination, 2009 (Centre for Reviews and Dissemination, 2009) was used as it has been tested for internal consistency, reliability, and validity and is relatively easy to use.

For a summary of the responses applied to each of the critical appraisal citeria, please see Appendix A (Appendix A, Table 4) Many of the studies did not report concealment practice or if there were any unexpected drop outs. However, the studies were judged to be of high quality and all were retrospective analyses of previous clinical trial data.

2.1.3. Results of the relevant cetuximab randomised trials

Data from the four relevant studies with RAS wild-type data have been included for cetuximab. Efficacy results for the *RAS* wild-type analysis for the CRYSTAL, OPUS, FIRE-3 and CALGB-80405 studies are presented below (Table 8). The CRYSTAL and OPUS trials compared cetuximab in combination with chemotherapy (FOLFIRI or FOLFOX) with chemotherapy alone, whereas the FIRE3 and CALGB-80405 studies examined the efficacy of cetuximab/chemotherapy with another biological agent, bevacizumab when combined with chemotherapy.

Table 8: Efficacy results for the RAS wild-type analysis

	CRYSTAL		OPUS		FIRE-3		CALGB-80405					
	CET + FOLFIRI N=178	FOL-FIRI N=189	CET + FOL-FOX N=38	FOLF-OX N=49	CET + FOLFIRI N=199	BEV + FOLFIRI N=201	Overall population CET plus FOLFOX or FOLFIRI vs. BEV plus FOLFOX or FOLFIRI		Sub population by chemotherapy CALGB-80405			
							Cet +chemo N=270	Bev+ chemo N=256	CET+ FOLFIRI N=72	BEV+ FOLFIRI N=64	CET + FOLFOX N=198	BEV+ FOLFOX N=192
Response rate												
Odds Ratio (95% CI) P value	3.1145 (2.03-4.78) p <0.0001		3.33 (1.375-8.172) p=0.0084		1.33 (0.88-1.99) p= 0.18		p<0.01		Data not currently available			
ORR (%) (95% CI)	66.3 (58.8-73.2)	38.6 (31.7-46.0)	57.9 (40.8-73.7)	28.6 (16.6-43.3)	65.3 (58.3-51.6)	58.7 (51.6-65.6)	68.6	53.8				
Progression free Survival												
HR(95% CI) P value	0.56 (0.406 -0.761) P=0.0002		0.53 (0.27-1.04) P= 0.0615		0.97 (0.78-1.20) P=0.77		(0.9-1.3) P=0.31		1.1 (0.7-1.5) P=0.7		1.1 (0.9-1.4) P=0.3	
Median (months) (95% CI)	11.4 (10.0-14.6)	8.4 (7.4-9.4)	12 (5.8 – NE)	5.8 (4.7-7.9)	10.3 (9.5– 11.8)	10.2 (9.3 – 11.7)	11.4	11.3	12.7	11.9	11.3	11.0
Overall Survival												
HR (95% CI) P value	O.69 (0.54-0.88) p 0.0024		0.94 (0.56 – 1.56) p=0.80		0.70 (0.54-0.90) p 0.0059		0.9 (0.7-1.1) p=0.40		1.1 (0.7-1.6) P=0.7		0.86 (0.6-1.1) P=0.2	
Median OS (95% CI)	28.4 (24.7-31.6)	20.2 (17.0-24.5)	19.8 (16.6-25.4)	17.8 (13.8-23.9)	33.1 (24.5 – 39.4)	25.0 (23.0-28.1)	32.0 (27.6-38.5)	31.2 (26.9-34.3)	32.0 (25.6-42.9)	35.2 (28.3-41.3)	32.5 (26.1-40.4)	29.0 (24.0-32.8)

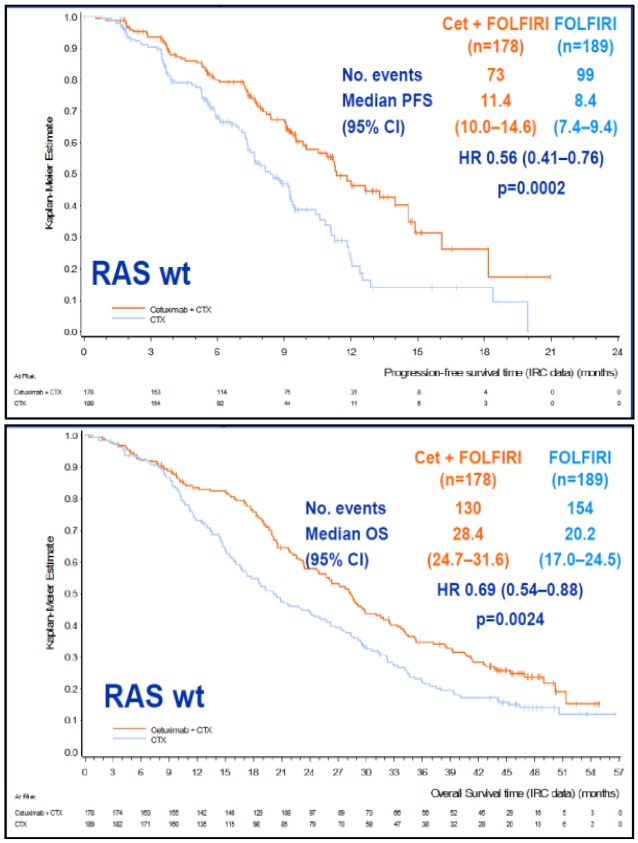
2.1.3.1. *Cetuximab plus Chemotherapy versus Chemotherapy alone trails – CRYSTAL and OPUS*

Cetuximab plus FOLFIRI vs. FOLFIRI Phase III RCT – CRYSTAL

CRYSTAL (Van Cutsem et al., 2009) , EMR 62 202-013, was an open-labelled, randomised, controlled, multicentre phase III study comparing 5-FU/FA plus irinotecan (FOLFIRI) plus cetuximab versus 5-FU/FA plus irinotecan (FOLFIRI) as a first-line therapy for EGFR-expressing mCRC. Of the 1198 patients who received therapy, 367 were identified as RAS wild-type patients in the post-hoc analysis. The representative RAS wild-type numbers in this study are much lower than the ITT, due to the limited number of tumour samples remaining that were available for pathology to test in order to determine their RAS status. The study met its primary endpoint, superior progression free survival, in the intent-to-treat (ITT population).

In the RAS wild-type subgroup, the study demonstrated superior PFS for cetuximab in combination with FOLFIRI compared to FOLFIRI alone (p=0.0002). The median time to progression was 11.4 months in the cetuximab plus FOLFIRI arm, and 8.4 months in the FOLFIRI alone arm, a 3 month benefit (Figure 3).

Figure 3: Progression Free & Overall Survival in RAS wild-type population in the CRYSTAL Study



In addition to a significant benefit in PFS there was an 8.2 month overall survival benefit when cetuximab was added to FOLFIRI compared to FOLFIRI alone in the RAS wild-type group, with cetuximab/ FOLFIRI demonstrating a median OS of 28.4 months (95% CI: 24.7-31.6) compared to 20.2 months (95% CI: 17-24.5) for the FOLFIRI alone arm (p=0.0024) (Figure 3).

Treatment with cetuximab/FOLFIRI increased response rates by over 27% with a statistically significant p value of 0.0001 compared to FOLFIRI alone (66.3 vs. 38.6%, OR 3.1145, p<0.0001).

There is a small group of patients with metastasis confined to the liver that after treatment with cetuximab/FOLFIRI may have their tumours downsized and then be eligible for surgery with curative intent. An analysis was carried out to compare survival in those patients with metastases confined to the liver (liver limited disease – LLD) compared to those with more widespread metastases. As can be seen in Table 9, the R0 resection rate, where all the tumour is removed, for patients with LLD was 16.3% with Cetuximab/FOLFIRI compared to 6.5% for FOLFIRI alone. For patients without LLD there is still also potential for R0 resection. These rates were 4.4% for cetuximab/FOLFIRI vs. 0.7% for FOLFIRI alone.

As can be seen in Figure 4, the overall survival benefit is maintained regardless of whether patients have metastasis which are confined to the liver or are more widespread, with a HR for LLD of 0.647 (95% CI 0.380-1.102) and for non-LLD of 0.707 (95% CI 0.539-0.927).

In the group of patients with non-liver limited disease the median overall survival was 27.1 months for the cetuximab plus FOLFIRI group compared with 17.4 months with the FOLFIRI alone group.

Figure 4 Overall survival in RAS wild-type patients grouped according to LLD or non-LLD

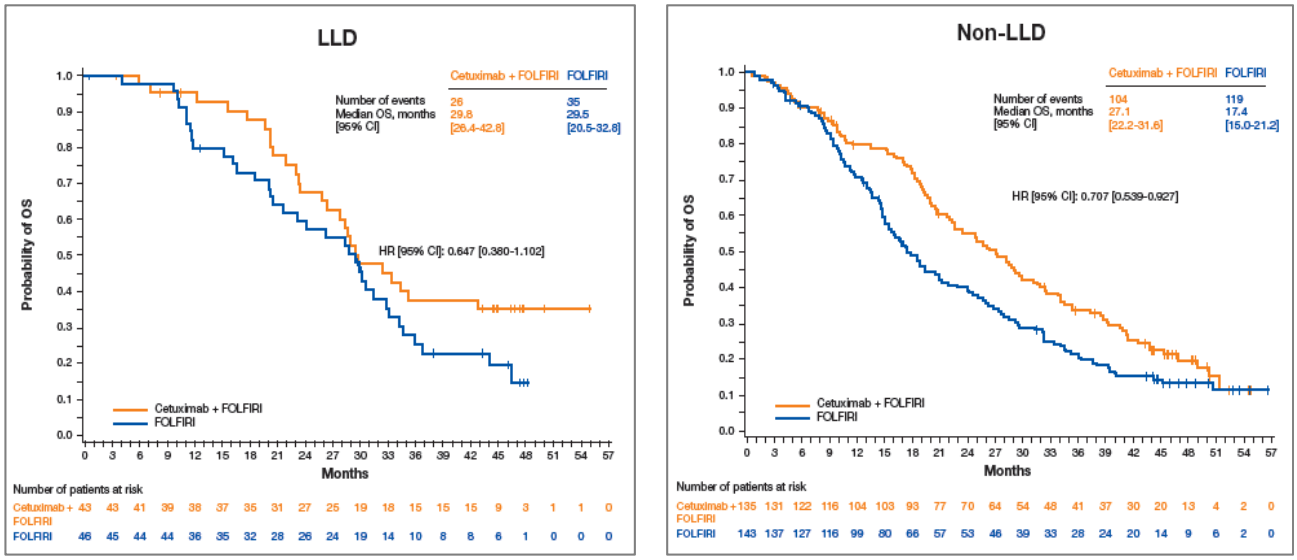


Table 9: R0 resection rates according to treatment arm in patients with RAS wild-type tumours, grouped by metastatic site

Subgroups (number of patients)	**Treatment (n value)**		**R0 Resection (Rate, %)**		
	FOLFIRI	**Cet + FOLFIRI**	**FOLFIRI**	**Cet + FOLFIRI**	**OR [95% CI}**
LDD (n=89)	46	43	6.5	16.3	2.68 [0.63-11.43]
Non-LDD (n=278)	143	135	0.7	4.4	5.94 [0.79-44.88]

Cetuximab plus FOLFOX vs. FOLFOX Phase II RCT – OPUS

OPUS (Bokemeyer et al., 2009) (EMR 62 202-047) was an open-labelled, randomised, controlled, multicentre phase II study comparing 5-FU/FA plus oxaliplatin (FOLFOX) plus cetuximab versus FOLFOX alone as a first-line treatment for EGFR-expressing metastatic colorectal cancer. The intention to treat population consisted of 169 patients in the cetuximab in combination with FOLFOX arm and 168 patients in the FOLFOX alone arm.

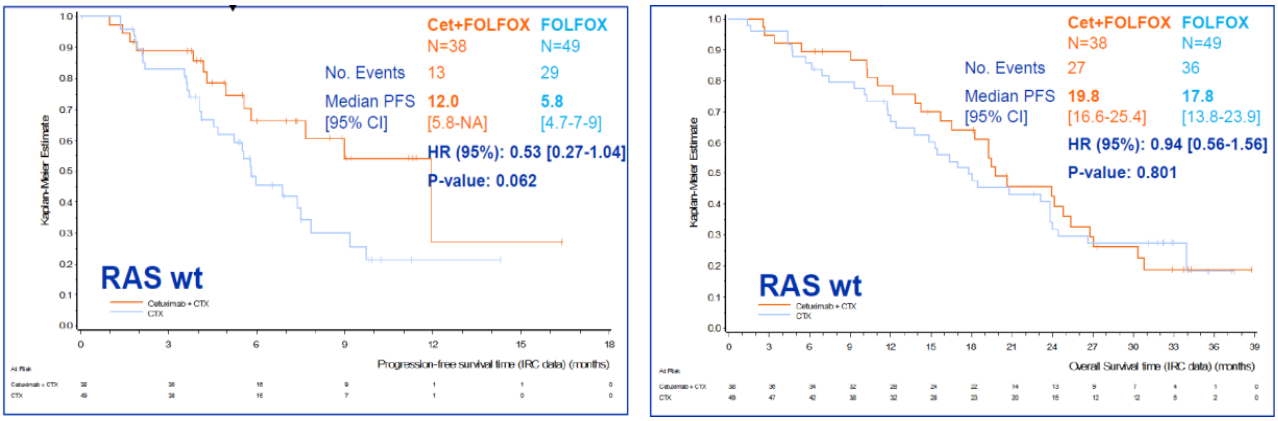
In contrast to CRYSTAL, OPUS was a phase II study and had much lower number of patients in the ITT group to begin with, which meant that for the post-hoc RAS analysis there were fewer samples available resulting in 38 RAS wild-type patients identified in the cetuximab/FOLFOX arm and 49 patients in the FOLFOX alone arm.

The response rates for the RAS wild-type patient population was significantly better in the cetuximab/FOLFOX arm versus FOLFOX alone (57.9 vs. 28.6%; p=0.0084). For median overall survival, cetuximab in combination with FOLFOX demonstrated an additional 2 months overall survival benefit when compared to FOLFOX alone (19.8 months versus 17.8 months, HR 0.94, p=0.8)

Figure 5). In addition to the benefit seen in overall response rates (ORR), there was a more than doubling of median PFS showing an increase of 6.2 months for patients treated with cetuximab/FOLFOX vs. FOLFOX alone (12.0 months vs. 5.8 months, HR 0.53, p=0.062)

Figure 5).

Figure 5: OPUS RAS wild-type Kaplan-Meier plot of progression free survival



2.1.3.2. *Cetuximab plus Chemotherapy versus Bevacizumab plus Chemotherapy trails – FIRE-3 and CALGB-80405*

Cetuximab plus FOLFIRI vs. bevacizumab plus FOLFIRI Phase III Clinical Trial – FIRE-3

The FIRE-3 trial (AIO CRC 0306) (Heinemann et al., 2013) is an investigator-sponsored phase III, open label, randomised study which investigated the efficacy of FOLFIRI in combination with cetuximab or bevacizumab in the first-line treatment of KRAS wild-type metastatic colorectal cancer. The primary endpoint of the study was overall response rate. There was no significant difference in the overall response rates between the two treatment arms (62% vs. 58%, p=0.18) and therefore the trial did not meet its primary endpoint for the KRAS wild-type population.

While response rates increased from 58.7% in the bevacizumab/FOLFIRI arm to 65.3% in the cetuximab/FOLFIRI arm in the RAS wild-type analysis, the difference was not statistically significant

(p=0.18). PFS was similar in both arms (10.2 vs. 10.3, bevacizumab/ FOLFIRI vs. cetuximab/FOLFIRI). The main difference seen between the two arms in the study was in mOS, 25.0 bevacizumab/FOLFIRI compared with 33.1 months for cetuximab/FOLFIRI, p=0.0059, a difference of 8.1 months and one of the highest increases in mOS seen in phase III studies with biological treatment.

Benefits seen in overall survival in the absence of a difference in PFS results may be due to the depth of response seen following treatment with cetuximab/FOLFIRI versus bevacizumab/FOLFIRI. A greater reduction in tumour load may lead to longer overall survival even though the time at which patients tumours start to grow (progression) may be the same. Please see Figure 2 for an illustration of depth of response.

The FIRE-3 study showed greater DpR in the cetuximab/FOLFIRI group when compared to the bevacizumab/FOLFIRI arm (Table 10). In the FIRE-3 study depth of response (DpR) was found to correlate significantly with OS and PFS (two-sided Bravais Pearson test) for the RAS wild-type patient population (Stintzing et al., 2014b).

Table 10: Evaluation of Depth of Response (DpR*)

	FOLFIRI + Cetuximab		FOLFIRI + Bevacizumab		p
Median DpR	%	SE	%	SE	
KRAS exon 2 wild-type N=493	-44.1	(±54.6%)	-32.9	(±44.3%)	0.0003
Final RAS wild-type n=330	-48.9	(±54.8%)	-32.3	(±42.3%)	<0.0001

*DpR: percentage of maximum tomour shrinkage observed at the nadir compared with baseline

The Kaplan-Meier curves for OS and PFS can be seen in Figure 6. These results are consistent with those found in the CRYSTAL study.

Figure 6: Overall Survival & PFS curves in RAS wild-type patients in the FIRE-3 Study

Overall Survival curves in RAS wild-type patients in the FIRE-3 Study

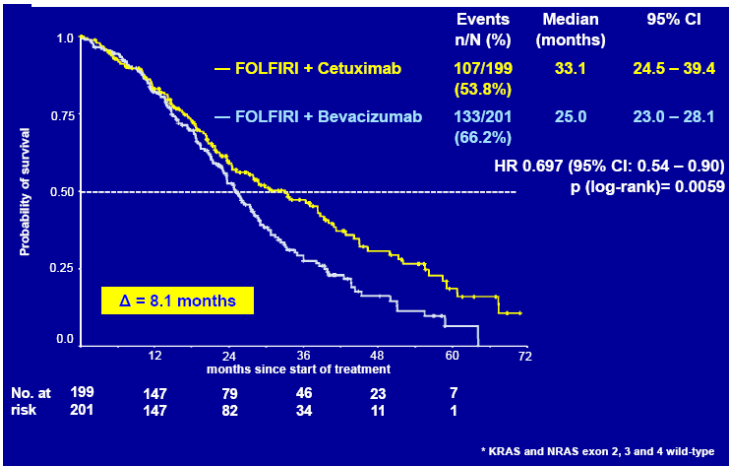
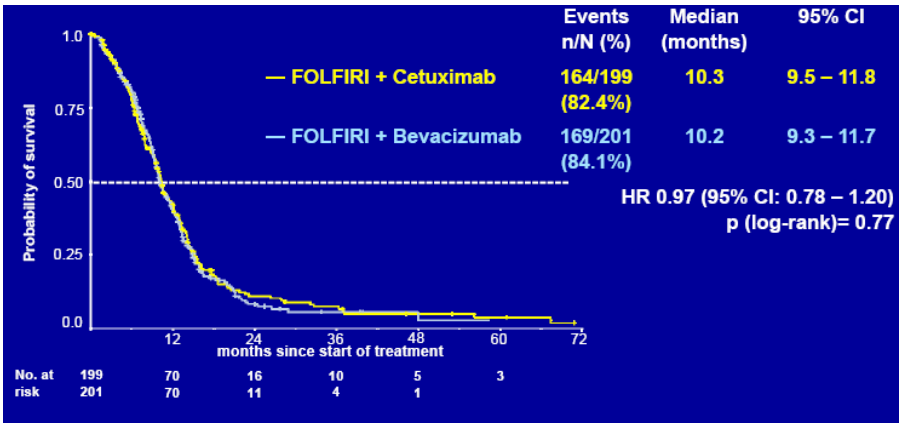


Figure 7: Progression-free Survival curves in RAS wild-type patients in the FIRE-3 Study



Cetuximab plus FOLFOX or FOLFIRI vs. bevacizumab plus FOLFOX or FOLFIRI CALGB-80405

CALGB-80405 (Lenz et al., 2014) is an investigator-sponsored, phase III, open label, randomized study which investigated the efficacy of chemotherapy (FOLFOX or FOLFIRI) in combination with cetuximab or bevacizumab. The trial was designed to investigate the difference in progression free survival and overall survival in KRAS wild-type metastatic colorectal cancer patients.

The study demonstrated a significant difference in response rate in favour of cetuximab/chemo (68.6 vs. 53.8%, p<0.01) vs bevacizumab/chemotherapy. The rates of PFS were similar between both arms (11.4 months for cetuximab/chemotherapy vs. 11.3 months for bevacizumab/chemotherapy, p=0.31). The median overall survival was high for both arms at 32.0 months for cetuximab/chemotherapy and 31.2 months for bevacizumab/chemotherapy (p=0.40). These median survivals are similar to the cetuximab arm in the FIRE3 study.

In the CALGB-80405 study, investigators were allowed to choose which chemo backbone (FOLFOX or FOLFIRI) they wished to use with about two thirds of patients being treated with FOLFOX, and a third being treated with FOLFIRI. Analysis was carried out of subpopulations by chemotherapy backbone and no statistically significant differences were found for PFS or OS between the treatment arms (Table 8) (Figure 8 and Figure 9).

Figure 8: Progression Free Survival for All RAS wild-type patients in CALGB-80405

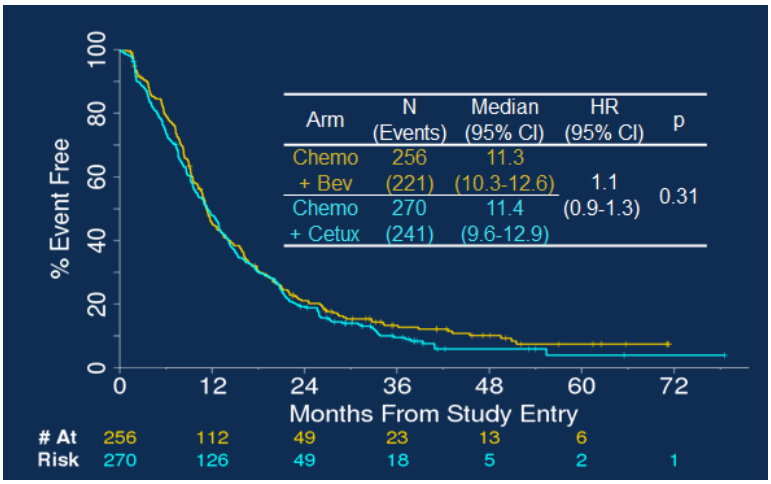
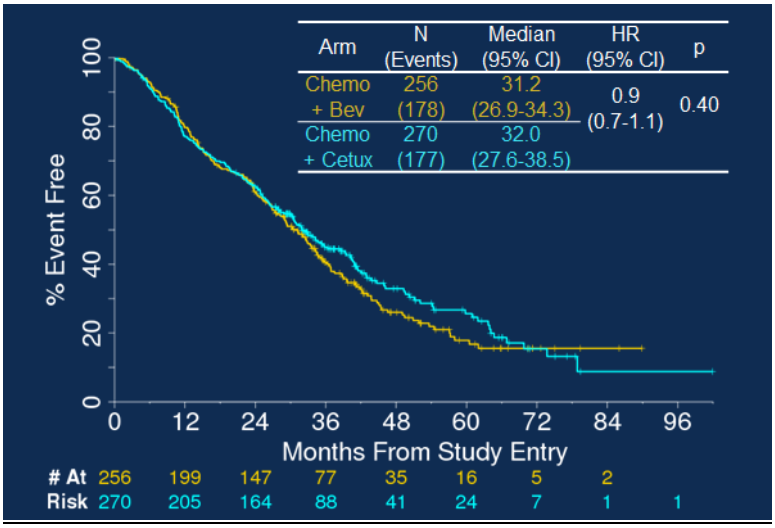


Figure 9: Overall Survival for All RAS wild-type patients in CALGB-80405



2.1.3.3. Health Related Quality of Life (HRQoL)

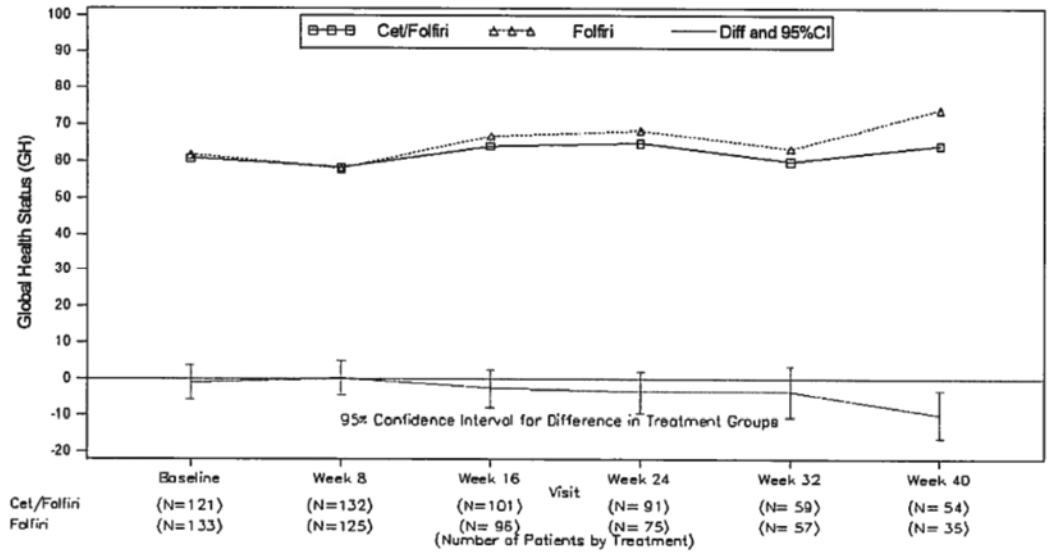
CRYSTAL study RAS wild-type QoL Study

A Quality of life analysis was performed for the RAS wild-type patient population from the CRYSTAL trial. The RAS wild-type subgroup appears to have similar patient characteristics as the KRAS wild-type subgroup (data on file). As can be seen in Figure 10, global health status scores between the FOLFIRI alone and cetuximab/FOLFIRI groups are comparable except for the 40 week timepoint. The LS mean score for Global Health Status at week 40 was 64.29 in the Cetuximab + FOLFIRI group (N=54) compared with 74.12 in the FOLFIRI alone group (N=35) suggesting that subjects in the FOLFIRI alone group have a better Global Health Status (p=0.0033). However this result should be viewed with caution are there are less patients in the FOLFIRI alone group at week 40.

With regard to the EORTC QLQ-C30 multi-item scales, a difference between treatment groups was observed for nausea/vomiting. From week 8, the LS mean score for nausea\vomiting is slightly higher in the FOLFIRI treatment group and at week 16 was 6.62 in the Cetuximab + FOLFIRI group (N=105) compared with 11.04 in the FOLFIRI alone group (N=98) suggesting that subjects in the Cetuximab + FOLFIRI group had less nausea\vomiting (P=0.0436); (data on file).

Overall the RAS wild-type QoL life data are reflective of the KRAS wild-type data and showed that there were no clinically meaningful differences between the two treatment arms.

Figure 10 Plot of the Least Squares Means Estimate of the EORTC QLQ-C30 Global Health Status\QoL Scores by Treatment Group, Evaluable for QLQ-C30 Population: RAS wild-type subgroup



In the CALGB 80405 study QOL was assessed using the EORTC QLQ-30 and the Dermatology-Specific Quality of Life (DSQL) Scale. 83% of patients completed a 3 month assessment. There were no differences in global health functioning (p=0.164) or other items/subscales of the EORTC at 3 months by treatment arm. However as expected, significant differences were found across arms in skin symptoms (p<.0001), limitations in social activities due to skin condition (p=0.008), and concerns about appearance (p<.0001), as measured by the DSQL in the cetuximab arm. The choice of chemotherapy (FOLFOX or FOLFIRI) had no bearing on these results. In summary, global QOL, as well as physical, role, social and emotional functioning, were not significantly different across treatment arms (Naughton et al., 2013).

2.1.4. Adverse Events

Adverse events overview

The adverse event profile was compared between the KRAS and RAS populations of the CRYSTAL and OPUS studies.

The cetuximab-treated patients exhibited side effects which are well established and listed in the Summary of Product characteristics for cetuximab e.g. skin reactions (mainly acne-like rash) and infusion-related reactions. The adverse events in the RAS and K*RAS* wild-type populations were comparable for both studies.

Grade 3 or 4 adverse event frequencies in the RAS wild-type populations were generally below 10%.

Neutropenia was observed slightly more frequently in the cetuximab plus FOLFIRI group vs. the FOLFIRI alone group in RAS wild-type populations. However, the frequency of febrile neutropenia was low and there was no increase in Grade 3 or 4 infectious complications with cetuximab plus FOLFIRI.

Safety summary: Overall, no new relevant safety findings were identified in the *RAS* wild-type compared with the corresponding *KRAS* populations.

Table 11: Summary of adverse events during the treatment phase (RAS wild-type and KRAS wild-type) in the CRYSTAL trial

	***RAS* wild-type**		**K*RAS*-wild-type**	
	Cetuximab + FOLFIRI	**FOLFIRI alone**	**Cetuximab + FOLFIRI**	**FOLFIRI alone**
	N=178	N=189	N=317	N=350
N	n(%)	n(%)	n(%)	n(%)
Any AE	178 (100)	187 (98.9)	316 (99.7)	347 (99.1)
Any AE Grade 3 + 4	144 (80.9)	110 (58.2)	257 (81.1)	211 (60.3)
Any SAE	69 (38.8)	62 (32.8)	136 (42.9)	111 (31.7)
Any Fatal AE	3 (1.7)	5 (2.6)	15 (4.7)	14 (4.0)
Any AE causing discontinuation of study treatment	46 (25.8)	23 (12.2)	94 (29.7)	44 (12.6)

Table 12: Special adverse events categories - any AE and Grade 3 and/or Grade 4 AE in the KRAS wild-type and RAS wild-type population in the CRYSTAL trial

	***RAS* wild-type**		**K*RAS*-wild-type**	
	Cetuximab + FOLFIRI	**FOLFIRI alone**	**Cetuximab + FOLFIRI**	**FOLFIRI alone**
	N=178	N=189	N=317	N=350
	n(%)	n(%)	n(%)	n(%)
Any Adverse Events				
Skin Reactions	162 (91.0)	33 (17.5)	274 (86.4)	54 (15.4)
Acne-like *Ras*h	157 (88.2)	30 (15.9)	263 (83.0)	46 (13.1)
Infusion related reactions	27 (15.2)	0	37 (11.7)	1 (0.3)
Cardiac Events	19 (10.7)	19 (10.1)	47 (14.8)	43 (12.3)
Mucositis	71 (39.9)	55 (29.1)	134 (42.3)	98 (28.0)
Any Grade 3 and/or Grade 4 Adverse Events				
Skin Reactions	39 (21.9)	2 (1.1)	67 (21.1)	1 (0.3)
Acne-like *Ras*h	32 (18.0)	1 (0.5)	52 (16.4)	0
Infusion related reactions	5 (2.8)	0	5 (1.6)	0
Cardiac Events	11 (6.2)	7 (3.7)	19 (6.0)	8 (2.3)
Mucositis	10 (5.6)	3 (1.6)	14 (4.4)	4 (1.1)

Table 13: Adverse events (Grade 3 and 4) known for cetuximab - comparison of frequencies in cetuximab plus FOLFIRI vs. FOLFIRI alone group in the RAS and KAS wild-type populations in the CRYSTAL trial

Number of Subjects with Grade 3 and 4 Adverse Events by Preferred Term	***RAS* wild-type**		**K*RAS*-wild-type**	
	Cetuximab + FOLFIRI	**FOLFIRI alone**	**Cetuximab + FOLFIRI**	**FOLFIRI alone**
	N=178	N=189	N=317	N=350
	n(%)	n(%)	n(%)	n(%)
Anorexia	6 (3.4)	2 (1.1)	11 (3.5)	6 (1.7)
Asthenia	5 (2.8)	4(2.1)	10 (3.2)	9 (2.6)
Conjunctivitis	0	0	1 (0.3)	0
Dehydration	4 (2.2)	7 (3.7)	13 (4.1)	10 (2.9)
Diarrhoea	26 (14.6)	18 (9.5)	52 (16.4)	35 (10.0)
Epistaxis	0	0	0	0
Fatigue	12 (6.7)	9 (4.8)	14 (4.4)	20 (5.7)
Headache	0	0	2 (0.6)	1 (0.3)
Hypertension	19 (10.7)	10 (5.3)		
Hypocalcaemia	1 (0.6)	0	3 (0.9)	0
Hypokalaemia	7 (3.9)	4 (2.1)	15 (4.7)	9 (2.6)
Hypomagnesaemia	6 (3.4)	0	11 (3.5)	0
Leukopenia	15 (8.4)	7 (3.7)	25 (7.9)	17 (4.9)
Nausea	4 (2.2)	5 (2.6)	10 (3.2)	8 (2.3)
Neutropenia	55 (30.9)	38 (20.1)	97 (30.6)	83 (23.7)
Neurotoxicity	6 (3.4)	6 (3.2)		
Palmar-plantar erythrodysaesthesia syndrome	6 (3.4)	0	13 (4.1)	1 (0.3)
Pulmonary embolism	8 (4.5)	8 (4.2)	14 (4.4)	12 (3.4)
Deep vein thrombosis	11 (6.2)	1 (0.5)	16 (5.0)	2 (0.6)
Vomiting	6 (3.4)	6 (3.2)	13 (4.1)	16 (4.6)
Weight decreased	3 (1.7)	2 (1.1)	3 (0.9)	4 (1.1)

Table 14: Summary of adverse events during the treatment phase in the RAS and KRAS wild-type populations in OPUS

	***RAS* wild-type**		**K*RAS*-wild type**	
	Cetuximab + FOLFIRI	**FOLFIRI alone**	**Cetuximab + FOLFIRI**	**FOLFIRI alone**
	N=38	N=49	N=82	N=97
	n(%)	n(%)	n(%)	n(%)
Any AE	38 (100)	49 (100)	82 (100)	95 (97.9)
Any AE Grade 3 + 4	30 (78.9)	31 (63.3)	67 (81.7)	62 (63.9)
Any SAE	15 (39.5)	8 (16.3)	29 (35.4)	19 (19.6)
Any Fatal AE	1 (2.6)	1 (2.0)	3 (3.7)	3 (3.1)
Any AE causing discontinuation of study treatment	18 (47.4)	16 (32.7)	35 (42.7)	27 (27.8)

Table 15: Special AE categories - Any AEs and Grade 3 and/or Grade 4 AEs in the RAS and KRAS wild-type populations in OPUS

	***RAS* wild-type**		**K*RAS*- wild-type**	
	Cetuximab + FOLFIRI	**FOLFIRI alone**	**Cetuximab + FOLFIRI**	**FOLFIRI alone**
	N=38	N=49	N=82	N=97
	n(%)	n(%)	n(%)	n(%)
Any Adverse Events				
Skin Reactions	33 (86.8)	4 (8.2)	72 (87.8)	7 (7.2)
Acne-like *rash*	31 (81.6)	3 (6.1)	69 (84.1)	6 (6.2)
Infusion related reactions	3 (7.9)	0	7 (8.5)	3 (3.1)
Cardiac Events	4 (10.5)	0	6 (7.3)	2 (2.1)
Mucositis	15 (39.5)	6 (12.2)	25 (30.5)	16 (16.5)
Neurotoxicity	22 (57.9)	25 (51.0)	44 (53.7)	55 (56.7)
Any Grade 3 and/or Grade 4 Adverse Events				
Skin Reactions	5 (13.2)	0	15 (18.3)	0
Acne-like *rash*	3 (7.9)	0	11 (13.4)	0
Infusion related reactions	0	0	1 (1.2)	2 (2.1)
Cardiac Events	2 (5.3)	0	3 (3.7)	0
Mucositis	1 (2.6)	1 (2.0)	2 (2.4)	2 (2.1)
Neurotoxicity	2 (5.3)	5 (10.2)	6 (7.3)	14 (14.4)

Table 16: Number of subjects with Grade 3 or 4 AEs in OPUS

Number of Subjects with Grade 3 and 4 Adverse Events by Preferred Term	***RAS* wild-type**		**K*RAS*- wild-type**	
	Cetuximab + FOLFIRI	**FOLFIRI alone**	**Cetuximab + FOLFIRI**	**FOLFIRI alone**
	N=38	N=49	N=82	N=97
	n(%)	n(%)	n(%)	n(%)
Anorexia	0	0	1 (1.2)	0
Asthenia	1 (2.6)	0	1 (1.2)	2 (2.1)
Conjunctivitis	1 (2.6)	0	2 (2.4)	0
Dehydration	0	0	1 (1.2)	0
Diarrhoea	1 (2.6)	2 (4.1)	7 (8.5)	5 (5.2)
Epistaxis	0	0	0	0
Fatigue	1 (2.6)	1 (2.0)	1 (1.2)	3 (3.1)
Headache	0	0	0	0
Hypocalcaemia	2 (5.3)	0	3 (3.7)	0
Hypokalaemia	2 (5.3)	0	3 (3.7)	0
Hypomagnesaemia	1 (2.6)	0	3 (3.7)	0
Leukopenia	1 (2.6)	3 (6.1)	6 (7.3)	5 (5.2)
Nausea	0	0	1 (1.2)	1 (1.0)
Neutropenia	12 (31.6)	14 (28.6)	29 (35.4)	31 (32.0)
Palmar-plantar erythrodysaesthesia syndrome	2 (5.3)	0	3 (3.7)	1 (1.0)
Peripheral sensory neuropathy	7 (18.4)	12 (24.5)		
Pulmonary embolism	3 (7.9)	0	4 (4.9)	1 (1.0)
Deep vein thrombosis	0	0	0	1 (1.0)
Vomiting	1 (2.6)	1 (2.0)	3 (3.7)	2 (2.1)
Weight decreased	0	0	0	1 (1.0)

Strengths of the evidence base

The evidence base from the four relevant studies presented above highlights the additional benefit seen when cetuximab is combined with chemotherapy compared to chemotherapy alone or combined with bevacizumab for:

- Response rates, median progression free survival and median overall survival.
- 4 well designed and conducted clinical studies providing robust results with additional supportive evidence in a total of 2813 patients in 916 study centres across the 4 studies.
- The network meta-analysis reflects these strong clinical results.
- The addition of cetuximab to chemotherapy also has proven benefit over standard chemotherapy of shrinking tumours in patients with initially unresectable metastases and enabling curative resection after treatment with cetuximab plus combination chemotherapy.

Limitations of the evidence base

Due to the retrospective nature of the RAS analysis, for some studies, there were a low number of samples available for analysis reducing the power of the studies to show statistical significance.

There was limited data available on safety for the CALGB-80405 study, resulting in many of the indirect comparison analyses having very wide confidence intervals and making interpretation from the indirect comparison difficult (full study publication is awaited).

2.1.5. Discussion of Efficacy and Safety Data

As can be seen from the studies presented, cetuximab combined with chemotherapy in patients with RAS wild-type mCRC shows consistent positive results:

- High tumour response rates ranging from 57.9% in the OPUS study to 68.6% in the CALGB-80405 study compared to 28.6% -38.6% for chemotherapy alone.
- Median PFS ranged from 10.3 months in the FIRE-3 study to 12.0 months in the OPUS study (in addition in the CALGB subgroup, cetuximab plus FOLFIRI, it is 12.7 months).
- Median overall survival results for the CRYSTAL, CALGB-80405 and FIRE3 Phase III studies ranged from 28.4 months in the CRYSTAL study to 33.1 months in the FIRE3 study. The mOS for the phase II OPUS study was 19.8 months and an outlier compared to the other studies. Of note, two thirds of patients in the CALGB-80405 study were treated with the FOLFOX chemotherapy backbone, with cetuximab/FOLFOX (n=198) showing a median overall survival of 32.5 months. In addition the mOS for cetuximab/FOLFOX in the CECOG study was 28.5 months, further suggesting that 19.8 months mOS from OPUS is an outlier.
- Furthermore, in patients with metastatic disease confined to the liver who are initially unresectable, the improvement in response to chemotherapy with the addition of cetuximab may permit liver resection.
- Overall clinical safety showed that RAS wild-type patients have a similar safety profile than the KRAS wild-type population in both the CRYSTAL and OPUS trials. The most common AEs were skin reactions, acne-like rash, and neutropenia.

2.2. Evidence Synthesis

2.2.1. Network meta-analysis

In line with the decision problem outlined in the introduction, a clinical systematic review of the literature was conducted for relevant RCT evidence to inform a potential NMA (See Appendix A). Panitumumab was included in the scope of the NMA as this therapy is currently used in clinical practice in the UK, however results are not reported below (but are available in Appendix A) as this comparison was not considered in the economic model. After final study selection, six studies were included and 27 clinical endpoints were extracted and considered in the feasibility analysis. The definition for each clinical endpoint is presented in Appendix A (Appendix A, Table 5).

As there were no head-to-head trial data comparing cetuximab + chemotherapy to bevacizumab + FOLFOX, an investigation into the feasibility of conducting a NMA was undertaken in order to assess the comparative efficacy and safety of cetuximab in combination with FOLFOX or irinotecan based chemotherapy versus the other comparators in the treatment of RAS wild-type mCRC patients.

The feasibility assessment consisted of addressing two key questions:

- Is there one network of interlinked RCTs to allow the comparisons of interest?

- Are there any differences in study and patient characteristics across comparisons that affect the treatment effects of the interventions of interest relative to the reference treatment?

The data identified in the systematic literature review provided sufficient evidence to draw one global network for 2 of the 27 outcomes considered (See Appendix A): OS and PFS. It was not possible to draw a global network for Overall Response as neither PEAK nor CALGB-80405 study reported this outcome. It was also not possible to include CALGB-80405 in any safety outcome network due to lack of reporting. No significant differences were found between trial populations, however there were some differences between trials in terms of disease progression. However, dropping any study from the synthesis set resulted in the networks no longer being feasible. All key trial characteristics, patient population details, and efficacy outcomes are provided in Appendix A.

Figure 11 presents the network of studies that was available for the main outcomes of interest: PFS and OS. This network was chosen as it allows a comparison between cetuximab/chemotherapy and chemotherapy alone or bevacizumab/chemotherapy. While the head to head trials are comparing against one chemotherapy, several studies have indicated that there is little difference between FOLFOX and FOLFIRI in terms of effectiveness (Colucci et al., 2005). This network also allows the inclusion of the CALGB-C80405 study, which included patients that were treated with both FOLFOX and FOLFIRI.

An analysis was also conducted by splitting the patients in CALGB-80405 into chemotherapy groups, however this breaks the randomisation in CALGB-80405 which could introduce bias into the analysis and therefore is not the preferred analysis. The safety analysis was conducted in separate networks for FOLFOX and FOLFIRI as CALGB-C80405 did not report any safety data for the RAS wild-type population.

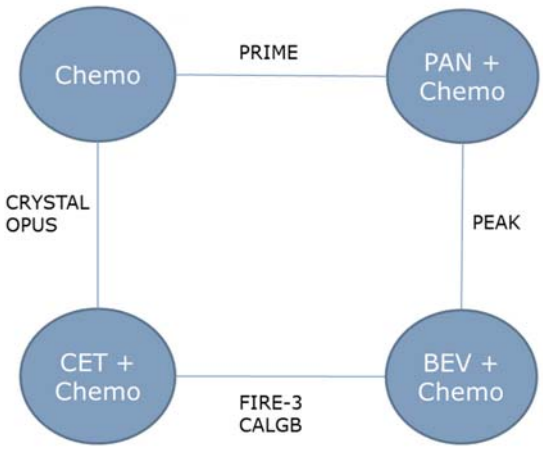
Both fixed and random effects models were used in the analysis, based upon the NICE DSU guidance (Dias et al., 2011). The analysis was conducted using WinBugs using a Bayesian framework and Markov Chain Monte Carlo (MCMC) method to estimate the parameters. A full description of the models, assessment of inconsistency, prior and posterior distributions, and the likelihood and link functions used are provided in Appendix D.

Table 17: Outcome definitions considered in the NMA

Endpoint	Definition
Clinical Endpoints	
Overall survival	The event is defined as death from any cause before or after progression. The Kaplan-Meier method should be used to calculate the event-free probabilities.
Progression free survival	The event is defined as time from randomization to disease progression or death from any cause.
Overall Response rate	This event is defined by the RECIST or WHO response definitions
Safety Endpoints	
Withdrawals	Number of withdrawals from study medication for any reason
Any adverse event	Number reporting any adverse event
Serious adverse event	Number reporting an AE grade III or above
Adverse events leading to withdrawal	Number reporting withdrawal from study medication due to adverse event of any severity
Hypertension	Number/percent reporting hypertension
GI perforation	Number/percent reporting GI perforation
Cardiac events	Number/percent reporting cardiac event
Venous thromboembolism (VTE)	Number/percent reporting VTE
Arterial thromboembolism (ATE)	Number/percent reporting ATE

Pulmonary embolism	Number/percent reporting pulmonary embolism
Skin reactions	Number/percent reporting skin reactions
Acne-like rash	Number/percent reporting acne-like rash
Infusion-related reactions	Number/percent reporting infusion related reactions
Mucositis	Number/percent reporting mucositis
Neutropenia	Number/percent reporting neutropenia
Febrile Neutropenia	Number/percent reporting febrile neutropenia
Nausea	Number/percent reporting nausea
Vomiting	Number/percent reporting vomiting
Leukopenia	Number/percent reporting leukopenia
Fatigue	Number/percent reporting fatigue
Neurological toxicity	Number/percent reporting neurological toxicity
Hypokalemia	Number/percent reporting hypokalaemia
Hypomagnesia	Number/percent reporting hypomagnesia
Paronychia	Number/percent reporting paronychia

Figure 11: Network of trials considered in the NMA for OS and PFS



For all models, the differences in DICs between the fixed and random effects models are relatively small, indicating there may be significant uncertainty in the analysis. When the difference is smaller than 5, it is difficult to make a choice with respect to the preferred model. However, for each endpoint analysed, the credible intervals were wide for the random effects model, therefore the results reported below are from the fixed effects models.

Table 18: DIC for fixed and random effects model for the main clinical outcomes

	FOLFOX and FOLFIRI pooled		FOLFOX and FOLFIRI separated		FOLFIRI	
	FE	FE	RE	RE	FE	RE
Overall Response	NA	NA	NA	NA	30.24	30.26
Overall Survival Proportional HR	-1.30	0.66	1.06	-0.70	NA	NA
Overall Survival FP	999.3	1048.1	1050.3	1000.4	NA	NA
Progression Free Survival Proportional HR	2.55	1.20	0.85	0.25	NA	NA
Progression Free Survival FP	923.8	960.2	946.7	910.5	NA	NA

The full results of the analyses are available in Appendix D. However, as there was significant uncertainty surrounding model choice, and head-to-head trial data was available for the key comparisons between chemotherapy alone and bevacizumab + chemotherapy, the information from the NMA is not discussed further here.

However, the results demonstrated that when compared to chemotherapy (FOLFOX and FOLFIRI), head-to-head trial results appear to be robust as similar hazard ratios were found for the main clinical outcomes. Overall, the results of this NMA demonstrate that cetuximab plus chemotherapy is more efficacious than chemotherapy alone (HR 0.76) and bevacizumab plus chemotherapy (HR 0.79) for overall survival. In terms of progression free survival, cetuximab plus chemotherapy is more efficacious than chemotherapy alone (HR 0.67), and comparable to bevacizumab plus chemotherapy (HR 0.98). The results of the split scenario (see Appendix D) reflected the results of the pooled scenario for OS and PFS.

While the safety results indicated comparable safety/tolerability or additional side effects typical of anti-EGFR therapy, safety results in the NMA are difficult to interpret as the data often had few or no events on which to base the comparison. These results indicate that cetuximab plus FOLFIRI or FOLFOX is a valid and life-extending treatment choice for RAS wild-type mCRC patients.

2.2.2. NMA Conclusion

Overall, the results of this NMA demonstrate that cetuximab plus chemotherapy appears to be more efficacious than chemotherapy alone in terms of overall survival and progression free survival. When compared to bevacizumab plus chemotherapy, cetuximab plus chemotherapy appears to be more efficacious in terms of overall survival, and comparable in terms of progression free survival. For objective response, cetuximab + FOLFIRI appears to have better tumour response when compared to FOLFIRI alone, and is comparable to bevacizumab plus FOLFIRI. These results echo that of the head-to-head clinical trials, which indicate that cetuximab plus FOLFIRI or FOLFOX is a valid and life-extending treatment choice for RAS wild-type mCRC patients. As there was significant uncertainty surrounding the results of the NMA, head-to-head trial data was preferred for use in the health economic model.

3. ECONOMIC EVIDENCE

3.1. Published cost-effectiveness studies

In the systematic review of the economic literature (See Appendix C for full details), 15 records were identified for studies conducting an economic analysis of cetuximab. The majority of studies reported that cetuximab in combination with chemotherapy was a cost effective option in various countries, including Scotland and Wales. However, none of these studies address the decision problem for this submission in its entirety. In particular, all economic analyses were not specific to RAS wild type mCRC patients and do not compare cetuximab in combination with chemotherapy to all the comparators included in the scope of this submission.

3.2. De novo analysis

A *de novo* economic model (executed in Microsoft Excel) was developed to assess the cost effectiveness of cetuximab in combination with chemotherapy in comparison to each of the comparators included in the NICE decision problem (where feasible). This model was developed for this evidence submission due to the absence of published economic studies which conduct this analysis specifically in the RAS wild type mCRC patient population and the absence of a single clinical trial that contains all the relevant evidence for each comparator included in the scope. Moreover, the benefit of cetuximab treatment extends beyond the clinical trials period, specifically in relation to those patients who receive surgical resection with curative intent. Excluding these patients from the economic analysis significantly underestimates the benefit and cost effectiveness of cetuximab.

As stated in the “Intervention technology and comparators” section, some analyses comparing cetuximab in combination with chemotherapy to certain comparators were deemed inappropriate for this submission. This was due to the lack of RAS wild-type patient data specific to these comparators in published studies consistent with the systematic literature review findings reported in this submission.

Table 19 outlines the main features of the de novo economic analysis.

Table 19: Key features of the de novo analysis

Factor	Chosen values	Justification	Reference
Time horizon	10 years	This value was selected as it reflects the patient population, in particular it allows the model to capture the benefits in patients who receive surgical resection with curative intent	Adam 2004 (Adam et al., 2004); clinical expert opinion
Cycle length	1 month	This cycle length allows the model to capture events relevant to beginning treatment	Clinical expert opinion
Half-cycle correction	Half cycle correction was applied to the first and final months spent in the model's time horizon	Transitions could occur at any time point in the model and not just at the end or beginning of a cycle. This is in line with NICE DSU guidance.	NICE DSU TSD* 15 (NICE DSU, 2014)
Discount of 3.5% for utilities and costs	Yes	NICE Reference Case	NICE DSU TSD* 15 (NICE DSU, 2014)
Perspective (NHS/PSS)	Yes	The burden of care would be on the NHS/PSS of England	
Were health effects measured in QALYs; if not, what was used?	Yes, and Life Years Gained	The two measures were chosen in line with the NICE reference case	NICE DSU TSD* 15 (NICE DSU, 2014)
NHS, National Health Service; PSS, personal social services; QALYs, quality-adjusted life years			

*NICE Decision Support Unit Technical Support Document

3.2.1. Patient population

All analyses reported in for the economic analyses consider patients with RAS wild type mCRC as characterised in the relevant clinical trials. This patient group is in line with the decision problem and is modelled based on available RAS biomarker data as described in the clinical effectiveness section.

Furthermore, a subgroup analysis is presented for RAS wild type mCRC where the metastatic disease is confined to the liver and is unresectable. This subpopulation represented the patient population in which cetuximab was assessed in the previous NICE Technology Appraisal 176 (2009) (NICE, 2009b) with the exception that the biomarker status required under the previous license was KRAS wild type, which encompasses a marginally larger patient population size than that of the RAS wild type population assessed in this submission. The rationale for including such subgroup analysis in this evidence submission is to assess the cost effectiveness of cetuximab in this subgroup with RAS wild type status, using recent published evidence, and prove that cetuximab remains a cost effective treatment since NICE recommended its use in Technology Appraisal 176.

Another subgroup analysis is presented for those patients with metastases not confined to the liver, which when combined with the aforementioned subgroup, forms the total RAS wild-type mCRC population covered in the scope of this submission. The purpose of presenting this subgroup analysis is to demonstrate that the use of cetuximab with chemotherapy is not only cost effective when used in liver-limited mCRC patients, but also in those who have metatstasis in other sites. It also proves that the cost effectiveness model results are valid in the wider RAS wild-type mCRC population as the model is not only driven by the additional benefit seen in liver-limited mCRC patients.

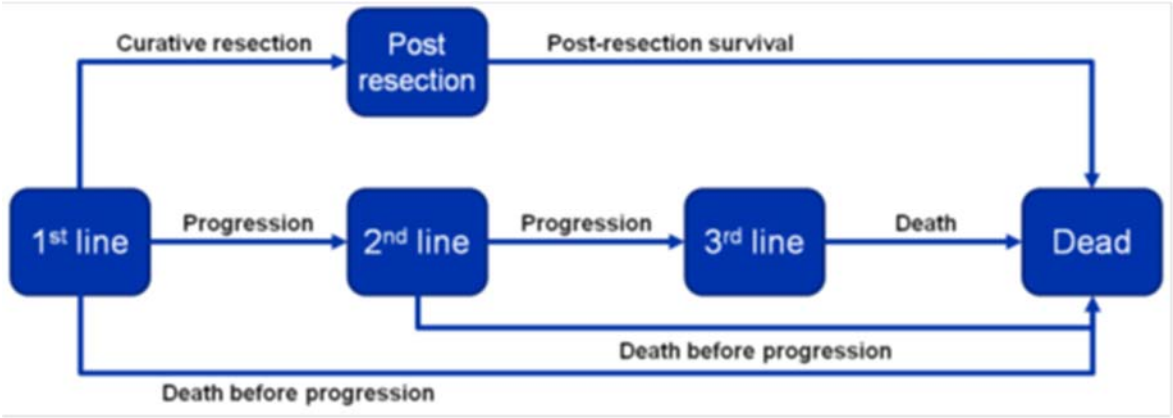
3.2.2. Model structure

A Markov cohort model was developed as it is the common structure used in economic modelling of cancer treatments and is in line with the findings of the economic systematic literature review [Appendix E].

Figure 12 presents the structure of the model and illustrates patient transitions between different health states. Patients in the cohort simulation start in the first-line therapy health state, then either undergo curative resection of liver metastases or enter a post-resection health state or transition to second-line followed by third line treatment health states upon disease progression from the previous state. For patients who receive liver resection, they are assumed to remain in a progression free state until death and do not require second-line treatment. Hence, they follow a different model pathway to those progressing to second-line treatment state. For patients who progress to third-line treatment they are assumed to remain in this state until death.

Transition probabilities used in the model are time-dependent and apply from the beginning of first-line treatment and to the time spent in any particular health state. In order to apply time-dependent transition probabilities for a sequence to treatments, the Excel model uses the mechanism of tunnel states.

Figure 12. Model structure diagram



State transitions in the model are based upon PFS and OS data from the relevant head-to-head clinical trials or from the indirect treatment comparison. Post resection survival is based on the study by Adam et al (Adam et al., 2004). The model assumes the same survival for all patients following liver resection. The possible transitions between health states are described in Table 20.

Table 20: Key model transition structure and implementation

Originating state	Transitions	Implementation
1st Line	Progression to 2nd line Or Death before progression Or Surgical resection with curative intent	Time dependent based upon individual patient data Time dependent based upon individual patient data At cycle/month 4 based upon Adam et al (Adam et al., 2004) which found that most resections occur before 4 months.
Post resection	Death	Based on background mortality as curative resection patients are considered cured.
2nd Line	Progression to 3rd line Or Death before progression	Time dependent based on the literature (Tournigand et al Time dependent
3rd Line	Death	AUC approach: The proportion of patients on third line treatment is calculated as the difference between the OS and the sum of the proportions of patients in the first and second-lines as reported in Jonker et al., 2009 as no patient level data is available from this study to model the disease in the third line treatment setting.

Table 21: Transition assumptions used in the model

Section of the model	Description of the state in the model	Outcomes and data sources	Service use and costs
1st line treatment	This is the treatment stage where the biggest incremental benefit is expected due to the addition of cetuximab to the treatment regimen. Based on either the *RAS* wild type CRYSTAL or OPUS datasets.	Patients remain in this state until: • they die before progression • progress into 2nd line • or are referred for curative intent liver surgery Death before progression and progression into second line are derived from survival analysis of the *RAS* wild type subgroup of either the CRYSTAL or OPUS study data.	Patients accrue costs in line with treatment duration, progression into the subsequent line, or are referred for curative surgery.
	All patients' start 1st line treatment and receive either cetuximab + FOLFIRI or FOLFIRI alone for the CRYSTAL evaluation. For the OPUS evaluation they will receive either cetuximab plus FOLFOX or FOLFOX alone	While patients stay progression-free their health-related utility of life is assumed constant at 0.77. For both evaluations we have used the cost of branded oxaliplatin as £3.10 per mg and not the generic price. The branded oxaliplatin price has been utilised in the model. Similarly for irinotecan with £1.16 for the 2ml vial and £1.20 for the 25ml vial.	No utility data is available for OPUS or CRYSTAL *RAS* wild-type population
	At 3 months in the model some patients can be referred for curative-intent resection of liver metastases.	The resection rates used in the model are R0 and R1 where 100% of patients are expected to have successful resection and continue to be in a disease free state until death. Since repeat hepatectomy is a feature of some patients enrolled in the Adam et al study, it is not included as a health state in the model as this may double count the benefit accrued. Costs of complex liver surgery have been included however.	Postoperative death was 0% in the CRYSTAL study and set to 0 in the model.

Section of the model	Description of the state in the model	Outcomes and data sources	Service use and costs
2nd line treatment upon progress-ion from the 1st line	Patients move to this health state after disease progression in the first-line health state	Patients remain in this health state until: • they die before progression • progress into 3rd line Progression-free survival in 2nd line is derived from the PFS curves published in Tournigand et al (Tournigand et al., 2004), regardless of the time of progression from the first line. It is assumed that the health related utility weight in the second line is lower than the utility weight in the 1st line (0.77 and 0.78 respectively) and higher than the utility weight in the 3rd line (0.68) and is represented by their average (0.73). Probability of [further] progression in the 2nd line is identical for both arms in the model. A slight difference in health gains in 2nd line can be observed due to the different mean times to progression in the cetuximab + FOLFIRI and FOLFIRI alone arms and the effect of discounting after year 1.	The clinical trial by Tournigand *et al* (Tournigand et al., 2004) forms the basis of the second line segment of the model. The main critique is the use of FOLFOX-6 It can be assumed that the FOLFOX 6 regimen has similar outcomes to the use of UK oxaliplatin based combinations. This is validated by reported results as follows: 4.6 months PFS reported by Rothenberg (Rothenberg et al., 2003); 4 months reported by Scartozzi (Scartozzi et al., 2005) for second-line FOLFOX4. This is not dissimilar to the 4.2 months reported for second-line FOLFOX6 by Tournigand *et al* (Tournigand et al., 2004)
3rd line	This is the final treatment line in the model.	Patients remain in this health state until: • Death before progression • Death after progression The probability of death is derived from the results of Jonker *et al (Jonker et al., 2009)* comparing treatment with cetuximab + best supportive care to best supportive care alone. Similar to 2nd line therapy, the risk of death does not depend on the time the patient progressed from the 2nd line.	It is assumed that most patients would receive best supportive care, with only 15-20% (average= 17.5%) receiving capecitabine monotherapy or cetuximab (Merck Serono, 2015). It is assumed in the model that patients would not be re-treated with cetuximab in third line setting and that 17.5% would receive capecitabine while the rest receive BSC only. The monthly cost from (Hoyle et al., 2013) of best supportive care from this study was applied in the model.

3.2.3. Intervention technology and comparators

The model compares cetuximab in combination with either FOLFOX or FOLFIRI versus FOLFOX and FOLFIRI alone as well as bevacizumab in combination with FOLFIRI. A comparison wih bevacizumab in combination with FOLFOX was not possible due to the reasons mentioned in section 2. In addition, an exploratory scenario analysis based on OPUS was conducted to compare XELOX (CAPOX), for which RAS wild-type specific data is unavailable at the time of submission, under the assumption that XELOX is equivalent in effect to FOLFOX as presented in the scenario analyses section.

All comparators in the model are implemented as per the marketing authorisations.

Table 22: Implementation of comparators within scope in the economic model

Comparator	**Implemented in economic model as comparator**	**Clinical trial used for modeling**	**Comment**
FOLFIRI	cetuximab + FOLFIRI	CRYSTAL	Only data for RAS wild type mCRC patients used
FOLFOX	cetuximab + FOLFOX	OPUS	Only data for RAS wild type mCRC patients used
Bevacizumab + FOLFIRI	cetuximab + FOLFIRI	FIRE 3	Only data for RAS wild type mCRC patients used
XELOX	cetuximab + FOLFOX	OPUS	There is no RAS wild type data available from a head-to-head study (cetuximab + chemotherapy against XELOX). This is an exploratory scenario analysis assuming that XELOX is equivalent to FOLFOX-4 in effect based on the OPUS study
Capecitabine	Analysis not performed	N/A	There is no RAS wild type data available from a head-to-head study (cetuximab + chemotherapy against capecitabine).
Tegafur folinic acid and fluorouracil	Analysis not performed	N/A	Tegafur was withdrawn from the market in 2013 and is not available through any distributor in the UK. Merck Serono was the marketing authorization holder at the time.

3.3. Clinical parameters and variables

3.3.1. Base case analysis

The economic model uses the disease modelling approach to estimate treatment benefit in terms of overall survival in the base case analysis. This approach is followed as it allows for the possibility that patients will survive beyond the trial time horizon and allows for patients to receive curative liver resection. The benefit of which was not fully captured over the duration of the clinical trials and therefore, using overall survival as reported in clinical trials is likely to underestimate the clinical benefit and overestimate the incremental cost effectiveness ratio for cetuximab in combination with chemotherapy. Alternatively, real progression hazard ratios were used for each disease state to estimate the overall survival of the cohort. For each relevant pairwise comparison, this was achieved using patient-level data from OPUS and CRYSTAL studies, digitised published Kaplan-

Meier curve for the FIRE3 study. Table 23 presents these hazard ratios with their respective sources.

Table 23: Hazard ratios applied in the model base case for PFS

	Hazard Ratio	Low 95% CrI	High 95% CrI	Source
Real progression HR Cetuximab + FOLFOX versus FOLFOX	0.57	0.38	0.85	OPUS
Real progression HR Cetuximab + FOLFIRI versus FOLFIRI	0.71	0.54	0.95	CRYSTAL
Real progression HR Cetuximab + FOLFIRI versus bevacizumab + FOLFIRI	0.97	0.78	1.20	FIRE - 3

Disease modelling assumes that PFS benefits of the first-line cancer treatments translate directly into OS benefits, with further progression in second and survival in the third-line applying equally to patients who progressed from the first-line at different times from the start of first-line treatment.

Parametric survival models (Weibull, exponential, log normal, log logistic, gamma and generalised gamma) were fitted to the PFS Kaplan-Meier curves from the CRYSTAL and OPUS trials. Single survival models were utilised so that a treatment effect is included in the output of the survival models, and a hazard ratio can be calculated under the proportional hazard model. Both the pivotal CRYSTAL and OPUS studies reported a numerically greater overall survival as well as a greater rate of curative resection of liver metastases in the groups that received cetuximab in combination with chemotherapy compared to chemotherapy alone. Therefore, the rate of curative resection and survival was included in the model to capture this treatment benefit. Where direct comparisons were not available, the hazard ratios from the NMA were applied to the trial Kaplan Meier data to adjust for the relative effectiveness.

Table 24: CRYSTAL, OPUS and FIRE3 economic models: Extrapolation technique employed for different model settings

	CRYSTAL Evaluation		**OPUS Evaluation**		**FIRE3 Evaluation**	
Setting	**Extrapolation technique**	**Source of distributional assumption**	**Extrapolation technique**	**Source of distributional assumption**	**Extrapolation technique**	**Source of distributional assumption**
First-line, death before progression	Log normal	CRYSTAL wild-type RAS analyses	Log normal	OPUS wild-type RAS analyses	Log normal	CRYSTAL wild-type RAS analyses
First-line time to progression	Weibull	CRYSTAL wild-type RAS analyses	Log normal	OPUS wild-type RAS analyses	Weibull	FIRE-3 KM Curves
Second-line time to progression	Log normal	Tournigand et al *(Tournigand et al., 2004)*	Log normal	Tournigand et al *(Tournigand et al., 2004*	Log normal	Tournigand et al *(Tournigand et al., 2004*
Third-line time to Death	Weibull	Jonker *et al (Jonker et al., 2009)*	Weibull	Jonker *et al (Jonker et al., 2009)*	Weibull	Jonker *et al (Jonker et al., 2009)*

	CRYSTAL Evaluation		OPUS Evaluation		FIRE3 Evaluation	
Setting	**Extrapolation technique**	**Source of distributional assumption**	**Extrapolation technique**	**Source of distributional assumption**	**Extrapolation technique**	**Source of distributional assumption**
Post curative surgery survival	Log logistic	Adam *et al (Adam et al., 2004)*	Log logistic	Adam *et al (Adam et al., 2004)*	Log logistic	Adam *et al (Adam et al., 2004)*
PFS following curative surgery	Log logistic	Adam *et al (Adam et al., 2004)*	Log logistic	Adam *et al (Adam et al., 2004)*	Log logistic	Adam *et al (Adam et al., 2004)*

The suitability of each fitted parametric model for the first-line time to progression data was assessed based on the NICE DSU technical support document 14. Models were deemed appropriate based on the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) and visual inspection. Tests were run on the selection of parametric models, ranging from the very simple, one-parameter Exponential distribution to more complex and flexible four-parameter Generalised Gamma distributions. The model fitting and analysis were performed using the flexsurv package in R.

Table 25 presents the AIC and BIC estimates for the extrapolated curves for each of the considered parametric models for CRYSTAL and OPUS.

Table 25: AIC/BIC results for goodness of fit for time to progression in first-line treatment

Parametric models	**CRYSTAL – AIC**	**CRYSTAL– BIC**	**OPUS–AIC**	**OPUS–BIC**
Weibull	**1203.130**	**1214.846**	280.224	287.622
Exponential	1274.576	1282.387	288.91	293.842
Gamma	1203.504	1215.22	279.075	286.473
Lognormal	1214.984	1226.7	**278.576**	**285.974**
Loglogistic	1208.494	1220.211	278.709	286.107
GenGamma	1204.785	1220.406	280.399	290.262

The fit of the parametric models explored for the analysis based on data from the CRYSTAL trial are presented on Figure 13. The results for the CRYSTAL trial indicate that the Weibull distribution provides the best fit (lowest AIC and BIC scores and visual inspection) to the Kaplan

Meier curves. The progression-free survival KM curves and the fitted Weibull curves for the CRYSTAL trial are shown on Figure 14.

Figure 13: Kaplan-Meier and fitted curves for progression free survival of *RAS* wild-type patients in CRYSTAL (all parametric models considered)

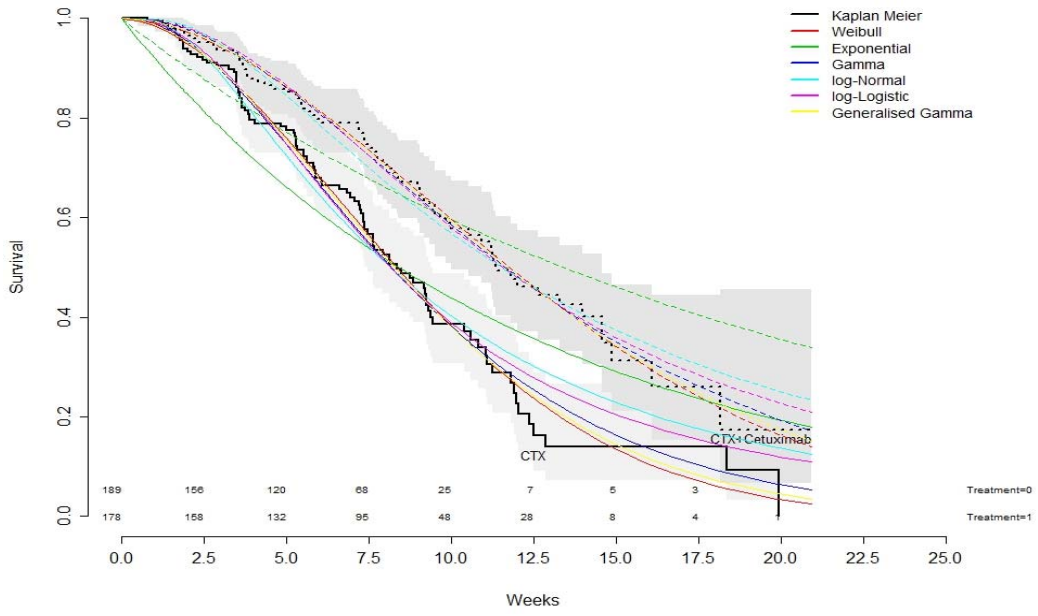
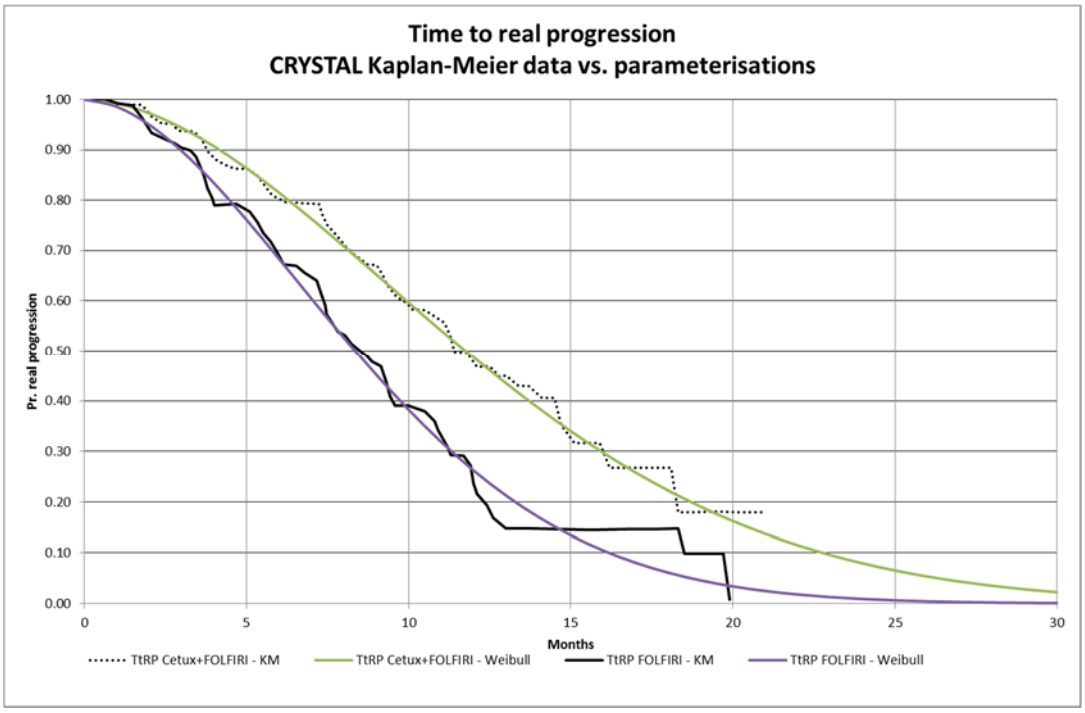


Figure 14: Kaplan-Meier and Weibull fitted curves for progression free survival of RAS wild-type patients in CRYSTAL



The fit of the parametric models explored for the analysis based on data from the OPUS trial are presented on Figure 15. For the OPUS trial, the log-normal distribution provided the best fit (lowest AIC and BIC scores) of the six parametric curves considered (Weibull, exponential, log-logistic, log-

normal, gamma and generalised gamma). The progression-free survival data and the fitted log-normal curves for the OPUS trial are shown in Figure 16.

Figure 15: Kaplan-Meier and fitted curves for progression free survival of RAS wild-type patients in OPUS (all parametric models considered)

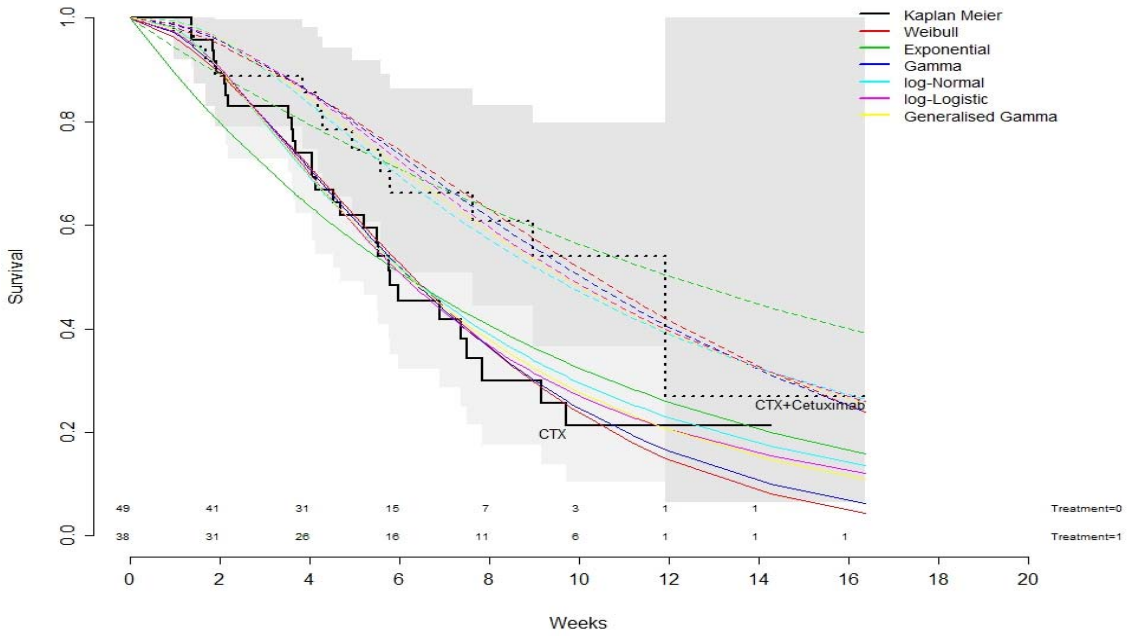
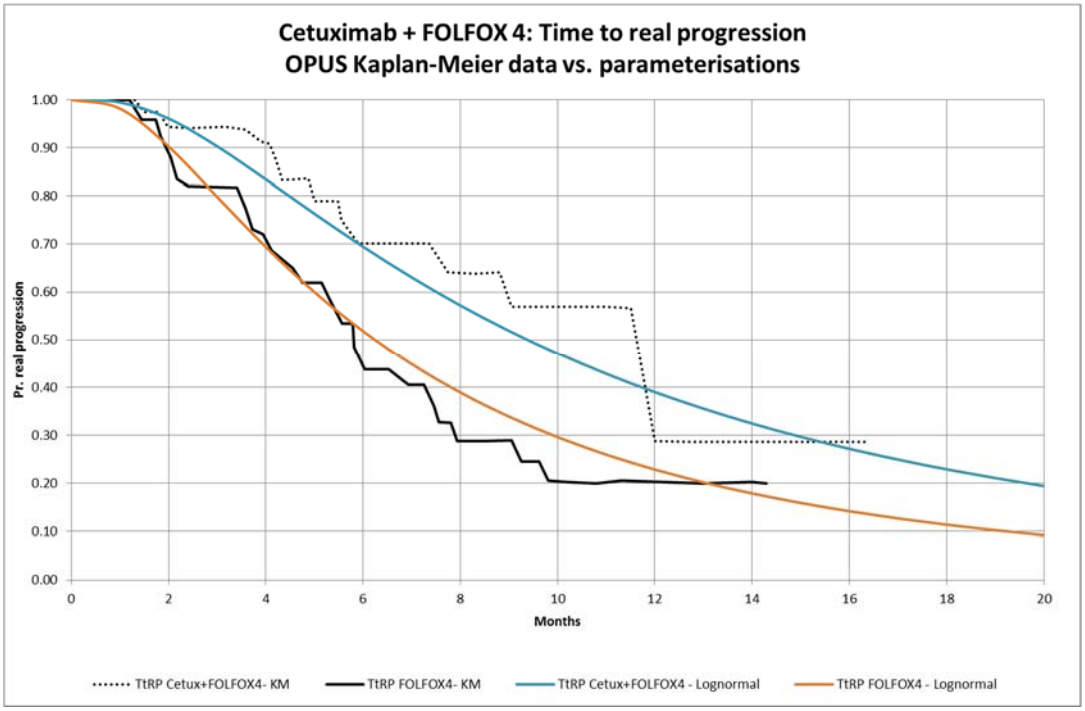


Figure 16: Kaplan-Meier and log-normal fitted curves for progression free survival of RAS wild-type patients in OPUS



In order to estimate the benefit of potentially curative resection of liver only metastases as a subgroup of the overall mCRC population, resection rates for cetuximab in combination with FOLFIRI and FOLFOX were obtained from a post hoc analysis of CRYSTAL study (Kohne, 2014)

as there is no other study reporting a resection rate specific to RAS wild type mCRC patients treated with cetuximab combination therapy. For bevacizumab plus chemotherapy, the respective R0 resection rates were obtained from the PEAK study post hoc analysis of RAS wild type patients enrolled in the study (Schwartzberg et al., 2014). Resection rates for either FOLFIRI or FOLFOX alone were obtained from Tournigand et al. study (Tournigand et al., 2004), which is not stratified per RAS mutation status since it does not have any impact on treatment outcome when treating patients with chemotherapy only. RAS mutation confers a poorer prognosis of response to cetuximab but not to conventional chemotherapy.

Table 26: Resection rates from retrospective analysis of RAS wild type mCRC patients enrolled in CRYSTAL study

Subgroups (number of patients	**Treatment (n Value)**		**R0 resection (Rate %)**		
	FOLFIRI	**Cet + FOLFIRI**	**FOLFIRI**	**Cet + FOLFIRI**	**OR [95% CI]**
Liver-limited disease (n = 89)	46	43	6.5	16.3	2.68 [0.63 -
Non Liver-limited disease (n=278)	143	135	0.7	4.4	5.94 [0.79 -
Overall RAS wild type population (n = 367)	189	178	**2.1**	**7.3**	-

***Cet**: cetuximab; **FOLFIRI**: 5-fluorouracil/leucovorin/irinotecan; **OR**, odds ratio.*

Survival was modelled according to those observed in Adam et al. (Adam et al., 2004) for the subgroup of patients who undergo resection of liver only metastases. The time patients stay in the third-line treatment state was based on patient survival as reported in Jonker et al (CO17 study) (Jonker et al., 2009).

Table 27 below provides further information on patient population in the aforementioned clinical trials upon which the model was based.

Table 27: Study characteristics of sources within the economic model

	CRYSTAL/ OPUS/FIRE-3/NMA (Van Cutsem et al., 2009, Heinemann et al., 2013, Bokemeyer et al., 2009)	**Tournigand et al** (Tournigand et al., 2004)	**Adam et al** (Adam et al., 2004)	**Jonker et al** (Jonker et al., 2009)
Inclusion Criteria	*RAS* wild-type Patients with mCRC who have unresectable metastases.	Patients with mCRC who have unresectable metastases.	Patients with mCRC who have undergone resection of hepatic metastases. Metastases have been rendered resectable by chemotherapy.	Studies cetuximab with best supportive care against best supportive care only. Best supportive care was defined in this study as those measures designed to provide palliation of symptoms and improve quality of life as much as possible
Patient Characteristics	N= 367/ 87 (*RAS* wild type analyses)	N= 220	N= 138	N=572
Mean Age (Yrs)	60/ 59.5	63	57.3	63.2
Male/Female (%)	62/38 (CRYSTAL) 50/50 (OPUS)	64.5/ 35.5	55.8/ 44.2	64.3/35.7
Metastases Confined To Liver Before Chemotherapy	Not an inclusion criteria - only 19.8% of patients with disease confined to liver (CRYSTAL)	Not an inclusion criteria - but 80% of patients had liver metastasis and overall 64% had only one site of metatstasis	78%	Not an inclusion criteria - but 80.9% of patients had liver metastasis
RAS Status	Determined post hoc –*RAS* wild type	Not determined	Not determined	Not determined

Adopting liver resection rates from Tournigand et al. (Tournigand et al., 2004) for chemotherapy alone can be justified by the fact that there was a large number of patients with liver only metastases enrolled in this study (80% of patients had liver metastases and 59% had one metastatic site only). In addition, the response rates for patients treated with FOLFIRI were comparable with those observed in the liver-only metastases population in CRYSTAL treated with FOLFIRI alone. Using Adam et al. (Adam et al., 2004) to model the survival of patients who undergo resection represents clinical practice as this population were patients whose liver tumour size was reduced with

chemotherapy before their resection. The population included patients with both microscopically "clear" and "not clear" resection margins.

3.4. Measurement and valuation of health effects

3.4.1. Health-related quality-of-life data from clinical trials

Health-related utility weights are applied to the time lived with disease at different stage of disease progression in the Markov model. A systematic review of the literature for health economic studies identified data for the first-, second- and third-line treatment health states (HRQoL systematic literature review is reported in Appendix C). No studies were identified reporting HRQoL data specifically for RAS wild-type mCRC patients. However an analysis has now been performed on the CRYSTAL RAS wild-type dataset as detailed in section 2.1.3.3. With the exception of this criterion, 10 studies were identified reporting HRQoL data not specific to RAS wild mCRC type patients. Expert clinicians indicated that quality of life within each disease state is unlikely to vary according to the biomarker status of patients receiving cetuximab treatment and hence it can be assumed that quality of life of KRAS wild-type or non-biomarker stratified patients is similar to those with RAS wild-type status for any disease state in the economic model (Merck Serono, 2015).

The utility data used in the model are presented in Appendix B. For the post-resection health state, a composite utility weight was calculated. It was assumed that the proportion of post-resection patients that were disease-free would have the same utility as the general (disease-free) population. For patients with progressive disease, a weighted average of second-line and third-line utilities were used based upon the mean time spent in those health states. This gives an average utility value of 0.789 which can be applied to the entire post-resection health state.

3.4.2. Disutilities for adverse events

The disutilities associated with experiencing adverse events have been obtained from previously published literature identified in the systematic review. For several adverse events, no data was found in the systematic literature review, and therefore a pragmatic approach to identifying relevant information was taken. Disutility values were assumed to occur in the first month of therapy only.

3.5. Cost and healthcare resource use identification, measurement and valuation

Costs and resource use were identified from the literature and validated with key clinical opinion leaders. Unit costs for treatment and adverse event costs were also taken from UK national sources including the British National Formulary (BNF, 2014), NHS Reference costs 2013/14 (NHS England, 2013). Full details of resource use and unit cost information can be obtained from Appendix B.

In the economic model, it is assumed that all mCRC patients entering the model simulation are tested for RAS status at the outset and those who are found to have mutations in their RAS codons are treated in the comparator arm of the model, therefore the cost of RAS testing is applied to both cetuximab arm and the comparator arm equally.

Although the base case economic analyses were based on cetuximab dose studied in clinical trials, parallel analyses were run based on fortnightly dosing of cetuximab (every 14 days). This represents the currently prescribed dose in clinical practice across England and Wales (Merck Serono, 2015) and is the standard dosing regimen upon which cetuximab is reimbursed through the National Cancer Drugs Fund in England. Refer to section 1.1.2 in the clinical effectiveness section for further detail on fortnightly dosing. In clinical practice, this translates to halving the frequency of patient visits to the chemotherapy unit for treatment and also represents a significant reduction in administration cost compared to the weekly cetuximab dosing regimen. This demonstrates that cetuximab is significantly more cost effective in real-world clinical practice. Analyses utilising fortnightly dosing for cetuximab in the model assume the same parameter and

variable values as analyses utilising the weekly dose with the exception of changing the dose and frequency of administration to 500mg/m^2 every 14 days.

3.6. Base-case results

3.6.1. Economic analyses results based on head-to-head clinical trial data

Table 28 presents the head-to-head trial results utilising cetuximab list price and a weekly dosing schedule. Table 29 presents results for the same analyses when considering fortnightly dosing of cetuximab in the model. The ICERs were reduced significantly due to the reduction in administration cost and frequency of patient visit to the chemotherapy unit for treatment.

Deterministic base-case results for Head-to-head trial results (OPUS, CRYSTAL, FIRE-3) based on fortnightly cetuximab dose

3.6.1.1. Base-case incremental cost effectiveness analysis results

Table 28: Deterministic base-case results for Head-to-head trial results (OPUS, CRYSTAL, FIRE-3) based on weekly cetuximab dose

	Costs	LYs	QALYs	ICER (cost per LY gained)	ICER (cost per QALY gained)
OPUS					
Cetuximab + FOLFOX	46,231.31	2.22	1.64		
FOLFOX	26,407.55	1.81	1.32		
Increment (Cetuximab + FOLFOX-4 - FOLFOX)	19,823.76	0.41	0.32	47,979.03	61.894.46
CRYSTAL					
Cetuximab + FOLFIRI	48,953.70	2.19	1.61		
FOLFIRI	27,138.74	1.81	1.32		
Increment (Cetuximab + FOLFIRI - FOLFIRI)	21,814.96	0.38	0.29	57,001.13	74,212.31
FIRE-3					
Cetuximab + FOLFIRI	42,491.25	2.16	1.60		
Bevacizumab + FOLFIRI	34,604.87	2.03	1.49		
Increment (Cetuximab + FOLFIRI - Bevacizumab + FOLFIRI)	7,886.38	0.14	0.10	56,553.18	76,505.41

Table 29: Deterministic base-case results for Head-to-head trial results (OPUS, CRYSTAL, FIRE-3) based on fortnightly cetuximab dose

	Costs	LYs	QALYs	ICER (cost per LY gained)	ICER (cost per QALY gained)
OPUS					
Cetuximab + FOLFOX	41,301.81	2.22	1.64		
FOLFOX	26,407.55	1.81	1.32		
Increment (Cetuximab + FOLFOX - FOLFOX)	14,894.26	0.41	0.32	36,048.26	46,503.39
CRYSTAL					
Cetuximab + FOLFIRI	43,591.52	2.19	1.61		
FOLFIRI	27,138.74	1.81	1.32		
Increment (Cetuximab + FOLFIRI - FOLFIRI)	16,452.78	0.38	0.29	42,990.08	55,970.70
FIRE-3					
Cetuximab + FOLFIRI	37,978.34	2.16	1.60		
Bevacizumab + FOLFIRI	34,604.87	2.03	1.49		
Increment (Cetuximab + FOLFIRI - Bevacizumab + FOLFIRI)	3,373.48	0.14	0.10	24,191.18	32,725.95

3.6.1.2. Clinical outcomes from the model

Table 30 compares the model results to those reported for each relevant clinical trial. For the OPUS-based comparison, the model potentially underestimates PFS, but overestimates the OS. For CRYSTAL, the model is very similar in terms of PFS, but underestimates OS. OPUS was a phase II study and the numbers of patients in the RAS analysis was relatively small. In terms of PFS, the underestimation of the OS in OPUS is largely due to the analysis containing a small number of patients, resulting in fitted curves that are a less accurate reflection of the trial results. For CRYSTAL, the curve fit appears to be relatively reflective of the trial in terms of PFS. For OS, it is likely that the constant hazard ratio associated with progression from 2nd to 3rd line, and 3rd line to death has resulted in an inflated difference in OPUS, but an underestimate for CRYSTAL. The OS estimates are also influenced by the addition of curative resection. As the number of patients refered for resection is the same in both analyses, this has resulted in similar overall survival estimates for both trials. For FIRE-3, the model appears to overestimates the difference in PFS and greatly underestimates the OS difference. As with CYRSTAL and OPUS, the constant hazard ratio

assumed for progression from subsequent therapy lines, and the assumption of the same resection rates between arms is likely to result in a lower OS difference between arms. Overall, the economic analyses underestimate the OS benefit attributed to cetuximab treatment and hence cetuximab is more likely to be more effective in practice and therefore the ICERs presented in this evidence submission are overestimated and cetuximab is likely to be more cost effective in reality.

Table 30: Summary of model results compared with clinical data

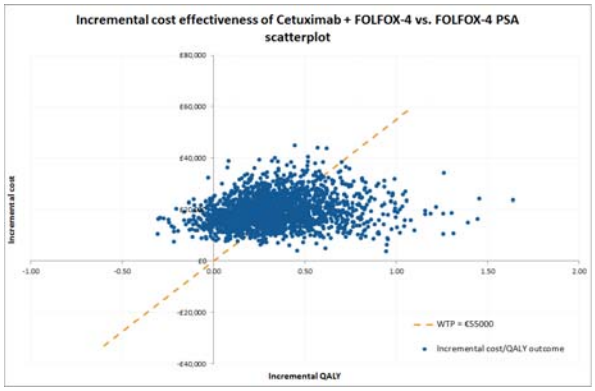
Outcome	Clinical trial	Clinical trial result			Model result		
		Cetuximab	Comparator	difference	Cetuximab	Comparator	difference
Progression -free survival (months)	OPUS	12	5.8	6.2	12.23	8.75	3.48
	CRYSTAL	11.4	8.4	3	11.67	8.73	2.94
	FIRE3	10.3	10.2	0.1	11.95	10.13	1.82
Post-progression survival (months)	OPUS	NR	NR	NR	14.43	12.95	1.48
	CRYSTAL	NR	NR	NR	14.65	13	1.65
	FIRE3	NR	NR	NR	14.03	14.17	-0.14
Overall survival (months)	OPUS	19.8	17.8	2	26.66	21.70	4.96
	CRYSTAL	28.4	20.2	8.2	26.32	21.73	4.59
	FIRE3	33.1	25.0	8.1	25.98	24.30	1.68

3.7. Sensitivity analyses

3.7.1. Probabilistic sensitivity analysis

The Probabilistic Sensitivity Analyses (PSA) indicated that while there was some uncertainty around the results, cetuximab + FOLFOX or FOLFIRI was consistently likely to be the most cost-effective treatment given a cost-effectiveness threshold range of £50,000 - £60,000 per QALY gained, when the fortnightly cetuximab dosing was administered. When the weekly dosing of cetuximab was administered, the likelihood of cost-effectiveness decreased. Largest uncertainty of the results was found for the comparison of cetuximab + FOLFOX versus FOLFOX, where a wide spread of the ICER iterations on the scatterplot was observed. The FOLFOX analysis reflects the relatively wide confidence intervals on the effectiveness estimates in the trial, whereas in the FOLFIRI analysis and the bevacizumab + FOLFIRI analysis, the uncertainty in effectiveness was less pronounced.

Figure 17: ICER scatterplot and CEAC for cetuximab + FOLFOX versus FOLFOX alone (weekly cetuximab dosing)



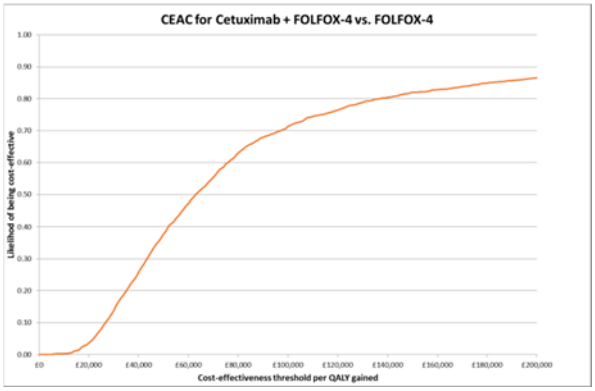
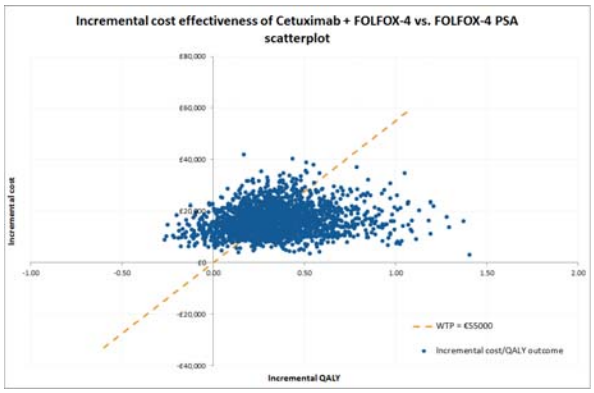


Figure 18: ICER scatterplot and CEAC for cetuximab + FOLFOX versus FOLFOX alone (fortnightly cetuximab dosing)



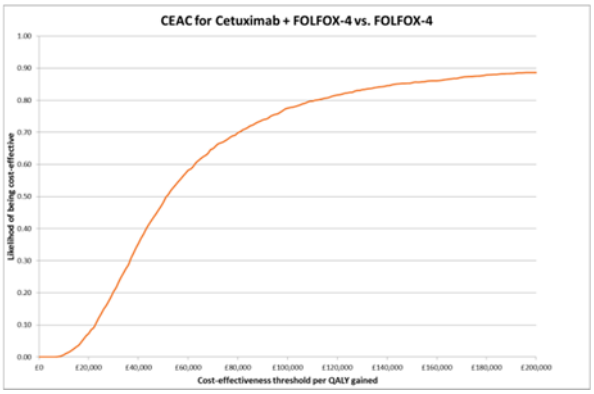
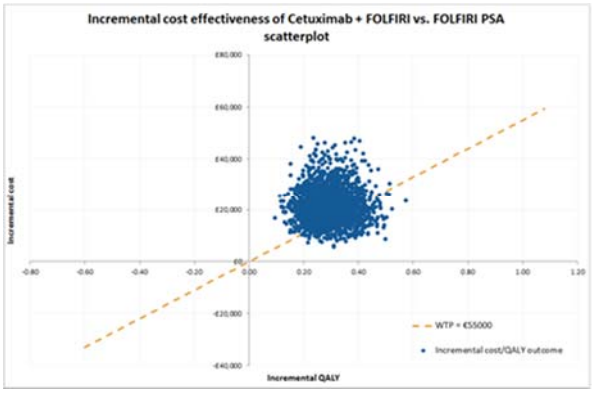


Figure 19: ICER scatterplot and CEAC for cetuximab + FOLFIRI versus FOLFIRI alone (weekly cetuximab dosing)



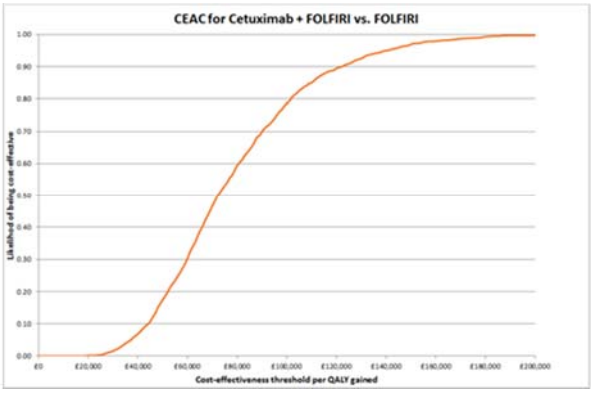
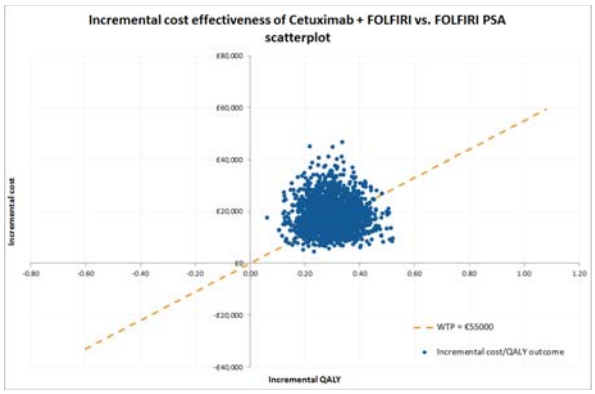


Figure 20: ICER scatterplot and CEAC for cetuximab + FOLFIRI versus FOLFIRI alone (fortnightly cetuximab dosing



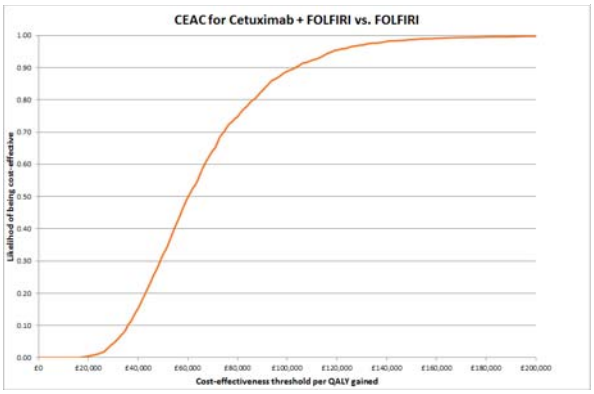
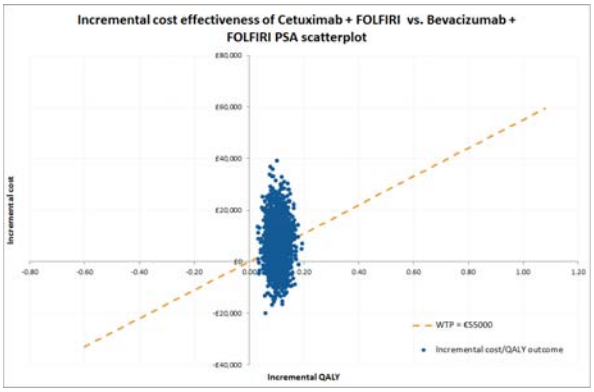


Figure 21: ICER scatterplot and CEAC for cetuximab + FOLFIRI versus bevacizumab + FOLFIRI (FIRE3 study) (weekly cetuximab dosing)



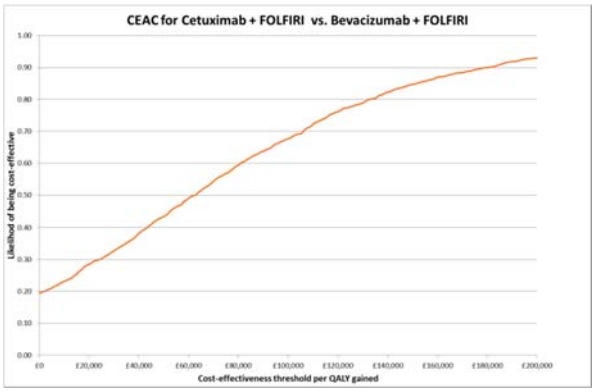
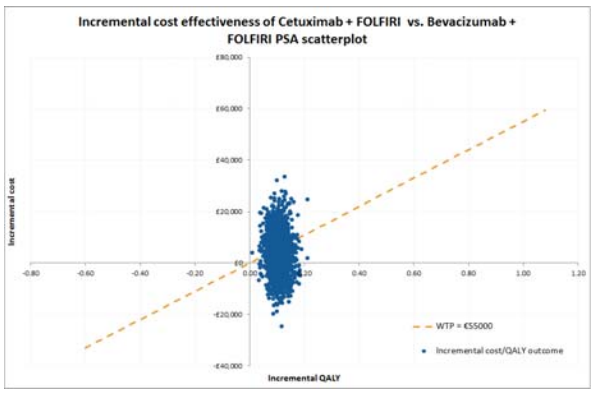
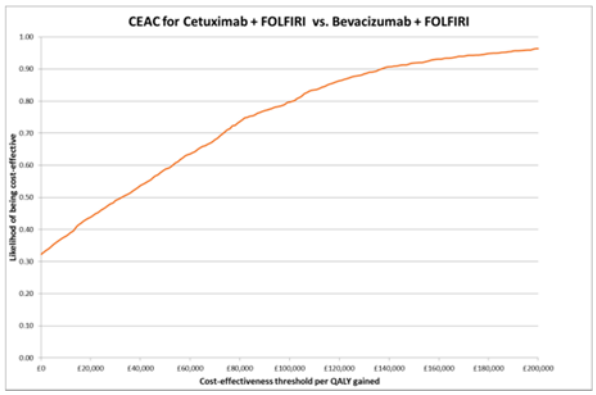


Figure 22: ICER scatterplot and CEAC for cetuximab + FOLFIRI versus bevacizumab + FOLFIRI (FIRE3 study) (fortnightly cetuximab dosing)





3.7.2. Univariate sensitivity analysis

To investigate the extent of uncertainty around the deterministic estimates, univariate sensitivity analyses (one-way sensitivity analysis) were run for all comparisons based on head-to-head clinical trial data. The results of the univariate sensitivity analyses indicate that the model was sensitive, in all analyses, to the hazard ratio for real progression, the number of months on cetuximab treatment and the average body surface area. These findings are commonly identified as the main drivers of

economic models for cancer treatments as they either have a direct impact on treatment cost or patients survival estimation in the model.

The period of treatment with cetuximab plus chemotherapy used in the model were obtained from the relevant clinical trials. As stated in the clinical evidence section, the period of treatment in the clinical trial represents clinical practice as Merck Serono research indicates that the period of cetuximab treatment is 25 weeks on average. Therefore, the cost effectiveness of cetuximab in the model should not vary according to this parameter.

The rate of liver resection with curative intent was also one of the drivers of the model. However, it did not have the same impact as the HR for real progression, the number of months on cetuximab treatment and the average body surface.

Figure 23: OWSA for cetuximab + FOLFOX versus FOLFOX alone

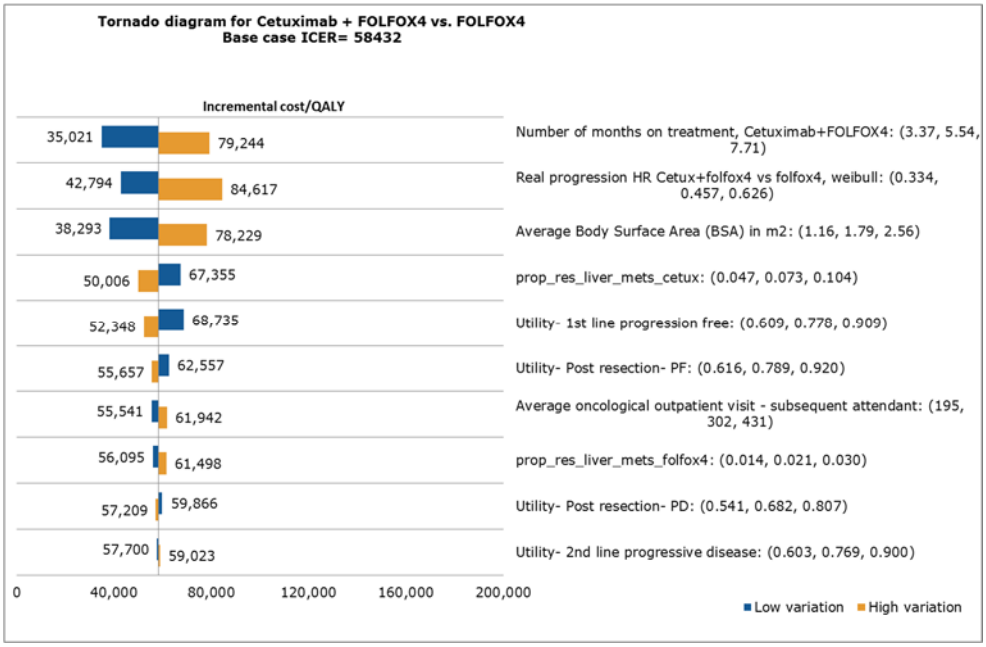


Figure 24: OWSA for cetuximab + FOLFIRI versus FOLFIRI alone

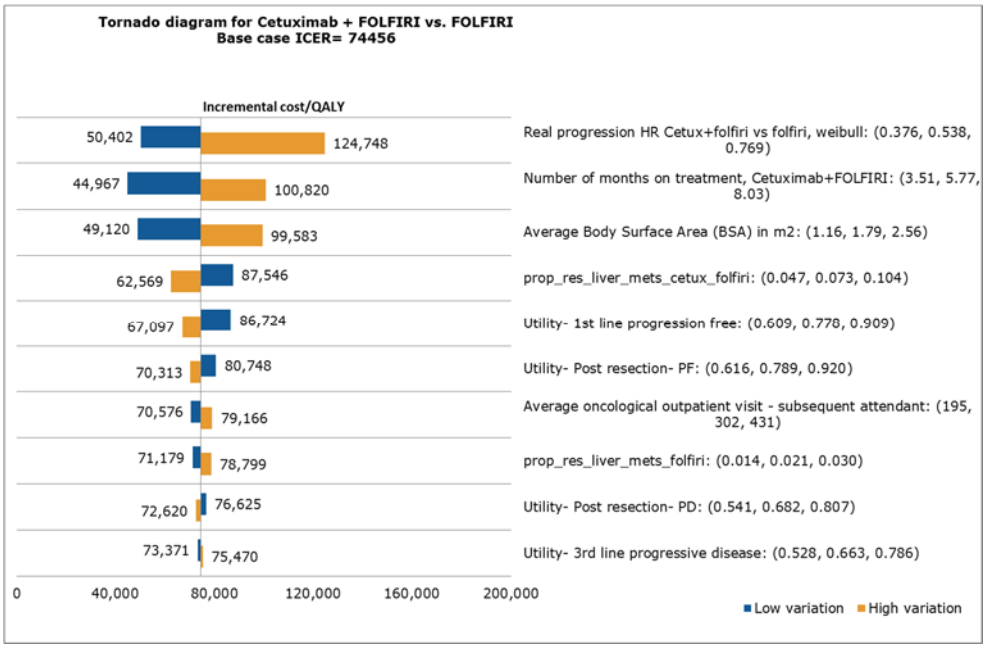
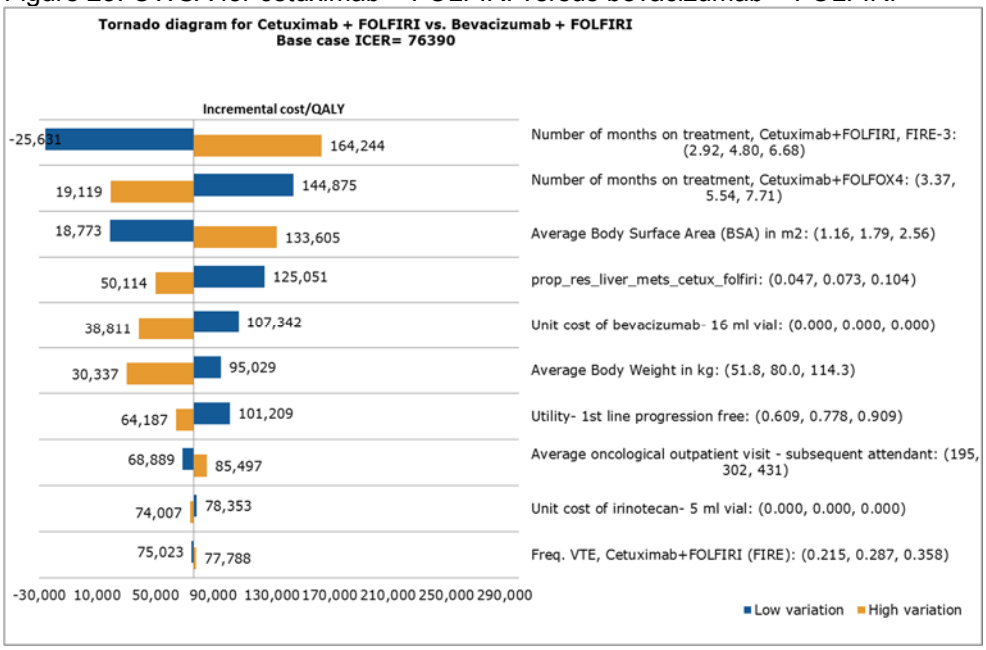


Figure 25: OWSA for cetuximab + FOLFIRI versus bevacizumab + FOLFIRI



3.7.3. Scenario analysis

3.7.3.1. Cost effectiveness of cetuximab in combination with FOLFOX compared to XELOX (CAPOX)

An exploratory analysis based on the OPUS study was conducted to compare cetuximab plus FOLFOX with CAPOX despite the lack of head to head data specific to RAS wild-type mCRC patients. Since CAPOX is commonly used in UK clinical practice for the treatment of mCRC, it is important to demonstrate the cost effectiveness of cetuximab versus this chemotherapy option, hence this scenario analysis.

To conduct the analysis, it was assumed that CAPOX is equivalent in outcomes to FOLFOX while the cost of treatment was different as 5-Fluorouracil (5-FU) cost was displaced by capecitabine cost in the economic analysis based on OPUS study. Cost of administration remained the same as patients would still be required to attend the chemotherapy unit to receive oxaliplatin despite receiving capecitabine orally.

There is evidence to support the assumption above. In a Phase III trial by Cassidy *et al* (Cassidy et al., 2006, Cassidy et al., 2007). CAPOX was shown to be non-inferior to FOLFOX-4 as a first-line treatment for mCRC. Therefore the two regimens are expected to be equivalent in terms of efficacy and can thus be treated as equal in terms of outcomes. In addition, this assumption was validated by clinical experts (Merck Serono, 2015) who stated that the combinations of different forms of 5FU (differing infusion regimens and oral analogues) along with both FOLFIRI and FOLFOX have equivalent efficacy.

The results of this analysis do not show great difference in ICER from the base case analysis based on the OPUS study. The ICER for cetuximab plus FOLFOX compared to CAPOX.

Table 31: Scenario analysis results (cetuximab+FOLFOX vs. CAPOX) based on fortnightly cetuximab dose

	Costs	LYs	QALYs	ICER (cost per LY gained)	ICER (cost per QALY gained)
OPUS					
Cetuximab + FOLFOX	41,301.81	2.22	1.64		
CAPOX	27,576.73	1.81	1.32		
Increment (Cetuximab + FOLFOX – CAPOX)	13,725.08	0.41	0.32	33,218.53	42,852.95

3.8. Subgroup analysis

3.8.1.1. Cetuximab use in mCRC patients with metastasis confined to the liver

A scenario analysis was conducted for the RAS wild-type mCRC with metastasis confined to the liver to compare the results to those estimated in NICE Technology Appraisal 176 and demonstrate that cetuximab plus chemotherapy remains a cost effective therapy.

In this analysis, it was assumed that only mCRC patients with unresectable tumor enter the model simulation where the aim of treatment is to reduce the size of the tumor to allow its surgical removal with a curative intent. Resection rates specific to this patient subgroup were reported in post hoc studies of OPUS study (13.3% with cetuximab + FOLFOX vs 0% with FOLFOX alone) and CRYSTAL study (16.3% with cetuximab + FOLFIRI vs 6.5% with FOLFIRI alone) (Kohne, 2014). The structure of the model with the remainder of the model inputs and variables used in this analysis remain the same as the base case analysis.

The most realistic scenario amongst the analyses presented below is when considering the fortnightly cetuximab dose. The results of these analyses demonstrate that cetuximab is a cost effective option against chemotherapy alone with ICERs of £39,545.17 per QALY gained for cetuximab + FOLFIRI versus FOLFIRI alone and £28,230.19 per QALY for cetuximab + FOLFOX versus FOLFOX alone.

Table 32: Deterministic results for cetuximab + FOLFIRI versus FOLFIRI alone for the liver limited disease population, fortnightly dosing

	Costs	LYs	QALYs	ICER (cost per LY gained)	ICER (cost per QALY gained)
Cetuximab + FOLFIRI	45,421.85	2.76	2.04		
FOLFIRI	27,789.93	2.18	1.60		
Increment (Cetuximab + FOLFIRI - FOLFIRI)	**17,631.92**	**0.59**	**0.45**	**29,954.55**	**39,545.17**

Table 33: Deterministic results for cetuximab + FOLFOX versus FOLFOX alone for the liver limited disease population, fortnightly dosing

	Costs	LYs	QALYs	ICER (cost per LY gained)	ICER (cost per QALY gained)
Cetuximab + FOLFOX	43,692.45	2.30	1.69		
FOLFOX	26,198.52	1.49	1.07		
Increment (Cetuximab + FOLFOX-FOLFOX)	**17,493.94**	**0.81**	**0.62**	**21,465.02**	**28,230.19**

In NICE Technology Appraisal 176, resection rates from the CELIM study[1] were used to reflect the high rate of successful liver resection in KRAS wild-type patients with metastasis confined to the liver. This is due to the fact that resection outcomes were the primary focus of this study, unlike CRYSTAL and OPUS, and patients were enrolled with the aim of performing curative resection of the liver in specialist cancer centres. In comparison, clinical experts consulted at the time of appraisal noted that liver resection rates reported in CRYSTAL and OPUS trials were lower than that seen in UK clinical practice. Therefore, an additional analysis was run using the suggested resection rates by clinical experts consulted in TA176 who suggested that cetuximab in combination with chemotherapy was likely to result in up to 35% of patients being eligible for resection after treatment, compared to 20% with FOLFOX alone. When these estimates are used in the model using the most plausible scenario setting (fortnightly dosing) and for both pairwise comparisons (cetuximab with FOLFIRI or FOLFOX versus FOLFIRI or FOLFOX alone), the ICER for cetuximab + FOLFIRI when compared FOLFIRI alone is ICER of £ 29,784.27 per QALY, and the ICER for cetuximab + FOLFOX when compared to FOLFOX has an ICER of £ 25,601.04 per QALY. Compared to the ICERs estimated in TA176, cetuximab remains as a cost effective treatment in this patient subgroup.

3.9. Interpretation and conclusions of economic evidence

Evidence from clinical trials demonstrate that cetuximab in combination with chemotherapy provides patients with significant clinical benefit compared to chemotherapy alone and to bevacizumab. The results of the network meta-analysis supported these findings, as well as showing that cetuximab was comparable to the other anti-EGFR therapies. When considering the cost effectiveness of cetuximab in light of these findings, the analyses reported in the previous sections demonstrate that cetuximab is likely to be cost effective, particularly when compare to chemotherapy alone.

In England, the most commonly prescribed palliative treatments for mCRC are FOLFOX, CAPOX and FOLFIRI (NCIN, 2014). Therefore economic analysis including these comparators represents the most plausible scenarios to reflect clinical practice in England. In addition to this, the most plausible scenario should consider cetuximab when prescribed as a fortnightly dosing regimen.

When considering our suggested most plausible scenario, the ICER for combining cetuximab with FOLFOX is £52,588 per QALY compared to FOLFOX alone and £63,126 per QALY when combining cetuximab with FOLFIRI compared to FOLFIRI alone. These ICERs demonstrate that cetuximab is a cost effective treatment, especially when considering End of Life criteria and the

[1] Gunnar Folprecht, Thomas Gruenberger, Wolf O Bechstein, Hans-Rudolf Raab, Florian Lordick, Jörg T Hartmann, et al. Lancet Oncol 2010; 11: 38–47.

significant survival benefit cetuximab brings to the relatively small RAS wild-type mCRC patient population compared to currently prescribed treatments, which do not extend disease prognosis beyond 2 years of survival.

Economic comparisons between cetuximab and bevacizumab do not reflect clinical practice as bevacizumab is no longer funded by NHS England or the National Cancer Drugs Fund for the treatment of colorectal cancer and therefore these comparisons are not meaningful.

When focusing the analysis on mCRC patients with initially unresectable liver-limited metastasis, cetuximab plus chemotherapy demonstrated ICERs between £31,555.24 and £40,166 per QALY compared to chemotherapy alone which shows that it remains cost effective following NICE recommendation of cetuximab treatment in this patient group in NICE Technology Assessment 176 (NICE, 2009b).

One-way sensitivity analysis (OWSA) reveals that the model was most sensitive to the parameters that have direct impact on cost of treatment or survival extension. In comparison, the model is less sensitive to the liver resection rates and this can be explained by the fact this parameter only affects the survival of a subgroup of the cohort population simulated in the model; patients who undergo surgical resection. Probabilistic sensitivity analysis (PSA) reveals that there is some uncertainty surrounding the deterministic ICERs. This could stem from the impact of post hoc analysis of RAS wild type patient outcomes on the statistical significance of these outcomes since the pivotal studies were not originally powered to focus on this biomarker-stratified patient subgroup. Despite this inherent limitation of post hoc analyses, outcomes from the CRYSTAL study were statistically significant. Outcomes from the OPUS study, despite the small number of RAS wild type patients identified in this study, remain comparable to those reported in the PEAK study in which they were statistically significant.

Given the significant healthcare and humanistic burden of metastatic colorectal cancer, and the relatively limited treatment options available, it is important to have additional effective treatment options. The results of this analysis indicate that cetuximab in combination with FOLFIRI or FOLFOX not only increases overall survival versus chemotherapy alone and other anti-EGFR inhibitors, but also provides a cost effective option for the health service.

3.10. Assessment of factors relevant to the NHS and other parties

Cetuximab is currently funded for treating NHS mCRC patients through two routes: baseline NHS commissioning for mCRC patients with liver-limited metastasis, and through the NCDF in England for first-line or third/fourth-line treatment of mCRC.

If cetuximab is to be recommended for use in the NHS for first-line RAS wild-type mCRC patients following this NICE assessment, the market share of cetuximab in England is unlikely to change in the short term; the impact of a NICE recommendation for cetuximab will be in the form of transferring its funding from the NCDF to baseline NHS commissioning. In the short term, when considering budget impact, the assumption is that there will be little impact, merely a transition of funding, followed by a likely modest increase due to growing acceptance of using biological agents in first-line treatment of mCRC and the organic population growth of RAS wild-type mCRC patients. Similar assumptions can be made for panitumumab, which is also funded through the NCDF and any growth would come at the expense of the existing costs of cetuximab or panitumumab.

Clinical experts advised that physicians in the UK are more likely to continue to prefer cetuximab as an addition to chemotherapy over panitumumab as they have been prescribing cetuximab for more than 10 years and are more familiar with its clinical benefits, safety profile and the management of its adverse events. NCDF data show that although panitumumab has been allowed funding through the NCDF, there has not been any significant uptake of this drug in the UK

Since bevacizumab is no longer funded through the NCDF for the first-line treatment of colorectal cancer. The budget impact analysis presented below assumes that all newly diagnosed RAS wild-type mCRC patients which were eligible for bevacizumab therapy in the past are now eligible for cetuximab therapy instead.

In Wales, a positive recommendation would allow Welsh patients much wider access to cetuximab as there is no cancer drugs fund in Wales. It is worth noting that cetuximab is currently being assessed by AWSMG for the same indication considered in the scope of this evidence submission.

3.10.1.1. Estimation of patient numbers

Table 34: List of parameters utilized to estimate number of patients eligible for mCRC treatment with a biological agent

Population level estimate	Proportion	Number of individuals in 2015	source
General population	-	53,063,456	Office of National Statistics 2014
Incidence of CRC (per 100,000)	46.15	24,489	National Cancer Intelligence network 2011
Patients with mCRC at diagnosis	52%	12,735	Tappenden et al 2007
Patients tested for RAS biomarker status	83%	10,571	Data on File Merck Serono
Patients with RAS wild type mCRC	53.2%	5,623	Calculated from Heinemann et al , 2014
Percent of 1st line RAS wild-type patients treated with a targeted therapy	72%	4,049	Data on File Merck Serono

As the estimates are derived from the general patient population in England, a projected general population growth rate of 0.7% (Office of National Statistics, 2014) was utilised to estimate the size of the population in the next 5 years.

Table 35: Estimated number of RAS wild type mCRC patients eligible for treatment with biological agent and chemotherapy combination

Year	2015	2016	2017	2018	2019
Number of patients	4,162	4,191	4,221	4,250	4,280

3.10.1.2. Market share assumptions

Based on Merck Serono's market research, market shares were estimated to start at 62% by the end of 2015 increasing gradually to 80% of RAS wild-type mCRC patients who would receive a targeted therapy by 2019 conditional on the recommendation of cetuximab upon this HTA. Paninumumab was included to reflect clinical reality despite it not being included in the scope. It was also assumed that a third of patients receiving cetuximab will receive FOLFOX chemotherapy with it. The remainder will receive FOLFIRI chemotherapy with cetuximab.

Table 36: Market share estimates for cetuximab + chemotherapy and panitumumab + FOLFOX

	2015	2016	2017	2018	2019
Cetuximab + Chemotherapy predicted uptake	62%	65%	70%	75%	80%

3.10.1.3. Results

All costs were based on cetuximab fortnightly dosing schedule as it is a reflection of clinical practice in England and Wales, and cetuximab's discounted NHS price.

As mentioned previously, the increase in cetuxiamb uptake is due to growing acceptance of biological agents as treatments for mCRC in the presence of a NICE recommendation. This increase is estimated to be 11.6% over the period of 5 years, which is a modest increase due to the fact that cetuximab is currently funded by the NCDF.

Table 37: Budget impact analysis results based on cetuximab (Erbitux) list price and fortnightly dose

	2015	2016	2017	2018	2019	Cumulative (5years)
World with current cetuximab uptake	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
World with increased cetuximab uptake	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net Budget Impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% increase/ decrease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

3.10.1.4. RAS biomarker testing

RAS biomarker testing is already an established practice in NHS hospitals. Merck Serono had funded (K)RAS testing in the UK (KRAS initially, but this was widened to include all RAS - KRAS & NRAS in codons 2, 3 & 4) until May 2014 when the NHS started funding these tests. Merck Serono helped increase the volume and quality of RAS testing and continues to drive the implementation of efficient RAS testing pathways for the NHS.

RAS biomarker testing is only conducted at the point of diagnosis of metastatic colorectal cancer (mCRC) when patients are deemed suitable for treatment with a targeted anti-EGFR therapy, such as cetuximab. It is estimated that 83% of mCRC patients are tested for RAS mutations but not all patients who are identified as RAS wild-type go on to receive an anti-EGFR therapy in combination with chemotherapy – patient and clinician choice and any medical contra-indications would determine that decision.

The purpose of the RAS test is to identify patients who do not have RAS mutations, which is a predictive factor to indicate potential response to treatment with a cetuximab regime. RAS testing is a cost-efficient way to determine the patients who are most likely to benefit and it avoids cetuximab treatment for patients who have RAS mutations who would not benefit. This position is recognised in the NIHR HTA report on KRAS mutation testing (Westwood et al., 2014).

The NIHR report also found that there was no strong evidence that any one method of KRAS mutation testing had greater accuracy than any other. All available assays were equally accurate for predicting tumour response for with cetuximab plus standard chemotherapy. With the advancement of biomarker testing methods, some molecular diagnostic laboratories in the UK are now using panel testing where multiple tests for KRAS, NRAS and many other mutations of potential interest are conducted simultaneously in order to be more efficient. The cost of RAS mutation testing applied in the cost effectiveness model described in the economic section represents the national NHS tariff for this type of test.

Appendices

List of the appendices (supplied separately)

Appendix A: Clinical Evidence

Appendix B: Economic Section

Appendix C: Systematic literature review

Appendix D: Network Metanalysis

Appendix G: Confidential information checklist and guidance note

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1 May 2015

Dear Mr Powell

Joint letter on behalf of Beating Bowel Cancer and Bowel Cancer UK - Re: Cetuximab (review of TA176) and panitumumab (partial review of TA240) for the first line treatment of metastatic colorectal cancer

Beating Bowel Cancer and Bowel Cancer UK both feel strongly that it is appropriate to recommend this treatment, in light of the enormity of bowel cancer prevalence and the number of patients who still present when the disease has reached an advanced stage. As the two leading charities that provide advice and support for people affected by bowel cancer, we take a keen interest in developments relating to the care and treatment of bowel cancer patients and their families.

The UK lags significantly behind Europe in its treatment options available to advanced bowel cancer patients on the NHS. At present, patients in England are only able to access proven, clinically effective treatments which could extend their lives through the Cancer Drugs Fund. In light of the current de-listing of cancer drugs from this fund we are facing the real possibility that treatments such as cetuximab first line may be at risk from further budgetary actions on behalf of NHS England.

To receive a diagnosis of advanced bowel cancer is devastating and of course has a huge psychological impact on the patient and their family. Given the poor prognosis for these patients, treatment options aim primarily to manage the range of related physical symptoms in order to maximise quality of life and extend survival. Following such a diagnosis it is vital that patients are assured that they have access to the best known and clinically proven treatment options for their stage of diagnosis.

The evidence we have from patients who contact both our organisations, both documented and anecdotal, stress the very real benefits that they obtain when treated with these new targeted therapies which have significant potential to improve their survival and their quality of life. They place great value on extended survival no matter how limited this may be, and desperately seek the opportunity to take a treatment which enables them to make the most of the time left to them and allow them time to address practical issues with their families and dependants. Many have been able to return to work, make personal preparations with their loved ones giving them the control and dignity they desire in the time they have left. This has also provided psychological relief to families, time to plan and time to say goodbye in some cases.

The value of experiencing extra months, allowing patients time with their partners, children, families and friends, should not be underestimated for a person diagnosed with advanced bowel cancer. We would also like to see that the importance of extended life expectancy is given the highest priority when measuring outcomes. Patients with advanced metastatic colorectal cancer have among the worst survival rates - only 7 per cent of people with advanced bowel cancer survive for more than five years – and they rely on combinations of surgery, radiotherapy and drug treatment to extend survival. 50% of patients will survive for less than 24 months from initiation of 1st line treatment for metastatic bowel cancer using standard chemotherapy options. Therefore there is an unmet need in improving survival in this patient population, that targeted therapies can help address.

Access to targeted therapies such as cetuximab and panitumumab are vital treatments at a stage when there are limited options and short life expectancy. These treatments, in combination with chemotherapy, are an essential component of the range of treatment options that must be available to patients with advanced bowel cancer – especially given the poor survival rates for patients with advanced disease. The fact that these drugs can be targeted to specific patients by identifying which patients have the potential to benefit the most from them, by simple genetic RAS tests, means that these options should offer both effective treatment options and value for the NHS.

Considerable progress has been made in recent years to understand and identify ways in which genetic tests can be carried out to identify groups of patients who are most likely to respond to modern therapies. For people with advanced bowel cancer, this means having access to a RAS test that can help clinicians decide the optimal treatment choice to allow them the chance of better survival. People with bowel cancer are still missing out on the test and therefore treatment. Having NICE guidance to support and encourage testing and offering people the right treatment option, could move a considerable way to bringing bowel cancer in line with the testing and treatment rates seen in the management of breast and lung cancers, where biomarker testing and treatment has become more routine.

We understand that NICE has to make decisions based on clinical and cost effectiveness. This current review is crucial to provide a long term funding solution and give patients access to these important targeted therapies. Effective stratification of patients based on identifying those who are more likely to respond to treatment offers an attractive option to maximise resources and improve outcomes – the principle of ‘the right treatment, for the right patient, at the right time’.

In the context of uncertainty over the future of the Cancer Drugs Fund in England as it comes under increasing cost pressures; as well as access for patients in Wales already being very limited, we are keen to see a step change towards more equal access.

In order to make sure bowel cancer survival rates in England are amongst the best in the world, a number of key steps must be taken. In addition to investment in screening and diagnosis, there must be better and equal access to treatment. The best way to ensure this is through a positive recommendation for the above review by NICE.

For these reasons Beating Bowel Cancer and Bowel Cancer UK urge NICE to recommend cetuximab (Erbitrux) for the treatment of metastatic bowel cancer.

Yours sincerely

[redacted], Beating Bowel Cancer

[redacted], Bowel Cancer UK

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

Cetuximab (review of TA176) and panitumumab (partial review of TA240) for the first line treatment of metastatic colorectal cancer – ID794

Name: Statement submitted by [redacted] on behalf of:

Organisation: NCRI/RCP/RCR/ACP

Comments coordinated by: [redacted]

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Patients with metastatic colorectal cancer (CRC) may be treated in a number of ways depending on patient characteristics such as performance status and co-morbidities, tumour burden and the potential toxicities of the treatment, previous exposure to adjuvant or neo-adjuvant systemic anti-cancer therapies as well as patient and clinician preference.

In patients with a poorer performance status, who are asymptomatic or have a low tumour burden, single agent therapy with capecitabine or infusional 5-fluorouracil (5FU) and folinic acid may be offered.

In patients with better performance status, who are symptomatic or have a high tumour burden, combination chemotherapy using either oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) in combination with 5FU and folinic acid or capecitabine, is more likely to be offered (NICE clinical guideline 131). Patients with liver metastases that may become resectable can receive cetuximab in combination with FOLFOX or FOLFIRI according to NICE guidance (TA176).

In England only, patients with more widespread metastatic disease can access cetuximab if they have RAS wild type tumours via the Cancer Drugs Fund (CDF) in combination with either FOLFIRI or FOLFOX as first line therapy. Until 12th March 2015 this was also true of bevacizumab, but this has now been removed from the CDF list for first line treatment. Panitumumab has not been available outside of clinical trials until the latest CDF update, but it is now available in the first line setting in combination with FOLFOX (but not FOLFIRI).

Chemotherapy may be given for 4 to 6 months followed by a treatment holiday, or continued until evidence of disease progression. Decisions regarding treatment duration are based upon response, toxicities and patient wishes.

This summary of options is fairly standard across the NHS, although access to biological agents through the CDF is only routinely available for patients in England, with limited and variable but evolving availability in Scotland, Wales and N. Ireland.

Initial studies investigated outcomes in all patients regardless of mutational status, but subsequent analysis showed those patients with wild type in exon 2 had improved outcomes compared with patients carrying mutation in this gene. In 2014, further evidence demonstrated that the population benefiting from these agents could be further defined by extending mutational analysis to additional exons in the gene (exons 3 and 4) and in the NRAS gene (exons 2, 3 and 4). In these patients overall survival was significantly increased.

The advantages of adding cetuximab to combination chemotherapy (FOLFIRI and in some trials FOLFOX) has been a demonstration of increased response rate, increased R0 surgical resection of metastases and in Ras wild type patients improved overall survival, but is associated with increase in some toxicities particularly related to the skin and infusional reactions. Similar findings have been demonstrated in Ras wt patients when panitumumab was added to FOLFOX.

This appraisal is addressing the role of both cetuximab and panitumumab in combination with chemotherapy in first line treatment of patients with metastatic CRC. Direct standard of care comparators are therefore various combinations of chemotherapy without an added biological or chemotherapy in combination with bevacizumab.

For patients who have RAS wild-type CRC, the addition of either cetuximab or panitumumab clearly improves overall survival and in those patients with liver-only disease, provides an increased chance of potentially curative resection. In those patients with RAS mutant tumours, there appears to be a detrimental effect. The FIRE-3 trial showed a clear advantage of FOLFIRI plus cetuximab over bevacizumab (median overall survival 33.1 months vs 25.0 months respectively (HR 0.697, p = 0.0059), while the CALGB 80405 trial in which FOLFOX was the predominant chemotherapy backbone showed similar outcomes from the addition of either cetuximab or bevacizumab (median overall survival 32 months vs 31.2 months respectively, p = NS).

There are no other licensed technologies targeting EGFR, although the role of multiple other EGFR targeting agents alone or in combination are currently in phase I, II and III trials in metastatic CRC.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

Patients with poor performance status and a life expectancy of less than 3 months are unlikely to benefit from the addition of cetuximab, unless a very rapid anti-tumour response will reverse these (this only applies to a small proportion of highly selected individuals).

In patients with small volume and relatively indolent disease, the excess toxicity of the addition of these agents to combination chemotherapy may outweigh the additional benefit, but this will be a decision come to by the patient with their oncologist.

However, in patients with good performance status who have high volume, rapidly progressive disease, clinicians routinely wish to treat with a combination of drugs offering high response rates in order to try and gain rapid control of their disease. The same is also true for patients with liver-only metastatic disease who may become resectable, and then may achieve a 25-44% 5 year survival rate.

Patients have previously been selected to received cetuximab and panitumumab based on EGFR over-expression (which we now know is not a useful predictive biomarker) and the

absence of activating mutations in exon 2 of the gene. More recent studies have investigated the effect of other activating mutations within the and NRAS genes.

The PRIME study initially enrolled patients with and without mutations in exon 2, but later just patients who were wild-type. The study showed that the use of panitumumab was detrimental in patients who carried mutations in exon 2 , but improved overall survival compared to chemotherapy alone in the wild-type group. Further mutational analysis was subsequently performed on the exon 2 wild-type patients to investigate the effect of additional mutations within exons 3 and 4 of and exons 2, 3 and 4 of NRAS. Additional mutations were detected in 17% of these patients. Analysis of efficacy on this population again showed that panitumumab was detrimental in patients with the additional mutations, but that the overall survival in the wild-type group improved further with an overall survival of 26.0 months in those who received panitumumab with chemotherapy compared to 20.2 months in those who received chemotherapy alone.

The FIRE-3 study comparing FOLFIRI plus cetuximab with FOLFIRI plus bevacizumab has also demonstrated the importance of additional mutational testing to further define a patient population who will benefit from cetuximab. Further mutations in exons 3 and 4 and NRAS exons 2, 3 and 4 were demonstrated in 15.8 % of the exon 2 wild-type population. Survival analysis showed additional benefit in terms of overall survival, increasing from 28.7 months in the exon 2 wild-type population to 33.1 months in the RAS wild-type group. Similar results have been demonstrated in the CALGB 80405 study, and in reanalysis of data from the OPUS and CRYSTAL studies after extended RAS mutational testing.

The use of expanded RAS testing therefore further defines a population who are most likely to benefit from these therapies. The presence of activating mutations in the BRAF gene (in approximately 6-10% of patients with metastatic CRC) or in exons 9 and 20 of the PIK3CA gene have not been definitively shown yet to be predictive markers for benefit or not for EGFR inhibitors, and thus are not in the recently updated license for either cetuximab or panitumumab.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

Cetuximab and panitumumab should only be prescribed by specialist colorectal oncologists in secondary care. Clear, rapid pathways for analysis of RAS mutations are required for all patients so that treatment decisions (and better information on patients on prognosis) can be made promptly. This may require further investment in molecular pathology and diagnostic services across the UK.

Education of all professionals involved in acute oncology services is required to ensure that the appropriate and prompt management of toxicities (particularly skin rash and hypomagnesaemia) occurs.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Cetuximab is currently available both via TA176 and through the SMC for patients with liver-only metastatic disease which may become resectable through downsizing from a good anti-tumour response. It is also available in England via the Cancer Drugs Fund for patients with more widespread metastases. It is used only in patients who have RAS wild type metastatic CRC.

Cetuximab is licensed to be given weekly, with an initial loading dose of 400 mg/m^2 and then 250 mg/m^2 per week. However, the CDF specifies use every 2 weeks at a dose of 500mg/m^2. This has been shown to be pharmacologically equivalent to the weekly regimen, and is less burdensome for patients and the NHS.

Until 12th March 2015 when panitumumab became available to patients in England via the CDF on 12th March 2015, again in RAS wild type patients, it had largely only been used in centres conducting clinical trials. Therefore experience of its use amongst clinicians is more limited. It is not available to the NHS in Scotland, Wales or N. Ireland.

Both drugs are used in CRC in clinical trials (eg in combination with BRAF inhibitors in BRAF mutant metastatic CRC).

P*lease tell us about any relevant* ***clinical guidelines*** *and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.*

The current NICE clinical guideline 131 suggests the use of oxaliplatin containing regimens as first line therapy for metastatic colorectal cancer followed by irinotecan either as single agent or in combination with infusional 5FU. The use of biological agents is not discussed.

The European Society of Medical Oncology published guidelines for the management of metastatic colorectal cancer in December 2014. They comment that EGFR positivity, as determined by immunohistochemistry (IHC), is not a relevant predictive marker, but recommend that testing is performed for activating mutations in exons 2, 3 and 4 of both KRAS and NRAS. In first-line RAS wild type metastatic CRC, ESMO recommend EGFR antibodies in the following situations: (i) added to FOLFIRI or FOLFOX to increase tumour shrinkage and secondary resectability, (ii) added to FOLFOX or FOLFIRI as palliative treatment, particularly in patients with relevant tumour-related symptoms who will benefit from the earlier onset of response (iii) as a possible addition to palliative chemotherapy in 'never-resectable' metastatic disease in selected patients

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

All patients with metastatic disease will require tumoural KRAS and NRAS mutational testing to be performed before decisions on treatment are made. These are important prognostic and predictive markers. The case for additional testing for activating mutations in BRAF is strong (both for prognostication and for decision on appropriate therapies in first-line such as avoidance of EGFR antibodies outside of relevant clinical trials), and this is the preference of our professional organisations.

If cetuximab and panitumumab were to be more widely available as first line therapy in addition to chemotherapy in patients with RAS wild type metastatic CRC, there are likely to be implications in delivery.

Patients receiving FOLFIRI as their first line combination have a PICC / central line inserted in order to give the infusional 5FU. Many patients receive Oxaliplatin in combination with

capecitabine as first line therapy rather than FOLFOX. Cetuximab and panitumumab is not recommended in combination with capecitabine, due to increased risk of diarrhoea and other toxicities, and possible diminished benefit compared to infusional 5FU. These patients would therefore be given FOLFOX which would require insertion of a PICC or central line.

Delivery time on chemotherapy day units would also increase, by moving from 3 weekly oxaliplatin and capecitabine to 2 weekly FOLFOX which would require extra visits. If cetuximab is given weekly, as per license, additional visits would also be required. We recommend that it should be given 2 weekly wherever possible.

Due to the risk of allergic reactions, patients receiving cetuximab routinely receive pre-medication with anti-histamines and steroids and require observation after the infusion. Panitumumab is a fully humanised antibody and therefore does not require pre-medication. Oral tetracycline antibiotics are often given to proactively manage the skin toxicity. Hypomagnesaemia can occur, and monitoring for this is needed and patients may require oral or intravenous magnesium supplementation.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

All patients with metastatic disease would require RAS testing to be performed before decisions on treatment options are made. Only patients with RAS wild type tumours should be offered these agents. For the reasons given above, we also recommend that BRAF mutational testing should be performed.

EGFR inhibitor treatment should be discontinued on disease progression assessed radiologically or where the patient's clinical condition means these are no longer appropriate or where unacceptable toxicities are experienced despite dose modifications/delays and adequate supportive care.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

The COIN and CRYSTAL trials were run in UK, but the other trials were run in the USA and other European countries. However, they are definitely representative of mainstream UK practice. Although patients with a performance status of 2 were eligible in the majority of the trials, they only accounted for 4-10% of patients randomised. In the current UK practice these patients would make up a greater percentage of the metastatic colorectal cancer population, but many would not be offered combination chemotherapy or EGFR inhibitors.

The most important outcome for patients with potentially resectable liver disease is R0 resection rate and a significant improvement in this was demonstrated with cetuximab in CRYSTAL, OPUS and FIRE-3 but not in COIN. The PRIME study using panitumumab also demonstrated an improvement in R0 liver resection rate.

For other patients with widespread, inoperable metastatic disease, progression-free survival (PFS) and overall survival are the most important outcomes and were measured in all the studies mentioned. In trials comparing chemotherapy with chemotherapy plus cetuximab, the

addition of cetuximab demonstrated improvement in both PFS and overall survival. However, this benefit was not demonstrated in trials using an EGFR inhibitor with oxaliplatin in combination with capecitabine. Panitumumab in combination with FOLFOX has also demonstrated improved PFS and overall survival when compared to FOLFOX alone.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

The principle increase in grade 3 to 4 toxicities seen with the addition of cetuximab to either FOLFOX or FOLFIRI or panitumumab added to FOLFOX are related to the skin (with acneiform rash and nail changes predominating), but also diarrhoea, mucositis, fatigue and hypomagnesaemia. Additional toxicities which are less commonly seen include conjunctivitis, keratitis, cardiovascular toxicity and interstitial pneumonitis. When severe, the acne-like skin rash can have a significant impact on quality of life, both in terms of appearance and in some severe dryness and itch. The rash can generally be controlled with topical or systemic antibiotics and tends to fluctuate in intensity over time. Cetuximab commonly causes infusional reactions, which are mild for most patients, but severe reactions can occur and in these cases cetuximab should be discontinued.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

These are not applicable, and abundant evidence for this review is available from multiple, large, randomised phase III trials.

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

NHS staff are already familiar with giving cetuximab. Fewer staff will have experience in giving panitumumab, unless involved in clinical trials, but this has less infusion reactions and adds no additional resource for that needed for cetuximab.

The main issue in terms of delivery would be the additional time required to give the monoclonal antibodies in Chemotherapy day units and the requirement for those patients receiving oxaliplatin-based chemotherapy to have infusional 5FU (rather than oral capecitabine) and the need for insertion, and maintenance of a central or PICC line.

Additional resources in molecular pathology for widespread KRAS and NRAS extended mutational testing (and also BRAF mutational testing) may be required in some regions of the UK, if approved for all appropriate patients with first-line RAS (and RAF) wild type metastatic disease.

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

We believe that the only impact on equality would be failure to ensure implementation of this NICE guidance equally across the UK.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Cetuximab (review of TA 176) and panitumumab (partial review of TA240) for first line metastatic CRC

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation The Christie Hospital NHS Trust, Manchester

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? YES
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? YES
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?
- other? (please specify)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

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Despite the use of modern systemic therapies the five year OS for patients with unresected stage IV colorectal cancer is in the region of 5-10%. In clinical practice, we are always looking out for patients with stage IV disease who could become candidates for resection of their metastasis. Primarily but not exclusively this involves resection of liver metastasis.

Unfortunately however in practice at initial presentation 75-90% of patients with liver spread are **not** candidates for curative liver resection. This is mostly on account of the proximity to critical structures, distribution and les often the size of the liver metastasis. Another very crucial factor is the volume of normal liver that can be safely left behind after removing the diseased section.

From an oncologist perspective therefore once potential resection cases identified (i.e. liver limited disease) then we maximise our efforts to send them for surgery. With good response however only additional 15% of the initially unresectable patients do proceed for surgery.

As per retrospective long term & large population studies they do significantly better compared to patients not having curative resection.

As treating clinicians therefore we maximise number of drugs that we can give to (fit) highly selected patients and use combinations of chemotherapy plus biological agent

esp. anti EGFR antibodies. There is a very good correlation between response rates to chemotherapy and resection rates in studies with liver limited CRC.

Clinical practice today (consistent with NCCN 03/2015 guidelines):

Currently NICE guidelines allow use of FOLFOX or FOLFIRI with cetuximab in Ras wild type populations (we only use it if kras + nras wild type). We do not combine cetuximab with capecitabine containing regimes (XELOX excluded). If ras mutant- we consider FOLFOXIRI in fit patients (not within scope of current discussion)

To limit the development of hepatotoxicity we recommend radiological (and MDT) re-evaluation after 2 months of systemic + targeted agent.

Some selected trials
Folprecht G Lancet Oncology Ann Oncology 2014 CELIM study
Tan BR (abstract) GI ASCO 2009
Ye LC JCO 2010
Petrelli F- a metanalysis Int J Colorectal Diseases 2012
ESMO guidelines Ann Oncology 2014

If patients have upfront clearly resectable disease use of anti – EGFR agents is **not recommended** as per New EPOC data (Primrose Lancet Oncology 2014)**.**

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology

be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

****

Cetuximab is already being used as part of TA176 guidelines and funded for NHS patients. As per licensed indication and data, clinicians and pharmacists have already restricted use to extended Ras wild type only tumours. Panitumumab is generally only used in TA176 type indication if there is cetuximab hypersensitivity.

Currently (and this is an ever dynamic situation) both these anti-EGFR agents are available within Cancer Drug Fund (CDF) in treatment naïve ras wild type patients in combination of chemotherapy. This is the second funding stream via which these drugs can be accessed (unless CDF rules change again).

Anti-EGFR agents are ubiquitously associated with cutaneous toxicities (as the main one). Considering the intent of therapy (taking patient to a curative paradigm) and the finite short duration of anti-EGFR in this indication, toxicity is generally not a concern and is manageable.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

No concerns

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

****

Already in implementation – no concerns

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Appendix K – clinical expert statement declaration form

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

Cetuximab (review of TA176) and panitumumab (partial review of TA240) for the first line treatment of metastatic colorectal cancer

Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the submission made by NCRI/RCP/RCR/ACP and consequently I will not be submitting a personal statement.

Name: [redacted]

Signed:

Date: 24/06/15

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient carer organisation submission (MTA)

Peninsula Technology Assessment Group (PenTAG)Thank you for agreeing to give us your views on the treatment(s) being evaluated by NICE in this appraisal and how it/they could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

1. About you and your organisation

Your name: [redacted]

Name of your organisation: Patient

Your position in the organisation: N/a

Brief description of the organisation: N/a

(For example: who funds the organisation? How many members does the organisation have?)

We are asking for your collective view as an organisation and will be asking patient experts for their individual input separately. If you have the condition, or care for someone with the condition, you may wish to complete a patient expert questionnaire to give your individual views as well.

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition

I have been living with Bowel cancer for 3 and a half years (DX March 2012) I have had major surgery on both my bowel and Liver and live with a permanent ileostomy.

I began a cetuximab Irinoteacan regimen after first and second line treatment failed and was given a terminal prognosis in February 2013 (6-12 month life expectancy) before commencing this treatment.

This was a particularly difficult time for me and my family as we came to terms with this (I have 3 young daughters). I have now been on this treatment for 2 and a half years. My family and I have made our lives work around the treatment cycle. Planning for good weeks where the effects of the treatment are less pronounced.

6 months into this treatment I began training for a marathon (this was a lifelong goal) and I have since run 18 marathons in as many months, as well as numerous shorter races and an 11 day fitness challenge that took in the National 3 peaks and 450 miles of cycling.

My quality of life has massively improved since commencing this treatment and I believe I would not be alive today without it.

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers (That is what would patients or carers like treatment to achieve) Which of these are most important If possible please explain why

Increased life expectentancy is obviously a massively important outcome for me. At the time I began this treatment it was the hope I would have an additional 6-12 months. This would have meant me seeing my youngest daughters 2nd birthday, my middle daughter starting Primary school and given me valuable time to prepare with my family. Given that I have outlived this by a significant amount I am grateful for everyday I have with them.

Part of this is also the quality of life I am able to have. In a 2 week cycle I usually have 3-4 days of feeling exhausted and nauseous. The other days I am able to live a fairly normal life, be sociable, take my children to school etc.

I have been lucky with the side effects from this treatment. If they were less controlled this would obviously have an impact on my quality of life. However, this doesn't effect the larger implication of a shorter life expectancy.

Another massive consideration is the way in which my oncology team have worked with us as a family to ensure we are able to fit family life around treatment They have been incredibly supportive

What do patients or carers consider to be the advantages of the treatment(s) being appraised?

Please list the benefits that patients or carers expect to gain from using the treatment(s) being appraised

These are the advantages I have personally experienced:

Extended life expectancy

Improved quality of life

Improved physical symptoms

Reduction in disease mass

Please explain any advantages described by patients or carers for the treatment(s) being appraised compared with other NHS treatments in England

The previous 2 treatment given to me did not work and disease continued to spread. This is the biggest advantage.

I also feel there have been fewer and more manageable side effects than I experienced on previous regimens.

If you know of any differences in opinion between patients or carers about the benefits of the treatment(s) being appraised please tell us about them

N/A

What do patients and/or carers consider to be the disadvantages of the treatment(s) being appraised?

Please list any concerns patients or carers have about current NHS treatments in England

Side effects from other treatments included:

Peripheral Neropathy

Sensitivity to cold

Effect on taste and appetite

Increased fatigue

Having to keep the pump on at home for 3 days

Decreased quality of life (unable to do much at all!)

Please list any concerns patients or carers have about the treatment(s) being appraised

I have a minor regarding the Cetuximab rash and also loss of hair that have been specific to this treatment. However, given the list of advantages and benefits, and in comparison to previous treatments, I am very happy continuing this treatment for as long as possible.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment(s) being appraised please tell us about them

4. Patient population

Are there any groups of patients who might benefit more from the treatment(s) than others If so please describe them and explain why

Are there any groups of patients who might benefit less from the treatment(s) than others If so please describe them and explain why

5. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment(s)

☐ Yes ☐X No

If you answered 'no' please skip the rest of section 7 and move on to

Equality

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

Are there groups of patients who would have difficulties using the treatment(s) being appraised or currently available treatments Please tell us what evidence you think would help the Committee to identify and consider such impacts

N/A

6. Other issues

Do you consider the treatment(s) being appraised to be innovative

☐ Yes ☐ No

If yes please explain what makes it significantly different from other treatments for the condition (If this applies to more than one treatment that is being appraised please give reasons for each one)

Are there any other issues that you would like the Appraisal Committee to consider

It has been my experience that Oncologists gain a wealth of practical knowledge throughout their working life that cannot always be quantifiable. They are able to use this to determine what they 'feel' will work for an individual patient and how they may or may not cope with the side effects. This experience cannot be underestimated. I know from discussing with many other patients that Cancer is an individual experience, both in qualitative and clinical aspects. Broad statements and research are not always applicable.

7. Key messages

In no more than 5 bullet points please summarise the key messages of your submission

- Cetuximab has enabled me to have extended life expectancy and increased quality of life
- The side effects are manageable

The treatment has reduced my disease mass significantly in Bowel, Liver and Lymph node

- Specialist Oncologists experience should not be underestimated

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

Cetuximab (review of TA176) and panitumumab (partial review of TA240) for the first line treatment of metastatic colorectal cancer [ID794]

Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the submission provided by Beating Bowel Cancer and consequently I will not be submitting a personal statement.

Name: .....

Signed: ..

Date: 15. 10. 15