NICE National Institute for Health and Care Excellence

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

Assessment Report

Redacted version for consultation – commercial-in-confidence and academic-in-confidence information removed

Produced by: Peninsula Technology Assessment Group, University of Exeter

STRICTLY CONFIDENTIAL

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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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.

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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/

Contents

List of tables

List of figures

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.

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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:

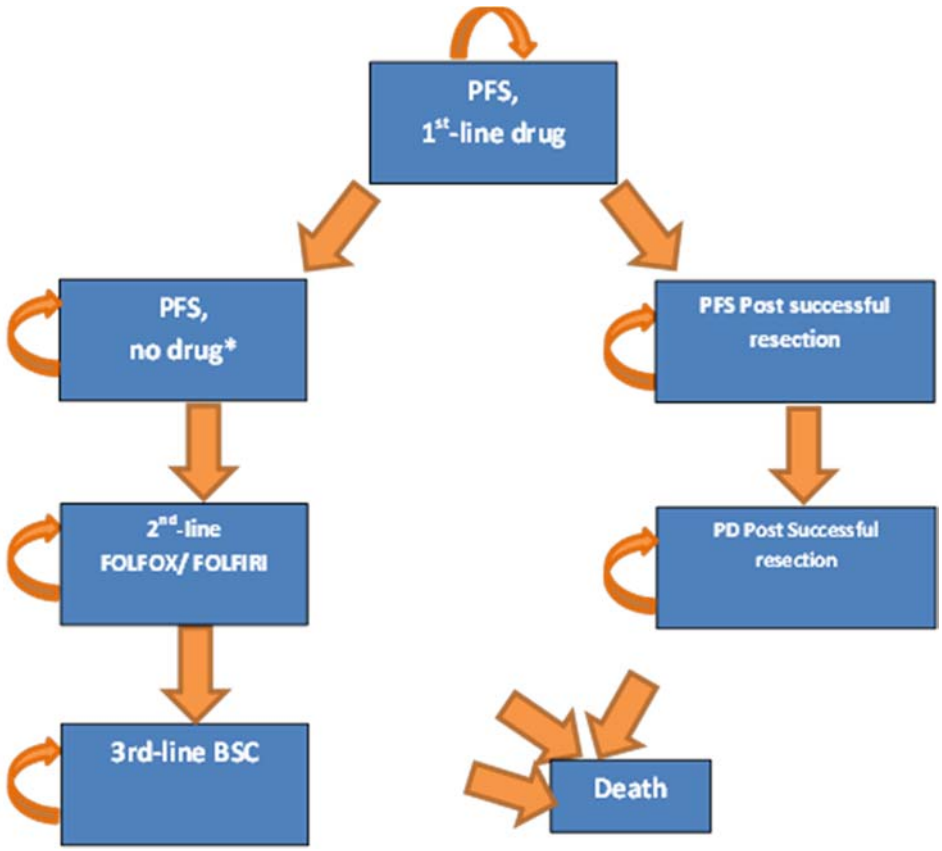
- Resection rates,
- PFS for unresected patients.
- Treatment duration

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.

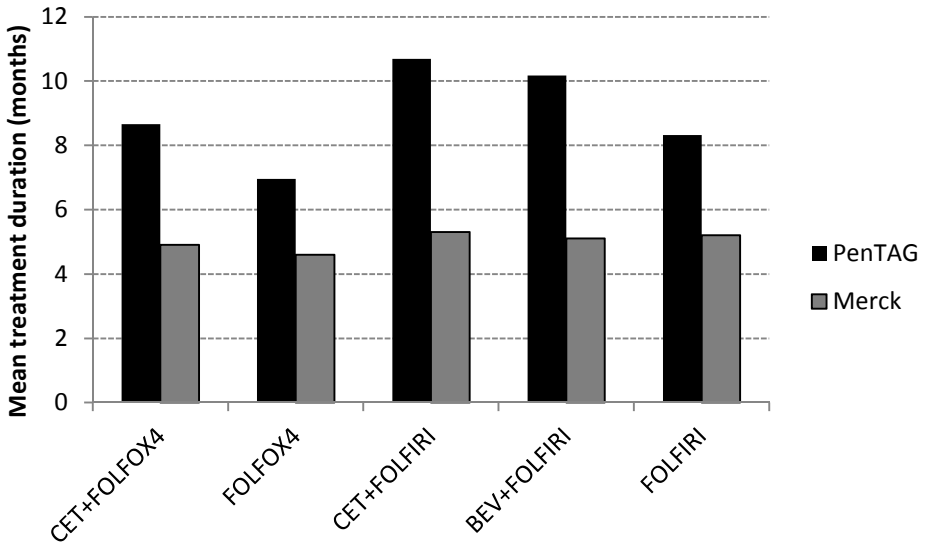
The model itself contained some minor errors and inconsistencies, but we found no major wiring errors.

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.

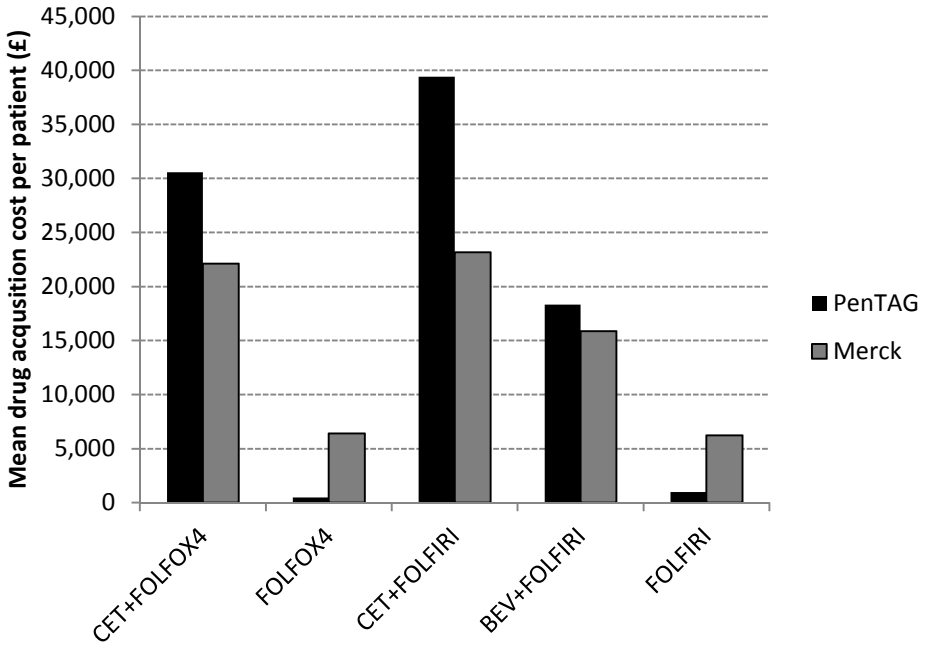
Merck Serono assume that no 1st-line drugs are given after a certain cut-off time, which varies slightly by treatment arm. Strangely, they provide no justification for the cut-off. Further, we note that Merck Serono assumed a similar cut-off time in their model for cetuximab and cetuximab+irinotecan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

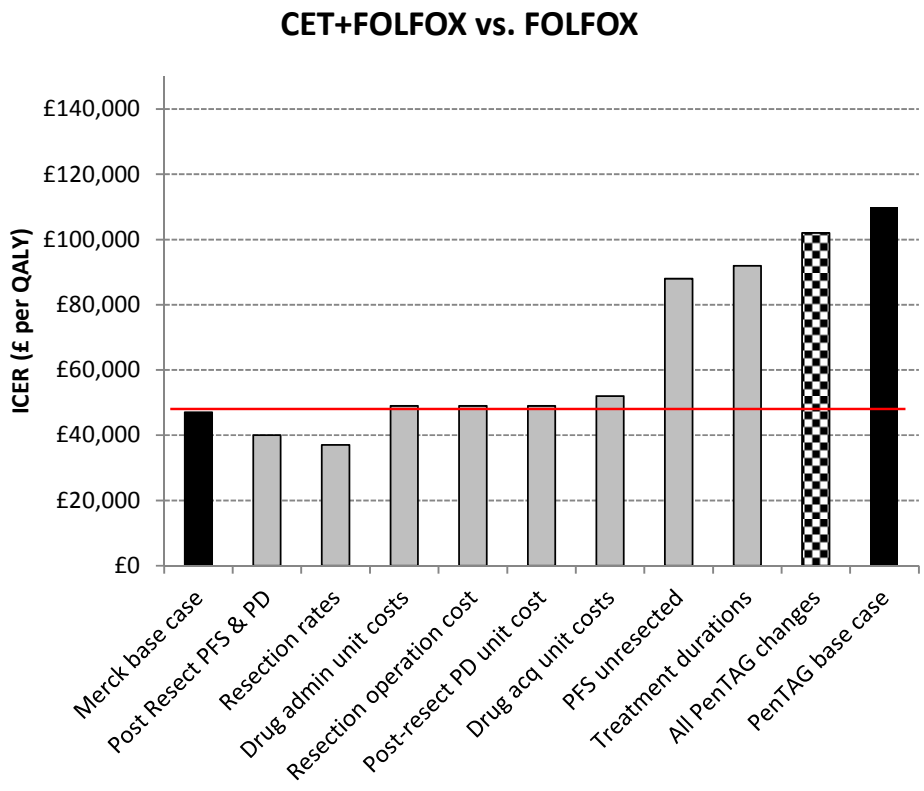
There are four other factors which contribute to the PenTAG model having higher ICERs than Merck Serono's model:

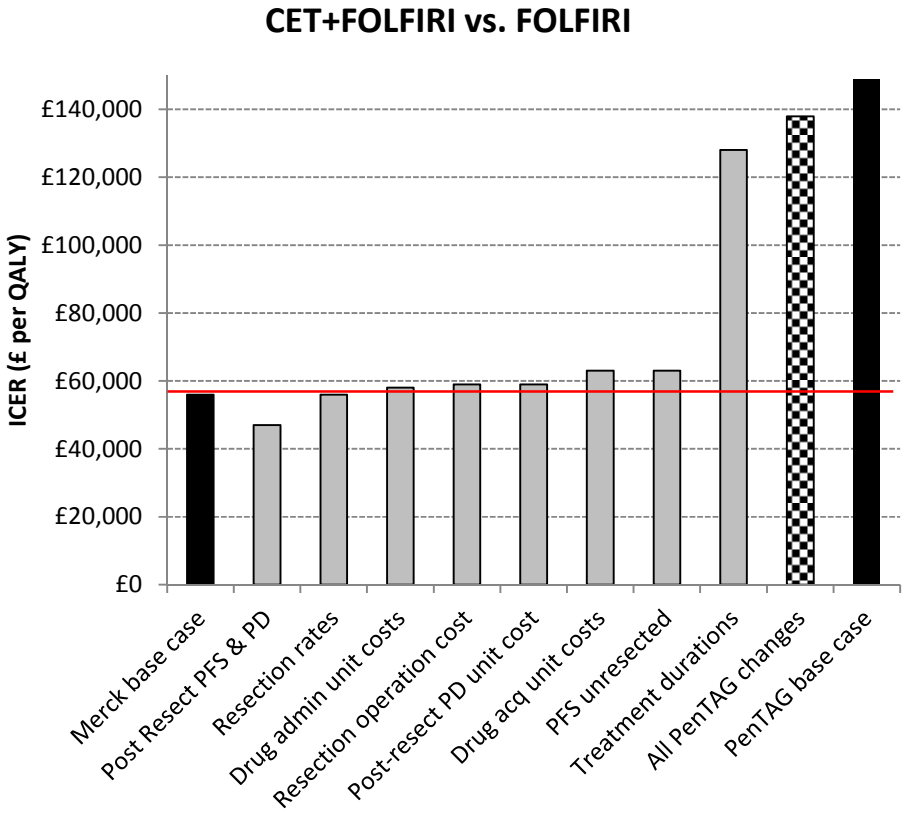
- We assume far higher unit costs of drug administration than Merck Serono. Our values yield slightly higher ICERs because we assume that patients are on treatment for longer on CET+FOLFOX than FOLFOX and for longer on CET+FOLFIRI than FOLFIRI.
- We assume a far higher cost for resection operation than 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]

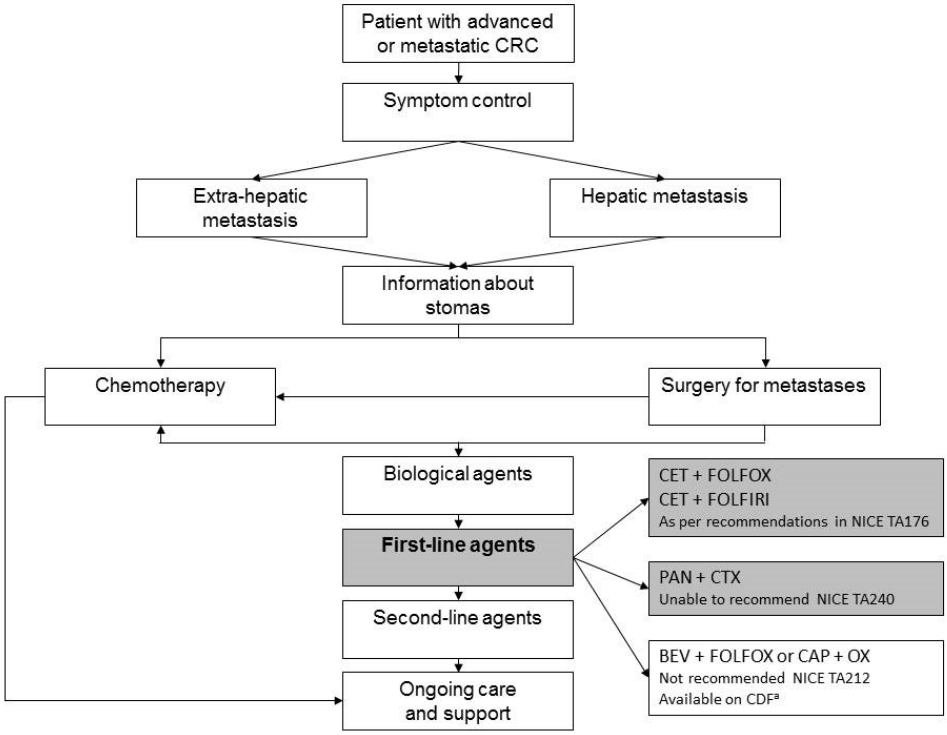
1.2.1. Management of disease

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]

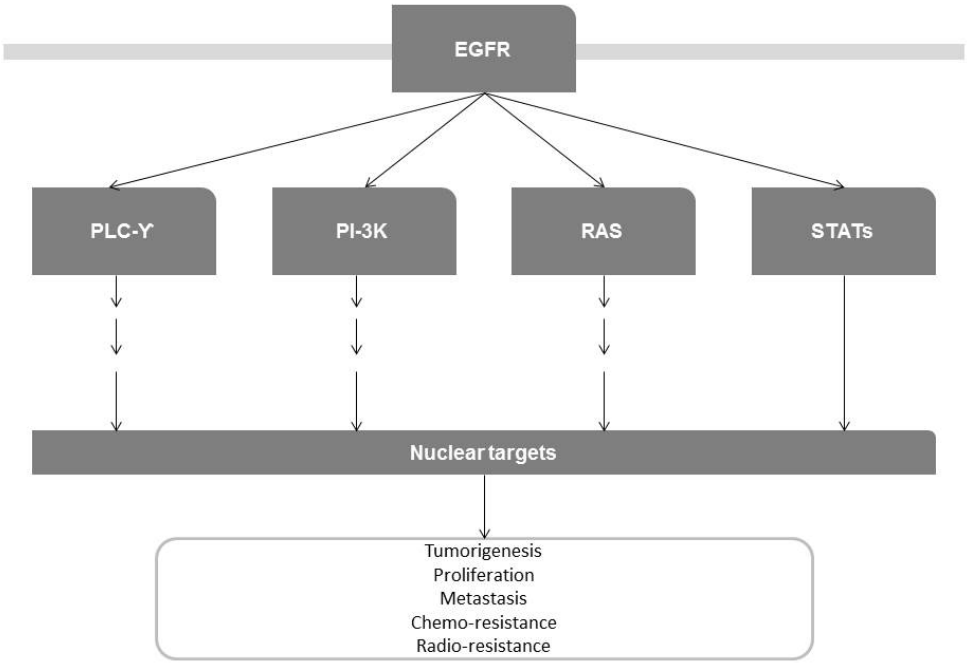
Chemotherapy may be combined with biological agents such as cetuximab (currently recommended for people satisfying criteria specified in NICE Technology Appraisal (TA) 176 [see Section 1.2.2.1]), panitumumab (see Section 1.2.2.2), and bevacizumab (see Section 1.2.2.3). Although bevacizumab is included 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]

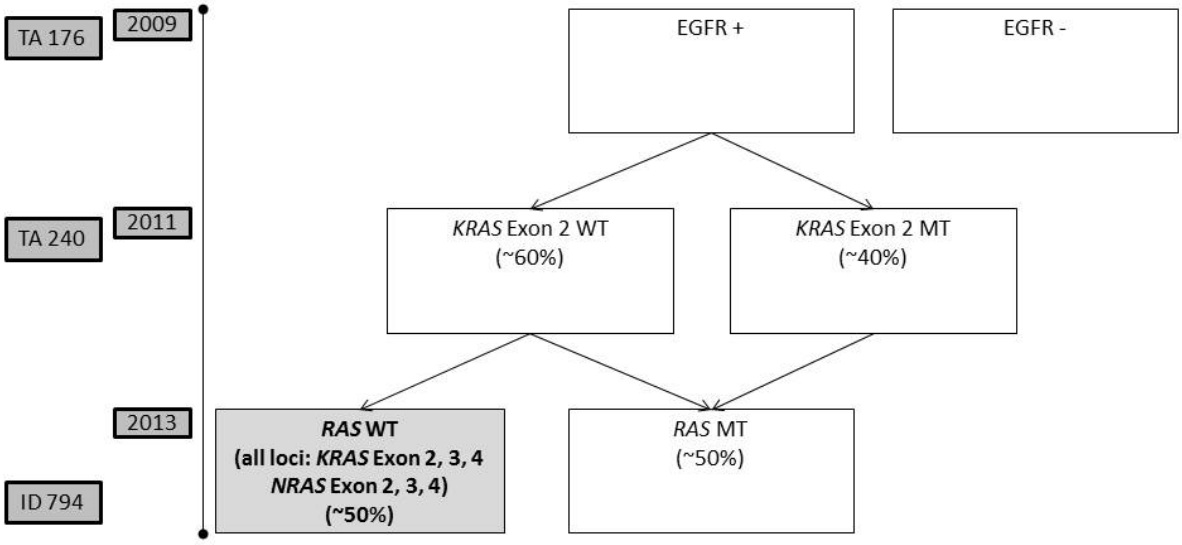
The three *RAS* genes: Kirsten rat sarcoma [*KRAS*]; Harvey rat sarcoma [*HRAS*]; and, neuroblastoma rat sarcoma [*NRAS*]) are the most common oncogenes in human cancer.[28, 29] All three are widely expressed, with *KRAS* expressed in almost all cell types.[28] Published research has demonstrated that 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

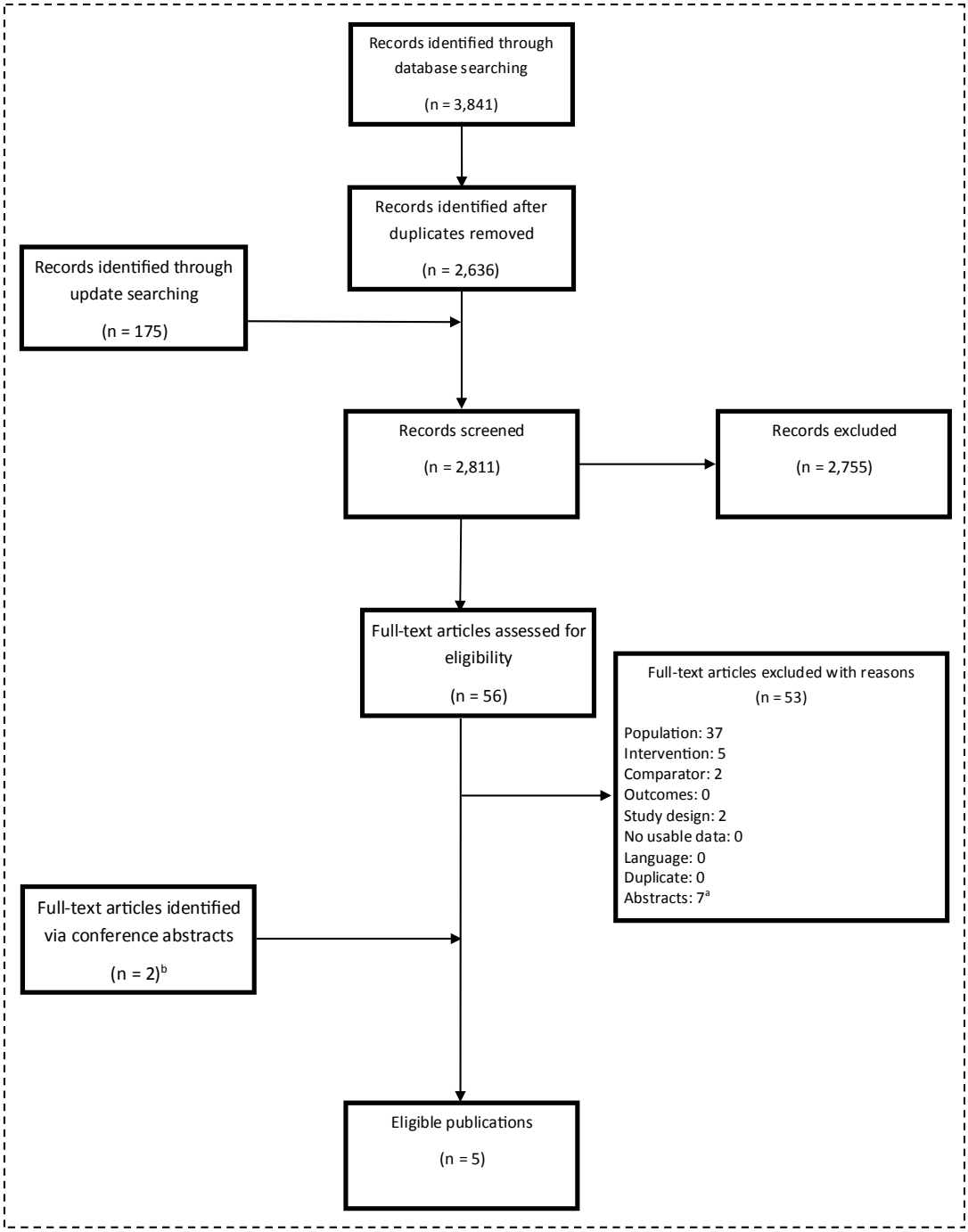
was substantial (κ=0.801). At the full-text stage, agreement was good (κ=0.636]). At both stages, initial disagreements were easily resolved by consensus.

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	PAN+FOLFOX4	253[b]	61 (27–81)	170 (67)	0: 150/253 (59)	1: 56/253 (22)	Colon: 165/253 (65)	48/253 (19)
					1: 88/253 (35)	2: 92/253 (36)	Rectum: 88/253 (35)	
Data on File, Amgen Ltd					2: 15/253 (6)	≥3: 104/253 (41)		
PRIME	FOLFOX4	252[b]	61 (24–82)	158 (63)	0: 137/252 (54)	1: 50/252 (20)	Colon: 164/252 (65)	41/252 (16)
					1: 98/252 (39)	2: 93/252 (37)	Rectum: 88/252 (35)	
					2: 16/252 (6)	≥3: 109/252 (43)		
Schwartzberg, 2014	PAN+ mFOLFOX6	88	62 (23–82)	58/88 (66)	0: 53/88 (60)	1: 32/88 (36)	Colon: 64/88 (73)	23/88 (26)
					1: 35/88 (40)	2: 28/88 (32)	Rectum: 24/88 (27)	
PEAK					Other[a]: NA	≥3: 28/88 (32)		
						Other[a]: 0/88 (0)		
	BEV+ mFOLFOX6	82	60 (39–82)	56/82 (68)	0: 52/82 (63)	1: 33/82 (40)	Colon: 57/82 (70)	22/82 (27)
					1: 29/82 (35)	2: 29/82 (35)	Rectum: 28/82 (30)	
					Other[a]: 1/82 (1)	≥3: 19/82 (23)		
						Other[a]: 1/82 (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; 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.

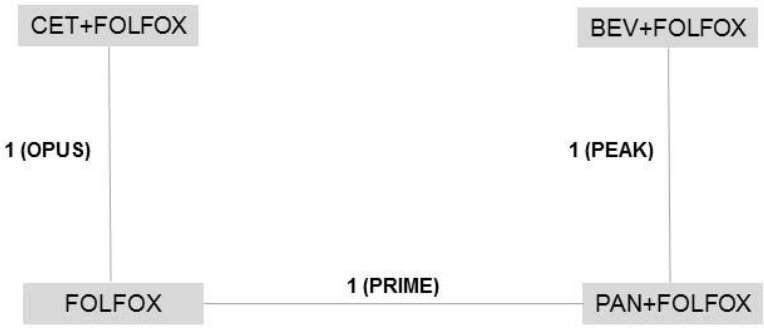
3.3. Network meta-analysis

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

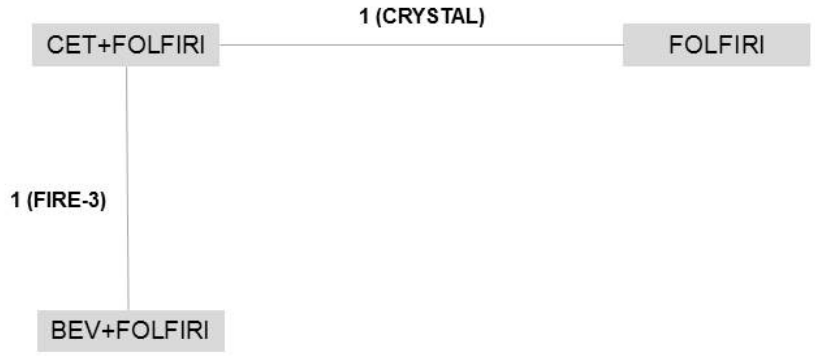
	Comparator treatment			Probability ranked			
Intervention treatment	FOLFOX	BEV+FOLFOX	PAN+FOLFOX	1st	2nd	3rd	4th
FOLFOX				<1%	3%	23%	73%
BEV+FOLFOX	4.22 (0.58, 30.68)			43%	39%	12%	6%
PAN+FOLFOX	2.20 (0.80, 6.07)**	[redacted]		7%	39%	49%	4%
CET+FOLFOX	4.63 (0.20, 104.60)****	1.09 (0.03, 44.34)	2.09 (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 (1.46, 5.49)		<1%	64%	36%
CET+FOLFIRI	3.06 (1.91, 4.95)**	1.09 (0.69, 1.72)***	0%	36%	64%

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 (0.18, 1177)		28%	72%	0%
CET+FOLFIRI	127.60 (11.12, 53970)**	47.60 (21.30, 129.40)***	0%	0%	100%

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.

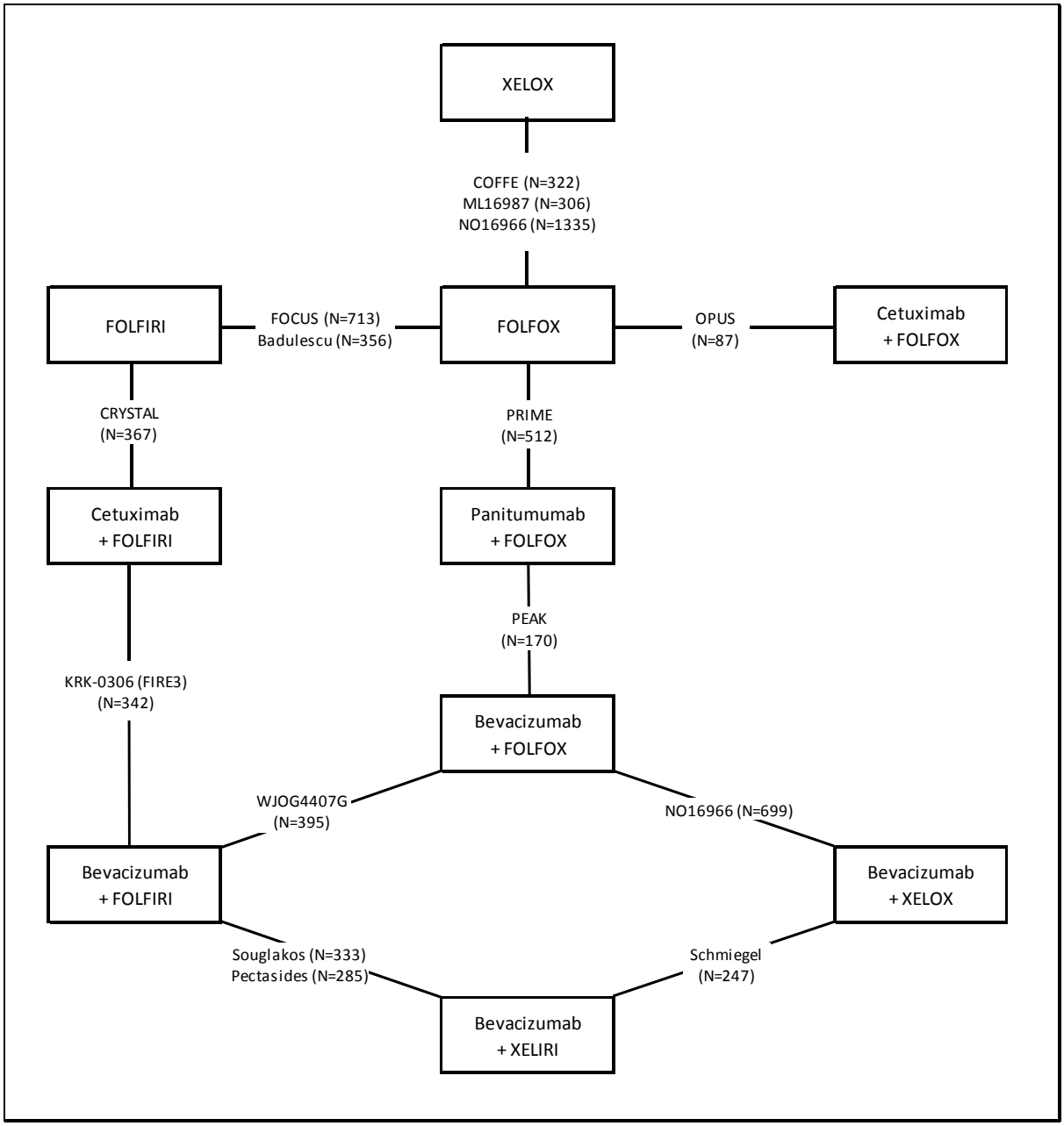
3.6.1.1. Network meta-analysis

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

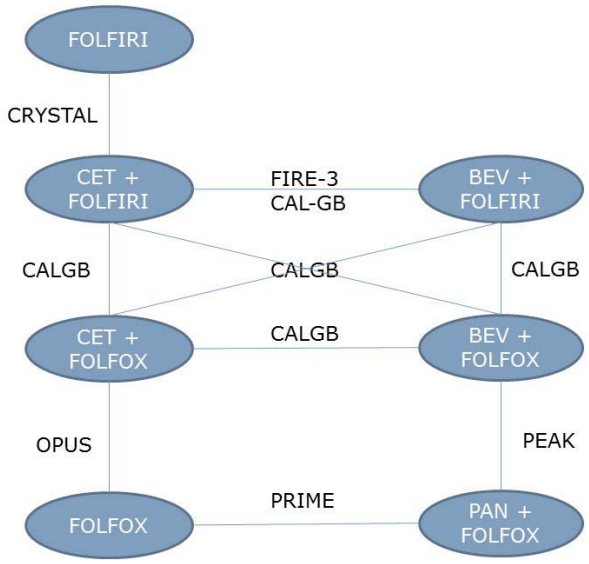
Merck Serono performed a network meta-analysis (NMA) to compare cetuximab plus chemotherapy (FOLFOX or FOLFIRI) for the treatment of *RAS* WT mCRC with other comparators specified in the NICE scope (see Section 2, p80).

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

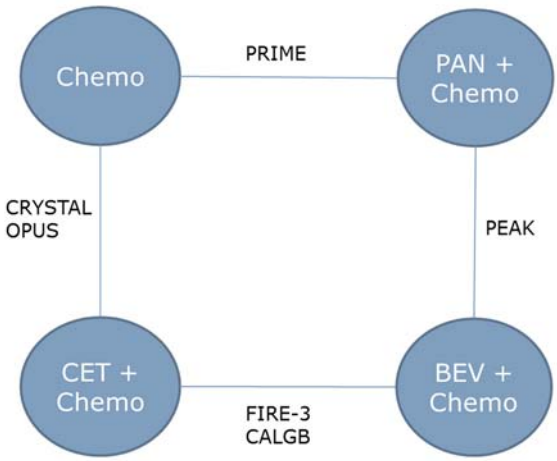
not possible for ORR as neither the PEAK nor CALGB-80405 study reported ORR and, as a result, only a FOLFIRI network was possible for this outcome. It was also not possible to include CALGB-80405 in any safety outcome network due to lack of reporting. Therefore two separate networks, one for FOLFOX and 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".

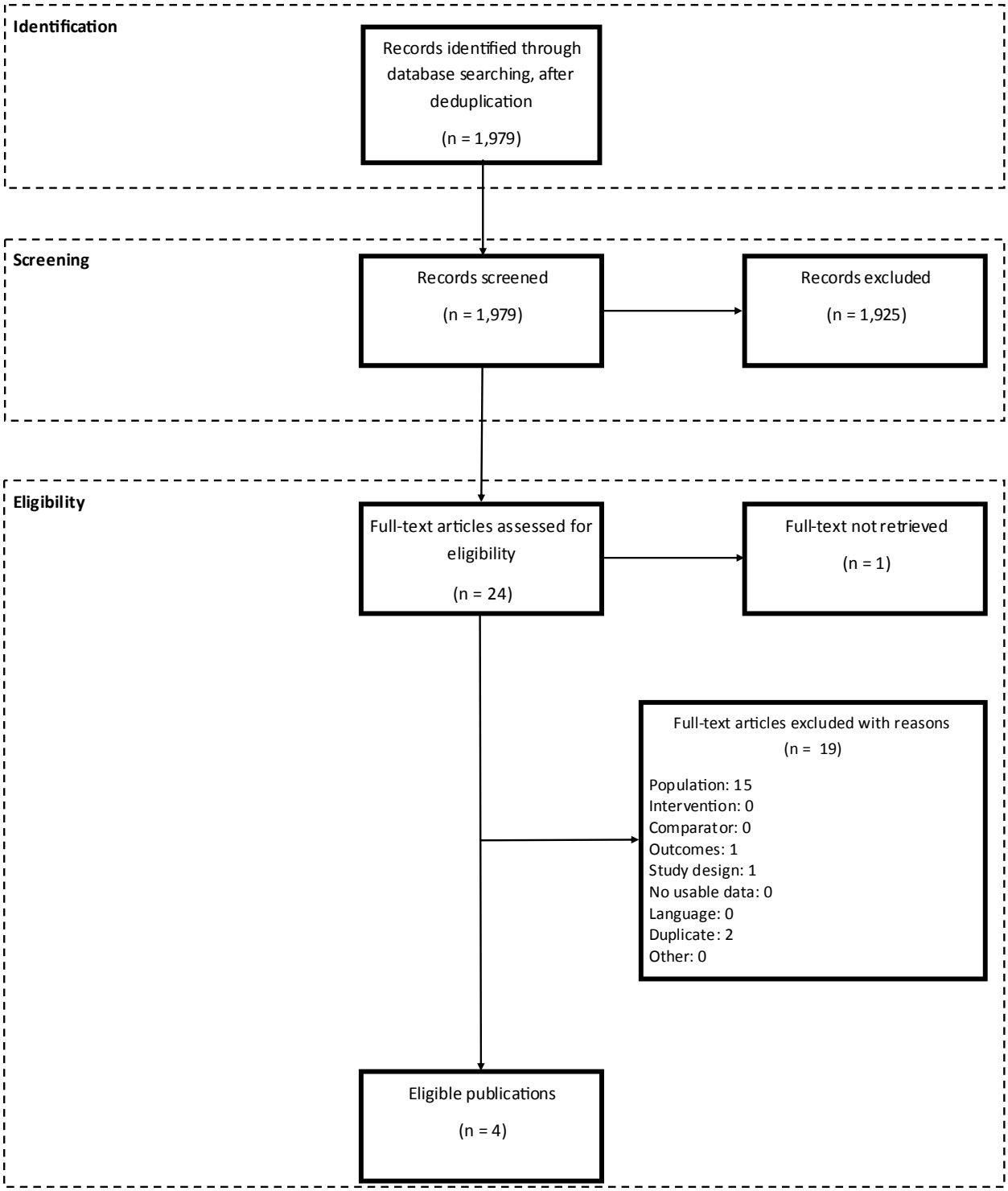
Where these studies were based on decision models, they were further quality assessed using the checklist developed by Philips et al. (2006).[2]

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.

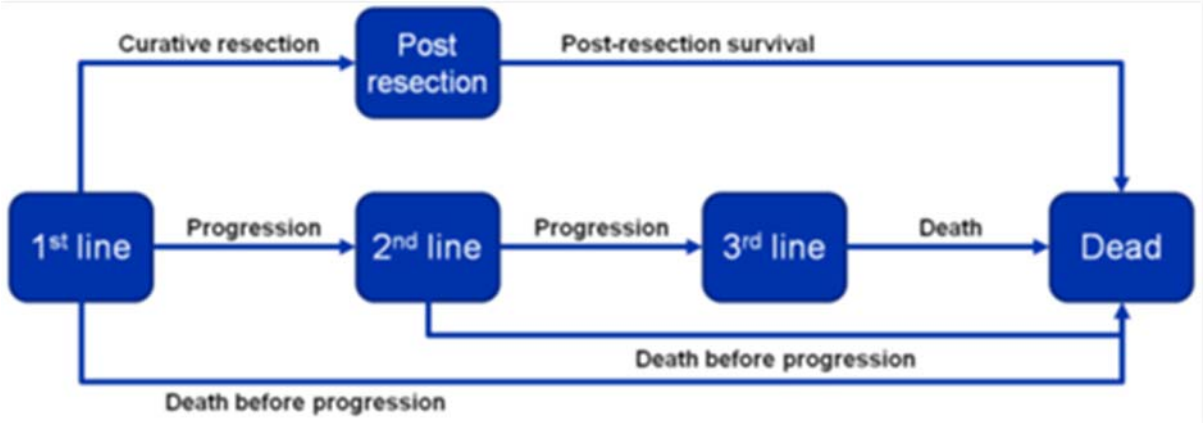
Model structure

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

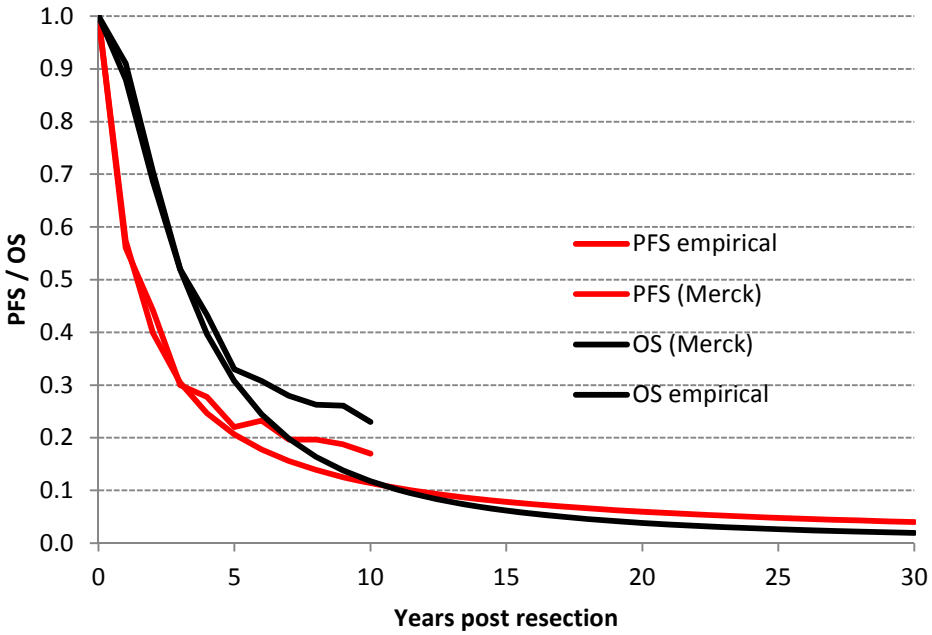
In their submission, Merck Serono state that they assume all patients who undergo curative liver resection for initially unresectable colorectal liver metastases, turned resectable by systematic chemotherapy, and are cured of the disease, "remain in a progression free state until death and do not require 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

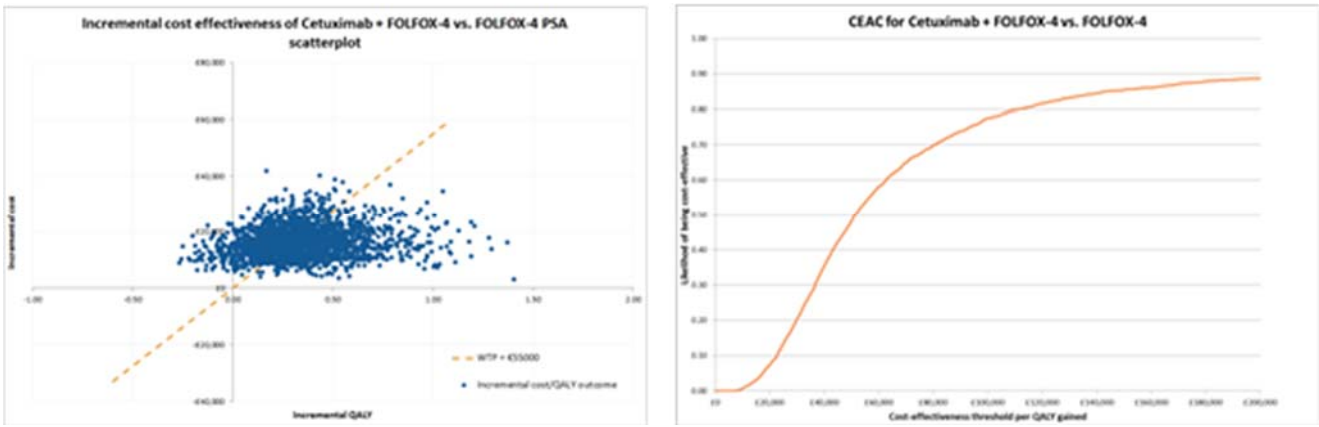
	Costs (£)	LYs	QALYs	ICER (£/LY)	ICER (£/QALY)
CET FOLFIRI	37,978	2.16	1.60		
BEV+ FOLFIRI	34,605	2.03	1.49		
Increment CET+FOLFIRI vs. BEV+FOLFIRI	**3,373**	**0.14**	**0.10**	**24,191**	**32,726**

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

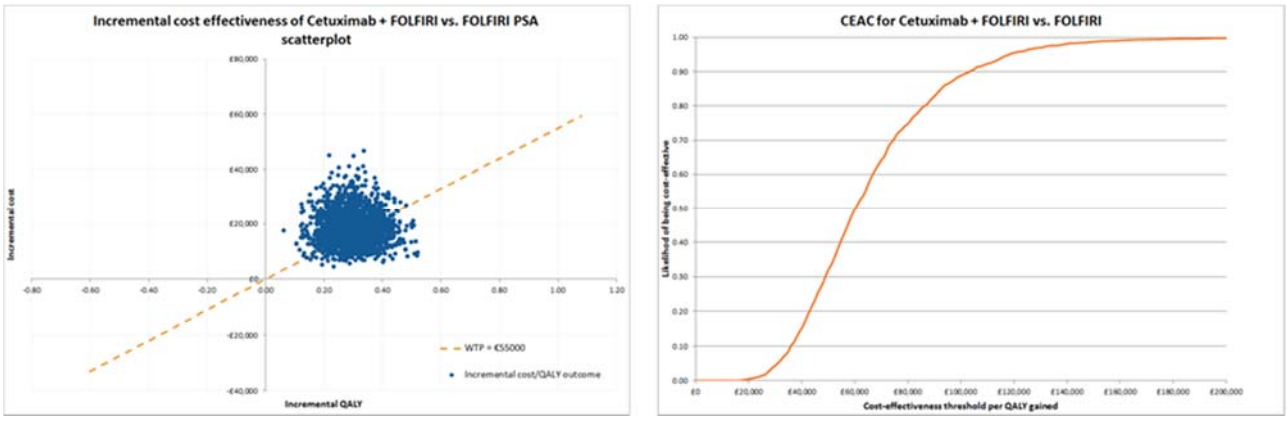
Merck Serono performed a probabilistic sensitivity analysis (PSA) for all of their base case comparisons. These were not all available in the model and so have been reproduced from the report in Figure 13 and Figure 14. CET+FOLFOX is the most likely cost-effective treatment compared to FOLFOX at a willingness 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

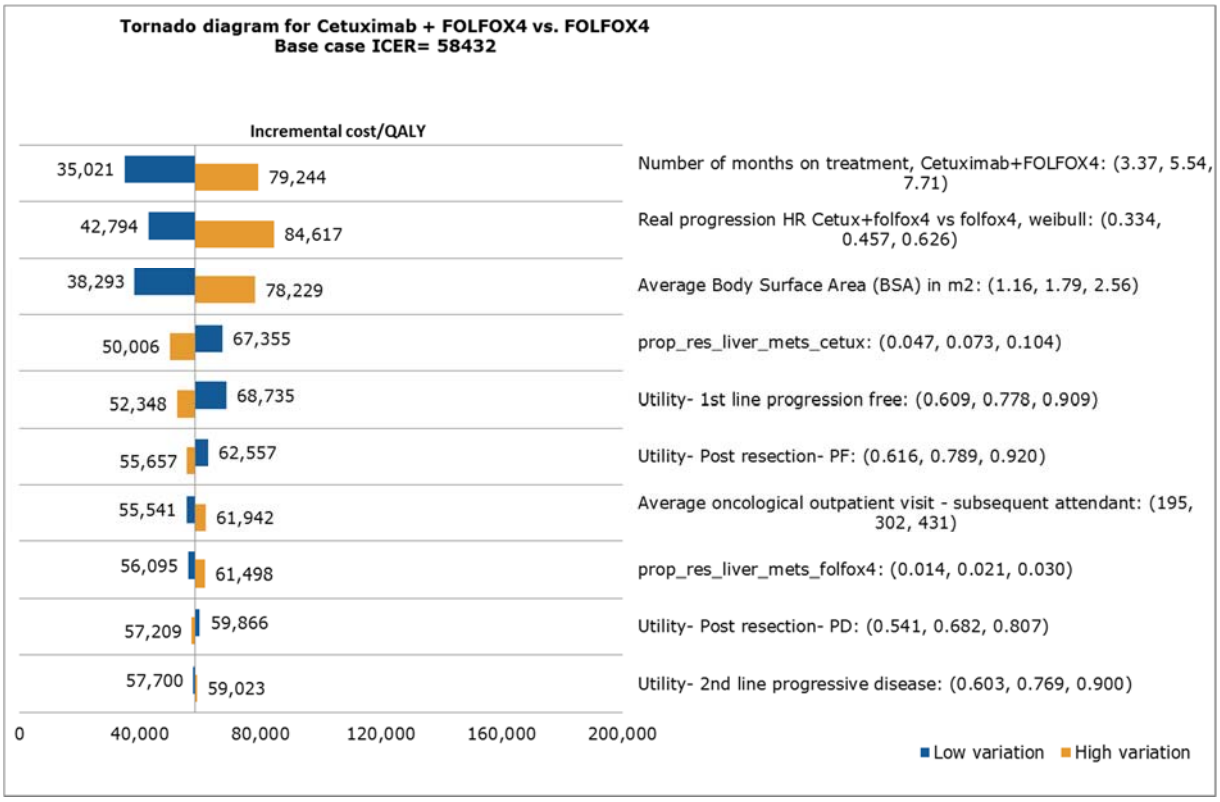


Key: CEAC = cost-effectiveness acceptability curve; ICER = incremental cost-effectiveness ratio
Source: Merck Serono submission, Figure 20, Section 3.7.1 page 63

Univariate sensitivity analysis

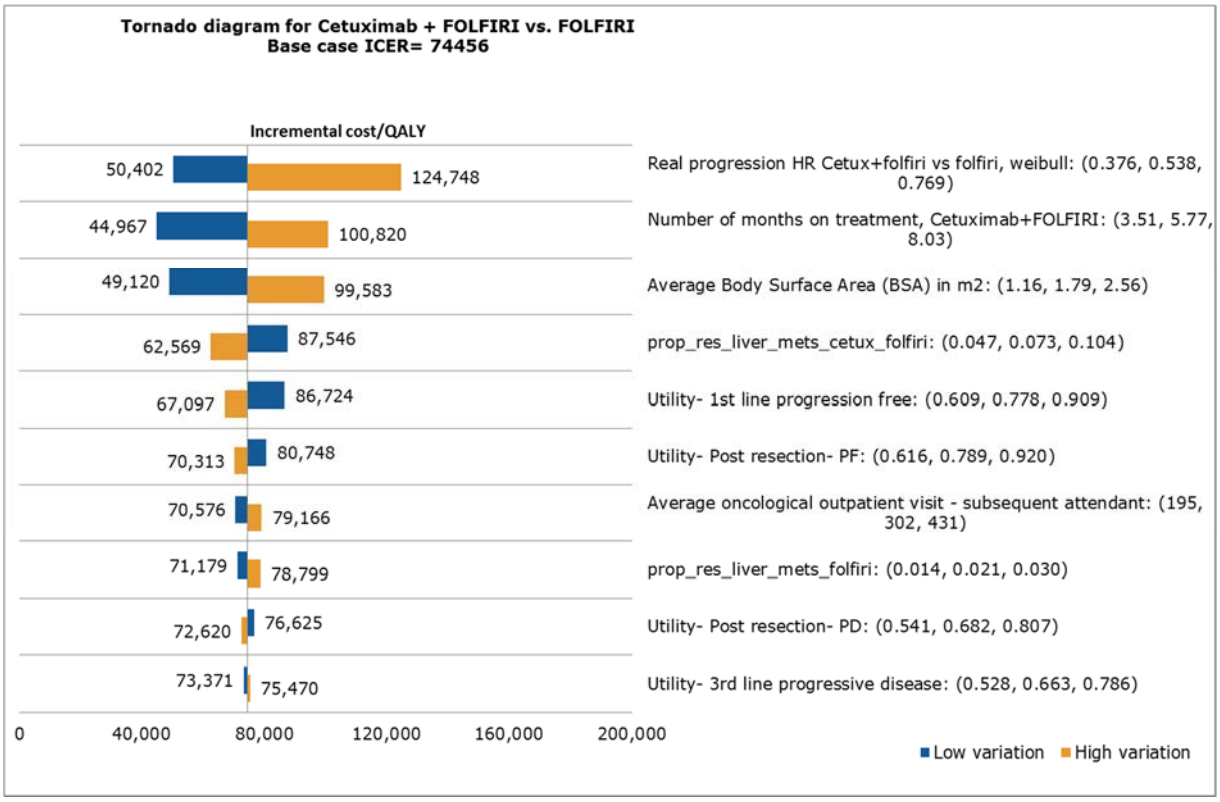
Merck Serono also conducted univariate sensitivity analyses to find the most influential parameters in the model. For both FOLFOX and FOLFIRI comparisons, parameters used to estimate the costs of treatment (number of months of treatment, average body surface area), time in progression free survival (PFS), 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)

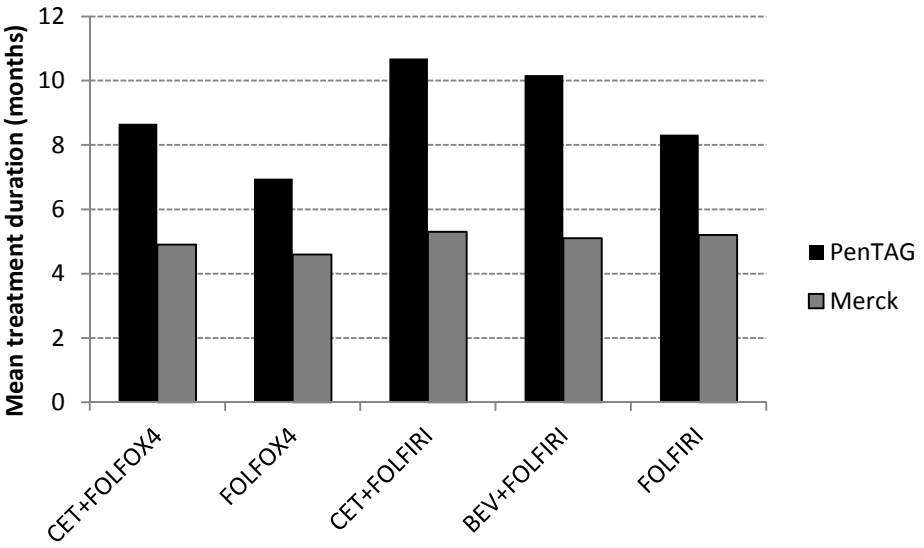
We show in Section 6.1.4.5, p.284, that there is good evidence treatment durations are approximately exponentially distributed, which leads to the followings estimates of **mean** treatment durations from the pivotal RCTs

- 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

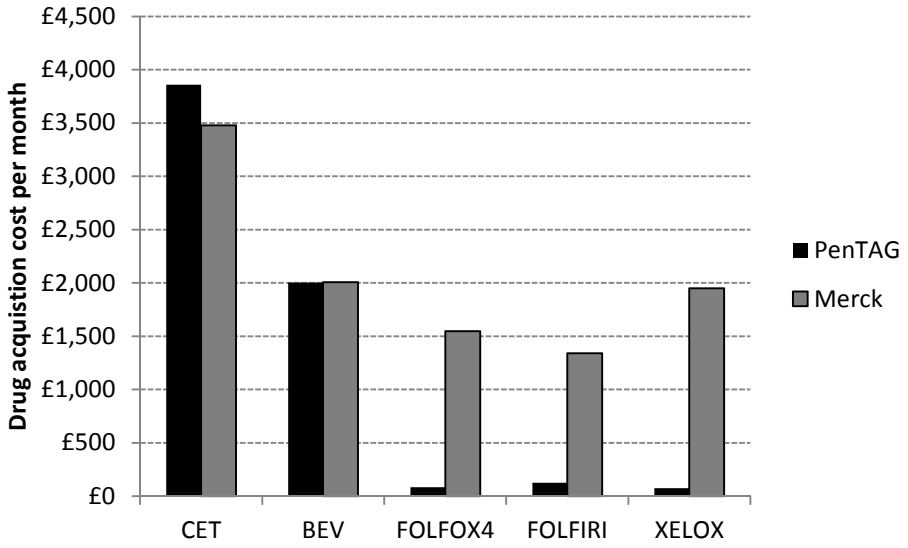
RAS mutation testing

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

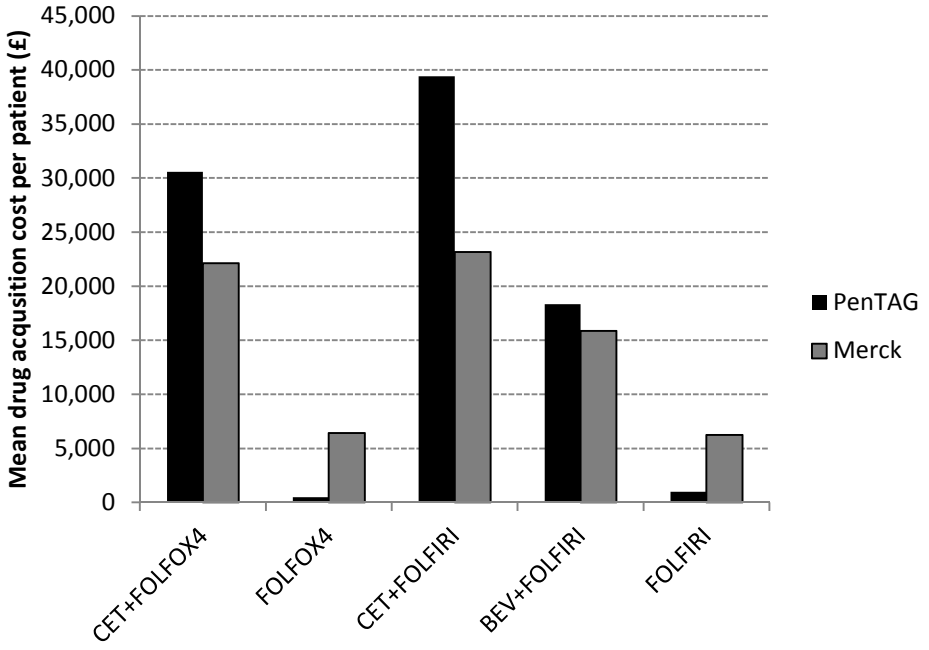


Key: BEV = bevacizumab; CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; XELOX = capecitabine + oxaliplatin

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

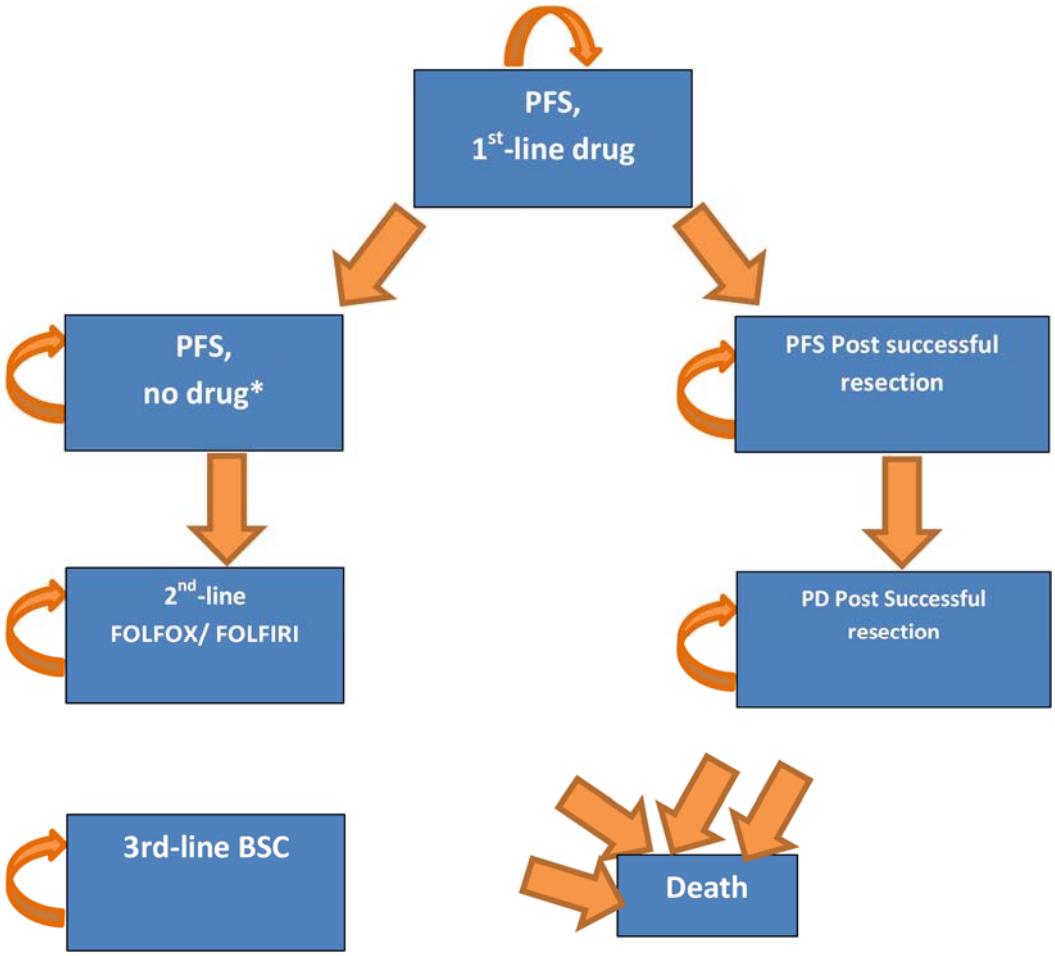
		Population	N	Anti-EGFR (Cetux/Pan)	Anti-VEGF (bevacizumab)	Oxaliplatin or irinotecan	Reference
FOLFOX network							
PRIME	PAN+FOLFOX	KRAS WT	325	13%	NR	59% chemo	Douillard, (2014)[35] (p1350)
	FOLFOX		331	25%	NR	65% chemo	
PEAK	PAN+FOLFOX	*RAS* WT	88	22% (presumably CET)	40%	Irinotecan-based 50%, oxaliplatin-based 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

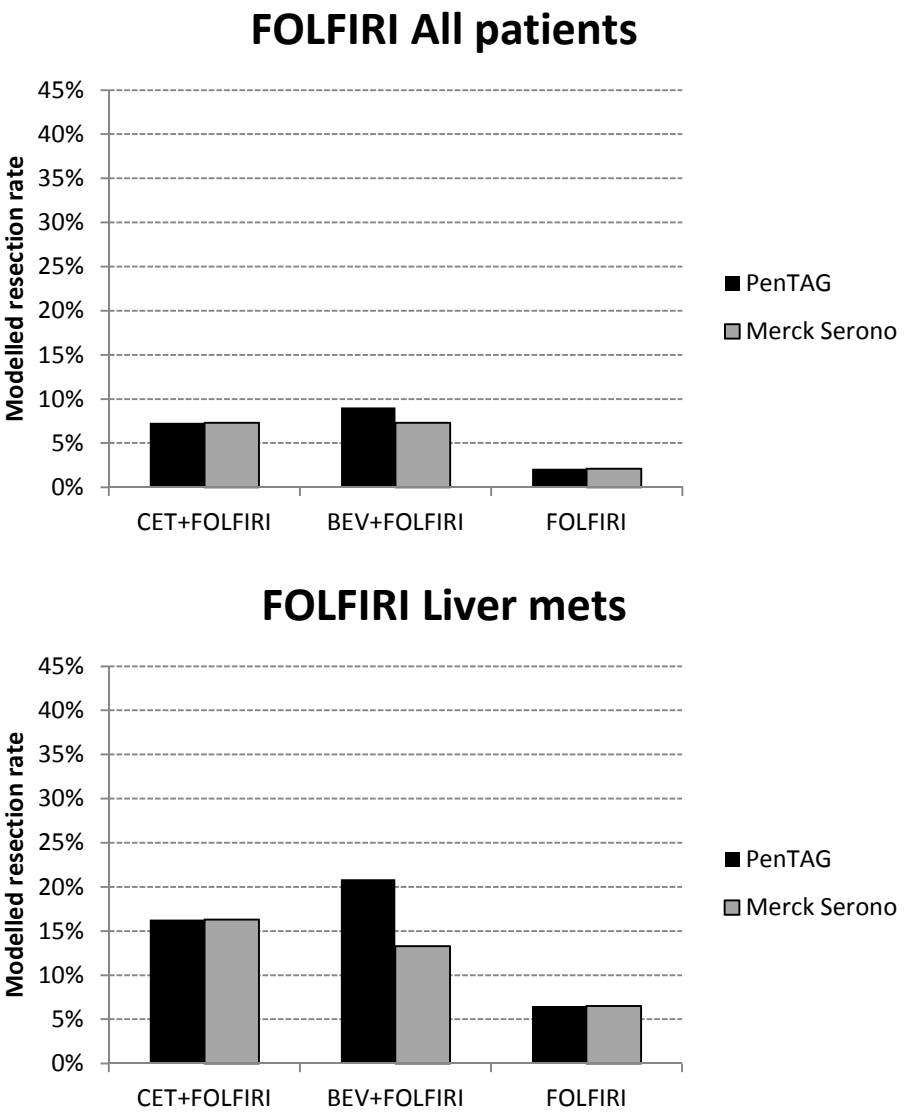
Treatment	Liver-limited mets subgroup *RAS* WT		All *RAS* WT patients	
	PenTAG	**Merck Serono**	**PenTAG**	**Merck Serono**
FOLFIRI network				
CET+FOLFIRI	16.3% (Merck Serono data).	16.3% (Merck Serono data).	7.3% (Merck Serono data).	7.3% (Merck Serono data).
FOLFIRI	6.5% (Merck Serono data).	6.5% (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).

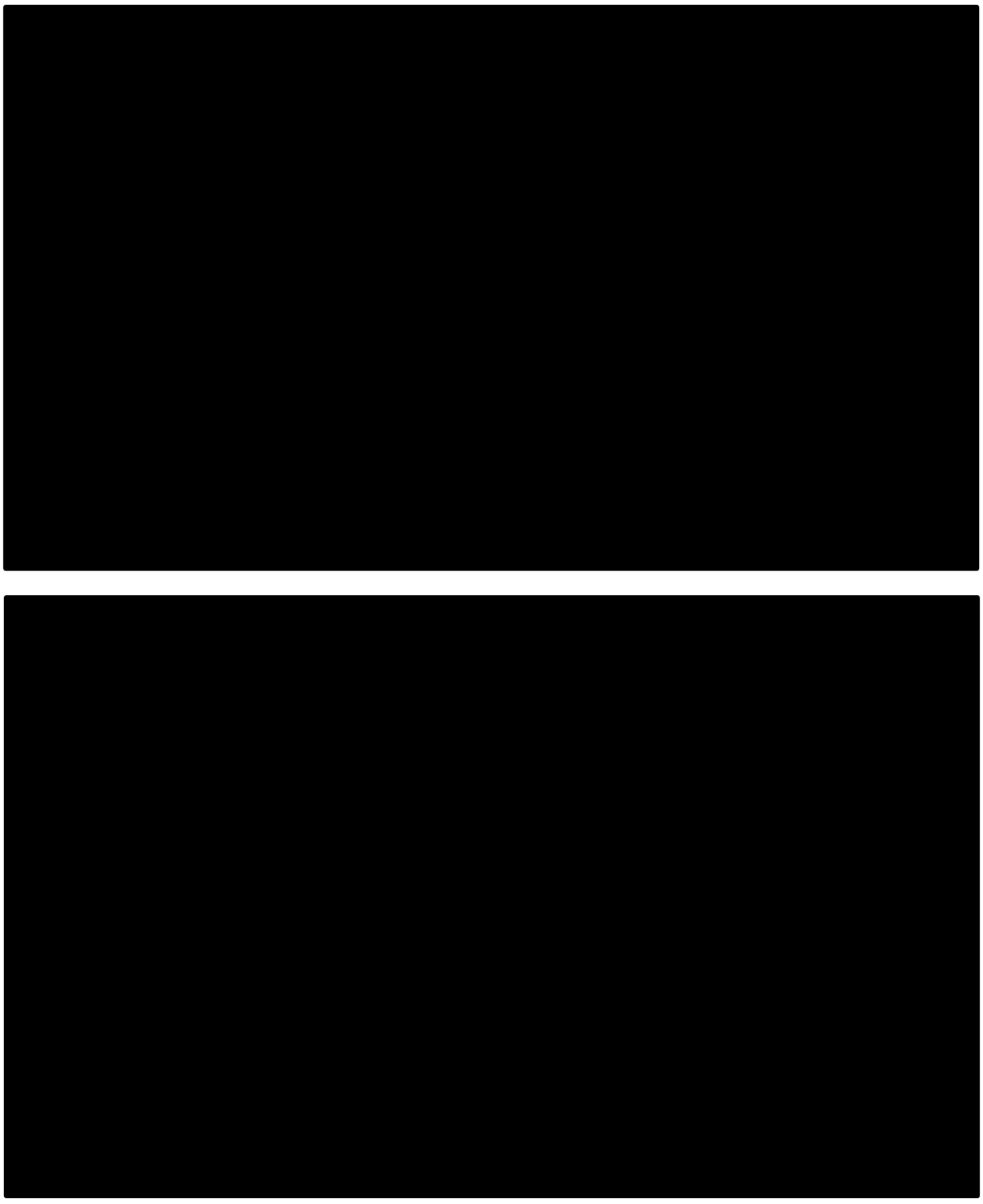
Next, we estimate the rate for *RAS* WT in FIRE-3 for BEV+FOLFIRI similarly, as 39.6% = 17.7% * (16.3% / 7.3%), where 17.7% is the estimated value for all patients, and 16.3% and 7.3% are as before.

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]

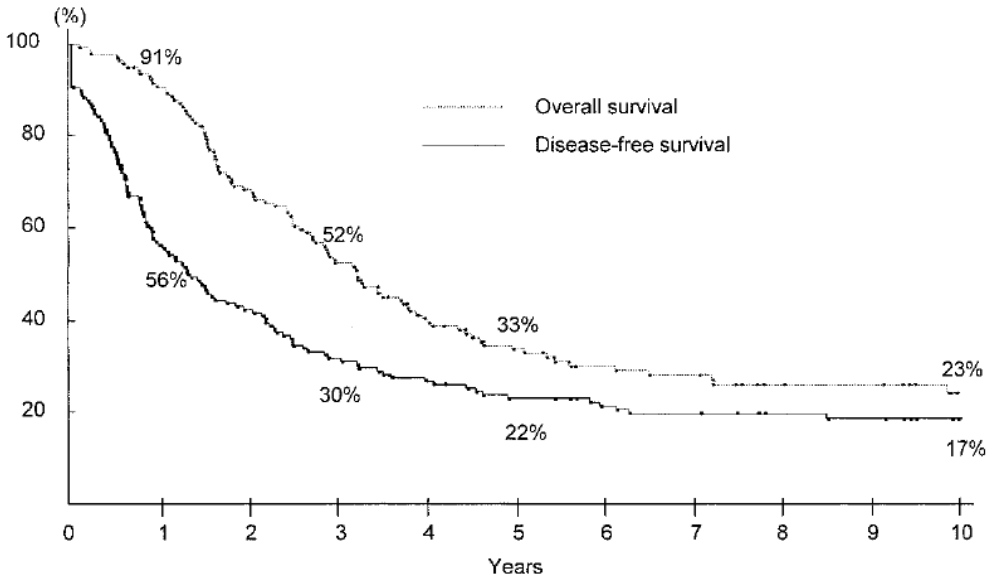
However, the choice of study has little impact on cost-effectiveness, as OS is similar across the three studies , and PFS is similar for Adam et al. (2004)[3] and Adam et al. (2009)[127] (Table 94).

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.

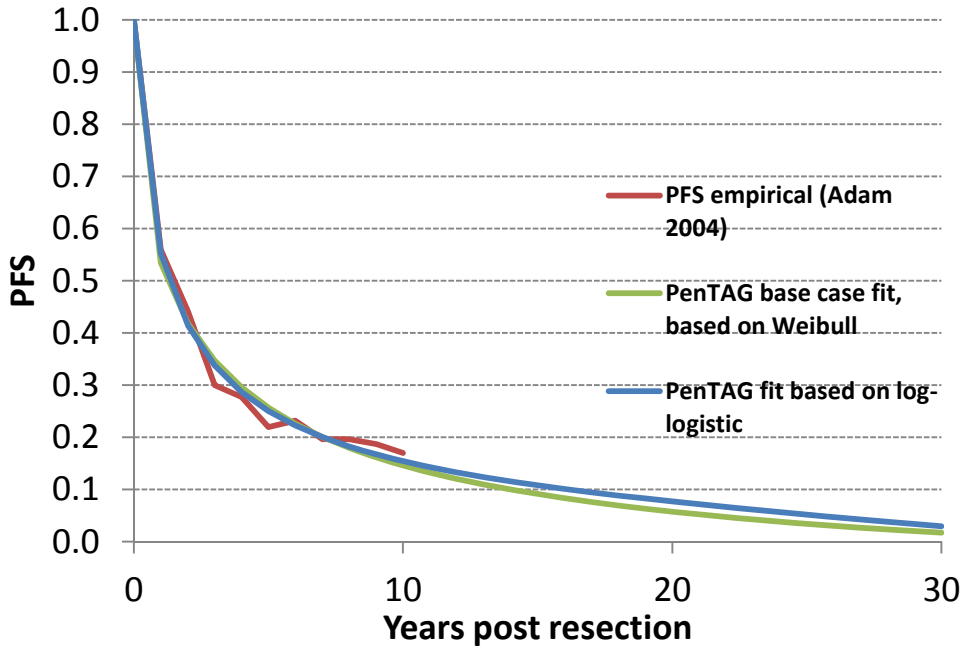
Figure 23. PFS & OS post-resection: Adam et al. (2004)



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).

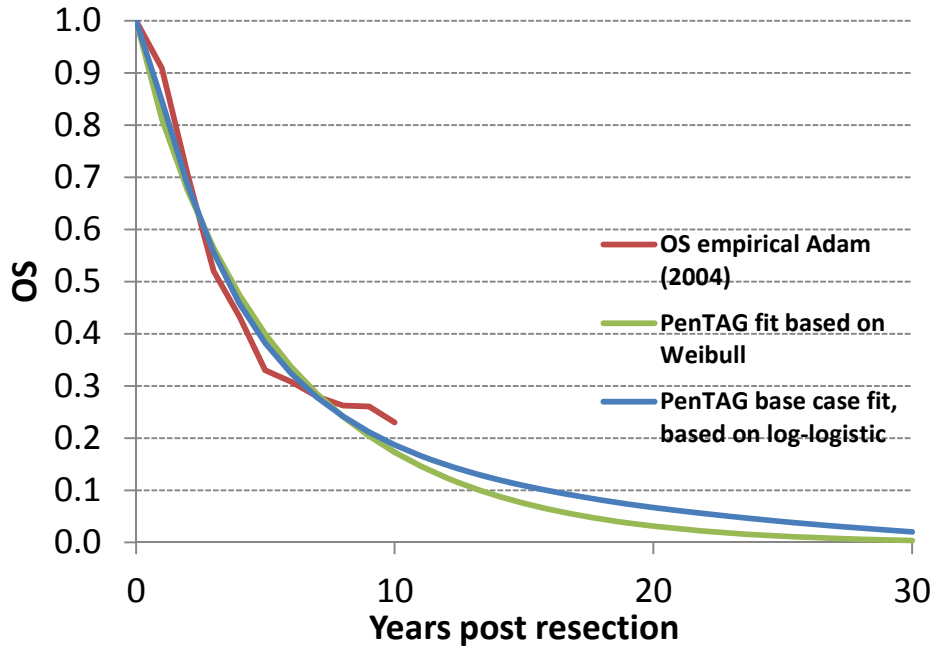
For our base case analysis, we chose the Weibull, as it is possible that the long tail in Adam et al. (2004)[3] is heavily influenced by the small numbers of patients at risk in the tail (e.g. 17 patients at 8 years, Figure 23), and the tail of the log-logistic is longer than the Weibull.

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

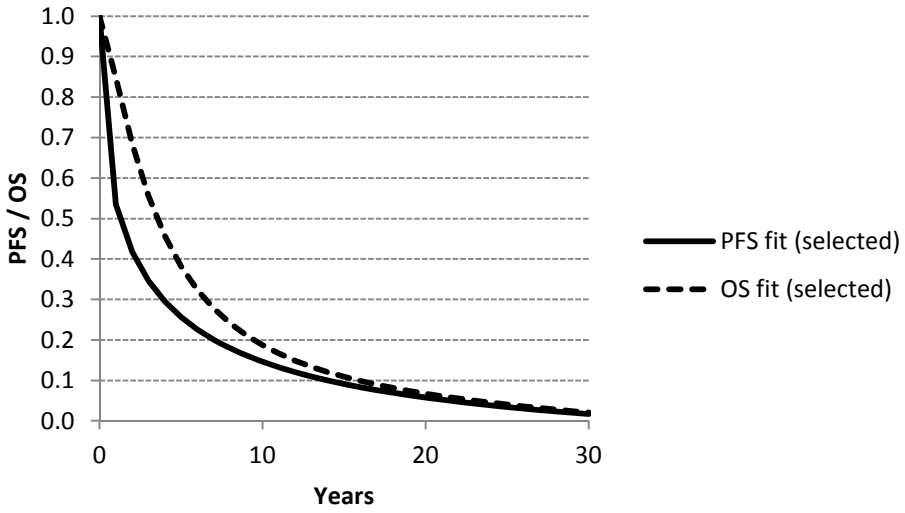


Key: OS = overall survival

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:

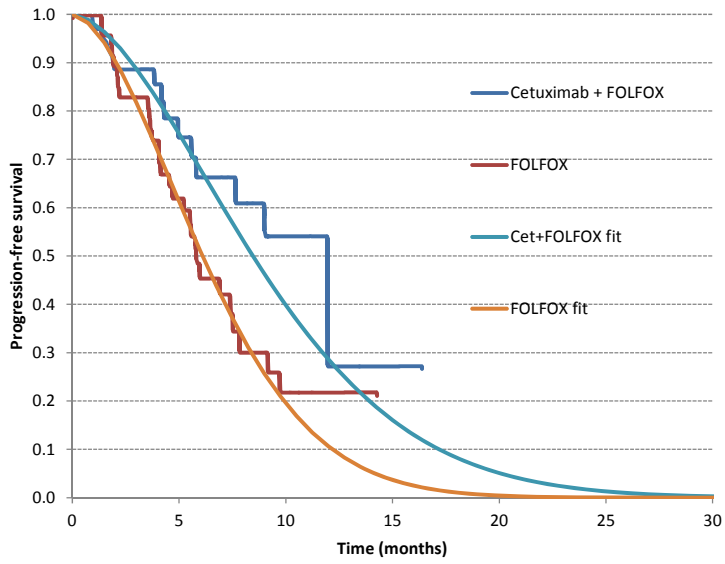
- The Weibull usually gave the lowest AIC and BIC values. If it did not, the values were nearly the lowest of all distributions.
- It seemed desirable to choose the same type of distribution for each treatment within the FOLFOX network, and separately for each treatment within the FOLFIR network, because 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.

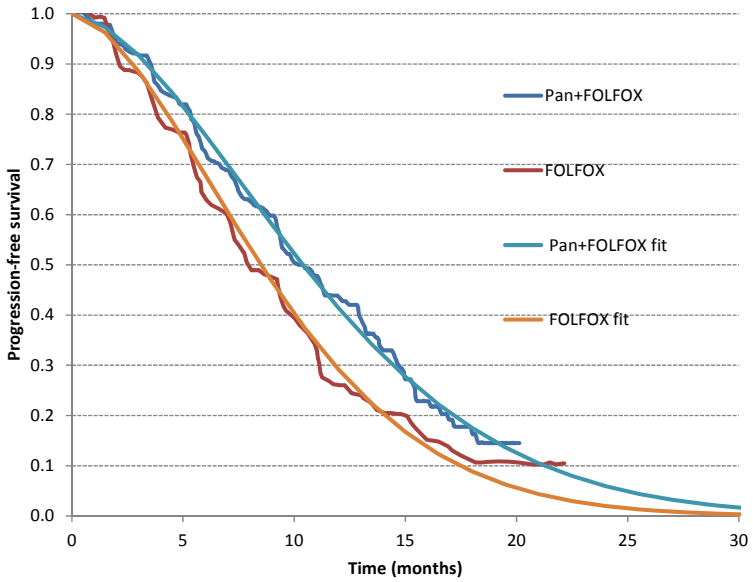
Our chosen curve fits are given in Figure 27 below. In each case, the mean and variance-covariance matrix of the parameters of the Weibull were recorded.

Figure 27 1st-line PFS (unresected patients) in PenTAG model

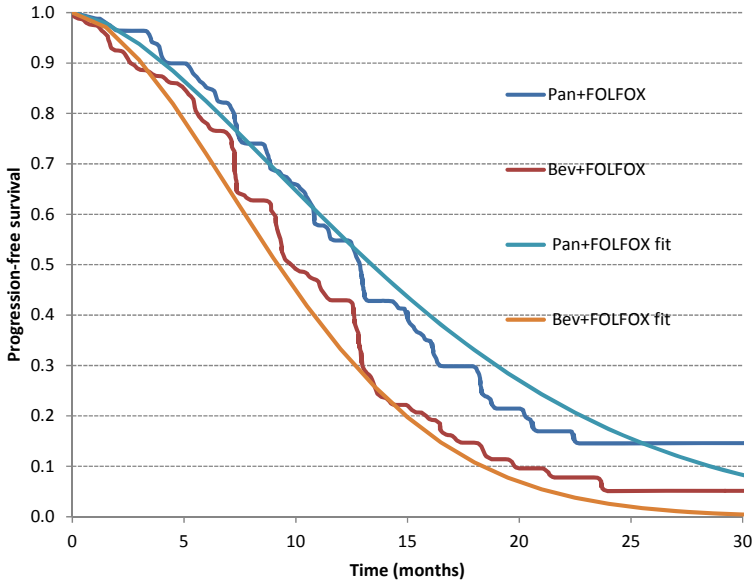
(a) CET+FOLFOX vs. FOLFOX from OPUS



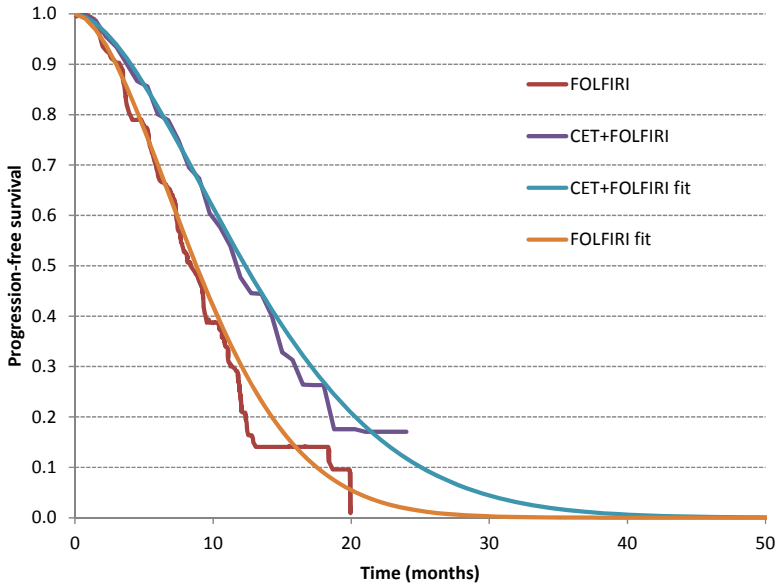
(b) PAN+FOLFOX vs. FOLFOX from PRIME



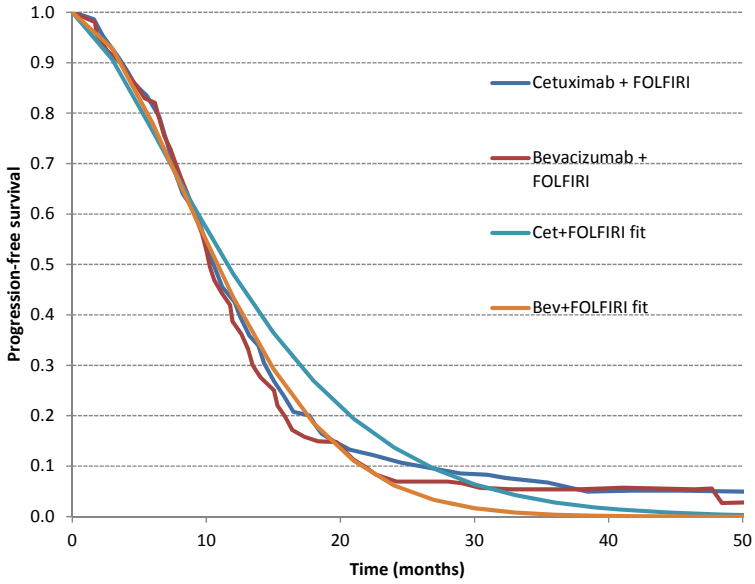
(c) PAN+FOLFOX vs. BEV+FOLFOX from PEAK



(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)

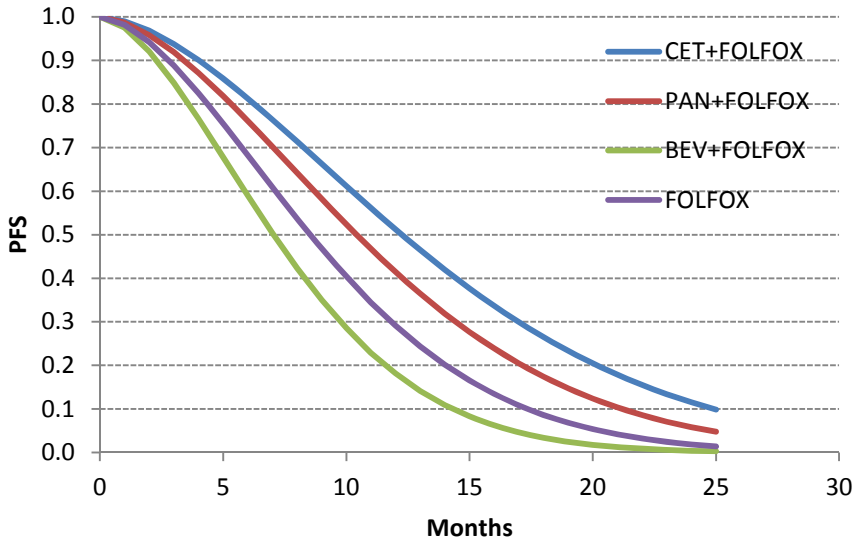
We assume PFS for non-resected patients follows same distribution as for all patients, the Weibull in all cases. The shape parameter for the Weibull was estimated from Step point A, and scale parameter estimated from the mean PFS for non-resected patients and shape parameter.

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.

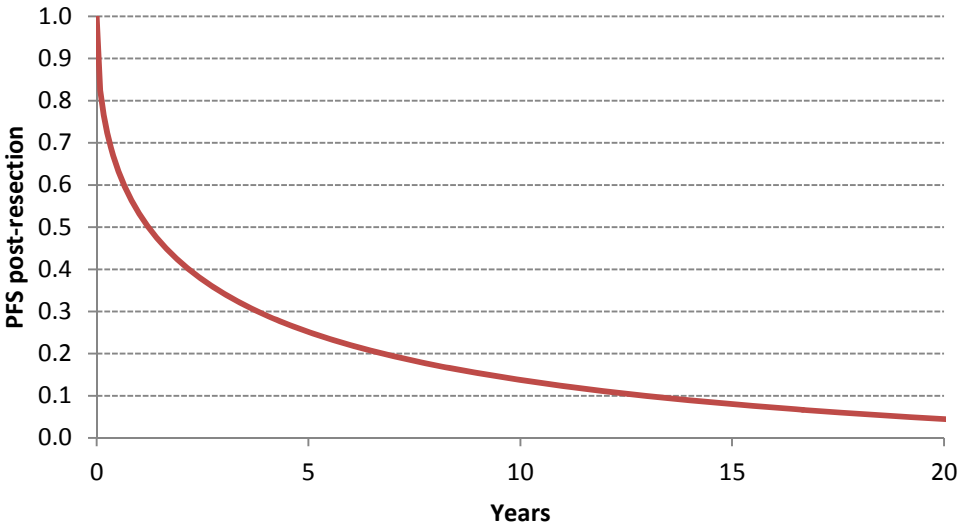
Notice that PFS for unresected patients is shorter than for all patients, as PFS for resected patients is substantially greater than for unresected patients (noting difference in scale of time axis).

Figure 28. 1st-line PFS for the FOLFOX network in PenTAG model

(a) all patients



(b) resected patients



(c) unresected patients

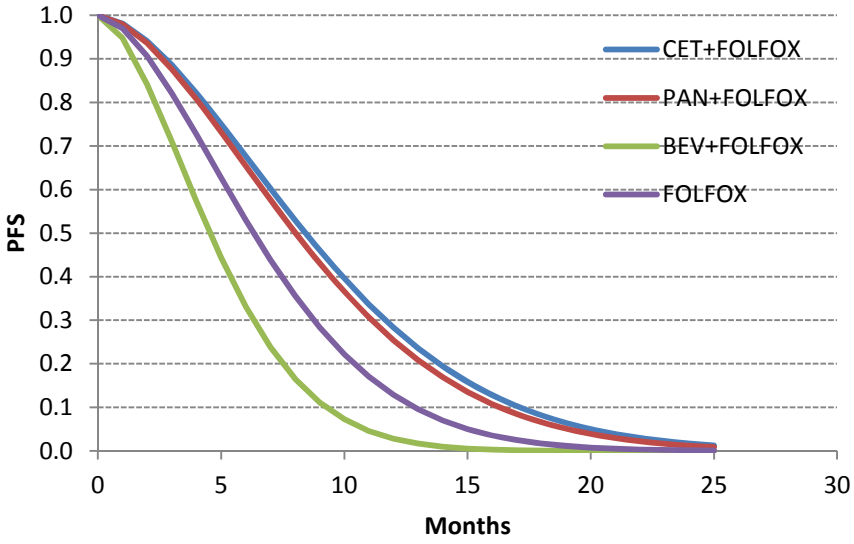
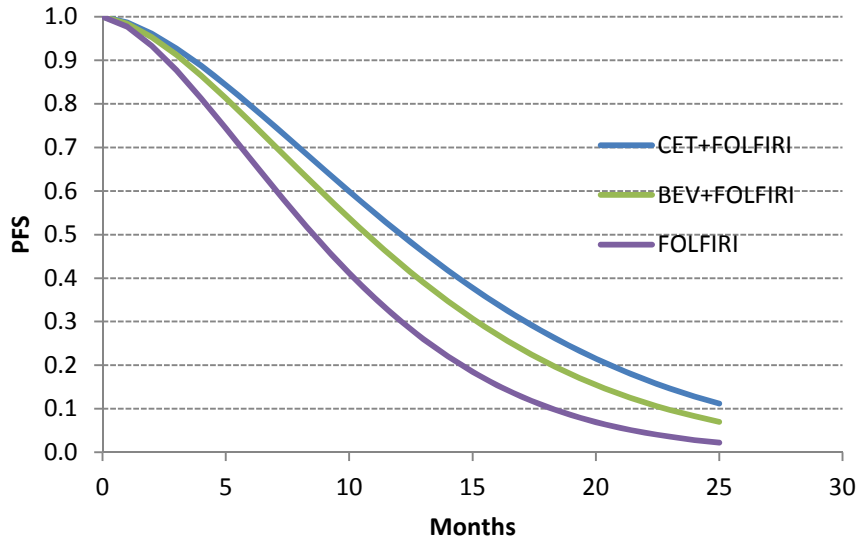
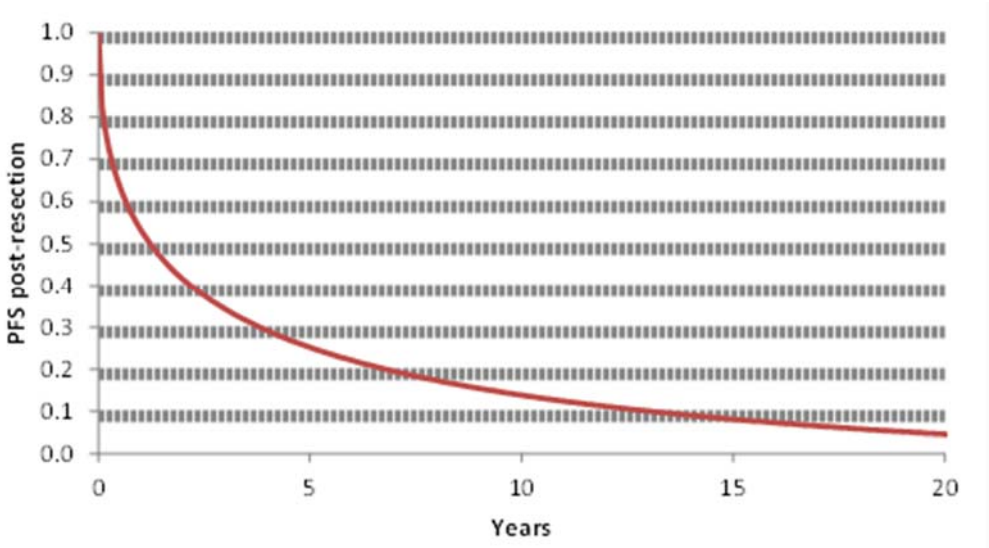


Figure 29. 1st-line PFS for the FOLFIRI network in PenTAG model

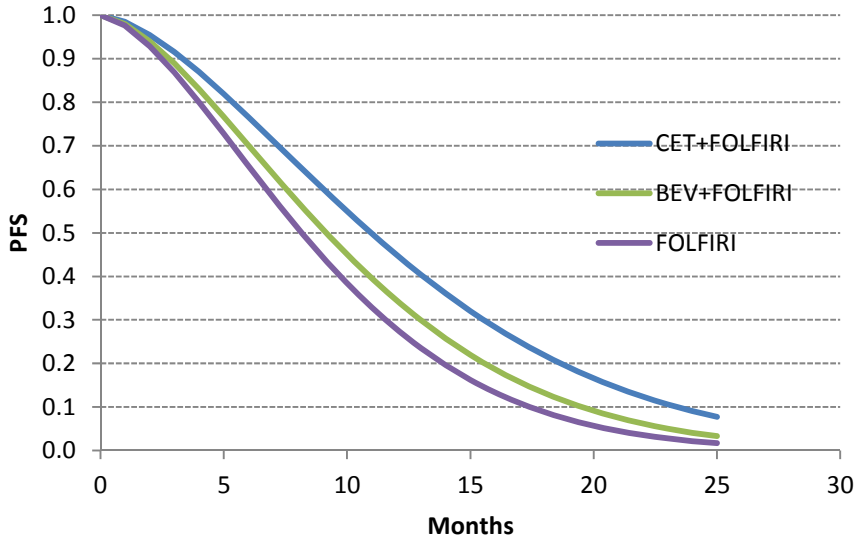
(a) all patients



(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

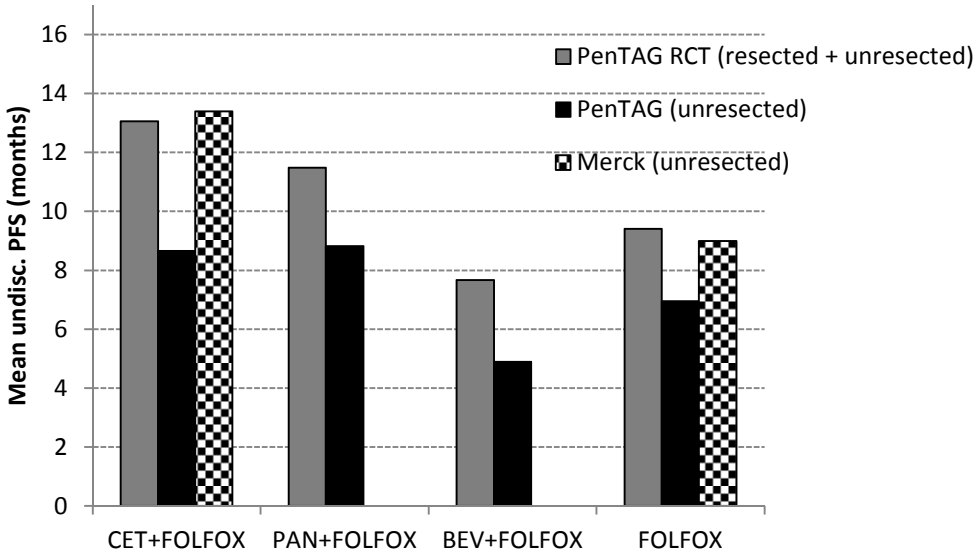
Comparison with Merck Serono

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.

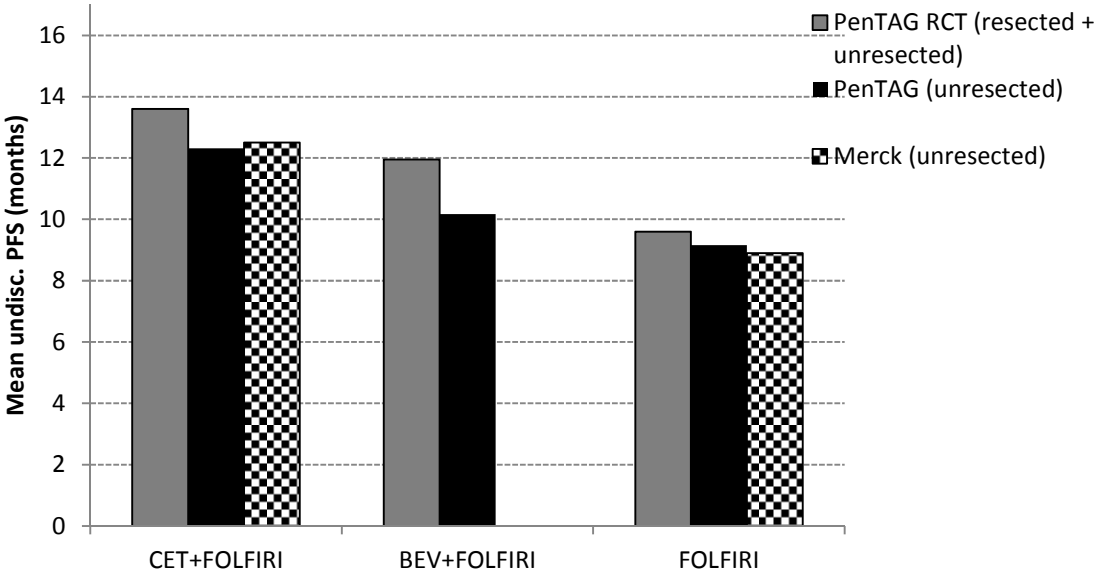
For the FOLFIRI network, our estimates of mean PFS for resected + unresected patients are slightly higher than those of Merck Serono for unresected patients only (Figure 30b). Coincidently, even though we have subtracted off PFS for resected patients, our estimates of mean PFS for unresected patients 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.

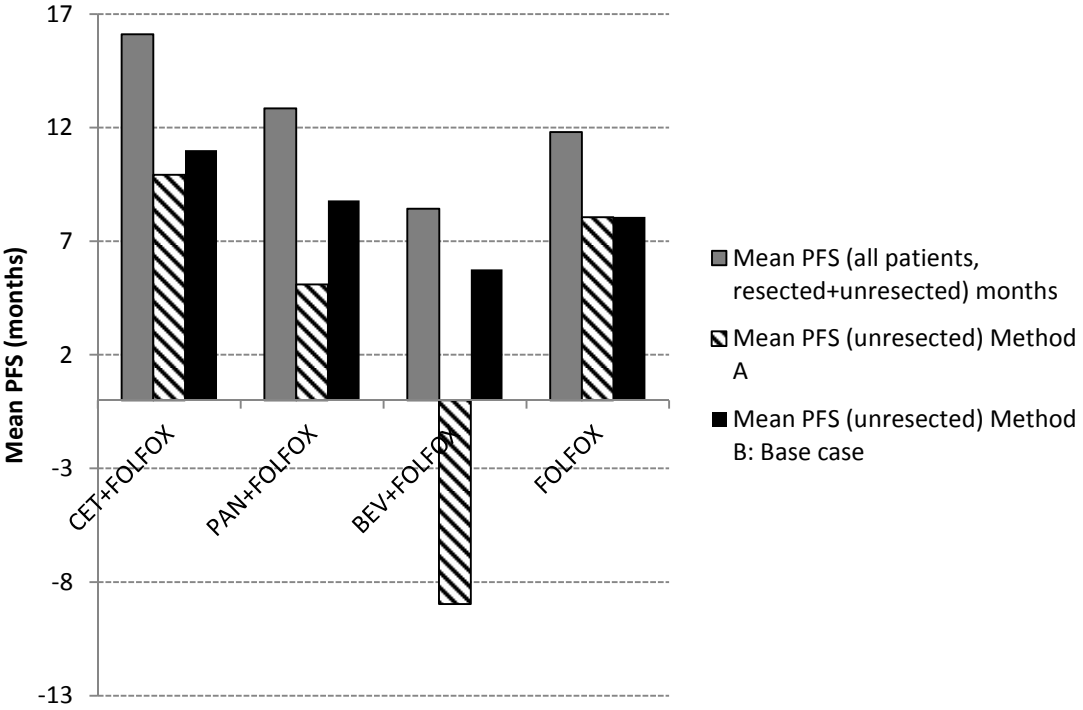
Next, estimated mean PFS for the unresected patients in the liver mets subgroup were first estimated by “Method A”, as above for all patients, by subtracting off mean PFS for resected patients, and using the resection rates specific to the subgroup. This yielded estimates of mean PFS for unresected patients 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)

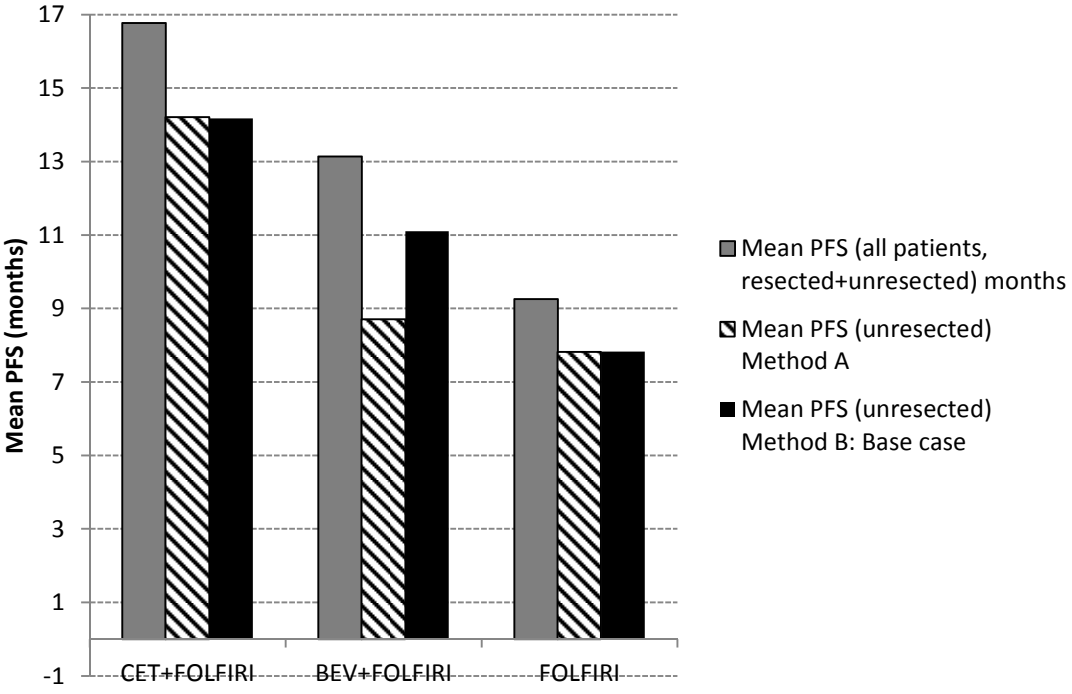
We stress that mean PFS for unresected patients for the liver metastases subgroup are highly uncertain for all treatments given the number of assumptions. Given that cost-effectivess is sensitive to this, then cost-effectivess is also highly uncertain for all treatments for the liver metastases subgroup.

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

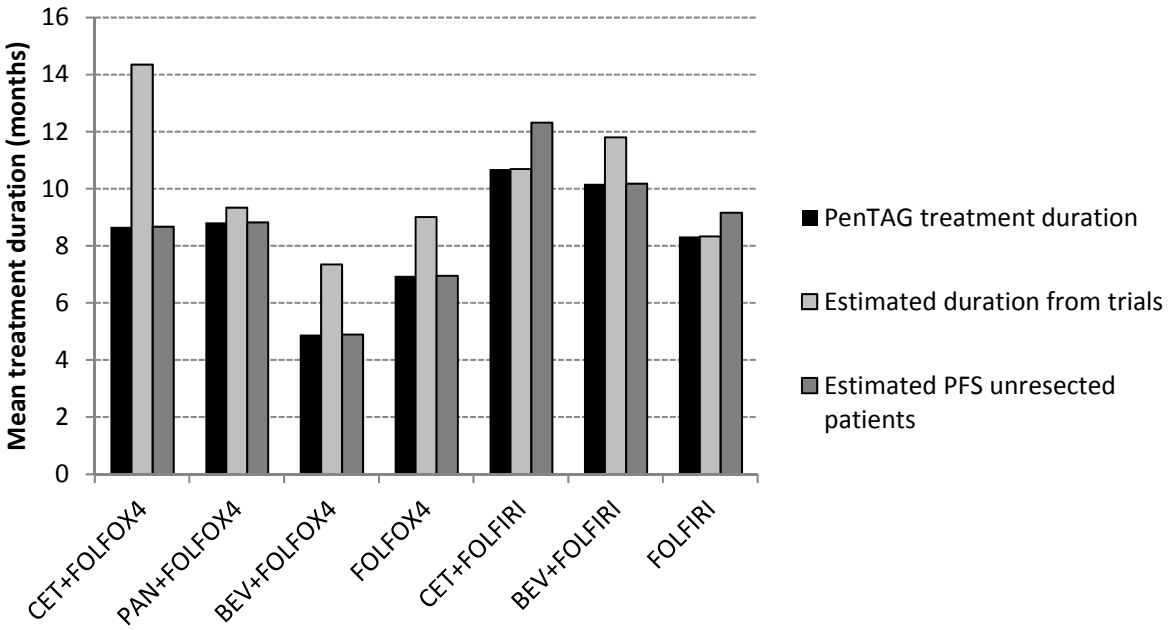
C. For each treatment, compare the estimated mean treatment duration with the estimated mean 1st-line PFS for unresected patients (Section 6.1.4.4, p267). We would expect the mean treatment duration to be lower, because in all RCTs, treatment was supposed to stop on progression. However, we show below 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).

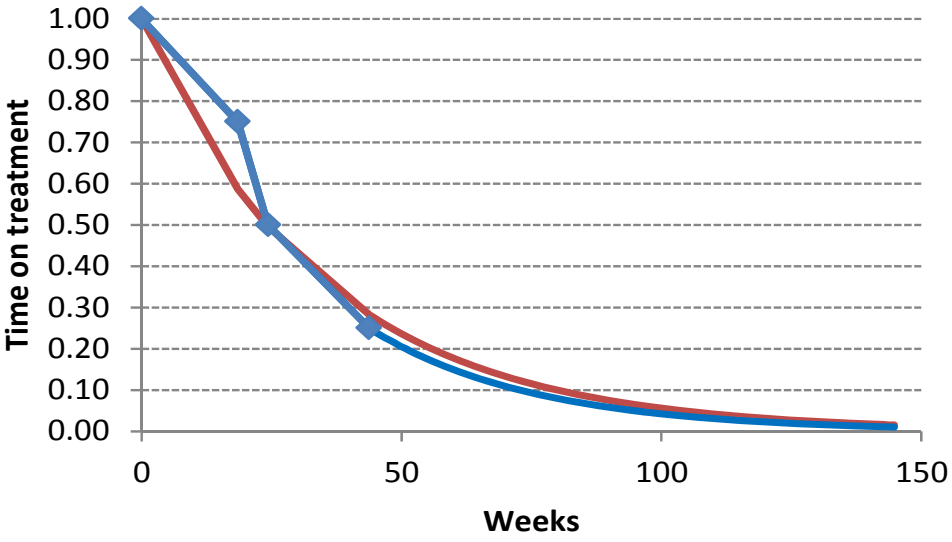
Table 101: Estimated treatment durations and cumulative doses from OPUS for RAS WT patients

	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

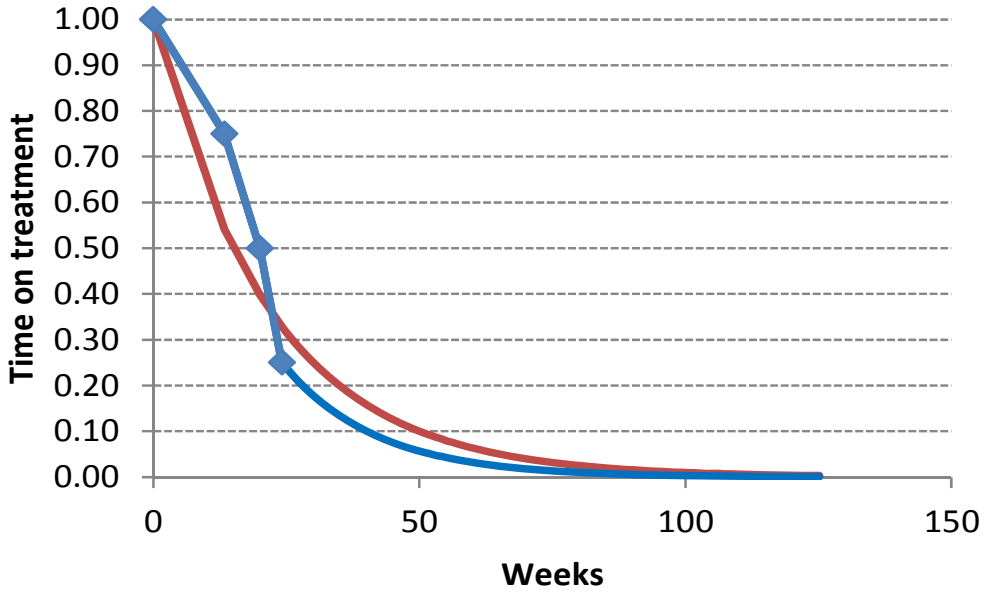
First, this data was used to estimate the mean time on cetuximab+FOLFOX for RAS WT patients. An exponential tail was fit to the 25% percentile (Figure 33), with hazard set equal to that at the 25% percentile. The mean was then estimated as 34.7 weeks, being the area under the empirical data and fitted tail.

Figure 33 Estimated time on CET+FOLFOX treatment for *RAS* WT patients in OPUS



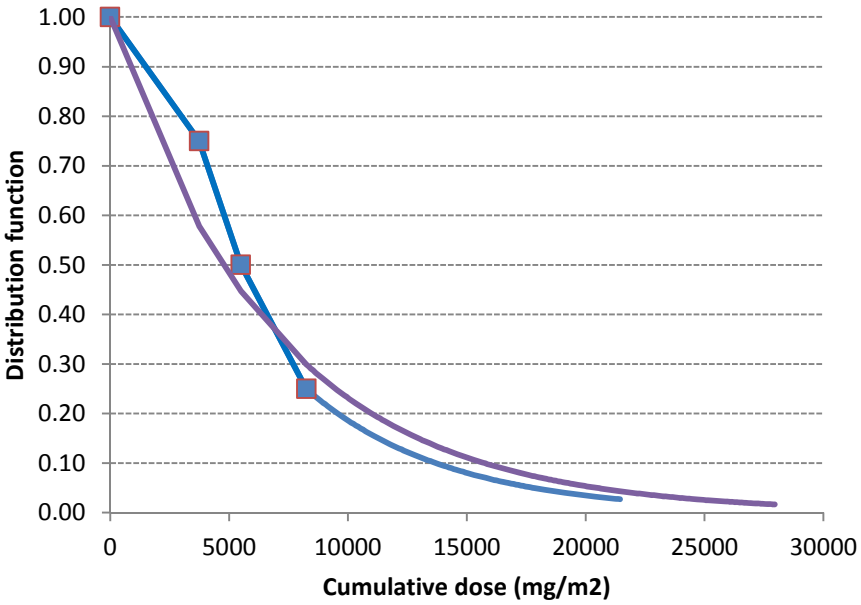
The same process was followed to estimate the mean time on FOLFOX in the FOLFOX arm as 21.7 weeks (Figure 34).

Figure 34 Estimated time on FOLFOX treatment in FOLFOX arm for *RAS* WT patients in OPUS



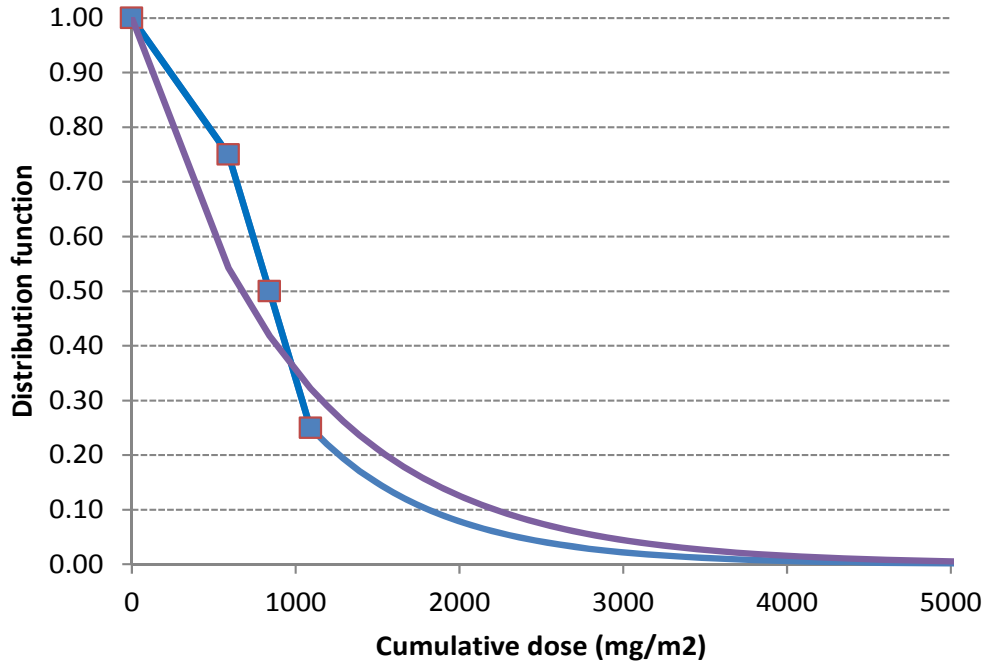
In a sensitivity analysis, we estimate treatment duration from cumulative drug doses. The total cumulative doses were calculated in a similar way. First, for cetuximab in OPUS (Figure 35). This yielded an estimated total dose of cetuximab of 6,838mg/m2.

Figure 35 Estimated cumulative total dose for cetuximab in CET+FOLFOX arm for *RAS* WT patients in OPUS



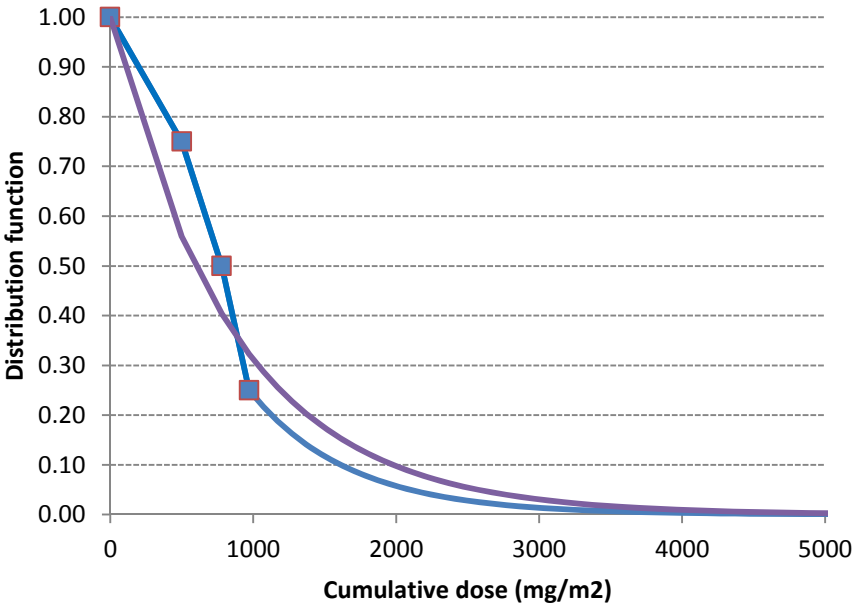
Similarly, the estimated mean total dose of oxaliplatin in the CET+FOLFOX arm in OPUS is 963mg/m2 (Figure 36).

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

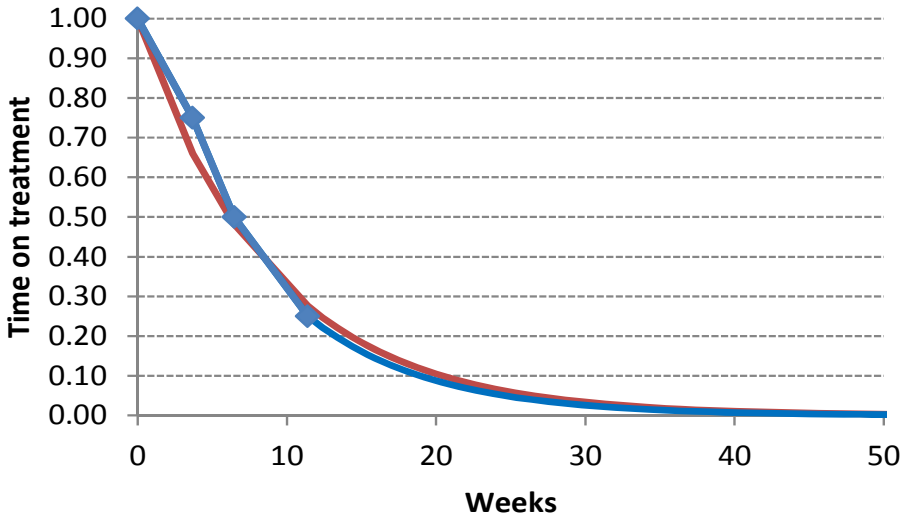
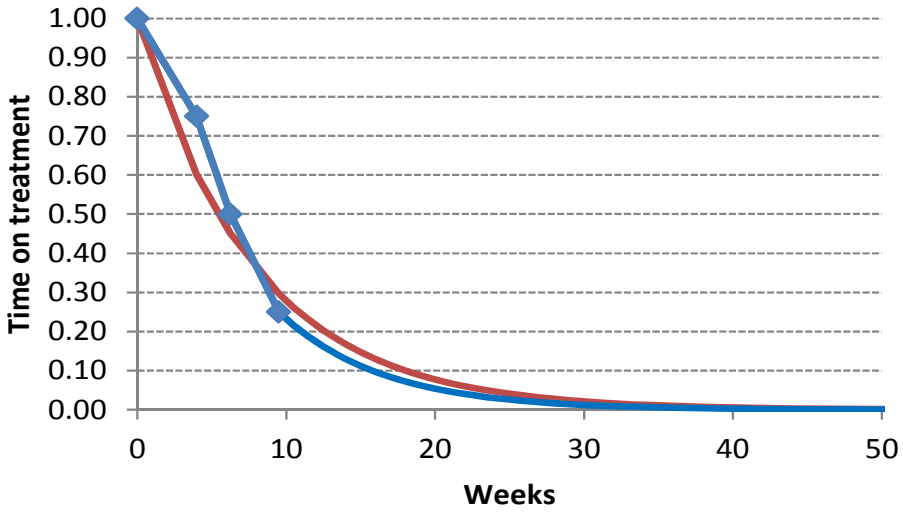


Figure 39 Duration of treatment in FOLFOX arm in PRIME



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

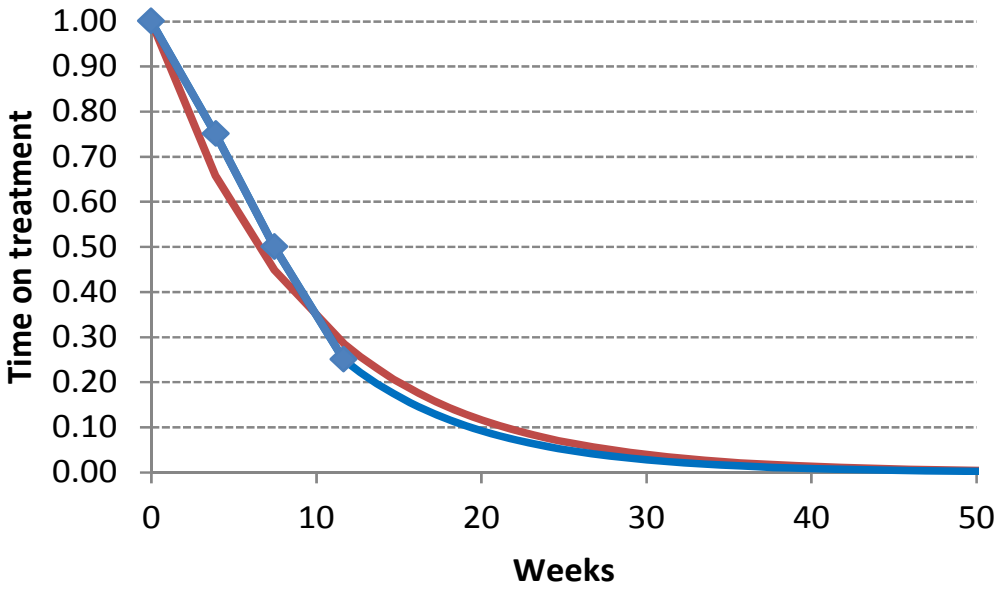
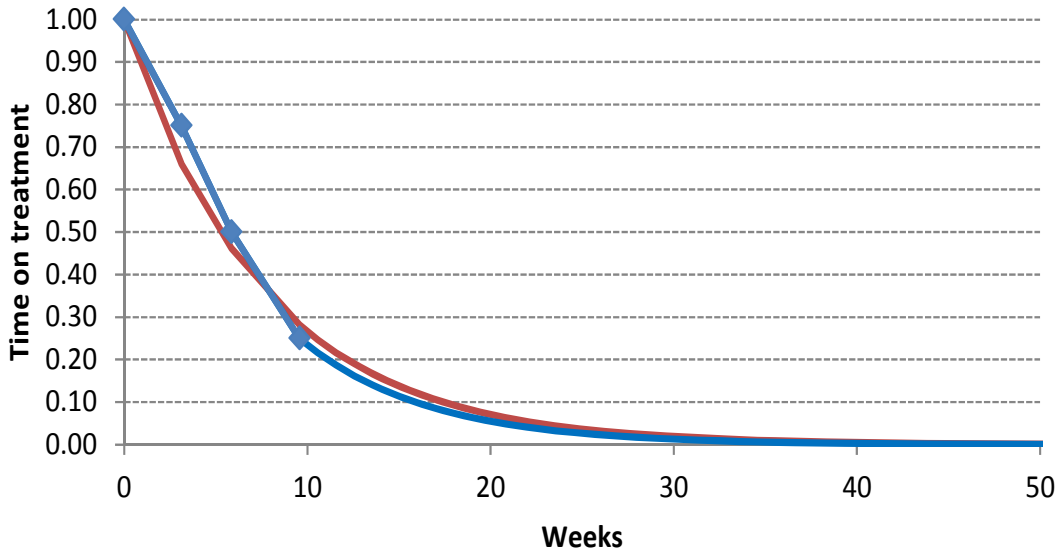


Figure 41. Duration of treatment in BEV+FOLFOX arm in PEAK



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:

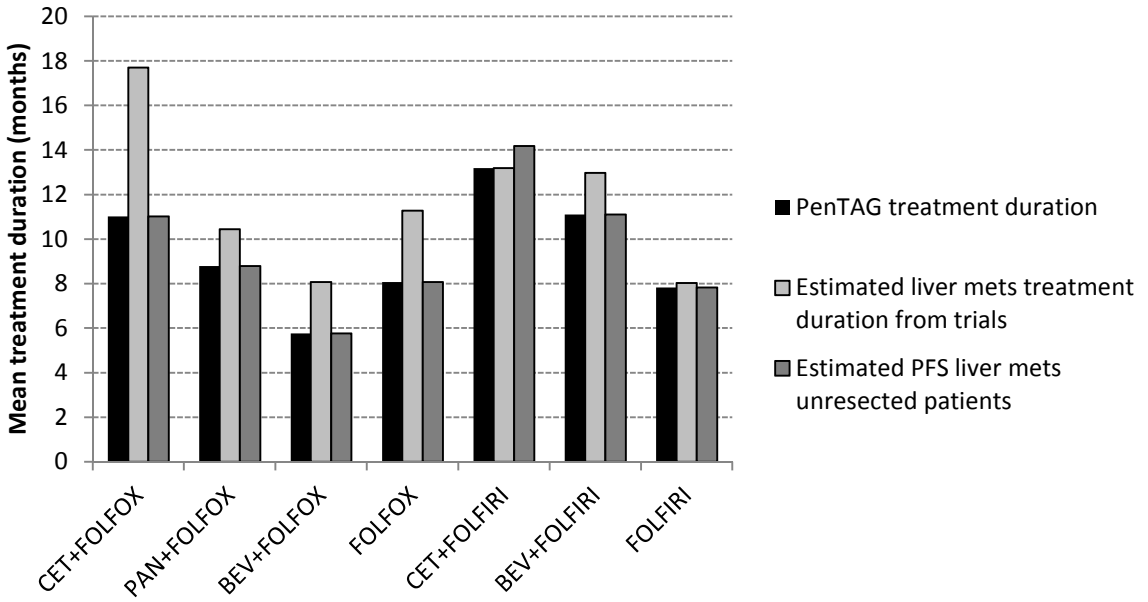
Mean PFS (resected + unresected) liver mets / Mean PFS (resected + unresected) all patients

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

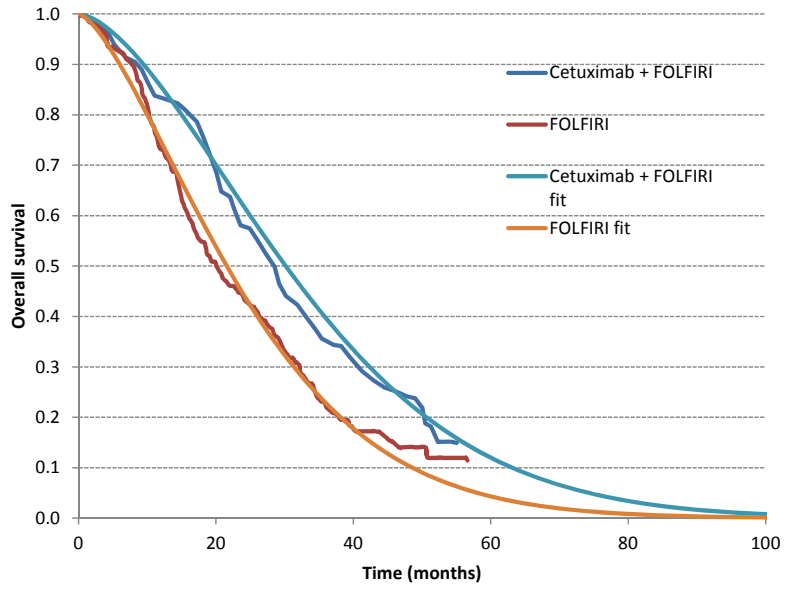
In our base case analysis, we model only PFS from the RCTs. As mentioned in Section 6.1.3.2, p243, in a sensitivity analysis, we model OS for unresected patients, in addition to PFS for unresected patients, from the RCTs. In particular, our method of estimating OS for unresected patients is the same 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.

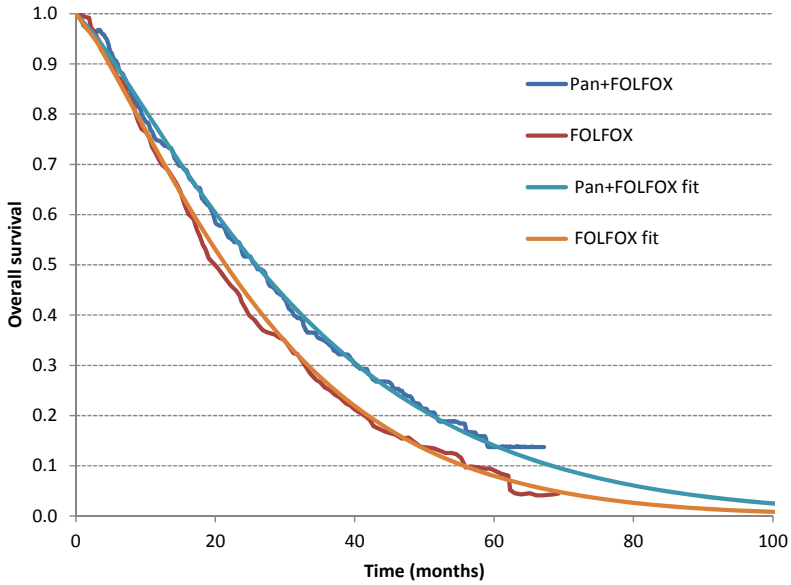
Our chosen curve fits are given in Figure 43 below.

Figure 43. 1st-line OS (unresected patients) in PenTAG model

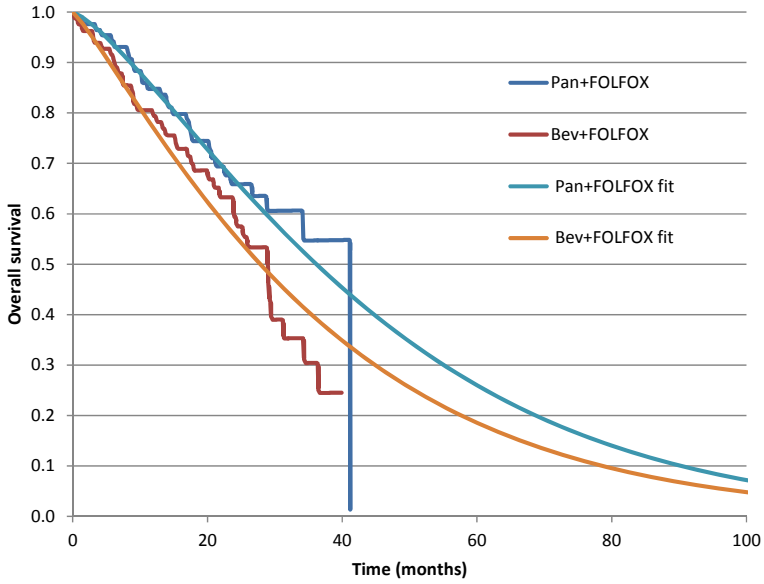
(a) CET+FOLFOX vs. FOLFOX from OPUS



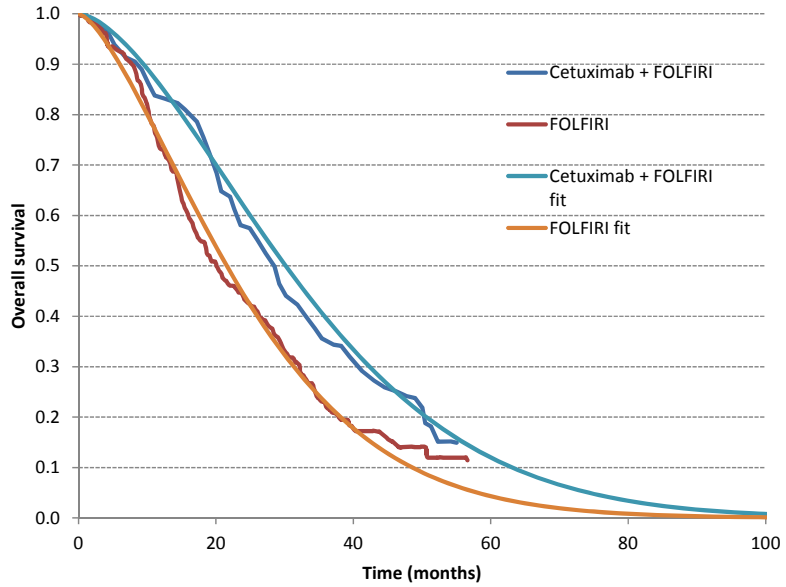
(b) PAN+FOLFOX vs. FOLFOX from PRIME



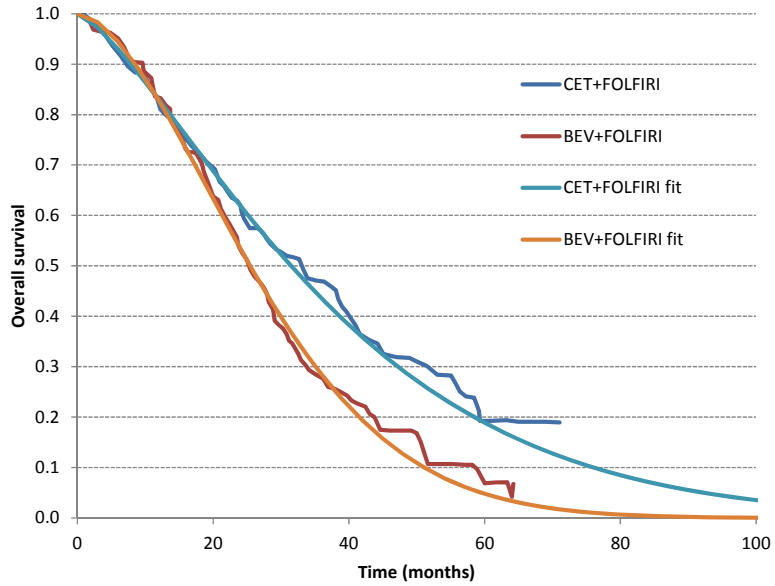
(c) PAN+FOLFOX vs. BEV+FOLFOX from PEAK



(d) CET+FOLFIRI vs. FOLFIRI from CRYSTAL



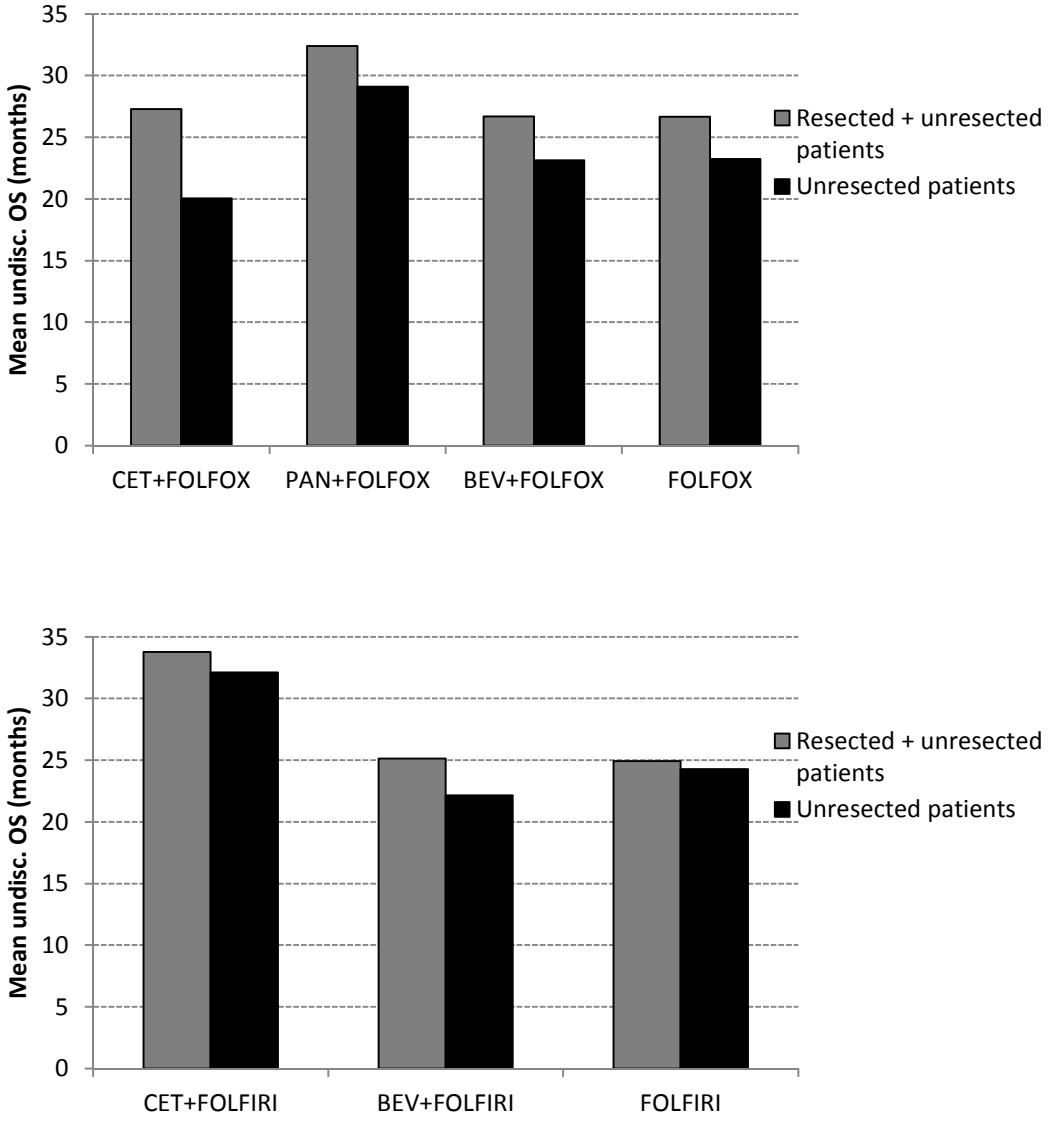
(e) CET+FOLFIRI vs. BEV+FOLFIRI from FIRE-3



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).

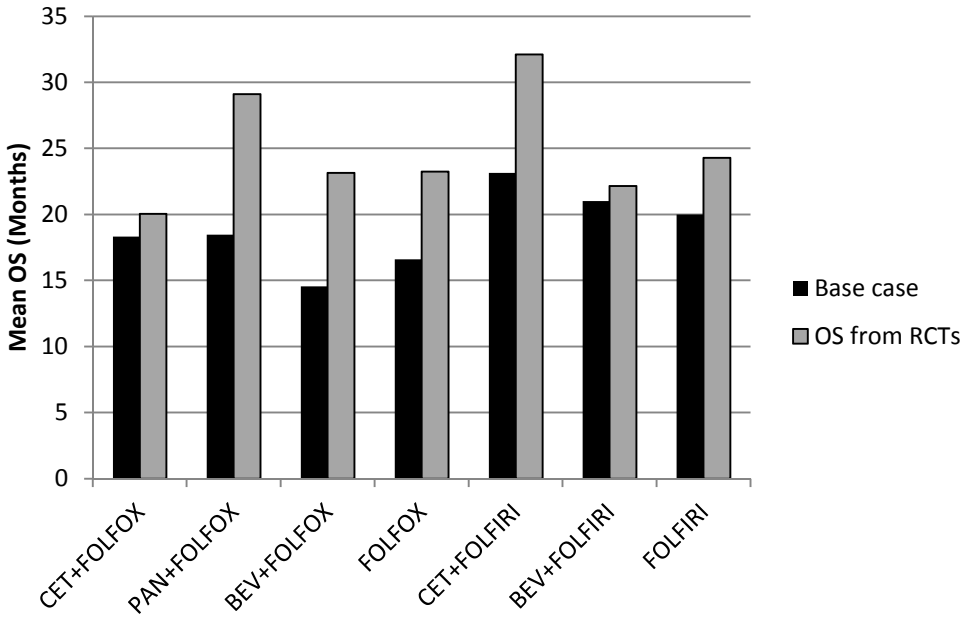
Figure 44. PenTAG mean OS from 1st-line RCTs



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

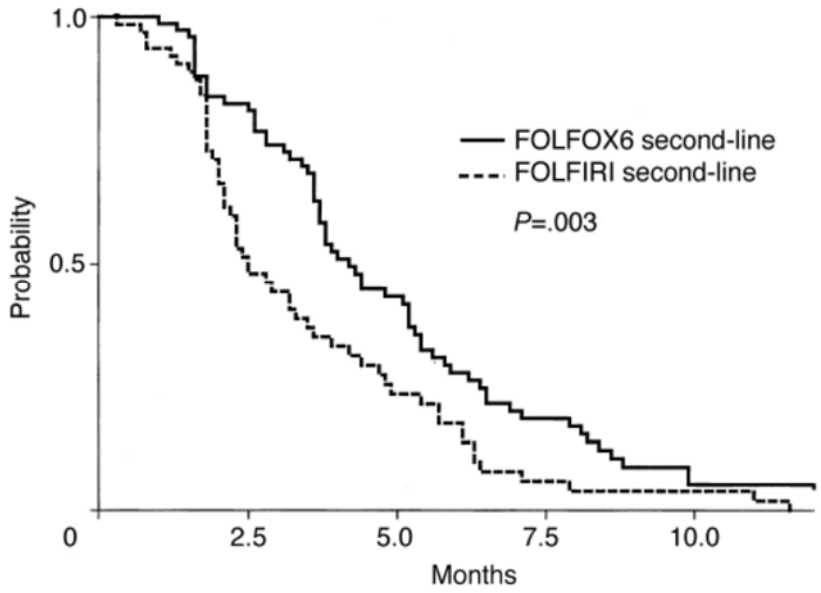
6.1.4.7. 2nd-line Progression-free survival: unresected patients

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)

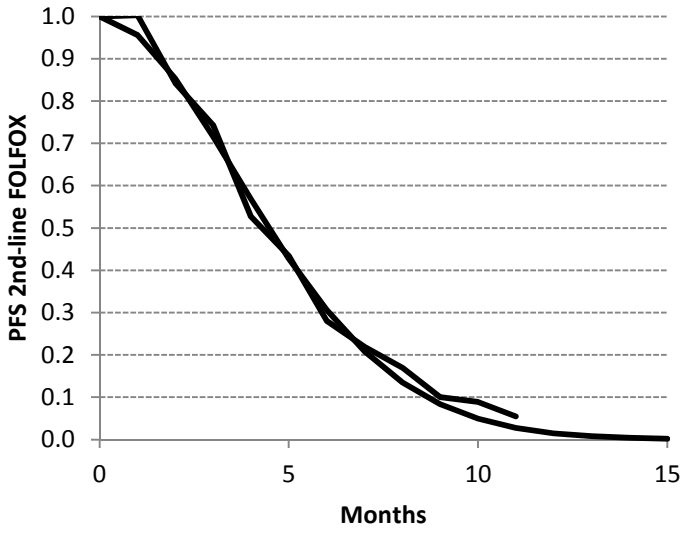


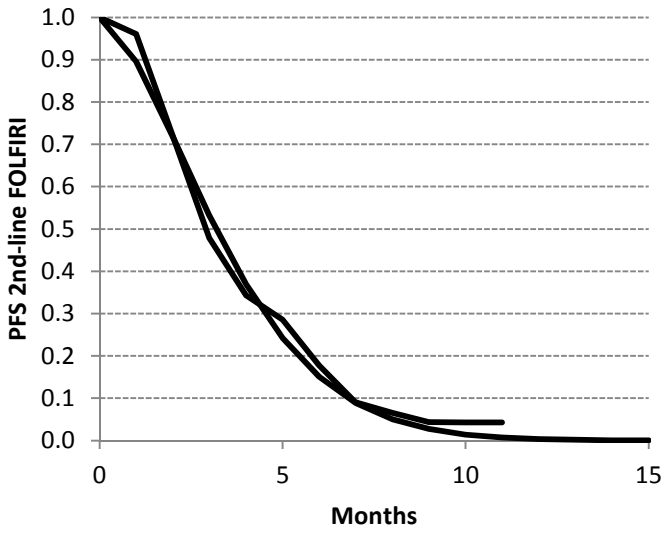
Source:Figure 2B, Tournigand et al. (2004).[113]

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.

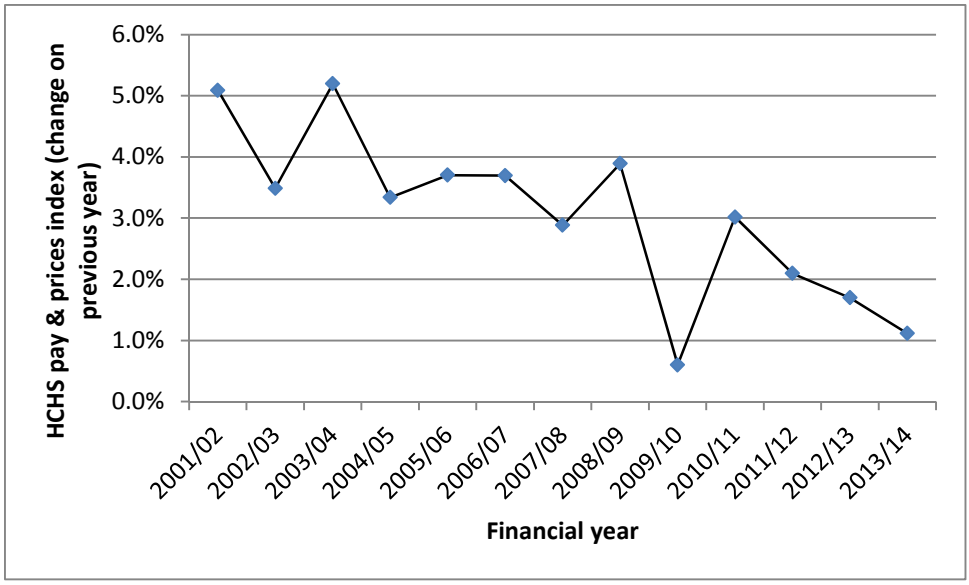
6.1.4.12. Costs

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)

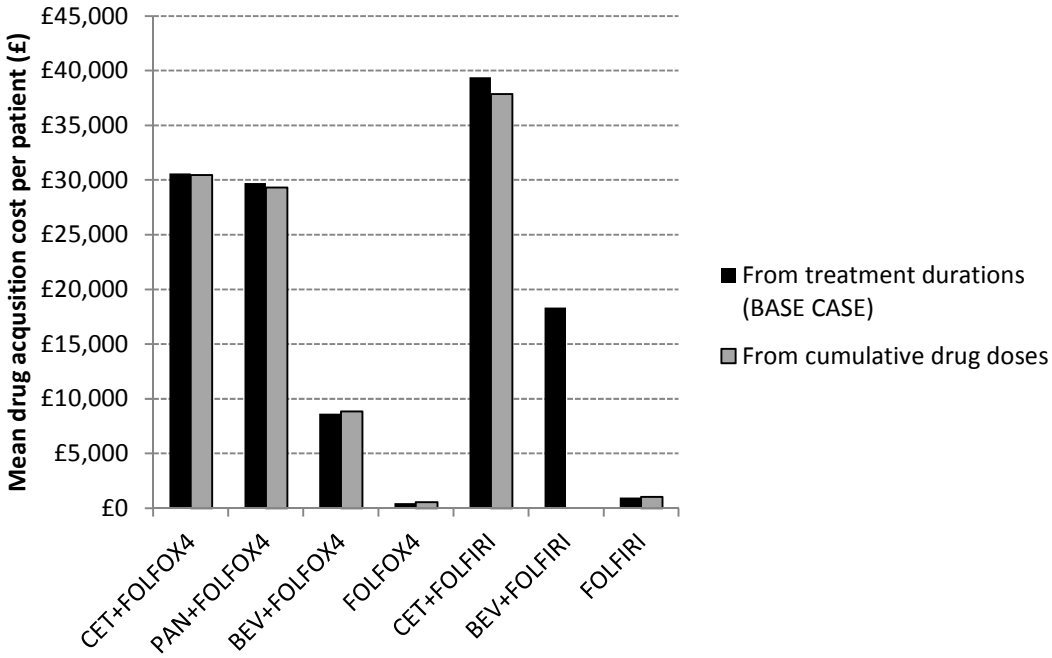
CET+FOLFIRI: 92% (CRYSTAL)

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.

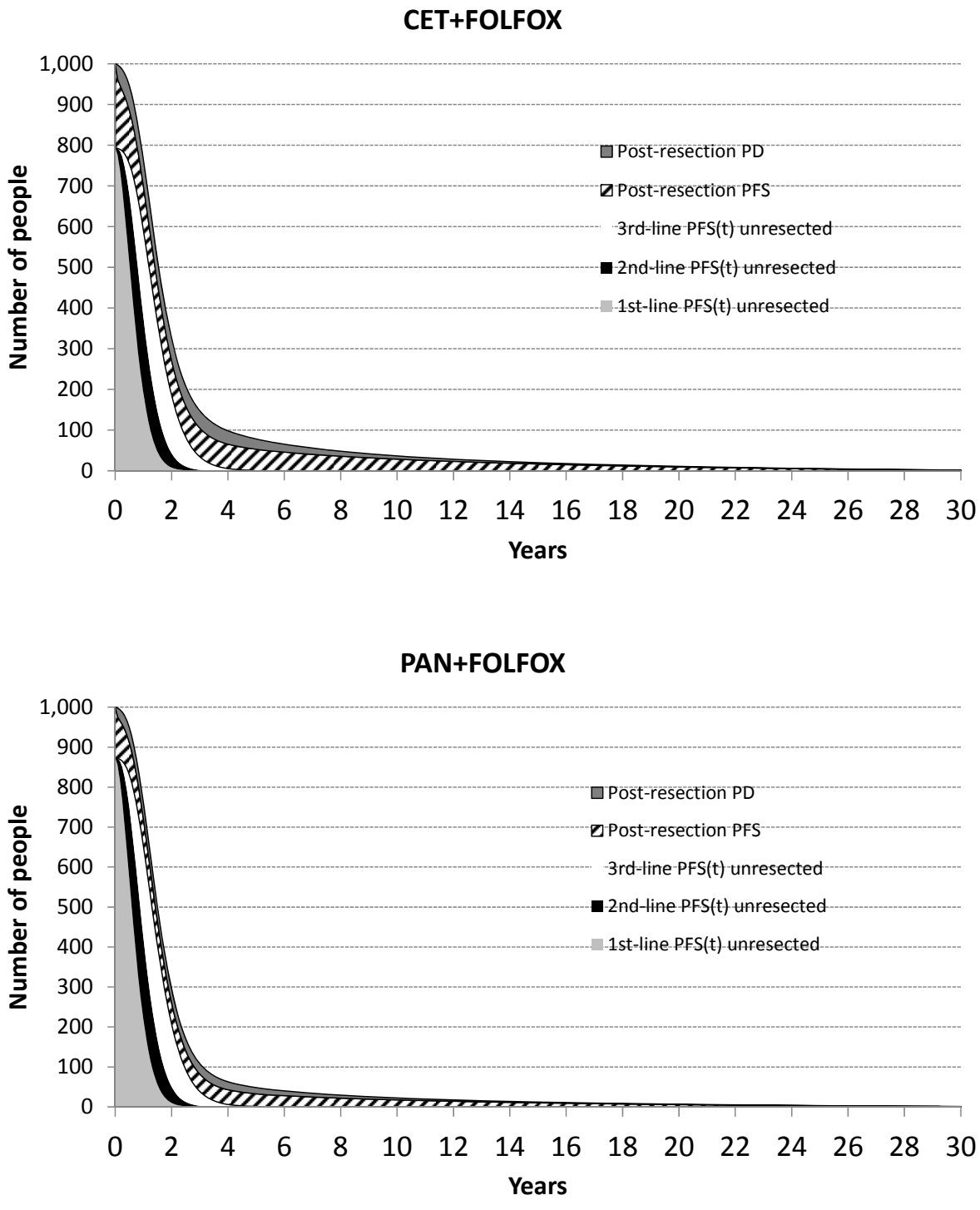
Notice that all graphs show two distinct features. The times on 1st-, 2nd- and 3rd-line for unresected patients are short, and last in total up to about 4 years. The time on PFS and PD post-resection are much longer. This reflects the substantial improvement in survival that we predict for patients post-resection.

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.

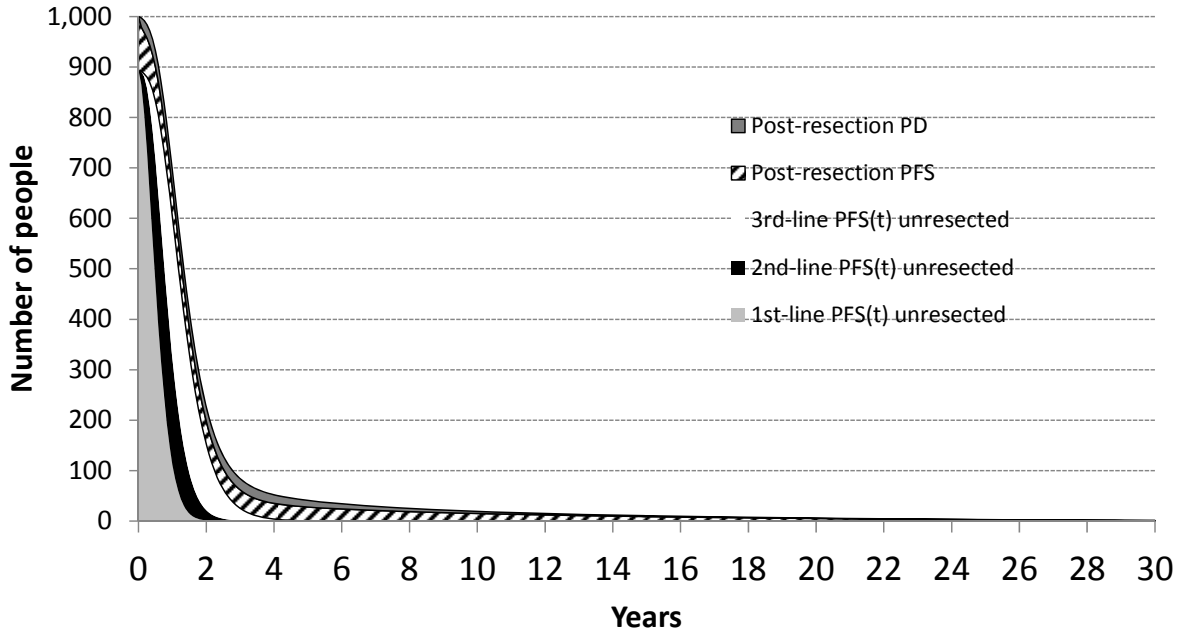
See see further than we expect slightly longer times in 1st-line PFS for unresected patients for CET+FOLFOX and PAN+FOLFOX compared to FOLFOX and for CET+FOLFIRI compared to FOLFIRI.

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”).

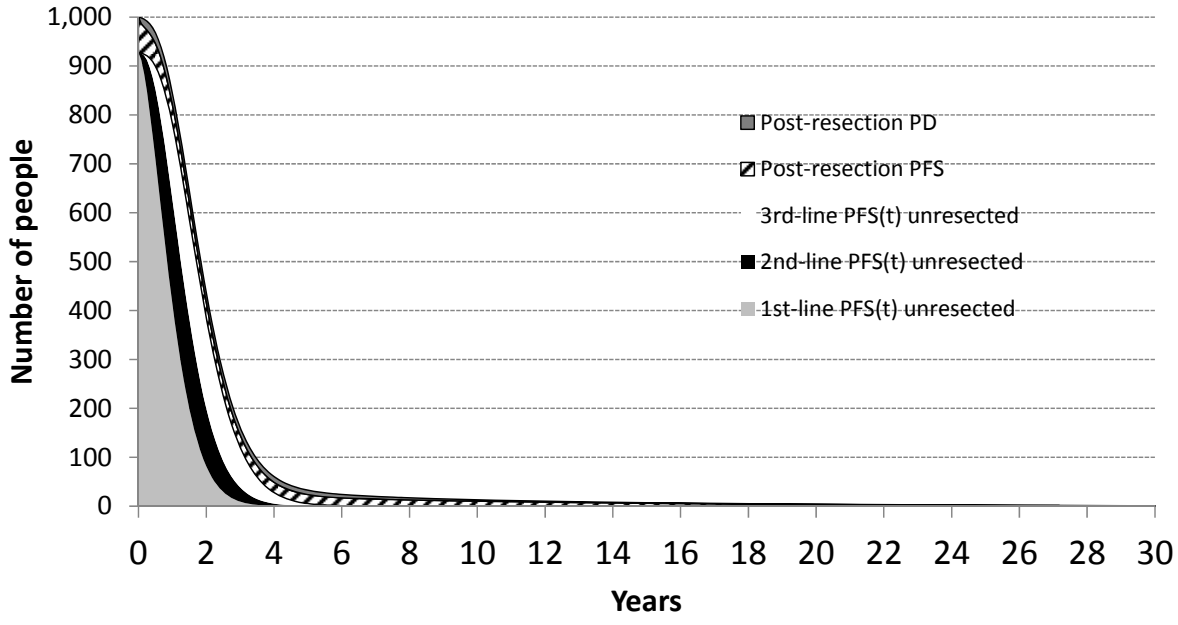
Figure 50. Cohort composition over time by treatment.

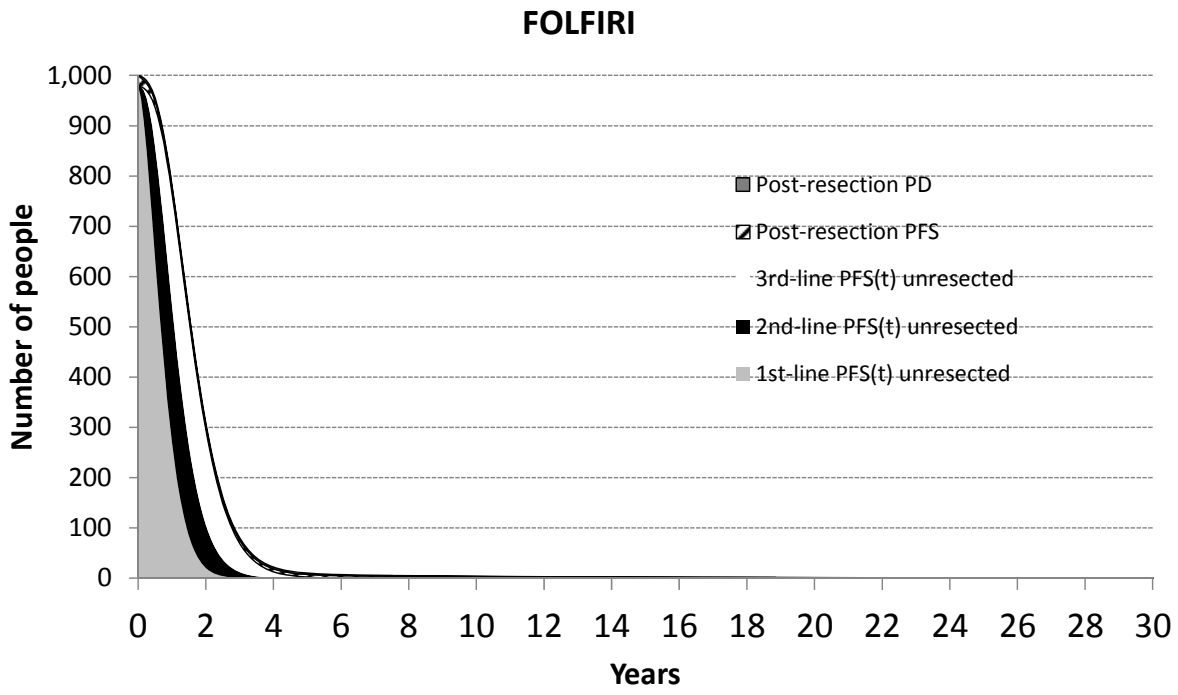


FOLFOX



CET+FOLFIRI





Key: PD = progressive disease, PFS = progression free survival

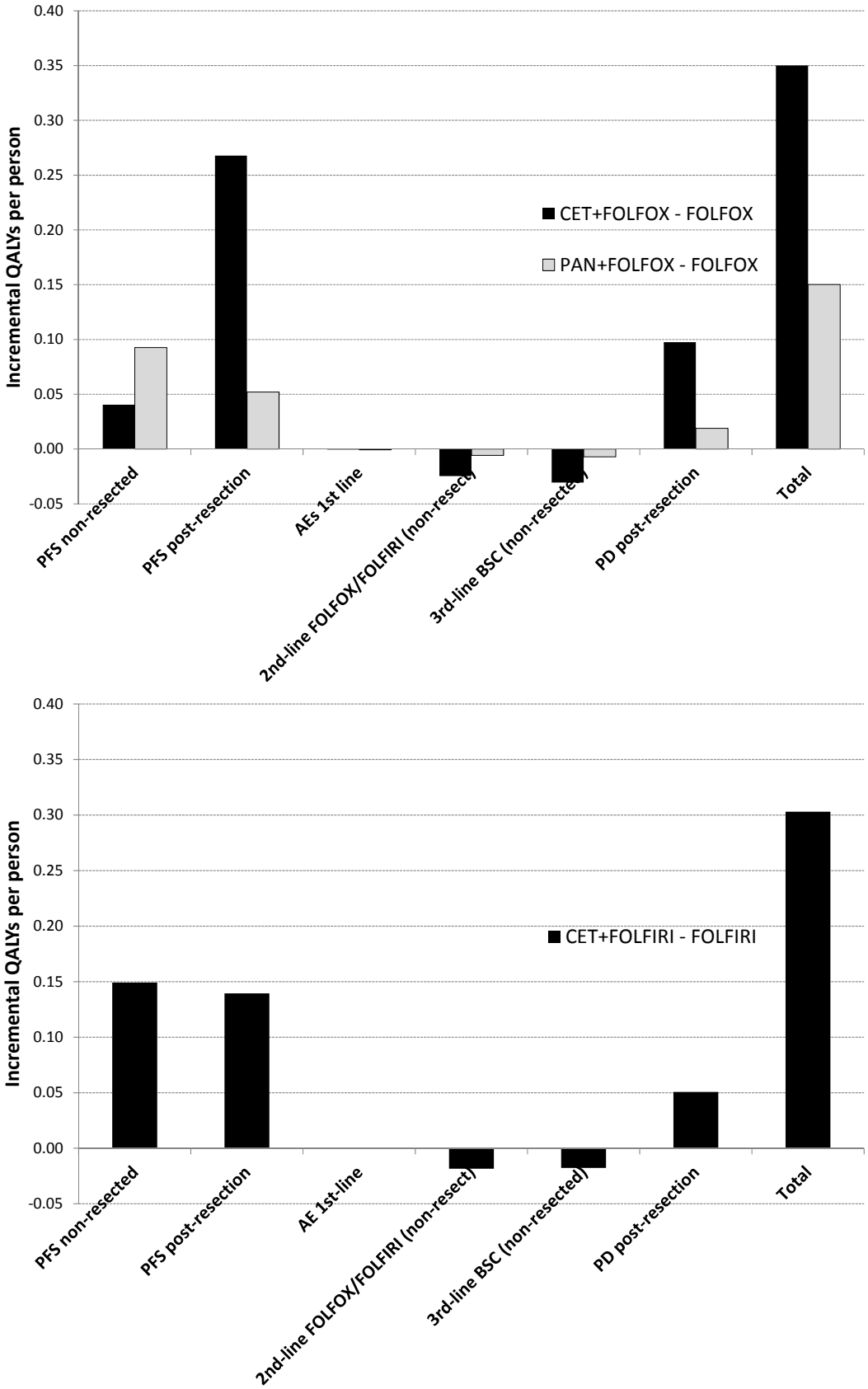
The relative magnitudes of the QALYs are similar to the relative magnitudes of the life years, as the QALYs are simply the life years, discounted and then multiplied by the utilities appropriate for each health state.

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

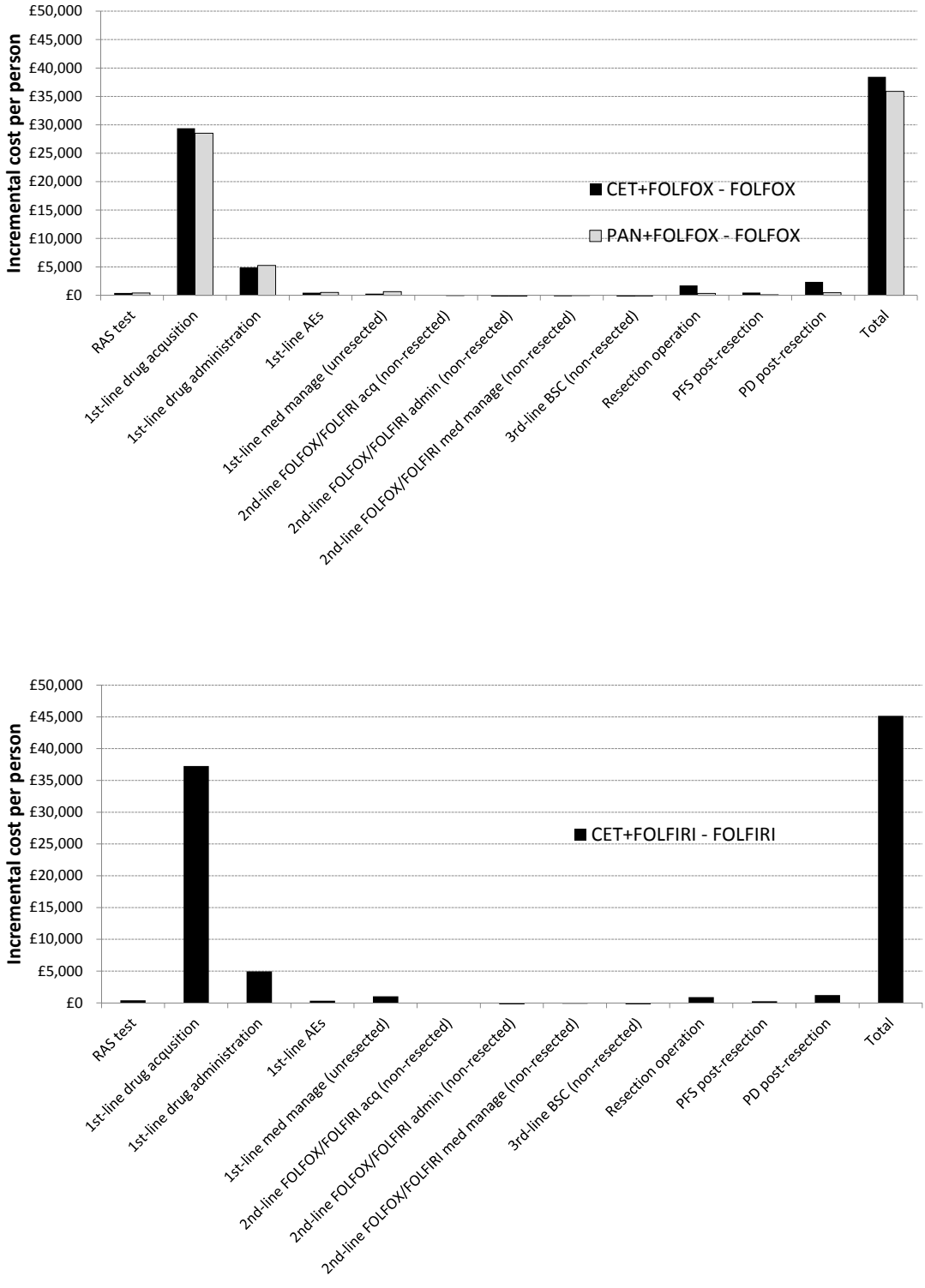
Costs results

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).

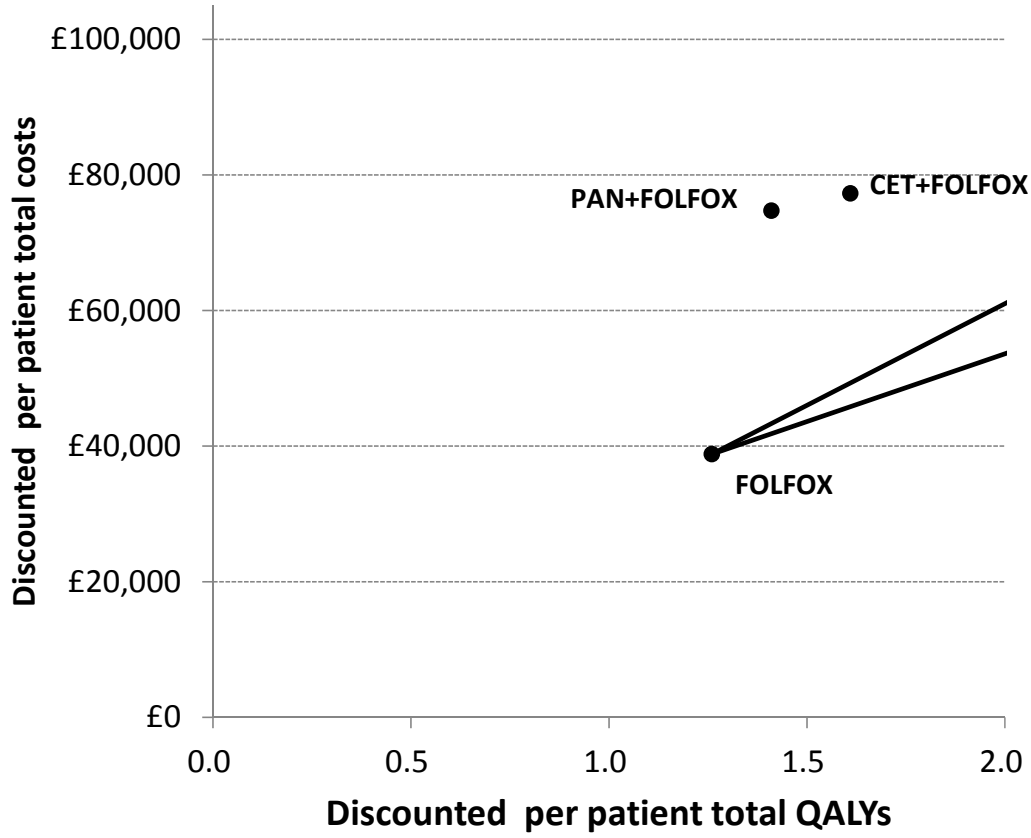
Given lack of data to suggest otherwise, we assume the same accuracy of the *RAS* test in clinical practice as in the 1st-line RCTs (Section 6.1.4.10, p307). Any differences are likely to render worse estimates of cost-effectiveness for cetuximab and panitumumab.

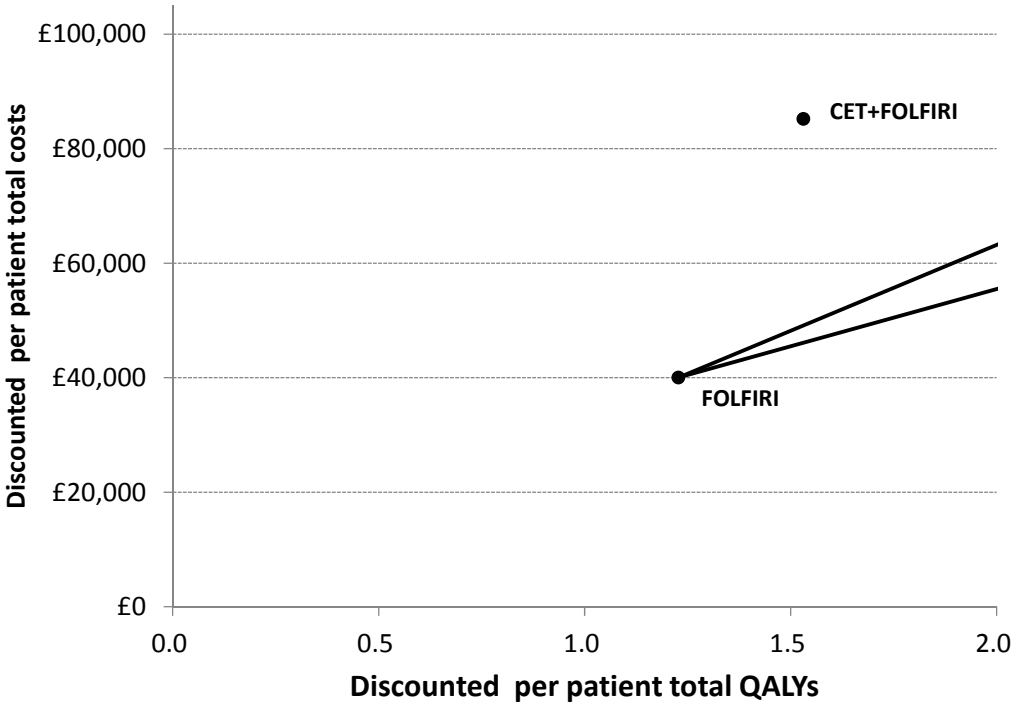
For FOLFOX, our clinical effectiveness is based on the PRIME RCT. Instead, we use the OPUS RCT in a scenario analysis (Section,1.1.1.1, p383).

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

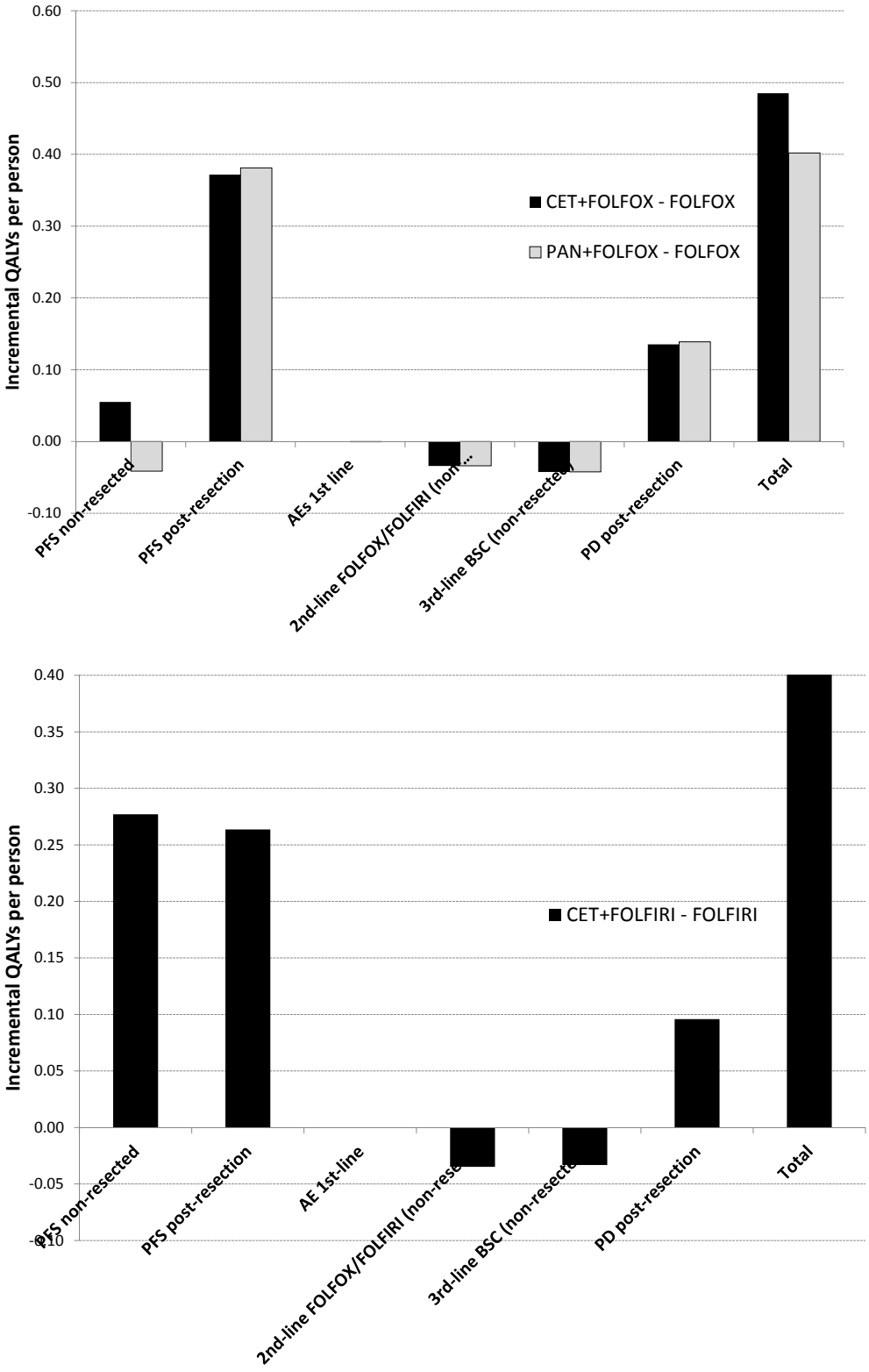
Many of the comments for all patients carry over to the liver mets subgroup. Here, we explain features unique to the liver mets subgroup.

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.



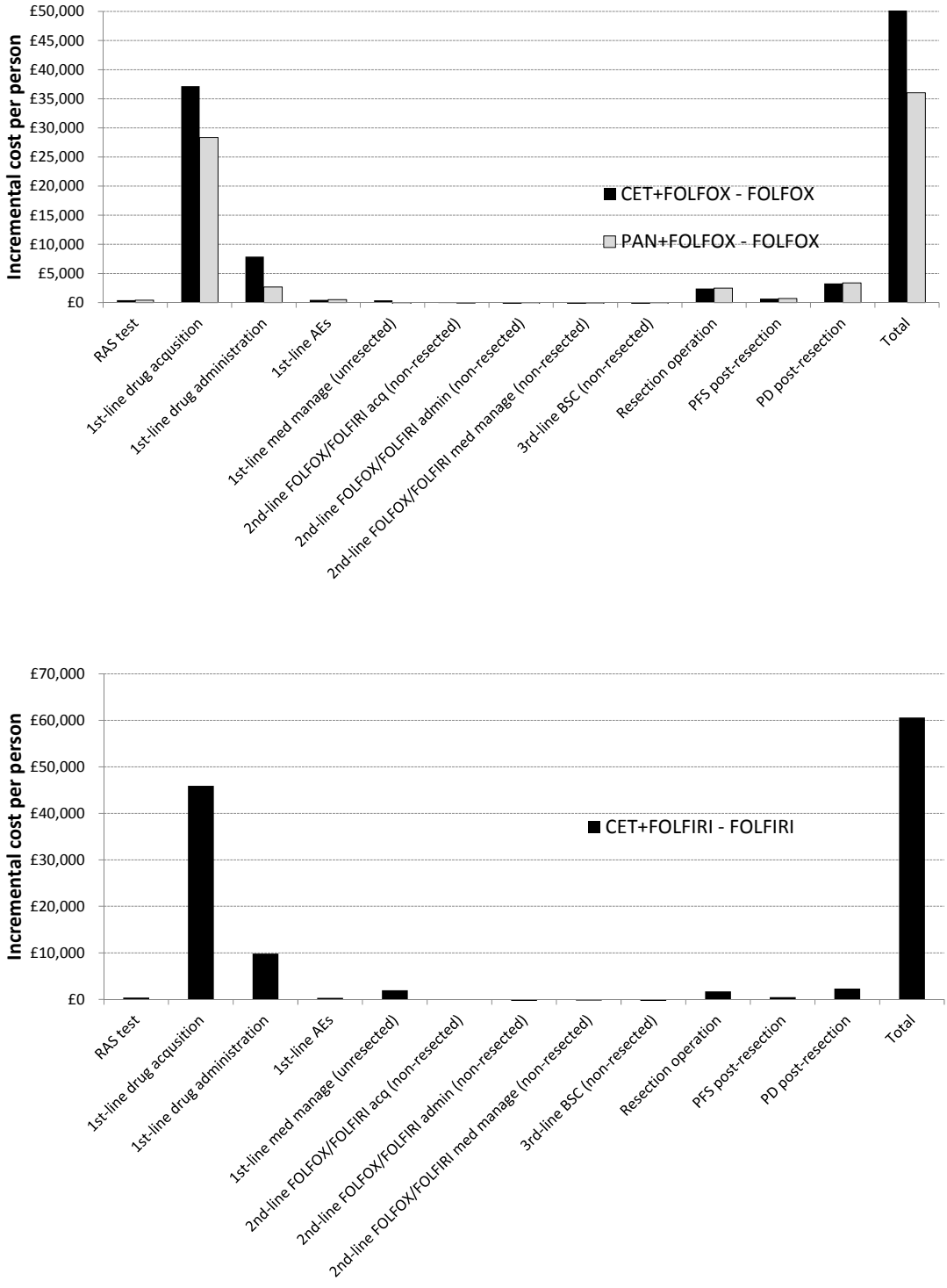
Key: AE = adverse event; BEV = bevacizumab; BSC = best supportive care; CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; PAN = panitumumab; PD = progressive disease; PFS = progression free survival QALY = quality adjusted life year

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

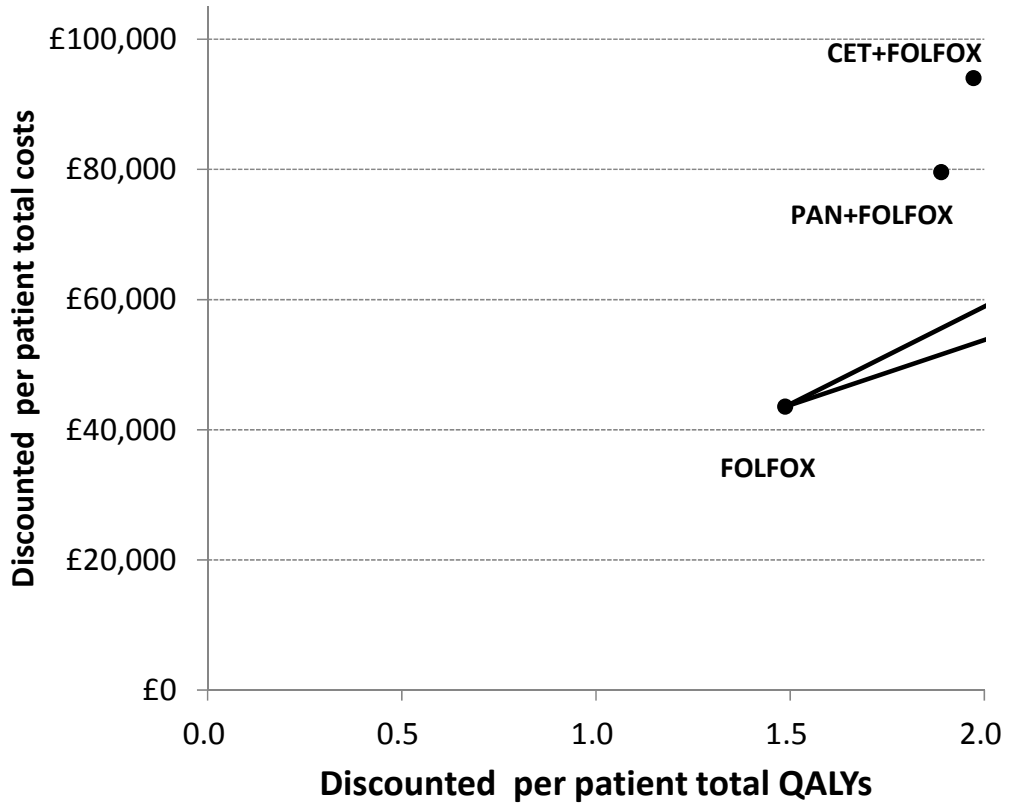
Combining all the information on expected costs and QALYs per person, we estimate the following ICERs for the liver mets subgroup:

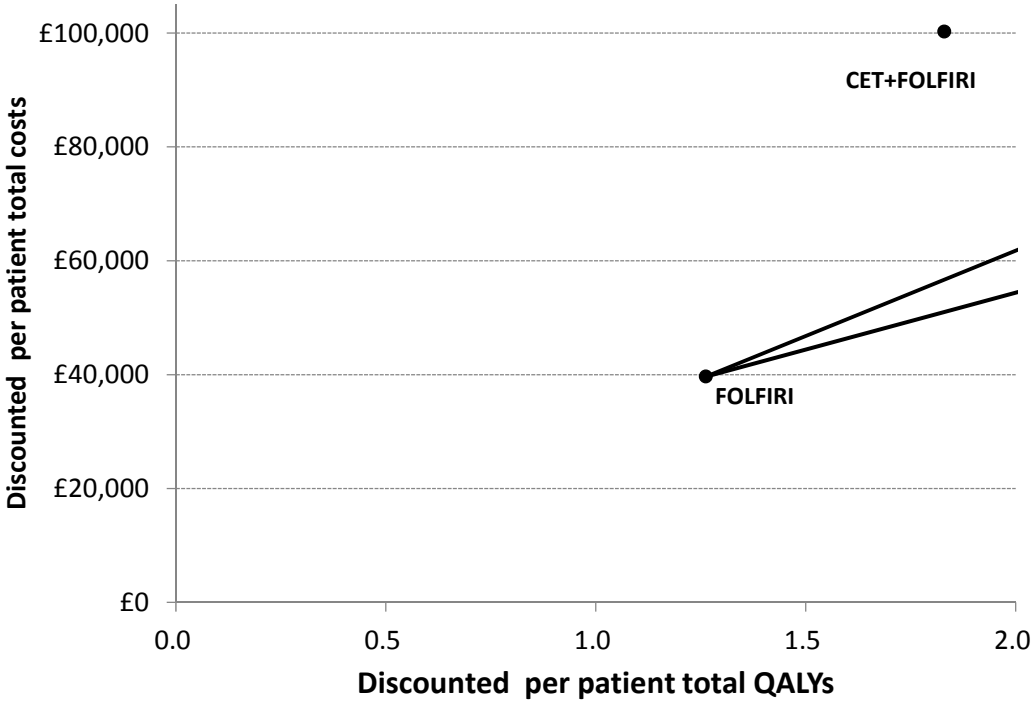
- CET+FOLFOX vs FOLFOX as £104,000 per QALY
- PAN+FOLFOX vs FOLFOX as £90,000 per QALY.
- CET+FOLFIRI vs FOLFIRI as £107,000 per QALY

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.

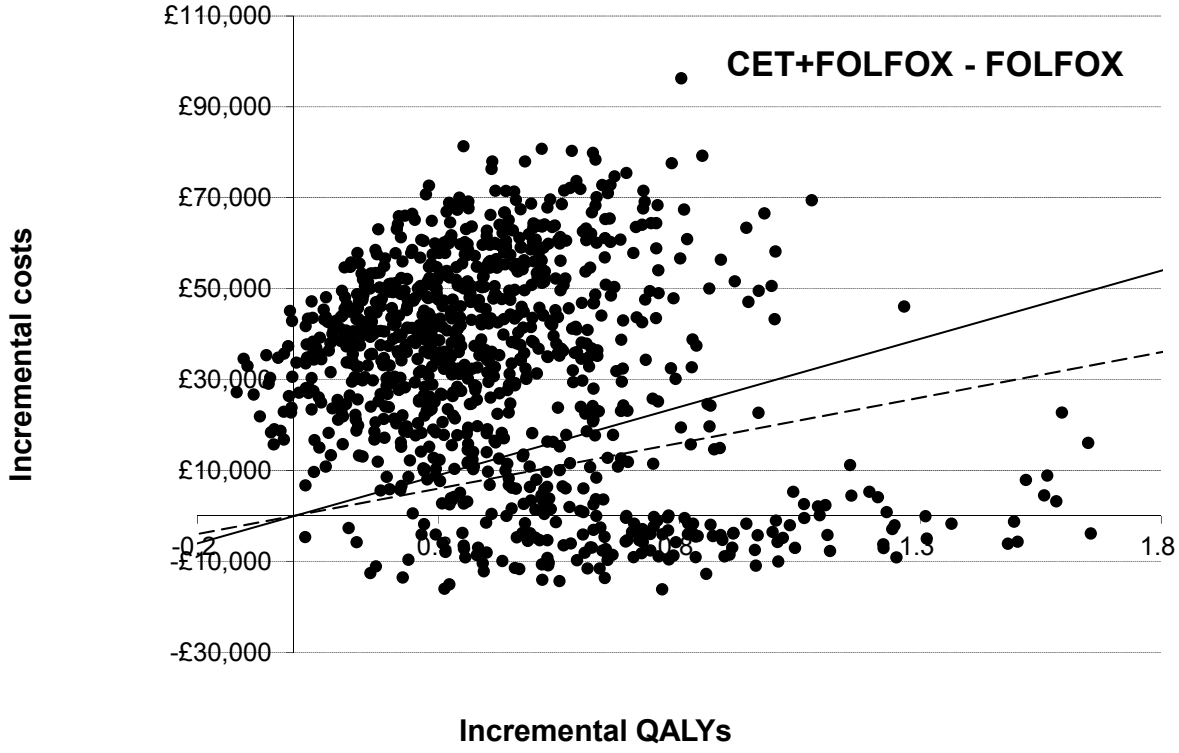
In the FOLFOX network, we predict that the probability is zero that PAN+FOLFOX provides the best value at any willingness to pay threshold investigated (£0 to £150,000 per QALY). The probability that CET+FOLFOX provides the best value exceeds 50% only at a willingness to pay of about £105,000 per QALY, 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:

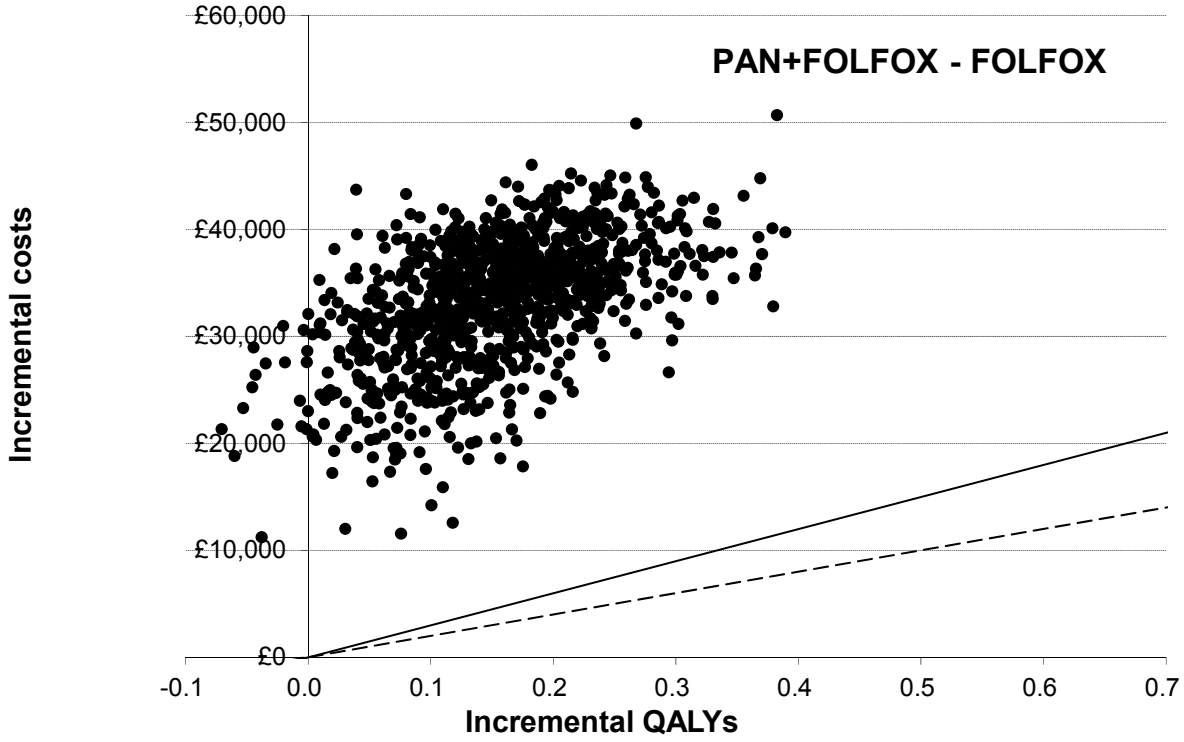
- CET+FOLFOX: 22%.
- PAN+FOLFOX: 0%.
- CET+FOLFIRI: 0%

Figure 57. PenTAG PSA results: incremental cost–utility per person of CET+FOLFOX vs. FOLFOX, all patients



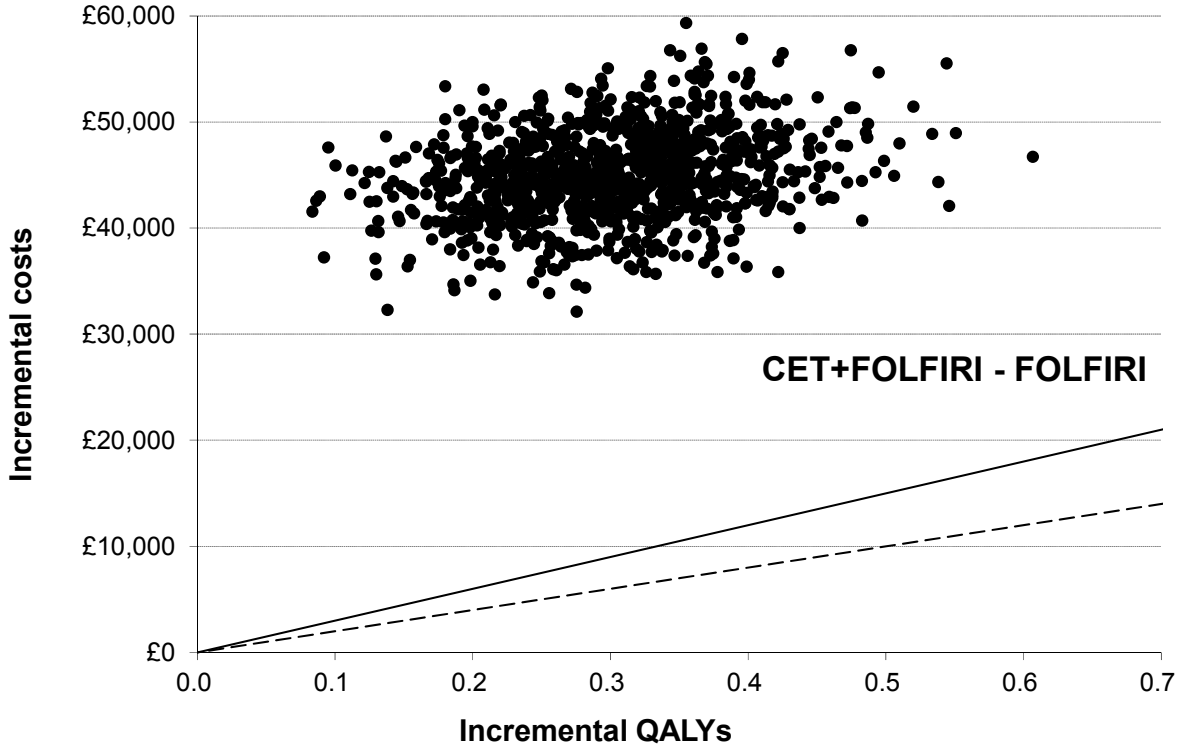
Key: CET = cetuximab; FOLFOX = folinic acid + fluorouracil + oxaliplatin; QALY = quality adjusted life year
Notes: - - - - = willingness to pay threshold £20,000 per QALY gained; ____ = willingness to pay threshold £30,000 per QALY

Figure 58. PenTAG PSA results: incremental cost–utility per person of PAN+FOLFOX vs. FOLFOX, all patients



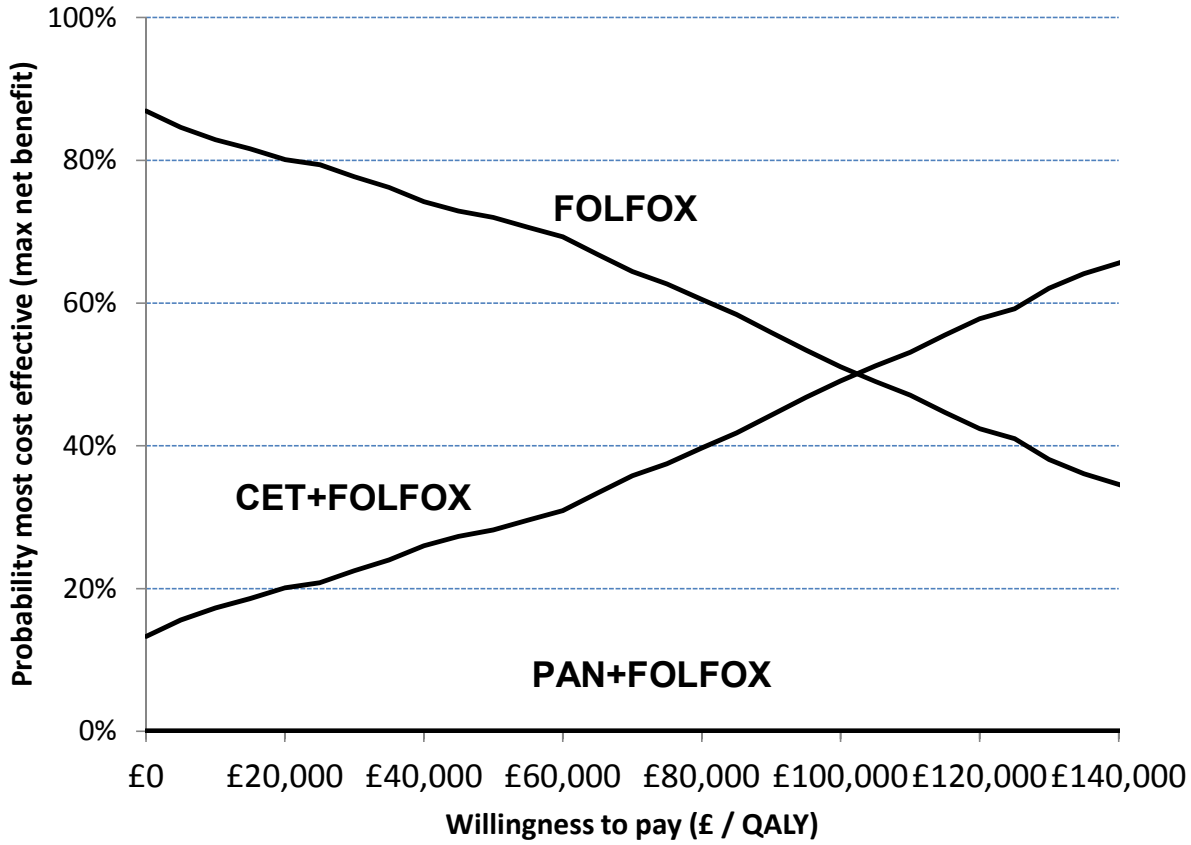
Key: FOLFOX = folinic acid + fluorouracil + oxaliplatin; PAN = panitumumab; QALY = quality adjusted life year
Notes: - - - - = willingness to pay threshold £20,000 per QALY gained; ____ = willingness to pay threshold £30,000 per QALY

Figure 59. PenTAG PSA results: incremental cost–utility per person of CET+FOLFIRI vs. FOLFIRI, all patients



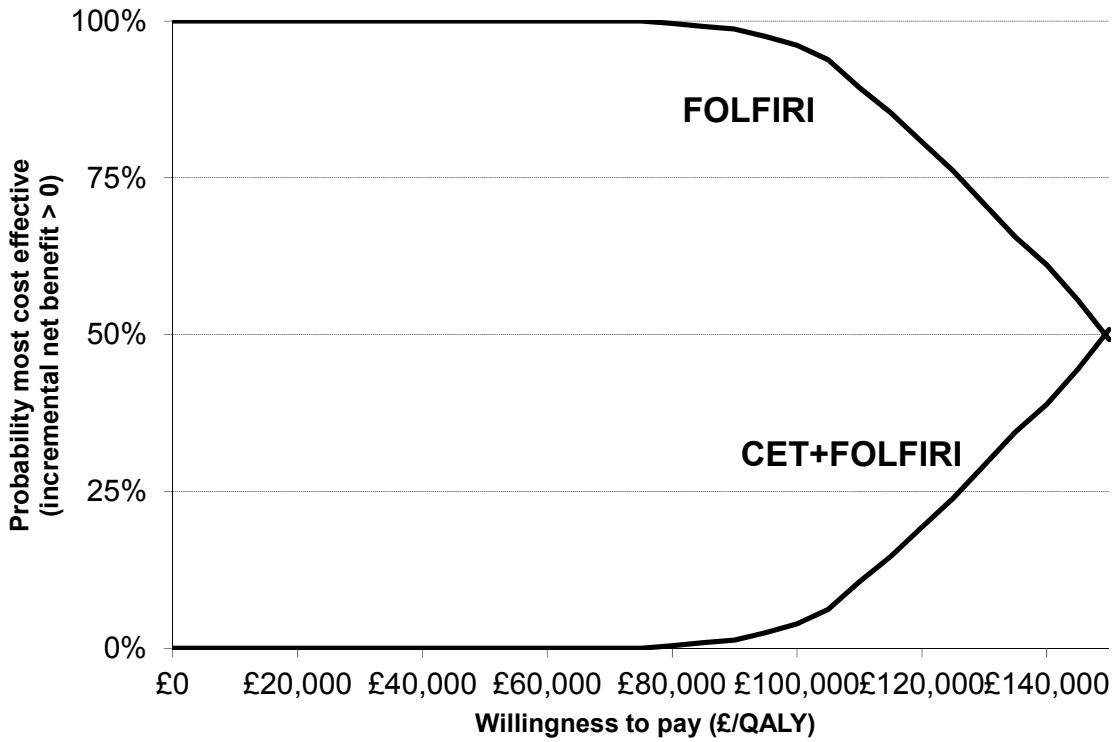
Key: CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irintoecan; QALY = quality adjusted life year
Notes: - - - - = willingness to pay threshold £20,000 per QALY gained; ____ = willingness to pay threshold £30,000 per QALY

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

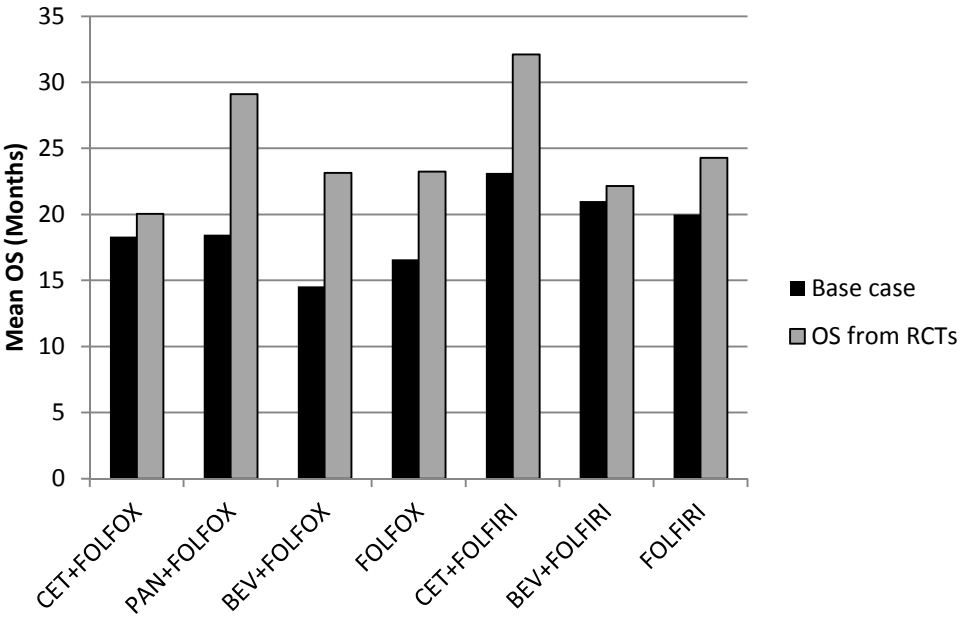
	Estimated treatment duration (months)			1st-line treatment: Estimated % patients on 2nd-line treatment		
2nd-line treatment	**1st-line**	**3rd-line**	**2nd-line**	**CET+FOLFOX**	**PAN+FOLFOX**	**FOLFOX**
CET+FOLFIRI	10.7	8.8	9.7	0%	12.9%	12.7%
PAN+FOLFIRI	8.8	8.8	8.8	14.1%	0%	12.7%
Estimated total cost 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.

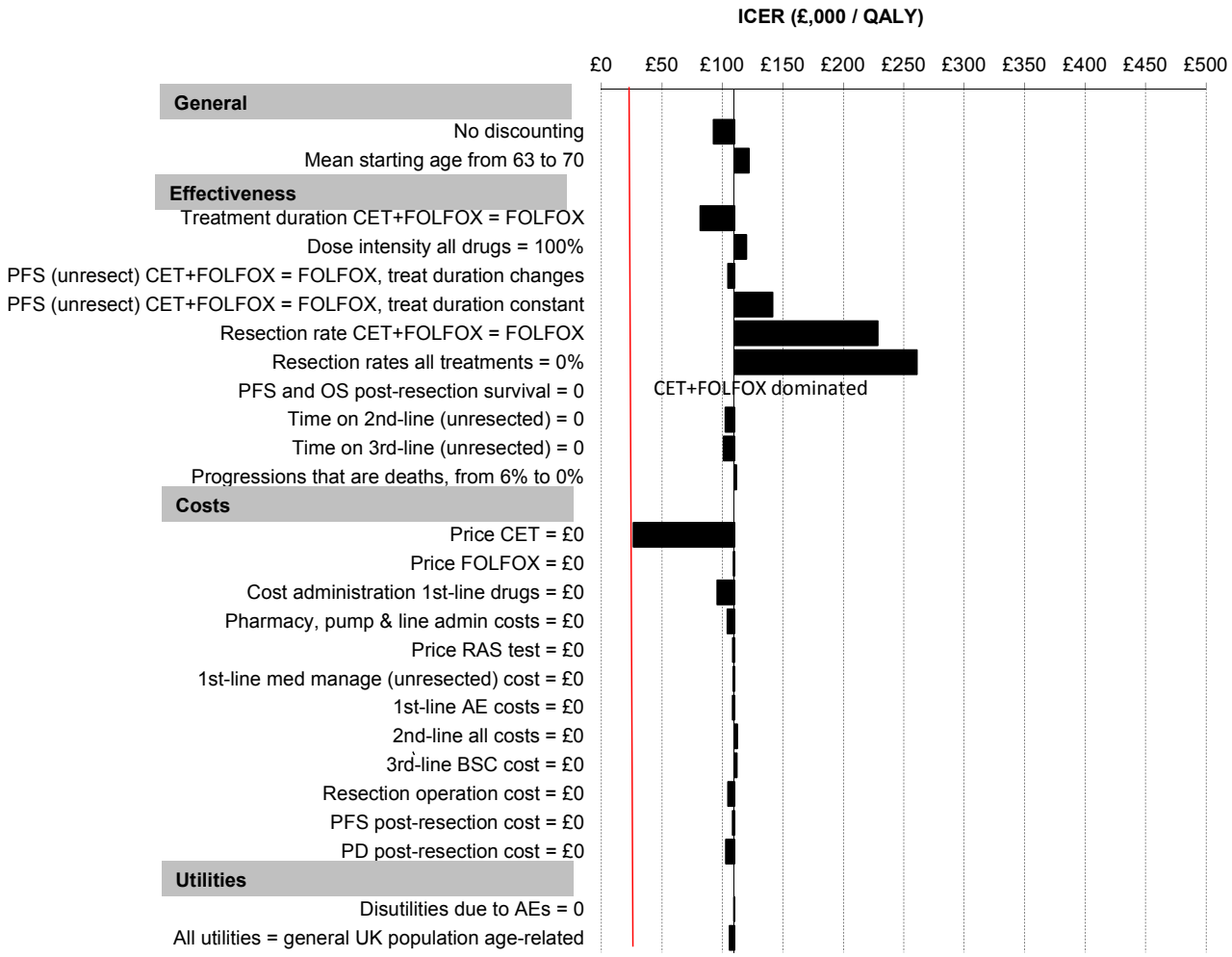
Cost-effectiveness is sensitive to the treatment durations. If we reduce the treatment duration for CET+FOLFOX from 8.7 to 7.0 months, the duration for FOLFOX, the ICER falls substantially.

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

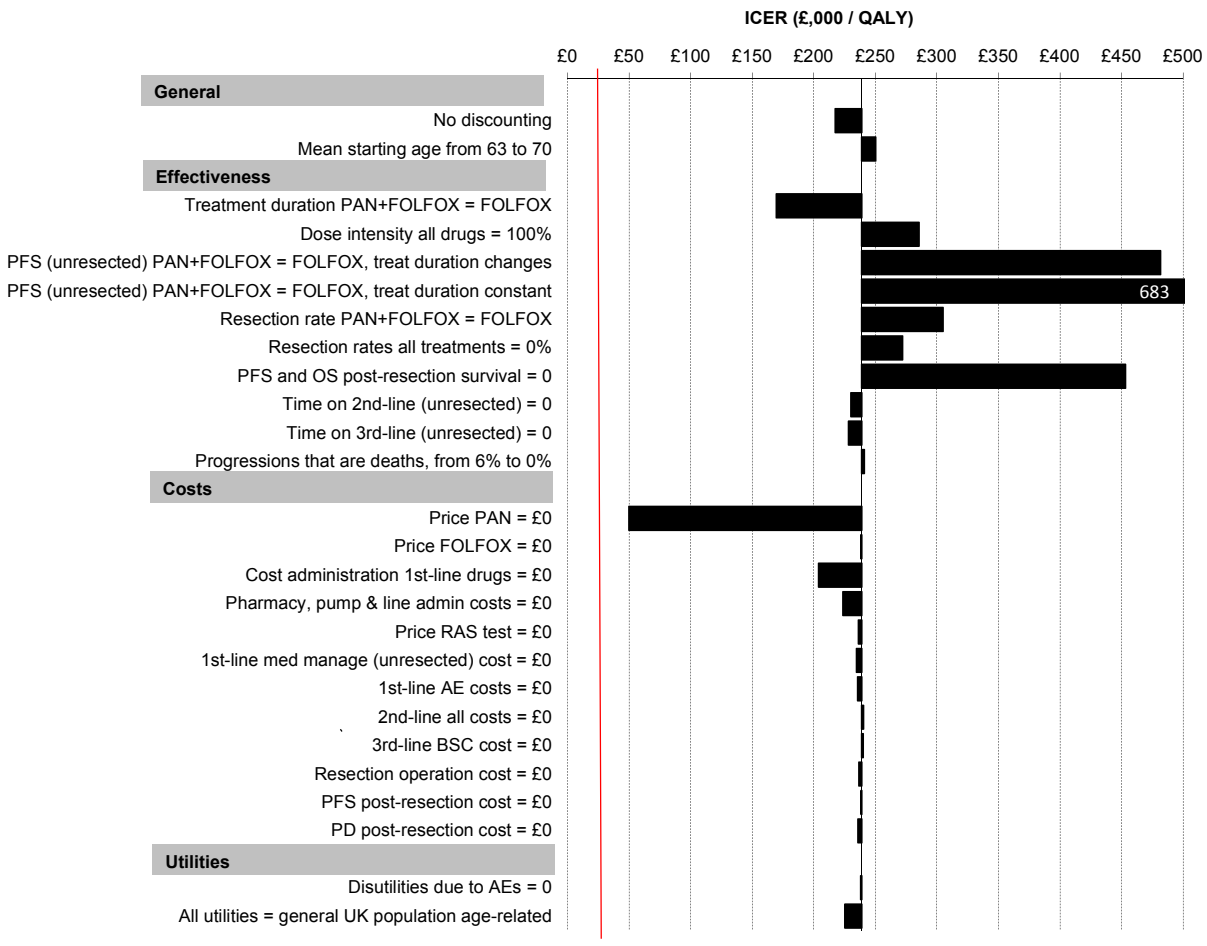
One-way deterministic sensitivity analyses for PAN+FOLFOX vs FOLFOX are reported in Figure 64. Again, none of these sensitivity analyses bring the ICER below usually accepted willingness-to-pay thresholds. There are many similarities with the CET+FOLFOX vs. FOLFOX sensitivity analyses. Here, we discuss 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.

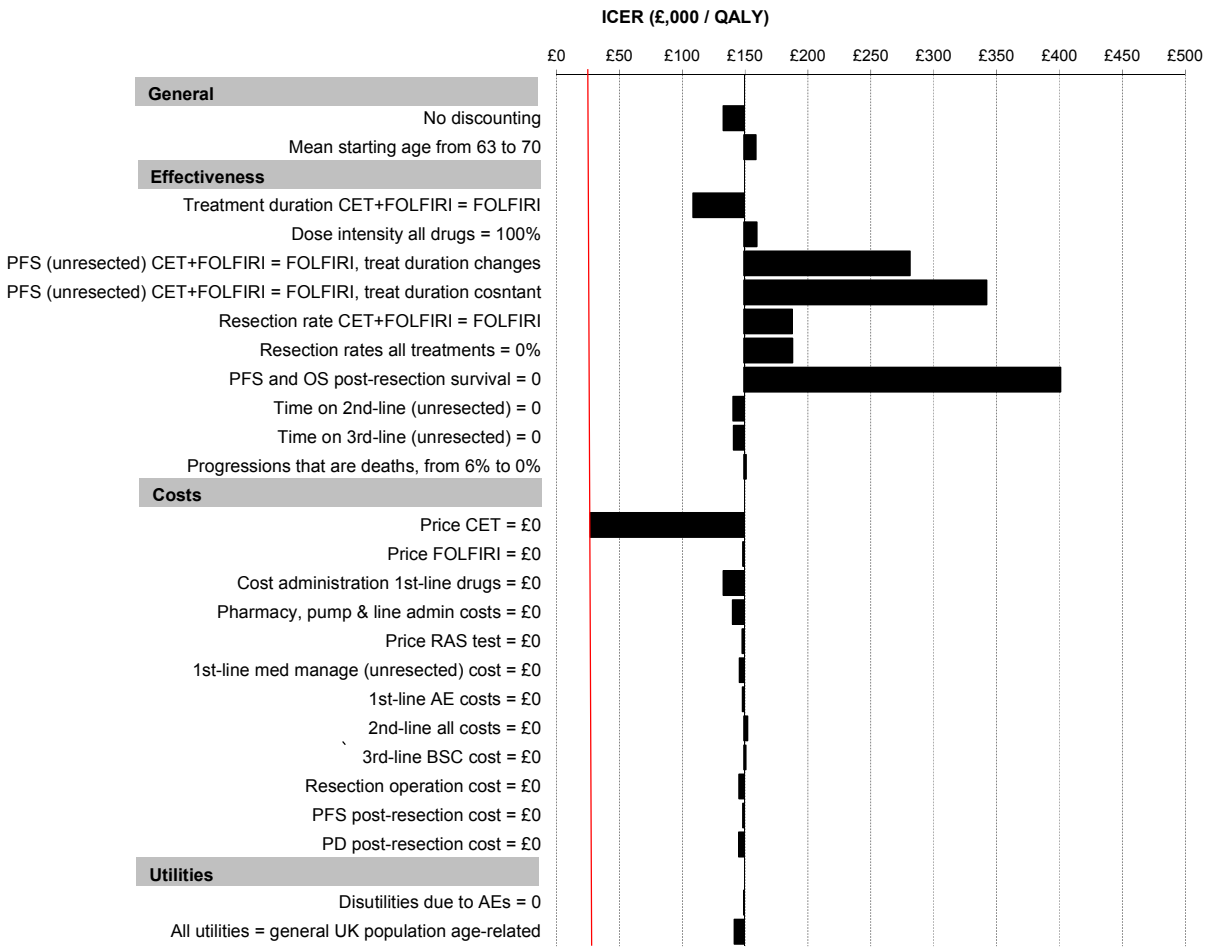
Again, there are many similarities with the CET+FOLFOX vs. FOLFOX sensitivity analyses. Here, we discuss the differences.

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 20.7%, 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).

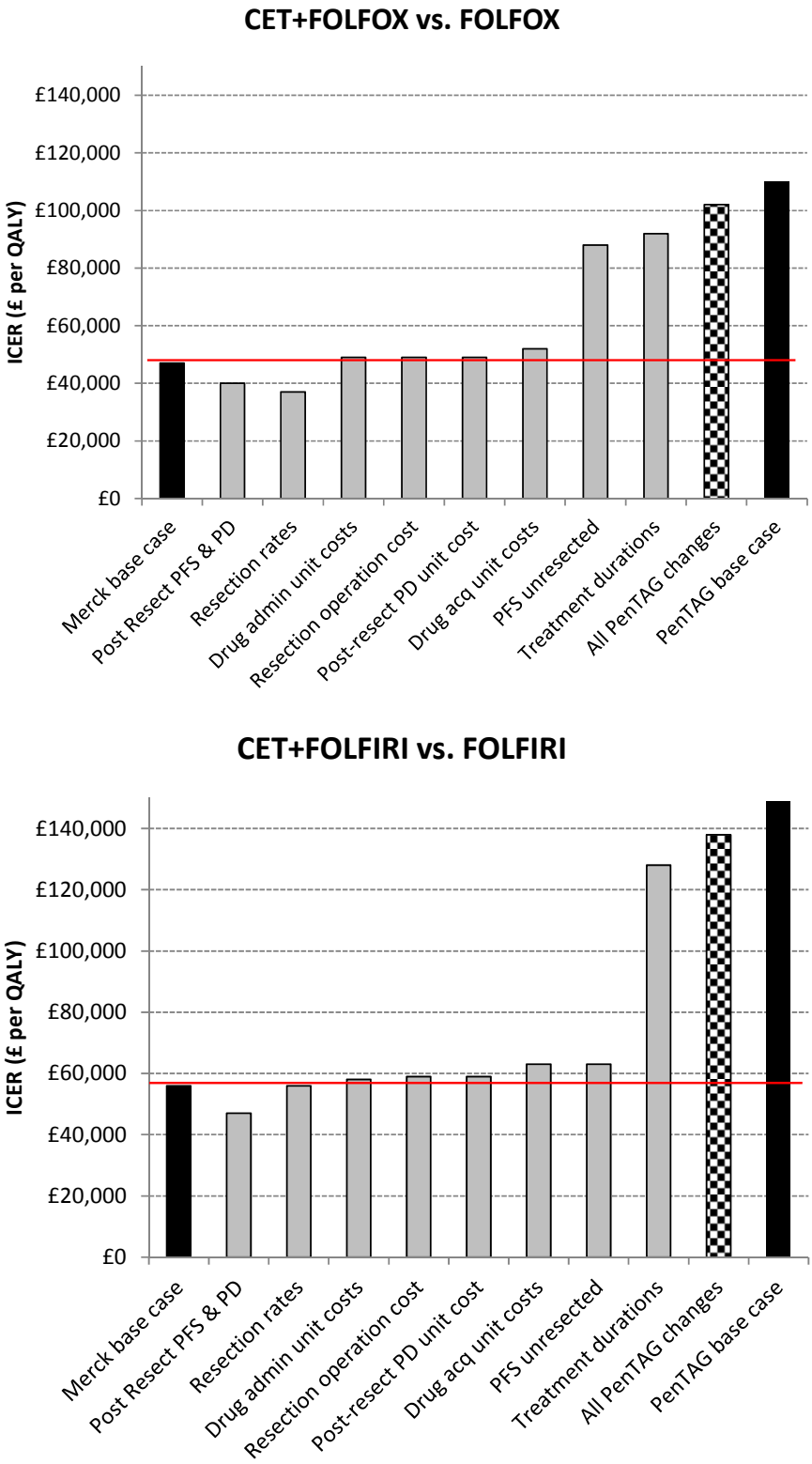
Of course, this does not in itself prove that there are no important differences between Merck's amended model and our model. However, we find no remaining large differences in incremental mean life years, QALYs and costs between Merck's amended model and our model (Figure 67, Figure 68). We conclude 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

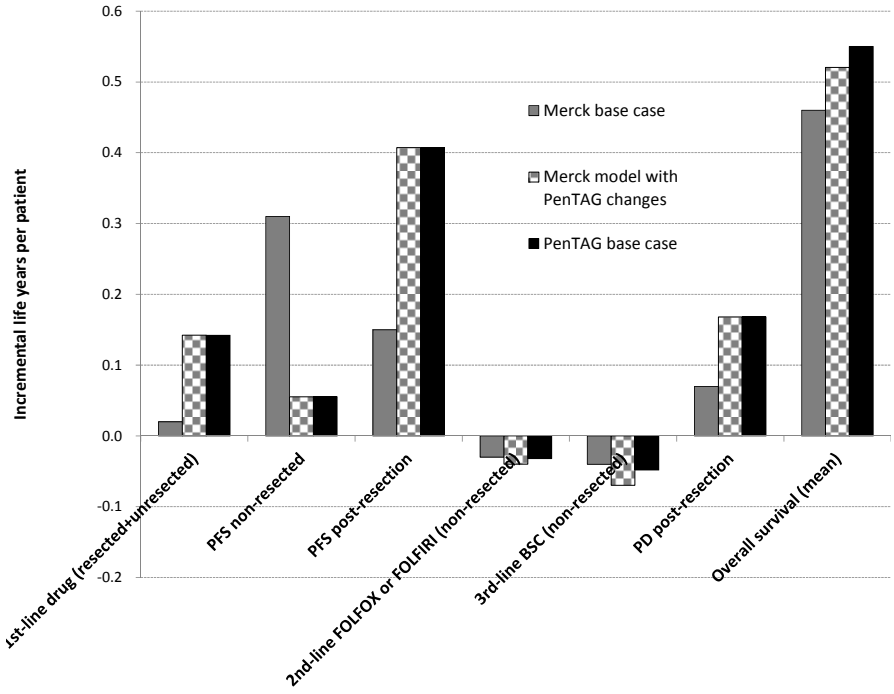
Key: PD = progressive disease; PFS = progression free survival

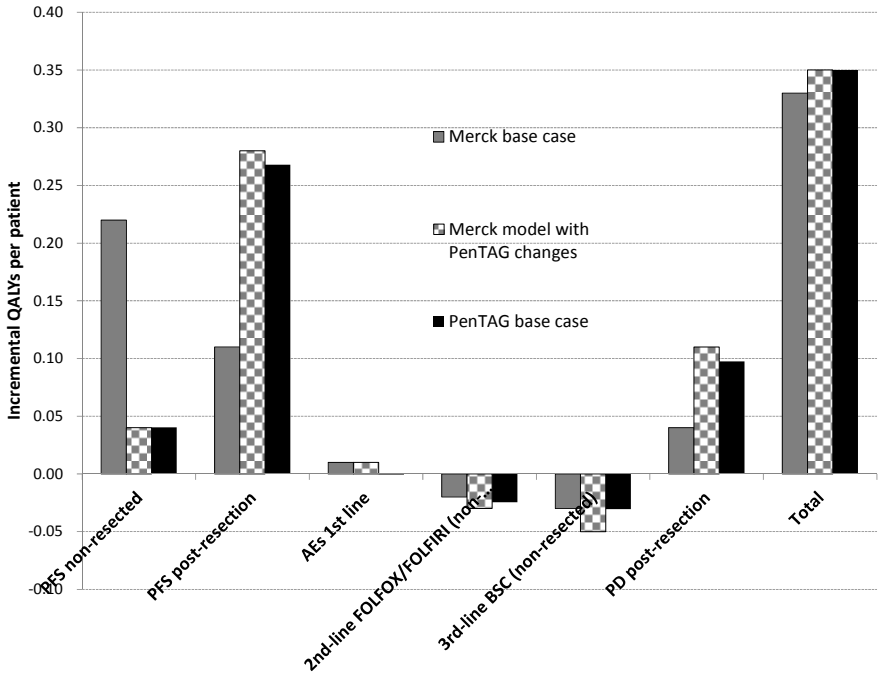
Figure 66. ICERs from Merck Serono model with PenTAG changes applied independently or in combination

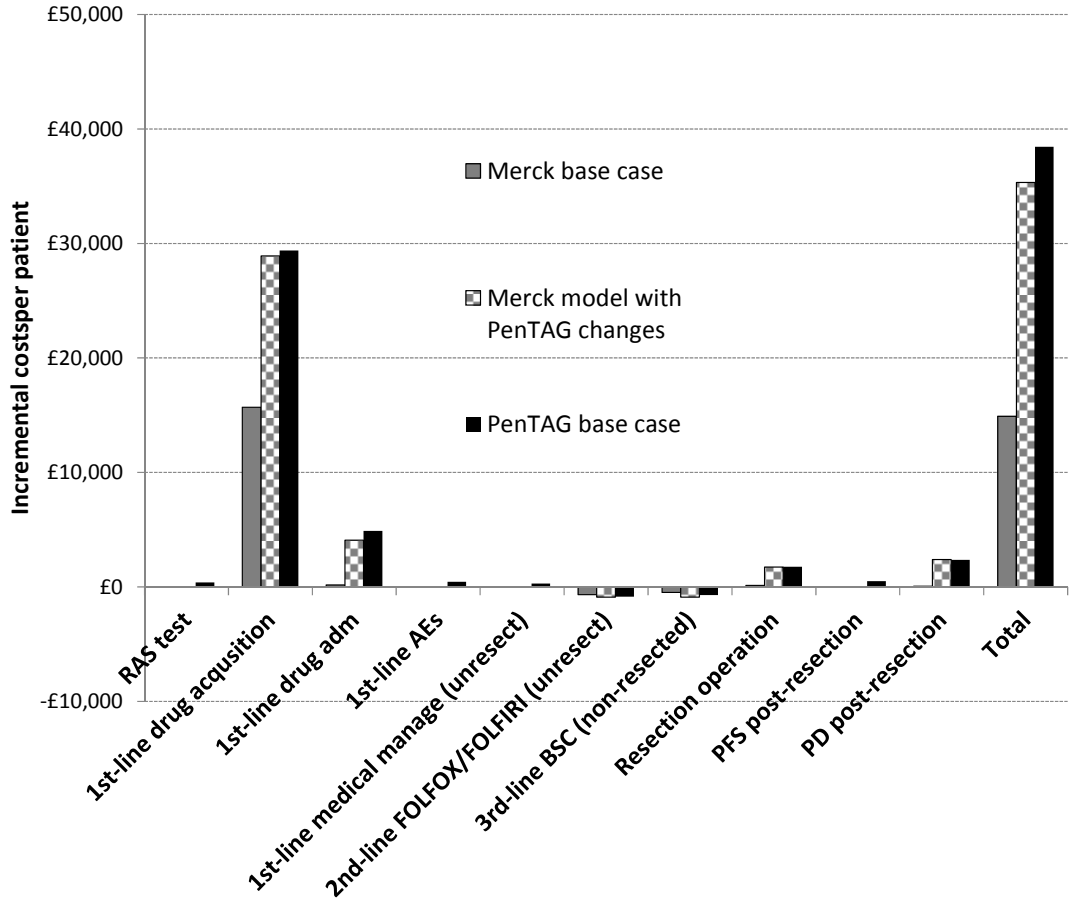


Key: CET = cetuximab; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; PD = progressive disease; PFS = progression free survival

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

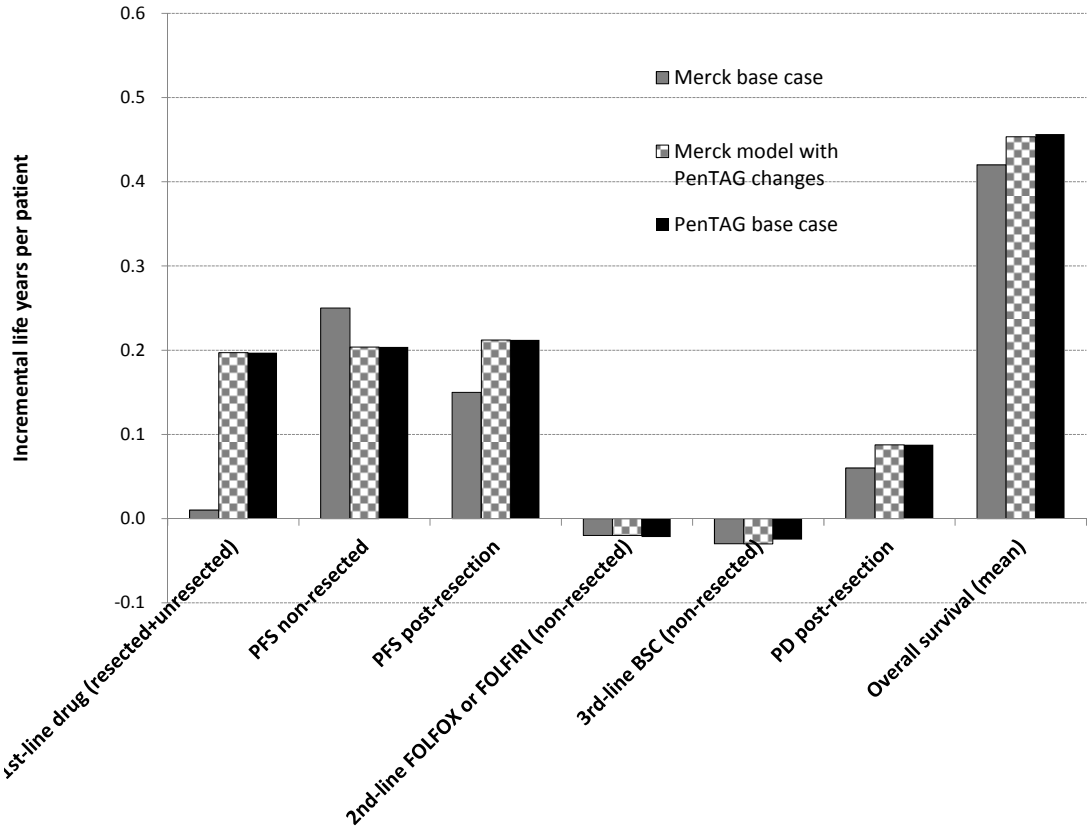


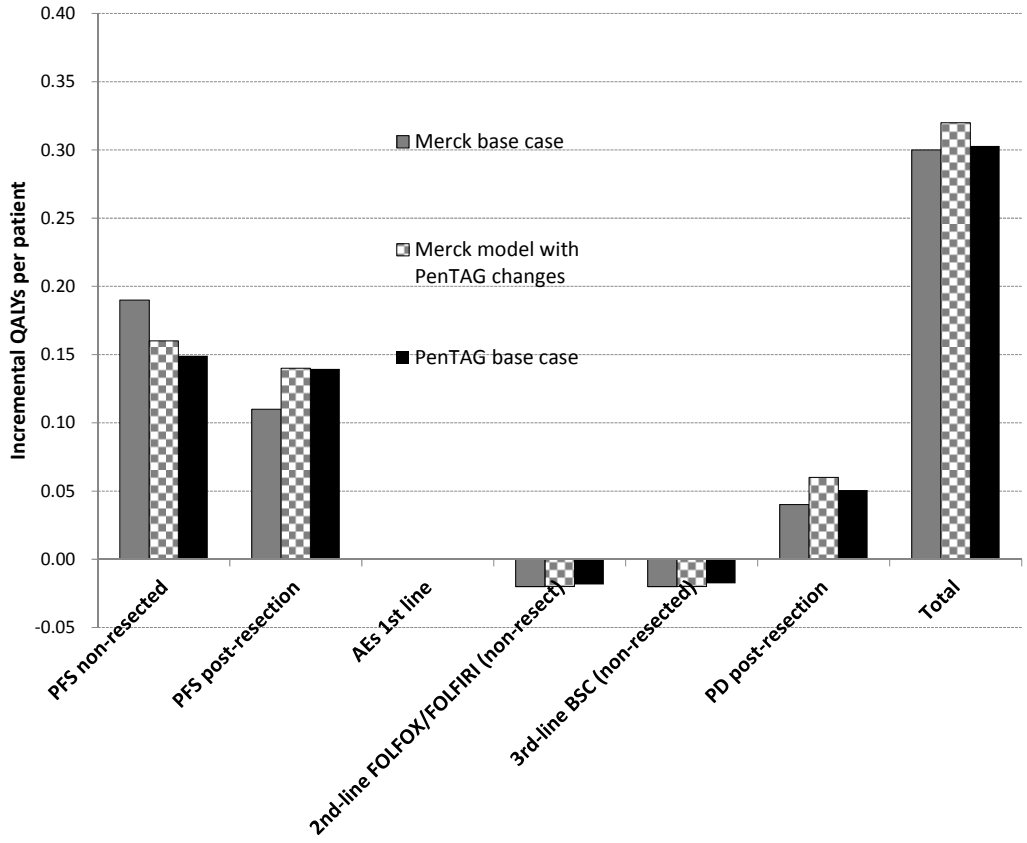


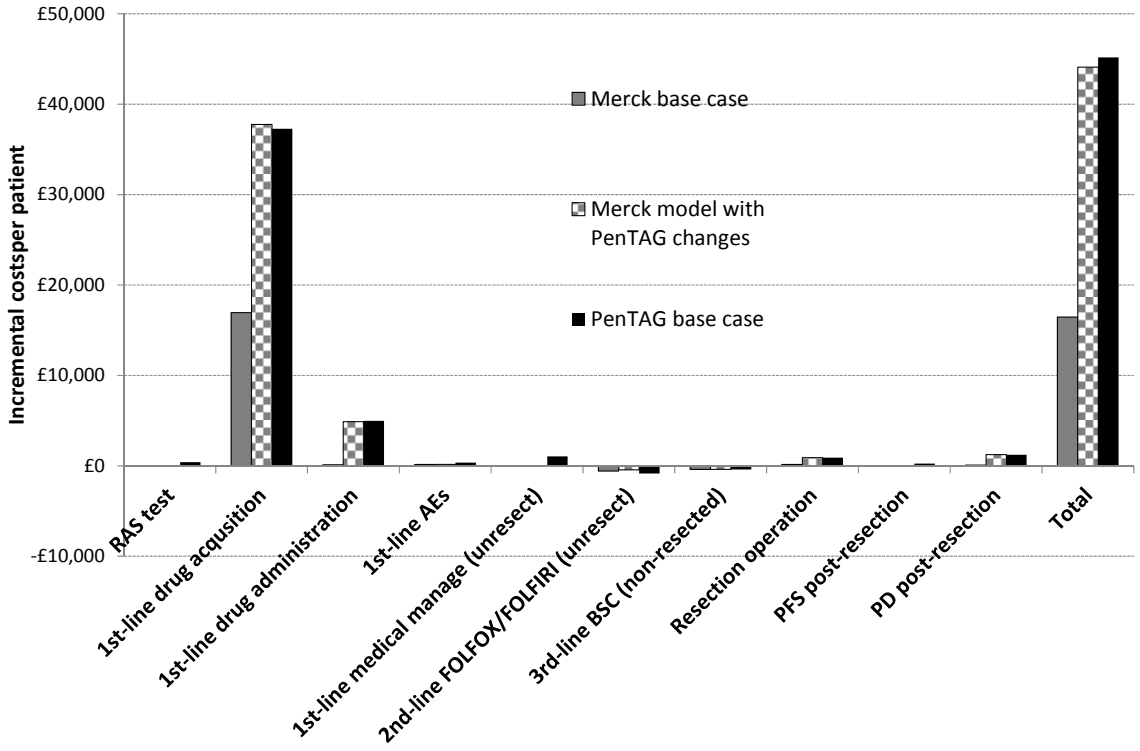


Key: AE = adverse event; BSC = best supportive care; FOLFIRI = folinic acid + fluorouracil + irinotecan; FOLFOX = folinic acid + fluorouracil + oxaliplatin; PD = progressive disease; PFS = progression free survival

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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