The effectiveness and cost-effectiveness of cetuximab (mono- or combination chemotherapy), bevacizumab (combination with (non-oxaliplatin chemotherapy) and panitumumab (monotherapy) for the treatment of metastatic colorectal cancer after first-line chemotherapy (review of technology appraisal 150 and part review of technology appraisal 118): a systematic review and economic model

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About the Peninsula Technology Assessment Group (PenTAG)

PenTAG is part of the Institute of Health Service Research at the Peninsula College of Medicine and Dentistry. PenTAG was established in 2000 and currently has two major work streams: independent health technology assessments (HTAs) for NICE and the NIHR HTA programme, and evidence synthesis work in relation to the needs of the SW Peninsula Collaboration for Applied Health Research and Care (PenCLAHRC), as well as for other local and national decision-makers.

The group is multi-disciplinary and draws on individuals' backgrounds in public health, health services research, computing and decision analysis, systematic reviewing, statistics and health economics. The Peninsula College of Medicine and Dentistry is a school within the Universities of Plymouth and Exeter. The Institute of Health Research is made up of discrete by methodologically related research groups, among which HTA is a strong and recurring theme.

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- The effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review of TA111): a systematic review and economic model
- Ofatumumab (Arzerra®) for the treatment of chronic lymphocytic leukaemia in patients who are refractory to fludarabine and alemtuzumab: a critique of the submission from GSK
- Everolimus for the second-line treatment of advanced and/or metastatic renal cell carcinoma
- The clinical and cost-effectiveness of sunitinib for the treatment of gastrointestinal stromal tumours: a critique of the submission from Pfizer
- The clinical- and cost-effectiveness of lenalidomide for multiple myeloma in people who have received at least one prior therapy: an evidence review of the submission from Celgene
- Bevacizumab, sorafenib tosylate, sunitinib and temsirolimus for renal cell carcinoma: a systematic review and economic model
- Machine perfusion systems and cold static storage of kidneys from deceased donors.

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- Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long-acting beta$_2$-agonists for the treatment of chronic asthma in adults and children aged 12 years and over.
- Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long-acting beta$_2$-agonists for the treatment of chronic asthma in children under the age of 12 years.
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- Surveillance of cirrhosis for the development of hepatocellular carcinoma: systematic review and economic analysis.
- Surveillance of Barrett's oesophagus: exploring the uncertainty.
- The cost effectiveness of testing for hepatitis C in former injecting drug users.
- Do the findings of case series vary systematically by methodological characteristics.
- The effectiveness and cost effectiveness of dual chamber pacemakers compared to single chamber pacemakers for bradycardia due to atrioventricular block or sick sinus syndrome: systematic review and economic evaluation.
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- Effectiveness and cost-effectiveness of imatinib for first-line treatment of chronic myeloid leukaemia in chronic phase: a systematic review and economic analysis.
- Systematic review of endoscopic Sinus Surgery for Nasal Polyps.
- Screening for hepatitis C in GUM clinic attenders and injecting drug users.
- The effectiveness and cost effectiveness of imatinib in chronic myeloid leukaemia: a systematic review.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA programme. Any errors are the responsibility of the authors.

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Martin Hoyle	Led the design, development and execution of the economic model and wrote the sections on the design and results of the economic model
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Chris Hyde	Led the systematic review of economic evaluations, contributed to the design of the model, contributed to the writing and editing of the report and was overall Director of the project and Guarantor of the report

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List of abbreviations

5-FU/FA	5-fluorouracil plus folinic acid
AE	adverse events
AIC	Akaike Information Criterion
AJCC	American Joint Committee on Cancer
APCGBI	Association of Coloproctology of Great Britain and Ireland
ASR	age standardised incidence rate
BEV	bevacizumab
BNF	British National Formulary
BSA	body surface area
BSC	best supportive care
CAN	Canadian
CCI	Charlson Comorbidity Index
CCT	controlled clinical trial
CEA	cost-effectiveness analysis
CEAC	cost-effectiveness acceptability curves
CET	cetuximab
CHEC	Consensus on Health Economic Criteria
CI	confidence interval
CRC	colorectal cancer
CRD	NHS Centre for Reviews and Dissemination
CRD	Centre for Reviews and Dissemination
CT	computed tomography
DLY	discounted life year
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EoL	end of life
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer - Quality of Life Questionnaire
EQ-5D	European Quality of Life - 5 Dimensions
FA	folinic acid
FOLFIRI	irinotecan + 5-FU/FA
FOLFOX	oxaliplatin + 5-FU/FA
FU	fluorouracil
GHS	global health status
HR	hazard Ratio
HRG	Healthcare Research Group
HRQL	health related quality of life
HTA	Health Technology Assessment
HUI	health utility index
ICER	incremental cost effectiveness ratio
IFL	irinotecan with fluorouracil and leucovorin

IPD	individual patient data
IRIN	irinotecan
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	intention to treat
KRAS	Kirsten rat sarcoma
LSM	least squares mean
LV	leucovorin
LYG	life-year gained
M1	distant metastases present
mCRC	metastatic colorectal cancer
MØ	no distant metastases
MTA	multiple technology assessment
N/A	not applicable
NCCN	National Comprehensive Cancer Network
NCCN FCSI	National Comprehensive Cancer Network FACT CRC Symptom Index
NCI-CTC	National Cancer Institute Common Terminology Criteria
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NIHR	National Institute for Health Research
NØ	no regional lymph node invasion
NR	not reported
OS	overall survival
PAN	panitumumab
PD	progressive disease
PenTAG	Peninsula Technology Assessment Group
PD	progressive disease
PF	physical function
PFS	progression free survival
PR	partial response
PSA	probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	quality-adjusted life year
QoL	quality of life
RCT	randomised controlled trial
RECIST	Response Evaluation Criteria In Solid Tumors
SD	Standard deviation
SE	Standard error
SMPC	Summary of Product Characteristics
ST	skin toxicity
T0	no evidence of tumour
T1, T2, T3, T4	stage of cancer
T_{is}	tumour in situ
TNM	tumour node metastases
UK	United Kingdom

VAS	visual analogue scale
VEGF	vascular endothelial growth factor
WHO	World Health Organisation
WT	wild type
XELOX	capecitabine with oxaliplatin

1. Summary

1.1. Background

Colorectal cancer (CRC) is a malignant neoplasm arising from the lining of the large intestine (colon and rectum). It is the third most commonly diagnosed cancer in the UK, with 32,644 new cases registered and approximately 14,233 deaths registered in England and Wales in 2008.

In metastatic colorectal cancer (mCRC) the tumour has spread beyond the confines of the locoregional lymph nodes to other parts of the body. This is described as Stage IV of the American Joint Committee on Cancer (AJCC) tumour node metastases (TNM) system or Stage D of the modified Dukes' classification. The five-year survival of patients with advanced disease (modified Dukes' D) is less than 7%.(1)

Individuals with metastatic disease who are sufficiently fit (normally those with World Health Organisation [WHO] performance status ≥2) are usually treated with active chemotherapy as first- or second-line therapy. First-line active chemotherapy options include:

- infusional 5-fluorouracil plus folinic acid (5-FU/FA)
- oxaliplatin plus infusional 5-FU/FA (FOLFOX)
- irinotecan plus infusional 5-FU/FA (FOLFIRI).
- oral analogues of 5-FU (capecitabine and tegafur with uracil) may also be used instead of infusional 5-FU.

For those patients first receiving FOLFOX, irinotecan-containing regimens may be a second-line treatment option, whereas for patients first receiving FOLFIRI, oxaliplatin-containing regimens may be a second-line treatment option. More recently, targeted agents have become available including anti-epidermal growth factor receptor (EGFR) agents; for example, cetuximab and panitumumab, and anti-vascular epidermal growth factor (VEGF) receptor agents; for example bevacizumab.

The EGFR signalling pathway has been the focus of new drug development for CRC because it is overexpressed in approximately 80% of colorectal carcinomas. KRAS mutation status – wild type (WT) or mutant can explain resistance to anti-EGFR therapy. There are multiple methods for determining the KRAS mutation status of a tumour which are considered to have adequate clinical sensitivity for predicting a lack of response to anti-EGFR agents. However, the possibility the sensitivity of the test is less than 100% could mean that some patients may be incorrectly diagnosed with KRAS WT status.

The National Institute for Health and Clinical Excellence (NICE) currently recommends FOLFOX and FOLFIRI as first-line treatment options for advanced colorectal cancer. FOLFOX or irinotecan alone are recommended as subsequent therapy options. The oral analogues of 5-FU, capecitabine and tegafur, in combination with uracil (and FA) are also recommended as first-line treatment options for mCRC. Cetuximab in combination with FOLFOX, or in combination with FOLFIRI, is recommended as an option for the first-line treatment of mCRC where the metastatic disease is confined to the liver and the aim of treatment is to make the metastases resectable. In Technology Appraisal (TA) 118, bevacizumab in combination with 5-FU/FA, with or without irinotecan, as a first-line treatment and cetuximab in combination with irinotecan, as a second or subsequent line treatment were not recommended for mCRC. TA150 on cetuximab for the treatment of mCRC following failure of oxaliplatin-containing chemotherapy in 2008 was terminated because the manufacturer submitted a no evidence response to NICE.(2)

This technology assessment report considered three pharmaceutical interventions. These are bevacizumab (Avastin®, Roche Products), cetuximab (Erbitux®, Merck Serono), panitumumab (Vectibix®, Amgen). All three have UK marketing authorisations:

- Bevacizumab is licensed in combination with fluoropyrimidine-based chemotherapy for the treatment of patients with mCRC
- Cetuximab is licensed for the treatment of patients with EGFR expressing mCRC kirsten rat sarcoma (KRAS) wild type (WT) status either in combination with chemotherapy or as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy, and who are intolerant to irinotecan
- Panitumumab is licensed for the treatment of EGFR expressing mCRC with KRAS WT status after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.

The following question was addressed by this report: „What is the clinical and cost-effectiveness of cetuximab (mono- or combination chemotherapy), bevacizumab (combination with non-oxaliplatin chemotherapy) and panitumumab (monotherapy) for the treatment of mCRC after first-line chemotherapy'.

The main comparators of interest are: irinotecan- or oxaliplatin-based chemotherapy regimens; and best supportive care (BSC). The populations of interest were limited to mCRC patients with KRAS WT status in the cases of cetuximab and panitumumab.

1.2. 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.

1.2.1. Clinical effectiveness systematic review

For the assessment of effectiveness, a literature search was conducted in a range of electronic databases including MEDLINE, EMBASE and the Cochrane Library (2005–17 November 2010).

Studies were included if they were:

- Randomised controlled trials (RCTs) or systematic reviews of RCTs of cetuximab, bevacizumab or panitumumab
  - in participants with EGFR expressing mCRC with KRAS WT status that has progressed after first-line chemotherapy (for cetuximab and panitumumab)
  - in participants with mCRC that has progressed after first-line chemotherapy (bevacizumab).

All steps in the review were performed by one main reviewer and checked independently by a second. Quality was assessed using criteria specified by the Centre for Reviews and Dissemination (CRD). Synthesis was mainly narrative.

1.2.2. Cost-effectiveness systematic review

For the cost-effectiveness review, the inclusion and exclusion criteria were the same as for the clinical effectiveness review excepting study design, where non-randomised studies, full cost-effectiveness analyses, cost-utility analyses, cost-benefit analyses and cost-consequence analyses were included.

1.2.3. Review of manufacturers' submissions

The cost-effectiveness analyses reported in the manufacturers' submissions to NICE were critically appraised using established frameworks, including the NICE reference case.

Three manufacturers' submissions were potentially available for this appraisal. However, only one full economic model was submitted: by Merck Serono (the manufacturer of cetuximab) for cetuximab+irinotecan and panitumumab+BSC vs BSC. Roche (the manufacturer of bevacizumab) submitted some basic cost calculations in their report for a

comparison between bevacizumab+FOLFIRI and cetuximab+FOLFIRI. Amgen did not provide any details of a cost-effectiveness model, nor make any comment upon the likely cost-effectiveness of panitumumab, its product.

1.2.4. PenTAG cost-effectiveness analysis

A decision analytic model was developed following the NICE reference case, from the perspective of NHS and Personal Social Services (PSS).

The model focused on third- and subsequent lines of treatment as agreed with NICE. The use of drugs of interest second-line was theoretically covered by the scope, but there was no clinical effectiveness data, no case for such a comparison was made by the manufacturers and there was no obvious clinical case for such use. We did not model bevacizumab in combination with non-oxaliplatin based chemotherapy due to the absence of clinical effectiveness data for this treatment.

The structure of the model is widely used for metastatic cancers. It uses an „area under the curve' method to determine state probabilities at each cycle of the model. The model has three health states: progression-free survival (PFS), progressive disease (PD) and dead. We performed an indirect four-way comparison of the cost-effectiveness of BSC, cetuximab, panitumumab and cetuximab+irinotecan.

The clinical effectiveness of BSC and cetuximab are taken from an RCT of cetuximab+BSC vs BSC, and of panitumumab from an RCT of panitumumab+BSC vs BSC. Both of these RCTs were those identified in the systematic review, see below. The clinical effectiveness of cetuximab+irinotecan was derived from an RCT of ceruximab+irinotecan vs cetuximab in which information on KRAS status was not available.

The following resource costs were included in the model: KRAS testing, drug acquisition, drug administration, consultant outpatient visits, computed tomography (CT) scans, BSC in progressive disease (PD) and treatment for adverse events. The currency and cost year were pounds sterling (GBP), for 2011.

One-way and probabilistic sensitivity analyses (PSA) were performed to explore structural and parameter uncertainty on the cost-effectivenes of each intervention.

1.3. Results

1.3.1. Number and quality of clinical effectiveness studies

The searches identified 7,745 titles and abstracts. Two clinical trials (reported in 11 papers) were included. No data were available for bevacizumab in combination with non-oxaliplatin based chemotherapy in previously treated patients. Neither of the included studies had KRAS status performed prospectively, but did report retrospective analyses of the results for the KRAS WT subgroups. Taken as a whole, the quality of the included studies was considered good.

1.3.2. Summary of benefits and risks

Third-line treatment with cetuximab+BSC or panitumumab+BSC appears to have clinically relevant and statistically significant advantages over treatment with BSC alone in patients with KRAS WT status. In both trials, median PFS almost doubles. For cetuximab+BSC, median PFS increases from approximately two months to approximately four months (HR 0.40; 95% CI 0.30, 0.54). For panitumumab+BSC from approximately two months to approximately three months (HR 0.45; 95% CI 0.34, 0.59).(3, 4)

For median overall survival (OS) in the KRAS WT population, the cetuximab arm is 9.5 months vs 4.8 months for BSC (HR 0.55; 95% CI 0.41, 0.75). The effect of panitumumab on OS is less convincing and not statistically significant. The median OS was 8.1 months vs 7.6 months for BSC (HR 0.99; 95% CI 0.75, 1.29). The rapid cross-over of 76% of patients originally allocated to BSC to treatment with panitumumab (median time to cross-over 7.1 weeks) is less likely to have had an extensive confounding effect.(4, 5)

For both PFS and OS the effects in patients with KRAS WT status are greater than those in the whole trial populations.

Data on adverse events (AEs) is difficult to compare between the interventions. The panitumumab trial does not confirm the AE scale used therefore it is unclear if they are analogous with cetuximab.

Skin toxicity was clearly an issue for both treatments, although again, reported differently. Patients in the cetuximab group had an 88% incidence of rash of any grade, compared to 90% for panitumumab. There appears to be a correlation between extent of skin toxicity and treatment efficacy, although one paper suggests exercising caution with these results since a patient remaining longer on a treatment due to its benefit is more likely to develop skin toxicity at some point.(6)

1.3.3. Number and quality of cost effectiveness studies

1.3.3.1. Summary of economic evaluations

Our literature search identified five published full economic evaluations meeting the inclusion criteria. Three abstracts were also identified, but these did not provide sufficient detail for a full critical appraisal.

All of the included studies assessed the cost-effectiveness of cetuximab used as third-line therapy.(7-11) However, only one of these by Mittmann and colleagues directly addressed a comparison of interest, cetuximab+BSC vs BSC, in the population of direct interest mCRC patients with KRAS WT status.(8) The trial-based cost-effectiveness analysis (2007) calculated a cost per quality-adjusted life year (QALY) of CAN$186,761 (95% CI = CAN$130,326 to CAN$334,940 per QALY gained). Updating this to 2011, converting to GBP and using the current UK price of cetuximab we estimated this to be approximately equivalent to £101,000 per QALY.

A Markov model considered the cost-effectiveness of a range of increasingly complex treatment strategies starting with well-established first-line treatments such as 5-FU/FA in a general mCRC population. It included third-line use of cetuximab and cetuximab+irinotecan, but concluded that the treatment of mCRC with the most effective regimens came at very high incremental costs.(11). The remaining three included studies considered the cost-effectiveness of cetuximab+irinotecan+BSC vs BSC generally finding unfavourable cost per QALY estimations,(7, 9, 10) the exception being when treatment was stopped in the case of non-response after six weeks.(7) However, the impact of KRAS status was not however considered in any of these three studies.

There were no fully published papers on the remaining agents. There was, however, one conference abstract on the cost-effectiveness of panitumumab on which further detail could not be obtained.

1.3.4. Industry submissions

Merck Serono (the manufacturer of cetuximab) focused their submission on third- and subsequent line use and presented base case incremental cost-effectiveness ratios (ICERs) of £47,000 per QALY gained for cetuximab+BSC vs BSC and £44,000 per QALY gained for cetuximab+irinotecan combination therapy vs BSC.

Our main critique of Merck Serono's model is that they underestimate the mean treatment duration leading to ICERs that are too low. Assuming that patients are treated for as long as

they remain progression free (which we believe is a more realistic assumption) leads to much larger ICERs: £75,000 and £67,000 per QALY gained for cetuximab monotherapy vs BSC and for cetuximab+irinotecan combined therapy vs BSC, respectively.

We also believe that Merck Serono have underestimated the costs of BSC drug administration leading us to the conclusion that more realistic ICERs from Merck Serono's model are around £82,000 and £75,000 per QALY gained for cetuximab+BSC vs BSC and for cetuximab+irinotecan combined therapy vs BSC, respectively.

There are, however, serious concerns that the clinical effectiveness evidence for cetuximab+irinotecan combined therapy used by Merck Serono (De Roock and colleagues(12)) is highly subject to bias, undermining confidence in the ICERs offered for cetuximab+irinotecan vs BSC.

Roche (the manufacturer of bevacizumab) did not estimate cost-effectiveness, but did present a case that used second-line, the cost of bevicuzumab+FOLFIRI would be less expensive than cetuximab+FOLFIRI.

Amgen presented reasonable analyses to adjust for cross-over in the study by Amado and colleagues(4), leading to an adjusted estimate of OS advantage of 2.74 or 3.13 months, depending on the method of adjustment used, for panitumumab vs BSC. They did not present any estimates of cost-effectiveness. However, one of the abstracts identified in the cost-effectiveness review (Graham and colleagues) clearly indicates that the cost-effectiveness of panitumumab has been estimated.

1.3.5. *De novo* economic model results

Based on our degree of certainty of clinical effectiveness and mean treatment duration, we estimate the cost-effectiveness of:

- Cetuximab vs BSC is £98,000 per QALY gained and is reasonably accurate
- Panitumumab vs BSC is £150,000 per QALY gained and is reasonably accurate
- Cetuximab+irinotecan vs BSC is £88,000 per QALY gained but is highly uncertain.

The incremental costs and QALYs for cetuximab and panitumumab vs BSC are similar (approximately £25,000 and 0.20 QALYs per person), whereas these quantities are both far greater for cetuximab+irinotecan vs BSC (approximately £53,000 and 0.60 QALYs per person).

The PSA suggests that for willingness-to-pay thresholds of £60,000 per QALY or lower, the probability that BSC is the most cost-effective treatment relative to the other three alternatives is approximately 100%.

The deterministic sensitivity analysis suggests that PFS, OS, time on drug treatment, drug acquisition costs and drug administration costs strongly influence cost-effectiveness estimates.

1.4. Discussion

1.4.1. Strengths and limitations of the systematic review of effectiveness studies

The strengths of this systematic review are that it was conducted by an independent research team using the latest evidence to a pre-specified protocol. The main limitation was lack of evidence on bevacizumab, cetuximab and cetuximab+irinotecan used second-line in the populations of interest and lack of evidence on bevacizumab and cetuximab+irinotecan used third-line.

1.4.2. Strengths and limitations of the systematic review of cost-effectiveness studies

The strengths of this systematic review are that it was conducted by an independent research team using the latest evidence to a pre-specified protocol. The main limitation was the incomplete reporting of the reports of the cost-effectiveness of panitumumab and the absence of cost-effectiveness estimates on bevacizumab.

1.4.3. Strengths and limitations of the critique of Industry submissions

This was conducted by an independent research team using a number of established frameworks to identify strengths and weaknesses. The scope of the submissions on bevacizumab and panintumumab, which did not directly estimate cost-effectiveness, was the main limitation.

1.4.4. Strengths and limitations of the economic modelling by PenTAG

1.4.4.1. Strengths

Our assessment of the cost-effectiveness of drugs for mCRC is independent. Our analysis is the second independent fully-published cost-effectiveness analysis of cetuximab vs BSC for patients with KRAS WT status, the first being that of Mittmann and colleagues, and the first specifically for the UK.(8) Our analysis is the first independent fully-published cost-effectiveness analysis of panitumumab vs BSC for patients with KRAS WT status and of cetuximab+irinotecan vs BSC for patients with KRAS WT status. We have carefully compared our model and the results of our analysis with those of Mittmann and colleagues and Merck Serono, and in so doing, we have highlighted areas in common and those where there is disagreement.

Our model adheres to the NICE reference case,(13) and has been extensively checked. In addition to our base case analysis, we also present numerous one-way sensitivity analyses, which we have chosen carefully to reflect the key areas of uncertainty and disagreements between ourselves and Merck Serono. We also present PSA, in which we vary the key parameters within plausible ranges.

Our certainty about the accuracy of our cost-effectiveness results for cetuximab vs BSC and panitumumab vs BSC is increased given that the effectiveness evidence that underpins these analyses is taken from high-quality RCTs whose data is mature. There is much greater uncertainty concerning the analysis for cetuximab+irinotecan vs BSC given the lack of effectiveness evidence particularly for patients with KRAS WT status.

We have confidence in the accuracy of our utility estimates for the BSC, panitumumab and cetuximab treatment arms. Indeed its accuracy is greater than is typically available for cost-effectiveness analysis, being derived from direct observation of patients in trials. This is not true for the utilities for cetuximab+irinotecan.

1.4.4.2. Limitations

There are some factors limit the accuracy of our analysis. For example, the mean duration of drug treatment for patients with KRAS WT status, a vital parameter, is available only for panitumumab. Indeed, the mean durations of cetuximab and cetuximab+irinotecan treatment are not published for patients with KRAS WT status. These are important

limitations in the evidence for our analysis, given that cost-effectiveness is very sensitive to these parameters.

The external validity of the results is uncertain given that we use efficacy data from RCTs in which people are relatively young (median age approximately 63 years) and fit (Eastern Cooperative Oncology Group [ECOG] 0–2), compared to people in actual clinical practice who are typically older and less fit (some with ECOG 3–4).

PFS and OS for cetuximab+irinotecan are available only for all people combined: KRAS WT and KRAS mutant status. Like Merck Serono we have therefore been forced to adjust these estimates to obtain estimates of PFS and OS in patients with KRAS WT status using other data sources. However, we have provided several possible methods of adjustment and the ICER for cetuximab+irinotecan vs BSC remains high regardless of which estimates for PFS and OS are used.

In common with Merck Serono, we do not stratify our analysis according to the line of treatment as the necessary individual patient data (IPD) were not available.

We estimate the cost of medical management in PD for all treatment groups based on a study of medical management in PD for women with breast cancer.(14) Like Merck Serono we believe that this is methodologically acceptable given the absence of suitable alternatives, but do caution that the data from this publication is now rather old, relating to practices from the Year 2000.

1.4.5. Main findings in the light of strengths and limitations

Clinical effectiveness: There is no consensus about the evidence on effectiveness of cetuximab and panitumumab for patients with KRAS WT status. Based on RCTs, both cetuximab and panitumumab are effective used third-line, particularly with respect to PFS. We broadly agree with Merck Serono's estimates of the effectiveness of cetuximab+irinotecan for patients with KRAS WT status even though it has not been directly measured in an RCT. There is an absence of RCT evidence of bevacizumab combined with non-oxaliplatin chemotherapy.

Cost-effectiveness of cetuximab+BSC: There are many similarities between Merck Serono's cost-effectiveness model for cetuximab vs BSC and the PenTAG *de novo* model. Importantly, we assume the same mean times as Merck Serono for PFS and OS for cetuximab and for BSC. Nonetheless, Merck Serono estimate a far lower ICER for cetuximab vs BSC than us: £47,000 vs £98,000 per QALY gained. This is explained almost entirely by Merck Serono's estimation of the total mean costs of cetuximab acquisition and

administration, which are far lower than our estimates. These differences in turn are due almost entirely to Merck Serono's far lower estimation of the mean time on cetuximab treatment: 2.6 vs 4.8 months. Merck Serono's derivation of their estimate is based on their imposition of an artificial maximum time on cetuximab treatment. When we use Merck Serono's model, and lift their cap on the time on cetuximab treatment, their ICER increases from £47,000 to £75,000 per QALY gained.

We are aware of only one other fully published cost-effectiveness analysis of any of the treatments in this appraisal for patients with KRAS WT status, that of Mittmann and colleagues (2009).(8) They perform a trial-based economic analysis to consider cost-effectiveness from the healthcare payer perspective in Canada. After we adjust their result for the cost per mg of cetuximab appropriate in the UK in 2011, and other costs for inflation to the Year 2011, we estimate their ICER is approximately equivalent to £101,000 per QALY gained. This is very close to our estimate of £98,000 per QALY gained, and much higher than Merck Serono's £48,000 per QALY gained.

Cost-effectiveness of cetuximab+irinotecan vs BSC: Again there are many similarities between Merck Serono's model for cetuximab+irinotecan vs BSC and the PenTAG *de novo* model. Importantly, we assume similar mean times as Merck Serono for PFS and OS for cetuximab+irinotecan and for BSC. Merck Serono estimate a far lower ICER for cetuximab+irinotecan vs BSC: £44,000 vs £88,000 per QALY gained. Similar to the case of cetuximab vs BSC, this is explained almost entirely by Merck Serono's estimation of the total mean costs of cetuximab+irinotecan acquisition and administration, which are far lower than our estimates. These differences, in turn, are due almost entirely to Merck Serono's far lower estimation of the mean time on cetuximab+irinotecan treatment than us: 4.4 vs 8.8 months. Merck Serono's derivation of their estimate is based on their imposition of an artificial maximum time on cetuximab+irinotecan treatment. When we use Merck Serono's model, and lift their cap on the time on treatment, their ICER increases from £44,000 to £67,000 per QALY.

Cost-effectiveness of panitumumab vs BSC: The estimate of cost-effectiveness from the PenTAG *de novo* model is £150,000 per QALY gained with no alternative estimate being offered by the manufacturer.

1.5. Conclusions

On balance we conclude that used for third- and subsequent line treatment relative to BSC, cetuximab+BSC, cetuximab+irinotecan+BSC and panitumumab+BSC are effective but not cost-effective if decision thresholds of £20,000 per QALY or £30,000 per QALY are used.

There is no additional evidence on the effectiveness and cost-effectiveness of cetuximab used in second-line treatment relative to that informing the guidance on second-line use provided by TA118.

In common with the manufacturer, we were not able to estimate the cost-effectiveness of bevacizumab in combination with non-oxaliplatin chemotherapy second- or subsequent line due to the absence of RCT evidence.

1.6. Suggested research priorities

- Given the lack of clinical data for patients with KRAS WT status receiving cetuximab+irinotecan, it would be useful to conduct a RCT for these patients, compared with cetuximab+BSC, or panitumumab+BSC. It would be helpful to collect health-related quality of life (HRQoL) data in such a trial.
- We cannot model the cost-effectiveness of bevacizumab in combination with non-oxaliplatin chemotherapy, due to the absence of relevant clinical evidence. Ideally an RCT should be conducted, but only if this was thought to be a potentially important use of the agent by the wider clinical community.
- Given that the mean treatment durations of cetuximab and cetuximab+irinotecan treatment strongly influence cost-effectiveness, and that they are uncertain, further data on these parameters from the RCTs of cetuximab vs BSC and cetuximab+irinotecan vs cetuximab would be helpful.
- Given that the medical management cost data come from a study of women with breast cancer over 10 years ago, collecting data on the medical management of mCRC would be useful.

Ongoing trials identified in the course of this appraisal indicate that some of the gaps in knowledge may already be being addressed.

2. Background

2.1. Description of health problem

CRC is a malignant neoplasm arising from the lining of the large intestine (colon and rectum). Over 95% of colon and rectal cancers are adenocarcinomas; cancers that start in the cells that line the inside of the colon and rectum. Cancer cells eventually spread to nearby lymph nodes (local metastases) and subsequently to more remote lymph nodes and other organs in the body. The liver and the lungs are common metastatic sites of CRC.

2.1.1. VEGF and EGFR

Two key elements in the growth and dissemination of tumours are the VEGF and the EGFR; both pathways are closely related, sharing common downstream signalling pathways.(15) VEGF and EGFR play important roles in tumour growth and progression through the exertion of both indirect and direct effects on tumour cells.(15) Biological agents targeting the VEGF and EGFR pathways have shown clinical benefit in several human cancers, either alone or in combination with standard cytotoxic therapies. Inhibition of VEGF-related pathways is thought to contribute to the mechanism of action of agents targeting the EGFR.(16) Conversely, (over)activation of VEGF expression independent of EGFR signalling is thought to be one way that tumours become resistant to anti-EGFR therapy.(17) Specific ongoing point mutations in the EGFR gene are also thought to convey resistance to anti-EGFR tyrosine kinase inhibitors.(18) The possibility that combined VEGF and EGFR pathway blockade could further enhance antitumor efficacy and help prevent resistance to therapy is currently being evaluated in clinical trials.(15)

2.1.2. KRAS

KRAS is a gene that codes for a protein that plays an important role in the EGFR pathway; a complex signalling cascade that is involved in the development and progression of cancer.

The KRAS protein regulates other proteins, downstream in the EGFR signalling pathway, that are associated with tumour survival, angiogenesis, proliferation and metastasis.(19) There are different types of the KRAS gene found in tumours, which either code for a „normal', non-mutated KRAS protein known as KRAS WT, or an abnormal, mutated protein known as mutant KRAS. The KRAS „status' (KRAS WT vs KRAS mutant) may be indicative of prognosis and predictive of response to certain drugs including those under consideration in this review. In tumours with KRAS WT status, the protein is only temporarily activated in response to certain stimuli such as EGFR signalling. This tight regulation warrants a close

control of downstream effects. In tumours with the mutated version of the KRAS gene, the KRAS protein is permanently „turned on' even without being activated by the upstream EGFR-mediated signalling. As a result the downstream effects that lead to tumour growth and spread continue unregulated.

The KRAS test is performed on a sample of tumour tissue which is sent to a laboratory for analysis of the KRAS mutation status – wild type (WT) or mutant. The process helps to enable the most effective treatment to be selected for the individual patient. There are multiple methods for determining the KRAS mutation status of a tumour (see Table 1);(20) all appear to have adequate clinical sensitivity to detect patients unlikely to respond to cetuximab or panitumumab. The limitation of sequencing technologies is the requirement of greater than 5% to 10% mutant alleles for pyrosequencing and greater than 20% for Sanger sequencing although newer approaches are being developed to increase the sensitivity of sequencing methods.(20)

Table 1. Methods used for KRAS mutation testing(20)

Method	Sensitivity, % of mutant alleles	Strengths	Weaknesses
Sanger sequencing	20	• Gold standard • Detects all possible mutations • Inexpensive	• Time consuming • Open PCR system requires strict control for contamination
Pyrosequencing	5–10	• Ability to sequence short PCR products (advantageous for DNA from fixed tissue) • Detects all possible mutations • Inexpensive • Faster than Sanger sequencing	• Short reading length for sequences used • Open PCR system requires strict control for contamination
Allele-specific real-time PCR	1	• Rapid, closed PCR system (eliminates risk • of contamination with previously generated • amplicons) • Available as a commercial kit	• Detects only the 7 most common mutations • Require more tissue for analysis as compared with other methods • Cost
Post-PCR fluorescent melting curve analysis with specific	5–10	• Rapid, closed PCR system • Detects all possible mutations (heterozygous and homozygous)	• Occasionally difficult to distinguish between mutation types • More expensive than Sanger sequencing

probes			
PCR clamping method	1	• Rapid, closed PCR system • Available as a commercial kit	• Does not allow to control quality of DNA and efficiency of PCR amplification

PCR, polymerase chain reaction

In CRC, up to 65% of patients are KRAS WT status; the remaining 35% are KRAS mutant.(5)

2.2. Epidemiology

2.2.1. Incidence and prevalence

CRC is a common form of malignancy in developed countries but occurs much less frequently in the developing world. It is the third most commonly diagnosed cancer in the UK, with around 39,991 new cases registered in the UK in (32,644 cases registered in England and Wales).(21) The number of cases of CRC and the incidence rates in each of the countries of the UK are shown in Table 2.

Table 2. CRC (C18-C21), number of new cases and European ASRs: England and Wales (2008)(21)

CRC (C18–C21)		England	Wales
Men	Cases	18,040	1,311
	Crude rate	71.2	89.8
	ASR (95% CI)	57.0 (56.2–57.8)	64.4 (60.9–67.9)
Women	Cases	14,604	989
	Crude rate	55.9	64.6
	ASR (95% CI)	36.9 (36.3–37.5)	39.3 (36.9–41.8)
Persons	Cases	32,644	2,300
	Crude rate	63.4	76.9
	ASR (95% CI)	46.1 (45.6–46.6)	50.7 (48.6–52.8)

ASR, age standardised incidence rate; CI, confidence interval

The occurrence of CRC is strongly related to age, with 86% of cases arising in people aged 60 years-plus.(21) Until age 50, men and women have similar rates for CRC but in later life the incidence rate for men is higher. In numerical terms, there are more cases of CRC in men among almost all age-groups up to the age of 84, after which cases of CRC in women are in the majority, even though their rates are lower, as women make up a larger proportion

of the elderly population.(21) Overall the male:female ratio is 11:10.(21) The lifetime risk for men of being diagnosed with colorectal cancer in the UK is estimated to be 1 in 16 for men and for women 1 in 20.(21)

Data for CRC patients diagnosed in England in 2000–04 did show a deprivation gradient for male patients with incidence rates 11% higher in the most deprived groups than in the affluent groups.(21)

2.2.2. Pathology

CRC includes malignant growths from the mucosa of the colon and rectum. Cancer cells eventually spread to nearby lymph nodes (local metastases) and subsequently to more remote lymph nodes and other organs in the body. The liver and the lungs are common metastatic sites of CRC.

The pathology of the tumour is usually determined by analysis of tissue taken from a biopsy or surgery. CRC 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 (see Table 3).

Knowing the stage of colon cancer is important for several reasons including: helping the physician to define an appropriate treatment plan; and, in predicting prognosis. In the UK, approximately 11% of patients are diagnosed at TNM Stage I, 32% at Stage II, 26% at Stage III (lymph node involvement), and 30% at Stage IV (metastatic disease). It is estimated that around 30% of patients present with metastatic disease and a further 20% may eventually develop metastatic disease. Metastatic disease often develops first in the liver, but metastases may also occur at other sites including the lungs.

Table 3. Staging of CRC(22)

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 Tumour invades submucosa (T1, N0, M0) Tumour invades muscularis propria (T2, N0, M0)	A
Stage II	No nodal involvement, no distant mestastases Tumour invades muscularis propria into pericolorectal tissues (T3, N0, M0) Tumour penetrates surface of visceral peritoneum or directly invades or is adherent to other organs or structures (T4a/b, N0, M0)	B
Stage III	Nodal involvement, no distant metastases (Any T, Any N, M0)	C
Stage IV	Distant metastases (Any T, Any N, M1a/M1b)	D

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

2.2.3. Prognosis

The treatment, prognosis and survival rate depend on the stage of disease at diagnosis.

The five-year relative survival rates for both men and women with CRC have doubled between the early 1970s and mid 2000s.(1) Five-year survival rates for men with CRC rose from 25% in the early 1970s to 51% in mid 2000s and from 27% to 55% for men with CRC.(1) These improvements are a result of earlier diagnosis and better treatment but there is still much scope for further progress.(1) Ten-year survival rates are only a little lower than those at five-years indicating that most patients who survive for five years are cured from this disease.(1)

Patients who are diagnosed at an early stage have a much better prognosis than those who present with more extensive disease.(1) Over 93% of patients diagnosed with Stage A on the modified Dukes classification system (the earliest stage of the disease) survived five years compared with less than 7% of patients with advanced disease (Stage D) (see Table 4)(1)

Table 4. Percentage of cases and five-year relative survival (%) by modified Dukes' stage at diagnosis, CRC patients diagnosed 1996-2002 (England)(1)

Modified Dukes stage at diagnosis	Percentage of cases	Five-year relative[a] survival
A	9%	93%
B	24%	77%
C	24%	48%
D	9%	7%
Unknown	34%	35%

[a]Defined as the ratio of the proportion of observed survivors in a cohort of cancer patients to the proportion of expected survivors in a comparable set of cancer free individuals

Treatment of CRC may be curative or palliative depending on the location of the tumour and the degree to which the tumour has penetrated the bowel and spread to other organs in the body. Treatment options differ considerably for colon and rectal tumours. Recurrence of CRC may be local or metastatic; however, local recurrence is less commonly reported in patients with colon cancer. Treatments of metastatic recurrence of CRC are typically palliative; however, hepatic resection and pulmonary resection may offer a chance of cure in a small proportion of patients. The mainstay of treatment for metastatic CRC involves chemotherapy; cytotoxic agents include 5-FU, capecitabine, oxaliplatin, irinotecan, tegafur with uracil, and mitomycin. Again, these may be given according to a variety of regimens across different lines of therapy.

2.3. Impact of health problem

2.3.1. Significance for patients in terms of ill-health (burden of disease)

CRC is a significant cause of morbidity and mortality. When treating patients with mCRC, the main aims of treatment are to relieve symptoms and to improve HRQoL and survival.(23) In 2008 there were 14,233 deaths from CRC in England and Wales. The majority of deaths occurred in older people, around 80% in people aged 65 years-plus and almost two-fifths aged 80 years-plus (see Table 5).(23)

Table 5. Number of deaths and mortality rates of CRC: England and Wales (2008)(23)

	England	Wales
Deaths		
Men	7,178	499
Women	6,138	418
Total	13,316	917
Crude rate per 100,000 population		
Men	28.4	34.1
Women	23.5	27.3
Total	25.9	30.6
ASR (European) per 100,000 population		
Men	21.8 (95% CI: 21.3–22.3)	23.6 (95% CI: 21.5–25.6)
Women	13.6 (95% CI: 13.3–14.0)	14.6 (95% CI: 13.2–16.0)
Total	17.3 (95% CI: 17.0–17.6)	18.6 (95% CI: 17.4–19.8)

ASR, age standardised incidence rate; CI, confidence interval; CRC, colorectal cancer

2.3.2. QoL

Assessment of health related quality of life (HRQoL) has become an important feature of cancer trials, enabling evaluation of treatment effectiveness from the perspective of the person with the condition and facilitating improved clinical decision making.

There are several general HRQoL instruments for people with cancer that can be used to assess QoL both in research studies and in clinical practice; for example, the National Comprehensive Cancer Network FACT CRC Symptom Index (NCCN FCSI) and the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 (QLQC-30).

2.4. Significance for the NHS

2.4.1. Current service provision

2.4.1.1. National Guidelines

In 2004, the NHS Executive published guidelines for the management of CRC in England and Wales.(22)

NICE has issued the following guidance:

- NICE: Irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer: review of TA33. (TA93). London: NICE, 2008.(24)

- NICE. Guidance on the use of capecitabine and tegafur with uracil for mCRC. (TA61). London: NICE, 2003.(25)
- NICE. Bevacizumab and cetuximab for the treatment of mCRC. (TA118) London: NICE, 2009.(26)
- NICE. Cetuximab for the first-line treatment of mCRC. (TA176) London: NICE, 2009.(27)
- NICE. Laparoscopic surgery for colorectal cancer: review of NICE Technology Appraisal 117. (TA105). London: NICE, 2009.(28)
- NICE. Bevacizumab in combination with oxaliplatin and either 5-FU/FA or capecitabine for the treatment of mCRC. (TA212) London: NICE, 2010.(29)
- NICE. Guidance on Cancer Services: Improving Outcomes in Colorectal Cancer: Manual Update. London: NICE, 2004.(22)

NICE's draft clinical guideline on the diagnosis and management of CRC, currently out for consultation with stakeholders, is due for publication in October 2011.

In addition, the Association of Coloproctology of Great Britain and Ireland (ACPGBI) have published guidelines for the management of CRC (2007).

2.4.1.2. Current management

Surgery to remove the primary tumour is the principal first-line treatment for approximately 80% of patients, after which about 40% will remain disease-free in the long term.(22) In 20-30% of cases, the disease is too far advanced at initial presentation for any attempt at curative intervention; many of these patients die within a few months.(22) Surgical skill is crucial to outcomes, and there is evidence of wide variation between the survival rates of patients operated on by individual surgeons.(22) Evidence showing large differences between surgeons in the outcomes they achieve was reviewed for the earlier edition of this guidance.(22) More recent studies suggest that variations between both surgeons and institutions persist.(22)

Metastatic disease usually develops first in the liver. 20–25% of patients have clinically detectable liver metastases at the time of the initial diagnosis and a further 40-50% of patients develop liver metastases within three years of primary surgery.(22) When the metastatic deposits are confined to a limited area of the liver, expert surgery offers the possibility of long-term cancer-free survival.(22) About 8% of patients are potential candidates for liver resection, which can be life-saving in about 35% of these cases.(22)

Chemotherapy is given as an adjuvant to surgery to a minority of patients, usually those whose tumour has spread to lymph nodes (Dukes' Stage C), for whom the benefit of chemotherapy has been most clearly demonstrated.(22) Adjuvant radiotherapy can be used to treat colorectal cancer; although, a minority of patients receive it.(22) For the majority of patients however, surgery with curative intent is not an option due to the widespread nature of their disease and/or their poor suitability for surgery.(22) In contrast, these patients are treated with palliative intent using a combination of specialist treatments: palliative surgery, chemotherapy, or radiotherapy to improve both the duration and the quality of the individual's remaining life.(22)

Individuals with metastatic disease who are sufficiently fit (normally those with World Health Organization [WHO] performance status ≥2) are usually treated with active chemotherapy as first- or second-line therapy.(24) More recently, targeted agents have become available including anti- EGFR agents; for example, cetuximab and panitumumab, and anti- VEGF agent; for example, bevacizumab (see Section 2.4.1.1).

Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine is not recommended for the treatment of people with mCRC.(29)

2.4.1.2.1.1. First-line treatment

First-line active chemotherapy options include FOLFOX and FOLFIRI; NICE TA93.(30) Additionally TA93 did not recommend raltitrexed for people with advanced CRC, unless they were taking part in a clinical trial.(25) Oral analogues of 5-FU (capecitabine and tegafur with uracil) may also be used instead of infusional 5-FU; NICE TA61.(25)

Cetuximab in combination with FOLFOX or in combination with FOLFIRI is also recommended by NICE as an option for the first-line treatment of mCRC where the metstatic disease is confined to the liver and the aim of treatment is to render the metastases resectable; NICE TA176.(31)

In 2009 NICE did not recommend bevacizumab in combination with oxaliplatin and either 5-FU/FA or capecitabine for people with mCRC.(32)

2.4.1.2.1.2. Second-line treatment

For those patients first receiving FOLFOX, irinotecan may be a second-line treatment option, whereas for patients first receiving FOLFIRI, oxaliplatin may be a second-line treatment option; NICE TA93.(24) Patients receiving 5-FU/FA or an oral analogue as first-line treatment may be offered FOLFOX or FOLFIRI as second-line and subsequent therapies.

NICE TA118 (2009) did not recommend cetuximab in combination with irinotecan for the treatment of people with mCRC previously treated with irinotecan.(32)

2.4.1.2.1.3. Third-line treatment

In the third-line setting the majority of patients will receive BSC.

2.5. Description of technologies under assessment

2.5.1. Bevacizumab (Avastin®, Roche)

Bevacizumab is a recombinant humanised monoclonal antibody that acts as an angiogenesis inhibitor. It targets the biological activity of human VEGF, which stimulates new blood vessel formation in the tumour.(33) Depriving tumours of VEGF has several effects that are relevant to the therapeutic use of bevacizumab. These include preventing the development of new tumour blood vessels, causing the regression of existing vasculature and normalising the function of the remaining tumour blood vessels resulting in enhanced delivery of concomitantly administered cytotoxic drugs.(34)

Bevacizumab is licensed in combination with 5-fluoropyrimidine based chemotherapy and is indicated for treatment of patients with mCRC.(33) The original European Medicines Agency (EMA) marketing authorisation for bevacizumab in mCRC restricted it to use in the first-line setting in combination with 5-FU based chemotherapy with or without irinotecan, based on the Phase III trial data then available. The EMA granted a broader marketing authorisation in 2010 licensing bevacizumab in combination with fluoropyrimidine-based chemotherapy for treatment of patients with metastatic cancer of the colon and rectum. The extension to the marketing authorisation followed publication of further studies showing that bevacizumab added to combinations of 5-FU or capecitabine in the first- or second-line setting settings also improved treatment outcomes.(35, 36)

It is contraindicated in patients who are pregnant, have untreated central nervous system metastases, have hypersensitivity to products derived from Chinese hamster ovary cell cultures or other recombinant human or humanised antibodies. Special warnings and precautions for use include gastrointestinal perforations, wound healing complications, hypertension, proteinuria, arterial thromboembolism, haemorrhage, congestive heart failure/cardiomyopathy.(33)

The most common AEs with bevacizumab (incidence >10% and at least twice the control arm rate) are epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, rectal haemorrhage, lacrimation disorder, and exfoliative dermatitis.

Bevacizumab must be administered under the supervision of a clinician experienced in the use of antineoplastic medicinal products.(33) It is administered over 90 minutes as an intravenous infusion at a dose of 5 mg/kg body weight once every 14 days, and is recommended until there is underlying disease progression.(33)

2.5.2. Cetuximab (Erbitux®, Merck Serono Pharmaceuticals)

Cetuximab is a recombinant monoclonal antibody that blocks the human EGFR. EGFR is found on the surface of some cells and plays a role in regulating cell growth. Cetuximab is believed to interfere with the growth of cancer cells by binding to EGFR so that the normal epidermal growth factors cannot bind and stimulate the cells to grow.

Cetuximab, used in combination with irinotecan, is indicated for the treatment of EGFR-expressing, KRAS WT mCRC in patients either in combination with chemotherapy; or as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan.(37) The Summary of Product Characteristics (SmPC) recommends that cetuximab must be administered under the supervision of a physician experienced in the use of antineoplastic medicinal products. Close monitoring is required during the infusion and for at least one hour after the end of the infusion in a setting with resuscitation equipment and other agents necessary to treat anaphylaxis. Patients requiring treatment should be monitored for longer.(37)

Special warnings and precautions for use include hypersensitivity reactions, dyspnoea and skin reactions. Only patients with adequate renal and hepatic function have been investigated to date (serum creatinine ≤1.5-fold, transaminases ≤5-fold, and bilirubin ≤1.5-fold the upper limit of normal).(37) Cetuximab has not been studied in patients presenting with one or more of the following laboratory parameters:(37)

- haemoglobin <9 g/dl
- leukocyte count <3,000/mm³
- absolute neutrophil count <1,500/mm³
- platelet count <100,000/mm³

The most common AEs with cetuximab (incidence ≥25%) are cutaneous adverse reactions (including rash pruritus and nail changes), headache, diarrhoea and infection.

The recommended initial dose, either as monotherapy or in combination with irinotecan, is 400 mg/m^2 administered as a 120-minute intravenous infusion (maximum infusion rate 10 mg/minute). The recommended subsequent weekly dose, either as monotherapy or in

combination with irinotecan is 250 mg/m^2 infused over 60 minutes (maximum infusion rate 10 mg/min) until disease progression or unacceptable toxicity).

There is limited experience in the use of cetuximab in combination with radiation therapy in CRC.(37)

2.5.3. Panitumumab (Amgen®, Vectibix)

Panitumumab is a recombinant monoclonal antibody which targets the EGFR receptor, thereby inhibiting the growth of EGFR-expressing tumours. Panitumumab is licensed as monotherapy for treating patients with EGFR-expressing mCRC with KRAS WT status after failure of prior chemotherapy regimens containing fluoropyrimidine, irinotecan and oxaliplatin.

Panitumumab treatment should be supervised by a physician experienced in the use of anti-cancer therapy.(38) The recommended dose of panitumumab is 6 mg/kg of bodyweight given once every two weeks.(38) Prior to infusion, panitumumab should be diluted in 0.9% sodium chloride injection to a final concentration not to exceed 10 mg/ml.(38)

Panitumumab is contraindicated in patients with a history of severe or life-threatening hypersensitivity reactions to the active substance or to any of the excipients.(38) Skin toxicities, hypomagnesaemia, and diarrhoea were the most common treatment-related toxicities observed.(38)

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.

3. Definition of the decision problem

3.1. Decision problem

The purpose of this report is to assess the clinical and cost-effectiveness of cetuximab (mono- or combination chemotherapy), bevacizumab (combination with non-oxaliplatin chemotherapy) and panitumumab (monotherapy) for the treatment of metastatic colorectal cancer after first-line chemotherapy.(39)

3.1.1. Population including subgroups

The population for this assessment is adults with mCRC who have failed first-line chemotherapy. This is further restricted to patients with EGFR-expressing mCRC with KRAS WT status for cetuximab and panitumumab in line with the marketing authorisations for these treatments.

3.1.2. Interventions

This technology assessment report will consider three pharmaceutical interventions:

- Bevacizumab in combination with non-oxaliplatin based chemotherapy
- Cetuximab monotherapy and in combination with chemotherapy
- Panitumumab monotherapy

Each should be being used in accordance with the marketing authorisation and in the populations indicated in Section 3.1.1.

3.1.3. Relevant comparators

Any clinically relevant alternative treatment for the population in question, but particularly including:

- Irinotecan- or oxaliplatin-based chemotherapy regimens (in the case of second-line treatment)
- BSC (in the case of third-line or later treatment) consisting of: pain control, anti-emetics, appetite stimulants (steroids); and, in some cases, radiotherapy
- One of the other interventions under consideration.

4. Assessment of clinical effectiveness

4.1. Methods for reviewing effectiveness

The clinical effectiveness of bevacizumab, cetuximab and panitumumab for mCRC was assessed by a systematic review of research evidence. The review was undertaken following the principles published by the NHS CRD.(40)

4.1.1. Identification of studies

Electronic databases were searched using terms related to population and intervention only, without recourse to methodological or outcome filters. The sensitivity here allowed the screening for the multiple requirements of the review.

Appendix 1 shows the databases searched and the strategies undertaken in a single database of results, these included: Medline, Embase, (both via OVID) The Cochrane Library, Web of Science (ISI)[1] and Econlit (EBSCo host). Clinical Trials.Gov, Current Controlled Trials, the FDA web-site and EMEA web-site were also searched. The search initially used as its basis a previous multiple technology assessment (MTA) by Tappenden and colleagues to construct the population aspect of the search.(41) Searches were not limited by language but did limit their findings by date (2005–17 November 2010), as stated in the protocol (see Appendix 2).

Included studies and industry submissions were analysed to ensure the saturation of relevant studies.

All references were exported into Endnote X4 (Thomson Reuters) for conversion to RIS format before being uploaded into EPPI reviewer (Version 4) where manual de-duplication was performed.

Relevant studies were then identified in two stages. Titles and abstracts returned by the search strategy were examined independently by two researchers (LC and TJH) and screened for possible inclusion. Disagreements were resolved by discussion. Full texts of the identified studies were obtained. Two researchers (LC and TJH) examined these independently for inclusion or exclusion, and disagreements were again resolved by discussion.

[1] This included, Conference Proceedings Citation Index

4.1.2. Inclusion and exclusion criteria

4.1.2.1. Study design

4.1.2.1.1. Inclusion criteria

For the review of clinical effectiveness, only systematic reviews of RCTs and RCTs were considered. The review protocol made provision for broadening search criteria to include some observational evidence if insufficient systematic reviews or RCTs were identified.

Systematic reviews were used as a source for finding further RCTs and to compare with our systematic review. For the purpose of this review, a systematic review was defined as one that has:

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

The preliminary screening of title and abstract did not discriminate according to KRAS status, to ensure trials were not excluded in error. However, during the full text screening process, it became apparent that no clinical trials existed with prospective analysis of KRAS status. Since this relatively recent understanding of KRAS WT status on intervention efficacy is key to this review, trials which retrospectively analysed outcomes according to this subgroup were therefore included.

4.1.2.1.2. Exclusion criteria

Studies were excluded if they did not match the inclusion criteria, and in particular were:

- Non-randomised studies (except for AEs)
- Animal models
- Pre-clinical and biological studies
- Narrative reviews, editorials, opinions
- Non-English language papers

- Reports published as meeting abstracts only, where insufficient methodological details were reported to allow critical appraisal of study quality.

4.1.2.2. Population

RCTs were included for panitumumab and cetuximab if they reported clinical outcomes for an adult population with EGFR expressing mCRC with KRAS status that has progressed after first-line chemotherapy. The justification for only including studies where the population had their KRAS status assessed revolves around recent evidence indicating that anti-EGFR targeted antibodies, such as cetuximab and panitumumab, are only effective in patients with KRAS WT, as opposed to KRAS mutant, oncogenes.(4)

For bevacizumab, studies were included if the population with mCRC had progressed after first-line chemotherapy. No stipulation for EGFR expression or KRAS status was required, since this has been shown to have no influence on bevacizumab activity.(42)

4.1.2.3. Interventions and comparators

Studies were included if the technologies they assessed fulfilled the following criteria:

- After first-line therapy with cetuximab as monotherapy or in combination with chemotherapy
- After first-line therapy with bevacizumab in combination with non-oxaliplatin based chemotherapy
- After first-line therapy with panitumumab as monotherapy

Alternative treatments for the population in question, clinically relevant comparators were:

- Irinotecan- or oxaliplatin-based chemotherapy regimens
- One of the interventions under consideration
- BSC

We have also considered the validity of indirect comparisons between interventions where appropriate.

4.1.2.4. Outcomes

Studies were included if they reported data on one or more of the following outcomes:

- OS
- PFS

- Tumour response rate
- AEs of treatment
- HRQoL
- Liver resection rates.

4.1.3. Data extraction strategy

Data were extracted by one reviewer (TJH) using a standardised data extraction form in Microsoft Access 2007 and checked by a second reviewer (LC). Disagreements were resolved by discussion, with involvement of a third reviewer if necessary. Data extraction forms for each included study can be found in Appendix 3.

4.1.4. Critical appraisal strategy

The methodological quality of the studies was assessed according to criteria specified by the CRD.(40) Quality was assessed by one reviewer and judgements were checked by a second. Any disagreement was resolved by discussion, with involvement of a third reviewer as necessary. The instrument is summarised below. Results were tabulated and the relevant aspects described in the data extraction forms.

4.1.4.1. Internal validity

The instrument sought to assess the following considerations:

- Was the assignment to the treatment groups really random?
- Was the treatment allocation concealed?
- Were the groups similar at baseline in terms of prognostic factors?
- Were the eligibility criteria specified?
- Were outcome assessors blinded to the treatment allocation?
- Was the care provider blinded?
- Was the patient blinded?
- Were point estimates and a measure of variability presented for the primary outcome measure?
- Did the analyses include an intention-to-treat (ITT) analysis?
- Were withdrawals and dropouts completely described?

In addition, methodological notes were made for each included study, with the reviewer's observation on: sample size and power calculations; participant attrition; methods of data analysis; and conflicts of interest.

4.1.4.2. External validity

External validity was judged according to the ability of a reader to consider the applicability of findings to a patient group and service setting. Study findings can only be generalisable if they provide enough information to consider whether a cohort is representative of the affected population at large. Therefore studies that appeared to be typical of the UK mCRC population with regard to these considerations were judged to be externally valid.

4.1.5. Methods of data synthesis

Details of the extracted data and quality assessment for each individual study are presented in structured tables and as a narrative description. Any possible effects of study quality on the effectiveness data are discussed. Survival data (OS and PFS) are presented as hazard ratios (HRs) where available.

Where data on head-to-head comparisons between interventions were not available we performed adjusted indirect comparisons using an adaption of the method described by Bucher and colleagues.(43) This method aims to overcome potential problems of simple direct comparison (i.e. comparison of simple arms of different trials), in which the benefit of randomisation is lost leaving the data subject to the biases associated with observational studies. The method is only valid when the characteristics of patients are similar between the different studies being compared. Further details of the methods used can be found in Appendix 4.

4.1.6. Use of manufacturers' submissions to NICE

A description and comment on whether the search strategy employed in each of the manufacturers' submissions was appropriate is detailed in Appendix 5. All the clinical effectiveness data included in the manufacturers' submissions was assessed. Where these met the inclusion criteria and had not already been identified from published sources, they were included in the systematic review of clinical effectiveness. However, it became apparent that the manufacturers' submissions were dependent on evidence which did not include KRAS status and would not fulfil the inclusion criteria for this section of the report. Therefore, to maintain consistency, the papers reported in the manufacturers' submissions are briefly critiqued here, with a more detailed discussion in Section 6 (page 45).

4.1.7. Interpreting the results from the clinical trials

4.1.7.1. Effectiveness

Most of the clinical trials in which the efficacy of these interventions have been evaluated, report results in terms of HRs: the ratio of hazard rates in two groups, such as a treatment group and a control group. The hazard rate describes the number of events per unit time per number of people exposed (i.e. the slope of the survival curve, or the instantaneous rate of events in the group). A HR of ≥1 indicates that the event is happening faster in the treatment group, whereas a HR of ≤1 indicates that the event of interest is happening more slowly in the treatment group. A HR of one suggests that there is no difference.

4.1.7.2. Adverse drug effects

The National Cancer Institute Common Terminology Criteria (NCI-CTC) (see Table 6) is frequently used by trials to report drug toxicities.(44) 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.

Table 6. NCI-CTC for AEs

Grade	Description
0	No AE or within normal limits
1	Mild AE
2	Moderate AE
3	Severe or medically significant AE but not immediately life threatening
4	Life threatening or disabling AE
5	Death related to an AE

AE, adverse event
Source: Common Terminology Criteria for Adverse Events, National Cancer Institute, 2009(44)

4.2. Results of clinical effectiveness

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 (see Table 7, page 48) and a summary table of key quality indicators (see Table 9, page 54).

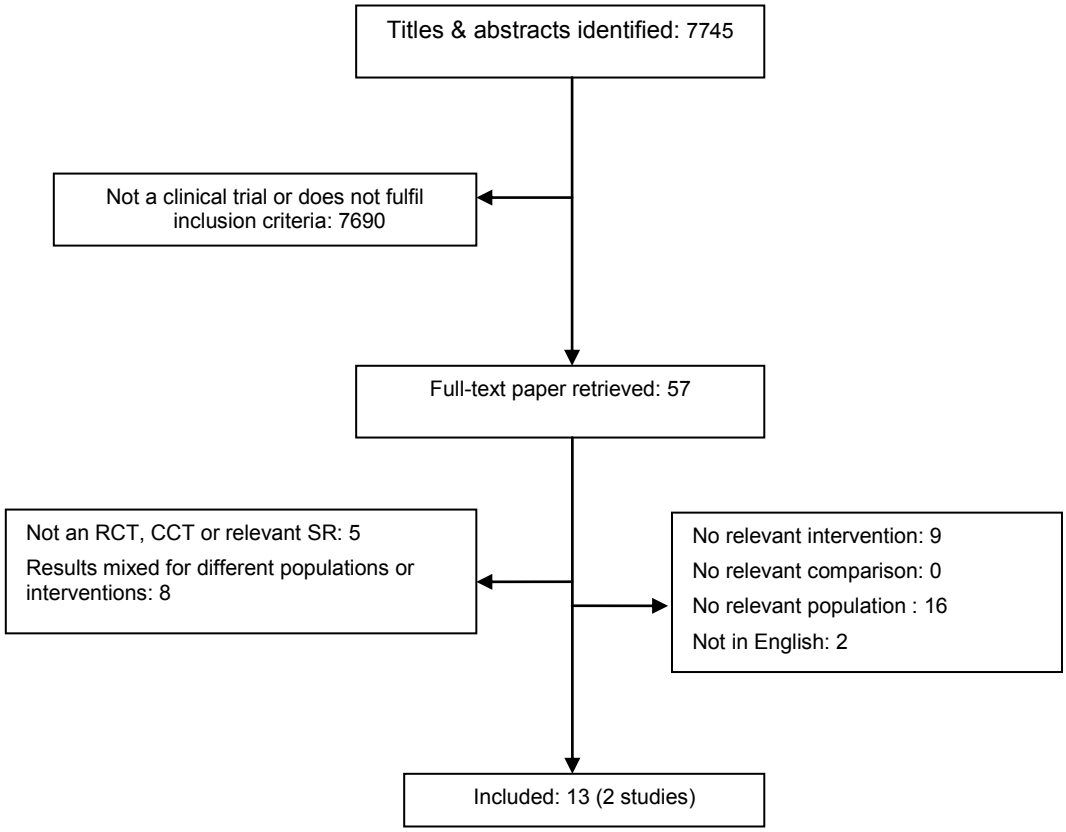
- A critical review of the available evidence for each of the stated research questions (see Section 4.2.1.4, page 48), covering:
    - the quantity and quality of available evidence,
    - a summary table of the study characteristics,
    - a summary table of the baseline population characteristics,
    - 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'. This is included to address the trials used by the manufacturers, none of which meet the inclusion criteria for this systematic review (see Section 4.2.1.4, page 48).

4.2.1. Quantity and quality of research available

4.2.1.1. Number of studies identified.

The electronic searches retrieved a total of 7,745 titles and abstracts. No additional papers were found by searching the bibliographies of included studies. A total of 7,690 papers were excluded, based on screening title and abstract. Full text of the remaining 55 papers was requested for more in-depth screening, to give a total of 13 papers included in the review. The process of study selection is shown in Figure 1 (page 47).

Figure 1. Summary of study selection



4.2.1.2. Number of studies excluded

Papers were excluded for at least one of the following reasons: duplicate publications, narrative reviews, uncontrolled studies (where evidence from controlled trials was available for the research question) and publications (systematic reviews and individual studies) not considering relevant intervention, population, comparison or outcomes. The bibliographic details of studies retrieved as full papers and subsequently excluded, along with the reasons for their exclusion are detailed in Appendix 6.

4.2.1.3. Number and description of included studies

Two clinical trials reported in 11 papers were included in the review for cetuximab+BSC and panitumumab+BSC. Both trials had retrospective KRAS status determination after the study had completed. All included citations are detailed in Table 7 (page 48) could be noted that no studies used in the previous NICE report which reviewed bevacizumab and cetuximab for the treatment of mCRC met the inclusion criteria in this instance, since the included trials for bevacizumab were first-line and KRAS status was not established for cetxuimab.(41)

Table 7. Summary information of all included clinical effectiveness studies

Study	Pub year	Study type	N	Intervention	Comparator	Supplementary publications
Cetuximab+BSC compared with BSC after first-line therapy						
Jonker, et al(45)	2007	R, O, C, BR, Phase III, international, multicentre	572	CET + BSC	BSC	(46) (47) (3) (8)
Panitumumab plus BSC compared with BSC after first-line therapy						
Van Cutsem, et al(5)	2007	R, O, C, BR, Phase III, international, multicentre	463	PAN + BSC	BSC	(4) (48) (6) (49)
Panitumumab after first-line therapy						
Van Cutsem et al(50)	2007	ES, O, single arm supplement (above)	176	PAN	N/A	–

BR, independent (blind) central review of radiological images used to assess primary outcome; BSC, best supportive care; C, controlled; CET, cetuximab; ES, extension study; O, open-label; PAN, panitumumab; R, randomised

We were unable to identify any suitable data on clinical effectiveness of bevacizumab with non-oxaliplatin based chemotherapy. However, a clinical trial is currently underway comparing bevacizumab with FOLFIRI against panitumumab with FOLFIRI after first-line treatment (Appendix 7).(51) No result data have yet been published.

4.2.1.4. Study characteristics

4.2.1.4.1. Bevacizumab

There is currently no clinical evidence for the effectiveness of bevacizumab with non-oxaliplatin therapy after first-line treatment in mCRC, although the EMA have granted marketing authorisation for its use in this clinical setting (Section 2.5.1, page 36).

However, Roche report three trials they consider relevant to the consideration of bevacizumab for first-line use in patients with mCRC, which were not included in the review. These studies are the „966 Study' by Saltz and colleagues for oxaliplatin-combined therapy,(52) Hurwitz and colleagues for irinotecan-combined therapy,(35) and Kabbinavar and colleagues(36) for 5-FU/FA combined therapy. For second-line combined treatment, Roche refer to the „E3200 Study' by Giantonio and colleagues for bevacizumab with

oxaliplatin therapy.(53) Further details can be found in Section 6 (page 98); however, the outcomes will be briefly discussed in this section for consistency.

4.2.1.4.2. Cetuximab+BSC vs BSC

Jonker and colleagues report the results of the CO.17 trial, an open-label, RCT, in which 572 patients across Canada and Australia, with advanced CRC expressing EGFR were randomised to receive either cetuximab+BSC or BSC alone. Note, this primary paper does not analyse results according to KRAS status. The trial has been reported in one publication(45) and four supplementary papers, one of which addresses the retrospective analysis of tissue samples for KRAS mutations and the others looking at cost-effectiveness, quality of life (QoL) and subgroup analysis.(8, 46, 47, 54)

The aim of the study was to demonstrate the effectiveness of cetuximab on survival and QoL in patients with advanced CRC. To that end, the primary endpoint was OS, defined as time from randomisation until death from any cause. Secondary outcomes investigated were PFS, QoL and response rates. Objective tumour response was evaluated modified Response Evaluation Criteria in Solid Tumours (RECIST)(55) and QoL was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30).

To be eligible for entry into the trial participants had to have advanced CRC expressing EGFR that was detectable by immunohistochemical methods in a central reference laboratory. The participants must have experienced tumour progression, unacceptable AEs or contraindications to treatment with either fluoropyrimidine, irinotecan or oxaliplatin.

Randomisation was performed centrally at a 1:1 ratio to cetuximab+BSC or BSC alone, with participants stratified according to ECOG performance status (0 or 1 vs 2) and centre. Patients in the treatment arm received intravenously administered cetuximab over 120 minutes with an initial dose of 400 mg/m^2 of body surface area, followed by a weekly maintenance infusion of 250 mg/m^2 over 60 minutes. An antihistamine was given 30–60 minutes before each dose of cetuximab. Treatment was continued until death, in the absence of unacceptable AEs, tumour progression, worsening symptoms of the cancer, or request by the patient.

The median duration of follow-up was reported as 14.6 months, although no range is given and it is not clear if this is for both arms. The median duration of cetuximab treatment was only 8.1 weeks (range 1–60) largely due to disease progression. The median dose intensity after the initial dose was 247 mg/m^2/week and the relative dose intensity of cetuximab; i.e.,

the ratio of the dose administered to the planned dose, was 90% or higher in 75% of patients.

The first supplementary paper by Karapetis and colleagues considers the association between KRAS status and clinical benefit from cetuximab.(3) The rationale for this investigation revolved around evidence to suggest that KRAS mutation rendered EGFR inhibitors, in this case cetuximab, ineffective.(12, 56) The retrospective analysis was performed on 394 tumour samples obtained from the 572 participants of the CO.17 trial, with the results of either KRAS WT or KRAS mutant status then correlated with OS, PFS and QoL.

The examination of tissue samples was performed by blinded assessors, with all statistical analysis performed in accordance with a protocol written before assessment of KRAS mutation was performed.(3) The primary and secondary outcomes were consistent with the main trial report.(45)

Au and colleagues focused on the HRQoL in patients participating in the CO.17 trial to include the influence of KRAS status in predicting benefit of cetuximab.(47) The primary HRQoL analyses were defined prospectively as a comparison of the change of scores on the EORTC QLQ-C30 from baseline to eight and 16 weeks for physical function (PF) and global health status (GHS) scales. Secondary HRQoL analyses included comparisons of the proportion of patients with worsened PF and GHS at eight and 16 weeks. A 10-unit change in score was predefined as clinically important.

The paper produced by Asmis considered the relationships between comorbidity, age and performance status as predictors of outcome.(46) The Charlson Comorbidity Index (CCI) was used to measure comorbidity, with the score determined by two physician reviewers. Variables of participant age and CCI score were dichotomised; age <65 vs ≥65 years and CCI score 0 vs ≥1, with higher scores indicating greater comorbidity. Univariate analysis was also performed for the association between age groups and baseline characteristics.

Finally the study by Mittmann and colleagues evaluated the cost-effectiveness of cetuximab with some preference-based health utility values, using the health utility index (HUI) Mark 3 (HUI3)e, which are relevant to this section.(8)

In addition to the CO.17 trial, Merck Serono provided details of the BOND trial (57) via De Roock and colleagues 2008.(12) This is a retrospective analysis of cetuximab+BSC vs cetuximab plus irinotecan according to KRAS status. Data is used from the following four trials: BOND,(57) EVEREST,(58) SALVAGE(59) and BABEL. Since De Roock is not

reporting a trial, nor a systematic review it is not formally included in this review of clinical effectiveness. However, the *de novo* model relies heavily on this evidence, therefore relevant information will be included throughout this section. Further details with a more substantial critique may be found in Section 6 (page 98).

4.2.1.4.3. Panitumumab+ BSC vs BSC

Van Cutsem and colleagues present the results of an open-label, Phase III, international[a] multicentre, RCT in which 463 patients with mCRC were randomised to receive either panitumumab and BSC or BSC alone. The trial has been reported in one main publication(5) with four supplementary publications which are summarised in Table 8 (page 53).(4, 6, 48-50)

Eligibility criteria included pathological diagnosis of metastatic colorectal adenocarcinoma and radiologic documentation of disease progression during or within six months following the last administration of fluoropyrimidine, irinotecan and oxaliplatin.

The aim of the study was to evaluate the effect of panitumumab monotherapy in patients with chemorefactory mCRC. The primary outcome was PFS assessed by blinded central radiology. Secondary outcomes were best objective response, OS, time to response and duration of response.

The study was designed to have 90% power for a two sided 1% significance level test given a HR of 0.67 (panitumumab relative to BSC). Eligible patients were required to have a pathological diagnosis of metastatic disease progression during or within six months following the last administration of fluoropyrimidine, irinotecan and oxaliplatin.

Patients were randomly assigned 1:1 to receive panitumumab+BSC or BSC alone, however, details of the randomisation procedure are not given. Random assignment was stratified by ECOG performance status (0 or 1 vs 2) and region (Western Europe vs Central and Eastern Europe vs the rest of the world). Patients allocated to intervention arm received panitumumab via a 60-minute intravenous infusion at 6 mg/kg once every two weeks until patients progressed or unacceptable toxicity developed.

All patients were followed for survival every three months for up to two years after randomisation; however, median follow-up reported in this paper was approximately 35 weeks (range 15–76) in the panitumumab arm.

a Western Europe, Central Europe, Eastern Europe, Canada, Australia, New Zealand

In the BSC group, 176 (76%) patients received panitumumab in a cross-over protocol, which is reported in a supplementary paper.(50) The median time to cross-over was seven weeks (range 6.6–7.3) and the median follow-up after cross-over was 61 weeks (range 1–103). Median duration of treatment and dose intensity was not reported.

Siena and colleagues examine the association of PFS with CRC symptoms, HRQoL and OS for the panitumumab trial.(48) Patient reported outcomes were measured using the National Comprehensive Cancer Network (NCCN) FACT Colorectal Symptom Index (FCSI) for CRC symptoms and HRQoL was measured using the EQ-5D Health Index Scale, the EQ-5D Visual Analog Scale (VAS) and the EORTC QLQ-C30 GHS/QoL Scale. In this paper median follow-up time for survival (enrolment to data cutoff for analysis) for all patients was reported as 72 weeks (range 52–113).

The efficacy and safety findings of panitumumab from the extension study of the main trial; i.e. the cross-over from BSC to panitumumab are presented by Van Cutsem and colleagues.(5, 50) Hence, this was a multicentre, open-label, single arm trial. To be eligible, participants must have documented disease progression and were required to have completed the last assessment on the Phase III study not more than three months before enrolment in the extension study, During the interim participants could not have received systemic chemotherapy, radiotherapy, investigational agents or anti-tumour therapies.

Patients were followed for survival approximately every three months for up to two years from the randomisation date into the Phase III study.(5) The primary endpoint was safety and, although not pre-specified in the protocol, PFS, objective response rate, time to and duration of response, duration of stable disease (SD) and survival were explored.

The sample size was limited to the patients enrolled in the BSC arm of the Phase III study who met the eligibility criteria. Assuming a true event rate of 1%, the probability of at least one patient experiencing a given AE was 87% for a sample size of 200. Median follow-up time was reported as 61 weeks (range 18–103).

Amado and colleagues reported on a retrospective study assessing the predictive role of KRAS status in the main panitumumab trial.(4) The primary objective was to determine whether the effect of panitumumab+BSC on PFS differed between patients with KRAS mutant and KRAS WT status.

Of the 463 patients originally enrolled, 427 were included in the KRAS analysis, although the assessable sample size was 380 due to unavailable or poor quality samples. The primary outcome was PFS between KRAS mutant and KRAS WT status, with secondary outcomes

including examining whether panitumumab improved PFS, OS and response rate in the KRAS WT group compared with the BSC group.

Estimating a 60% KRAS WT status prevalence, power was calculated at more than 99% if the HR was 1.0 in the mutant group and at 87% if the HR was 0.80 in the KRAS mutant group, assuming an overall HR of 0.54 among all patients.

The final supplementary paper by Peeters and colleagues uses data from the main trial to investigate the association of skin toxicity severity and patient reported skin toxicity with PFS, OS, disease-related symptoms and HRQoL.(6) Associations by KRAS status were also evaluated.

Table 8. Summary of primary and supplementary papers for PAN

	Description	Median follow-up (months)
Van Cutsem et al (2007)	Main trial of PAN+BSC vs BSC	8.8 (range 3.8–19)
Siena et al (2007)	Analysis of association of PFS with CRC symptoms, HRQoL and OS	18 (range 13–28.3)
Van Cutsem et al (2007)	Cross-over extension study	15.3 (range 4.5–25.8)
Amado et al (2008)	Retrospective KRAS analysis of main trial	14.1 (for 36 remaining patients at time of analysis)
Peeters et al (2009)	Analysis of association of skin toxicity severity with efficacy of PAN	18 (range 13–28.3)

BSC, best supportive care; CRC, colorectal cancer; HRQoL, health-related quality of life; KRAS, kirsten rat sarcoma; OS, overall survival; PAN, panitumumab

4.2.1.5. Assessment of study quality

A summary of the quality assessment of studies included in this review are shown in Table 9 (page 54); study characteristics are summarised in the narrative below and in Appendix 3.

Table 9. Summary of quality assessment: clinical effectiveness all included trials

	Jonker et al 2007(45)	Van Cutsem et al 2007(5)	Van Cutsem et al 2007 (50)
Study design	RCT	RCT	single arm/ cross-over
Is a power calculation provided?	Yes	Yes	N/A
Is the sample size adequate?	Yes	Yes	N/A
Was ethical approval obtained?	?	Yes	Yes
Were the study eligibility criteria specified?	Yes	Yes	N/A
Were the eligibility criteria appropriate?	Yes	Yes	N/A
Were patients recruited prospectively?	Yes	Yes	N/A
Was assignment to the treatment groups really random?	Yes	?	N/A
Was the treatment allocation concealed?	No	No	No
Were adequate baseline details presented?	Yes	Yes	Yes
Were the participants representative of the population in question?	Yes	Yes	Yes
Were the groups similar at baseline?	Yes	Yes	N/A
Were baseline differences adequately adjusted for in the analysis?	N/A	N/A	N/A
Were the outcome assessors blind?	?	Yes	N/A
Was the care provider blind?	No	No	N/A
Are the outcome measures relevant to the research question?	Yes	Yes	Yes
Is compliance with treatment adequate?	Yes	?	?
Are withdrawals/dropouts adequately described?	Yes	Yes	Yes
Are all patients accounted for?	Yes	Yes	Yes
Is the number randomised reported?	Yes	Yes	N/A
Are protocol violations specified?	No	No	No
Are data analyses appropriate?	Yes	Yes	Yes
Is analysis conducted on an ITT basis?	Yes	Yes	N/A
Are missing data appropriately accounted for?	Partial	No	Yes
Were any subgroup analyses justified?	Yes	Yes	No
Are the conclusions supported by the results?	Yes	Yes	Yes

?, unclear or unknown; ITT, intention to treat; N/A, not applicable; RCT, randomised controlled trial

4.2.1.5.1. Cetuximab+BSC vs BSC

The CO.17 trial reported by Jonker and colleagues is a good quality, open-label, randomised Phase III trial.(45) The evaluation of the trial in relation to study quality is shown in Table 9 (page 54).

Randomisation methods and withdrawal were adequately reported. As previously mentioned, dose intensity was also noted to be adequate at 90%. However, blinding of assessors was not reported. A reason for the open-label nature of the study was also not given, although this may be due to the anticipated skin toxicity of anti-EGFR agents. The assessment of tissue samples for KRAS status was confirmed as performed in a blinded manner.(3)

The De Roock study (12), not formally included in this review but cited by Merck Serono for clinical effectiveness, analyses KRAS status from several cetuximab-based studies. However, the data reveals several key issues as follows:

- Of the relatively small sample size (n=113), a total of 67 patients had KRAS WT status, with 40% of the patients (n=27) from the BOND trial, 42% (n=28) from the EVEREST trial, 15% (n=10) from SALVAGE and 3% (n=2) from BABEL.
- In the BOND trial, 50% of patients from the cetuximab+BSC arm received irinotecan after disease progression, indicating potential cross-over and subsequent underestimate in the OS of those treated with cetuximab+irinotecan.(57)
- The EVEREST trial is described as an RCT comparing cetuximab+irinotecan, escalating doses of cetuximab+irinotecan and cetuximab+BSC. However, it is unclear why only data from cetuximab+irinotecan patients are included in De Roock and colleagues.(12, 58, 60, 61)
- The SALVAGE study (59), is a non-comparative study on patients receiving cetuximab+BSC only, who have received at least two prior lines of therapy.
- The BABEL study appears to be investigating the effect of tetracycline to alleviate a rash in cetuximab therapy, although further details on this study have been difficult to identify.
- Patients were included on the basis of availability of formalin-fixed paraffin-embedded tumour tissue; however there are no details on what this percentage was for each of the four studies contributing patient data.

As such, there are concerns regarding the disease progression and effectiveness estimates calculated using De Roock and colleagues.(12) The estimates are likely to be subject to high levels of bias and confounding, although it is unclear what impact this will have.

4.2.1.5.2. Panitumumab+ BSC vs BSC

This is a large, good quality, open-label, international, multicentre, randomised Phase III study.(5) The lack of participant and clinician/investigator blinding due to expected skin toxicity is discussed; however, to mitigate this, tumour assessments were performed by blinded central review. Unfortunately, it is unclear whether randomisation was performed centrally. [redacted] Further details of the quality assessment can be found in Table 9 (page 54).

4.2.1.5.3. Population baseline characteristics

4.2.1.5.3.1. Cetuximab+BSC vs BSC

For the main trial the demographic characteristics and disease status were well matched (Table 10, page 58).(45) The baseline characteristics were re-examined by Karapetis and colleagues according to KRAS status, which are also included in Table 10 (page 58).(3) Of the original 572 samples, 394 were available for analysis. Fifty eight percent were revealed to be WT, with 51% assigned to cetuximab+BSC and 49% to BSC. The relative proportions of each characteristic remained similar between arms.

4.2.1.5.3.2. Panitumumab+BSC vs BSC

At baseline, the two groups were well matched in the original trial.(5) A slight difference was noted with disease status, where the BSC arm had 34% participants with ECOG 0 and 50% with ECOG 1, whereas the treatment arm had 46% participants with ECOG 0 and 41% with ECOG 1 (Table 10, page 58). The supplementary study ascertained KRAS status in 92% of the original participants, showing the distribution of KRAS WT and KRAS mutant status between arms and ECOG performance status to be broadly similar.(4)

4.2.1.5.3.3. Comparability of baseline population characteristics

Participants in the two main trials of cetuximab+BSC vs BSC were similar in terms of age, gender distribution and site of primary cancer.(5, 45) However, as is usually the case with cancer trials, the study populations were significantly younger than the general population presenting with CRC, where the peak in number of cases in the UK, for example, is between 70 and 79 for men and 75 to 85-plus for women, as opposed to a median of 62– 64 shown in Table 10 (page 58).

Reporting of disease status in the panitumumab trial was limited to only ECOG status, rather than providing details of primary or metastatic sites. A higher proportion of participants were

noted to have an ECOG 0 in the treatment arm as opposed to BSC (46% vs 25%), which, according to the National Cancer Institute equates to: *'fully active, able to carry on all pre-disease performance without restriction'*. This therefore suggests a fitter population in the intervention arm.

Table 10. Population baseline characteristics: CET+BSC vs BSC after first-line therapy and PAN+BSC vs BSC

Study	Jonker et al 2007(45)		Karapetis et al 2008(3)				Van Cutsem, et al 2007(5)		Amado et al 2008(4)			
Intervention	CET	BSC	CET	BSC	CET	BSC	PAN	BSC	PAN (M)	PAN (WT)	BSC (M)	BSC (WT)
			MUTANT (M)		WILD TYPE (WT)							
N[a]	287	285	81	83	117	113	231	232	84	124	100	119
Diagnosis	Advanced colorectal cancer expressing EGFR						Chemorefractory mCRC					
Age, median yrs (range)	63 (29−88)	64 (29−86)	62 (37−88)		64 (29−86)		62 (27−82)	63 (27−83)	62 (27−79)	63 (29−82)	62 (27−83)	63 (32−81)
Male: n (%)	186 (65)	182 (64)	101 (62)		156 (68)		146 (63)	148 (64)	47 (56)	83 (67)	64 (64)	76 (64)
ECOG performance status (%)												
0	72 (25)	64 (23)	34 (21)		56 (24)		107 (46)	80 (34)	43 (51)	53 (43)	37 (37)	40 (34)
1	148 (52)	154 (54)	94 (57)		127 (55)		94 (41)	115 (50)	28 (33)	56 (45)	47 (47)	62 (52)
2	67 (23)	67 (24)	26 (22)		47 (20)		29 (13)	35 (15)	13 (15)[b]	15 (12)[b]	16 (16)[b]	17 (14)[b]
3	–	–	–		–		1 (0)	2 (1)	–	–	–	–
Site n (%)												
Colon only	171 (60)	161 (57)	108 (66)		137 (60)		153 (66)	157 (68)	53 (63)	86 (69)	65 (65)	82 (69)
Rectum only	63 (22)	70 (25)	32 (20)		50 (22)		78 (34)	75 (32)	31 (37)	38 (31)	35 (35)	37 (31)
Colon and rectum	53 (19)	54 (19)	24 (15)		43 (19)		–	–	–	–	–	–
Previous adjuvant chemotherapy												
n (%)	108 (38)	99 (35)	50 (31)		77 (34)		86 (37)	78 (34)	27 (32)	50 (40)	40 (40)	32 (27)
No of regimens												
1 or 2	50 (17)	54 (19)	27 (17)		46 (20)		230 (100)	232 (100)	54 (64)	79 (64)	74 (74)	63 (53)

3	109 (38)	108 (38)	69 (42)	86 (37)	84 (36)	88 (38)	23 (27)	41 (33)	24 (24)	49 (41)
4	87 (30)	72 (25)	46 (28)	63 (27)	–	–	–	–	–	–
≥5	41 (14)	51 (18)	22 (13)	35 (15)	–	–	–	–	–	–
TSI	287 (100)	285 (100)	164 (100)	230 (100)	–	–	–	–	–	–
Irin	277 (97)	273 (96)	161 (98)	219 (95)	–	–	–	–	–	–
Ox	281 (98)	278 (98)	163 (99)	222 (97)	–	–	–	–	–	–
Site of disease n (%)										
Liver	230 (80)	233 (82)	129 (79)	189 (82)	–	–	–	–	–	–
Lung	188 (66)	180 (63)	98 (60)	144 (63)	–	–	–	–	–	–
Lymph nodes	130 (45)	117 (41)	64 (39)	103 (45)	–	–	–	–	–	–
Peritoneal cavity (ascites)	45 (16)	41 (14)	23 (14)	38 (17)	–	–	–	–	–	–
No. of sites of disease										
1	40 (14)	53 (19)	27 (17)	40 (17)	–	–	–	–	–	–
2	84 (29)	69 (24)	45 (27)	63 (27)	–	–	–	–	–	–
3	84 (29)	89 (31)	42 (26)	75 (33)	–	–	–	–	–	–
≥4	79 (28)	74 (26)	50 (31)	52 (23)	–	–	–	–	–	–
Treatment n (%)										
CET+BSC	N/A	N/A	81 (49)	117 (51)	–	–	–	–	–	–
BSC	N/A	N/A	83 (51)	113 (49)	–	–	–	–	–	–

BSC, best supportive care; CET, cetuximab; ECOG: Eastern Cooperative Oncology Group score; EGFR, epidermal growth factor receptor; irin, irinotecan; M, mutant; mCRC, metastatsic colorectal cancer; ox, oxaliplatin; PAN< panitumumab; TSI, thimidylate synthase inhibitor; WT, wild type

[a]Number randomised; [b]ECOG ≥2

4.2.1.6. Assessment of clinical effectiveness

4.2.1.6.1. OS (Table 11, page 62)

4.2.1.6.1.1. Bevacizumab

There is currently no clinical evidence for the effectiveness of bevacizumab with non-oxaliplatin therapy after first-line treatment in mCRC. However, the trials reported by Roche, which are not included in this review, will be briefly mentioned as follows.

First-line

Saltz and colleagues conducted an RCT for first-line bevacizumab combined with oxaliplatin in 1,401 patients, 75% of whom had not previously received chemotherapy.(52) Treatment arms were: capecitabine+oxaliplatin (XELOX)+bevacizumab, XELOX+placebo, fluorouracil, folinic acid and oxaliplatin (FOLFOX-4)+bevacizumab or FOLFOX-4+placebo. The HR for OS for bevacizumab vs placebo was not statistically significant (HR=0.89, 97.5% CI: 0.76, 1.03, p=0.077) where the median OS for bevacizumab was 21.3 months compared to 19.9 months in the placebo arm.

Hurwitz and colleagues randomised 813 people to receive either irinotecan, bolus fluorouracil and leucovorin (IFL) plus bevacizumab or IFL alone for first-line treatment (28% of IFL patients and 24% of IFL+bevacizumab patients had received previous adjuvant chemotherapy).(35) ITT analyses showed median survival was 20.3 months for those treated with IFL+bevacizumab and 15.6 for those receiving IFL alone (HR=0.6, p<0.001).(35)

Subsequent treatment

Kabbinavar and colleagues(36) randomised 209 patients to receive fluorouracil and leucovorin (FU/LV)+bevacizumab or FU/LV only. Twenty one percent of the FU/LV+bevacizumab patients and 19% of the FU/LV patients had prior adjuvant chemotherapy. The primary endpoint of OS produced a non-statistically significant HR of 0.76 (95% CI 0.56, 1.10) for FU/LV+bevacizumab compared to FU/LV, with a median OS of 16.6 months in the FU/LV+bevacizumab arm and 12.9 months in the FU/LV arm. The authors argue that the large number of patients receiving post-progression treatment could partly explain the lack of statistical significance in the primary endpoint of OS. A similar percentage of patients from both treatment arms received irinotecan, oxaliplatin or both, post-progression (39% of the FU/LV+bevacizumab patients and 46% of the FU/LV patients).

Giantonio and colleagues (53) report a RCT with 820 patients previously treated with a fluoropyrimidine and irinotecan randomised to one of three arms: FOLFOX-4+bevacizumab, FOLFOX-4 or bevacizumab alone. Median OS was greater in the FOLFOX-4+bevacizumab arm: 12.9 months compared to 10.8 for FOLFOX-4 and 10.2 for bevacizumab alone. The HR for OS associated with FOLFOX-4+bevacizumab compared to FOLFOX-4 was 0.75 (p=0.01).

4.2.1.6.1.2. Cetuximab+BSC vs BSC

OS, defined as the time between date of randomisation and death from any cause, was the primary endpoint in the CO.17 trial.(45) The analysis was performed on an ITT basis, with the final analysis conducted after at least 445 patients were known to have died.

The median OS was 6.1 months in the cetuximab group and 4.6 months in the BSC group with a HR of 0.77 (95% CI 0.64 to 0.92; p=0.005). It should be noted that the addition of cetuximab to the BSC arm may have resulted in longer OS; however, it was reported that only 7% of patients receiving BSC were administered cetuximab after cross-over, which would bias the results against treatment.(45)

No significant differences were seen in the benefit of cetuximab on the basis of ECOG performance status at baseline, age or sex in subgroup analysis. However, unplanned analysis indicated that grade of rash in patients receiving cetuximab was correlated with OS, with median survival of 2.6 months in patients with no rash, as compared with 4.8 months in patients with Grade 1 rash and 8.4 months is patients with Grade 2 rash (p<0.001).(45)

For patients with KRAS mutant status, analysis by Karapetis and colleagues showed a median OS of 4.5 months for cetuximab and 4.6 months for BSC with an HR of 0.98 (95% CI 0.70 to 1.37; p=0.89).(3) Among patients with WT, the median OS was 9.5 months in the cetuximab group as compared with 4.8 months in the BSC group with an HR of 0.55 (95% CI 0.41 to 0.74; p<0.001). Subsequent to adjustment for potential prognostic factors which are reported as specified in the protocol but not described in the paper, the HR increases to 0.62 (0.44 to 0.87; p=0.006); however, these results remain favourable towards cetuximab+BSC.

4.2.1.6.1.3. Panitumumab+BSC vs BSC

At the time of analysis, the study had achieved the event rate required for 90% power.(5) OS was calculated from the day of random assignment until death, censoring patients at the last day known to be alive. Median OS values were not given; however, it was reported that no significant difference was found between arms (HR of 1.00; 95% CI 0.82–1.22; p=0.81). The authors cite confounding due to the rapid cross-over of 76% of patients from the BSC arm to receive active

treatment for the lack of significant difference between arms;(4) which would bias the results against treatment.

Exploratory analysis of skin toxicity demonstrated that favoured longer OS in patients with a skin toxicity of Grade 2 to 4 vs Grade 1, resulting in an HR of 0.59 (95% CI 0.42–0.85).

The retrospective investigation of panitumumab efficacy and KRAS status revealed no statistically significant OS difference between treatment arms in either of the KRAS groups.(4) The HR for OS was 1.02 (95% CI 0.75–1.39) and 0.99 (95% CI 0.75–1.29) for the mutant and KRAS WT groups, respectively, which is in contrast to the analysis for skin toxicity which apparently favours OS and only occurs in WT patients.(6)

Median OS is also unclear. Patients with KRAS WT status treated with panitumumab show a median survival of 8.1 months vs 7.6 months for those treated with BSC; and, patients with KRAS mutant status treated with panitumumab show a median OS of 4.9 months vs 4.4 months for BSC.(4)

Table 11. Summary of OS: CET+BSC and PAN+BSC vs BSC after first-line therapy

Study	Intervention[a]	N	Median OS (months)	HR	95% CI for HR	p value
Jonker et al 2007(45)	All: CET+BSC	287	6.1	0.77	0.64−0.92	p=0.005
	All: BSC	285	4.6			
Karapetis et al 2008(3)	WT: CET+BSC	117	9.5	0.55[b]	0.41−0.74	p<0.001
	WT: BSC	113	4.8	–	–	–
Van Cutsem et al (2007)(5)	All: PAN+BSC	231	NR	1.00	0.82−1.22	p=0.81
	All: BSC	232	NR	–	–	–
Amado et al 2008(4)	WT: PAN+BSC	124	8.1	0.99	0.75−1.29	NR
	WT: BSC	119	7.6	–	–	–

BSC, best supportive care; CET, cetuximab; CI, confidence interval; NR, not reported; OS, overall survival; PAN, panitumumab; HR, hazard ratio; WT, wild type

[a]All, mutant and wild type patients; WT, wild type status only; [b]These results are prior to adjustment for potential prognostic factors. The difference remained significant following adjustment.

4.2.1.6.2. PFS (Table 12, page 64)

4.2.1.6.2.1. Bevacizumab

Roche mention a number of papers which did not fulfil the inclusion criteria for this review, but their results will be briefly summarised here for completeness. Further details can be found in Section 6 (page 98).

Saltz and colleagues (52) report the HR for PFS for bevacizumab vs placebo was 0.83 (97.5% CI: 0.72, 0.95) with median PFS of 9.4 months for bevacizumab and eight months for placebo.

The HR for PFS determined by Hurwitz and colleagues was 0.54 ($p<0.001$), with patients treated with irinotecan, bolus fluorouracil and leucovorin (IFL) plus bevacizumab having a PFS of 10.6 months compared to 6.2 months for patients in the IFL arm.(35)

Kabbinavar and colleagues showed a statistically significantly longer PFS in the fluorouracil and leucovorin (FU/LV) plus bevacizumab arm (9.2 months) than the FU/LV arm alone (5.5 months) (HR = 0.5, 95% CI: 0.34, 0.73).(36)

Finally, Giantonio and colleagues(53) showed a median PFS which was also greater in the FOLFOX-4 plus bevacizumab arm, with 7.3 months as compared to 4.7 months for FOLFOX-4 and just 2.7 months for bevacizumab alone.

4.2.1.6.2.2. Cetuximab+BSC vs BSC

PFS was defined in the CO.17 study as the time from randomisation until the first objective observation of disease progression or death from any cause.(45) It should be noted that it was not reported whether assessors were blinded. Treatment with cetuximab significantly improved PFS with a HR of 0.68 (CI 0.57–0.80; $p<0.001$). No median PFS is reported for either arm, however, the estimated proportions of patients who were alive without documented objective progression of the disease at three and six months were 41% and 15%, respectively, in the cetuximab group and 24% and 3%, respectively, in the BSC group.

For patients with KRAS mutant status, median PFS was 1.8 months in both the cetuximab and BSC groups, HR of 0.99 (95% CI 0.73–1.35; $p=0.96$).(3) For patients with KRAS WT status, the median PFS was 3.7 months in the cetuximab group and 1.9 months in the BSC group, to give an HR of 0.40 (95% CI 0.30–0.54; $p<0.001$).

4.2.1.6.2.3. Panitumumab+BSC vs BSC

PFS (primary endpoint) for this trial was calculated from the day of random assignment until determination of radiologic progression or death by blinded assessors. (5) A statistically significant improvement was observed with patients receiving panitumumab giving an HR of 0.54 (95% CI 0.44–0.66). The difference in median PFS time was statistically significant at two months (95% CI 7.9–8.4) for panitumumab and 1.8 months (95% CI 7.1–7.7) for BSC; however, the difference in mean PFS time was more substantial at 3.5 months (SE 0.2) for panitumumab and 2.1 months (SE 0.1) for BSC.

The supplementary KRAS analysis revealed a beneficial effect of panitumumab for patients with KRAS WT status (HR 0.45; 95% CI 0.3–0.59) with a median PFS of 12.3 weeks in contrast to 7.3 weeks for BSC.(4)

Table 12. Summary of PFS: CET+BSC and PAN+BSC vs BSC after first-line therapy

Study	Intervention[a]	N	Median PFS (months)	HR	95% CI for HR	p value
Jonker, et al 2007 (45)	All: CET+BSC	287	NR	0.68[†]	0.57−0.80	<0.001
	All: BSC	285	NR	–	–	–
Karapetis, et al 2008 (3)	WT: CET+BSC	117	3.7	0.40[b]	0.30−0.54	<0.001
	WT: BSC	113	1.9	–	–	–
Study	**Intervention**	**N**	**Median PFS (weeks)**	**HR**	**95% CI for HR**	**p value**
Van Cutsem et al (2007) (5)	PAN+BSC	231	2	0.54	0.44−0.66	–
	BSC	232	1.8	–	–	–
Amado et al 2008 (4)	PAN+BSC*	124	3.1	0.45	0.34−0.59	–
	BSC*	119	1.8	–	–	–

BSC, best supportive care; CET, cetuximab, CI, confidence interval; HR, hazard ratio; NR, not reported; PAN, panitumumab; PFS progression-free survival; WT, wild type

[a]All, mutant and wild type (WT) patients; WT, wild type status only; [b]These results are prior to adjustment for potential prognostic factors. The difference remained significant following adjustment

4.2.1.6.3. Tumour response (Table 13, page 66)

4.2.1.6.3.1. Cetuximab+BSC vs BSC

In the cetuximab RCT, response rates (defined according to RECIST criteria) were assessed; however, it is unknown whether the assessors were blinded.(45) All patients were assessed every four weeks. Chest radiographs and cross-sectional imaging were performed at baseline and every eight weeks in both study groups until tumour progression occurred. In the cetuximab group, 23 patients (8%) had partial responses (PRs), with none in the BSC group ($p<0.001$). SD occurred in 90 patients in the cetuximab group (31.4%) and 31 patients in the BSC group (10.9%; $p<0.001$).(45) No data were provided on time to response and duration.

Subsequent KRAS assessment revealed that for patients with KRAS WT status in the cetuximab group, the response rate was 12.8%, whereas only 1.2% with KRAS mutant status displayed a response.(3)

4.2.1.6.3.2. Panitumumab+BSC vs BSC

Objective response was evaluated by blinded central review using modified RECIST at Weeks 8, 12, 16, 24, 32, 40 and 48 and every three months thereafter until disease progression.(5) At the discretion of the investigator, patients could be evaluated for radiographic tumour assessment after developing symptoms consistent with disease progression.

Objective response rates were greater in those treated with panitumumab compared to those treated with BSC. After a 12-month minimum follow-up, 10% of patients in the panitumumab had a partial response (PR), whereas no patients in the BSC group had an objective response ($p<0.0001$). Median time to response was 7.9 weeks (range 6.7–15.6) and median duration of response was 17.0 weeks (range 7.9–76.7). Twenty seven percent of patients in the panitumumab group and 10% of patients in the BSC group had a best response of SD.(5)

According to Amado and colleagues, best overall response (OR) data were unassessable or missing for 15% patients receiving panitumumab and for 23% of BSC patients, although this was not reported in the main trial report.(4) For the KRAS assessable patients receiving panitumumab, response was 10%, SD was 25% and disease progression was 50%. In the BSC arm, 0% had a response and 10% had SD. In the panitumumab group with KRAS WT status, 21 patients (17%; 95% CI 11–25%) had a PR, 34% had SD, whereas no responders were identified in the panitumumab group with KRAS mutant status. Median time to response was 7.9 weeks (range 7.0–15.6) and median duration of response was 19.7 weeks (range 7.9–88.7 weeks).(4)

Table 13. Summary of tumour response: CET+BSC and PAN+BSC vs BSC after first-line therapy

Study	Intervention	N	Objective response rate % (n)				p value for OR
			OR	CR	PR	SD	
Jonker et al 2007(45)	All: CET+BSC	287	8.0 (23)	0	8.0 (23)	31.4 (90)	<0.001
	All: BSC	285	0	0	0	10.9 (31)	–
Karapetis et al 200(3)	WT: CET+BSC	117	–	0	12.8 (15)	NR	<0.001
	WT: BSC	113	–	0	0	NR	–
Van Cutsem et al (2007)(5)b	All: PAN+BSC	231	10 (22)	0	10 (22)	27 (62)	<0.0001
	All: BSC	232	0	0	0	10 (23)	–
Amado et al 2008(4)	WT: PAN+BSC	124	17 (21)	0	17 (21)	34 (42)	NR
	WT: BSC	119	–	0	0	12 (14)	–

BSC, best supportive care; CET, cetuximab; CR, complete response; NR, not reported; OR, overall response; PAN, panitumumab PR, partial response; SD, stable disease; WT, wild type

[a]All, mutant and wild type (WT) patients; WT, wild type status only; [b]Results from independent central view of radiological images

4.2.1.6.4. HRQoL (Table 14, page 67)

A summary of the HRQoL results for cetuximab+BSC vs BSC are shown in Table 14 (page 67).

Table 14. Summary of HRQoL: CET+BSC and PAN+BSC vs BSC after first-line therapy

Study	Intervention		N	Mean	SD	95% CI	p value[a]
Jonker et al 2007(45)	All: CET+BSC	Wk 8 PF	NR	-3.9	–	–	<0.05
		Wk 16 PF		-5.9	–	–	0.03
		Wk 8 GHS		-0.5	–	–	0.008
		Wk 16 GHS		-3.6	–	–	<0.001
	All: BSC	Wk 8 PF		-8.6	–	–	–
		Wk 16 PF		-12.5	–	–	–
		Wk 8 GHS		-7.1	–	–	–
		Wk 16 GHS		-15.2	–	–	–
Karapetis et al 2008(54)	WT: CET+BSC	Wk 8 GHS	NR	3.2	–	4.2−17.6[b]	0.002
		Wk 16 GHS		-0.2	–	7.6−28.2[b]	<0.001
	WT: BSC	Wk 8 GHS		-7.7	–	–	–
		Wk 16 GHS		-18.1	–	–	–
Au et al 2009(47)	CET+BSC	Week 8 PF					
		All	185	-3.9	15.6	–	0.046
		WT	90	-0.69	13.59	–	0.11
		Week 8 GHS					
		All	185	-0.5	20.4	–	0.008
		WT	88	3.22	19.63	–	0.0016
		Week 16 PF					
		All	125	-5.9	17.7	–	0.027
		WT	69	-3.43	17.93	–	0.0078
		Week 16 GHS					
		All	128	-3.6	-3.6	–	<0.001
		WT	70	-0.24	-0.24	–	<0.001
	BSC	Week 8 PF					
		All	147	-8.6	20.4	–	–
		WT	62	-7.15	20.26	–	–
		Week 8 GHS					
		All	149	-7.1	22.4	–	–
		WT	63	-7.67	21.34	–	–

		Week 16 PF					
		All	76	-12.5	21.6	–	–
		WT	36	-13.8	21.47	–	–
		Week 16 GHS					
		All	75	-15.2	25.8	–	–
		WT	36	-18.1	27.64	–	–
Mittmann et al (2009)(8)	All: CET+BSC	Baseline	263	0.72	0.23	–	–
		Wk 4 HUI	220	0.73	0.26	–	–
		Wk 8 HUI	190	0.73	0.24	–	–
		Wk 16 HUI	119	0.73	0.24	–	–
		Wk 24 HUI	82	0.77	0.33	–	–
	All: BSC	Baseline	260	0.71	0.24	–	–
		Wk 4 HUI	184	0.68	0.26	–	–
		Wk 8 HUI	149	0.66	0.28	–	–
		Wk 16 HUI	72	0.63	0.30	–	–
		Wk 24 HUI	36	0.70	0.24	–	–
Odom et al 2011(49)	All: PAN+BSC	FCSI	188	3.63	–	-0.05, 7.31	p≤0.05
		EQ-5D		0.26[a]	–	0.16, 0.37	–
	WT: PAN+BSC	FSCI	112	5.75 [a]	–	1.45, 10.04	p≤0.05
		EQ-5D		0.32 [a]	–	0.18, 0.45	p≤0.05

BSC, best supportive care; CET, cetuximab; FCSI, Functional Assessment of Cancer Therapy Colorectal Symptom Index; GHS, global health status; HUI,health utility index; NR, not reported; PF, physical function; Wk, Week; WT, wild type

[a]p value between cetuximab and BSC; [b]mean difference

4.2.1.6.4.1. Cetuximab+BSC vs BSC

HRQoL for the CO.17 trial was reported in several papers. However, since this study was not blinded there is the potential for bias in the QoL measures.

QoL reported in the main trial paper was assessed by the EORTC QLQ-C30 at baseline and at four, eight, 16 and 24 weeks after randomisation.(45) Compliance with the questionnaire reduced from 94% at baseline in both groups to 67% at 16 weeks in the cetuximab group, and 43% at 16 weeks in the BSC group.(45) Missing data is acknowledged as having systematic difference in compliance between treatment groups and HRQoL data were not missing at random. Au and colleagues suggest that patients in the BSC arm were subject to worse PFS and OS and therefore less able to complete questionnaires. Lack of blinding was also recognised as potential bias, due to the placebo effect.(47)

In comparison with BSC, the reported results indicate that cetuximab was associated with reduced deterioration in PF at eight weeks (mean change score, -3.9 vs -8.6; p=0.05) and 16 weeks (mean change score, -5.9 vs -12.5; p=0.03). The cetuximab arm also demonstrated less deterioration in GHS at eight weeks (mean change score, -0.5 vs -7.1; p=0.008) and 16 weeks (mean change score, -3.6 vs -15.2; p<0.001).(45) The data for HRQoL at 24 weeks are not reported.

According to Karapetis and colleagues, patients with KRAS WT status in the cetuximab arm had an improvement in GHS at eight weeks, whereas those in the BSC group deteriorated (mean change score, 3.2 vs -7.7; 95% CI 4.2 to 18.6; p=0.002).(3) Pateints with KRAS WT status in the cetuximab group also had less deterioration at 16 weeks than the BSC group (mean change score, -0.2 vs -18.1; 95% CI 7.6– 28.2; p<0.001).

Mittmann and colleagues (8) report on HUI3 data collected during the CO.17 trial, where patients assess their own health attributes; vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain. The assessments were performed at four weeks, eight weeks, 16 weeks and 24 weeks after randomisation, and the results show that the scores were relatively unchanged for the cetuximab arm, but declined for BSC. However, these are not displayed according to KRAS status; in addition, bias is likely since patients in the BSC arm may deteriorate more quickly than those in the cetuximab arm, and therefore be less able to complete the questionnaire.

4.2.1.6.4.2. Panitumumab plus BSC vs BSC

Patient-reported outcomes were analysed using the EUROQOL EQ-5D VAS, the NCCN FCSI , EORTC QoL subscales, and a dermatology question. Results in the main trial report by Van Cutsem and colleagues were included in an online appendix.(5) No data were given, just a summary concluding that patients were more concerned by their skin conditions in the cetuximab group rather than the BSC group. It was reported that no clinically meaningful differences in overall QoL were observed between the groups.(5)

A subsequent study by Odom and colleagues reported more information on this study.(49) They report on data collected using the NCCN FCSI and the EQ-5D Index. The results were analysed according to the KRAS status, which was ascertained in 92% of participants. (49) The authors acknowledged the large amount of missing patient reported data and attributed this to declining health, since approximately 50% of patients in the BSC arm, and patients with KRAS mutant status in the panitumumab+BSC arm had progressed by Week 8. Sensitivity analysis was performed to evaluate the effect of attrition on QoL between treatment arms.

Overall, information on KRAS status together with post-baseline patient reported outcome data was available for 78% of the overall study population. Baseline characteristics were broadly similar across groups, other than the panitumumab+BSC group had a slightly higher percentage of people in ECOG 0. Less deterioration was observed in the FCSI score and EQ-5D Index in the panitumumab+BSC group compared with the BSC group alone, both overall and for those with KRAS WT status.

For the FCSI scores, an average least squares mean (LSM) difference between treatment groups across all weeks favoured panitumumab by 3.60 (95% CI, 0.90–6.30) overall and 5.62 (95% CI, 2.38–8.86) for patients with KRAS WT status. The EQ-5D Index results also favoured panitumumab, with an average LSM difference between treatment groups across all weeks of 0.17 (95% CI, 0.09–0.25) overall and 0.22 (95% CI, 0.12–0.32) for those with KRAS WT status. Analysis of the KRAS mutant group did not show any significant differences in QoL between those treated with panitumumab+BSC and those treated with BSC. Odom and colleagues suggest a limitation of the study concerned skin toxicity, which was associated with higher HRQoL, since the rash may be seen as a predictor of benefit by the patient. However, the majority of KRAS mutant status patients on panitumumab who also experienced a rash, did not report this benefit.(49)

4.2.1.7. Indirect comparison of cetuximab and panitumumab

There are no RCTs directly comparing the effectiveness of cetuximab to panitumumab. However, an indirect comparison between the two treatments can be made if it is assumed that the BSC arm of Karapetis and colleagues(54) and Amado and colleagues(4) are equivalent in terms of the care and treatment received. Based on this assumption the HRs for OS and PFS can be calculated for an indirect comparison of cetuximab vs panitumumab(43). Details of the method used can be found in Appendix 4.

Two sets of results are given in Table 15 (page 71), those using the unadjusted OS and PFS HRs from Karapetis and colleagues and those using the KRAS adjusted OS and PS HRs. Given that KRAS status is assessed retrospectively in Karapetis and colleagues and that KRAS status was not determined for all participants, there may be some selection bias in the study (even though the authors report that there were similarities between patient characteristics for those with KRAS WT status and those with KRAS mutant status), therefore it would seem reasonable to attach more importance to the HRs adjusted for patient characteristics than those not adjusted. Note that Amado and colleagues do not report HRs adjusted for patient characteristics, only the unadjusted HRs. It is therefore possible that the unadjusted HRs from Amado and colleagues are subject to selection bias as well, but the magnitude of this bias is difficult to quantify.

Table 15. Direct and indirect HRs (and 95% CIs) for OS and PFS

Outcome	HR from Karapetis et al(54)	CET+BSC vs BSC(54)	PAN+BSC vs BSC (4)	CET+BSC vs PAN+BSC (calculated by PenTAG(43))
PFS	Unadjusted	0.40 (0.30, 0.54)	0.45 (0.34, 0.59)	0.89 (0.59, 1.33)
	Adjusted	0.42 (0.30, 0.58)		0.93 (0.61, 1.43)
OS	Unadjusted	0.55 (0.41, 0.74)	0.99 (0.75, 1.29)	0.56 (0.37, 0.83)
	Adjusted	0.62 (0.44, 0.87)		0.63 (0.41, 0.97)

BSC, best supportive care; CET, cetuximab; HR, hazard ratio; OS, overall survival; PAN, panitumumab; PFS, progression free survival

The indirect comparisons indicate that there is no statistically significant difference in the hazard for PFS between those receiving cetuximab+BSC and those receiving panitumumab+BSC, regardless of whether the adjusted or unadjusted HR from Karapetis and colleagues is used. On the other hand, the results suggest that there is a statistically significant difference in hazard for OS between cetuximab+BSC and panitumumab+BSC, with patients receiving cetuximab+BSC having longer OS. However, the study by Amado and colleagues is subject to a large number of patients randomised to receive BSC actually receiving panitumumab+BSC during the progressed disease stage, potentially biasing the results against cetuximab. Thus, the HR for OS from this study is subject to confounding. No published analyses have addressed this issue of cross-over in the study by Amado and colleagues. In Amgen's submission analyses were undertaken to address the cross-over (see Section 6, page 98), but the results are not presented in terms of HRs and so are not included in the indirect comparisons described here.

4.2.1.7.1. AEs (Table 16, page 72)

Comparison between the cetuximab and panitumumab trials, even indirectly, is troublesome, since it is not clear whether similar scales were used to grade the level of AE for both. For example, Merck Serono (cetuximab [Erbitux®]), report that 30% of patients suffered Grade 3 or higher fatigue in the BSC arm, whereas Amgen (panitumumab [Vectibix®]) report only 3% of patients in the BSC arm experienced the same level of fatigue. Since the population characteristics between studies are similar, this suggests the AEs may have been measured differently. It also appears that different criteria were used; for example, the cetuximab trial combined all skin-related AEs as a rash, whereas the panitumumab trial employed a variety of conditions, such as erythema and pruritus.

Table 16. AEs (Grade 3 & 4): CET+BSC vs BSC vs PAN+BSC vs BSC after first-line therapy

Study	Jonker et al (2007) (45)		Van Cutsem et al (2007) (5)		Van Cutsem et al (2007)(50)
Intervention	CET+BSC	BSC	PAN+BSC	BSC	PAN+BSC
N	288	274	229	234	176
Grade 3/4 AEs	**% of patients**				
Erythema	–	–	5	0	6
Dermatitis acneiform	–	–	7	0	6
Pruritis		–	2	0	1
Skin exfoliation	–	–	2	0	1
Fatigue	33	30	4	3	–
Paronychia	–	–	1	0	2
Abdominal pain	13	16	7	4	–
Anorexia	8	6	3	2	–
Nausea	6	6	1	0	–
Diarrhoea	–	–	1	0	1
Rash	12	0	1	0	5
Skin fissures	–	–	1	0	–
Constipation	3	5	3	1	–
Vomiting	6	6	2	1	–
Dyspnoea	16	12	5	3	–
Pyrexia	–	–	0	2	–
Asthenia	–	–	3	2	–
Cough	–	–	0	0	–
Back pain	–	–	2	0	–
Oedema	5	6	1	0	–
Conjunctivitis	–	–	–	–	1
General physical health deterioration	–	–	7	2	–
Other pain[a]	15	7	–	–	–
Non-neutropaenic infection	13	6	–	–	–
Confusion	6	2	–	–	–
Hypomagnesia	6	0	–	–	4
Infusion reactions	5	0	–	–	–

BSC, best supportive care; CET, cetuximab; PAN, panitumumab

[a]Excludes arthralgia, myalgia, earache, headache and abdominal, bone, chest, hepatic, neuropathic, pelvic, pleuritic, rectal, perirectal, and tumour pain

4.2.1.7.1.1. Bevacizumab

For consistency, the following is a brief overview of papers cited by Roche, not applicable for inclusion in the review. Further details are available in Section 6 (page 98).

Saltz and colleagues(52) report that 30% of patients in the bevacizumab arm discontinued treatment due to AEs as compared to 21% in the placebo arm. Hurwitz and colleagues report statistically significantly more Grade 3 or 4 AEs in the IFL+bevacizumab arm than in the IFL arm ($p<0.01$), due to hypertension.(35) Kabbinavar and colleagues also experienced an increase in Grade 3 or 4 AEs with bevacizumab (87% for FU/LV+bevacizumab vs 71% for FU/LV) (36) as did Giantonio and colleagues (53) (75% for FOLFOX-4+bevacizumab vs 61% for FOLFOX-4).

4.2.1.7.1.2. Cetuximab+BSC vs BSC

Safety analysis for the CO.17 trial was conducted on an on-treatment basis, contrasting patients who had at least one dose of cetuximab (including those who crossed over) with patients assigned to supportive care alone, and omitting patients who withdrew consent before any intervention.(45) Grades were determined according to the NCI-CTC, Version 2.0.

It should be noted that the data are presented with the patient as the unit of measurement. No information is given as to whether patients experienced more than one AE.

No statistically significant differences were apparent between the cetuximab group and the BSC group in the incidence of Grade 3 or higher AEs, with the exception of rash (11.8% for cetuximab vs 0.4% for BSC; $p<0.001$), infection without neutropeania (12.8% vs 5.5%; $p=0.003$), confusion (5.6% vs 2.2%; $p=0.05$) and pain defined as other according to the NCI-CTC (14.9% vs 7.3%; $p=0.005$). Hypomagnesia was also more common in the cetuximab group than BSC (5.8% vs 0.0%; $p<0.001$).(45)

Grade 3 or 4 infusion reactions occurred in 4.5% of patients assigned to cetuximab, with 11 patients having an AE leading to discontinuation of cetuximab, most frequently because of an infusion reaction. Patients in the cetuximab group also had a higher incidence of rash of any grade in comparison to the BSC group (88.6% vs 16.1%; $p<0.001$).(45)

In total, 59 patients died within 30 days after the last date of the cetuximab infusion. All died of CRC except one patient who had a pulmonary embolus.

Unfortunately, safety data was not retrospectively analysed in relation to KRAS status for cetuximab.

4.2.1.8. Panitumumab plus BSC vs BSC

It should also be noted that the safety data are presented with the patient as the unit of measurement, as opposed to the number of AEs in each arm. No information is given as to whether patients experienced more than one AE.

Skin-related toxicities occurred in 90% of patients in the panitumumab group and in 9% of the BSC group. One patient in the panitumumab group discontinued treatment because of Grade 2 dermatitis acneiform and another due to a Grade 2 hypersensitivity reaction.(5) Grade 3 or 4 hypomagnesia occurred in 3% of patients in the panitumumab group.

Eighty one percent of patients in the panitumumab group and 84% in the BSC group died during the study, none of which were treatment related. Nearly all deaths were related to disease progression.

Specific AEs according to KRAS status in each arm were not reported. However, in the group with KRAS WT status, 100% of patients receiving panitumumab and 90% of patients receiving BSC had an AE, although no level of statistical significance is given.(4) Consistent with previous reports,(5) patients with the worst grade skin toxicity in the KRAS WT group appeared to experience better PFS and OS. The other main AE in the panitumumab arm, was a higher incidence of diarrhoea of any grade (KRAS WT 24%; KRAS mutant 19%). Amado reports the incidence of AEs leading to withdrawal in the panitumumab arm to be 7% for the group with KRAS WT status, with 2% withdrawing for panitumumab-related events.(4)

In regard to the single arm extension study, 92% of patients experienced adverse events considered related to panitumumab, 16% had a Grade 3 treatment-related AE and 2% had a Grade 4 treatment-related AE (acute renal failure, pulmonary embolism, erythema and pustular acne).(50) There were no fatal AEs related to panitumumab.

Fifty three percent of patients had at least one serious AE, most of which were typical of mCRC disease progression, with 6% experiencing serious AEs considered at least possibly related to panitumumab. AEs leading to discontinuation of the treatment phase occurred in 11% of patients with 4% discontinued treatment because of skin and subcutaneous tissue disorders that were possibly related to panitumumab.(50)

All deaths were attributed to disease progression with 10% of patients dying during the treatment period, 20% within 30 days of treatment discontinuation and 52% after 30 days of receiving the last panitumumab infusion.

4.2.1.8.1. Summary of safety data

Skin toxicity is the most common AE associated with EGFR inhibitors, although it has been shown that skin toxicity severity may be associated with efficacy.(6) With panitumumab treatment this association was only seen for patients with KRAS WT status; however, the trial authors advise caution on the apparent correlation since the analysis was not a randomised comparison and patients remaining longer on the study because of benefit treatment are more likely to develop skin toxicity.(6)

4.2.2. Overall conclusion: cetuximab+BSC vs BSC and panitumumab+BSC vs BSC

From the limited clinical data available, treatment with both interventions (cetuximab+BSC and panitumumab+BSC) appears to have clinically relevant and statistically significant advantages over treatment with BSC alone (Table 16, page 72). In both trials, median PFS in patients with KRAS WT status appears to almost double due to active treatment. For cetuximab, median PFS increases from approximately two months to approximately four months and for panitumumab from approximately two months to approximately three months (HR for cetuximab vs BSC 0.40; 95% CI 0.30 to 0.54 and HR for panitumumab vs BSC 0.45; 95% CI 0.34–0.59).(3, 4)

For median OS in the clinically relevant KRAS WT population, the cetuximab arm exhibits 9.5 months vs 4.8 months for BSC (HR 0.55; 95% CI 0.41–0.75). The evidence for panitumumab is less convincing. Although a median OS of 8.1 months vs 7.6 months for BSC is presented, the HR of 0.99 (95% CI; 0.75–1.29) indicates a lack of significant difference. The rapid cross-over of 76% of patients (median time to cross-over 7.1 weeks is likely to have had an extensive confounding effect.(4, 5)

Tumour response, in the cetuximab group indicated SD occurred in 31.4% of patients and 10.9% patients in the BSC group ($p<0.001$); however, it is unclear whether the assessors were blinded.(45) PR was seen in 8% of patients in the cetuximab group, with no PR was seen in the BSC group. Subsequent KRAS analysis revealed that for patients with KRAS WT status in the cetuximab group, the partial response rate was 12.8%, whereas only 1.2% with KRAS mutant status had a response.(3) SD was not reported.

Objective response for the panitumumab study was evaluated by blinded central review and was shown to favour panitumumab vs BSC. After a 12-month minimum follow up, 10% of patients in the panitumumab group had a PR, whereas no patients in the BSC group had an objective response ($p<0.0001$). In the panitumumab group with KRAS WT status, 17% had a PR and 34%

had SD, whereas no responders were identified in the panitumumab group with KRAS mutant status.

Data on AEs is difficult to compare between the interventions. The panitumumab trial does not confirm the AE scale used therefore it is unclear if they are analogous with cetuximab.

Skin toxicity was clearly an issue for both treatments, although again, reported differently. Patients in the cetuximab group an 88% incidence of rash of any grade, compared to skin toxicity of 90% for panitumumab. There appears to be a correlation between extent of skin toxicity and treatment efficacy, although one paper suggests exercising caution with these results since a patient remaining longer on a treatment due to its benefit are more likely to develop skin toxicity at some point.(6)

HRQoL was at risk of bias for both trials, due to lack of blinding and the knowledge that skin toxicity may also have been a predictor of benefit. Missing data may also have systematic differences in compliance between treatment groups' for example, patients in the BSC arm were subject to worse PFS and OS and therefore less able to complete questionnaires. For patients receiving cetuximab+BSC, a slower deterioration in GHS and PF was noted in comparison to BSC alone. According to Karapetis and colleagues, patients with KRAS WT status in the cetuximab+BSC arm had an improvement in GHS at eight weeks, whereas those in the BSC group deteriorated.

For patients receiving panitumumab+BSC, it was initially reported that no clinically meaningful differences in overall QoL were observed between the groups.(5) However, subsequent analysis revealed less deterioration in the FCSI score and EQ-5D Index in the panitumumab+BSC group compared with the BSC group alone, both overall and for those with KRAS WT status.(49)

As there is no head-to-head comparison data available for cetuximab vs panitumumab, we carried out an indirect comparison to consider which intervention might be the most clinically effective. The results indicate that there is no statistically significant difference in the hazard for PFS between those receiving cetuximab+BSC and those receiving panitumumab+BSC. In contrast, there is, a statistically significant difference in hazard for OS between cetuximab+BSC and panitumumab+BSC, with patients receiving cetuximab+BSC having longer OS. However, the study by Amado and colleagues (4) is subject to a large number of patients randomised to receive BSC actually receiving panitumumab+BSC during the PD stage. Thus, the HR for OS from this study is subject to confounding.

Table 17. Summary of clinical effectiveness results

CET+BSC vs BSC	Significant > PFS Significant > OS
PAN+BSC vs BSC	Significant > PFS No significant effect on OS[a]
CET+BSC vs PAN+BSC[b]	No significant difference between PFS Significant > OS for cetuximab[a]

BSC, best supportive care; CET, cetuximab; OS, overall survival; PAN, panitumumab; PFS, progression-free survival
[a]At risk of confounding; [b]Calculated by PenTAG

5. Assessment of cost-effectiveness: systematic review

The cost-effectiveness of bevacizumab, cetuximab and panitumumab, against relevant comparators within their licensed indications for the treatment of mCRC after first-line chemotherapy was assessed in a systematic review of the literature. An outline discussion is presented on the literature searching undertaken in the general literature on mCRC, covering the costs associated with the treatment of mCRC, HRQoL associated with mCRC states, and the modelling of disease progression in mCRC.

5.1. Systematic review of existing cost-effectiveness evidence

5.1.1. Cost-effectiveness evidence which supported existing guidance

A review by Tappenden and colleagues evaluated the clinical and cost-effectiveness of bevacizumab and cetuximab for the treatment of individuals with mCRC; this informed previous NICE guidance TA118.(41) Both were identified in the literature searches and are summarised in Table 18 (page 79) and Section 5.1.1.1 (page 80). The assessment of bevacizumab in the Tappenden review falls beyond the scope of this current appraisal as it considered evidence of the use of bevacizumab in untreated mCRC patients (i.e. first-line treatment). The review of cetuximab is relevant to this appraisal as it considered patients with EGFR expressing mCRC who had failed irinotecan-including therapy. It was not, however, restricted to patients with KRAS WT status as this was not part of the cetuximab licence at the time TA118 was developed.

Table 18. Summary of systematic review and economic evaluation of CET+IRIN for the treatment of mCRC: Tappenden and colleagues(41)

	Tappenden et al, 2007(41)
Study purpose	To assess the clinical and cost-effectiveness of bevacizumab[a] and cetuximab in the treatment of individuals with mCRC
Country setting	UK
Base-year prices	Not stated explicitly but manufacturer's submissions are 2005
Intervention/comparator	CET+IRIN vs ASC/ BSC
Line of treatment	Second- or subsequent line (CET)
Study type	Threshold analysis; based on Merck Serono's submission to NICE in 2005
Model duration / cycle length	Unclear
Number of health states	Unclear. Description of utilities suggests two alive health states: SD and PD.
Study group	Patients with EGFR-espressing mCRC after failure of irinotecan-including cytotoxic therapy.
Perspective	NHS/PSS perspective
Discount rate p.a.	Not included; distribution of costs incurred over time is not included in the model although given the short time horizon this omission is unlikely to have a substantial impact upon the cost-effectiveness or cost-utility estimates
Source of funding	Funding for this review was provided by NIHR
Base case findings	The calculation of the mean OS durations for ASC/BSC treatment groups range from 0.60 LYs to 0.77 LYs. Based on these estimates of OS the cost per LYG for CET+IRIN given according to the proposed continuation rule may be as low as £58,048 per LYG or as high as £462,889 per LYG. When health outcomes are measured in terms of QALYs, the equivalent range is likely to be £77,210–£335,358 per QALY gained. When the proposed continuation rule is not applied the cost per LYG may be as low as £77,345 per LYG or as high as £375,487 per LYG; or, between £104,747 and £370,044 per QALY gained (again depending on calculation of mean OS duration for ASC/BSC groups). Minimum OS advantage required by CET+IRIN over ASC/BSC is 0.65 years assuming the continuation rule.
Sensitivity analyses	**Scenario** / **Min OS (yrs) adv for CET+IRIN over comparator to have a cost/QALY gained of £30,000** Base case (with continuation rule) / 0.65 Base case (without continuation rule) / Not possible for the incr cost-utility of CET+IRIN vs ASC/BSC to be below £30,000/QALY gained Alt HRQoL data source (MABEL) / 0.6 Comparator is oxaliplatin+5-FU/FA / Approx 0.8 Comparator is BSC alone / Not possible for CET+IRIN to have a cost/QALY which is better than £30,000 Incl of indirect effectiveness evidence / 0.14

Adv, advantage; Alt, alternative; ASC, active supportive care; BEV, bevacizumab; BSC, best supportive care; CEA, cost-effectiveness ratio; CET, cetuximab; CI, confidence interval; FA, folinic acid; FU, fluorouracil; ICER, incremental cost effectiveness ratio; IRIN, irinotecan; LYs, life years; LYG, life years gained; mCRC, metastatic colorectal cancer; NHS, National Health Service; NIHR, National Institute for Health Research; OS, overall survival; p.a., per annum; PSS, Personal Social Services; QALY, quality-adjusted life year; yrs, years

[a]Bevacizumab was considered in combination with 5-FU containing / releasing regimens in previously untreated mCRC patients which falls outside the scope of the current review

5.1.1.1. Considerations for cetuximab from TA118

Main guidance:

'Cetuximab in combination with irinotecan is not recommended for the second-line or subsequent treatment of mCRC after the failure of of an irinotecan-containing chemotherapy regimen. People currently receiving … cetuximab should have the option to continue therapy until they and their consultants consider it appropriate to stop.'(32)

Key economic considerations:

Effectiveness data representative of third-line not second-line usage:

'The Committee considered the cost-effectiveness for cetuximab. It noted that the economic modelling from both the manufacturer and the assessment group had been completed using effectiveness data from the RCT of cetuximab where approximately 80% of patients received cetuximab plus irinotecan as a third-line or subsequent therapy. It [the Appraisal Committee] was also aware that the comparator used in both models was ASC/BSC, which meant the modelled scenario and corresponding estimates of cost-effectiveness more closely resembled third-line or subsequent use of cetuximab rather than second-line use.'(32)

Uncertainties surrounding the utility estimates were discussed:

The Committee discussed the uncertainties around the estimates of utility for patients with mCRC. The manufacturer had provided estimates between 0.95 and 0.71, both constant over the lifetime of the patient. The Committee considered that the utility for a patient with mCRC was likely to reflect the lower end of this range, based on additional data submitted by the manufacturer from the MABEL study. The [Appraisal] Committee concluded that, using the most realistic utility estimates, the cost effectiveness estimates provided by both the manufacturer and the assessment group were not compatible with the best use of NHS resources. The [Appraisal] Committee also noted that these estimates were associated with a high level of uncertainty because they were based on indirect comparisons.'(32)

Results from the threshold analysis were considered:

'The Committee therefore considered threshold analyses completed by the assessment group, where the survival in the comparator arm was held as unknown. The base-case threshold analysis suggested that, with the application of the continuation rule, a cost per QALY gained of £30,000 could only be achieved if survival with ASC/BSC is less than two months. A sensitivity analysis adjusting the assumptions to reflect utility values from the MABEL study did not materially alter the results. The Committee noted that the manufacturer had provided an estimate

of mean survival of 5.6 months for patients receiving ASC/BSC in their economic model, while studies of ASC/BSC identified in their assessment report provided estimates of median survival ranging from six to nine months. The Committee therefore considered that an estimate of mean survival while receiving ASC/BSC of approximately two months was an unrealistic underestimate. Considering all the available evidence on clinical and cost effectiveness, the Committee therefore concluded that cetuximab, either as a second-line or a subsequent line treatment for mCRC would not be a cost-effective use of NHS resources.'(32)

5.1.2. Methods

Electronic databases were searched using population and intervention sets only, without restricting to methodological or outcome filters; see Section 4.1.1 (page 40) and Appendix 1.

5.1.3. Study selection criteria and procedures

The inclusion and exclusion criteria for the systematic review of economic evaluations are similar to those for the systematic review of clinical effectiveness (see Section 4.1.2, page 41), subject to the following exceptions:

- Non-randomised studies were included (for example, 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 included if the incremental ratios can be easily calculated from the published data.)
- Standalone cost analyses based in the UK NHS were also sought and appraised.

Relevant studies to the cost-effectiveness analysis were identified in two stages based on the above inclusion/exclusion criteria. Titles and abstracts returned by the search strategy were examined independently by two researchers (CH and LC) and screened for possible inclusion. Disagreements were resolved by discussion. Full texts of the identified studies were obtained. Two researchers (CH and LC) examined these independently for inclusion or exclusion, and disagreements were again resolved by discussion.

5.1.3.1. Study quality assessment

The methodological quality of included economic evaluations was assessed according to internationally accepted criteria such as the Consensus on Health Economic Criteria (CHEC) list questions developed by Evers and colleagues and the critical appraisal checklist developed by

Drummond and colleagues.(62)re(63) The studies were assessed by one reviewer (LC) and checked by a second reviewer (CH).

5.1.3.2. Data extraction strategy

For those studies which were of relevance to the current decision problem, data were extracted by one researcher (LC) into one summary table describing the study design and main results. The table includes: author and year; model type or trial based; study design (for example, cost-effectiveness analysis or cost-utility analysis); service setting/country; study population; comparators; research question; perspective; time horizon and discounting; main costs included; base-case findings, sensitivity analyses conducted; and, other notable design features. Finally the reviewers' comment on study quality and generalisability (in relation to the final scope) of their results were recorded (see Table 21 (page 86), Table 22 (page 87) and Appendix 9).

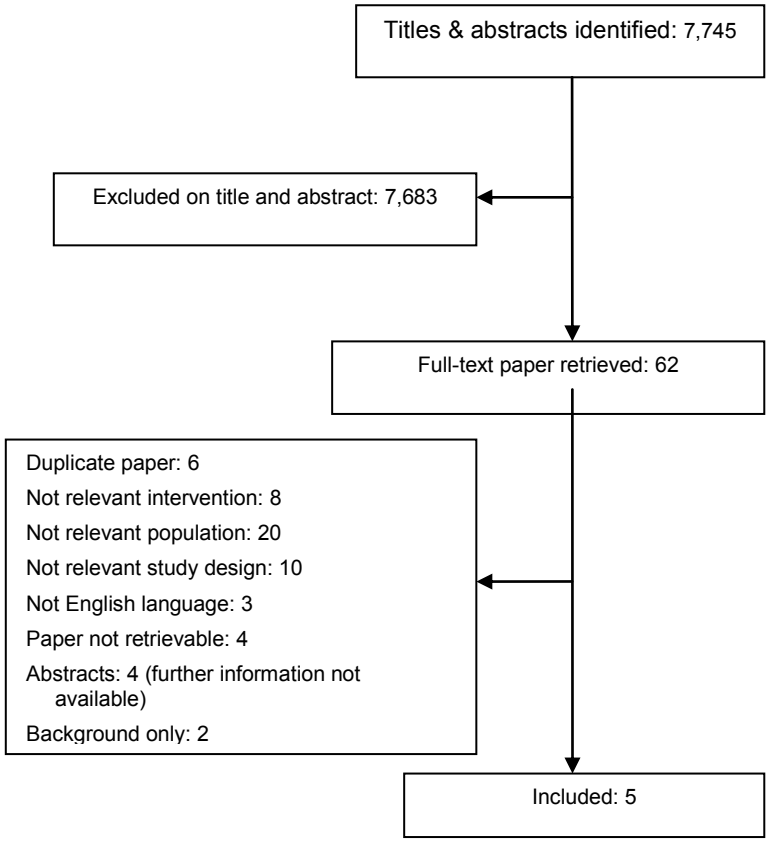
5.1.3.3. Synthesis of extracted evidence

Narrative synthesis, supported by abridged data extraction tables (Appendix 3), were used to summarise the available evidence base.

5.1.4. Results

The flow of papers is summarised in Figure 2 (page 83). In brief over 7,745 citations were identified; 85 of which were ordered in full; six of these could not be retrieved but from the information in the title seemed to offer a low probability of representing additional included studies. Of the 79 which were retrieved 71 were excluded. Of the remaining eight, three were abstracts for which more information was requested but not received and five were formally included. Further details and references for these excluded papers are available in Appendix 10.

Figure 2. Flow diagram for search, retrieval and inclusion of articles in systematic review of evidence on the economic evaluations of BEV, CET and PAN for the treatment of mCRC



One published systematic review (Tappenden and colleagues)(41) was identified in the literature search which informed previous guidance (NICE TA118) These were not included in the main review but are summarised in Table 18 (page 79), and Section 5.1.1 (page 78).(32)

Five published full economic evaluations meeting the inclusion criteria were included.(7-11) Four abstracts were identified which met the specified inclusion criteria.(64-67) Additional information was requested from the corresponding authors of each of the four abstracts, but at the time of writing no responses have been received. Three of the abstracts are referred to in the discussion in this section.(64-66)

5.1.4.1. Summary of cost-effectiveness studies

Table 19. Summary of cost-effectiveness studies

Author	Intervention	Comparator	Location	Notes
Mittmann (2009)(8)	CET+BSC	BSC	Canada	Based on CO.17 study
Annemans(2007)(7)	CET+IRIN	BSC	Belgium	Based on BOND study
Norum (2004)(9)	CET+IRIN	BSC	Norway	–
Starling (2007)(10)	CET+IRIN	BSC	UK	–
Wong (2009)(11)	Treatment sequences to measure the cost implications of treatments that include chemotherapy for the treatment of mCRC; five sequences consider either cetuximab+BSC or cetuximab+irinotecan use as a third-line treatment option.		US	–

BSC, best supportive care; CET, cetuximab; IRIN, irinotecan; mCRC, metastatic colorectal cancer; UK, United Kingdom; US, United States of America

5.1.4.1.1. Cetuximab+BSC vs BSC

There was one included study addressing the cost-effectiveness of cetuximab+BSC vs BSC, see Table 20 (page 85). The study is quality assessed in Table 21 (page 86) and Table 22 (page 87). The study by Mittmann and colleagues was a trial-based cost-effectiveness analysis based on the CO.17 study; the CO.17 study is also included in the clinical effectiveness review see Section 4.2.1.4.2 (page 49).

Table 20. Summary of cost-effectiveness analyses of CET+BSC

	Mittmann et al (2009)(8)
Study purpose	To investigate the cost-effectiveness of cetuximab in mCRC
Country setting	Canada
Base-year prices	2007
Intervention/ comparator	Cetuximab vs BSC
Line of treatment	Third-line
Study type	Trial-based CEA; CO.17 study
Model duration / cycle length	18-19 months
Number of health states	Not applicable
Study group	Participants in the CO.17 study; 572 patients with chemorefractory colorectal cancer
Perspective	Payer perspective; Canadian government
Discount rate p.a.	Not used
Source of funding	Funding for the CO.17 study was provided by NCIC CTG; AGIGT, B-MS and ImClone Systems
Base case findings	**For all patients**, the incremental cost with cetuximab compared with BSC was CAN$23,969. The ICER was CAN$199,742 per LYG (95% CI = CAN$125,973 to CAN$652,492 per LYG), and the incremental cost-utility ratio was CAN$299,613 per QALY gained (95% CI = CAN$125,973 to CAN$898,201 per QALY gained). **For patients with KRAS WT tumours**, the incremental cost with cetuximab was $33,617 and ICER was CAN$120,061 per LYG (95%CI = CAN$88, 679 to CAN$207,075 per LYG), The incremental cost-utility ratio was CAN$186,761 per QALY gained (95% CI = CAN$130,326 to CAN$334,940 per QALY gained).
Sensitivity analyses	A sensitivity analysis was performed on every cost, resource and effectiveness variable. The ICERs were most sensitive to changes in the cost of cetuximab and patient survival.

Variable	Range	ICER over range, CAN$/LYG
Entire study population		
Cost of CET (base case CAN$3.24/kg)	CAN$2.94–CAN$6.73/kg	188,734–384,823
OS with CET (base case = 7.7 mths [0.64 yr])	6.2 mths (0.52 yr)–9.2 mths (0.77 yr)	166,451–249.677
KRAS WT patients		
Cost of CET (base case CAN$3.24/kg)	CAN$2.94–CAN$6.73/kg	112,939–228,591
OS with CET (base case = 9.5 mths [0.79 yr])	7.6 mths (0.63 yr)–11.4 mths (0.95 yr)	100,051–150,076

AGIGT, Australasian Gastrointestinal Trials Group; B-MS, Bristol-Myers Squibb; BSC, best supportive care; CAN, Canadian; CEA, cost-effectiveness ratio; CI, confidence interval; ICER, incremental cost effectiveness ratio; LYG, life years gained; mCRC, metastatic colorectal cancer; NHS, National Health Service; p.a., per annum; QALY, quality-adjusted life year

Table 21. Summary of quality assessment: Mittmann and colleagues using critical appraisal checklist from Evers and colleagues(62)

	Item	Yes / No
1	Is the study population clearly described?	Yes. The results of all study patients from the CO17 study were used in this analysis: a total of 572 patients with chemorefractory colorectal cancer all had received prior chemotherapy with a fluoropyrimidine; 98% of patients had received prior treatment with oxaliplatin and 96% had received prior treatment with irinotecan.
2	Are competing alternatives clearly described?	Yes. The study prospectively evaluated the cost effectiveness of cetuximab when given in addition to BSC.
3	Is a well-defined research question posed in answerable form?	Yes. Cetuximab+BSC vs BSC for patients with chemorefractory colorectal cancer
4	Is the economic study design appropriate to the stated objective?	Yes. A trial-based cost effectiveness analysis
5	Is the chosen time horizon appropriate to include relevant costs and consequences?	Yes. The time horizon of the analysis was the duration of the clinical trial (i.e. 18–19 months) because more than 77% of the patients on cetuximab and 82% of those on best supportive care alone had died by the end of the collection period.
6	Is the actual perspective chosen appropriate?	Yes. The study was calculated from a payer perspective; the Canadian government.
7	Are all important and relevant costs for each alternative identified?	Yes. Most main categories of cost were captured (drug; outpatient visits; hospitalisation and surgical procedures; serious adverse events; laboratory tests and diagnostic procedures). KRAS testing was not however included.
8	Are all costs measured appropriately in physical units?	Yes. For instance the total dosage of cetuximab used by each patient in the trial was the basis for drug cost calculations.
9	Are costs valued appropriately?	Yes. For instance cetuximab drug cost/mg was the median value in the countries that were reviewed by the Patented Medicines Prices Review Board.
10	Are all important and relevant outcomes for each alternative identified?	Yes.
11	Are all outcomes measured	Yes. Treatment benefit was defined in terms of

	appropriately?	mean survival gain after random assignment Self reported HUI3 was prospectively collected to assess preference-based measures of health status throughout the study (baseline, Week 4, Week 8, Week 16 and Week 24 after random assignment)
12	Are outcomes valued appropriately?	Yes; quality-adjusted life years
13	Is an incremental analysis of costs and outcomes of alternatives performed?	Yes and subjected to sensitivity analysis
14	Are all future costs and outcomes discounted appropriately?	No. No discounting appears to have been done.
15	Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	Yes. One-way deterministic sensitivity analyses to test the robustness of the incremental ratios were performed on every cost, resource and effectiveness variable. Uncertainty surrounding the estimates of cost-effectiveness was illustrated by means of cost effectiveness acceptability curves.
16	Do the conclusions follow from the data reported?	Yes. The ICERs were acknowledged to be "high" which is consistent with the ICERs reported.
17	Does the study discuss the generalisability of the results to other settings and patient/ client groups?	Yes. The authors state that the results may not be generalisable to all patients under routine care for advanced colorectal cancer.
18	Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	Funding for the CO.17 study was provided by National Cancer Institute of Canada Clinical Trials Group; Australasian Gastrointestinal Trials Group, Bristol-Myers Squibb and ImClone Systems.
19	Are ethical and distributional issues discussed appropriately?	Yes. Fully explored in discussion section.

Table 22. Summary of quality assessment: Mittmann and colleagues using critical appraisal checklist from Drummond and colleagues(63)

Item	Critical Appraisal	Reviewer Comment
Is there a well-defined question?	✓	Cetuximab+BSC vs BSC for patients with chemorefractory colorectal cancer. . Whole population and KRAS WT analysed.

Item	Critical Appraisal	Reviewer Comment
Is there a clear description of alternatives (i.e. who did what to whom, where, and how often)?	✓	Patients in the CO17 study, cetuximab vs BSC in patients with chemorefractory colorectal cancer.
Has the correct patient group / population of interest been clearly stated?	✓	Yes. The study prospectively evaluated the cost effectiveness of cetuximab when given in addition to BSC.
Is the correct comparator used?	✓	BSC, reflective of current standard of care
Is the study type reasonable?	✓	Trial-based economic evaluation.
Is the perspective of the analysis clearly stated?	✓	Healthcare payer perspective – Canadian government
Is the perspective employed appropriate?	✓	Costs and benefits are appropriate with the perspective.
Is effectiveness of the intervention established?	✓	The CO.17 study population demonstrated a clinically and statistically significant overall survival advantage for cetuximab in chemorefractory colorectal cancer patients (median survival 6.1 months vs 4.6 months; HR for death = 0.77; p=0.005). The survival advantage was even greater in the subset of patients with KRAS WT status (median OS for cetuximab vs BSC 9.5 months vs 4.8 months; HR for death 0.55; p<0.001).
Has a lifetime horizon been used for analysis, if not has a shorter time horizon been justified?	✓	The time horizon of the study was the duration of the clinical trial (i.e. 18–19 months) because more than 77% of the patients on cetuximab and 82% of those on BSC alone had died by the end of the data collection period. Median survival time in the study was less than one year.
Are the costs and consequences consistent with the perspective employed?	✓	The main categories of cost were: drugs; outpatient visits; hospitalisation and surgical procedures; serious adverse events; laboratory tests and diagnostic procedures. This is consistent with the health care payer perspective.
Is differential timing considered?	X	No. No discounting appears to have been done.
Is incremental analysis performed?	✓	Yes.

Item	Critical Appraisal	Reviewer Comment
Is sensitivity analysis undertaken and presented clearly?	✓	One-way deterministic sensitivity analyses were performed and presented in Table 20.

The analysis by Mittmann and colleagues(8) was based on the CO.17 study; a Phase III, multicentre, open-label, randomised study(45) in which resource utilisation and utility values were collected prospectively for 572 patients with advanced CRC expressing EGFR who received cetuximab+BSC or BSC. Quality assessment suggests that this study was generally well conducted.

Mean improvement in OS for the entire study population was 0.12 years and mean improvement in quality-adjusted survival was 0.08 QALYs. The incremental cost with cetuximab (all patients) compared with BSC was CAN$23,969. The ICER for cetuximab+BSC vs BSC alone was CAN$199,742 per life-year gained (LYG) (95% CI = CAN$125,973 to CAN$652,492 per LYG) and the incremental cost-utility ratio was CAN$299,613 per QALY gained (95% CI = CAN$187,440 to CAN$898,201 per QALY gained).

For patients with KRAS WT status, the incremental cost with cetuximab was CAN$33,617 and mean gains in overall and quality-adjusted survival were 0.28 years and 0.18 QALYs, respectively. The ICER was CAN$120,061 per LYG (95% CI = CAN$88,679 to CAN$207,075 per LYG) and the incremental cost utility ratio was CAN$186,761 per QALY gained (95% CI = CAN$130,326 to CAN$334,940 per QALY gained). Updating this to 2011, converting to pounds sterling and using the current UK price of cetuximab we estimate this to be approximately equivalent to £101,000 per QALY.

5.1.4.1.2. Cetuximab+irinotecan vs BSC

There were three included studies addressing the cost-effectiveness of cetuximab+irinotecan vs BSC (see Table 23 [page 90]).

Table 23. Summary of cost-effectiveness analyses: CET+IRIN vs BSC

	Annemans et al (2007)(7)	Norum et al (2006)(9)	Starling et al (2007)(10)
Study purpose	To investigate the cost-effectiveness of cetuximab+irinotecan with current approaches to treatment	To compare the cost-effectiveness of including cetuximab in the treatment of mCRC in Norway	Cost-effectiveness of cetuximab+irinotecan vs BSC
Country setting	Belgium	Norway	UK
Base-year prices	Not reported, but study analysis based on carried out in 2007	2005	Not reported; study carried out in 2004
Intervention /comparator	Cetuximab+irinotecan vs current care[a]	Cetuximab+irinotecan vs BSC	Cetuximab+ irinotecan vs BSC
Line of treatment	Third-line	Third-line	Third-line
Study type	Trial-based CEA; BOND study	Model-based CEA	Trial-based CEA; Cunningham et al(57, 68)
Model duration / cycle length	Six-week and 12-week rule[b]	Unclear	Lifetime
Number of health states	Not applicable	Unclear but likely two states	Not applicable
Study group	Belgian participants from the BOND trial (n=218) vs eligible participants in the three largest study centres (Belgium, France and Italy) who fell outside the recruitment period (retrospective (n=66)	Patients with mCRC	mCRC patients with disease progression following irinotecan failure; patients in the BOND trial
Perspective	Healthcare perspective	Third-party payer	NHS perspective
Discount rate p.a.	Not reported	No discounting applied	Not reported

Source of funding	Not reported	A research grant from the Norwegian Cancer Union	Evaluation carried out on behalf of Merck KGaA
Base case findings	The ICER for cetuximab+irinotecan compared to current care administered according to the six-week rule was markedly better than that for the 12-week rule (€16,766 vs €40,273 per LYG)	Lifetime gain 1.7–2.0 months in addition to the 18–21 months expected lifetime standard chemotherapy. The total cost per patient treated with CET+IRIN in mCRC was calculated as €34,256 and €45,764 (depending on time on therapy), yielding a cost per LYG in the range between €205,536 and €323,040	The incremental cost per LYG with cetuximab and irinotecan therapy compared with BSC was £42,975. The incremental cost per QALY was £57,608.
Sensitivity analyses	In case of the six-week rule, the maximal ICER (worst-case scenario [defined as higher end survival and lowed end cost for the control group]) is €30,288 and for the 12-week rule €59,064.	A multivariate sensitivity analysis was conducted; the two factors having the major influence on the conclusions were the cost of CET (25% reduction in CET cost = €200,781–€313,823/LYG; 50% reduction in CET cost = €122,520–€195,106); and, the survival gain (25% improvement €164,429–€258,432; and, 50% improvement €137,024–€215,360/LYG).	Sensitivity analyses involving health outcome and cost variables. The cost-effectiveness of CET+IRIN was most sensitive to the survival adjustment factor: improvement [2.00] on base case [1.71] = £37,587; and, reduction [1.50] on base case [1.71] = £49,999.

BSC, best supportive care; CEA, cost-effectiveness analysis; ICER, incremental cost effectiveness ratio; LYG, life years gained; mCRC, metastatic colorectal cancer; p.a., per annum

[a]Current care was based on a retrospective review of treatment received by patients in the three largest BOND study centres (Belgium, France, Italy) who met the eligibility for inclusion in the BOND study but who fell outside the recruitment period for the study. 15% had received one prior line of chemotherapy, 77% at least two lines of prior chemotherapy for metastatic disease. Approximately 80% of these patients went on to receive chemotherapy, including capecitabine, 5-FU, raltitrexed and rechallenge with irinotecan or oxaliplatin.

[b]Two scenarios were considered in which cetuximab was discontinued at six weeks or 12 weeks if there was no tumour response at those time points

Of the three included studies evaluating cetuximab+irinotecan vs BSC one was a model-based cost-effectiveness analysis and the other two trial-based cost-effectiveness analyses.

Unfortunately none of the studies considered patients with KRAS WT status reducing their relevance to this assessment.

An analysis by Annemans and colleagues(7) compared the cost-effectiveness of cetuximab+irinotecan with current care in the treatment of EGFR-expressing mCRC that has failed irinotecan-containing therapy. Treatment outcomes and medical resource use data for patients receiving cetuximab+irinotecan from the BOND study (Phase III, multicentre, open-label, randomised study), were compared with those from a matched group of patients (current care). Current care was based on a retrospective review of treatment received by patients in the three largest BOND study centres (Belgium, France, Italy) who met the eligibility for inclusion in the BOND study but who fell outside the recruitment period for the study. Fifteen percent had received one prior line of chemotherapy, 77% at least two lines of prior chemotherapy for metastatic disease. Approximately 80% of these patients went on to receive chemotherapy, including capecitabine, 5-FU, raltitrexed and rechallenge with irinotecan or oxaliplatin. Annemans and colleagues considered two scenarios in which cetuximab was discontinued at six weeks or at 12 weeks if there was no tumour response at those time points. The ICERs were €17,000 per LYG and €40,000 per LYG for the six- and 12-week rule respectively vs current care. Sensitivity analyses showed an acceptable robustness of the results, with generally acceptable ICERs for the six-week rule, even in the worst case scenario for cetuximab (defined as higher end survival and lower end cost for the control group). The study concluded that cetuximab+irinotecan was cost-effective compared with current care when treatment was stopped in the case of non-response after six weeks.

Norum and colleagues(9) explored the cost-effectiveness of including cetuximab+irinotecan in the treatment of mCRC in Norway via a model-based cost-effectiveness analysis. Based on randomised trial data the increased lifetime gain was in the range between 1.7 and 2.0 months; in addition to the 18–21 months expected lifetime with standard chemotherapy. The median cost per patient treated was calculated as €34,256 to €45,764 yielding a cost per LYG in the range between €205,536 and €323,040. Sensitivity analysis documented the price of cetuximab and survival gain to be the major factors influencing the ICER. The efficacy data for this analysis were based on one RCT and single-arm Phase II or III studies; the randomised study did not measure OS as its primary endpoint and had a cross-over following progressive disease, whereby 50% of the patients crossed over from cetuximab alone to cetuximab+irinotecan. Sensitivity analysis documented price of cetuximab and survival gain to be the major factors influencing the ICER. The study, funded by the Norwegian Cancer Union, concluded that cetuximab+irinotecan was a promising but expensive treatment.

Starling and colleagues compared the cost-effectiveness of cetuximab+irinotecan vs BSC for the treatment of mCRC patients who have failed previous chemotherapy treatment from an NHS perspective.(10) The economic evaluation presented was a trial-based cost-effectiveness study of cetuximab+irinotecan vs BSC. Effectiveness estimates for the treatment groups were modelled from key clinical trials: Cunningham and colleagues (2004) compared cetuximab+irinotecan with cetuximab+BSC;(57) and, Cunningham and Colleagues (1998) compared irinotecan monotherapy in a secondline setting with supportive care.(68) The discounted life expectancy of patients treated with cetuximab+irinotecan was 0.91 years vs 0.47 for patients receiving BSC. Patients treated with cetuximab+irinotecan accumulated mean additional costs of £18,901 per patient relative to BSC, with £11,802 attributable to drug costs of cetuximab. The incremental cost per LYG with cetuximab+irinotecan vs BSC was £42,975. The incremental cost per QALY gained was £57,608. The study concluded that the incremental cost per LYG for cetuximab+irinotecan is relatively high compared with other interventions.

5.1.4.2. Cetuximab vs BSC and cetuximab+irinotecan vs BSC

There was one included study (Wong and Colleagues)(11) which evaluated the cost implications of treatment with sequential regimens that include chemotherapy and/or monoclonal antibodies. Nine possible treatment sequences were selected to reflect the sequential advances in CRC treatment. Of these, five were considered relevant to the current review considering cetuximab or cetuximab plus irinotecan third-line. The general characteristics of this study are set out in Table 24 (page 94).

Table 24. Summary of cost-effectiveness analyses: CET+BSC and CET+IRIN

	Wong et al(11)
Publication type	Full paper
Study purpose	To measure the cost implications of treatment with sequential regimens that include chemotherapy and/or monoclonal antibodies
Country setting	US
Base-year prices	2008
Intervention/ comparator	Nine possible treatment strategies selected to reflect the sequential advances in colorectal cancer treatment. Of these, five treatment sequences involving cetuximab third-line were considered relevant to this review[a]
Line of treatment	Sequences of relevance to the review consider third-line treatment
Study type	Model-based CEA
Model duration / cycle length	Unclear
Number of health states	Unclear but likely four states
Study group	A hypothetical cohort of 1,000 patients with newly diagnosed mCRC. Patients supposedly received up to three lines of treatment before supportive care and death. (As stated above only the five treatment sequences that considered cetuximab third-line were considered relevant to this review.)
Perspective	Third-party payer
Discount rate pa	Life expectancy[b] and costs at 3% per year
Source of funding	Three authors had acted as consultants for industry: Amgen sanofi-aventis, B-MS, Pfizer and Genentech; and one author had received a research grant from B-MS and was supported during the research by funding from the ASCO Young Investigator Award
Base case findings	The ICER per discounted life-year gained for adding the modern chemotherapy agents is approximately $100,000/DLY gained. The benefits of adding monoclonal antibodies come at higher costs ($170,000/DLY). The modest additional benefit of the most effective regimen (using both cetuximab and irinotecan in the third-line setting) generate even higher costs ($240,00/DLY).
Sensitivity analyses	One-way sensitivity analyses on progression, toxicity, drug cost and second progression demonstrated that the ICERs for sequences containing monoclonal antibodies are very high. The most significant changes in the ICERs occurred when the parameters for first-line treatment were changed.

B-MS, Bristol-Myers Squibb; DLY, discounted life year; ICER, incremental cost-effectiveness ratio; mCRC, metastatic colorectal cancer

[a] Sequence E: FOLFOX (first-line), Irinotecan (second-line), cetuximab (third-line); BSC (fourth line); Sequence F: FOLFOX and bevacizumab (first-line), Irinotecan (second-line), cetuximab (third-line); BSC (fourth line); Sequence G: FOLFIRI and bevacizumab (first-line), FOLFOX (second-line), cetuximab (third-line); BSC (fourth line); Sequence H: FOLFIRI and bevacizumab (first-line), FOLFOX (second-line), cetuximab+ irinotecan (third-line); BSC (fourth line); Sequence I: Sequence H: FOLFOX and bevacizumab (first-line), irinotecan (second-line), cetuximab+ irinotecan (third-line); BSC (fourth line). Sequences G and I were 2 of the 4 sequences used to calculate ICERs and perform sensitivity analysis

[b] Life expectancy used rather than quality-adjusted life expectancy because patients with life threatening diseases may choose treatments associated with a high risk of toxicity but low potential benefit. In addition, using life expectancy rather than utilities results in a conservative (lower) estimate for ICERs, because preference weights for patients with advanced cancer generally are <1.

Wong and colleagues(11) used a Markov model to evaluate a hypothetical cohort of 1,000 patients with newly diagnosed mCRC. Patients received up to three lines of treatment before supportive care and subsequent death. Data were obtained from published, multicentre, Phase III clinical trials. The study considered nine possible treatment sequences; of these, five were considered relevant to this review; i.e. drug of interest in the third-line setting (three sequences cetuximab+BSC and two sequences cetuximab+irinotecan). Based on drug costs alone, treatment that included new chemotherapeutic agents increased survival at an ICER of $100,000 per discounted life year (DLY). The addition of monoclonal antibodies improved survival at an ICER of >US$170,000 per DLY. The results were most sensitive to changes in the initial regimen. Even with significant improvements in clinical characteristics (efficacy and toxicity), treatment with the most effective regimens have very high ICERs. The authors concluded that treatment of mCRC with the most effective regimens came at very high incremental costs.

Of the three abstracts identified in the review, one (Wei and colleagues) examined the cost-effectiveness of cetuximab use among elderly mCRC patients.(66) Despite further information being requested from the authors none was received. It should be noted that the title of the abstract suggests the analysis was undertaken in an elderly patient population.(66) In the patients with mCRC, the incremental cost per QALY was $336,218 for cetuximab, and $318,609 for cetuximab+irinotecan, in comparison with BSC. PSA demonstrated that BSC is more cost-effective than cetuximab treatments until the threshold of willingness-to-pay is raised up to $240,000. The authors conclude that cetuximab is not cost-effective, either in monotherapy or in combination with irinotecan, as the cost-effectiveness ratios are far beyond the accepted threshold of $50,000 / QALY gained.(66)

5.1.4.3. KRAS testing with cetuximab treatment

Mittmann and colleagues concluded that restricting cetuximab to patients with KRAS WT status reduced the ICER resulting in a more efficient use of healthcare resources. However, Mittmann and colleagues also note that as the KRAS WT patient group had a greater survival gain with cetuximab vs BSC (3–4 months = 0.25–0.33 years) compared with the overall group (1.5 months = 0.13 years), the drug cost was also greater in the group with KRAS WT status because cetuximab was used for a longer time. However, the ICER was still high for the group with KRAS WT status (CAN$120,061/LYG and CAN$189,761 per QALY gained), and would generally be considered unfavourable. The authors hypothesise that to achieve a generally accepted level of cost-effectiveness, the survival gain would need to be in the order of six to eight months.

One of the abstracts identified (Carlson and colleagues) examined the cost-utility of using KRAS mutation testing prior to initiating monotherapy for patients with mCRC from a US payer

perspective.(64) Although further information was requested none was received and more detailed assessment was not possible. It is worth noting, however, that the results suggest that the use of KRAS testing to select patients for cetuximab treatment in mCRC can reduce costs (US$10,037) with a negligible impact on QALYs compared to using cetuximab for all patients.(64)

5.1.4.4. Panitumumab+BSC vs BSC

Graham and colleagues assessed the cost-effectiveness of panitumumab+BSC compared with BSC alone in chemorefractory mCRC patients with KRAS WT status in the Netherlands.(65) In the base case analysis, the ICERs for mCRC patients with KRAS WT status receiving panitumumab+BSC vs BSC alone were €51,314 per life year gained and €59,440 per QALY gained. Univariate sensitivity analysis analyses and PSA showed the results to be robust to assumptions around input parameters. We requested more information on this abstract from the authors, but none was received to allow a more detailed assessment of the study for inclusion. Interestingly despite a number of Amgen-linked authors, no mention was made of this abstract in Amgen's submission.

No other studies looking at the cost-effectiveness of panitumumab in the relevant patient population were found in the literature review.

5.1.4.5. Bevacizumab + non-oxaliplatin containing regimens

No studies looking at the cost-effectiveness of bevacizumab in the relevant patient population were found in the literature review.

5.1.4.6. Conclusions

There were five included studies in the review that considered cetuximab or cetuximab+irinotecan in third-line therapy. In addition, three abstracts were identified for which we received no further information; of these, one considered the cost-effectiveness of KRAS testing prior to cetuximab treatment,(64) one considered the cost-effectiveness of cetuximab (mono- and combination therapy),(66) and one considered panitumumab in third-line therapy.(65)

Of the full papers, Annemans and colleagues concluded that, in comparison with BSC, cetuximab was a cost-effective treatment option in one of the scenarios tested (six-week rule; i.e. cetuximab was discontinued at six weeks if there was no tumour response at that time point).(7) The other studies concluded that although clinically effective cetuximab is an expensive intervention.(8-11, 46, 64) The study by Wong and colleagues which evaluated treatment strategies that included one, two, three or four therapies, concluded that in general the treatment of mCRC with the most effective regimens came at very high incremental costs.(11)

Of the identified studies in the review the study by Mittmann and colleagues was the only published full paper to consider mCRC patients with KRAS WT status. Mittmann and colleagues concluded that although the ICER for cetuximab over BSC in mCRC patients was high and sensitive to drug cost it was lower when analysis was limited to patients with KRAS WT tumours.(8) We consider this in greater detail and in comparison to the PenTAG cost-effectiveness model in Section 7 (p134). In addition results from a study by Carlson and colleagues also suggest that the use of KRAS testing to select patients for cetuximab treatment in mCRC can reduce costs with a negligible impact on QALYs compared to using cetuximab for all patients.(64)

One abstract, Graham and colleagues, identified in the review found panitumumab to be a cost-effective treatment option in mCRC patients with KRAS WT status. However, no further information was made available for analysis.

Most of the available studies were supported by grants from Industry. In some cases the cost-effectiveness studies received independent funding; for example, Norum and colleagues,(9) yet many of the RCTs on which they were based had received funding, either in full or in part, from Industry.

6. Assessment of industry submissions to NICE

6.1. Introduction

Three manufacturer submissions were potentially available for this MTA. However, only one full economic model was submitted; by Merck Serono for cetuximab. Roche submitted some basic cost calculations in their report for a comparison between bevacizumab+FOLFIRI and cetuximab+FOLFIRI, while Amgen did not provide any details of a cost-effectiveness model, nor make any comment upon the likely cost-effectiveness of panitumumab. In this section the full economic model submitted by Merck Serono, the cost calculations presented by Roche and the trial analysis submitted by Amgen are critiqued.

6.2. Industry submission critique 1: Merck Serono, cetuximab

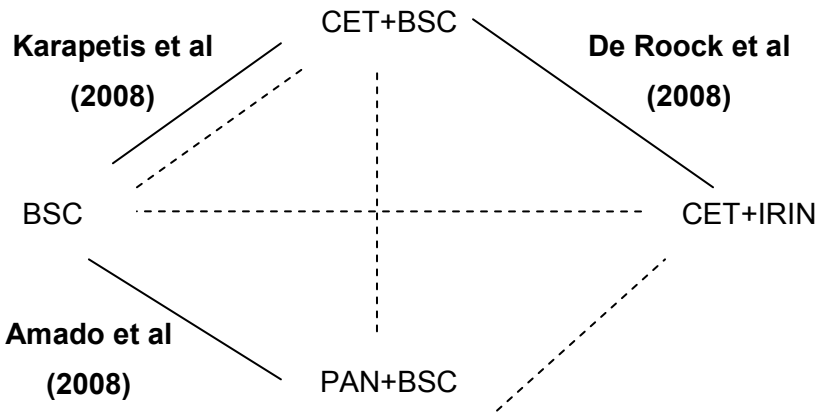
6.2.1. The decision problem: cetuximab

Merck Serono restrict the evaluation of cetuximab to third- and subsequent lines of treatment. Bevacizumab is disregarded by Merck Serono as an inappropriate treatment comparator for cetuximab due to the lack of published clinical data on the effectiveness of bevacizumab for mCRC patients with KRAS WT status in third-line treatment. In summary, Merck Serono report estimates of cost-effectiveness for the following four comparisons:

- Cetuximab+BSC vs BSC
- Cetuximab+irinotecan vs BSC
- Cetuximab+BSC vs panitumumab+BSC
- Cetuximab+irinotecan vs panitumumab+BSC

There are three points of interest relating to these comparisons. First, the pairwise cost-effectiveness comparisons are selective in the sense that several relevant comparisons, while possible, are not presented. Figure 3 (page 99) shows the data available to Merck Serono (the bold lines) and cost-effectiveness comparisons they have undertaken (the dashed lines). They have not compared cetuximab+irinotecan with cetuximab+BSC despite the data being available.

Figure 3. Diagram of the available data and the cost-effectiveness comparisons modelled by Merck Serono



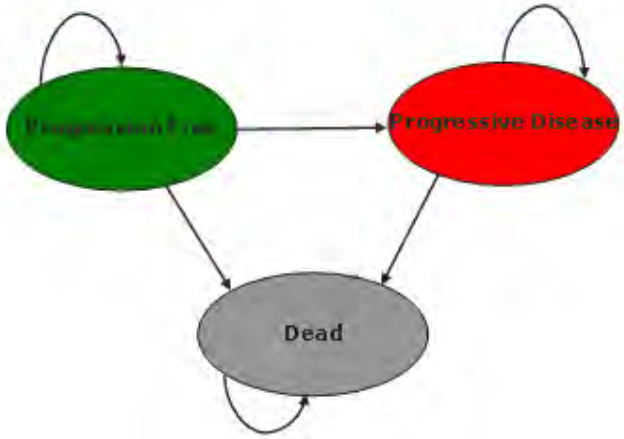
Bold lines represent published effectiveness data, dashed lines represent the cost-effectiveness comparisons made by Merck Serono.

Second, depending on the active comparator arm, the BSC arm is modelled slightly differently (hence post hoc incremental analysis could not be undertaken by the Assessment Group). This difference in the modelling of the BSC arms appears to depend on data availability and flexibility in modelling and is discussed in Section 6.2.10 (page 120). Third, Merck Serono only assess cost-effectiveness in third-line treatment and do not consider the second-line scenario which the scope of this guidance also covers (see Section 6.2.4, page 102).

6.2.2. Overview of model design: cetuximab

A three-state Markov model, with health states defined as progression free, progressed disease (PD) and death is used by Merck Serono to compare BSC with cetuximab+BSC and cetuximab+irinotecan in third-line treatment for mCRC patients with KRAS WT status (Figure 4, [page 100] [taken directly from Merck Serono's submission]). Treatment-specific utilities are assigned to the progression free and PD states (discussed further in Section 6.2.6.6 [page 109]). The costs associated with KRAS testing, drug acquisition and administration, BSC and AEs are accounted for in the model (discussed further in Section 6.2.6 [page 103]). Merck Serono state that all patients in the progression free state are assumed to receive active treatment while those in the PD state receive BSC only (see page 94, Meck Serono's submission). As will be discussed in Section 6.2.6.1 (page 103), this is not how the base case analysis is modelled and so the reported base case ICERs are misleading.

Figure 4. Three-state Markov model used by Merck Serono [see page 94, Merck Serono's submission]



6.2.3. Summary of results: cetuximab

The base case results are reproduced from the Merck Serono submission Table 25 (below) and Table 26 (page 101) for cetuximab+BSC vs BSC and cetuximab+irinotecan vs BSC, respectively. Merck Serono show that the biggest cost component for cetuximab+BSC and cetuximab+irinotecan arms is the drug acquisition costs, followed by the BSC and drug administration costs. The QALYs gained for cetuximab+BSC are similar between the PF and PD health states. As is also the case for cetuximab+irinotecan. Merck Serono conducted a PSA of their base case assumptions. They report that the probability that cetuximab+BSC is cost-effective compared to BSC is 0.1% at a willingness to pay of £30,000 per QALY gained and 65% at willingness-to-pay of £50,000 per QALY gained. Merck Serono report a 16% probability that cetuximab+irinotecan is cost-effective compared to BSC at a willingness-to-pay of £30,000 per QALY gained, with a probability of 68% of cetuximab+irinotecan being cost-effective at a willingness-to-pay of £50,000 per QALY gained. Merck Serono argue that the End of Life (EoL) criteria are appropriate for both cetuximab+BSC and cetuximab+irinotecan.

Table 25. Base case results from Merck Serono for CET+BSCvs BSC[a]

Comparators	Total costs	Total LYG	Total QALY	Inc. costs	Inc. LYG	Inc. QALY	ICER £/QALY
BSC	£7,580	0.512	0.359				
CET+BSC	£21,836	0.829	0.662	£14,256	0.317	0.303	£47,095

BSC, best supportive care; CET, cetuximab; ICER, incremental cost-effectiveness ratio; Inc., incremental; LYG, life years gained; QALY, quality-adjusted life year

[a]Taken from Merck's Excel spreadsheet

Table 26. Base case results from Merck Serono for CET+IRIN vs BSC[a]

Comparators	Total costs	Total LYG	Total QALY	Inc. costs	Inc. LYG	Inc. QALY	ICER £/QALY
BSC	£7,947	0.547	0.391				
CET+irin	£37,248	1.325	1.059	£29,301	0.779	0.68	£43,887

BSC, best supportive care; CET, cetuximab; ICER, incremental cost-effectiveness ratio; Inc., incremental; irin, irinotecan; LYG, life years gained; QALY, quality-adjusted life year

[a]Taken from Merck's Excel spreadsheet

Merck Serono have followed NICE's reference case as far as is possible given the evidence limitations. A NHS and PSS perspective has been taken, with costs and outcomes discounted at an annual rate of 3.5% (see Table 27, page 101). The only exception is for the health-related utility values for which HUI3 not EQ-5D data were used. The impact of this on the results is unknown.

Sensitivity analyses suggest that the important drivers for the cost-effectiveness analysis are the cetuximab acquisition and administration costs, the utility values assigned to progression free and PD, and the cost of BSC. In Section 6.2.6 (page 103) a number of uncertainties regarding the cetuximab administration and BSC costs, and the utilities used in the Merck Serono model are discussed. Furthermore, Merck Serono did not assess the sensitivity of the model to the effectiveness data.

Table 27. NICE reference case and the Merck Serono model

Element	NICE reference case(69)	Merck Serono model
Perspective on costs	NHS & PSS	☑
Perspective on outcomes	All health effects on individuals	☑
Type of economic evaluation	Cost-effectiveness	☑ Cost-utility
Synthesis of evidence on outcomes	Based on systematic review	☑ Except that data relating to cetuximab+irinotecan vs cetuximab+BSC(De Roock et al(12)) are not from a RCT and is of questionable quality
Measure of health effects	QALYs, EQ-5D preferred measure of HRQoL	☑ QALYs used, but utilities based on HUI3.
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	☑ Reported directly by patients. Valuation based on Canadian public preferences(8)
Discount rate	Annual rate of 3.5% for costs and health effects	☑

Equity weighting	Same QALY weight regardless of other characteristics of the individuals receiving the health benefit	☑

BSC, best supportive care; cetux, cetuximab; EQ-5D, EuroQol 5-dimension; HRQoL, health-related quality of life; HUI, health utility index; irin, irinotecan; NHS, National Health Service; PSS, personal social services; QALY, quality adjusted life year; RCT, randomised controlled trial

6.2.4. Line of treatment: cetuximab

Merck Serono argues that they only consider third-line use of cetuximab in their submission because this is: *'based on clinical need, the strength of the evidence, expert opinion and current usage'* (page 21, Merck Serono's submission). Accordingly, the studies informing estimates of effectiveness in the model mainly involve patients who have previously received two or more lines of treatment. The EPIC study(70-72) is available to model second-line treatment comparing cetuximab+irinotecan with irinotecan. Merck Serono argues that irinotecan is an appropriate second-line treatment comparator, and our clinical expert agrees that it is part of current practice in second-line treatment. There are, however, a number of issues related to the EPIC study: first, 46.9% of patients randomised to irinotecan crossed-over to receive cetuximab at some stage, and; second, KRAS status is not known for the participants. It is understood that the manufacturer did not have access to the IPD and could not address this accurately, however it would have been possible for some assumptions to have been made to find some indication of the likely cost-effectiveness of cetuximab+irinotecan vs irinotecan in second-line therapy.

6.2.5. PenTAG corrections for errors: cetuximab

In the rest of this section all ICERs reported from the Merck Serono model have been corrected for the following three logical errors identified in Merck Serono's Excel spreadsheet:

- Cetuximab+irinotecan cost of administration: the cost of £180 is modelled when Merck Serono report in their submission that this calue should be £196
- Incorrect proportion in progression free state at Cycle 0 for BSC arm in comparison with cetuximab+BSC
- Cost of non-serious AE in BSC arm: cost of £200 is modelled when Merck Serono report in their submission that this value should be £174.

Note that correction for these errors leads to slightly increased base case ICERs compared to those reported by Merck Serono. From £47,095 to £48,238 per QALY for cetuximab+BSC vs BSC and from £43,887 to £44,429 per QALY for cetuximab+irinotecan vs BSC.

6.2.6. Critique of Merck Serono's model for cetuximab

In this section we detail our main concerns with the assumptions made in the model submitted by Merck Serono. Where possible we present the impact on the ICERs of alternative assumptions. In Section 6.2.7 (page 112) the cumulative effect of different assumptions on Merck's base case results are presented.

6.2.6.1. Drug acquisition costs and dose intensity: cetuximab

Merck Serono assumes a guaranteed NHS price of £136.50 for 20 ml (100 mg) vial for cetuximab'. We believe that this price is that which would be available nationally. Merck assume the cost for generic irinotecan of £120.30 for 5 ml vial (100 mg) from BNF 60, September 2010.(73)

The manufacturer states that dose intensity is included in the model and present details in Table 81 of their submission for dose intensity of cetuximab+BSC, cetuximab+irinotecan and irinotecan (see Table 28, page 103). However, examination of the Excel model indicates that only the calculations for the cost of cetuximab include consideration of dose intensity. The value used in the Excel model is 94%, but the value reportedly used in the submission is 98% (*'based on CO.17 study'* [page 110, Merck Serono's submission]). Thus, for cetuximab+BSC, lower dose intensity is assumed in the model than specified in the report. For irinotecan 100% dose intensity is modelled even though the report indicates a dose intensity of 90% is modelled. Adjusting the drug costs for these discrepancies has negligible impact on the PenTAG corrected base case ICERs.

Table 28. Reported and modelled dose intensities in Merck Serono submission

Treatment	Reported	Modelled	Impact
CET (in CET+BSC)	98%	94%	Negligible
CET (in CET+IRIN)	94%	94%	Negligible
IRIN	90%	100%	Negligible

BSC, best supportive care; CET, cetuximab; IRIN, irinotecan

Merck Serono assume vial wastage for cetuximab in their base case analysis, but do not assume wastage for treatment with irinotecan, instead assuming vial sharing. Although inconsistent, this is unlikely to have much of an impact n the ICERs, as the cost of irinotecan is very small relative to the cost of cetuximab; however, vial sharing of irinotecan does not happen in the UK.

6.2.6.2. Administration costs: cetuximab

Merck Serono assume that administration takes place in the daycare setting, with a cost of £180 for cetuximab+BSC for „Deliver simple parenteral chemotherapy at first attendance' from the NHS Reference Costs for 2009–09,(74) and £196 for cetuximab+irinotecan (the average of £180 for delivery of cetuximab+BSC and £213 „Deliver more complex chemotherapy at first attendance').

The costs of administration of cetuximab used by Merck Serono could be too low as they refer to drugs at first delivery, whereas „delivery of subsequent elements of chemo cycle' is likely to be more relevant. This would incur costs of £227 per administration at 2008–09 prices. Note that this is the cost of drug administration assumed by Roche in their cost calculations for bevacizumab (see Section 6.3.3, page 126). Merck Serono do not account for pharmacy preparation costs in their model. In the PenTAG model we assume a pharmacy preparation cost of £15 per infusion informed by data from a pharmacist at the Royal Devon and Exeter Hospital (see Section 7.1.3.3.6, page 165).(75) Although these pharmacy preparation costs are small, they are incurred for every administration. Thus, assuming an administration cost of £242 (including pharmacy preparation costs: £227+£15) for cetuximab+BSC at 2008–09 costs (consistent with Merck's model) increases the ICER slightly (see Table 29, page 104).

Table 29. Assumptions on administration costs (including pharmacy preparation) per infusion

Treatment	Cost used by Merck	Alternative cost value	Impact
CET (in CET+BSC)	£180	£242	Alternative cost value increase ICER from £43,238 to £50,624 per QALY gained
CET (in CET+IRIN)	£196	£242 per CET infusion; £128.50 per IRIN infusion	Alternative cost value increases ICER from £44,429 to £47,624 per QALY gained

BSC, best supportive care; CET, cetuximab; IRIN, irinotecan

It is difficult to assess the administration costs of irinotecan in addition to cetuximab. In the PenTAG model a best estimate of the average cost of no additional administration time being required (£0) and the same administration time as that for cetuximab being required (£227) is

assumed (see Section 7.1.3.3.5, page 165). This leads to an administration cost, including pharmacy preparation time, for irinotecan of £128.50 per infusion (£113.50 + £15). Using this cost estimate, the ICER for cetuximab+irinotecan vs BSC increases slightly (see Table 29, page 104).

Within their sensitivity analyses Merck Serono examine the impact of assuming different dosing regimens for irinotecan for the cetuximab+irinotecan vs BSC comparison. It is reported that the ICER increases when assuming 350 mg/m^2 administration every three weeks, and decreases assuming 125 mg/m^2 every three weeks. However, the base case analysis assuming that administration of irinotecan is every two weeks at a dose of 180 mg/m^2 nationally is reasonable.

6.2.6.3. Treatment duration: cetuximab

In the Excel model, for the base case analyses, drug acquisition and administration costs are modelled for all patients in the progression free state until Week 13 for cetuximab+BSC and Week 24 for cetuximab+irinotecan. At these times approximately 60% of patients are still in the progression free state for all active treatments. After these times, no drug acquisition or administration costs are assumed for patients but they remain in the progression free health state. In the Excel model the 13- and 24-week cut-offs imply an estimated mean time on drug treatment of 11.4 weeks and 19.4 weeks for cetuximab+BSC and cetuximab+irinotecan, respectively. This is our main concern with Merck Serono's model.

In their report, Merck Serono give no explanation for the value of these cut-offs for cetuximab (+BSC or irinotecan). Instead they state in their list of model assumptions (Table 59 [page 96], Merck Serono's submission) that: *'The model is adjusted with clinical data related to the mean number of weeks on chemotherapy'*. However, Merck Serono do not report the mean number of weeks on treatment for cetuximab+BSC or cetuximab+irinotecan in their submission nor do they provide sufficient detail concerning the proper justification for these very important assumptions. Their rationale for this assumption, cited in their report is*: 'The model offers the option to adjust the number of chemotherapy cycles in order to 1) generate the mean number of cycles corresponding to the estimated mean number of doses in clinical studies, 2) ensure that the chemotherapy costs stay within plausible ranges in the probabilistic sensitivity analysis when the parameters of the progression-free survival can be sampled from a distribution and generate an unrealistic amount of time spent on active treatment.'* (page 97, Merck Serono's submission).*'*

We asked Merck Serono to clarify their assumptions regarding mean time on treatment as it was not sufficiently reported in their submission. In their response (see Appendix 11),they state that only the median time on treatment for the total cetuximab+BSC population (KRAS WT and KRAS mutant status) is available, and this is 8.1 weeks.(45) It is reported in the panitumumab+BSC vs

BSC study by Amado and colleagues,(4) that a mean of 10 panitumumab infusions was received by patients with KRAS WT status. For all patients (KRAS WT and KRAS mutant status combined) the mean number of panitumumab infusions is reported to be seven. Using these two sources of data from the panitumumab+BSC vs BSC study. Merck Serono multiplies the median 8.1 weeks on cetuximab for all patients by 10/7 to estimate the mean number of infusions on cetuximab treatment for patients with KRAS WT status. This gives a value of 11.57 infusions for patients with KRAS WT status. Merck Serono then adjust the mean number of weeks on treatment in the model to be 11.4 which corresponds: *'as close as possible to 11.57'* assuming one infusion per week. This approach assumes that the relative difference in the *mean number of infusions* for patients with KRAS WT status and all patients in panitumumab+BSC is the same as the: *„median weeks on treatment'* for patients with KRAS WT status and all patients. First, there is no evidence to suggest that the relative difference between the mean number of infusions for patients KRAS WT status and all patients in panitumumab+BSC can be assumed for cetuximab+BSC. Second, there is no evidence to suggest that the relative difference in means is the same as the relative difference in medians. Furthermore, the median 8.1 weeks on cetuximab treatment from Jonker and colleagues is very similar to the median PFS in Jonker and colleagues (8.2 weeks). This suggests but does not prove that treatment is received throughout the progression free state, which our clinical expert believes is reasonable. For more information on this see Section 7.1.3.1.4.3 (page 150).

For cetuximab+irinotecan, Merck Serono state in their response to our request that in the cetuximab+irinotecan vs cetuximab+BSC study (BOND) the mean number of infusions for all patients (KRAS WT and KRAS mutant status combined) receiving cetuximab+BSC and cetuximab+irinotecan was seven and 18, respectively. In fact, these figures refer to the median, not mean, number of infusions.(57) Second, it is not clear how this mean of 18 infusions was then translated by Merck Serono into their assumed mean 19.4 weeks of treatment for cetuximab+irinotecan. Note again that, as for cetuximab+BSC, the trial data suggest that treatment duration is very similar to PFS. It is reported in BOND that median PFS for all patients on cetuximab+BSC is 6.5 weeks while the median number of infusions of cetuximab was seven, corresponding to seven weeks of treatment.(57) For more information on this see Section 7.1.3.1.4.3 (page150).

Merck Serono's assumption that drug treatment ceases at the cut-off times (of 13 and 24 weeks), even if patients have not progressed, has a large impact on the base case ICERs, as the costs associated with drug treatment are reduced, yet there is no impact on time to progression or death and therefore on QALYs. This contradicts another of Merck Serono's assumptions that: *'Patients in the progression free state are assumed to be on therapy whereas patients in the*

progressive disease health state are assumed to receive no active treatment' (see page 94, Merck Serono's submission*)*, Assuming that all patients continue to receive active treatment as long as they remain in the the progression free state increases the ICER substantially, as shown in Table 30 (page 107).

Table 30. Results from PenTAG's calculations using the model assuming treatment continues for all patients for the entire time in the progression free state

	CET+BSC vs BSC	CET+IRIN vs BSC
ICER (£/QALY)	**£75,417**	**£67,429**
Incr costs (£)	£22,289	£45,018
Incr QALYs	0.296	0.668
Total costs (CET+BSC/IRIN)	£29,868	£52,927
Total costs (BSC)	£7,580	£7,909
Total QALYs (CET+BSC/IRIN)	0.662	1.059
Total QALYs (BSC)	0.367	0.391

BSC, best supportive care; CET, cetuximab; incr, incremental; IRIN, irinotecan; QALYs, quality adjusted life-years

These ICERs are much larger than those reported by Merck Serono (£47,000 vs £75,417 per QALY gained for cetuximab+BSC vs BSC and £44,000 vs £67,429 per QALY gained for cetuximab+irinotecan vs BSC). The estimates in Table 30 are likely to be slight overestimates as some patients in the progression free state may discontinue active treatment for reasons other than disease progression. However, the trial data indicate that very few patients discontinue treatment due to AEs (for example, Jonker and colleagues report 11 patients (4%) receiving cetuximab+BSC withdrew to AEs).(45) Merck Serono themselves argue that: *'patient[s] dropping out of treatment are not doing so due to an injection site reaction but more probably due to non efficacious treatment. At this point patients are in PD'* (see Table 59 [page 96], Merck Serono's submission). Therefore the ICERs above are more likely to be closer to reality than those presented in Merck Serono's base case where it is assumed that treatment ceases for all patients at 13 or 24 weeks.

In Merck Serono's submission it is stated: *'Patients dropping out of active treatment are allocated to the progressive disease state'* (Table 59 [page 96], Merck Serono's submission). However, in Merck Serono's model patients remaining in the progression free state after stopping active treatment continue to receive the utilities for being in progression free, not those associated with PD as their assumption would indicate.

6.2.6.4. BSC costs: cetuximab

Merck Serono use a monthly value of £785 for BSC costs in their model. They cite Remak and Brazil for the source of this cost but do not provide the actual value extracted from Remak and Brazil.(14) It is therefore assumed that the cost of BSC of £675 is extracted (from Table 5, page 80 of Remak and Brazil). We believe that Merck Serono have made two errors in their use of the Remak and Brazil data. First, by the methods of inflating this value; and second, by their use of this value in both the progression free and PD health states. Inflating £675 from 2004 to 2008–09 costs using the Retail Price Index(76), as reported by Merck Serono, gives the value used by the manufacturer of £785. However, the manufacturer's inflating of the BSC costs from Remak and Brazil are incorrect as they assume the costs reported by Remak and Brazil are at 2004 prices, when in fact they are at 2000 prices.(14) Using Merck's method of inflating using the Retail Price Index from 2000 leads to a monthly cost of BSC of £856 (rather than £785). In addition to this, Merck Serono have used the incorrect index to inflate this value. They use the Retail Price Index as opposed to the Hospital and Community Health Service Index from Curtis(76) which is widely used in health technology assessment (HTA) economic analyses since it refers specifically to hospital and health service costs. Using the Hospital and Community Health Service Index and inflating the Remak and Brazil value of £675 from 2000 to 2008–09 gives a cost of £917, a 17% increase on the value used by Merck Serono. This increase in the cost of BSC leads to slight increases in the ICERs: £49,938 per QALY gained for cetuximab+BSC vs BSC, and £46,276 per QALY gained for cetuximab+irinotecan vs BSC (assuming PenTAG's corrections to Merck Serono's base case ICERs as reported in Section 6.2.5 [page 102]).

This value is not appropriate to use for both the progression-free and the progressed disease health states as Merck Serono do. Remak and Brazil(14) present costs for four periods of Stage IV breast cancer treatment: (1) active drug treatment, (2) follow-up after active treatment until disease progression, (3) active supportive care (ASC) after disease progression, and (4) EoL care. The value assumed to have been extracted by Merck Serono, £675, relates to ASC after disease progression. However, Merck Serono applys this value to all patients in all treatment arms regardless of whether they are in the progression free or PD health state. Remak and Brazil report the combined monthly cost for the progression free state (covering periods (1) and (2) above). This cost is £679, which is very similar to the cost of ASC Merck Serono use from Remak and Brazil £675 for the progression free state. However, the progression free state costs from Remak and Brazil included active treatment (including drugs specifically for breast cancer), and so is likely to be an overestimate of the BSC costs appropriate to the progression free state in the Merck Serono model, because this should reflect non-drug related costs. This will lead to the total costs of the BSC arms being overestimated with the consequence that the ICERs for

cetuximab+BSC vs BSC and cetuximab+irinotecan vs BSC are underestimated. Given these issues related to the BSC costs Merck Serono have used from Remak and Brazil, we believe that the BSC cost assumed by Merck Serono is an underestimate for the PD state, and an overestimate for the progression free state.

6.2.6.5. KRAS testing costs: cetuximab

Merck Serono only account for the KRAS costs associated with those patients who subsequently receive cetuximab; i.e. those who test KRAS WT. In practice, all patients considered for cetuximab will have a KRAS test, therefore it is appropriate that the cost of the KRAS test should also account for those patients tested but who are KRAS mutant. Previous cost-utility models for cetuximab have assumed a KRAS testing cost of £300,(31) However, data from the All Wales Molecular Genetics Laboratory suggests that the cost of a KRAS test is £160.(77) The real cost of KRAS testing (including the cost of those identified to be KRAS mutant) is likely to be £296 (£160/0.54) (see Section 7.1.3.3.1, page 159). Updating Merck's model with this assumption increases the ICER very slightly.

6.2.6.6. Utilities: cetuximab

Merck Serono use utilities from the cost-effectiveness analysis of CO.17 by Mittmann and colleagues cost-effectiveness analysis of CO.17 who report the analysis of HUI3 scores according to values taken from the CO.17 study and valued by the general Canadian population(8). As Merck Serono state, the utility analysis by Mittmann and colleagues are presented at baseline and 2, 8, 16 and 24 weeks after random assignment and are therefore not useful for the Merck Serono model where the health states are defined as progression free and progressed disease. Thus, Merck Serono have re-analysed the utility data from the CO.17 study by these health states. The re-analysis produces mean HUI values that are generally greater than those reported by Mittmann and colleagues (see Table 31).

Table 31. HUI values in the literature for mCRC

Article	Stage of disease	Treatment arm	Number patients	Utility values
Ramsey et al(78)	Stage IV	N/A	13	0.76−0.95
Mittmann et al(8)	Study baseline	CET+BSC	263	0.72
		BSC	260	0.71
	24 weeks from baseline	CET+BSC	82	0.77
		BSC	36	0.70
Merck Serono	Progression free state	CET+BSC	294	0.81
		BSC	170	0.75
	PD state	CET+BSC	83	0.79
		BSC	85	0.69

BSC, best supportive care; CET, cetuximab; N/A, not applicable; PD, progressive disease

Assessment of the CO.17 study indicates that at baseline all patients were progression free.(3, 45) Therefore we can assume that the baseline mean HUI values reported by Mittmann and colleagues could give some idea of the likely progression free utility values the manufacturer may obtain in their analysis (cetuximab+BSC utility = 0.72; BSC utility=0.71). However, the utility values the manufacturer reports are considerably greater for the progression free state (utility cetuximab+BSC=0.81, BSC utility = 0.75).

The number of patients included in the calculations of the utility values differs between the analysis by Mittmann and colleagues(8) and the manufacturer's re-analysis (see Table 31, page 110). There is no explanation as to why this has occurred. We asked Merck to clarify the population base for which their utility estimates are based. They reported that their utility estimates are restricted to patients with KRAS WT status (see Appendix 12). However, given the number of patients contributing to the utility estimates, it is unlikely that this is the case. The number of patients reported by Merck Serono (see Table 80 [page 110], Merck Serono's submission) states that; for example, 294 patients receiving BSC and 170 patients receiving cetuximab contribute to their re-analysis of utilities in the progression free health state. However, in Karapetis and colleagues it is reported that the total number of patients with KRAS WT status receiving BSC and receiving cetuximab+BSC is 113 and 117, respectively. By considering all patients (KRAS WT and KRAS mutant status combined), the mean utility for those receiving cetuximab could have been underestimated by Merck Serono, as patients with KRAs mutant status would not experience a treatment effect. It would be difficult to quantify this underestimation without access to the IPD. Moreover, it is highly unlikely that the utility values

used by Merck Serono are larger than would be expected in the absence of all sources of bias, as is now discussed.

The PD utility estimates from the analysis by Mittmann and colleagues and the Merck Serono re-analysis are based on a much lower number of patients than those for the progression free state (see Table 31, page 110). Furthermore, there is likely to be unequal drop-out between the treatment arms with those in the BSC arm more likely to drop-out because of a lack of treatment effect, mean that they progress more quickly and are perhaps less able to complete the questionnaire. In addition, the CO.17 study(45) is not blinded and so there is the potential for bias in the QoL measures. The unequaldrop-out and lack of blinding in the CO.17 study, could lead to overestimates of the utilities in both treatment arms. Placing these utility values in context, the HUI values from Ramsey and colleagues(78) are of a similar magnitude to, or even greater than, those reported by Merck Serono: 0.76 to 0.95 for Stage IV, depending on time since diagnosis, compared to 0.69 to 0.81 (see Table 31, page 110). However, Ramsey and colleagues note that the study design is likely to have excluded more severely ill patients, and are based on just 13 patients, therefore these values are likely to be overestimates. This seems probable when the EQ-5D UK norm is 0.73 for people aged ≥75 years.(79) EQ-5D values collected alongside the MABEL study for mCRC patients receiving cetuximab+irinotecan also suggest such high values: mean utility of 0.746.(10)

In the Merck Serono cost-utility model, although the utility data are from the cetuximab+BSC vs BSC study (CO.17), all active treatments are assumed to have utilities as reported for cetuximab+BSC. There is a concern here that irinotecan is a particularly toxic chemotherapy, therefore it would seem unreasonable to assume that the utility for cetuximab+BSC is equivalent to that for cetuximab+irinotecan. In fact our clinical expert agrees that quality of life is unlikely to be equivalent for cetuximab+BSC and cetuximab+irinotecan, therefore the utilities associated with cetuximab+irinotecan in the Merck Serono model are likely to be overestimates. Merck Serono's assumption of equivalent utilities leads to a more favourable ICER for cetuximab+irinotecan over any comparator but, in the absence of data, it is difficult to quantify the extent to which this is an overestimate.

As can be seen in Table 31 (page 110), the utility values calculated by Merck Serono associated with cetuximab+BSC are greater than those for BSC, regardless of the health state. Au and colleagues(47) found a similar pattern in their analysis of the EORTC QlQ-C30 data from CO.17: higher QoL with cetuximab than for BSC. For the progression free state this finding appears reasonable given that patients are more likely to be responding with cetuximab+BSC than with BSC and therefore have a greater QoL even though they are more likely to experience treatment-related AEs (see Section 4.2.1.7.1, page 71).

The PD utilities are also different between treatment arms with cetuximab+BSC utilities higher than BSC utilities. This is difficult to explain since it is assumed in Merck Serono's model that all progressed patients cease cetuximab+BSC, therefore they will no longer be responding to treatment. The magnitude of this difference in utility is difficult to explain. The mean utility value in the progression free state for those on cetuximab+BSC is 0.063 greater than those on BSC alone. In the PD state this difference is even greater: a difference of 0.097. This is inconsistent as patients are receiving the same care once in PD regardless of whether they received cetuximab+BSC or BSC alone in the progression free state. Given the possibilities for bias in the analysis of these data (lack of blinding, unequal drop-out and healthier patients more likely to complete the quality of life survey), it does not seem reasonable that QoL in PD should differ between the treatment arms. By assuming higher utilities in the PD state for those receiving cetuximab+BSC in the progression free state, greater total QALYs will be associated with cetuximab+BSC than with BSC.

As a sensitivity analysis, if the utility of 0.693 is assumed for both treatment arms in the PD state and leaving unchanged Merck Serono's utility assumptions in the progression free state, the following ICERs are obtained by PenTAG re-running Merck Serono's model:

- cetuximab+BSC vs BSC: £56,132 per QALY gained (vs £48,238 per QALY gained)
- cetuximab+irinotecan vs BSC: £49,233 per QALY gained (vs £44,439 per QALY gained)

It is worth noting that Merck Serono is aware that: *'There are uncertainties around whether the utilities are truly representative of likely quality of life when in progression free and PD states'* (page 136 [scenarios 3a and b], Merck Serono's submission), and the utilities used in both health states were found to be important drivers in their model. The trial contributing evidence to the utility estimates is open-label, which introduces the possibility of bias in favour of cetuximab+BSC for the QoL estimates, but is difficult to avoid.

6.2.7. Impact on the ICERs: cetuximab

In the above sections the impact on the PenTAG corrected base case ICERs have been assessed for the specific individual issues discussed. In this section, the simultaneous impacts of a number of the important assumptions on the ICER are presented. As can be seen in Table 32 (page 113) and Table 33 (page 114), the simultaneous adjustment of a number of the assumptions regarding the costs associated with treatment and care for patients with mCRC has quite a large impact on the PenTAG corrected base case ICERs: from £48,238 per QALY gained to £95,238 per QALY gained for cetuximab+BSC vs BSC and from £44,429 per QALY gained to

£83,215 per QALY gained for cetuximab+irinotecan vs BSC. However, removing Merck's cap on the mean duration of treatment and instead assuming that patients are treated throughout the progression free state has the greatest impact on the ICER (see Section 6.2.6.3, page 105).

Table 32. Impact of changes in assumption on the base case ICERs reported by Merck Serono: CET+BSC vs BSC

CET+BSC = vs BSC	ICER	Incr costs	Incr QALYs	Total costs		Total QALYs	
				CET+BSC	BSC	CET+BSC	BSC
Merck base case	£47,095	£14,256	0.303	£21,836	£7,580	0.662	0.359
PenTAG corrected base case[a]	£48,238	£14,256	0.296	£21,836	£7,580	0.662	0.367
Drug admin costs £242; BSC costs £917; KRAS test cost £296; treated throughout progression free state	£81,922	£24,211	0.296	£32,601	£8,390	0.662	0.367
Drug admin costs £242; BSC costs £917; KRAS test cost £296; treated throughout progression free state; PD utilities 0.693	£95,328	£24,211	0.254	£32,601	£8,390	0.621	0.367

BSC, best supportive care; CET, cetuximab; incr, incremental; ICER, incremental cost-effectiveness ratio; IRIN, irinotecan; PD, progressive disease; PF, progression free; QALYs, quality adjusted life-years

[a]see Section 6.2.5, page 102

Table 33. Impact of changes in assumption on the base case ICERs reported by Merck Serono: CET+IRIN vs BSC

CET+IRIN vs BSC	ICER	Incr costs	Incr QALYs	Total costs		Total QALYs	
				CET+IRIN	BSC	CET+IRIN	BSC
Merck base case	£43,887	£29,301	0.668	£37,248	£7,947	1.059	0.391
PenTAG corrected base case[a]	£44,429	£29,663	0.668	£37,571	£7,909	1.059	0.391
Drug admin costs £306; BSC costs £917; KRAS test cost £296; treated throughout progression free state	£75,015	£50,083	0.668	£58,857	£8,774	1.059	0.391
Drug admin costs £306; BSC costs £917; KRAS test cost £296; treated throughout progression free state; PD utilities 0.693	£83,125	£50,083	0.603	£58,857	£8,774	0.994	0.391

BSC, best supportive care; CET, cetuximab; incr, incremental; ICER, incremental cost-effectiveness ratio; IRIN, irinotecan; PD, progressive disease; PF, progression free; QALYs, quality adjusted life-years

[a]see Section 6.2.5, page 102

6.2.8. Effectiveness evidence: cetuximab

6.2.8.1. Karapetis and colleagues 2008 (CO.17)

Merck Serono use the IPD from the CO.17 study to inform time to disease progression and death for patients receiving cetuximab+BSC vs BSC. The data used are from the Karapetis and colleagues(3) retrospective analysis of the CO.17 study which stratifies by KRAS status (see also Section 4.2.1.4.2, page 49). Karapetis and colleagues present both HRs adjusted for patient characteristics for PFS and OS, as well as the unadjusted HRs (see Table 34, page 115). In the Merck Serono model, the unadjusted HRs are used. However, given that KRAS status is assessed retrospectively in Karapetis and colleagues and that KRAS status was not determined for all participants, there may be some selection bias in the study (even though the authors report that there were similarities between patient characteristics for those identified to be KRAS WT and those KRAS mutant). Therefore it would seem more reasonable for Merck Serono to have used the adjusted HRs, rather than the unadjusted HRs. The adjusted HRs from Karapetis and

colleagues(3) are less favourable to the effectiveness of cetuximab+BSC vs BSC (i.e. the adjusted HR is closer to one than the unadjusted HR) than Merck Serono suggest in their submission (Table 52 [page 76], Merck Serono's submission).

Table 34. Unadjusted and adjusted HRs (95% CIs) from Karapetis and colleagues(3)

	Unadjusted	Adjusted for potential prognostic factors
OS	0.55 (0.41, 0.74)	0.62 (0.44, 0.87)
PFS	0.40 (0.30, 0.54)	0.42 (0.30, 0.58)

OS, overall survival; PFS, progression free survival

6.2.8.2. De Roock and colleagues

Although details of the BOND trial(57) are presented throughout the submission by Merck Serono, the BOND trial only impacts upon their submission via De Roock and colleagues 2008.(12) De Roock and colleagues(12) is a retrospective analysis of cetuximab+BSC vs cetux+rin using data from four studies (BOND, EVEREST, SALVAGE and BABEL) based at four centres in Belgium, in which KRAS status has been retrospectively determined for a selection of patients. Note that the four studies included in De Roock and colleagues(12) did not distinguish KRAS status, therefore these studies are not covered in the clinical effectiveness systematic review (see Section 4, page 40), but are briefly described below.

Restricting the De Roock and colleagues(12) data to only those patients with KRAS WT status (as done by the manufacturer) leads to a rather small sample of 67 patients. 40% of the patients (n=27) in De Roock and colleagues are from the BOND trial (whereas the total number of patients in BOND is 329), 42% (n=28) are from the EVEREST trial, 15% (n=10) from SALVAGE and 3% (n=2) from BABEL (see Table 35, page 116).

Table 35. KRAS WT data contributing to De Roock and colleagues(12)[a]

Original study	Treatment arms in original study	Total number patients contributing to De Roock et al(12)	Number (%) of patients receiving CET+BSC	Number (%) of patients receiving CET+IRIN
BOND(57)	CET+IRIN vs CET+BSC	27	8	19
EVEREST(58, 60, 61)	CET+IRIN vs CET+BSC	28	0	28
SALVAGE(59)	CET+BSC	10	10	0
BABEL	Unclear	2	0	2
Total	–	67 (100%)	18 (27%)	49 (73%)

BSC, best supportive care; cetux, cetuximab; irin, irinotecan
[a]Calculated from Table 2 in the appendices for De Roock and colleagues(12)

The BOND trial consists of 329 patients randomly assigned to cetuximab+BSC(n=111) or cetuximab+irinotecan (n=218), with 80% of those randomised having received at least two previous lines of therapy.(57) Importantly, 50% (n=56) of patients from the cetuximab+BSCarm received irinotecan after disease progression, thus there is a great deal of cross-over in the BOND trial which does not appear to have been dealt with, or even discussed, by De Roock and colleagues(12) or Merck Serono. Ignoring this cross-over underestimates the OS effectiveness of cetuximab+irinotecan vs cetuximab+BSC.

In their submission, Merck Serono categorise the EVEREST trial(58, 60, 61) as relating to second-line treatment, yet comment that the study is: *'not fully published. It is unclear what proportion of patients received the experimental treatment in the second-line compared to the third-line'* (page 42, Merck Serono's submission). Although EVEREST is described as a RCT comparing cetuximab+irinotecan, escalating doses of cetuximab+irinotecan and cetuximab+BSC, it is surprising that only data from cetuximab+irinotecan patients are included in De Roock and colleagues (see Table 35, page 116).

The SALVAGE study,(59) although only representing 15% of patients in De Roock and colleagues,(12) is not mentioned in the manufacturer's submission. Our investigations indicate that this is a non-comparative study on patients receiving cetuximab+BSC only who have received at least two prior lines of therapy. The BABEL study also appears to be a single arm study, although further details have been difficult to find.

More generally, De Roock and colleagues comment that patients were included on the basis of availability of formalin-fixed paraffin-embedded tumour tissue; however, there are no details on what this percentage was for each of the four studies contributing patient data.(12) In addition to this, there are uncertainties as to the inclusion of some patients and the exclusion of others. For instance, EVEREST is a three arm trial (cetuximab+irinotecan, cetuximab(escalating)+irinotecan and cetuximab+BSC) but only data from patients receiving cetuximab+irinotecan has been included and it is unclear if this is from the escalating or non-escalating cetuximab+irinotecan arm. Given these issues, there are concerns that the disease progression and effectiveness estimates calculated using De Roock and colleaguesare likely to be subject to high levels of bias and confounding.(12) This is in addition to the possibility of chance findings given that only 18 patients with KRAS WT status contribute to the cetuximab+BSC arm of De Roock and colleagues.(12)

The manufacturer used data from the Kaplan-Meier curves reported in De Roock 2008 to calculate HRs for PFS and OS for cetuximab+irinotecan vs cetuximab+BSC.(12) As described in the next section, Merck Serono used data from De Roock and colleagues 2010 in the calculation of the indirect HRs.(80) De Roock and colleaguesis a non-comparative dataset, consisting of 773 cetuximab+irinotecan treated patients from 11 European centres.(80) Eighty-seven percent of patients had two or more previous lines of therapy, with 58% of patients (N=448) found to have KRAS WT status. Note that De Roock and colleagues point out that PFS and OS are appropriate outcomes given the differences in the studies combined.(80)

6.2.9. Indirect comparison: cetuximab

Merck Serono use the Bucher method(43) to calculate indirect comparisons for PFS and OS HRs (see Figure 3 [page 99] for comparison network). There are a number of concerns with the method employed by Merck Serono to calculate the indirect HRs, these are: (1) combining randomised and non-randomised evidence, (2) no assessment of the similarities/appropriateness for comparison between the patient populations of the studies, (3) adjusting the indirect HR for OS using De Roock and colleagues,(80) (4) use of unadjusted HRs from CO.17 and (5) no accounting for cross-over in De Roock and colleagues(12) (i.e. BOND(57)).

With respect to the first concern, in the indirect comparisons, because of limitations in the available evidence data from an RCT(3) and a non-RCT(12) have been combined without considering the fact that different study designs are being used. These different study designs are subject to different sources of bias and confounding, in particular we have serious concerns over the use of De Roock and colleagues 2008. It is difficult to ascertain what impact the synthesis of randomised and non-randomised data may have on the subsequent HR estimates.

Related to this is the second point, that Merck Serono makes no assessment of the patient population from the different studies involved in the indirect comparison. In any form of evidence synthesis, there should be some consideration of whether the populations and interventions are comparable across studies. While Merck Serono reports the baseline characteristics for CO.17(3) and for De Roock and colleagues(12), they do not explicitly evaluate the appropriateness of combining these studies. A quick assessment of the baseline characteristics suggests that patients in De Roock and colleagues 2008 are slightly younger, and more likely to have had fewer lines of therapy (see Table 36, page 118) than those in the CO.17 study.(3) It is unclear what impact this may have on the results of the indirect comparison.

Table 36. Baseline characteristics of patients with KRAS WT status in the studies used by Merck Serono

Characteristic		Karapetis et al(3) CET+BSC vs BSC	De Roock et al(12) CET+IRIN vs CET+BSC
Male		67.8%	58.1%
Age [Median (range)]		63.5 (28.6, 85.9)	61 (22, 86)
ECOG 0		24.3%	–
ECOG 1		55.2%	–
ECOG 2		20.4%	–
Number of lines of previous therapy	**≤2**	20%	62.2%
	3	37.4%	24%
	4	27.4%	9.2%
	≥5	15.2%	3.6%

BSC, best supportive care; CET, cetuximab; ECOG, Eastern Cooperative Oncology Group; IRIN, irinotecan

The third concern with the indirect comparison is specific to the calculation of the OS HR for cetuximab+irinotecan vs BSC. The manufacturers use data from De Roock 2008(12) and CO.17(3) for this comparison(see Table 46 [page 72], Merck Serono's submission). After calculating the HR using the Bucher approach, plots of the observed Kaplan-Meier curves and fitted parametric curves for this comparison are shown (see Figure 29 [page 72], Merck Serono's submission), but Merck Serono states that advice from clinical experts indicated that the modelled curves were not a good fit. As a consequence, the manufacturer uses data from the non-comparative study by De Roock and colleagues(80) to adjust the HR obtained from the indirect comparison from 0.29 (0.14, 0.59) to 0.32 (0.14, 0.59). It is unclear why model fit was determined by clinical experts as the submission suggests, rather than by statistical methods. There is no explanation from Merck Serono as to how exactly this adjustment was made, regardless of the fact that De Roock and colleagues is a non-comparative study. Given that, as

stated in the previous section, De Roock and colleagues(80) themselves state that PFS and OS are not the best outcomes to assess given differences in the studies combined, there are further issues of bias and confounding associated with the indirect estimates obtained by the manufacturer for the OS HR for cetuximab+irinotecan vs BSC.

However, the adjustment made to the indirect HR using De Roock and colleagues(80) data is less favourable to cetuximab+irinotecan than the initial indirect comparison results (from a HR of 0.29 to 0.32). (Interestingly, a similar estimate of HR to that using the De Roock and colleagues 2010 data is obtained if the adjusted HR from CO.17 is used in this indirect comparison instead of the unadjusted HR (0.33 (0.16, 0.68)) (as discussed in Section 6.2.8.1, page 114). After adjustment of the HR using De Roock and colleagues 2010, Merck Serono assume the same 95% CI for the HR adjusted by the data from De Roock and colleagues as that from the initial indirect comparison. This will lead to more favourable estimates for cetuximab in the PSA even though the mean value is slightly different. It is very unsual to externally adjust an indirect comparison as Merck Serono have reported for the OS of cetuximab+irinotecan vs BSC. Within the other indirect comparisons reported by Merck Serono there is no indication that such an assessment of the Kaplan-Meier curves using clinical experts was undertaken. Although this adjustment leads to a less favourable estimate for cetuximab+irinotecan, it is unclear whether the manufacturers went through a similar process including experts for the other calculations and outcomes.

The fourth concern is that already expressed in Section 6.2.8.1 (page 114) that unadjusted HRs from CO.17(3) were used by the manufacturer in the indirect comparison, when adjusted HRs would have been more appropriate. Consequently, this means the effectiveness of cetuximab in all comparisons is likely to be overestimated, particularly for OS where the difference between the adjusted HR and unadjusted HR is most pronounced.

The fifth point for concern is that there appears to be no accounting for the cross-over in the BOND data used in De Roock and colleagues 2008. Such cross-over during progressive disease will underestimate the effectiveness of cetuximab+irinotecan in terms of OS.

Note further that Merck Serono did not investigate uncertainty surrounding the effectiveness within their sensitivity analyses.

6.2.10. Modelling PFS and OS: cetuximab

6.2.10.1. Cetuximab+BSC vs BSC

Merck Serono use the IPD from Karapetis and colleagues(54) to model disease progression for cetuximab+BSC and BSC: *'[IPD] allows the progression-free health state (over time) for cetuximab monotherapy and BSC arms (from CO.17 study) to be determined by two processes based on death before progression and 'real progression'* (page 98, Merck Serono's submission). Merck Serono fit four parametric functions to the IPD: exponential, Weibull, lognormal and log-logistic. Akaike's Information Criterion (AIC) was used to identify the best fitting function. For both time to „real progression' and time to „death before progression', a log-logistic function was the best fit (although the AIC results for „real progression' are illegible in their report). The parametric log-logistic curves have a reasonable fit to the Kaplan-Meier curve (see Figure 35 [page 100], Merck Serono's submission).

For OS, the same four parametric are fitted to the cetuximab+BSC and BSC IPD. The Weibull function was found to give the best fit according to the AIC and appears to give a reasonable fit to the Kaplan-Meier data. Note, however, that 20% and 10% of patients receiving cetuximab+BSC and BSC, respectively, have not died before the end of the study. Therefore, the appropriateness of the Weibull function to extrapolate beond the data cannot be assessed.

6.2.10.2. Cetuximab+irinotecan vs BSC

Merck Serono fit a Weibull curve to the PFS and OS IPD for the BSC arm of the study by Karapetis and colleagues.(3) Using the indirect PFS and OS HRs for cetuximab+irinotecan vs BSC calculated as described and critiqued in Section 6.2.9 (page 117), Merck Serono assume proportional hazards and use the following equation to calculate the corresponding Weibull function foe PFS and OS in the cetuximab+irinotecan arm where HR is the indirect HR for cetuximab+irinotecan vs BSC: $S(t) = \exp(-(\lambda HR)t^{\gamma})$

Merck Serono present the Kaplan-Meier curves of the BSC arm from Karapetis and colleagues and the cetxuiman+irinotecan arm from De Roock and colleagues (2008) alongside the Weibull fitted curves.(12, 54) Since the indirect HR has been used for the cetuximab+irinotecan Weibull fit, onewould not necessarily expect a good fit to the Kaplan-Meier curve from De Roock and colleagues (2008).(12) Nevertheless, the parametric curve seems to fit reasonably well to the Kaplan-Meier curve for both PFS and OS. There is no explanation as to why a Weibull curve was used to model the BSC, PFS and OS data and no statistical assessment of the goodness-of-fit of this curve (for example, using AIC). Presumably, a Weibull model was used for simplicity to allow

calculation of the cetuximab+irinotecan curve using the indirect HR. Given the lack of direct evidence for cetuximab+irinotecan vs BSC, Merck Serono have taken a reasonable approach to calculate the fitted curves for PFS and OS in the cetuximab+irinotecan arm, but we still have concerns regarding the use of the data from De Roock and colleagues (2008) and the „adjustment' to the indirect OS HR using data from De Roock and colleagues (2010) (see Section 6.2.9, page 117).(12, 81) Note that the Weibull curve does not appear to be a particularly good fit to the BSC PFS Kaplan-Meier data; however, this is likely to lead to an underestimate of the PFS in the BSC arm and can therefore be considered conservative. The Weibull fit to the BSC OS data, however, appears to be reasonable.

Finally, note that Merck's log-logistic modelling of „real progression' and „death before progression' in the BSC arm for the cetuximab+BSC vs BSC comparison and Weibull parametric modelling of PFS in the BSC arm for cetuximab+irinotecan vs BSC is the source of the difference in the BSC arm depending on the comparator (see Section 6.2.1, page 98)

6.2.11. AEs: cetuximab

Merck Serono includes the costs associated with treatment for Grade 3 or 4 AEs in the model (see Table 37 [page 122] for the AE costs applied to each treatment arm). The manufacturer assumes that the utilities used in the model reflect the impact of any AEs experienced, and so do not calculate disutilities for AEs. As Merck Serono's results suggest, the cost of the AEs has very little impact on the ICERs. Yet for completeness, we report assessment of the costing and inclusion of AEs in the Merck model having identified a number of points worth highlighting. The AE data used by Merck Serono is taken from the subset of patients with KRAS WT status and ECOG 0 or 1 of the CO.17 study.(3) Merck Serono assumes that all Grade 1 or 2 AEs are minor and do not require treatment, therefore are not associated with any costs. Grade 3/4 AEs reported in CO.17 are divided into three categories: non-serious (requiring outpatient treatment only), serious but not leading to hospitalisation, and serious leading to, or prolonging, hospitalisation.

Table 37. The number (%) and costs of AEs used in the Merck Serono submission

	CET+BSC	CET+IRIN	BSC (in CET+BSC)	BSC (in CET+IRIN)
No. non serious AEs	245 (63%)	245 (63%)	129 (58%)	129 (58%)
No. serious (no hosp) AEs	21 (5%)	21 (5%)	7 (3%)	7 (3%)
No. serious (hosp) AEs	126 (32%)	126 (32%)	88 (40%)	88 (40%)
Total number of AEs	392 (100%)	392 (100%)	224 (100%)	224 (100%)
Total patients	97	97	87	87
Cost of non serious AE	£174	£174	£174	£200[a]
Cost of serious (no hosp) AE	£165	£165	£165	£165
Cost of serious (hosp) AE	£2,460	£2,460	£2,460	£2,460
Total cost of AEs	£3,671	£3,671	£2,760	£2,799

AEs, adverse events; BSC, best supportive care; cetux, cetuximab; hosp, hospitalised; irin, irinotecan

[a]Reported to be £174 in Merck's report (this has been corrected for in PenTAG's re-analysis of the base case ICERs (see Section 6.2.5, page 102)

Merck Serono has calculated the cost of AEs by assigning each type of AE experience in CO.17 (non-serious, serious not requiring hospitalisation, serious requiring hospitalisation) to a body type/system. For the non-serious and serious but not requiring hospitalisation AEs, the corresponding body type/system is matched to appropriate Healthcare Resource Group (HRG) codes and a mean cost (from the NHS reference costs 2008(74)) is assigned to the body type/system AE. The average cost per body type/system ranges from £106 for ocular AEs to £259 for infection and influenza-like symptom AEs. Note that the AEs from the BSC and cetuximab+BSC arms are combined to obtain a cost per non-serious or serious not requiring hospitalisation AE across treatment arms. For serious AEs requiring hospitalisation, the AEs were also assigned to body type/system, but allocated in-patient procedure costs based on the HRG codes. Note that the AEs are assigned to body type/system, not reported by the actual AE experienced.

Based on the CO.17 data analysed by Merck Serono, the cost of a non-serious AE is slightly greater than that of a serious AE not requiring hospitalisation (£175 vs £165). There are a greater percentage of serious AEs requiring hospitalisation (the AE associated with the most costs) in the BSC arm than in the cetuximab+BSC arm: 32% of AEs in the cetuximab+BSC arm require hospitalisation compared to 40% in the BSC arm. Both of these findings appear unintuitive.

Merck Serono assumes the same proportion of different types of AEs for cetuximab+irinotecan as their analysis suggests for cetuximab+BSC. However, given that irinotecan is known to have significant toxicities, the assumption made by Merck Serono is likely to underestimate the costs of AEs associated with cetuximab+irinotecan. Given the lack of available evidence it is difficult to quantify what the level of AEs should be for cetuximab+irinotecan. Nevertheless, we have no better evidence for the AEs associated with BSC, cetuximab+BSC or cetuximab+irinotecan.

6.2.12. Summary of cost-effectiveness

6.2.12.1. Cetuximab monotherapy

We have major concerns with a number of Merck Serono's important assumptions including the adjustment for modelling mean time on cetuximab+BSC treatment, the utilities used and the costs associated with BSC. Simultaneously modelling alternative assumptions for these concerns leads to an ICER of £82,000 to £95,000 per QALY gained for cetuximab+BSC vs BSC.

6.2.12.2. Cetuximab combined therapy

We have major concerns with a number of important assumptions including the adjustment Merck Serono make for modelling mean time on treatment, the utilities used, the costs associated with BSC and the effectiveness data for cetuximab+irinotecan. Simultaneously modelling alternative assumptions for these concerns leads to an ICER of £75,000 to £83,000 per QALY gained for cetuximab+irinotecan vs BSC. However, there is a great deal of uncertainty regarding the impact of the questionable quality of the effectiveness data on which the cetuximab+irinotecan arm is modelled from (De Roock and colleagues(12)). Thus, we have very little confidence in the ICER estimated by Merck for cetuximab+irinotecan vs BSC.

6.3. Industry submission critique 2: Roche, bevacizumab

Roche did not submit a decision model for the cost-effectiveness of bevacizumab in combination with non-oxaliplatin chemotherapy for the treatment of metastatic colorectal cancer after first-line therapy. Instead they present some cost calculations for bevacizumab+FOLFIRI compared to cetuximab+FOLFIRI. Below we critique the effectiveness evidence submitted by Roche and their basic cost calculations.

6.3.1. Effectiveness evidence: bevacizumab

Although there is no clinical evidence for the effectiveness of bevacizumab with non-oxaliplatin therapy after first-line treatment in metastatic colorectal cancer, the main focus of Roche's argument for the effectiveness of bevacizumab in this setting is that there is evidence for the

effectiveness of bevacizumab in first-line treatment and for second-line treatment in combination with oxaliplatin. From this, Roche argue that the benefits of bevacizumab in addition to chemotherapy are therefore not dependent on regimen nor line of therapy, suggesting that there is no reason to expect bevacizumab+non-oxaliplatin after first-line would not provide added benefits. This argument was adequate for the EMA to grant marketing authorisation for bevacizumab with non-oxaliplatin therapy after first-line treatment in mCRC; however, ths does not make a case for the cost-effectiveness of bevacizumab in the scope of this review.

Roche report three trials relevant to the consideration of bevacizumab for first-line use in patients with metastatic colorectal cancer: the „966 Study' by Saltz and colleagues for oxaliplatin combined therapy,(52) Hurwitz and colleagues for irinotecan combined therapy,(35) and Kabbinavar and colleagues(36) for 5-FU/FA combined therapy. For second-line combined treatment, Roche refer to the „E3200 Study' by Giantonio and colleagues(53) for bevacizumab with oxaliplatin therapy.

Saltz and colleagues conducted a 2x2 factorial design RCT and randomised 1,401 patients, 75% of whom had not previously received chemotherapy. Treatment arms were: capecitabine plus oxaliplatin (XELOX)+bevacizumab, XELOX+placebo, FOLFOX-4+bevacizumab or FOLFOX-4+placebo. In ITT analyses, patients receiving XELOX+bevacizumab or FOLFOX-4+bevacizumab were pooled, as were those receiving XELOX+placebo or FOFLOX-4 + placebo as no statistically significant treatment difference was identified between XELOX and FOLFOX-4. The HR for progression-free survival for bevacizumab vs placebo was 0.83 (97.5% CI: 0.72, 0.95) with median PFS of 9.4 months for bevacizumab and eight months for placebo. The HR for OS for bevacizumab vs placebo was not statistically significant (HR=0.89, 97.5% CI: 0.76, 1.03) where the median OS for bevacizumab was 21.3 months compared to 19.9 months in the placebo arm. Saltz and colleagues report that 30% of patients in the bevacizumab arm discontinued treatment due to AEs as compared to 21% in the placebo arm.(52) Furthermore, they note that the percentage of patients receiving treatment until progression (as defined in the protocol) was particularly low: 29% of the bevacizumab arm and 47% of the placebo arm.

Hurwitz and colleagues randomised 813 patients from the US, Australia and New Zealand to either IFL plus bevacizumab or IFL alone for first-line treatment (28% of IFL patients and 24% of IFL+bevacizumab patients had previously received adjuvant chemotherapy).(35) ITT analyses showed median survival was 20.3 months for those treated with IFL+bevacizumab and 15.6 for those receiving IFL alone (HR=0.6, $p<0.001$). The HR for PFS was 0.54 ($p<0.001$), with patients treated with IFL+bevacizumab having a PFS of 10.6 months compared to 6.2 months for patients in the IFL arm. The authors report statistically significantly more Grade 3 or 4 AEs in the

IFL+bevacizumab arm than in the IFL arm (p<0.01), mainly explained by differences in hypertension rates between the arms.

Kabbinavar and colleagues randomised 209 patients to fluorouracil and leucovorin (FU/LV) plus bevacizumab or FU/LV only.(36) Twenty-one percent of the FU/LV+bevacizumab patients and 19% of the FU/LV patients had prior adjuvant chemotherapy. The primary endpoint of OS was associated with a HR of 0.76 (95% CI 0.56, 1.10) for FU/LV+bevacizumab compared to FU/LV, with a median OS of 16.6 months in the FU/LV+bevacizumab arm and 12.9 months in the FU/LV arm. PFS, however, was statistically significantly longer in the FU/LV+bevacizumab arm (9.2 months) than the FU/LV arm (5.5 months) (HR = 0.5, 95% CI: 0.34, 0.73). Treatment with FU/LV+bevacizumab was associated with a greater experience of Grade 3 or 4 AEs than FU/LV (87% for FU/LV+bevacizumab vs 71% for FU/LV). The authors argue that the large number of patients receiving post-progression treatment could partly explain the lack of statistical significance in the primary endpoint of OS. A similar percentage of patients from both treatment arms received irinotecan, oxaliplatin or both post-progression (39% of the FU/LV+bevacizumab patients and 46% of the FU/LV patients).

Giantonio and colleaguesreport the ITT analyses of a RCT with 820 patients previously treated with fluoropyramide and irinotecan randomised in to one of three arms: FOLFOX-4+bevacizumab, FOLFOX-4 or bevacizumab alone.(53) Median OS was greater in the FOLFOX-4+bevacizumab arm: 12.9 months compared to 10.8 for FOLFOX-4 and 10.2 for bevacizumab alone. The HR for OS associated with FOLFOX-4+bevacizumab compared to FOLFOX-4 was 0.75 (p=0.01). Median PFS was also greater in the FOLFOX-4 + bevacizumab arm: 7.3 months compared to 4.7 months for FOLFOX-4 and just 2.7 months for bevacizumab alone. A greater number of Grade 3/4 AEs were reported in the FOLFOX-4+bevacizumab arm (75%) than in the FOLFOX-4 arm (61%).

As Roche point out in their submission, these four trials suggest that bevacizumab in combination with therapies is associated with a benefit to PFS and OS, which is statistically significant for PFS in all four trials. None of these trials are included in our systematic review of clinical effectiveness in Section 4 (page 40) as they do not meet the inclusion criteria for this review.

6.3.2. The decision problem: bevacizumab

The manufacturer argues that due to the lack of clinical evidence on the effectiveness of bevacizumab after first-line therapy, a decision model comparing bevacizumab+FOLFIRI with FOLFIRI: *'would be subject to sizeable uncertainty'* (page 8, Roche's submission). Therefore no economic evaluation or cost calculations for bevacizumab+FOLFIRI vs FOLFIRI are presented by the manufacturer. In comparison with cetuximab, Roche argue that bevacizumab is likely to be

less expensive given the purchase prices of each drug. The manufacturer does, however, provide very basic cost calculations for a comparison of bevacizumab+FOLFIRI with cetuximab+FOLFIRI in patients who have failed one previous line of therapy, and these are critiqued in the sections below. Note that even though Roche state that there is considerable uncertainty with the bevacizumab+FOLFIRI vs cetuximab+FOLFIRI comparison, cost calculations are still presented, it is reasonable to query why such basic cost calculations were not performed for the bevacizumab+FOLFIRI vs FOLFIRI comparisons with the same caveat of: *'sizeable uncertainty'*.

6.3.3. Costs: bevacizumab

Roche focus on the incremental cost differences between bevacizumab+FOLFIRI and cetuximab+FOLFIRI over a seven-cycle (14-week) treatment regime. Roche account for differences in KRAS testing and drug acquisition and administration costs between bevacizumab+FOLFIRI and cetuximab+FOLFIRI. Roche use the: *'guaranteed NHS cost'* for cetuximab as reported in the submission from Merck Serono. Roche assume a cost of £462 for KRAS testing associated with each patient KRAS WT status as in TA176.(26) This cost is defined to account for the costs of all KRAS testing including patients who are KRAS mutant (who would not go on to receive cetuximab treatment). However, Roche's assumption for KRAS test costs may be too high as it is based on a KRAS test cost of £300. Data indicate that the test cost is £160,(77) thus the cost for testing for KRAS, accounting for those identified as KRAS mutant status(54%), is likely to be around £296 (as discussed in Section 6.2.6.5, page 109).

The drug preparation and administration costs assumed by Roche include an additional hospital visit for cetuximab+FOLFIRI per cycle for administration at £218 per visit (from NHS Reference Costs 2008–2009, SB15Z). However, this value is actually reported as £227 in NHS Reference Costs 2008–2009. This is based on the assumption that bevacizumab+FOLFIRI requires one administration per two-week cycle, while cetuximab+FOLFIRI requires two administrations per two-week cycle. Similarly, an additional pharmacy preparation cost of £9 (12 minutes of pharmacy time) per cycle is assumed for cetuximab+FOLFIRI. Thus, Roche assume an incremental cost per cycle for drug preparation and administration associated with cetuximab+FOLFIRI of £227, when in fact this value should be £236, if the £9 pharmacy cost is assumed. Data given to PenTAG on pharmacy preparations suggests that pharmacy costs are £15 (see Appendix 13 [Pharmacy drug preparation times]). The impact of changing the preparation and administration costs from £227 to £242 (£227+£15) is assessed below.

To calculate the dose of bevacizumab required per administration Roche assume a mean weight of 75 kg referencing TA118, and a mean body surface area (BSA) of 1.75m^2 for calculation of

dose of cetuximab required (although this estimate of BSA is not referenced). Using the BSA-to-weight calculations used by Merck Serono in their submission (page 112, Merck Serono's submission), assuming 75 kg weight is equivalent to a BSA of 1.91 m^2. Therefore Roche's estimate of cetuximab dose required per administration could be an underestimate if we are to accept the equations used by Merck. The impact of this is assessed below.

The total incremental cost of cetuximab+FOLFIRI over bevacizumab+FOLFIRI calculated and reported by Roche is therefore £5,408 (KRAS testing costs of £462 plus drug costs of £3,357 plus administration costs of £1,589).

6.3.4. Threshold analysis assumptions and results: bevacizumab

To undertake threshold analyses on the incremental costs for bevacizumab+FOLFIRI vs cetuximab+FOLFIRI, Roche assume a utility of 0.6 for PD. This is taken from TA118 and does not appear to be based on any evidence. The threshold analyses reported by Roche using this utility value indicate that cetuximab+FOLFIRI would have to provide a survival advantage of 3.6 months over bevacizumab+FOLFIRI to be considered cost-effective at a willingness-to-pay of £30,000 per QALY gained.

Adjusting the drug preparation, administration and KRAS test costs and BSA estimates for cetuximab+FOLFIRI has no impact on the estimated survival advantage of 3.6 months required by cetuximab+FOLFIRI to be considered cost-effective compared to bevacizumab+FOLFIRI at a willingness to pay of £30,000 per QALY gained. Note that the PD utility of 0.6 is lower than that used by Merck Serono for either BSC or active treatment. If a utility of 0.693 is assumed in addition to the updated KRAS testing administration costs and the BSA, a survival advantage of 3.2 months would be required.

6.3.5. Summary of cost calculations: bevacizumab

As Roche themselves state, these are very basic cost calculations and given the lack of effectiveness evidence for bevacizumab+FOLFIRI, they do not really help with the decision-making. Only KRAS test, drug acquisition and administration costs associated with a seven-cycle treatment regimen are accounted for. Roche assume that no patients (either those receiving cetuximab+FOLFIRI or bevacizumab+FOLFIRI) progress or die within that 14-week (seven-cycle) period. Furthermore, by assuming a utility for PD in the threshold analysis, Roche are implicitly assuming that time in progression free is the same for bevacizumab+FOLFIRI as for cetuximab+FOLFIRI. The differential cost of treating AEs between cetuximab+FOLFIRI and bevacizumab+FOLFIRI is not considered. Given the lack of evidence for AEs associated with

bevacizumab+FOLFIRI, it is difficult to state what the impact of AEs may have on the cost calculations, but is likely to be slight.

Roche only conducted a comparison of bevacizumab+FOLFIRI vs cetuximab+FOLFIRI, but another appropriate comparison would be between bevacizumab+FOLFIRI and cetuximab+BSC. This can be crudely estimated by subtracting the costs of irinotecan from the cetuximab+FOLFIRI costs calculated by Roche. We assume, as done by Merck, that irinotecan administration is every two weeks at a dose of 180mg/m^2 and that the mean BSA is 1.75m^2 as Roche assume. At a cost of £1,203 per mg of irinotecan (from Merck Serono) and assuming wastage, the cost of one cycle of irinotecan is £385. Over seven cycles this is a cost of £2,695. Thus, the incremental cost of cetuximab+FOLFIRI is adjusted by subtracting £2,695 from £5,408 to roughly estimate the incremental cost of cetuximab monotherapy compared to bevacizumab+FOLFIRI (£2713). Assuming this incremental cost and a willingness-to-pay threshold of £30,000 per QALY, leads to the estimation of an incremental QALY of 0.09. Assuming a PD utility of 0.6 leads to cetuximab monotherapy requiring an additional 1.8 months survival over bevacizumab+FOLFIRI. As with the threshold analysis undertaken by Roche, this is a very basic calculation which only considers the costs of the first 14 weeks of treatment, and it is difficult to evaluate the likeliness of the finding that cetuximab would need a 1.8 month survival over bevacizumab+FOLFIRI to be considered cost-effective at a willingness-to-pay of £30,000 per QALY gained.

6.4. Industry submission critique 3: Amgen, panitumumab

Amgen did not submit an economic model for this appraisal and do not argue that panitumumab could be a cost-effective treatment option for patients with KRAS WT status after first-line treatment in mCRC. Their submission consists of an analysis of the only RCT of panitumumab after first-line treatment where KRAS status is known: Amado and colleagues.(4) Here we critique their analysis of this trial data, in particular their adjustment for the large proportion of patients who crossed over from BSC to panitumumab+BSC at disease progression.

6.4.1. Effectiveness evidence: panitumumab

An important feature in Amado and colleagues is that 76% of patients randomised to BSC received panitumumab+BSC once they had progressed.(4) Thus, estimates of OS are confounded by this cross-over, and no effect of panitumumab+BSC over BSC was found in Amado and colleagues. The manufacturer has made adjustments to the calculation of OS to account for this cross-over. As they note, there are a number of techniques available for adjusting for cross-over, but, given the specific nature of the relationship between the effectiveness of panitumumab+BSC by KRAS status, Amgen uses a simple method for adjustment.

Amgen estimates OS for patients with KRAS WT status in the BSC treatment arm adjusted for cross-over as equal to that for patients with KRAS mutant status in the BSC treatment arm, regardless of whether patients crossed-over at progression (Table 38).

Table 38. Patient populations used by Amgen to adjust for cross-over in calculations of OS

BSC	Panitumumab arm
KRAS mutant patients randomised to receive BSC (N=100)	KRAS WT patients randomised to receive panitumumab (N=124)

In coming to this approach, Amgen argues that including all patients as they were randomised (i.e. ignoring the fact that many BSC patients crossed over to panitumumab+BSC at progression) will underestimate the effectiveness of panitumumab+BSC relative to BSC in terms of overall survival. Similarly, they argue that censoring all patients who crossed over from BSC to panitumumab+BSC at progression would overestimate the effectiveness of panitumumab+BSC, because patients who crossed over were generally fitter with a better prognosis than those patients who did not cross-over. They further argue that just censoring those who crossed-over and achieved stable disease or a complete or partial response would also lead to an overestimate of the effectiveness of panitumumab+BSC, for the same reason.

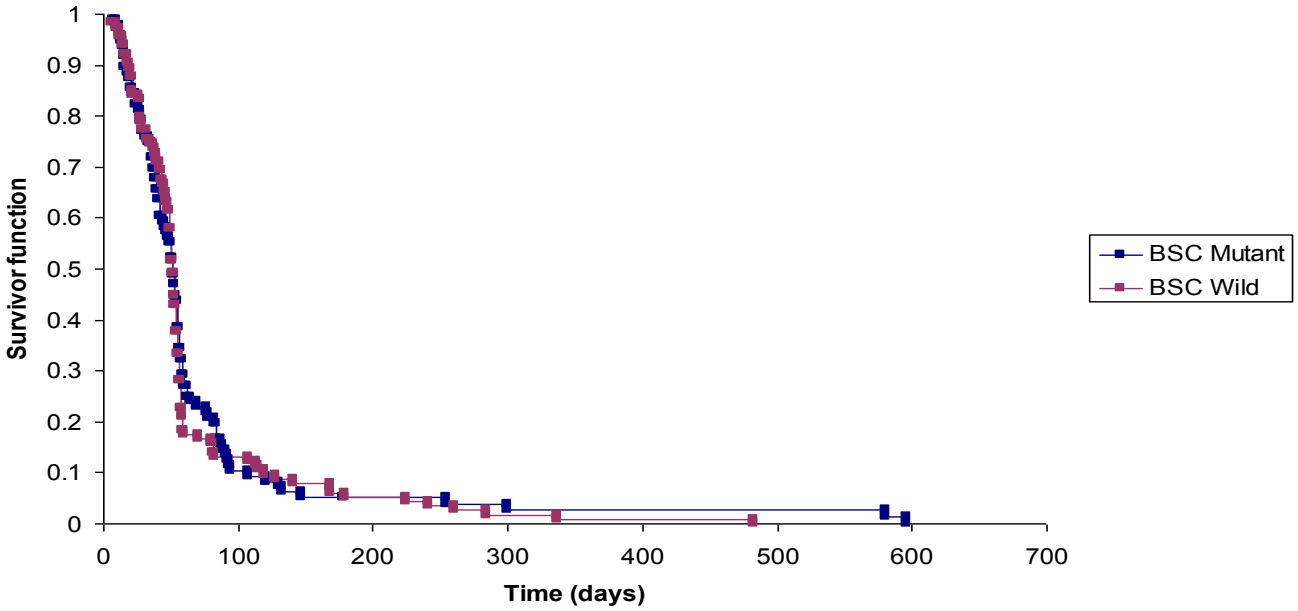
The approach used by Amgen depends upon two main assumptions. First, to be able to include KRAS mutant patients randomised to the BSC arm as a substitute for KRAS WT patients in the BSC arm, even though they may have crossed over to panitumumab+BSC at progression, it must be assumed that panitumumab+BSC is not effective for patients with KRAS mutant status. Second, to use only patients with KRAS mutant status randomised to BSC (see Table 38, page 129), it must be assumed that survival in patients with KRAS mutant status assigned to BSC is similar to survival in patients with KRAS WT status assigned to BSC (had these patients with KRAS WT status not crossed over to receive panitumumab).

The first assumption is based on the retrospective analysis of effectiveness by KRAS status by Amado and colleagues. As reviewed in Section 4.2.1.4.3 (page 51) the evidence indicates that this is a fair assumption; i.e. that panitumumab+BSC is not effective for patients with KRAS mutant status.

The second assumption is also based on data from Amado and colleagues(4) and involves an additional important assumption that similarities in PFS between patients with KRAS mutant and KRAS WT status randomised to BSC can predict similarities in OS between these two groups of

patients. Amgen state there are few differences between the Kaplan-Meier curves for PFS for patients with KRAS mutant and KRAS WT status randomised to BSC (Figure 5).

Figure 5. Kaplan-Meier Curves: time from randomisation until disease progression for BSC - KRAS mutant and KRAS WT (see Figure 2 [page 29], Amgen's submission)



As can be seen, there is very little difference between the two curves, in fact Amgen reports that mean PFS is 71 days for patients who are KRAS mutant and 64 days for those who are KRAS WT. Thus, if anything, their assumption for the survival benefit of panitumumab+BSC may be biased against panitumumab+BSC. In further analyses, Amgen compares baseline characteristics across the four groups (treatment x KRAS status) to identify any statistically significant differences between the groups. They then carry out Cox regression on three groups of patients ((a) all patients, (b) patients with KRAS mutant status and (c) patients with KRAS mutant status receiving BSC and patients with KRAS WT status receiving panitumumab+BSC) to determine whether any of the baseline variables are statistically significant predictors of survival. In doing this, Amgen is evaluating whether any differences in the survival between the KRAS mutant BSC arm and the KRAS WT panitumumab+BSC arm can be attributed to factors other than treatment.

Amgen appears to have taken a reasonable approach to this evaluation of characteristics, however their focus on 5% level of statistical significance does not help to fully assess whether any variables important to predicting time to death are different across the groups. For instance, there may be important factors that Amgen has not included because they were found to have a p-value above the p=0.05 cut-off used (i.e. p=0.051).

The additional point that the similarity in PFS in patients with KRAS mutant status receiving BSC and patients with KRAS WT status receiving BSC translating to a similarity in OS, is difficult to assess given the limited data available. However, there is evidence which could shed some light on this. In an evaluation of KRAS status on response to bevacizumab for mCRC, Ince and colleagues 2005,(82) and Hurwitz and colleagues 2009,(42) reported a greater median OS for patients with KRAS WT status treated with placebo than for patients with KRAS mutant status (17.6 vs 13.6 months). Hurwitz and colleagues do not report whether any patients randomised to BSC received bevacizumab, however since KRAS status has no impact on the effectiveness of bevacizumab, these data suggest that in this trial OS between KRAS WT and mutant patients was not similar. However, neither was PFS between the KRAS subgroups (7.4 months for patients with KRAS WT status and 5.5 months for patients with KRAS mutant status), plus the sample sizes are small (67 patients with KRAS WT status and 34 patients with KRAS mutant status).

[redacted]

129

[redacted]

Once PFS and OS have been calculated for each „best response' group, these are then aggregated to obtain the mean estimates given in Table 39 (page 131). Alongside these estimates, those obtained by ignoring the response rates are shown. As can be seen, the two approaches lead to similar estimates of mean PFS and OS.

Table 39. Mean estimates (months) of PFS and OS after adjusting for cross-over* confidential information removed

Treatment arm	Analysis method	PFS	Time from progression to death	OS
BSC	Accounting for response rates			
	Ignoring response rates			
Panitumumab	Accounting for response rates			
	Ignoring response rates			

Incr survival gains	Accounting for response rates			2.74
	Ignoring response rates			3.13

BSC, best supportive care; Incr, incremental; OS, overall survival; PFS, progression free survival
* when assuming base case effectiveness data as in Table 38

Amgen reports that the alternative methods for adjusting for cross-over in the BSC arm give a mean survival gain of 3.43 months when all patients crossing over are censored, or 4.79 when those achieving a stable, complete or partial response are censored. Thus, their approach is conservative compared to these other methods and is reasonable given all the uncertainties

6.4.2. QoL data: panitumumab

Amgen summarises the analyses of QoL data from the Van Cutsem and Amado study published by Odom and colleagues.(49) It is reported that the HRQoL, as measured by the EQ-5D and NCCN FCSI, was greater for patients receiving panitumumab+BSC rather than BSC alone (a mean difference of 0.22 on the EQ-5D scale). Furthermore, average estimates from both measures were greater than the minimally clinically important differences reported in the published literature. Note that Odom and colleagues report that HRQoL was only reported for patients in the PF health state, and that there was a great deal of patient drop-out. Amgen reports that the analysis suggested that drop-out was treatment related, being much higher in patients in the BSC arm. Note that neither Odom and colleagues nor Amgen reports the absolute EQ-5D utility values for the BSC or panitumumab+BSC arm, only the mean difference between them (0.22).(49)

6.4.3. Safety data: panitumumab

Amgen report the number of patients experiencing AEs from the Van Cutsem study where KRAS status was unknown, and from the retrospective analysis by Amado and colleagues where KRAS status was available for 92% of patients.(4) One hundred per cent of panitumumab patients with KRAS WT status developed an AE, and 90% of BSC patients developed an AE. Table 40 (page 132) is taken from Amgen's report detailing the percentage of patients with KRAS WT status receiving panitumumab who experienced Grade 3 or 4 AEs or withdrew due to AEs.

Table 40. AEs experienced by patients with KRAS WT status receiving PAN in Van Cutsem et al

	% developing AE	
AE	**KRAS WT**	**KRAS mutant**
Grade 3/4	44	28

Treatment-related (Grade 3)	25	12
Withdrawal due to AE (non-specified)	7	5
Withdrawal due to AE (panitumumab related)	2	1

AE, adverse event, KRAS, kirsten rat sarcoma; WT, wild type

6.4.4. Liver resection: panitumumab

Amgen reports on a Delphi consultation of 15 clinical specialists in the UK on the expected rates of liver resection within patients with mCRC after first-line therapy. They suggest that 5–9% of these patients could be expected to undergo liver resection. Amgen summarises the results of the Delphi consultation which includes that*: 'a majority of the clinical experts agreed that treating chemorefractory patients with panitumumab as a single agent may lead to downsizing of liver metastases'* and *'mean survival following successful liver resection in a chemorefractory patient on panitumumab was three years; estimates of five years and 10 years were expected in 20–24% and 10–14% of patients respectively'*.

6.5. Overall summary of industry submissions

The base case ICERs reported by Merck Serono (£47,000 per QALY gained for cetuximab+BSC vs BSC and £44,000 per QALY gained for cetuximab+irinotecan vs BSC) are highly likely to be underestimates given the concerns we have with their estimate of treatment duration, and the costs assumed for BSC, drug administration and KRAS testing. Alternative ICERs using Merck Serono's model of £82,000 per QALY gained for cetuximab+BSC vs BSC are more likely.

The very basic cost calculations submitted by Roche for bevacizumab+FOLFIRI vs cetuximab+FOLFIRI are reasonably robust to alternative drug acquisition, drug administration and KRAS test cost estimates, but offer very little information for the decision-making process.

Amgen makes no claims for cost-effectiveness of panitumumab, but their analysis for the cross-over in the study by Amado and colleagues is reasonable, suggesting an OS advantage of 2.74 or 3.13 months (depending on the method used) for panitumumab+BSC vs BSC.

7. PenTAG cost effectiveness analysis

7.1. Independent economic assessment

7.1.1. Scope of economic evaluation

Our economic evaluation is restricted to patients with KRAS WT status on third-line or further lines of treatment for mCRC for reasons described below. We estimate the cost-effectiveness of cetuximab+BSC versus BSC, panitumumab+BSC vs BSC and cetuximab+irinotecan vs BSC. We are not able to model cost-effectiveness as a function of the line of treatment because we do not have access to the required underlying individual patient data from the clinical trials.

The scope of our analysis is reduced relative to the original NICE Scope in two respects. First, although the NICE Scope refers to second-line treatment, we do not model the cost-effectiveness of any drugs for second-line treatment due to the lack of relevant clinical data. There is only one RCT of any of the assessed drugs for second-line use the RCT of cetuximab+irinotecan vs irinotecan (EPIC trial);(71) however, the clinical results are not stratified according to KRAS status. In addition, we note that MerckSerono do not model the cost-effectiveness of cetuximab+BSC or cetuximab+irinotecan for second-line treatment and that there appears to be little clinical demand for second-line use. Second, due to the lack of clinical evidence, we did not model treatment with bevacizumab in combination with chemotherapy not containing oxaliplatin for people on second or subsequent lines of treatment.

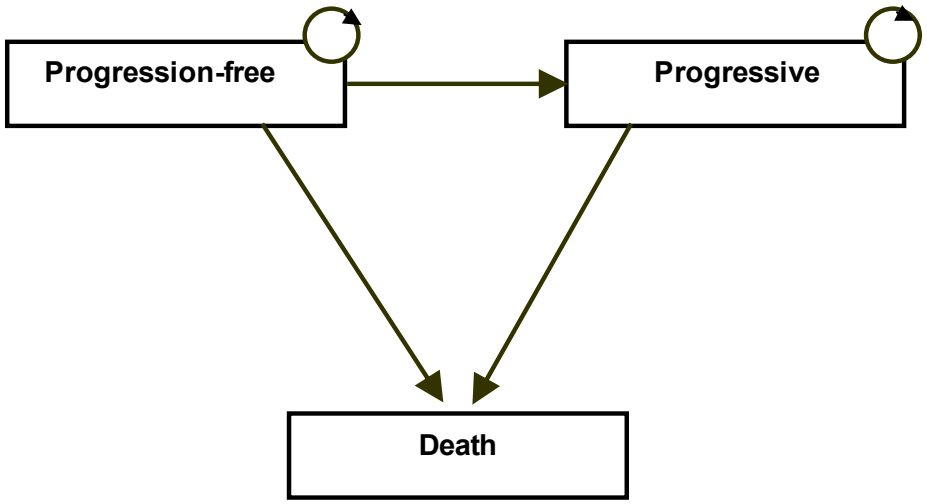
Both of these issues were agreed with NICE during the preparation of this report.

The following section describes the structure of our cost-effectiveness model. Subsequent sections describe the parameterisation of the model, and a comparison of the results of our model with other relevant models, including that submitted by Merck Serono, the manufacturer of cetuximab.

7.1.2. Model structure

The cost-effectiveness model, implemented in Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA), simulates a cohort of people with KRAS WT mCRC on third- or subsequent lines of treatment. The structure of the model was informed by a review of the literature and expert opinion. The basic design of the model is simple and has been previously used to simulate the progression of metastatic cancers; for example. for metastatic renal cell carcinoma.(83) There are three health states: PFS, PD and death (Figure 6, page 135).

Figure 6. Structure of PenTAG cost-effectiveness model



In Figure 6, 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.

Although our model closely resembles a Markov state-transition approach, it differs in that an „area under the curve' / „cohort partition' method is used to determine state populations at each cycle of the model (rather than using transition probabilities). In this method, the number of people in each health state at each successive model cycle is determined by using survival curve data to apportion the overall cohort between the states. This approach has been used in previous HTAs.(83) Using this method, there is no requirement to calculate the probabilities of transition between health states (depicted by the arrows in Figure 6), since estimates of populations for each health state are derived directly from the survival curves.

Differences in clinical effectiveness between treatments are represented by the differences between PFS and OS curves (and hence the respective populations of each disease state at each successive cycle of the model). Estimates of cost and utility per cycle are assigned to the PFS and PD states, and these provide an aggregated output over the modelled time horizon for the total costs and utility per person for each treatment. The main economic outcome presented is the incremental cost per QALY gained.

The model cycle length is one month, and the model time horizon is 10 years, after which time virtually all people in all cohorts have died. 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.(13)

After treatment with any of the comparator drugs, in common with MerckSerono, we assume no further lines of drug treatment.

7.1.2.1. Sensitivity of KRAS test

We assume that everyone tested as KRAS WT is indeed WT, i.e. that the sensitivity of the KRAS test (to test for KRAS mutant status) in routine clinical practice is 100%. However, if the sensitivity of the test used in routine clinical practice is less than 100%, some people may be incorrectly diagnosed with KRAS WT status. These people will then receive panitumumab+BSC or cetuximab+BSC, even though they will not benefit from these drugs. Therefore, these drugs vs BSC will actually have higher costs per QALY compared to BSC than the figures produced from our model. To be more precise, we should consider the relative sensitivities of the testing for patients with KRAS mutant status as used in the RCTs of panitumumab+BSC and cetuximab+BSC vs that used in the routine testing of patients. If the sensitivities are equal, the cost-effectiveness of these drugs will be the same as calculated in our model. If the sensitivity of the tests used in the RCTs is greater than used in routine practice, the cost-effectiveness of these drugs will actually be worse than predicted by our model. In this case, we should model the clinical effectiveness of people who are assessed as KRAS mutant status from the RCTs, in addition to that for people assessed as KRAS WT status.

We asked Merck Serono and Amgen for the sensitivity of KRAS tests used in routine practice. Amgen replied that the probability of a patient with KRAS mutant status being incorrectly diagnosed as KRAS WT *„using the standard KRAS test assured by appropriate external quality assurance*' is 14 in every 10,000 tests; i.e. 0.14% (see Appendix 11). In summary, Merck Serono does not quantify the probability of incorrectly diagnosing a patient as KRAS WT, but instead claim that it is *'slim'*. If insufficient tumour sample is available for testing then the test result is reported as not available.

7.1.2.2. PFS and OS

The distribution of PFS and OS times across people in:

- the BSC treatment group is taken directly from the RCT of cetuximab+BSC vs BSC(3)
- the cetuximab+BSC treatment group is also taken directly from the RCT of cetuximab+BSC vs BSC(3)
- the panitumumab+BSC treatment group is taken from the RCT of panitumumab+BSC vs BSC,(4) adjusted for the indirect comparison with BSC and cetuximab+BSC

- the cetuximab+irinotecan treatment group is taken from a variety of sources, and is adjusted for the indirect comparison with BSC and cetuximab+BSC.

Details are given in Section 7.1.3.1 (page 138).

7.1.2.3. Time on treatment

The mean duration of drug treatment is a key determinant of the mean drug acquisition costs, and therefore of cost-effectiveness. Ideally, we would model the mean duration of drug treatment as experienced in the RCTs. This is reported as a mean of 10 treatment cycles for patients with KRAS WT status on panitumumab+BSC,(4) but this is not reported for patients with KRAS WT status on cetuximab+BSC or for cetuximab+irinotecan. However, in the pivotal trials of cetuximab+BSC vs BSC, panitumumab+BSC vs BSC and cetuximab+irinotecan vs cetuximab (BOND), all drugs were taken until disease progression, intolerable AEs or death. In the RCT of cetuximab+BSC vs BSC, treatment with cetuximab was additionally stopped due to: *'worsening symptoms of the cancer, or request by the patient'*.(45) Therefore, we modelled treatment duration by treatment group (see Table 41).

Table 41. Treatment duration: PAN+BSC, CET+BSC and CET+IRIN

Drug	Treatment duration modelled	Source/rationale
PAN+BSC	Mean of 20 weeks (one dose every two weeks; mean of 10 doses)	As reported in Amado et al for patients with KRAS WT status
CET+BSC	Until disease progression	Assume main reason for stopping treatment is disease progression. Based on median treatment duration in Jonker et al trial being very similar to median PFS in Jonker et al (8.1 weeks vs 8.2 weeks) and clinical opinion
CET+IRIN	Until disease progression	Based on median treatment duration in BOND being very similar to median PFS (seven weeks vs 6.5 weeks)

BSC, best supportive care; CET, cetuximab; IRIN, irinotecan; KRAS, kirsten rat sarcoma; PAN, panitumumab; PFS, progression-free survival

Details are given in Section 7.1.3.1 (page 138).

7.1.2.4. Post-progression survival

Post-progression survival is calculated as OS minus PFS.

7.1.2.5. Severe AEs

We do not model disutilities due to AEs associated with drug treatment directly. Instead, as Merck Serono, we allow for disutilities indirectly in that we use utilities specific to each treatment.

We base our estimates of the costs of treating adverse events on those calculated by Merck Serono, see Section 7.1.3.3.7 (page 168) for details.

7.1.3. Evidence to inform model parameters

7.1.3.1. OS, PFS and treatment duration

Given that there is no single RCT with all treatment groups, it was necessary to perform an indirect comparison between some pairs of treatments. For PFS, OS and time on drug treatment, we chose the baseline treatment for the indirect comparison to be BSC taken from the RCT of cetuximab+BSC vs BSC.(3) The clinical effectiveness of people on BSC is also available from the RCT of panitumumab+BSC vs BSC.(4) However, this was not considered an appropriate estimate for the baseline treatment for BSC because the effectiveness of this treatment group was confounded by substantial cross-over (76% of patients).

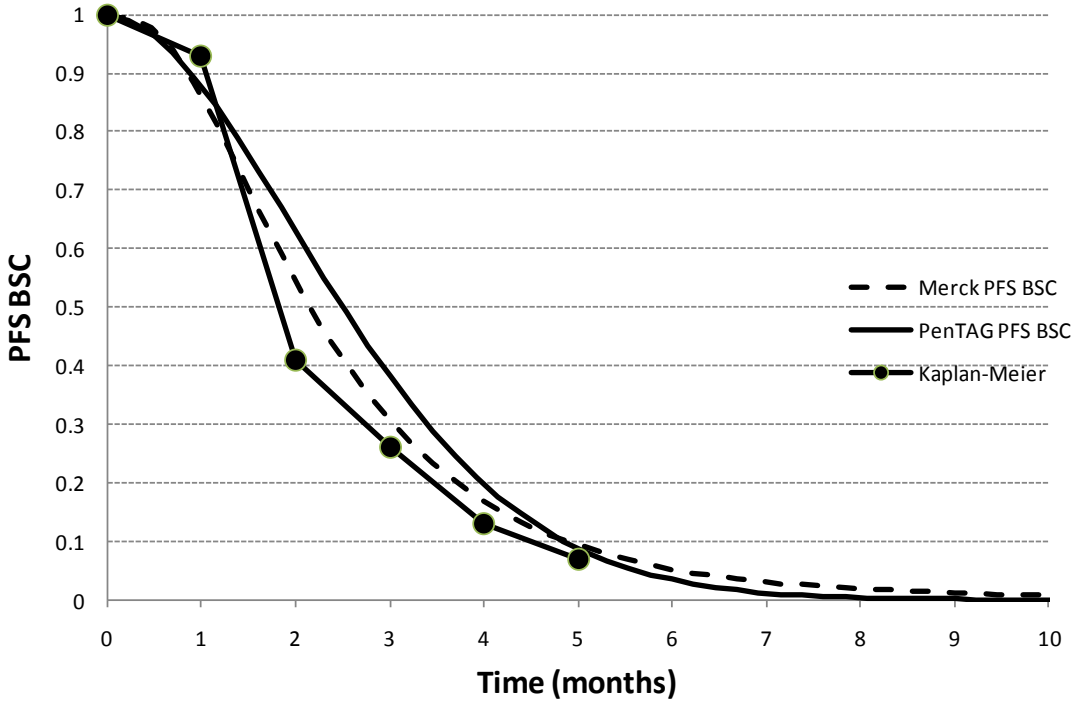
7.1.3.1.1. BSC

7.1.3.1.1.1. PFS for BSC

We have based our estimate of PFS for BSC on the analysis of the IPD by Merck Serono. In particular, we have assumed the same mean time in PFS as Merck Serono, namely 2.72 months. This is the most important summary statistic of PFS given that cost-effectiveness is a function of mean values. We did not use precisely the same PFS curve as Merck Serono, because this function is commercial in confidence (CiC). We specified that PFS follows a Weibull distribution, as this is a flexible function, widely used in cancer survival analysis. We read off the PFS probabilities at monthly intervals from the published Kaplan-Meier graphs for patients with KRAS WT status.(3) We then fitted a Weibull curve to this data by minimising the sums of squares of differences between actual and fitted probabilities. We estimated the shape parameter, γ, of the Weibull from this fit to the Kaplan-Meier curve. However, note that the shape is not important, because cost-effectiveness is almost completely insensitive to it. Instead, it is the mean PFS that is critical which we fix to be the same as that reported by Merck Serono. Finally, given that we have specified the mean, this then specifies the scale parameter, λ, of the Weibull, given that the mean of the Weibull is:

$\left(\frac{1}{\lambda}\right)^{\frac{1}{\gamma}}\Gamma\left(1+\frac{1}{\gamma}\right)$, see Figure 7.

Figure 7. PenTAG and Merck Serono PFS for BSC group for patients with KRAS WT status



We estimated the uncertainty in PFS for the PSA purely by modelling the uncertainty in the mean PFS. This is valid, given that it is the mean PFS that drives cost-effectiveness. First, for simplicity, we fixed the shape value gamma of the Weibull. Next, we specified that the mean PFS follows a gamma distribution with mean of 2.72 months, as above. We then estimated the standard error of the mean PFS by making two simplifying assumptions. The first was that PFS approximately follows an exponential distribution. We can then say that the standard deviation of PFS across patients approximately equals the mean PFS, as this is a property of the exponential distribution. The second simplifying assumption was that no patients in the BSC arm in the RCT of cetuximab+BSC vs BSC were censored, which is probably approximately true, given that progression occurs quickly. In this case, the standard error of the mean PFS equals:

$$\frac{\text{standard deviation of PFS for BSC}}{\sqrt{\text{no. of patients on BSC in CET + BSC vs BSC RCT}}} \approx \frac{\text{mean PFS for BSC}}{\sqrt{\text{no. of patients on BSC in CET + BSC vs BSC RCT}}}$$

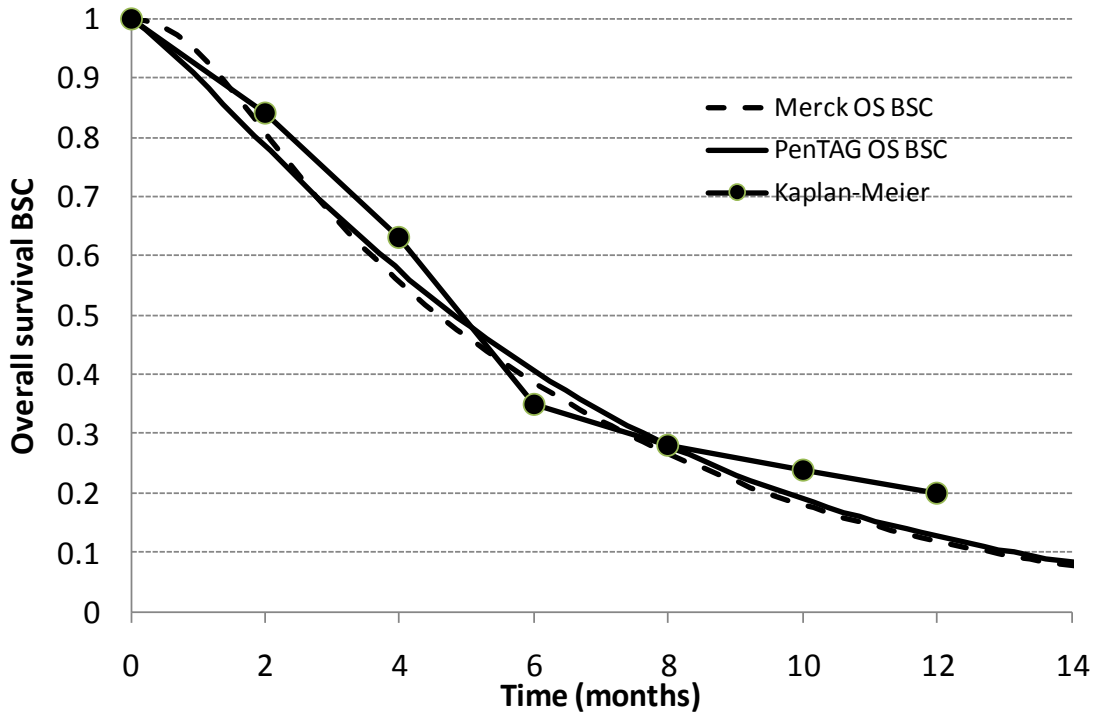
$$= \frac{2.72}{\sqrt{105}} = 0.27 \text{ months}$$

Finally, the scale parameter, λ, of the Weibull is back-calculated from the fixed gamma and variable mean, using the formula of the mean of the Weibull described above.

7.1.3.1.1.2. OS for BSC

As for PFS for BSC, we based our estimate of OS for BSC on the analysis of the IPD by Merck Serono. In particular, we assume the same mean OS as that calculated by Merck Serono of 6.2 months. Next, we again specified that OS for BSC follows a Weibull function, and we read off the OS probabilities at monthly intervals from the published Kaplan-Meier graphs for patients with KRAS WT status.(3) We then fitted a Weibull curve to this data by minimising the sums of squares of differences between actual and fitted probabilities. We estimated the shape parameter, γ, of the Weibull from the shape parameter of this fit to the Kaplan-Meier curve. Finally, given that we have specified the mean, this then specifies the scale parameter, λ, of the Weibull (see Figure 8).

Figure 8. PenTAG and Merck OS for patients with KRAS WT status in BSC group



We estimated the uncertainty in OS for the PSA in exactly the same way as for the uncertainty in PFS on BSC, as explained in the last section. Our estimation of the standard error of mean OS assumes that no patients were censored in the BSC arm of the cetuximab+BSC vs BSC RCT. This assumption is less likely to hold for OS than to PFS, but given the lack of further data, and the need for simplicity, this was again our assumption.

It is impossible to know the correlation between OS and PFS for BSC without access to the underlying IPD from the RCT of cetuximab+BSC vs BSC. Nonetheless, it seems intuitive that these quantities will be highly correlated. Therefore, given the lack of further evidence, we

assumed that OS and PFS are perfectly correlated. This was implemented in the model by using the same random number to draw values for mean PFS and OS.

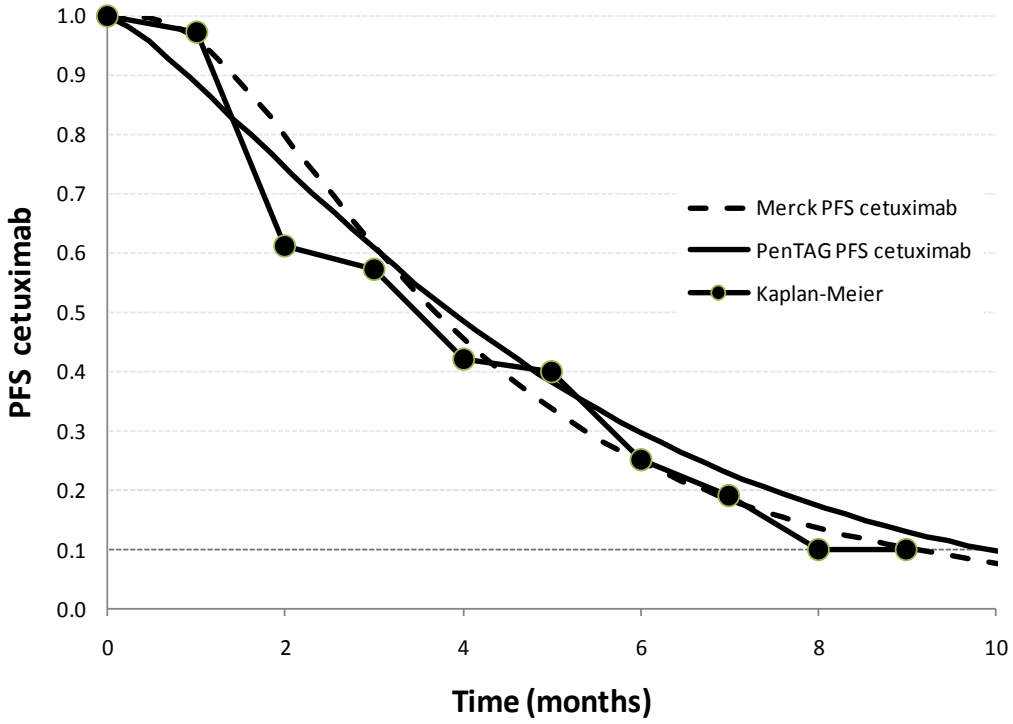
7.1.3.1.2. Cetuximab monotherapy

We modelled the time on cetuximab treatment, PFS and OS for the cetuximab+BSC group directly from the RCT of cetuximab+BSC vs BSC.(3)

7.1.3.1.2.1. PFS for cetuximab+BSC

As in the BSC group, given that Merck Serono have the underlying IPD from this trial, we have based our estimate of PFS for cetuximab+BSC on the analysis of the IPD by Merck. In particular, we assume the same mean PFS for cetuximab+BSC as that calculated by Merck of 4.78 months = 0.40 years. Next, we again specified that PFS for cetuximab+BSC follows a Weibull function, and again, we read off the PFS probabilities at monthly intervals from the published Kaplan-Meier graphs for patients with KRAS WT status.(3) We then fitted a Weibull curve to this data by minimising the sums of squares of differences between actual and fitted probabilities. We estimated the shape parameter, γ, of the Weibull from the shape parameter of this fit to the Kaplan-Meier curve. Finally, given that we have specified the mean, this then specifies the scale parameter, λ, of the Weibull (see Figure 9).

Figure 9. PenTAG and Merck Serono PFS for CET+BSC group for patients with KRAS WT status



We estimated the uncertainty in PFS for the PSA in exactly the same way as we estimated the uncertainty in PFS on BSC, as described above. Again, we modelled the uncertainty in the mean PFS, by specifying that the mean PFS follows a gamma distribution with mean of 4.78 months, as above. In this case, the standard error of the mean PFS equals;

$$\approx \frac{\text{mean PFS for cetuximab}}{\sqrt{\text{number of patients taking cetuximab in CET + BSC vs BSC RCT}}}$$

$$= \frac{4.78}{\sqrt{110}} = 0.46 \text{ months}$$

7.1.3.1.2.2. Time on cetuximab treatment

The time on cetuximab treatment is an extremely important quantity because it affects the total mean cost of cetuximab acquisition and administration per person, and the former in particular is a critical driver of the cost-effectiveness of cetuximab vs BSC.

Ideally, we would model the mean total dose of cetuximab per patient with KRAS WT status, allowing for wastage of cetuximab. However, this data is not published. Alternatively we would model the dose intensity of cetuximab and the mean number of doses of cetuximab per patient with KRAS WT status (as for pantiumumab, see Section 7.1.3.1.3.2 [page 145]). Unfortunately, this information is also not published and could not be made available upon request (see Appendix 11). We have therefore assumed that people in the cetuximab+BSC vs BSC RCT received cetuximab for the entire duration of PFS. This is mainly informed by the finding that the median time on cetuximab treatment for patients with KRAS WT and KRAS mutant status combined was 8.1 weeks in the RCT of cetuximab+BSC vs BSC, which is virtually identical to the median PFS for all patients (i.e. KRAS WT and KRAS mutant status combined) of 8.2 weeks.(45) Both our model and Merck Serono's model predict that patients with KRAS WT status are progression free for a median of approximately 16 weeks. Therefore, we predict that patients with KRAS WT status also took cetuximab for the entire duration of PFS, for a median of 16 weeks, and a mean of 21 weeks.

In the RCT of cetuximab+BSC vs BSC, people took cetuximab until death, serious adverse events, progression, worsening symptoms of the cancer, or request by the patient, with or without the withdrawal of consent for continued follow-up.(45) While our assumption that people took cetuximab until progression allows for only the „death' and „progression' causes for cetuximab cessation, cetuximab treatment was rarely discontinued because of serious adverse events, given that Merck Serono note that: *'In the CO.17 study 11 patients discontinued cetuximab therapy among the 287 treated subjects, and only 3 patients amongst the 117 KRAS WT patients*

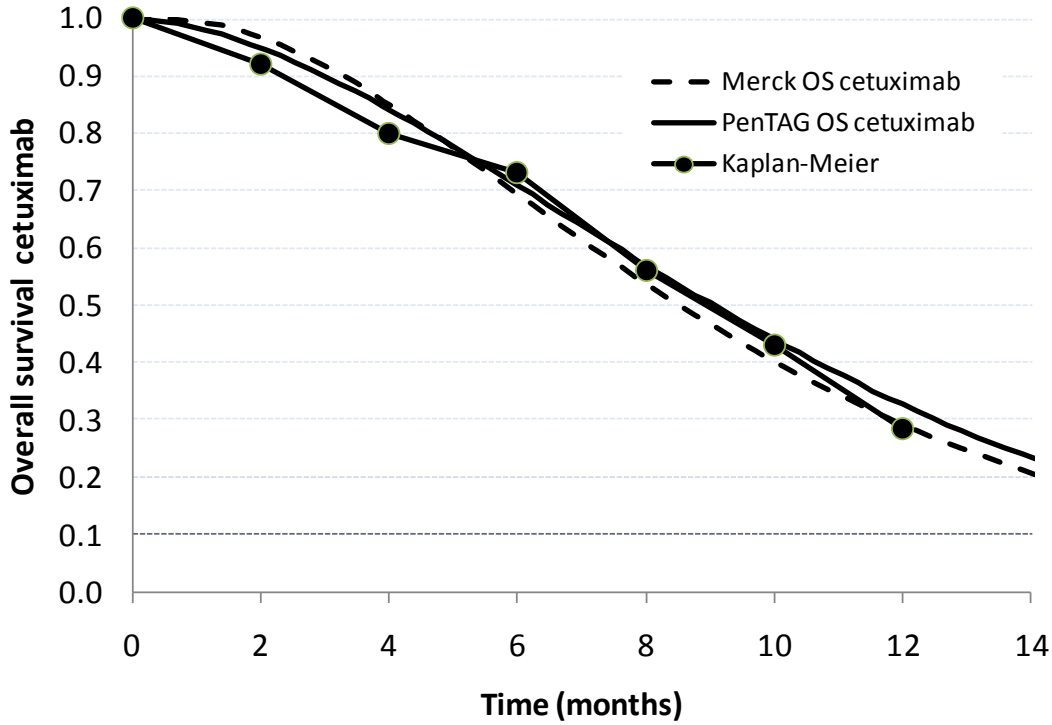
taking cetuximab stopped the therapy due to adverse events.' (see Appendix 11). We have no data on cetuximab cessation due to worsening symptoms of the cancer or request by the patient, with or without the withdrawal of consent for continued follow-up. Therefore, it is impossible to quantify cessation due to these factors.

For the PSA, the mean time on cetuximab treatment was assumed to equal the mean time in PFS, which we varied stochastically as explained in Section 7.1.3.1.2.1 (page 141).

7.1.3.1.2.3. OS for cetuximab+BSC

As for PFS for cetuximab+BSC (see Section 7.1.3.1.2.1, page 141.), we have based our estimate of OS for cetuximab+BSC on the analysis of the IPD by Merck Serono. In particular, we assume the same mean OS for cetuximab+BSC as that calculated by Merck Serono of 10.0 months. Next, we again specified that OS for cetuximab+BSC follows a Weibull function, and we read off the OS probabilities at monthly intervals from the published Kaplan-Meier graphs for patients with KRAS WT status.(3) We then fitted a Weibull curve to this data by minimising the sums of squares of differences between actual and fitted probabilities. We estimated the shape parameter, γ, of the Weibull from the shape parameter of this fit to the Kaplan-Meier curve. Finally, given that we have specified the mean, this then specifies the scale parameter, λ, of the Weibull, see Figure 10.

Figure 10. PenTAG and Merck Serono OS for CET+BSC group for KRAS WT people



We estimated the uncertainty in OS for the PSA in exactly the same way as for the uncertainty in PFS on cetuximab+BSC, as explained above (see Section 7.1.3.1.2.1, page 141). Our estimation of the standard error of mean OS assumes that few patients were censored in the cetuximab+BSC arm of the cetuximab+BSC vs BSC RCT. This assumption is less likely to hold for OS compared to PFS, but given the lack of further data, and the need for simplicity, this was again assumed.

Given the lack of further evidence, we set OS and PFS for cetuximab+BSC to be perfectly correlated, just as we did for OS and PFS for BSC.

7.1.3.1.3. Panitumumab+BSC

As explained above (Section 7.1.3.1, page 138), for the purposes of the indirect comparison, we chose the BSC treatment group from the cetuximab+BSC vs BSC RCT to represent the clinical effectiveness of the BSC treatment group. Therefore, in modelling the clinical effectiveness of panitumumab+BSC (time on treatment, PFS and OS), it is necessary to adjust the clinical effectiveness of panitumumab+BSC as reported in the RCT of panitumumab+BSC vs BSC(4) in the manner of the Bucher indirect comparison.(43) The implicit assumption is that the baseline patient characteristics in the two RCTs are reasonably similar, and indeed this is true (see Table 10, page 58).

7.1.3.1.3.1. PFS for panitumumab

In this section, we estimate PFS for panitumumab+BSC for the indirect comparison. First, we estimate the mean PFS for the BSC group corresponding to the panitumumab+BSC vs BSC RCT as 2.2 months, by calculating the area under the BSC PFS Kaplan-Meier graph, using probabilities at four-weekly intervals.

[redacted] Next, we estimated the mean PFS for the panitumumab+BSC group corresponding to the panitumumab+BSC vs BSC RCT as 4.0 months, by calculating the area under the panitumumab+BSC PFS Kaplan-Meier graph, using probabilities at four-weekly intervals.

[redacted]

Adjusting PFS for panitumumab+BSC for the indirect comparison using the Bucher method,(43) yields a mean of:

(mean PFS panitumumab+BSC from panitumumab+BSC vs BSC RCT)

X (mean PFS BSC from cetuximab+BSC vs BSC RCT) / (mean PFS BSC from panitumumab+BSC vs BSC RCT)

= 4.0 X 2.7 / 2.2 = 5.1 months.

This is our estimate of the mean PFS for the panitumumab+BSC group if panitumumab+BSC had been included as a third treatment group in the cetuximab+BSC vs BSC RCT.

Next, we specified that PFS for panitumumab+BSC follows a Weibull distribution. We then estimated the shape parameter γ of the Weibull by fitting a Weibull curve to the Kaplan-Meier panitumumab+BSC PFS curve at four-weekly intervals, by minimising the sums of squares of differences between actual and expected PFS.

Finally, given that we have specified the mean PFS for panitumumab+BSC and the shape parameter γ, this then specifies the scale parameter, λ, of the Weibull, given the formula for the mean of the Weibull.

We estimated the uncertainty in PFS on panitumumab+BSC for the PSA in exactly the same way as for BSC and cetuximab+BSC (Section 7.1.3.1.1.1 [page 138] and Section 7.1.3.1.2.1 [page 141]). Again, we modelled the uncertainty in the mean PFS by specifying that the mean PFS follows a gamma distribution, given that this appropriately models positive random variables, with mean of 5.1 months. In this case, the estimated standard error of the mean panitumumab+BSC PFS equals:

$$\approx \frac{\text{mean PFS for PAN + BSC}}{\sqrt{\text{number of patients taking PAN in PAN + BSC vs BSC RCT}}}$$

$$= \frac{5.1}{\sqrt{124}} = 0.45 \text{ months}$$

7.1.3.1.3.2. Time on panitumumab treatment

The mean time on panitumumab is a very important parameter in the estimation of the cost-effectiveness of panitumumab+BSC vs BSC. The RCT of panitumumab vs BSC reports a mean of 10 doses of panitumumab per person for those with KRAS WT status.(4) However, for the indirect comparison, we require the estimated number of doses of panitumumab if panitumumab+BSC had been a treatment group in the cetuximab vs BSC RCT. This is estimated by the Bucher indirect comparison method as:(43)

(number of doses of panitumumab in the panitumumab+BSC vs BSC RCT)

x (estimated mean PFS panitumumab+BSC for indirect comparison

/ mean PFS panitumumab in panitumumab+BSC vs BSC RCT)

For the deterministic analysis, this quantity equals:

= 10 x (5.1 / 4.0) = 12.7 doses.

Given that panitumumab is taken every two weeks, this corresponds to a treatment duration of 5.8 months = 0.49 years. Discounting has only a very small impact on the total drug acquisition costs, given that PFS is such a short duration. Nonetheless, we approximated for discounting in the cost of panitumumab acquisition by assuming that all panitumumab doses were taken at the mean time in PFS. We also used the adjusted number of panitumumab doses of 12.7 to estimate the total per person mean administration cost of panitumumab, as described below.

To estimate the mean number of doses of panitumumab for the PSA, we needed two further assumptions. First, we modelled the mean number of doses from the RCT of panitumumab+BSC vs BSC as a normal distribution, which is appropriate given the relatively small coefficient of variation, with mean 10 and standard error 10% of the mean, given that the standard error of mean PFS for panitumumab+BSC is approximately 10% of the mean PFS. Second, we modelled the mean PFS from the panitumumab+BSC vs BSC RCT as a normal distribution, with mean 4.0 and standard error of 0.36, with standard error estimated with two simplifying assumptions. The first was that PFS for panitumumab+BSC from the panitumumab+BSC vs BSC RCT approximately follows an exponential distribution. Indeed, we find this to be approximately true (gamma of Weibull = 1.2). We can then say that the standard deviation of PFS across patients equals the mean PFS, as this is a property of the exponential distribution. The second simplifying assumption is that no patients who started treatment with panitumumab+BSC in the RCT of panitumumab+BSC vs BSC were censored. Indeed, this also approximately true: only 7% of patients were censored.(4) In this case, the standard error of mean panitumumab+BSC PFS equals:

$$\frac{\text{standard deviation of PFS}}{\sqrt{\text{number of patients taking panitumumab in RCT}}} = \frac{\text{mean PFS}}{\sqrt{\text{number of patients taking panitumumab in RCT}}}$$

$$= \frac{4.0}{\sqrt{124}} = 0.36 \text{ months}$$

The estimated number of doses of panitumumab if panitumumab+BSC had been a treatment group in the cetuximab+BSC vs BSC RCT for the PSA is then calculated as described above for the deterministic case.

7.1.3.1.3.3. OS for panitumumab+BSC

In this section, we estimate OS for panitumumab+BSC for the indirect comparison using a similar method as we estimated PFS for panitumumab+BSC for the indirect comparison. First, we fitted a Weibull curve to OS for the panitumumab+BSC group corresponding to the panitumumab+BSC vs BSC RCT, by minimising the sums of squares of differences between the actual and estimated survival probabilities, using survival probabilities at four-weekly intervals. This gives a mean OS of 9.9 months. [redacted] based on analysis of the underlying IPD (see page 37, Amgen's submission).

Next we estimated the mean OS as 9.4 months for BSC from the panitumumab+BSC vs BSC,(4) again fitting a Weibull curve and by minimising the sums of squares of differences between the actual and estimated survival probabilities, using survival probabilities at four-weekly intervals. This is the mean OS for BSC without adjustment for the substantial cross-over of people from the BSC to the panitumumab+BSC treatment groups. Amgen's analysis of the IPD suggested that, after adjusting for cross-over, the mean OS in the BSC group is 2.7 months less than for the panitumumab+BSC group. This is discussed in detail in our critique of Amgen's submission (see Section6.4, page 128), and assumes that we can model OS for BSC patients with KRAS mutant status (including some people who cross-over) as an approximation for OS for BSC patients with KRAS WT status. We therefore estimate the mean OS for the BSC group as the mean OS for the panitumumab+BSC group minus the 2.7 months = 9.9 – 2.7 = 7.2 months.

Adjusting mean OS for panitumumab+BSC for the indirect comparison using the Bucher method yields:(43)

(mean OS panitumumab+BSC from panitumumab+BSC vs BSC RCT)

x (mean OS for BSC in cetuximab+BSC vs BSC RCT)

/ (mean OS for BSC in panitumumab+BSC vs BSC RCT)

= 9.9 X 6.2 / 7.2 = 8.5 months.

This is our estimate of the mean OS for the panitumumab+BSC group if panitumumab+BSC had been included as a treatment group in the cetuximab+BSC vs BSC RCT.(3)

Next, we specify that OS for panitumumab+BSC follows a Weibull distribution. We then use the shape parameter γ of the Weibull from our fit to the Kaplan-Meier panitumumab OS curve, described above. Finally, given that we have specified the OS mean and the shape parameter γ, this then specifies the scale parameter, λ, of the Weibull.

We estimated the uncertainty in OS for panitumumab+BSC for the PSA in exactly the same way as for the uncertainty in PFS on panitumumab+BSC (see Section 7.1.3.1.3.1 [page 144]). Our estimate of the standard error of mean OS assumes that few patients were censored in the panitumumab+BSC arm of the panitumumab+BSC vs BSC RCT: 14% of patients were censored.(4)

Given the lack of further evidence, we set OS and PFS for panitumumab+BSC to be perfectly correlated, just as we did for OS and PFS for BSC and for cetuximab+BSC.

7.1.3.1.4. Cetuximab+irinotecan

The pivotal BOND trial and supportive study MABEL trial used to confirm the clinical efficacy of cetuximab in combination with irinotecan in the pre-treated mCRC setting did not have KRAS status as a prerequisite for recruitment, and no retrospective KRAS analysis has been systematically undertaken. Given that we do not have direct randomised evidence for PFS, time on treatment, and OS for patients with KRAS WT status on cetuximab+irinotecan, some assumptions to estimate these quantities have to be made. These complex assumptions are critical to an understanding of the estimation of the cost-effectiveness of cetuximab+irinotecan, and the associated uncertainty. Details of the methods used are given in Appendix 15 (PFS) and Appendix 16 (OS).

7.1.3.1.4.1. PFS for cetuximab+irinotecan

PFS is estimated in three stages:

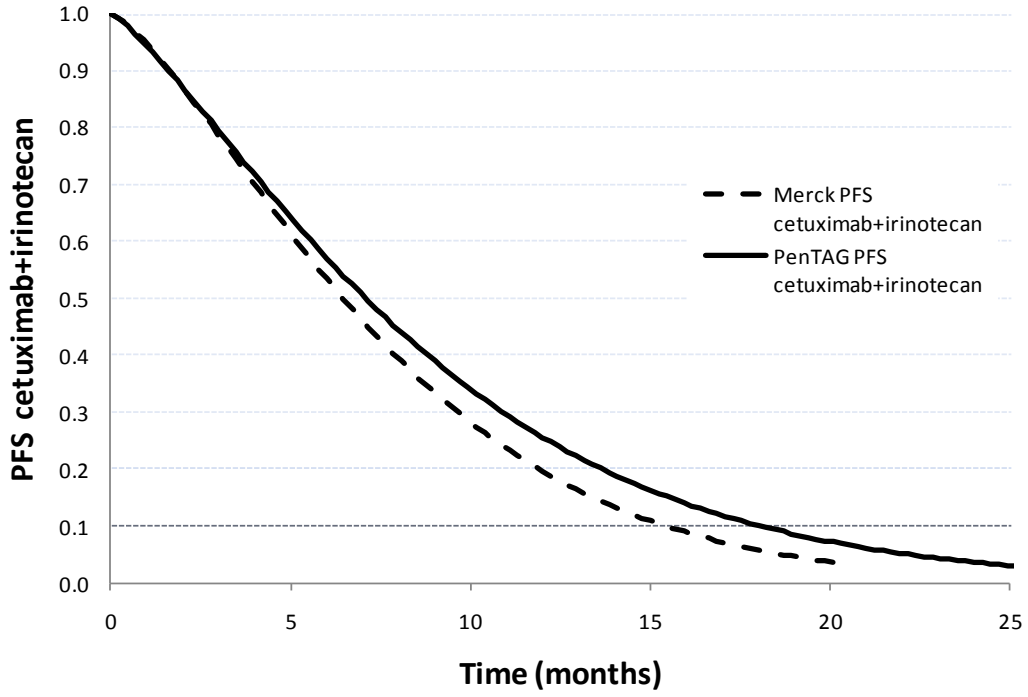
- First, we estimate the median PFS for patients with KRAS WT status on cetuximab+irinotecan in the BOND RCT of cetuximab+irinotecan vs cetuximab+BSC (as this is not reported).
- Next, we adjust this to estimate the median PFS for patients with KRAS WT status on cetuximab+irinotecan for our model.
- Finally, we assume that PFS follows a Weibull distribution (as for cetuximab+BSC) with the same shape parameter as for cetuximab+BSC.

Detailed description of these three stages and the assumptions made is given in Appendix 15. We estimate a mean PFS of 8.8 months for patients receiving cetuximab+irinotecan. This is similar to Merck Serono's estimated mean of 7.8 months see Figure 11 (page 149).

We note briefly that Merck Serono estimate PFS for patients with KRAS WT status on cetuximab+irinotecan by applying the HR of 0.47 between cetuximab+irinotecan (patients with KRAS WT status) and cetuximab monotherapy (patients with KRAS WT status) from De Roock

to their curve fit to PFS for cetuximab monotherapy (patients with KRAS WT status) (which they estimated from the cetuximab+BSC vs BSC RCT) (page 104, Merck Serono's submission). Merck Serono state that they estimated the HR by reading off survival data from the PFS curves published in De Roock and colleagues (2008)(12) (see Appendix 11). However, it is difficult to verify the HR, because it is not published in De Roock and colleagues (2008). Furthermore, the method used by Merck Serono introduces a good deal of uncertainty because it relies on data on cetuximab monotherapy (patients with KRAS WT status) for whom there are only 18 people.

Figure 11: PenTAG and Merck Serono PFS for CET+IRIN for patients with KRAS WT status



7.1.3.1.4.2. Uncertainty in PFS for cetuximab+irinotecan

We estimated the uncertainty in PFS on cetuximab+irinotecan for the PSA in a similar, but slightly different way to cetuximab+BSC and panitumumab+BSC. In this case, we modelled the uncertainty in the median PFS, not the mean PFS, given that our estimation of PFS for cetuximab+irinotecan is based on the median. First, for simplicity, we fixed the shape value gamma of the Weibull for PFS. Next, we specified that the median (not the mean) PFS follows a gamma distribution, which is appropriate for positive random variables, with mean of 7.1 months, (see Stage 2, Appendix 15). We then estimated the standard error of the median PFS as simply equal to 20% of the mean: 1.4 months. This method was chosen as being the most pragmatic, given the lack of evidence on this quantity. Note that the ratio of the standard error to the mean of the median, at 20%, is greater than the corresponding ratio for the mean PFS for BSC, cetuximab and panitumumab (all approximately 10%), to reflect the extra uncertainty in PFS for

cetuximab+irinotecan. Finally, the scale parameter, λ, of the Weibull for PFS is back-calculated from the fixed gamma and variable median, using the following formula for the median t* of the Weibull: $0.5 = \exp(-\lambda t^{*\gamma})$.

7.1.3.1.4.3. Time on cetuximab+irinotecan treatment

The time on cetuximab+irinotecan treatment is an extremely important quantity because it affects the total mean cost of cetuximab+irinotecan acquisition per person, which is a critical driver of the cost-effectiveness of cetuximab+irinotecan vs BSC.

Unfortunately, the mean duration of cetuximab+irinotecan treatment for patients with KRAS WT status in the BOND RCT is not reported. In the absence of this crucial information, we assume that all patients take cetuximab+irinotecan treatment for the entire duration of PFS. This gives a median duration of cetuximab+irinotecan treatment of 31 weeks, and a mean duration of 38 weeks.

Given the importance and uncertainty of the mean duration of cetuximab+irinotecan treatment, we vary the mean duration of irinotecan treatment and the mean duration of cetuximab treatment in our sensitivity analyses.

There is some support for our base case assumption that patients in the cetuximab+BSC and cetuximab+irinotecan treatment groups in the BOND RCT took cetuximab until progression as follows. The median PFS for all patients (KRAS WT and KRAS mutant status combined) in the cetuximab+BSC treatment group was 1.5 months = 6.5 weeks, and the median number of cetuximab doses in the cetuximab+BSC treatment group was seven.(57) Given that cetuximab was given once per week in the BOND RCT, this suggests that it was taken until disease progression. Similarly, the median PFS for all patients (KRAS WT and KRAS mutant status combined) in the cetuximab+irinotecan treatment group was 4.1 months = 17.8 weeks, and the median number of cetuximab doses in the cetuximab+irinotecan treatment group was virtually identical, at 18.(57)

As for treatment with cetuximab (see Section 7.1.3.1.2, page 141), Merck Serono forced the mean time on cetuximab+irinotecan treatment in their model to equal their estimate of the mean time on cetuximab+irinotecan treatment for patients with KRAS WT status in the BOND RCT of cetuximab+irinotecan vs cetuximab+BSC (see Table 59 [page 97], Merck Serono's submission). However, we believe that it was a very serious limitation that Merck Serono did not state their assumed mean time on cetuximab+irinotecan treatment of 19 weeks = 4.4 months (although this was stated in their model), and also a very serious omission that they did not explain the derivation of this figure in their report. We questioned Merck Serono on the derivation of the 19

weeks, and they replied as follows: *'The BOND study compared cetuximab plus irinotecan vs cetuximab monotherapy, but was undertaken before KRAS status was identified as a marker for response; hence the mean number of infusions is not available for the KRAS WT population. For the ITT analysis, the mean number of infusions was 18 for those on cetuximab plus irinotecan and 7 for those on cetuximab monotherapy (Cunningham et al, 2004) ... The mean number of cetuximab and irinotecan combination therapy infusions within the model for the KRAS WT population was not increased proportionately as per cetuximab monotherapy. The increasing side effects with combination therapy are likely to limit the treatment duration'* (see Appendix 11).

We strongly disagree with Merck Serono's derivation of the mean duration of cetuximab+irinotecan treatment for three important reasons. First, it seems highly unlikely that patients with KRAS WT status would take cetuximab+irinotecan for the same time as those patients with KRAS mutant status. It is far more likely that the duration of treatment would be longer for patients with KRAS WT status than for those who with KRAS mutant status, and therefore longer for patients with KRAS WT status than all patients combined. This is because cetuximab is known to improve PFS for patients with KRAS WT status, but not for those with KRAS mutant status. Furthermore, in BOND, drug treatment was given until disease progression or adverse events and three sources cite a substantially longer PFS time for cetuximab+irinotecan treatment for patients with KRAS WT status compared to those with KRAS mutant status: 7.8 months vs 2.8 months,(12) 7.4 months vs 2.1 months,(84) 5.5 months vs 2.8 months.(81) Second, Merck Serono has equated means with medians: they set the mean duration of cetuximab+irinotecan treatment for patients with KRAS WT status equal to the median duration of cetuximab+irinotecan treatment for all patients. Given that the mean is usually greater than the median; for example, by a factor of 1.44 for the exponential distribution, Merck Serono's estimate for the mean treatment duration of cetuximab+irinotecan for all patients in BOND is probably an underestimate. Third, Merck Serono has made no attempt to adjust the treatment duration from BOND for the indirect comparison with BSC.

For the PSA, the mean time on cetuximab+irinotecan treatment was assumed to equal the mean time in PFS, which we varied stochastically as explained in the previous section.

7.1.3.1.5. OS for cetuximab+irinotecan

Here, we estimate OS for cetuximab+irinotecan for patients with KRAS WT status for the purposes of the indirect comparison. We first note that both our estimate and Merck Serono's estimate of OS are highly uncertain given the lack of randomised evidence, and that we have both had to make substantial assumptions. Furthermore, we believe that the uncertainty in OS for cetuximab+irinotecan is considerably greater than for PFS.

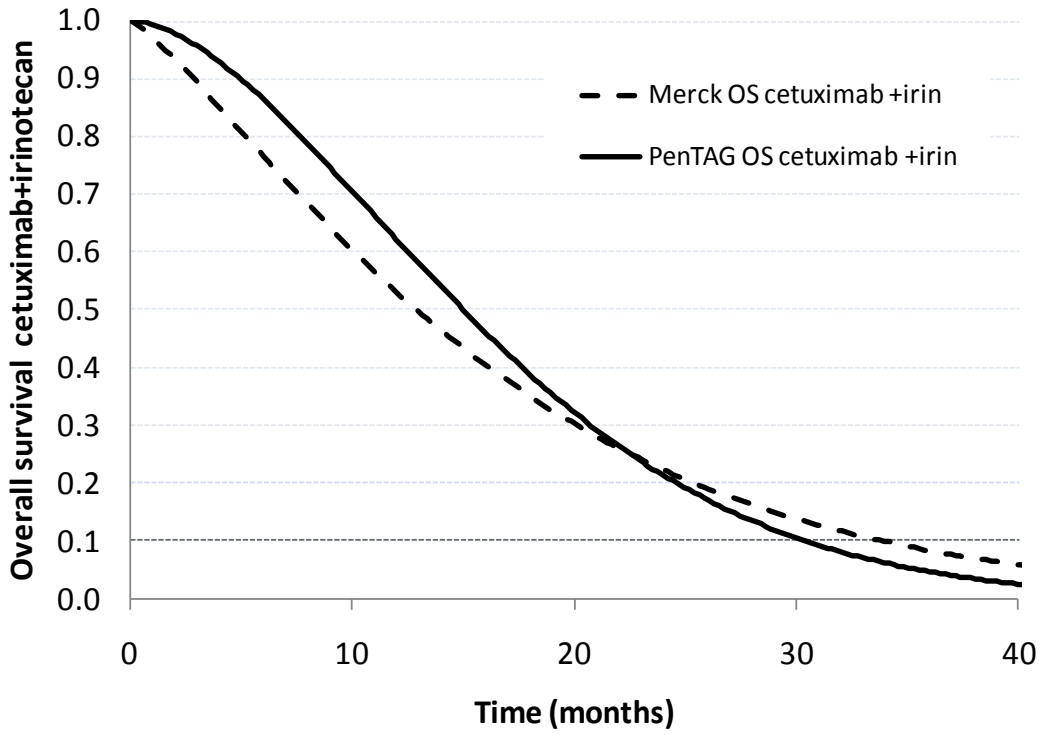
Our method to estimate OS proceeds in two stages:

- First, we estimate the median OS for patients with KRAS WT status on cetuximab+irinotecan for our model.
- Next, we assume that OS follows a Weibull distribution (as for cetuximab) with the same shape parameter as for cetuximab+BSC.

Detailed description of these two stages and the assumptions made is given in Appendix 16. We estimate a mean OS of 16.6 months for patients receiving cetuximab+irinotecan. This is similar to Merck Serono's estimated mean of 16.3 months (see Figure 12).

Both our estimate and Merck Serono's estimate of OS for patients with KRAS WT status on cetuximab+irinotecan are highly uncertain given that we have both had to make substantial assumptions. Therefore, we also present sensitivity analyses where we use different methods of estimating OS (see Appendix 16).

Figure 12. PenTAG and Merck Serono OS for CET+IRIN for patients with KRAS WT status



7.1.3.1.6. Uncertainty in OS for cetuximab+irinotecan

We estimated the uncertainty in OS for the PSA in exactly the same way as for the uncertainty in PFS on cetuximab+irinotecan, namely by modelling the uncertainty in median OS. We estimated the standard error of the median OS as equal simply to 20% of the mean of the median, to reflect the substantial uncertainty in OS.

Given the lack of further evidence, we set OS and PFS for cetuximab+irinotecan to be perfectly correlated, just as we did for BSC, panitumumab+BSC and cetuximab+BSC.

7.1.3.2. Utilities

7.1.3.2.1. HRQoL literature

Au and colleagues (2009) describe the HRQoL information collected using the EORTC QLQ-C30 during the cetuximab+BSC vs BSC RCT.(47)

Compliance was high at baseline (>90%), but declined over time, particularly for BSC. The authors believe that this selective non-compliance may make QoL for cetuximab+BSC conservative because more people on BSC than on cetuximab+BSC who were in poor health stopped completing the questionnaire. Conversely, given that the RCT was not blinded, people's judgement of their QoL could have been biased downward for people on BSC, and biased upwards for those on cetuximab (due to a potential placebo effect). Also, given that those people who complete the questionnaire are likely to be healthier, on average, than those who do not, all utilities from Au and colleagues (2009) are likely to be overestimates.(47)

For patients with KRAS WT status, treatment with cetuximab+BSC resulted in less PF deterioration over time than for people receiving BSC. Treatment with cetuximab+BSC resulted in improved GHS at eight weeks compared to baseline, whereas the GHS of people on BSC worsened. At 16 weeks, the GHS for people on cetuximab+BSC was approximately unchanged from baseline, whereas the GHS for people on BSC was much reduced from baseline.

The cost-effectiveness study of Mittmann and colleagues (2009)(8) reports that the HUI3 was also used in the RCT of cetuximab+BSC vs BSC. Whilst the NICE reference case(13) states a preference for the EQ-5D, Mittmann and colleagues (2009) present the only utility data from the RCT of which we are aware. Health was assessed at baseline, and at four weeks, eight weeks, 16 weeks, and 24 weeks after randomisation (Table 42, page 154). Merck Serono claims that these values relate to patients with KRAS WT status only (see Appendix 11). However this is difficult to believe given that there were more patients in the utility data set than there were patients with KRAS WT status in the RCT.

Table 42. Health utilities from RCT of CET+BSC vs BSC reported by Mittmann and colleagues (2009)(8)

Time of assessment	Cetuximab+BSC Mean±SD (N)	BSC Mean±SD (N)
Baseline	0.72 ± 0.23 (263)	0.71 ± 0.24 (260)
Week 4	0.73 ± 0.26 (220)	0.68 ± 0.26 (184)
Week 8	0.73 ± 0.24 (190)	0.66 ± 0.28 (149)
Week 16	0.73 ± 0.24 (119)	0.63 ± 0.30 (72)
Week 24	0.77 ± 0.22 (82)	0.70 ± 0.24 (36)

BSC, best supportive care; SD, standard deviation

At each follow-up time, mean utility scores for cetuximab+BSC were higher than for BSC. For the cetuximab+BSC arm, utilities remained largely unchanged over time. By contrast, utilities in the BSC arm generally declined over time, with the exception of the last time point, which may have been unrepresentative, due to the relatively small sample size.

Merck Serono assumed the utilities from the RCT of cetuximab+BSC vs BSC in their economic model given in Table 43 (below). These utilities were calculated from the HUI3 index, although Merck Serono provides very little detail of the calculations. We agree with Merck Serono's claim that the QoL data reflects both the positive aspects of a response to treatment with cetuximab+BSC and the negative aspects of treatment such as AEs.

Table 43. Utilities used by Merck Serono in their economic model

	CET+BSC	BSC
Progression-free survival		
No.of patients	294	170
Mean utility (se)	0.809 (0.011)	0.746 (0.017)
Progressive disease		
No. of patients	83	85
Mean utility (se)	0.789 (0.025)	0.693 (0.027)

BSC, best supportive care; CET, cetuximab; se, standard error

However, we are concerned that, although both Mittmann and colleagues (2009)(8) and Merck Serono both report utilities estimated by the HUI3, the values reported by Merck do not always tally with the values quoted in Mittmann and colleagues (2009). For example, the Mittmann

values would suggest that the utility for PFS for cetuximab+BSC should be about 0.73, whereas Merck Serono report 0.81.

Merck Serono's estimated utilities in PD are also a limitation of the approach. First, due to high drop-out rates, there are far fewer utility observations for people in PD than in PFS. Second, at the point of data cut-off, a large proportion of patients were still alive in both treatment arms.(45) This means that the utilities for PD do not include many time points when patients are close to death. Therefore, we suspect the true mean utilities for PD for BSC and cetuximab+BSC, averaged over the total time in PD, may be lower than the values used by Merck Serono.

In the economic evaluation of bevacizumab for first-line treatment and cetuximab plus irinotecan for second-line and further treatment of mCRC, Tappenden and colleagues (2007)(41) assumed a utility of 0.80 in PFS and 0.60 in PD, independent of treatment. The PFS value of 0.80 was taken from HUI3 responses from a small study of 173 people with CRC of various stages taken from the US SEER database. The PD value of 0.60 appears to have been a „best guess' given the dearth of relevant literature.

Odom and colleagues (2011) assessed the HRQoL of people in the RCT of panitumumab+BSC vs BSC.(49) QoL was assessed using the EQ-5D, NICE's preferred instrument,(13) using the VAS, and using the NCCN FCSI. Data was available for 208 patients with KRAS WT status (112 panitumumab+BSC arm, 96 BSC arm). Only outcomes before disease progression up to Week 17 of the study were used due to small sample sizes after this time. The QoL of patients with KRAS WT status taking panitumumab+BSC was better than for people on BSC, with a significant difference in the EQ-5D utility of 0.22 (95% CI: 0.12 – 0.32).(49) Similar to the QoL study in the cetuximab+BSC vs BSC RCT, there was much missing data, particularly in the later weeks, although patients receiving panitumumab+BSC had a higher percentage of available data for each post-baseline week compared with those receiving BSC. This could bias against panitumumab, and this is confirmed by analysis in Odom and colleagues (2011). Also as in the cetuximab+BSC vs BSC RCT, the panitumumab+BSC vs RCT was not blinded. Therefore, people's judgement of their QoL could have been biased downward for people on BSC, and biased upwards for those on panitumumab+BSC. Also, given that those people who complete the questionnaire are likely to be healthier, on average, than those who do not, all utilities from Odom and colleagues (2011) are likely to be overestimates.

7.1.3.2.2. Utilities in PenTAG model

Our choice of utilities is given in Table 44 (page 156) and is based on those supplied by Merck Serono. This seems appropriate because the utilities were collected in the RCT of cetuximab+BSC vs BSC, the same source as our baseline efficacy estimates. These utilities are

probably overestimates because people who complete HRQoL questionnaires are likely to be healthier, on average, than those who do not. In addition, given that both RCTs were not blinded, people's judgement of their QoL could have been biased upwards for those on cetuximab+BSC and panitumumab+BSC, due to the placebo effect. However, without further information, it is not possible to quantify the bias in either case.

It is impossible to accurately model the correlation between the utilities. Therefore, we took the pragmatic view of assuming correlation between all utilities, as shown in Table 44. This then captures various common-sense ideas; for example, that the utility in PD should always be less than the utilities in PFS, and that if the utility for BSC PFS is higher than expected, then so too should be the utility for all the other treatments in PFS.

Table 44. Utilities used in PenTAG model

	PFS			PD		
	Mean (se)	**Correlation**	**Source**	**Mean (se)**	**Correlation**	**Source**
BSC	0.75 (0.08)	Baseline	MS submission	0.69 (0.07)	Correlated with BSC PFS	MS submission
CET+BSC	0.81 (0.08)	Correlated with BSC PFS	MS submission	0.69 (0.07)	Set equal to BSC PD	Adjusted from MS submission
PAN+BSC	0.87 (0.09)	Correlated with BSC PFS	Based on Odom et al. See also calcs. in Appendix 12	0.69 (0.07)	Set equal to BSC PD	MS submission
CET+IRIN	0.75 (0.08)	Set equal to BSC PFS	MS submission	0.69 (0.07)	Set equal to BSC PD	Adjusted from MS submission

BSC, best supportive care; CET, cetuximab; IRIN, irinotecan; MS, Merck Serono; PAN, panitumumab; PD, progressive disease; PFS, progression free survival; se, standard error

For BSC, we use the mean utilities quoted by Merck Serono, 0.75 in PFS and 0.69 in PD, taken from the RCT of cetuximab+BSC vs BSC.(3) For cetuximab monotherapy, as Merck Serono, we used the mean utility of 0.81, also taken from the RCT of cetuximab+BSC vs BSC. Our clinical advisor believes that it is indeed plausible that people taking cetuximab+BSC in PFS have a higher HRQoL than people in PFS in the BSC group, as follows. First, HRQoL for cancer patients is broadly affected by two factors: tumour bulk and the degree of drug toxicity. Given

that cetuximab is not particularly toxic (for example, compared to chemotherapy drugs such as irinotecan), the HRQoL of people in PFS on cetuximab+BSC would be similar to that for people in PFS on BSC. Second, tumour bulk will, on average, be lower in PFS for patients taking cetuximab, because some patients respond to cetuximab; i.e. their tumour shrinks.

However, the mean utility of 0.79 for patients in the cetuximab+BSC treatment group in PD seems too high. This value is only marginally lower than the 0.81 for patients in the cetuximab+BSC group in PFS, and is substantially higher than the utility of 0.69 for patients in the BSC group in PD. This may result from differential time spent in PD by those treated with BSC and CET+BSC, leading to questionnaires being completed by patients who had been in PD for a longer time, on average, in the BSC group than in the cetuximab+BSC group. This is due to the fairly short data cut-off time, and the fact that patients in the BSC group progressed faster than those in the cetuximab+BSC group. We sought clarification from Merck Serono on this point. Merck Serono did not deny this assertion, but replied: *'The assumption in the model simplifies the detailed observations by assuming one utility weight per disease state. There may be biases caused by the fact that the model assumes the same utility in PFS and from progression until death, but it is not likely to affect the cost effectiveness.'* (see Appendix 11).

A mean utility of 0.69 for patients in the cetuximab+BSC treatment group in PD, the same as for patients in the BSC group in PD seems more appropriate. Indeed, we set the mean utility for patients in all groups in PD equal, at 0.69, and for the PSA, we set the utility for all patients in all groups in PD equal within each simulation. Our justification is as follows: all patients in PD, regardless of treatment group, are, by definition, off active drug treatment and as such there is no drug toxicity. Second, tumour bulk will be similar for all patients, regardless of treatment group in PD, given that tumour bulk is a major criterion for disease progression.

The value of 0.69 for all patients in PD is probably an overestimate because it is likely that many patients were alive for several months after their last HRQoL questionnaires, because of the limited data cut-off time. However, it is impossible to quantify the magnitude of any such bias without access to the detailed utility IPD.

Next, we used the utilities measured in the RCT of panitumumab+BSC vs BSC, published in Odom and colleagues (2011)(49) to estimate that the mean utility in PFS for people taking panitumumab+BSC is 0.12 higher than for people in PFS on BSC. Similar to the assertion that the utility of patients receiving cetuximab+BSC is higher than for patients in PFS in the BSC group, our clinical expert is satisfied with the analogous finding for patients receiving panitumumab+BSC. Odom and colleagues (2011) do not provide absolute utilities, only difference from baseline. Detailed calculations are given in Appendix 12, but broadly, we

calculate the increment in utility by weighting the PFS curve for panitumumab by the decrease in utility from baseline for panitumumab+BSC over time, and weighting the PFS curve for BSC by the decrease in utility from baseline for BSC over time. We then estimate the mean utility for people in PFS on panitumumab+BSC in the manner of an indirect comparison, as the utility for people on BSC from the cetuximab+BSC vs BSC RCT plus the difference in utility between panitumumab+BSC and BSC from the panitumumab+BSC vs BSC RCT, which equals 0.75 + 0.12 = 0.87. Although this value is evidence based, we caution that it is high compared with that corresponding to the UK general population.

Finally, we assume that the mean utility for people in PFS taking cetuximab+irinotecan is equal to 0.75, which is the utility for people in PFS in the BSC group. Furthermore, in the PSA, we assume that the PFS utilities for people in the BSC and cetuximab+irinotecan groups are equal within each simulation. Conversely, Merck Serono chose a mean utility of 0.81 for people in PFS taking cetuximab+irinotecan, the same as for patients in PFS taking cetuximab+BSC. As stated above, HRQoL is influenced both by tumour mass and drug toxicity. On the one hand, we might expect the HRQoL for people in PFS on cetuximab+irinotecan to be higher than for patients in PFS in the BSC group because the tumour mass for patients in PFS on cetuximab+irinotecan is, on average, smaller than for patients in PFS in on BSC. On the other hand, one might expect the HRQoL for people in PFS on cetuximab+irinotecan to be lower than for patients in the BSC group because irinotecan is a toxic chemotherapy. On balance, our clinical advisor suggests that the mean utility for patients taking cetuximab+irinotecan is probably lower than for patients in PFS in the BSC treatment group. It is difficult to estimate the net effect, but note that Starling and colleagues (2007)(10) report that in the MABEL single-arm study of cetuximab+irinotecan, the mean utility, as assessed by the EQ-5D, was 0.746, which equals our estimate of 0.75.

For the PSA, we modelled all utilities as beta distributions. We could have taken the standard errors of the utilities for cetuximab+BSC and BSC from the RCT of cetuximab+BSC vs BSC; however, this would only capture uncertainty within the RCT. Instead, we attempted to capture broader uncertainty, for example, to allow for the fact that utilities in PD were not collected throughout the PD of all patients, and to allow for extra uncertainty given that not all people completing the HRQoL questionnaires. This broader uncertainty was achieved by setting the standard errors of all utilities equal to 10% of the mean of each utility. Indeed, this is similar to Merck Serono's approach of setting the standard error equal to 20% of the mean for variables for which data on uncertainty is not available. We chose the standard error as 10% because this gave a plausible range of simulated utilities, given our experience of the utilities in other disease areas. Although the standard errors are clearly approximate, our method seems to be reasonably pragmatic.

It is impossible to accurately model the correlation between the utilities. Therefore, we took the pragmatic view of assuming correlation between all utilities, as shown in Table 44 (page 156). This then captures various common-sense ideas; for example, that the utility in PD should always be less than the utilities in PFS, and that if the utility for BSC PFS is higher than expected, then so too should be the utility for all the other treatments in PFS.

We did not model additional utility decrements associated with adverse events in the base-case, as our utilities reflect the experiences of people on treatment and therefore include treatment-related adverse events which did not result in treatment discontinuation.

7.1.3.3. Costs

We model the following costs: KRAS testing, drug acquisition, drug administration, consultant outpatient visits, CT scans, BSC in PD and treatment for adverse events. All costs are inflated to 2011–12 values where appropriate.

In addition to the cost of drug acquisition, mean drug costs per person allow for treatment duration (see Section7.1.3.1, page 138) and dose intensity (Section 7.1.3.3.3 , page 162).

7.1.3.3.1. Costs of EGFR and KRAS testing

Before treatment with cetuximab+BSC, tumour tissue samples must be tested for both KRAS status and EGFR expression before initiation of treatment (page 16, Merck Serono's submission). The same is true for treatment with panitumumab+BSC and cetuximab+irinotecan. There are no testing costs for people on BSC.

When we model the mean cost of testing per EGFR expressing mCRC patient with KRAS WT status, we need to cost for all patients who take test the tests, not just for those who are EGFR expressing and KRAS WT status. This is because, although people who test negative will not receive the drug treatment, they will nonetheless incur the testing costs. The total cost of the EGFR test per person in the model is then taken as the cost of a test divided by the proportion of people who are EGFR expressing, and similarly for the KRAS test.(85)

In common with Merck Serono, we assume a cost per KRAS test of £160.(86) We assume no cost for an EGFR test on the basis that the test is automatically calculated from a patient's creatinine level, which would routinely be measured as part of standard the urea and electrolytes blood test.

We set the proportion of people with KRAS WT disease as 54%. This is taken from Merck Serono's submission: *'Global clinical trial data indicates that ... approximately 30-50% have KRAS WT disease (Erbitux SmPC, November 2010). A more accurate estimate for the proportion*

of patients with KRAS WT disease is available from local KRAS testing facilities in Wales. The figure of 54% with KRAS WT disease from the local laboratories has consequently been used throughout the submission' (page 16, Merck Serono's submission).

Combining this information, we assume a cost for KRAS testing per person tested as £160 / 54% = £296 for all treatments apart from BSC, for which the cost was set at zero. This cost is very low compared with other costs, such as for drug acquisition. For the PSA, we modelled the cost of a KRAS test as a gamma distribution, independent of all other model parameters. It is very difficult to select an appropriate standard error. Therefore, we chose the pragmatic solution of setting the standard error equal to 20% of the mean.

7.1.3.3.2. Drug prices

Table 45 presents the drug prices, which have been taken from BNF 61 2010(73) for panitumumab and irinotecan. The price of cetuximab was provided by Merck Serono, and NICE have instructed us to use this value.

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Table 45. Drug prices used in the PenTAG model

Dose and frequency	Price	Cost per month model cycle	
		No vial wastage	With vial wastage
Cetuximab (Eribitux®)			
Initially 400 mg m^{-2} body area, followed by weekly 250 mg m^{-2}	£136.50 per 20 ml (100 mg) vial, £682.50 per 100 ml (500 mg) vial[a]	£3,108 first month, £2,730 subsequently	£3,421 first month, £3,026 subsequently
Panitumumab (Vectibix®)			
6 mg/kg every 2 weeks	20 mg/mL, net price 5-mL vial = £379.29, 20-mL vial = £1517.16	£3,693	£4,104
Irinotecan (generic)			
180 mg m^{-2} every 2 weeks	2-mL vial, 20 mg/mL = £49.03	£882	£935

[a] The price of cetuximab is given by Merck. The price quoted in BNF 61(73) is higher, at £178.10 per 20 ml (100 mg) vial, £890.50 per 100 ml (500 mg) vial.

In common with Merck Serono, we assumed a dosage of irinotecan of 180mg m^{-2} every two weeks. Indeed, members of Merck Serono's advisory board (see Appendix 1, Merck Serono's submission) agreed that most clinicians in the UK follow this regime. In common with Merck

Serono, we assumed the generic price for irinotecan, although this is not an important assumption because the price of the branded version of irinotecan, Campto®, is very similar.

All drugs are given intravenously in fixed vial sizes. Any unused drug left in the vials after administration is discarded, partly to avoid contamination; this is thought to be common practice across the UK.(75) Therefore, in our base case, we assumed total wastage of all drugs that remain in vials at the end of the infusion for each patient. Also in common with Merck Serono, we assumed the smallest vial sizes for all drugs to minimise the drug costs per patient, after allowing for wastage of drugs.

The doses of cetuximab and irinotecan are given proportional to BSA. Merck Serono assumed a BSA of 1.79m^2, representing the mean value from Sacco and colleagues (2010).(87) In this study, the authors calculated the BSA of 3,613 patients receiving chemotherapy for various cancers in the UK in 2005 from the height and weight, using the Dubois and Dubois method (also quoted by Merck Serono): BSA (m^2) = 0.007184 x weight $(kg)^{0.425}$ X height $(cm)^{0.725}$. Merck Serono's value of 1.79 m^2 is the mean over several cancers and over men and women.

As is standard practice in HTA, Merck Serono then assumed that the BSAs of all patients are the same, 1.79 m^2. However, in reality weights, heights and surface areas vary across people and, as such, the amount of drug wastage will also vary. As suggested by Sacco and colleagues, we captured this by modelling the distribution of body surface areas in a population of people receiving palliative chemotherapy for CRC, with 66% males, 34% females, and assumed the typical sex mix in the RCTs for mCRC. We then calculated the total drug used, including wastage, for each patient in this range, and then took the average of these dosages. The details are given in Appendix 13.

The mean BSA 1.79 m^2 cited by Merck Serono refers to people with a range of cancers. To be more precise, the mean is 1.85 m^2 for people receiving palliative chemotherapy for colon cancer with 66% males, 34% females. If we assume all patients have the same BSA of 1.85 m^2, the dose per administration for all patients, allowing for wastage, is 500 mg (after the first dose). However, using our methodology of assuming a distribution for doses across patients, the mean dose per patient per administration, allowing for wastage, is 511 mg. Similarly, the corresponding figures for irinotecan are 360 mg and 352 mg. In these cases, the effect of assuming a distribution for dosages has little effect on the mean dose per patient, and hence on cost-effectiveness. However, this is coincidental. Sacco and colleagues found that cost-effectiveness can change substantially.

The dose of panitumumab is proportional to weight, not BSA. Merck Serono assumed that the weights of all patients are the same, at 64 kg. Again, we modelled the distribution of body

weights in a population receiving palliative chemotherapy for CRC, with 66% males, 34% females. The details are given in Appendix 13 and we calculate the mean weight as 74.9 kg.

[redacted]

If we assume that all patient have the same mean weight of 74.9 kg, the dose per administration, allowing for wastage, is 500 mg. However, assuming a distribution for the doses across patients, the mean dose per patient per administration, allowing for wastage, is 499 mg. Again, assuming a distribution for dosages has little effect on the mean dose per person, and hence on cost-effectiveness.

We assume no drug costs for patients in the BSC treatment arm. This reflects the experience of the cetuximab vs BSC RCT; i.e. only a very small proportion of patients in the BSC arm took expensive drug treatment (for example, 2.5% of patients took irinotecan before progression) (see page 164, Merck Serono's submission).

7.1.3.3.3. Dose intensities

For consistency between the costs of the drugs and the clinical outcomes, it is necessary to model the amounts of the drugs actually taken in the relevant clinical trials. The dose intensity of a drug is defined as the amount of drug administered in a trial as a proportion of the amount that would have been administered if there had been no dose reductions or dose interruptions. This does not include people who withdraw from treatment due to adverse events. Mean dose intensities per person used in our model are given in Table 46. We assume a dose intensity of panitumumab+BSC of 100%,

[redacted]

Table 46. Dose intensities used in the PenTAG model

Drug	Treatment arm	Mean dose intensity[a]	Standard error	Source
CET	CET+BSC	98%	0.8%	Merck Serono submission, page 110
CET	CET+IRIN	94%	1.6%	Merck Serono submission, page 110
IRIN	CET+IRIN	90%	2.0%	Merck Serono submission, page 110
PAN	PAN+BSC	100%	0.0%	Amgen response to PenTAG questions

BSC, best supportive care; CET, cetuximab; IRIN, irinotecan; PAN, panitumumab

[a]Dose intensities from Merck are mean values, not medians

For the PSA, we modelled the dose intensities as beta distributions, where we assumed that the dose intensity for any one patient lies between 0% and 100%. The standard error for cetuximab+BSC was calculated as:

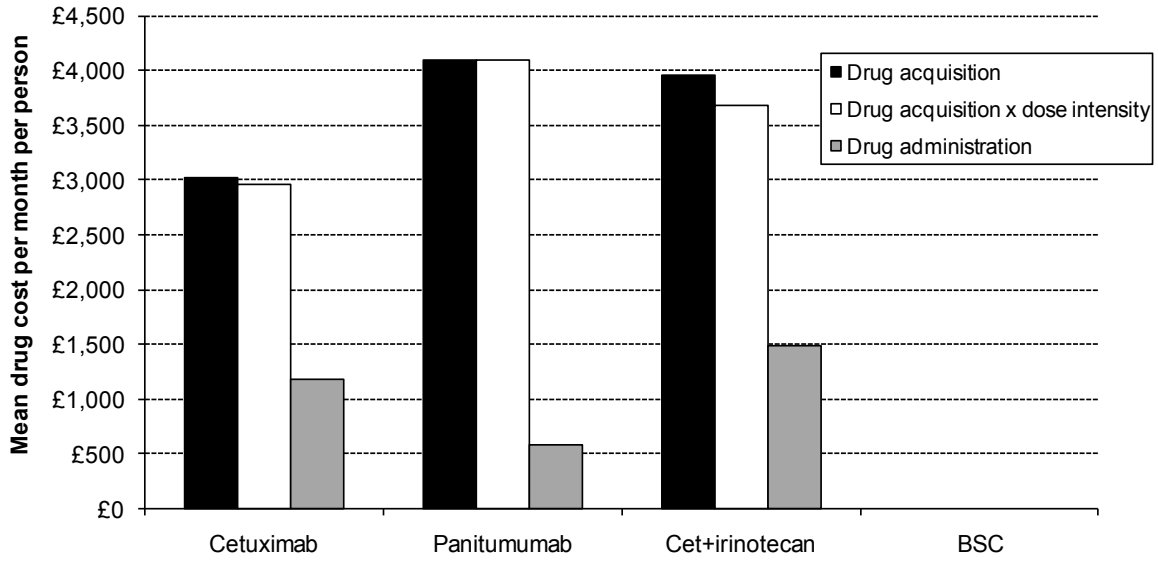
$$\sqrt{\frac{(\text{mean dose intensity})\ (100\% - \text{mean dose intensity})}{N}}$$

where N = 287 the number of people taking cetuximab in the RCT of cetuximab+BSC vs BSC.

The standard error for cetuximab in combination with irinotecan was calculated in the same way, but setting N=218 people from the BOND RCT of cetuximab+irinotecan vs irinotecan. The standard error for irinotecan in combination with cetuximab was calculated in the same way, again setting N=218 people. Given that we assumed a mean dose intensity for panitumumab+BSC of 100% and that we specify that the dose intensity per person lies between 0% and 100%, then this forces the standard error of the dose intensity for panitumumab+BSC to be 0%. Clearly, there should be no correlation between the dose intensities across drugs.

Drug costs per month, drug costs adjusted for dose intensity, and drug administration costs (see Section 7.1.3.3.4 [page 163]) are shown in Figure 13.

Figure 13. Drug acquisition costs, drug acquisition costs adjusted for dose intensity, and drug administration costs by treatment assumed in PenTAG model



7.1.3.3.4. Drug administration costs

According to the SmPC the administration of drugs should be as follows:

- Cetuximab: the first dose is administered as a 120-minute intravenous infusion, and all subsequent doses as 60-minute infusions(37)
- Panitumumab is administered as a 60-minute intravenous infusion(38)
- Irinotecan for use in combination therapy is administered as an intravenous infusion over 30–90 minutes, followed by infusion with folinic acid and 5-FU(88)

Merck Serono assume that cetuximab and panitumumab cost £180 per infusion, corresponding to the HRG „Deliver simple parenteral chemotherapy at first attendance', „Daycase and Regular Day / Night', from the NHS Reference Costs 2008–09.(89) Merck Serono also assume an infusion of cetuximab and irinotecan, when given together, costs £213, corresponding to the HRG „Deliver more complex chemotherapy at first attendance', „Daycase and Regular Day / Night' also from the NHS Reference Costs 2008–09.

By contrast, Roche assume a cost of £218 for the administration of bevacizumab, cetuximab and for cetuximab plus irinotecan, corresponding to the HRG „Deliver subsequent elements of a Chemotherapy cycle', „Outpatients', also from the NHS Reference Costs 2008-09, although we note that the database costs this as £227, not £218.

In common with Roche, and unlike Merck Serono, we assume the cost of £227 in 2008–09 prices for the intravenous administration of cetuximab monotherapy and panitumumab, corresponding to the HRG SB15Z „Deliver subsequent elements of a Chemotherapy cycle', „Outpatients', from the NHS Reference Costs 2008-09.(89) We calculate that non-drug NHS costs have typically increased at approximately 4% per annum over the last five years, using the Hospital & Community Health Services Pay & Prices Index.(76) Inflating the administration costs over three years at 4% per annum from 2008-09 to 2011–12, the date of this appraisal, gives £255 per administration.

For patients in the cetuximab+irinotecan group, when irinotecan is administered (every two weeks), it is given during the same visit to the hospital as cetuximab (every week). We assumed a cost of £255 for the administration of cetuximab, and half this amount, £128, for the subsequent administration of irinotecan. We did not assume the same cost, £255, for the administration of irinotecan because, according to our clinical advisor, the patient will already be mostly set up to receive the second drug, irinotecan, after the first drug, cetuximab. At the other extreme, we do not assume £0 for the administration of irinotecan, because there will still be some nursing functions to perform for the administration of irinotecan. In the absence of further information, we assume the average of these costs; i.e. £128.

When we estimated the total acquisition cost per patient of cetuximab and cetuximab+irinotecan, we assumed that patients took these drugs whilst in PFS. Also, we estimated the total

acquisition cost per patient of panitumumab based on the mean of 10 doses reported in the panitumumab+BSC vs BSC RCT.(4) For the purpose of calculating the total administration cost per patient of all these treatments, we assumed the same mean number of administrations as we did in our calculation of the total acquisition cost per patient. Figure 13 displays one important component of this calculation, the mean administration cost per person, per month, by treatment.

7.1.3.3.5. Pharmacy drug preparation costs

All drugs require preparation by a hospital pharmacist. We costed for the time of drug preparation as follows: the preparation times per infusion of bevacizumab, irinotecan and cetuximab according to the task (for example, clinical check of prescription, drug reconstitution and labelling of product) as being equal, as shown in Appendix 12.(75) We assume the same schedule applies to panitumumab. Using the information in Appendix 12, we calculate the total cost of the preparation of one infusion as £15 for all drugs.

7.1.3.3.5.1. PSA: drug administration and pharmacy preparation

For the PSA, we modelled the cost of a single drug administration (including pharmacy preparation) as a gamma distribution. We tried to capture the broader uncertainty of this variable given that there may be alternative sources for this cost in addition to the source we chose, namely, the NHS Reference Costs 2008–09. This was achieved by setting the standard error equal to 20% of the mean cost. This is the same approach as used by Merck Serono; i.e. setting the standard error equal to 20% of the mean for variables for which data on uncertainty is not available. We assumed perfect correlation between cetuximab+BSC and panitumumab+BSC by setting the administration costs equal for each simulation. The cost of administration of cetuximab+irinotecan was also set to correlate perfectly with the other drug administration costs, and for each simulation, we set it equal to the cost for the other drugs multiplied by the ratio of the mean cost for cetuximab+irinotecan to the mean cost for the other drugs.

7.1.3.3.6. Medical management costs

Our clinical expert advised us on the nature and frequency of medical management, see Table 47 (page 166).

Table 47. Medical management costs in PenTAG model

Health state	Population	Freq.	Mean cost	Mean cost per one month model cycle	Source
Consultant outpatient visits					
PFS	During all active drug treatment[a]	1 visit per 2 weeks	£136 per visit	£295	£121 per visit (n=106), National Schedule of Reference Costs Year : '2008-09' - NHS Trusts and PCTs combined Consultant Led: Follow up Attendance Non-Admitted Face to Face Service Code 370: Medical oncology.(74) £136 inflated to 2011/12 at 4% p.a.(76)
	BSC group	Never		£0	
CT scans					
PFS	During all active drug treatment[a]	Every 3 months	£112 per scan	£37	£100 (interquartile range £75-£109, n=162).(74) National Schedule of Reference Costs Year : '2008-09' - NHS Trusts and PCTs combined Diagnostic Imaging: Outpatient Computerised Tomography Scan, one area, no contrast. Currency code RA08Z.. £112 inflated to 2011/12.(76)
	BSC group	Never		£0	
Medication, hospitalisations, hospice stays, outpatient visits, scans and laboratory test					
PD	All treatment groups	N/A		£1,039	Remak & Brazil (2004)(14) inflated by 4% p.a. from, 2000 to 2011.

BSC, best supportive care; CT, computed tomography; N/A, not applicable; NHS, National Health Service; PCT, primary care trusts; PD, progressive disease; PFS, progression free survival

[a] cetuximab, cetuximab+irinotecan, bevacizumab or panitumumab

In common with Merck Serono, we took our estimate of the cost of medical management for all treatment groups in PD from a study of UK patients with breast cancer, reported by Remak and Brazil (2004).(14) Once off active drug treatment, and at the end stage of metastatic cancer, resources to alleviate pain and other symptoms is similar across cancer types, and therefore that

the data from the breast cancer study is appropriate. Table 5 of Remak & Brazil reports the monthly cost in progressive disease as £675 per patient, in Year 2000 prices. This represents mostly medication, hospitalisations, hospice stays, outpatient visits, scans and laboratory test. Inflating the cost at 4% per annum over 11 years, from 2000–11, gives £1,039 per month. This is noticeably higher than the £785 used by Merck Serono, even though they also used Remak and Brazil to estimate this quantity. We believe this difference arises because Merck Serono incorrectly inflated the cost over a shorter time period.

Our clinical expert believes that blood tests would be performed once every two weeks for people taking cetuximab+irinotecan and once per month for people on all other active drug treatments. Patients in the BSC group would have no blood tests. We have not modelled the cost of blood tests, because the cost per test is negligible, at about £3.28 (=£2.92 Department of Health. NHS reference costs 2006-07. Specialty code DAP823. Haematology [Excluding Anti-Coagulant Services](89) inflated by 4% per annum over three years).

Unlike Merck Serono, we assumed no magnetic resonance imaging (MRI) scans. Our clinical advisor suggests that scans would be performed only for patients for whom tumour resection is an option. There would be very few such patients in this patient population, because they are taking late-line drugs.

Merck Serono state that some people in the RCT of cetuximab+BSC vs BSC received radiotherapy for palliation of symptoms in PD in both treatment groups (see page 203 Merck Serono's submission). They calculate the total cost of radiotherapy per patient as £34 for patients in the cetuximab+BSC group and £46 for patients in the BSC group. However, given that these figures are dwarfed by other costs in the model, we do not cost for radiotherapy received in PD. Similarly, Merck Serono state that some people in the RCT of cetuximab+BSC vs BSC received chemotherapy for palliation of symptoms (see page 204, Merck Serono's submission). They calculate the total cost of chemotherapy per patient as £359 for patients in PFS in the BSC group, £624 in PD in the cetuximab+BSC group, and £827 in PD in the BSC group. We do not cost for palliative chemotherapy, first, because use of palliative chemotherapy in clinical practice may differ from that in the RCT, second because the figures are very small compared to other costs, and third because the PD chemotherapy costs for the two treatment arms nearly cancel out.

For the PSA, we modelled each medical management cost as a gamma distribution. We tried to capture the broader uncertainty of these variables given that there may be alternative sources for these costs in addition to the sources we chose. This was achieved by setting the standard errors of all costs equal to 20% of the mean costs, which reflects much uncertainty and because

this gives a plausible range of simulated costs. Also, we assumed that all medical management costs are independent of all other model parameters.

7.1.3.3.7. Costs of treating AEs

As explained in Section 7.1.2.5 (page 138), in our base case, we base our estimates of the mean costs of treating adverse events on those calculated by Merck Serono. The mean costs per person assumed by Merck Serono are: £2,760 for BSC, £3,671 for cetuximab+BSC, £880 for panitumumab+BSC, £3,671 for cetuximab+irinotecan; however, we use only Merck Serono's values for BSC, cetuximab+BSC, and cetuximab+irinotecan. This approach seems reasonable given that (a) Merck Serono have performed an extensive analysis of these costs from their RCT of cetuximab vs BSC,(3) (b) we have found no logical flaws in their calculations (see Section 6, page 98), and (c) the costs estimated by Merck Serono are very small compared to other costs; for example, drug costs.

We have not used Merck Serono's cost of £880 for treating AEs for panitumumab+BSC because their justification for this figure seems invalid (see Section 6, page 98). In particular, it seems unreasonable that the cost for panitumumab+BSC should be less than for BSC given that the incidence of Grade 3 and 4 adverse events is greater for panitumumab+BSC than for BSC for virtually every AE category.(5) Instead, we set the mean cost of treating AEs for panitumumab+BSC equal to that for BSC, at £2,760 per person. The true value for panitumumab+BSC may be somewhat higher than for BSC, and we explore this in a sensitivity analysis.

For the PSA, we model all costs of treating adverse events as gamma distributions. Given the lack of an obvious choice for the standard errors, we chose the pragmatic solution of setting all standard errors equal to 20% of each mean. It is also very difficult to parameterise the correlations between these costs, across treatments. For simplicity, we set the cost for panitumumab+BSC equal to BSC for each simulation, and these costs were independent of the cost for cetuximab+BSC, which itself was independent of the cost for cetuximab+irinotecan.

7.1.4. Deterministic one-way sensitivity analysis

We performed several one-way sensitivity analyses for the cost-effectiveness of cetuximab vs BSC, panitumumab vs BSC and cetuximab+irinotecan vs BSC.

7.1.5. PSA

We performed PSA to incorporate parameter uncertainty in the cost-effectiveness analysis. Values for each stochastic parameter in each of 1,000 simulations of the cost-effectiveness

model were drawn at random from a specified distribution. The distributions, standard errors and correlations for all parameters are given in Section 7.1.3 (page 138). The results are plotted on cost-effectiveness planes and cost-effectiveness acceptability curves, which shows the probability that a treatment is the most cost-effective given a particular willingness-to-pay threshold.

7.2. PenTAG cost-effectiveness results

We present our cost-effectiveness results in this section. We first present and discuss the base-case results, and then the results of the sensitivity analyses.

Table 48 presents the aggregated totals for the base-case results for the four treatments, and Table 49 (page 170) displays the incremental results vs BSC and the corresponding cost-effectiveness ratios.

Table 48. PenTAG base case results – patients with KRAS WT status

	CET	PAN	CET+IRIN	BSC
Life years (mean, undiscounted)				
Time on drug treatment	0.40	0.49	0.73[a]	N/A
Progression-free	0.40	0.42	0.73	0.23
Post-progression	0.44	0.29	0.65[b]	0.29
Total (mean)	**0.84**	**0.71**	**1.38**[b]	**0.51**
Total (median)	0.75	0.60	1.25[b]	0.40
QALYs (mean, discounted)				
Progression-free	0.32	0.36	0.54	0.17
Post-progression	0.29	0.19	0.43[b]	0.19
Total	**0.61**	**0.56**	**0.97**[b]	**0.36**
Costs (mean, discounted)				
KRAS test	£296	£296	£296	£0
Drug costs	£14,408	£23,643	£32,022[a]	£0
Drug administration	£5,546	£3,374	£12,714[a]	£0
Consultant monitoring appt.	£1,397	£1,479	£2,533	£0
CT scans	£178	£188	£322	£0
BSC in PD	£5,304	£3,473	£7,790 [b]	£3,496
Adverse events	£3,671	£2,760	£3,671	£2,760
Total	**£30,800**	**£35,213**	**£59,348**	**£6,256**

BSC, best supportive care; CET, cetuximab;CT, computed tomography; IRIN, irinotecan; N/A, not applicable; PAN, panitumumab; PD, progressive disease; QALYs quality-adjusted life years

[a]Uncertain because time on cetuximab+irinotecan treatment not reported

[b]Highly uncertain due to uncertainty in OS (see Section 7.1.3.1.5, p151)

Table 49. PenTAG base case incremental results vs BSC for patients with KRAS WT status

	CET - BSC	PAN - BSC	CET+IRIN – BSC
Life years (mean, undiscounted)			
Progression-free	0.17	0.20	0.50
Post-progression	0.15	0.00	0.37[b]
Total (mean)	**0.32**	**0.19**	**0.87**[b]
Total (median)	0.35	0.20	0.85[b]
QALYs (mean, discounted)			
Progression-free	0.15	0.19	0.37
Post-progression	0.10	0.00	0.24[b]
Total	**0.25**	**0.19**	**0.60**[b]
Costs (mean, discounted)			
KRAS test	£300	£300	£300
Drug costs	£14,400	£23,600	£32,000[a]
Drug administration	£5,500	£3,400	£12,700[a]
Consultant monitoring appt.	£1,400	£1,500	£2,500
CT scans	£200	£200	£300
BSC in PD	£1,800	£0	£4,300[b]
AEs	£900	£0	£900
Total	**£24,500**	**£29,000**	**£53,100**
Cost / life year gained	£78,000	£145,000	£64,000[c]
Cost / QALY	**£98,000**	**£150,000**	**£88,000**[c]

BSC, best supportive care; CET, cetuximab; CT, computed tomography; PAN, panitumumab; IRIN, irinotecan; PD, progressive disease; QALYs, quality-adjusted life years

[a]Uncertain because time on cetuximab+irinotecan treatment not reported

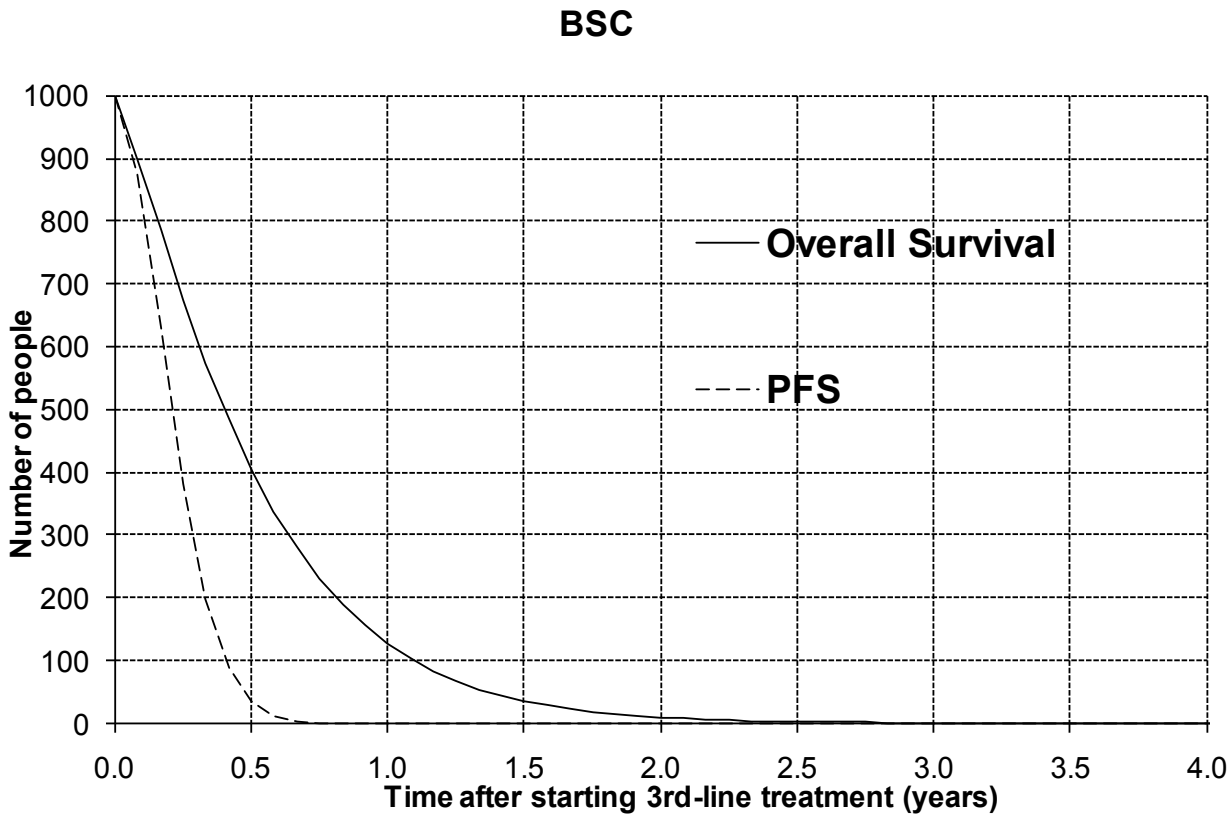
[b]Highly uncertain due to uncertainty in OS (see Section 7.1.3.1.5, p151)

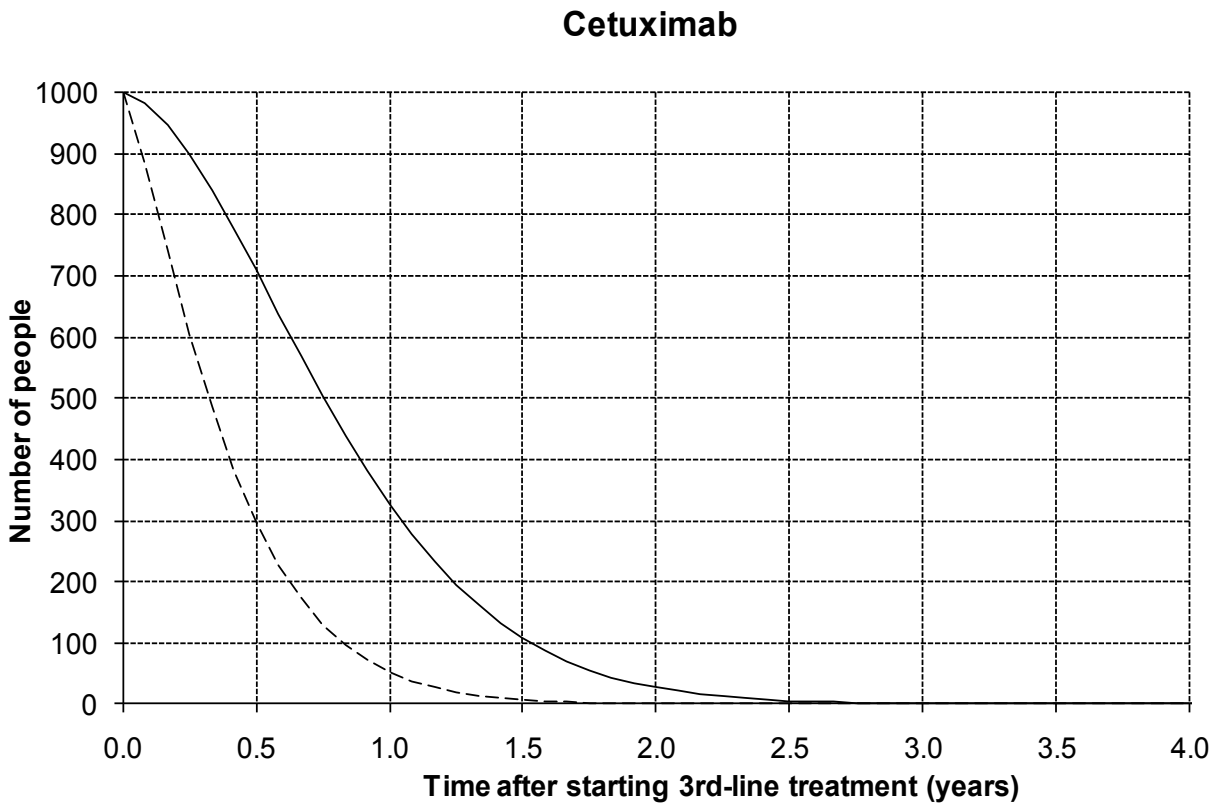
[c]Highly uncertain due to uncertainty in OS and because time on cetuximab+irinotecan treatment not reported

7.2.1. Survival results

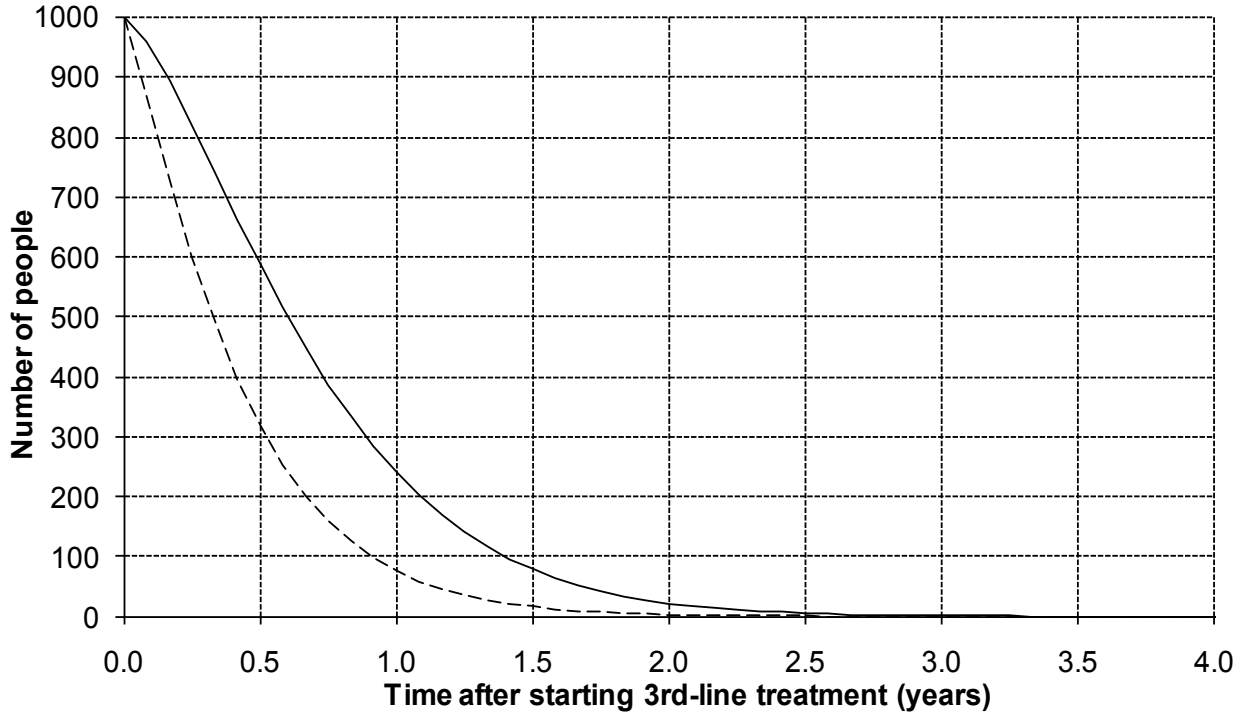
The relative proportions of patients in each health state for each treatment throughout the time horizon of the model is displayed in Figure 14 (page 171). The mean duration in each health state for each treatment (as reported in Table 48, page 169) is represented in these graphs by the area under each curve. Accordingly, mean PFS is represented by the area under the dotted line, and the area between the dotted line and the solid OS curve represents the mean PD time. As expected, virtually all patients are predicted to have died three years from start of treatment.

Figure 14. Base-case cohort composition over time by treatment.

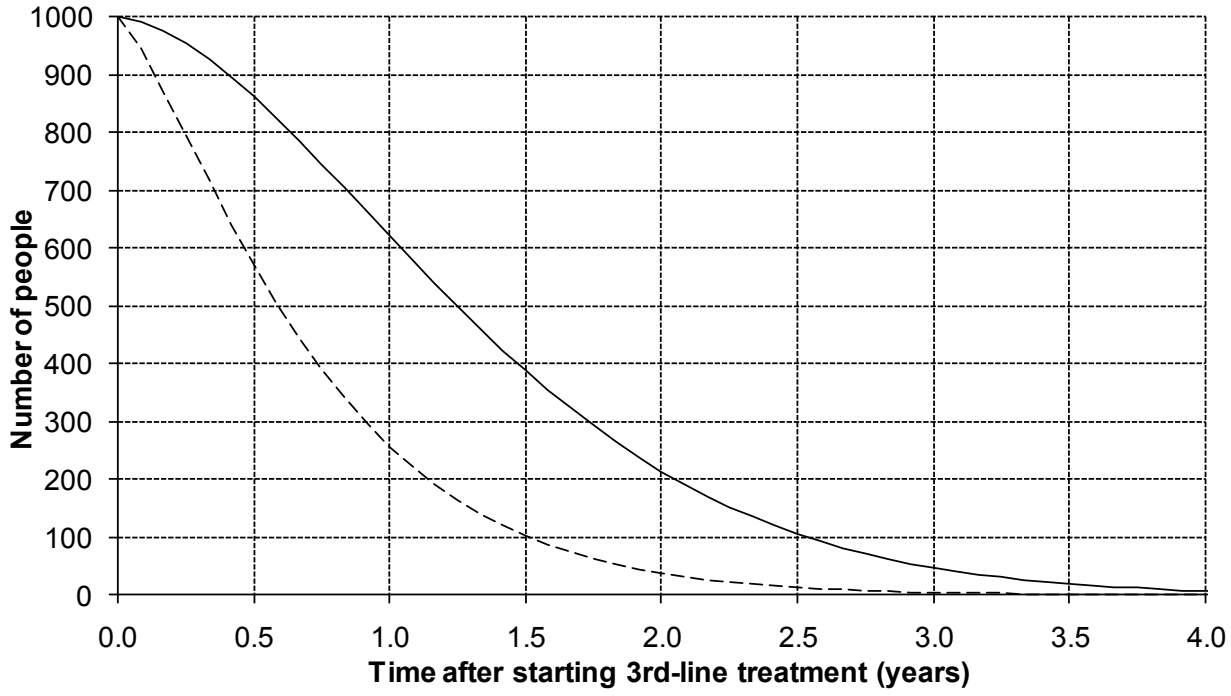




Panitumumab



Cetuximab + irinotecan



We predict that average PFS is least for people under BSC (0.23 years = 2.7 months), greater for cetuximab+BSC and panitumumab+BSC (0.40 and 0.42 years respectively (approximately five

months), and greatest for cetuximab+irinotecan (0.73 years = 8.8 months) (Table 48 [page 169], Figure 14 [page 171]). Given that drugs are taken largely until progression, cetuximab+BSC and panitumumab+BSC are taken for similar times (0.40 and 0.49 years respectively), and cetuximab+irinotecan is taken for longer (0.73 years).

Next, we predict that people spend a similar time in PD on BSC and panitumumab+BSC (0.29 years = 3.4 months), longer in PD on cetuximab (0.44 years = 5.2 months), and longer still on cetuximab+irinotecan (0.65 years = 7.8 months). But note that the time in PD on panitumumab+BSC is uncertain, because it is calculated from OS for BSC in the panitumumab+BSC vs BSC RCT, which is confounded due to cross-over of people from the BSC to the panitumumab+BSC arm. The time in PD on cetuximab+irinotecan is even more uncertain, because it is calculated from OS for cetuximab+irinotecan, which is highly uncertain (see Section 7.1.3.1.4, page 148). Average OS, the sum of PFS and PD, is least for BSC (0.51 years = 6.2 months), greater for cetuximab+BSC and panitumumab+BSC (0.84 and 0.71 years, or 10.0 and 8.5 months respectively), and greatest for cetuximab+irinotecan (1.38 years = 16.6 months), which we repeat is very uncertain.

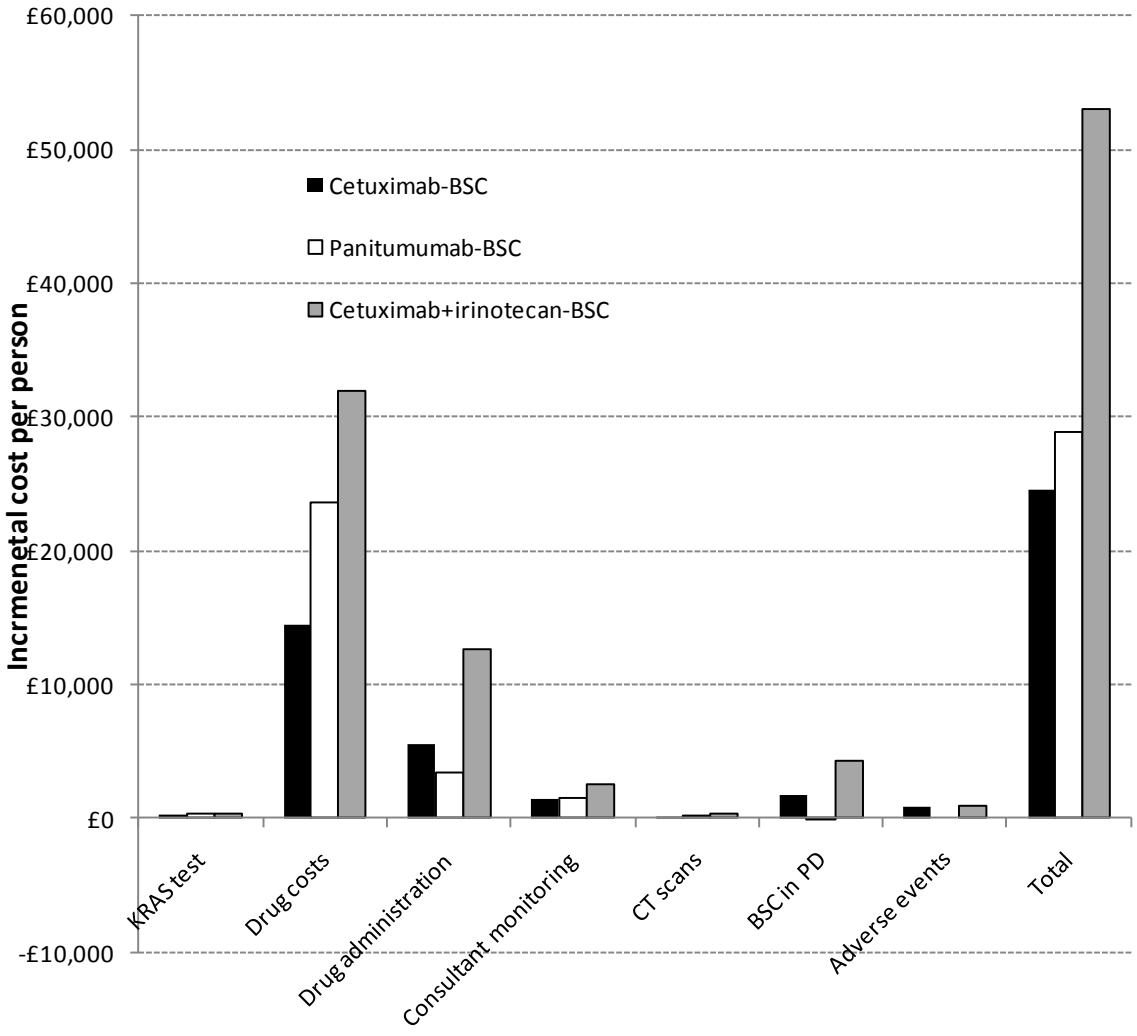
The relative QALYs in PFS and PD are similar to those for life years in PFS and PD. To be more precise the relative mean QALYs in PFS for cetuximab+BSC and panitumumab+BSC vs BSC (for example, QALYs in PFS for cetuximab vs QALYs in PFS for BSC) are greater than the relative mean life years (for example, PFS for cetuximab vs PFS for BSC), because we assume that the QoL of people on these drugs is better than on BSC. This is not the case for cetuximab+irinotecan because we assume that the QoL of people on this treatment is the same as for BSC. This is also not the case for QALYs and life years in PD, because we assume that the QoL of all people is equal in PD.

7.2.2. Costs results

We now turn to the expected costs per person. The expected drug acquisition costs are by far the largest single cost item (Table 48 [page 162]) and account for the largest incremental costs vs BSC (Figure 15 [page 174]). This is least for cetuximab+BSC (about £14,000), greater for panitumumab+BSC (about £24,000) and greatest for cetuximab+irinotecan (£32,000), although the last figure is particularly uncertain given that the mean duration of cetuximab+irinotecan treatment is not reported. The expected drug acquisition costs are calculated as the product of the mean drug acquisition cost per person per unit time and the discounted mean duration of drug treatment. Figure 13 (page 163) suggests that the mean drug acquisition cost per person per unit time, allowing for dose intensity, is lowest for cetuximab monotherapy (£3,000 per month), greater for cetuximab+irinotecan (£3,700 per month) and greatest for

panitumumab+BSC (£4,100 per month). From Table 48 (page 162), we repeat that cetuximab+BSC and panitumumab+BSC are taken for similar times (0.40 and 0.49 years respectively), and cetuximab+irinotecan is taken for much longer (0.73 years). Combining these two pieces of information, the expected drug acquisition cost is least for cetuximab+BSC because it is both the cheapest per person per unit time, and it is taken for the least time. The expected drug acquisition cost is greatest for cetuximab+irinotecan because the acquisition cost per unit of time is nearly as great as for panitumumab+BSC and because we predict that it is taken for far longer than the other two treatments.

Figure 15. Base case incremental costs vs BSC



The expected drug administration costs and expected costs in PD are the next largest single cost items (Table 48 [page 162]). However, the cost-effectiveness of the drugs vs BSC is influenced more by expected drug administration costs, since these account for larger incremental costs vs BSC (Figure 15 [page 174]). Similar to the total per person drug acquisition costs, these are calculated as the product of the mean drug administration cost per person per unit time and the

discounted mean duration of drug treatment. From Figure 13 (page 163), the mean drug administration cost per person per unit time is lowest for panitumumab (£600 per month) because it is given relatively infrequently, every two weeks, the mean administration cost per person per unit time is greater for cetuximab+BSC (£1,200 per month) because it is given relatively frequently, once per week, and the cost is greatest for cetuximab+irinotecan (£1,500 per month) because cetuximab+BSC is given every week and there are two drugs to administer every second week. From Table 48 (page 162), we repeat that cetuximab+BSC and panitumumab+BSC are taken for similar times (0.40 and 0.49 years respectively), and cetuximab+irinotecan is taken for much longer (0.73 years). Combining this information, the expected total drug administration cost is least for panitumumab+BSC because it is easily the least expensive per person per unit time, and it is taken for much less time than cetuximab+irinotecan and for a similar time as cetuximab+BSC. The expected total drug administration cost for cetuximab+irinotecan is by far the greatest because it has the greatest administration cost per unit of time and because we predict that it is taken for far longer than the other two treatments.

Absolute costs for BSC in PD are fairly large for all treatments (between £3,500 and £7,800), but the incremental costs vs BSC are small, with the exception of the cetuximab+irinotecan group, because the mean times spent in PD are fairly similar between treatments, again with the exception of cetuximab+irinotecan (Table 48, page 169).

All other costs: KRAS testing, consultant monitoring appointments, CT scans and treatment of serious adverse events, are all much smaller, and therefore have very little impact on cost-effectiveness.

7.2.3. Costs-effectiveness results

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

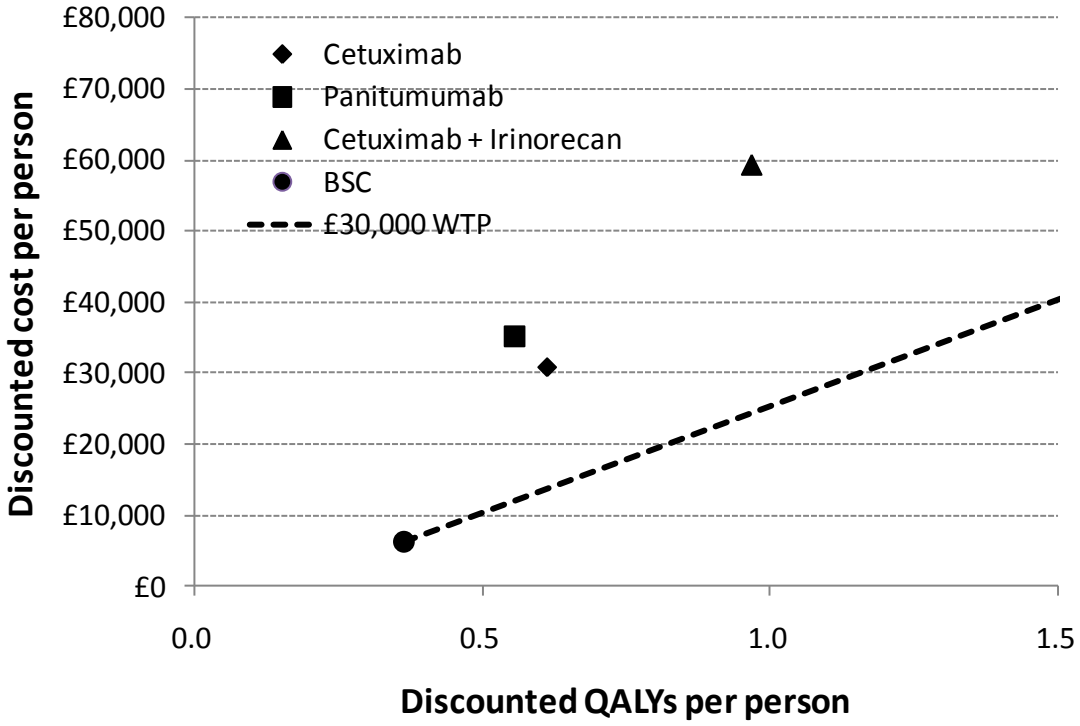
- cetuximab+BSC vs BSC as £98,000 per QALY
- panitumumab+BSC vs BSC as £150,000 per QALY
- cetuximab+irinotecan vs BSC as £88,000 per QALY.

Our estimate of the ICER for cetuximab+BSC vs BSC is based on the relevant clinical effectiveness evidence from a high quality RCT, although we caution that although we have some evidence for the mean treatment duration of cetuximab, the precise information is not published. The ICER for panitumumab+BSC vs BSC is based on relevant clinical effectiveness evidence from another high quality RCT. However, there remains some uncertainty because we

rely on an adjustment for the crossing-over of many people from the BSC to the panitumumab+BSC treatment group, and there is uncertainty about the accuracy of the adjustment. The ICER for cetuximab+irinotecan vs BSC is the most uncertain because there is much uncertainty about PFS for cetuximab+irinotecan, and hence treatment duration, and even more uncertainty about OS (Section 7.1.3.1.4, page 148).

The incremental costs and QALYs for cetuximab+BSC and panitumumab+BSC vs BSC are similar, whereas these quantities are far greater for cetuximab+irinotecan (Figure 16, and Table 49 [page 170]).

Figure 16. PenTAG base case cost-effectiveness results



7.2.4. End of life criteria

In Tables 50–52 (pages 180–182) we assess the treatments against all of NICE's EoL criteria except that concerning the patient population size for indications which are outside the scope of this appraisal. Merck Serono considers that both cetuximab+BSC and cetuximab+irinotecan qualifies for EoL criteria.

Table 50. Assessment of CET+BSC treatment for mCRC against NICE's EoL criteria

EoL criteria	CET+BSC for mCRC	Meets criteria	Justification
Life expectancy on current standard care <24 months	6.2 months	Yes	Clear
Treatment provides extension to life expectancy compared to current standard care of >3 months	Mean 3.9 months extension to life expectancy. Probability life extension >3 months = 0.78	Yes	Clear
No alternative treatment with comparable benefits is available through the NHS	True	Yes	Clear
The treatment is licensed or otherwise indicated, for small patient populations	MS estimate 260−390 people per year eligible for CET for mCRC (page 149, MS's report). We do not assess use of cetuximab for other indications	Unsure	Population is small for mCRC, but we do not assess use of cetuximab for other indications
The estimates of the extension to life are robust[a]	True	Yes	Probability extension to life >3 months = 0.78 estimated directly from high quality RCT. No adjustment for cross-over needed.
Overall assessment		**Unsure**	**We do not assess the size of the patient population for other indications, but all other EoL criteria are met**

CET, cetuximab; EoL, end of life; mCRC, metastatic colorectal cancer; MS, Merck Serono; NHS, National Health Service; RCT, randomised controlled trial

[a]and can be shown or reasonably inferred from either progression free survival or overall survival (taking account of trials in which cross-over has occurred and been accounted for in the effectiveness review).

Table 51. Assessment of CET+irinotecan treatment for mCRC against NICE's EoL criteria

EoL Criteria	CET+IRIN for mCRC	Meets criteria	Justification
Life expectancy on current standard care < 24 months	6.2 months	Yes	Clear
Treatment provides extension to life expectancy compared to current standard care of >3 months	Mean 10.4 months extension to life expectancy. Probability life extension >3 months = 0.99	Yes	Clear
No alternative treatment with comparable benefits is available through the NHS	True	Yes	Clear
The treatment is licensed or otherwise indicated, for small patient populations	MS estimate 260−390 people per year eligible for CET for mCRC (page 149, MS's report). We do not assess use of cetuximab for other indications	Unsure	Population is small for mCRC, but we do not assess use of cetuximab for other indications
The estimates of the extension to life are robust[a]	Estimate of extension to life expectancy relies on two important assumptions, concerning splitting of OS for KRAS WT and mutant people and use of non-RCT data	Unsure	If „robust' means we have high confidence in our mean estimate of OS, then evidence is not „robust'. If „robust' means we have high confidence that treatment increases overall survival by at mean 3 months, then evidence is „robust'.
Overall assessment		**Unsure**	**We are not sure whether all criteria passed**

CET, cetuximab; IRIN, irinotecan; mCRC, metastatic colorectal cancer; MS, Merck Serono; OS, overall survival; RCT, randomised controlled trial;

[a]and can be shown or reasonably inferred from either progression free survival or overall survival (taking account of trials in which cross-over has occurred and been accounted for in the effectiveness review).

Table 52. Assessment of PAN+BSC treatment for mCRC against NICE's EoL criteria

EoL criteria	PAN+BSC for mCRC	Meets criteria	Justification
Life expectancy on current standard care < 24 months	6.2 months	Yes	Clear
Treatment provides extension to life expectancy compared to current standard care of >3 months	**Indirect comparison:** Mean 2.3 months extension to life expectancy. Probability life extension >3 months = 0.25 **Direct comparison:** Mean 2.7 months extension to life expectancy. Probability life extension >3 months = 0.39	No	Probability that panitumumab provides extension to life expectancy compared to current standard care of >3 months is low
No alternative treatment with comparable benefits is available through the NHS	True	Yes	Clear
The treatment is licensed or otherwise indicated, for small patient populations	MS estimate 260−390 people per year eligible for CET for mCRC (page 149, MS's submission).	Yes	Population small
The estimates of the extension to life are robust[a]	False	Yes	Although extension to life expectancy from high quality RCT, adjustment for cross-over introduces much uncertainty
Overall assessment		**No**	**Not all EoL criteria passed**

CET, cetuximab; EoL, end of life; mCRC, metastatic colorectal cancer; MS, Merck Serono; PAN, panitumumab; RCT, randomised controlled trial

[a]and can be shown or reasonably inferred from either progression free survival or overall survival (taking account of trials in which cross-over has occurred and been accounted for in the effectiveness review).

7.2.5. Deterministic sensitivity analyses

7.2.5.1. Cetuximab+BSC vs BSC

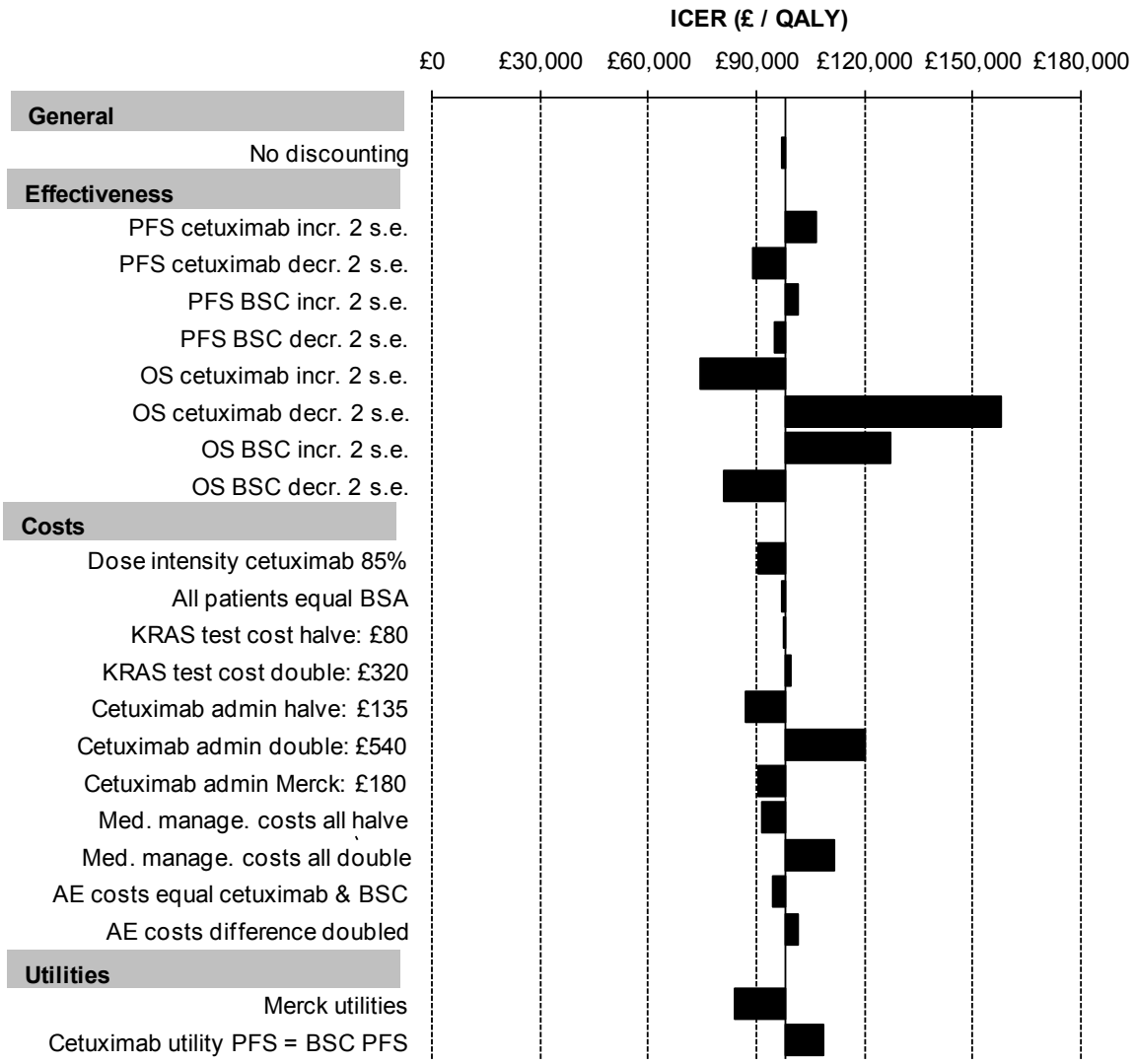
One-way deterministic sensitivity analyses for cetuximab+BSC vs BSC are reported in Table 53 (page 181) and Figure 17 (page 182), which shows the impact on the deterministic ICER of various alterations in model parameters. The sensitivity analyses were chosen on the basis of either general interest (for example, assuming no discounting), plausibility (for example, varying mean PFS and OS by two standard errors), or using Merck Serono's assumptions. None of these sensitivity analyses brings the ICER within usually accepted willingness-to-pay thresholds.

Table 53. Sensitivity analyses: CET+BSC vs BSC

Parameter	Base case	Sensitivity analysis	ICER
Base case	N/A	N/A	**£98,000**
General			
Discounting costs & benefits	3.5% p.a.	0% p.a.	£97,000
Effectiveness			
Mean PFS CET+BSC	0.40 years	0.47 years (increased by 2 SE)	£107,000
		0.32 years (decreased by 2 SE)	£89,000
Mean PFS BSC	0.23 years	0.27 years (increased by 2 SE)	£101,000
		0.18 years (decreased by 2 SE)	£95,000
Mean OS CET+BSC	0.84 years	1.00 years (increased by 2 SE)	£74,000
		0.68 years (decreased by 2 SE)	£158,000
Mean OS BSC	0.51 years	0.61 years (increased by 2 SE)	£127,000
		0.41 years (decreased by 2 SE)	£81,000
Costs			
Dose intensity CET	98%	85%	£91,000
Mean mg CET per person	511 mg CET (allowing for distribution of body surface area)	500 mg CET (all assumed same body surface area)	£97,000
KRAS test cost	£160 per test	Halve cost: £80	£98,000
		Double cost: £320	£99,000
CET administration	£270 per administration	Halve cost: £135	£87,000
		Double cost: £540	£120,000
		Merck assumption: £180	£91,000
Medical management (consultant visit, CT scans, BSC in PD) costs		Halve all unit costs or frequencies	£91,000
		Double all unit costs or frequencies	£112,000
AEs costs	CET+BSC = £3,671, BSC = £2,760	CET+BSC and BSC equal	£95,000
		CET+BSC - BSC doubled	£102,000
Utilities			
Utilities	CET+BSC PFS = 0.81, PD = 0.69; BSC PFS = 0.75, PD = 0.69	MS values: CET+BSC PFS = 0.81, PD = 0.79; BSC PFS = 0.75, PD = 0.69	£84,000
PFS	CET+BSC PFS = 0.81; BSC PFS = 0.75	CET+BSC PFS = BSC PFS = 0.75	£108,000

AEs, adverse events; BSC, best supportive care; CET, cetuximab; CT, computed tomography; MS, Merck Serono; p.a., per annum; PD, progressive disease; PFS, progression-free survival;

Figure 17. Sensitivity analyses: CET+BSC vs BSC



The ICER remains above £70,000 per QALY in all cases. The ICER is most sensitive to OS for BSC and cetuximab+BSC, noting that we have varied these quantities to the most extreme values (two standard errors from the mean) that are consistent with the RCT of cetuximab+BSC vs BSC.(3) The ICER is reasonably sensitive to mean PFS for cetuximab+BSC, because this is proportional to the mean duration of cetuximab+BSC treatment and hence the cost of cetuximab acquisition, which strongly influences the ICER. The ICER is less sensitive to mean PFS for BSC because this is not associated with any drug costs.

The ICER is fairly sensitive to the administration cost of cetuximab when this is varied within a plausible range, because cetuximab is given regularly, once per week. The ICER falls moderately when we use Merck Serono's utilities, although we disagree with these values. The ICER increases moderately when we assume that the HRQoL of people in PFS is equal for people on cetuximab+BSC and BSC, but we have good evidence that the QoL is higher for

people on cetuximab+BSC. The ICER is insensitive to all other parameters when they are varied within plausible ranges. For example, it is insensitive to the discount rates for costs and benefits because patients typically have short life expectancy. Also, for the calculation of the mean cost of cetuximab acquisition, the ICER is insensitive to whether we assume all people have the same body surface area, or whether we more realistically assume a range of surface areas. Although, as stated above, this is purely coincidental in this case, and we recommend that the distribution should be routinely modelled whenever drugs are administered in patient-related doses.

7.2.5.2. Panitumumab+BSC vs BSC

One-way deterministic sensitivity analyses for panitumumab+BSC vs BSC are reported in Table 54 (page 184) and in Figure 18 (page 185). None of these sensitivity analyses bring the ICER below usually accepted willingness-to-pay thresholds.

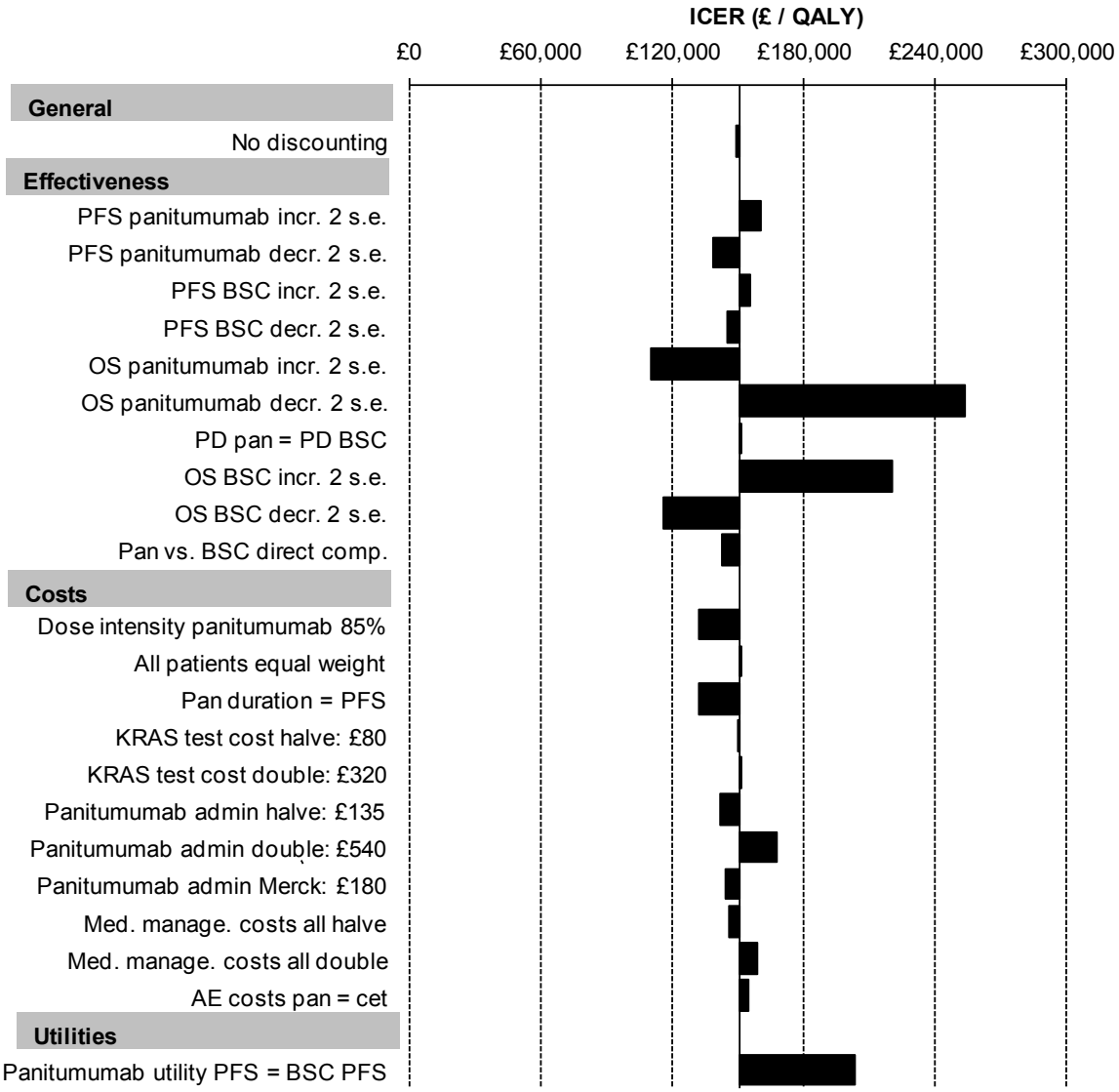
Table 54. Sensitivity analyses: PAN+BSC vs BSC

Parameter	Base case	Sensitivity analysis	ICER
Base case	N/A	N/A	**£150,000**
General			
Discounting costs & benefits	3.5% p.a.	0% p.a.	£149,000
Effectiveness			
Mean PFS PAN+BSC	0.42 years	0.50 years (increased by 2 se)	£161,000
		0.35 years (decreased by 2 se)	£138,000
Mean PFS BSC	0.23 years	0.27 years (increased by 2 se)	£155,000
		0.18 years (decreased by 2 se)	£145,000
Mean OS PAN+BSC	0.708 years	0.86 years (increased by 2 se)	£110,000
		0.58 years (decreased by 2 se)	£254,000
		0.709 years, so that PD PAN = PD BSC	£150,000
Mean OS BSC	0.51 years	0.61 years (increased by 2 se)	£221,000
		0.41 years (decreased by 2 se)	£116,000
PAN+BSC & BSC effectiveness	BSC from CET+BSC vs BSC RCT, PAN from PAN+BSC vs BSC RCT, adjusted for indirect comparison	All from PAN+BSC vs BSC RCT only (direct comparison)	£142,000
Costs			
Dose intensity PAN	100%	85%	£132,000
Mean mg PAN per person	499 mg (allowing for distribution of weights)	500 mg (all people assumed same weights)	£150,000
Mean duration PAN therapy	0.49 years	Same as mean PFS: 0.42 years	£132,000
KRAS test cost	£160 per test	Halve cost: £80	£150,000
		Double cost: £320	£152,000
PAN administration	£270 per administration	Halve cost: £135	£142,000
		Double cost: £540	£168,000
		Merck assumption: £180	£144,000

Medical management (consultant visit, CT scans, BSC in PD) costs		Halve all unit costs or frequencies	£146,000
		Double all unit costs or frequencies	£159,000
Adverse events costs	PAN+BSC = BSC = £2,760	PAN+BSC same as CET+BSC = £3,671, BSC = £2,760	£155,000
Utilities			
Utilities	PAN+BSC PFS = 0.87 ; BSC PFS = 0.75	PAN+BSC PFS = BSC PFS = 0.75	£203,000

BSC, best supportive care; CET, cetuximab; CT, computed tomography; p.a., per annum; PAN, panitumumab; PD, progressive disease; PFS, progression-free survival;

Figure 18. Sensitivity analyses: panitumumab+BSC vs BSC



The ICER remains very high, above £110,000 per QALY in all cases. As for the comparison of cetuximab+BCS vs BSC, the ICER is most sensitive to OS for BSC and panitumumab+BSC. As for cetuximab+BSC vs BSC, the ICER is reasonably sensitive to mean PFS for panitumumab+BSC, because this is proportional to the mean cost of panitumumab acquisition. The ICER is less sensitive to mean PFS for BSC because this is not associated with any drug costs. Further concerning the clinical effectiveness, we addressed the confounding due to substantial cross-over of people from the BSC to panitumumab+BSC arms in the RCT as follows. We performed a sensitivity analysis whereby we varied OS for panitumumab+BSC so that the time in PD is equal for the panitumumab+BSC and BSC arms. This models the plausible scenario whereby mortality is affected only whilst patients are on panitumumab. Once they are off panitumumab, in PD, the mortality rate is equal to that in PD in the BSC arm. This analysis was performed by adjusting OS for panitumumab+BSC only very slightly, from a mean of 0.708 years to 0.709 years. Not surprisingly, the ICER changed only incrementally. In the base case, we took the clinical effectiveness for the BSC arm from the RCT of cetuximab+BSC vs BSC, not the RCT of panitumumab vs BSC. Instead, when we use the RCT of panitumumab+BCS vs BSC; i.e. we perform a direct comparison of panitumumab+BSC vs BSC using data only from the panitumumab+BSC vs BSC RCT, the ICER decreases only slightly.

In our base case, we assume that panitumumab is typically taken for slightly longer, 0.49 years, than patients are in PFS, 0.42 years. Indeed, we have good evidence for the treatment duration of panitumumab for patients with KRAS WT status, as this is reported directly from the RCT. However, in cost-effectiveness analyses of drugs for terminal cancers, it is normal to assume that drugs are taken until disease progression. Under this assumption, the ICER decreases moderately. The ICER is less sensitive to the drug administration cost than the ICER for cetuximab+BSC vs BSC, because panitumumab is taken less frequently than cetuximab (once every two weeks vs once per week respectively). The ICER increases substantially when we assume that the quality of life of people in PFS is equal for people on panitumumab+BSC and BSC, but we have good evidence that the QoL is higher for people on panitumumab+BSC. The ICER is insensitive to all other parameters when they are varied within plausible ranges. For example, for the calculation of the mean cost of panitumumab acquisition, the ICER is insensitive to whether we assume all people are the same weight, or whether we more realistically assume a distribution of weights.

7.2.5.3. Cetuximab+irinotecan vs BSC

One-way deterministic sensitivity analyses for cetuximab+irinotecan vs BSC are reported in Table 55 (page 187) and in Figure 19 (page 189).

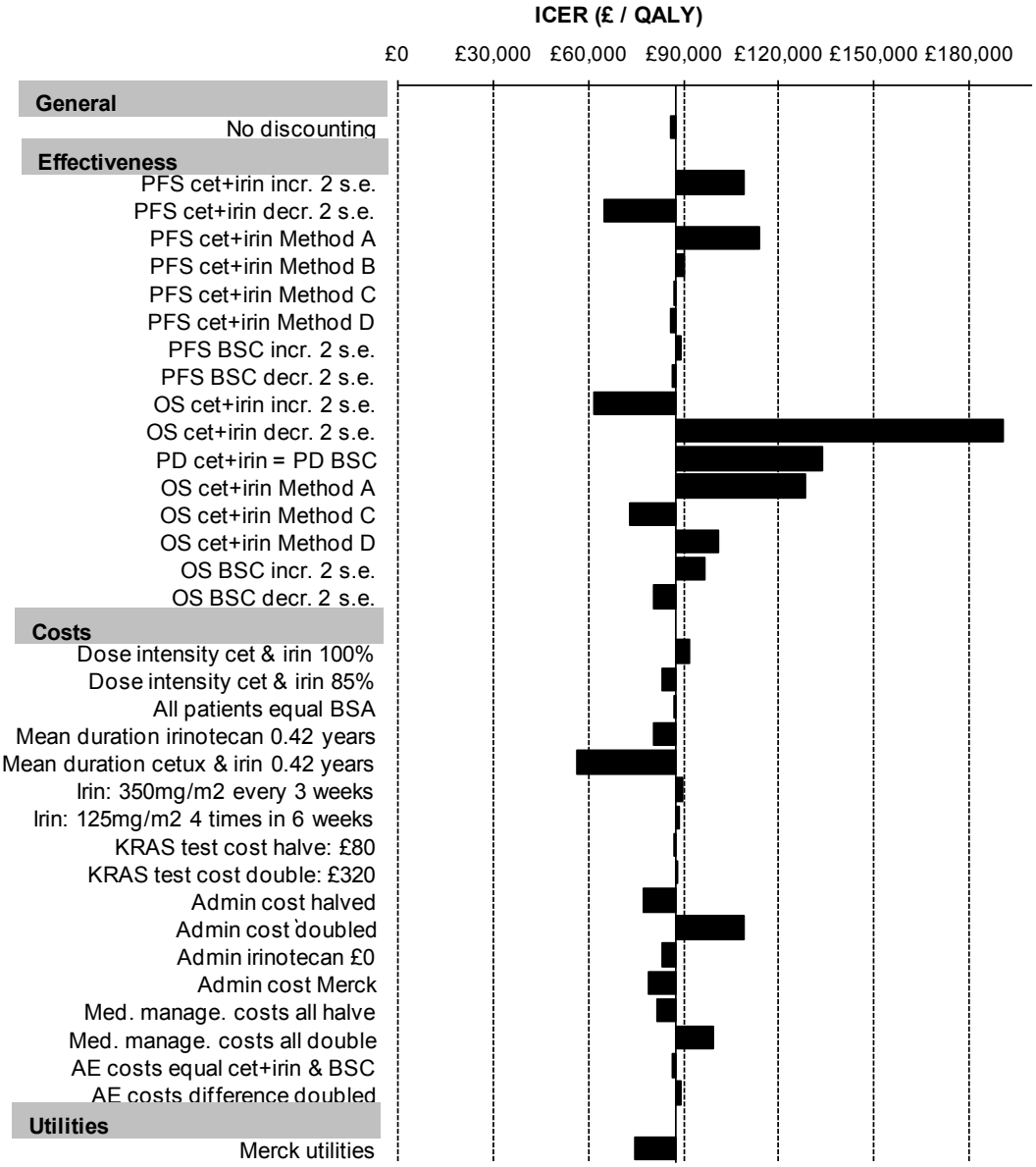
Table 55. Sensitivity analyses: CET+IRIN vs BSC

Parameter	Base case	Sensitivity analysis	ICER
Base case	N/A	N/A	**£88,000**
General			
Discounting costs & benefits	3.5% p.a.	0% p.a.	£86,000
Effectiveness			
Median PFS cetuximab+irinotecan	0.59 years	0.82 years (increased by 2 SE)	£109,000
		0.36 years (decreased by 2 SE)	£65,000
		0.88 years, using CET vs BSC RCT (see Method A, Appendix 15)	£114,000
		0.61 years, using De Roock et al. (2008) (see Method B, Appendix 15)	£90,000
		0.59 years, using Lievre et al. (2008) (see Method C, Appendix 15)	£87,000
		0.57 years, using De Roock et al. (2010) (see Method D, Appendix 15)	£86,000
Mean PFS BSC	0.23 years	0.27 years (increased by 2 SE)	£89,000
		0.18 years (decreased by 2 SE)	£86,000
Median OS cetuximab+irinotecan	1.25 years	1.75 years (increased by 2 SE)	£62,000
		0.75 years (decreased by 2 SE)	£191,000
		0.91 years, so that PD CET+IRIN = PD BSC	£134,000
		0.94 years (see Method A, Appendix 16)	£129,000
		1.48 years (see Method C, Appendix 16)	£73,000
		1.12 years (see Method D, Appendix 16)	£101,000
Mean OS BSC	0.51 years	0.61 years (increased by 2 SE)	£96,000
		0.41 years (decreased by 2 SE)	£80,000
Costs			
Dose intensity	94% CET, 90% IRIN	100% CET, 100% IRIN	£92,000
		85% CET, 85% IRIN	£83,000
Mean quantity CET+IRIN per person	511 mg CET, 352 mg IRIN (allowing for distribution of body surface area)	500 mg CET, 360 mg IRIN (all people assumed same body surface area)	£87,000
Mean duration therapies	0.73 years CET 0.73 years IRIN	0.73 years CET, 0.42 years IRIN	£81,000
		0.42 years CET+IRIN	£56,000

		(same as all people in BOND)	
Dosing schedule IRIN	180 mg/m^2 once every 2 weeks	350 mg/m^2 every 3 weeks	£90,000
		125 mg/m^2 for each of 4 weeks with 2 weeks rest	£88,000
KRAS test cost	£160 per test	Halve cost: £80	£88,000
		Double cost: £320	£88,000
CET+IRIN administration	£270 per admin CET, £143 per admin IRIN	Halve both costs	£77,000
		Double both costs	£109,000
		IRIN: £0	£83,000
		MS assumption total: £196	£79,000
Medical management (consultant visit, CT scans, BSC in PD) costs		Halve all unit costs or frequencies	£82,000
		Double all unit costs or frequencies	£100,000
Adverse events costs	CET = £3,671 BSC = £2,760	CET and BSC equal	£86,000
		CET - BSC doubled	£89,000
Utilities			
Utilities	CET+IRIN PFS = 0.75, PD = 0.69, BSC PFS = 0.75, PD = 0.69	MS values: CET+IRIN PFS = 0.81, PD = 0.79, BSC PFS = 0.75, PD = 0.69	£75,000

BSC, best supportive care; CET, cetuximab; CT, computed tomography; IRIN, irinotecan; MS, Merck Serono; p.a., per annum; PD, progressive disease; PFS, progression-free survival; SE, standard error

Figure 19. Sensitivity analyses: CET+IRIN vs BSC



The ICER remains very high, above £55,000 per QALY in all cases. The ICER is most sensitive to OS for cetuximab+irinotecan. In particular, it is more sensitive to OS for cetuximab+irinotecan than to OS for BSC because we have imposed a higher coefficient of variation (ratio of standard error to mean) for OS for cetuximab+irinotecan to reflect its greater uncertainty. The alternative method of estimating OS for cetuximab+irinotecan; i.e. where we do not adjust for cross-over in the BOND RCT, yields a substantially higher ICER (see Method A, Appendix 16). However, we do not favour this approach because we should make some adjustment for treatment cross-over. The ICER changes moderately when we use two other alternative methods to estimate OS for cetuximab+irinotecan; i.e. where we use information on PFS, and where we simply set our estimate of the median OS for patients with KRAS WT status on cetuximab+irinotecan for our

model equal to that from the BOND RCT without adjustment for indirect comparison (Methods C and D, Appendix 16). .

The ICER increases substantially when we adjust OS for cetuximab+irinotecan so that the mean time in PD for cetuximab+irinotecan equalled the mean time in PD for BSC. As explained in the last section, this models the plausible scenario whereby mortality is affected only whilst people are on active treatment, in this case, cetuximab+irinotecan. We believe that this is a useful sensitivity analysis given the substantial uncertainty in OS for cetuximab+irinotecan.

The ICER is sensitive to mean PFS for cetuximab+irinotecan, because this is proportional to the mean cost of cetuximab+irinotecan acquisition, and because it is very uncertain. The ICER is less sensitive to mean PFS for BSC because this is not associated with any drug costs, and because it is more certain. The ICER increases substantially when we model PFS for cetuximab+irinotecan using the cetuximab+BSC vs BSC RCT (see Method A, Appendix 15). The ICER is largely unchanged when we model PFS for cetuximab+irinotecan using alternative methods (see Methods B to D, Appendix 15); i.e., using only additional information from De Roock and colleagues (2008),(12) or Lievre and colleagues (2008),(84) or De Roock and colleagues (2010).(81)

In our base case, we predict that people take both irinotecan and cetuximab for a mean of 0.73 years; i.e. nearly nine months. We understand that irinotecan may typically be tolerated by patients for rather less than this period, given its toxicity. Therefore, we also modelled the scenario whereby irinotecan is taken for substantially less time, 0.42 years; i.e. five months, but leaving the treatment duration of cetuximab unchanged at 0.73 years. In this case, the ICER decreases only marginally because irinotecan is substantially less expensive than cetuximab. In a different sensitivity analysis, we modelled the time on treatment for both irinotecan and cetuximab as 0.42 years; i.e. five months. This corresponds approximately to the mean PFS time for all patients (KRAS WT and KRAS mutant status combined) on cetuximab+irinotecan in the BOND RCT, where the median PFS time is 4.1 months. However, we do not suggest that this treatment duration of cetuximab+irinotecan of 0.42 years is realistic. Instead it should be seen as being lower than the true value, because the 0.42 years represents the treatment duration for all patients (KRAS WT and KRAS mutant status combined), whereas we are modelling patients with KRAS WT status only, and PFS and hence treatment duration for patients with KRAS WT status is longer than for those with KRAS mutant status. This correlates with other sources of evidence; for example, in the cetuximab+BSC vs BSC RCT,(3) and from De Roock and colleagues (2008),(12) De Roock and colleagues (2010),(81) and Lievre and colleagues (2008).(84)

The ICER is fairly sensitive to the drug administration cost. In addition, the ICER falls moderately when we use Merck Serono's utility assumptions, but we disagree with their values for cetuximab+irinotecan. The ICER is insensitive to all other parameters when they are varied within plausible ranges. For example, the ICER is insensitive to the dosing regimen of irinotecan, partly because irinotecan is much less expensive than cetuximab, and partly because the dose of irinotecan per unit time is similar for all regimes.

7.2.6. PSA

The scatter-plots shown in Figure 20, Figure 21, and Figure 22 (pages 195–196) depict the results of the 1,000 simulations of the PSA, in terms of the incremental cost–utility of cetuximab+BSC, panitumumab+BSC, and cetuximab+irinotecan compared to BSC. In all simulations, all treatments generated more QALYs and more costs than BSC. There is clearly more uncertainty in the incremental costs and QALYs of cetuximab+irinotecan vs BSC compared to cetuximab+BSC vs BSC or panitumumab+BSC vs BSC. This is because we have assumed more uncertainty in the mean PFS and OS of cetuximab+irinotecan compared to cetuximab+BSC and panitumumab+BSC, to reflect the fact that we were forced to make assumptions about the effectiveness of cetuximab+irinotecan, whereas the effectiveness of the other two treatments were taken directly from RCTs. In all cases, the incremental costs and QALYs are correlated. This is because we have assumed correlations between PFS and OS for all treatments. So; for example, the longer people are in PFS, and hence the higher the total drug cost (as this is proportional to the time in PFS), the longer the OS, and hence total QALYs.

Figure 23 (page 193) shows the cost-effectiveness acceptability curves for the four treatments, showing the probability that each provides best value for money given a range of willingness-to-pay thresholds. We predict that panitumumab+BSC is never the most cost-effective option, and cetuximab monotherapy is unlikely to be the most cost-effective option regardless of the willingness-to-pay threshold. For willingness to pay below about £90,000 per QALY, BSC is likely to be the most cost-effective treatment, and above £90,000 per QALY, cetuximab+irinotecan is likely to be most cost-effective. For willingness-to-pay values of £60,000 per QALY or below, we predict that the probability that BSC is the most cost-effective treatment is approximately 100%.

Figure 20. PSA results: incremental cost–utility per person of: cetuximab+BSC

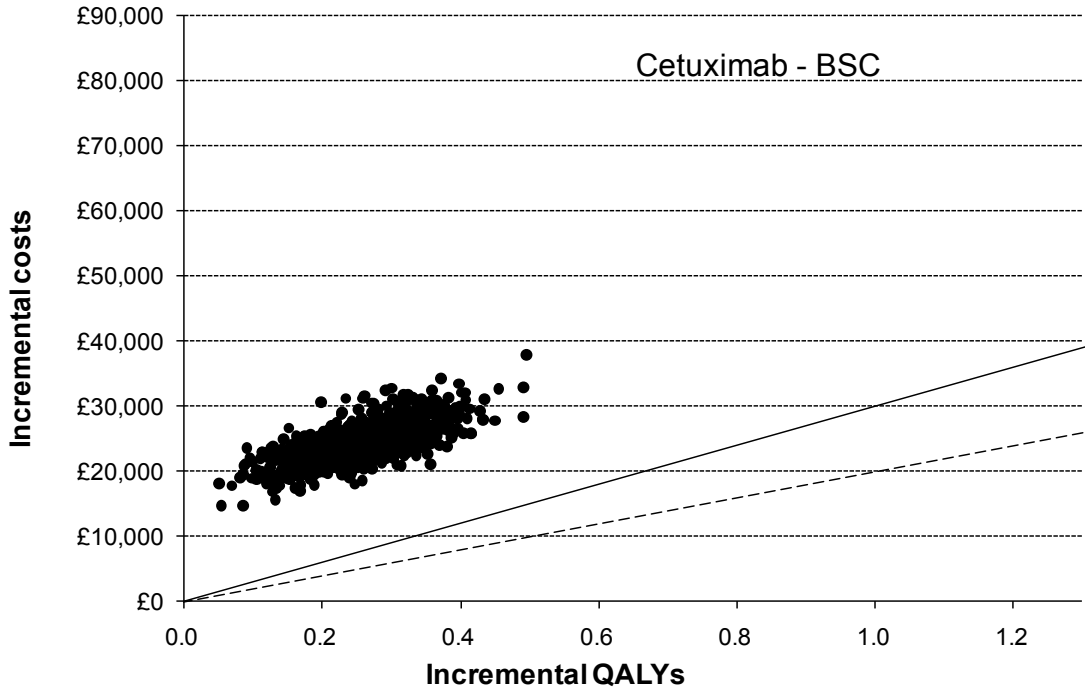


Figure 21. PSA results: incremental cost–utility per person of: panitumumab+BSC

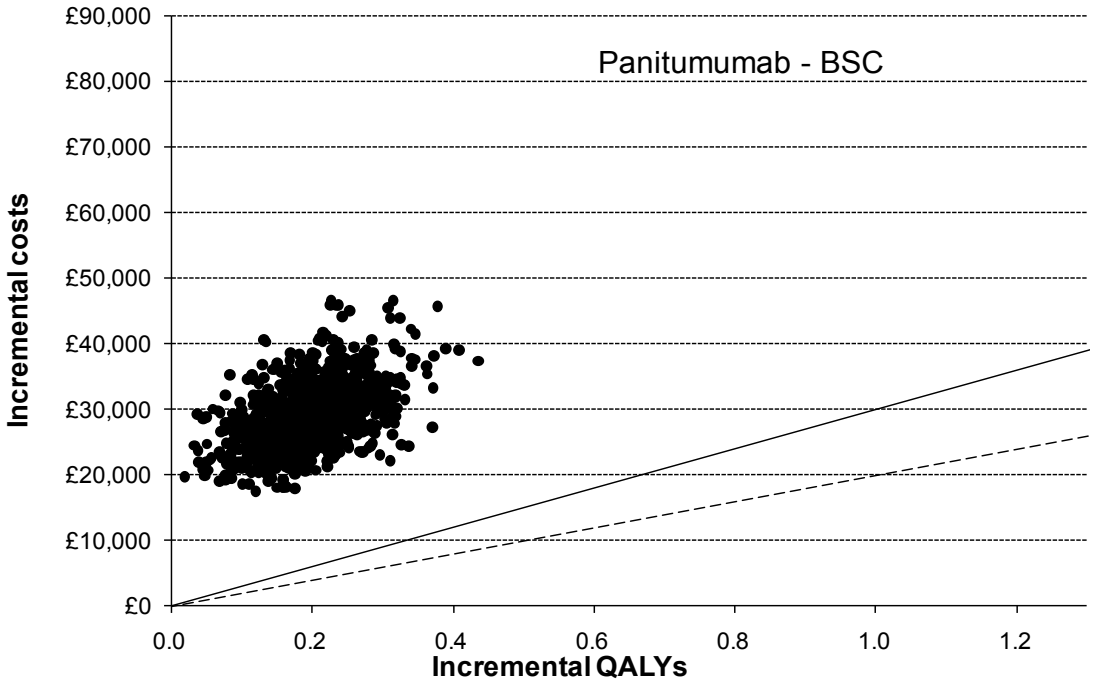


Figure 22. PSA results: incremental cost–utility per person of: cetuximab+irinotecan compared to BSC

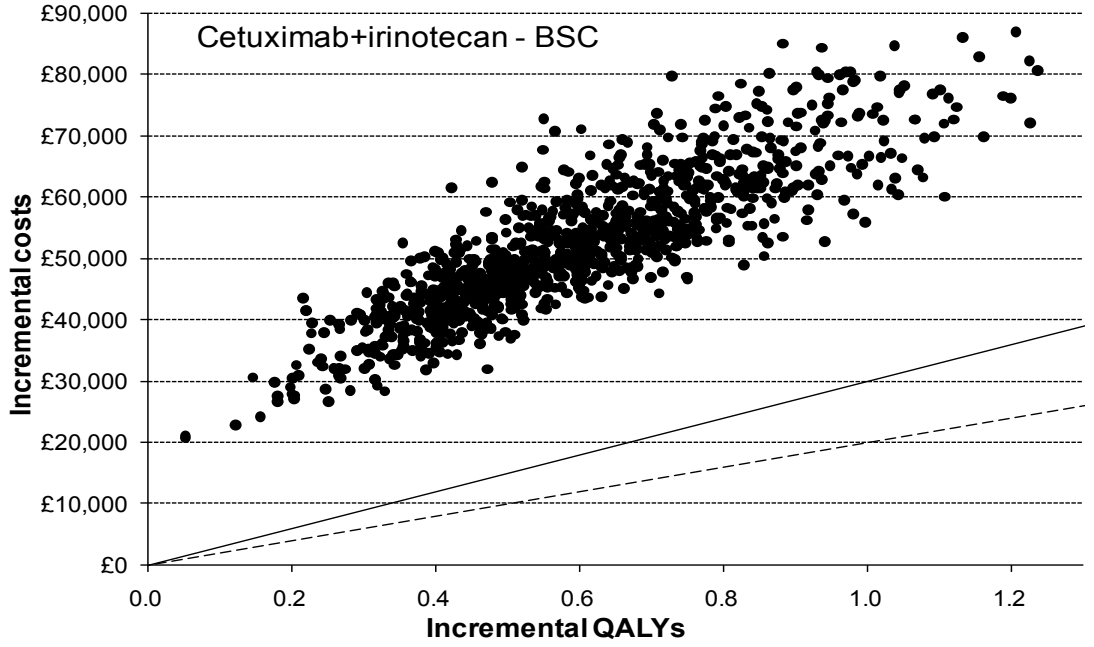
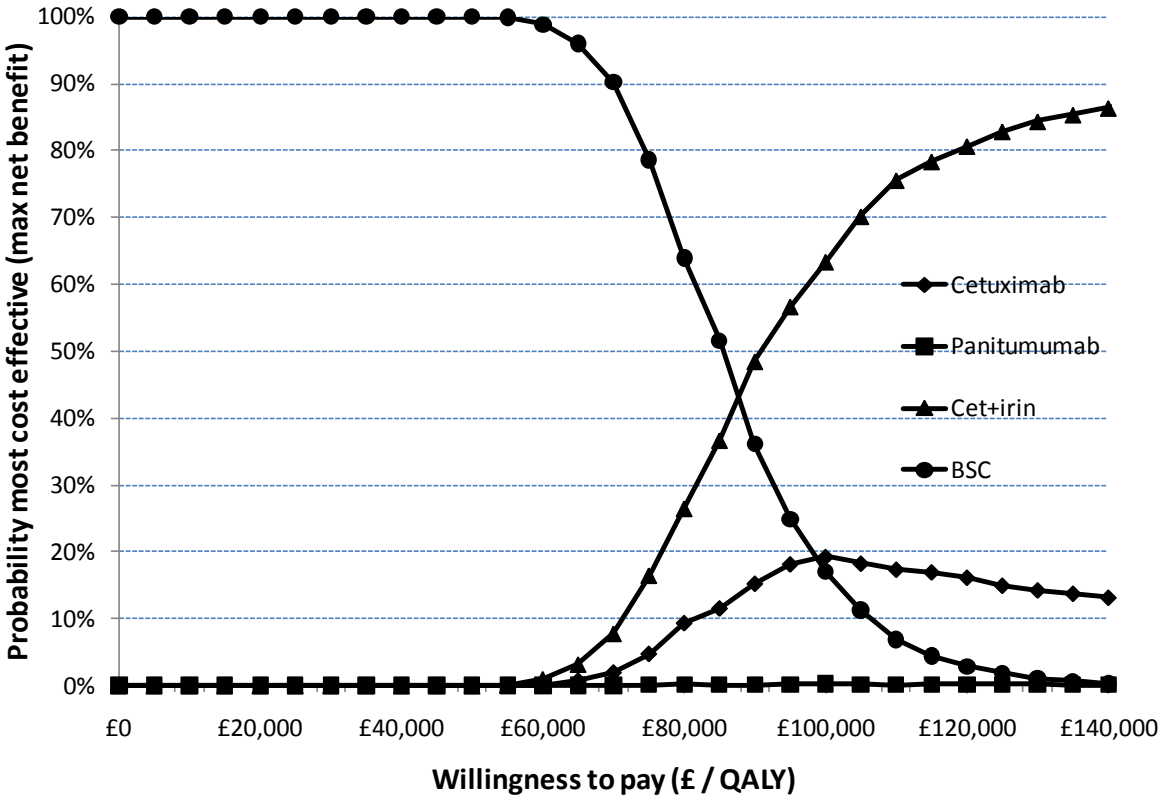


Figure 23. PSA results: cost-effectiveness acceptability curves



7.3. Comparison of results of PenTAG, Merck Serono, and Mittmann and colleagues

In the preceding sections, we described our cost-effectiveness analyses, and those of Merck Serono, the manufacturer of cetuximab, and of Mittmann and colleagues (2009).(8) In this section, we compare the results of these analyses and discuss the reasons for the different predictions of cost-effectiveness from the PenTAG model and Mittmann evaluation of cetuximab+BSC vs BSC in contrast with Merck Serono's model; and, the PenTAG model of cetuximab+irinotecan vs BSC relative to Merck Serono's model.

No comparisons of cost-effectiveness of panitumumab+BSC vs BSC for patients with KRAS WT status are possible because Amgen, the manufacturer of panitumumab, did not submit a cost-effectiveness analysis to NICE, and because we are not aware of any other relevant fully published models.

We have adjusted the results of Mittmann's evaluation in three ways, so that it is as comparable as possible with our model and Merck's model. First, we have separated out the estimated mean acquisition and administration costs of cetuximab from the values reported by Mittmann. We did this by assuming the same ratio of mean drug acquisition cost to administration cost as in our model. Second, and most importantly, we used the same cost per mg of cetuximab in our model as Merck Serono used in its model, which is relevant to the UK at today's date. Mittmann assumed a cost of CAN$3.24 per mg, which equals £2.05 per mg, assuming an exchange rate of GBP£1 = CAN$1.58 (as at 6th May 2011), whereas we use a cost of £1.37 per mg as do Merck Serono. Third, we inflated all non-drug costs at 4% per annum over four years, because all costs reported by Mittmann are given at 2007 prices.

7.3.1. Cetuximab+BSC vs BSC

A summary of the cost-effectiveness results for cetuximab+BSC vs BSC is given in Table 56, Table 58 and Table 59 (pages 195, 198 and 199). We believe that Mittmann's results are worthy of close scrutiny because they focus on the relevant KRAS WT population, and the trial-based economic evaluation appears to have been conducted to a high standard.

Table 56. Comparison of deterministic results per patient with KRAS WT status of PenTAG, Merck Serono, and Mittmann and colleagues

	CET+BSC			
	PenTAG	**Merck**	**Mittmann unadjusted[b]**	**Mittmann adjusted[b]**
Life years (mean) (undiscounted)				
Time on CET	**0.40**	**0.22**	NR	
Progression-free	0.40	0.40	N/A[a]	
Post-progression	0.44	0.44	N/A[a]	
Total (mean)	**0.84**	**0.84**	**0.79**	
QALYs (mean) (discounted)				
Progression-free	0.32	0.32	N/A[a]	
Post-progression	0.29	0.34	N/A[a]	
Total (mean)	**0.61**	**0.66**	**0.51**	
Costs (mean) (discounted)				
KRAS testing	£300	£200	[c]	
Drug costs	£14,400	£8,200	£18,500	£8,900
Drug administration	£5,500	£2,000		£6,000
Medical management in PFS	£1,600	£3,700	£5,100	
BSC in PD	£5,300	£4,100		£6,000
AEs	£3,700	£3,700		
Total	**£30,800**	**£21,800**	**£23,600**	**£20,900**

AEs, adverse events; BSC, best supportive care; CET, cetuximab, PD, progressive disease; PFS, progression-free survival; QALYs, quality-adjusted life years

[a] Mittmann's analysis does not split into PFS / PD; [b]Assuming an exchange rate of £1 = $1.58 Canadian (as at 6th May 2011); All values undiscounted in Mittmann et al (2009); [c]Not included because cancels out, as Mittmann assume testing in both treatment groups.

Importantly, the ICER for cetuximab+BSC vs BSC from our analysis (£98,000 per QALY), is similar to that from the adjusted results from the Mittmann analysis (£101,000 per QALY), but very different to that from Merck Serono's (£48,000 per QALY).

First, note that there are very many similarities between our model and Merck Serono's model; for example, we assume the same:

- clinical effectiveness for cetuximab+BSC and BSC
- health states progression free and PD
- cost per mg of cetuximab
- dose intensity of 98% for cetuximab
- costs of treating AEs

In addition, we used similar utilities, the only difference being that we assume a lower utility for cetuximab+BSC in PD than Merck Serono.

The difference between Merck Serono and our assessment of cost-effectiveness is virtually entirely caused by the large difference in total mean costs of acquisition and administration of cetuximab: for drug acquisition, we estimate £14,400, whereas Merck Serono estimate £8,200, and for drug administration, we estimate £5,600, whereas Merck Serono estimate £2,000 (Table 56, page 195). This itself is mostly due to the fact we estimate a far higher mean time on cetuximab treatment than Merck Serono: we assume 0.40 years (4.8 months), Merck Serono assume 0.22 years (2.6 months) (see Section 7.1.3.1.4 [page 148] for justification of this input). We both assume that cetuximab is taken whilst patients are in PFS, and we assume the same mean time in PFS. However, Merck Serono additionally impose an artificial maximum time on cetuximab treatment. When we use Merck Serono's model, and lift their cap on the time on treatment, their estimate of the mean time on cetuximab treatment increases from 0.22 to 0.40 years, equal to our estimate, and their ICER increases from £48,000 to £75,000 per QALY. Merck Serono estimate a lower mean total administration cost of cetuximab per person than us mostly because they assume a shorter mean time on treatment, but also because they assume a lower cost per administration than us, £180 vs £270.

We estimate that Mittmann and colleagues (2009) estimate the mean total acquisition cost per person of cetuximab as £8,900 (see final column Table 56, page 195), using the UK 2011 cost per mg of cetuximab, and assuming the same proportionate split of costs between cetuximab acquisition and administration as in our model. This value is similar to that of Merck, but far lower than our value of £14,400. Unfortunately, Mittmann and colleagues (2009) do not give their estimated mean duration of cetuximab treatment for patients with KRAS WT status. Instead, they mention only that the median duration of cetuximab treatment in the RCT was 8.1 weeks for whole population (i.e. those with KRAS WT and KRAS mutant status). Their mean total acquisition cost of cetuximab as £8,900, given a cost of cetuximab of £1.37 per mg, equates to a mean time on cetuximab of approx. 0.23 years, which is similar to that assumed by Merck, and far lower than assumed by us.

There are several further differences between Mittmann's evaluation versus Merck Serono's and our model (Table 57, page 197). Mittmann considers costs and consequences over 18–19 months, the duration of the cetuximab+BSC vs BSC RCT. At this the end of the study, 77% of patients on cetuximab+BSC and 82% on BSC had died, limiting but not eliminating the impact of this difference. However, we believe they should have extrapolated OS. Mittmann and colleagues speculate that if they had extrapolated OS, their estimated ICER would have fallen.

The final major difference is that Mittmann used different utilities, even though they also took utilities from the cetuximab+BSC vs BSC RCT.

Table 57. Comparison of PenTAG and Merck Serono models with the trial-based analysis by Mittmann and colleagues

	PenTAG	Merck Serono	Mittmann et al
Cost data	Modelled	Modelled	Directly measured
Discounting costs and benefits	3.5% per annum	3.5% per annum	None
Perspective	UK payer	UK payer	Canadian payer
Duration	Lifetime	Lifetime	18–19 months
Utilities	Progression free and PD from Merck Serono (CO.17)	Progression free and PD from CO.17 trial	Baseline and follow-up from CO.17 trial
Effectiveness estimates	Same mean PFS and OS assumed for CET+BSC vs BSC		No extrapolation of OS beyond end of CO.17 trial

BSC, best supportive care; CET, cetuximab; OS, overall survival; PFS, progression-free survival

None of the differences in assessed cost-effectiveness between our model and Merck Serono's model are due to differences in effectiveness assumptions; we both assume the same mean PFS and OS for cetuximab+BSC and BSC, see tables above and the survival curves shown in Figure 7 (page 139), Figure 8, (page 140), Figure 9 (page 141), Figure 10 (page 143). Given that Mittmann and colleagues (2009) do not split out the PFS and PD health states, we can only compare their estimates of mean OS. Their estimated OS for cetuximab+BSC of 0.79 years is slightly less, but very similar, to the 0.84 years used in both our model and that presented in the Merck Serono submission (Table 56 [page195]). Mittmann's value is lower probably because they did not extrapolate OS beyond the trial follow-up period. Their estimated OS for BSC of 0.51 years is exactly the same as the value used in both our model and Merck Serono's model.

Merck Serono's total discounted QALYs for cetuximab+BSC, at 0.66 is slightly higher than our estimate of 0.61 because they assume a slightly higher utility for people in PD. Mittmann's total QALYs of 0.51 is slightly lower than our value because they assume slightly lower mean OS and because they use slightly different utilities to those used in our model and Merck Serono's model. Our estimated total QALYs for BSC of 0.36 is virtually the same as Merck Serono's value of 0.37 because we use the same mean OS and utilities for BSC. Mittmann's estimated total mean QALYs of 0.33 is similar, but not the same as our value, because they have used different utilities.

Merck Serono's estimate of the cost of medical management in PFS for cetuximab at £3,700 is substantially higher than our estimate of £1,600. However, as we state in Section 6 (page 98) we

believe that Merck Serono's estimated cost per unit time for people in PFS is logically flawed. They have based their estimate of this figure on a value from Remak and Brazil (2004),(14) however, this refers specifically to the treatment of breast cancer, not CRC. Similarly, Merck Serono's flawed estimate of the total mean cost of medical management in PFS for BSC at £2,100 is substantially higher than our estimate of £0. However, coincidentally, we estimate the same mean incremental costs for medical management in PFS, at £1,600 (Table 59, page 199).

Our estimates for the mean costs of BSC in PD for both treatments are slightly higher than those of Merck Serono because we have inflated the cost of BSC in PD per unit time, quoted in Remak and Brazil over a greater period of time than Merck Serono.

Table 58. Comparison of deterministic results for KRAS WT population of PenTAG, Merck Serono, and Mittmann and colleagues for BSC (for comparison with cetuximab)

	BSC			
	PenTAG	**Merck**	**Mittmann unadjusted[b]**	**Mittmann adjusted[b]**
Life years (mean) (undiscounted)				
Progression-free	0.23	0.23[c]	N/A[a]	
Post-progression	0.29	0.29	N/A[a]	
Total (mean)	**0.51**	**0.51[c]**	**0.51**	
QALYs (mean) (discounted)				
Progression-free	0.17	0.17[c]	N/A[a]	
Post-progression	0.19	0.20	N/A[a]	
Total (mean)	**0.36**	**0.37[c]**	**0.33**	
Costs (mean) (discounted)				
KRAS testing	£0	£0	[d]	
Drug costs	£0	£0	£0	
Drug administration	£0	£0	£0	
Medical management in PFS	£0	£2,100	£2,300	£2,700
BSC in PD	£3,500	£2,700		
AEs	£2,800	£2,800		
Total	**£6,300**	**£7,600**	**£2,300**	**£2,700**

AEs, adverse events; BSC, best supportive care; PD, progressive disease; PFS, progression free survival; [a]Mittmann's analysis does not split into PFS / PD; [b]Assuming an exchange rate of £1 = $1.58 Canadian (as at 6th May 2011); All values undiscounted in Mittmann et al (2009); [c]After PenTAG corrected for error in calculation of proportion in PFS at Week 0; [d]Not included because cancels out, as Mittmann assume testing in both treatment groups

Table 59. Comparison of deterministic results of PenTAG, Merck Serono, and Mittmann and colleagues for cetuximab+BSC

	CET–BSC			
	PenTAG	Merck	Mittmann unadjusted[b]	Mittmann adjusted[b]
Life years (mean) (undiscounted)				
Progression-free	0.17	0.17	N/A[a]	
Post-progression	0.15	0.15	N/A[a]	
Total (mean)	**0.32**	**0.32**	**0.28**	
QALYs (mean) (discounted)				
Progression-free	0.15	0.15	N/A[a]	
Post-progression	0.10	0.14	N/A[a]	
Total (mean)	**0.25**	**0.30**	**0.18**	
Costs (mean) (discounted)				
KRAS testing	£300	£200	£0	
Drug costs	£14,400	£8,200	£18,500	£8,900
Drug administration	£5,500	£2,000		£6,000
Medical management in PFS	£1,600	£1,600	£2,800	£3,300
BSC in PD	£1,800	£1,400		
AEs	£900	£900		
Total	**£24,500**	**£14,300**	**£21,300**	**£18,200**
ICER (incr cost per QALY)	**£98,000**	**£48,000***	**£118,000**	**£101,000**

BSC, best supportive care; ICER, incremental cost effectiveness ratio; PD, progressive disease; PFS, progression free survival; QALYs, quality-adjusted life years

[a]Mittmann's analysis does not split into PFS / PD; [b]Assuming an exchange rate of £1 = $1.58 Canadian (as at 6th May 2011). All values undiscounted in Mittmann et al (2009); [c]After PenTAG corrected for Merck's error in calculation of proportion in PFS at Week 0

7.3.2. Cetuximab+irinotecan vs BSC

A summary of the results from our model and Merck Serono's model is given in Table 60–62 (pages 200–202)

Table 60. Comparison of deterministic results of PenTAG and Merck Serono models for cetuximab+irinotecan for KRAS WT population

	CET+IRIN	
	PenTAG	**Merck**
Life years (mean) (undiscounted)		
Time on CET+IRIN	**0.73**	**0.37**
Progression-free	0.73	0.65
Post-progression	0.65	0.70
Total (mean)	**1.38**	**1.36**
QALYs (mean) (discounted)		
Progression-free	0.54	0.53
Post-progression	0.43	0.53
Total (mean)	**0.97**	**1.06**
Costs (mean) (discounted)		
KRAS testing	£300	£160
Drug costs	£32,000	£17,400
Drug administration	£12,700	£3,800[a]
Medical management in PFS	£2,900	£6,100
BSC in PD	£7,800	£6,400
AEs	£3,700	£3,700
Total	**£59,300**	**£37,600[a]**

AEs, adverse events; BSC, best supportive care; CET, cetuximab; IRIN, irinotecan; KRAS, kirsten rat sarcoma; PD, progressive disease; PFS, progression free survival; PenTAG, Peninsula Technology Assessment Group; QALYs, quality-adjusted life years

[a]After we correct for Merck's error where model cell referred to CET+BSC admin, not CET+IRIN admin

Table 61. Comparison of deterministic results of PenTAG and Merck Serono models for BSC (for comparison with CET+IRIN) for KRAS WT population

	BSC	
	PenTAG	Merck
Life years (mean) (undiscounted)		
Progression-free	0.23	0.24
Post-progression	0.29	0.31
Total (mean)	**0.51**	**0.55**
QALYs (mean) (discounted)		
Progression-free	0.17	0.18
Post-progression	0.19	0.21
Total (mean)	**0.36**	**0.39**
Costs (mean) (discounted)		
KRAS testing	£0	£0
Drug costs	£0	£0
Drug administration	£0	£0
Medical management in PFS	£0	£2,200
BSC in PD	£3,500	£2,900
AEs	£2,800	£2,800
Total	**£6,300**	**£7,900**

AEs, adverse events; BSC, best supportive care; CET, cetuximab; incr, incremental; ICER, incremental cost-effectiveness ratio; IRIN, irinotecan; KRAS, kirsten rat sarcoma; PD, progressive disease; PenTAG, Peninsula Technology Assessment Group; PFS, progression-free survival; QALYs, quality-adjusted life years

Table 62. Comparison of deterministic results of PenTAG and Merck Serono models for CET+IRIN vs BSC for the KRAS WT population

	CET+IRIN – BSC	
	PenTAG	Merck
Life years (mean) (undiscounted)		
Progression-free	0.50	0.42
Post-progression	0.37	0.39
Total (mean)	**0.87**	**0.81**
QALYs (mean) (discounted)		
Progression-free	0.37	0.35
Post-progression	0.24	0.32
Total (mean)	**0.60**	**0.67**
Costs (mean) (discounted)		
KRAS testing	£300	£200
Drug costs	£32,000	£17,400
Drug administration	£12,700	£3,800
Medical management in PFS	£2,900	£3,900
BSC in PD	£4,300	£3,500
AEs	£900	£900
Total	**£53,100**	**£29,600**
ICER (incr cost per QALY)	**£88,000**	**£44,000**

AEs, adverse events; BSC, best supportive care; CET, cetuximab; incr, incremental; ICER, incremental cost-effectiveness ratio; IRIN, irinotecan; KRAS, kirsten rat sarcoma; PD, progressive disease; PenTAG, Peninsula Technology Assessment Group; PFS, progression-free survival; QALYs, quality-adjusted life years

The ICER for cetuximab+irinotecan vs BSC from our analysis, £88,000 per QALY, is much higher than Merck Serono's £44,000 per QALY.

As for the comparison of cetuximab+BSC vs BSC, first note that there are many similarities between our model and Merck Serono's model; for example we assume:

- similar PFS and OS for BSC and for cetuximab+irinotecan,
- the same health states PFS and PD,
- the same cost per mg of cetuximab and irinotecan,
- the same dose intensities of 94% for cetuximab and 90% for irinotecan,
- the same costs of treating AEs
- the same utilities for BSC, but we assume lower utilities for cetuximab+irinotecan in PFS and in PD.

As for the comparison for cetuximab+BSC vs BSC, the difference between Merck Serono and our assessment of cost-effectiveness is almost entirely due to the large difference in total mean costs of acquisition and administration of cetuximab+irinotecan: for drug acquisition, we estimate £32,000, whereas Merck Serono estimate £17,400, and for administration, we estimate £12,700, whereas Merck Serono estimate £3,800.

Very little of the difference in estimated cost-effectiveness between our model and the Merck Serono model is due to differences in effectiveness assumptions, because we assume very similar mean PFS and OS for BSC, and similar PFS and OS for cetuximab+irinotecan (even though our method of estimating the effectiveness for cetuximab+irinotecan is rather different to Merck Serono's method) see tables above and the survival curves for cetuximab+irinotecan in Figure 11 (page 149), Figure 12 (page 152).

Instead, the substantial differences in mean costs of drug acquisition and administration are mostly due to the fact we estimate a far longer mean time on cetuximab+irinotecan treatment than Merck Serono: we assume 0.73 years (8.8 months), Merck Serono assume 0.37 years (4.4 months). As we explained in Section 7.1.3.1.4 (page 148), we strongly disagree with Merck Seorno's derivation of mean time on cetuximab+irinotecan treatment. We both assume that cetuximab is taken while patients are in PFS. However, Merck Serono additionally impose an artificial maximum time on cetuximab+irinotecan treatment. When we use Merck Serono's model, and lift their cap on the time on treatment, their estimate of the mean time on cetuximab+irinotecan treatment increases from 0.37 to 0.65 years (equal to mean PFS), slightly below our estimate of 0.73 years, and their ICER increases from £44,000 to £67,000 per QALY. Notice also that if we use Merck Serono's estimated mean PFS for cetuximab+irinotecan of 0.65 years, then our ICER decreases slightly, from £88,000 to £82,000 per QALY. Merck Serono's estimate of the mean total administration cost of cetuximab+irinotecan per person is lower than our estimate mostly because they assume a far shorter mean time on treatment, but also because they assume a lower cost per administration per month than us, £840 vs £1,480.

Although we estimate slightly longer OS on cetuximab+irinotecan than Merck Serono (1.38 vs 1.36 years), we estimate slightly lower total QALYs than Merck Serono (0.97 vs 1.06 years). This is because we estimate lower utilities for cetuximab+irinotecan in PFS and PD than Merck Serono. Our estimated total QALYs for BSC of 0.36 years is very similar to Merck's value of 0.39 years because we use very similar mean OS and the same utilities for BSC.

Merck Serono's estimate of the cost of medical management in PFS for cetuximab+irinotecan at £6,100 is substantially higher than our estimate of £2,900. However, we believe that Merck Serono's estimated cost per unit time for people on cetuximab+irinotecan whilst in PFS is

logically flawed. Similarly, Merck Serono's flawed estimate of the mean total cost of medical management in PFS for BSC at £2,200 is substantially higher than our estimate of £0. However, coincidentally, we estimate similar mean total incremental costs for medical management in PFS.

Our estimates for the mean costs of BSC in PD for both treatments are slightly higher than those of Merck Serono because we inflate the cost per unit time of BSC in PD, quoted in Remak & Brazil (2004),(14) over a longer period of time than Merck Serono.

8. Discussion

8.1.1. Aim

The question addressed was, „What is the clinical and cost-effectiveness of cetuximab (mono- or combination chemotherapy), bevacizumab (combination with non-oxaliplatin chemotherapy) and panitumumab (monotherapy) for the treatment of metastatic colorectal cancer after first-line chemotherapy'.

The populations of interest were limited to KRAS WT mCRC in the cases of cetuximab and panitumumab.

The aim was addressed through a health technology assessment comprising a systematic review of clinical and cost-effectiveness studies, a review and critique of manufacturer submissions and a *de novo* economic analysis.

8.2. Stengths and limitations of the systematic review of effectiveness

The strengths of this systematic review are that it was conducted by an independent research team using the latest evidence in line with a pre-specified protocol. The main limitation of evidence on bevacizumab, cetuximab and cetuximab+irinotecan used third-line.

8.3. Stengths and limitations of the systematic review of economic evaluations

Again the strengths of this systematic review are that it was conducted by an independent research team using the latest evidence in line with a pre-specified protocol. The main limitation was the incomplete reporting of the reviews of the cost-effectiveness of panitumumab and the absence of cost-effectiveness estimates on bevacizumab.

8.4. Stengths and limitations of critique of manufacturer's submissions

This was conducted by an independent research team using a number of established frameworks to identify strengths and weaknesses. The scope of the submissions on bevacizumab and panitumumab, which did not directly estimate cost-effectiveness, was the main limitation.

8.5. Strengths and limitations of the PenTAG model

8.5.1. Strengths

Our assessment of the cost-effectiveness of drugs for mCRC is independent. Our analysis is the second independent fully-published cost-effectiveness analysis of cetuximab vs BSC for KRAS WT patients, the first being that of Mittmann and colleagues.(8) Our analysis is the first independent fully-published cost-effectiveness analysis of panitumumab+BSC vs BSC for patients with KRAS WT status and of cetuximab+irinotecan vs BSC for patients with KRAS WT status. We have carefully compared our model and the results of our analysis with those of Mittmann and colleagues and Merck Serono, and in so doing, we have highlighted areas in common and those where there is disagreement.

Our model adheres to the NICE reference case,(13) and has been extensively checked. In addition to our base case analysis, we also present numerous one-way sensitivity analyses, which we have chosen carefully to reflect the key areas of uncertainty and disagreements between ourselves and Merck Serono. We also present probabilistic analyses, in which we vary the key parameters within plausible ranges.

Our certainty about the accuracy of our analyses for cetuximab+BSCvs BSC and panitumumab+BSC vs BSC is increased given that the effectiveness evidence that underpins these analyses are taken from high-quality RCTs whose data is mature. There is much greater uncertainty concerning the analysis of cetuximab+irinotecan vs BSC given the lack of effectiveness evidence particularly for patients with KRAS WT status.

We have confidence in the accuracy of our utility estimates for the BSC, panitumumab and cetuximab treatment arms. Indeed, its accuracy is greater than is typically available for cost effectiveness analysis, being derived from direct observation of patients in trials. This is not true for the utilities for cetuximab+irinotecan.

8.5.2. Limitations

There are some factors that limit the accuracy of our analysis. For example, the mean duration of drug treatment for the KRAS WT population, a vital parameter, is available only for panitumumab. Indeed, the mean durations of cetuximab and cetuximab+irinotecan treatment are not published for patients with KRAS WT status. These are important limitations of our analysis, given that cost-effectiveness is very sensitive to these parameters.

The external validity of the results is uncertain given that we use efficacy data from RCTs in which people are relatively young (median age approximately 63 years) and fit (ECOG 0–2),

compared to people in actual clinical practice who are typically older and less fit (some with ECOG 3–4).

PFS and OS for cetuximab+irinotecan are available only for whole population: KRAS WT and KRAS mutant. Like Merck Serono we have therefore been forced to adjust these estimates to obtain estimates of PFS and OS in the KRAS WT population using other data sources. However, we have provided several possible methods of adjustment and the ICER for cetuximab+irinotecan vs BSC remains high regardless of which estimates for PFS and OS are used.

In common with Merck Serono, we do not stratify our analysis according to the line of treatment as the necessary IPD were not available.

We estimate the cost of medical management in PD for all treatment groups based on a study of medical management in PD for women with breast cancer.(14) Like Merck Serono we believe that this is methodologically acceptable given the absence of suitable alternatives, but do caution that the data from this publication is now rather old, relating to practices from the year 2000.

8.6. Main findings in the light of limitations

8.6.1. Effectiveness review

There is consensus about the evidence on effectiveness of cetuximab and panitumumab for patients with KRAS WT status. Based on RCTs, both cetuximab and panitumumab are effective used third-line, particularly with respect to PFS. For cetuximab, median PFS increases from approximately two months to approximately four months (HR 0.40; 95% CI 0.30, 0.54). For panitumumab median PFS increase from approximately 1.8 months to approximately three months (HR 0.45; 95% CI 0.34, 0.59).

We broadly agree with Merck Serono's estimates of the effectiveness of cetuximab+irinotecan for KRAS WT people even though it has not been directly measured in an RCT.

There is an absence of RCT evidence of bevacizumab combined with non-oxaliplatin chemotherapy.

8.6.2. Economic evaluations

Cost-effectiveness of cetuximab vs BSC: There are many similarities between Merck Serono's model for cetuximab vs BSC and the PenTAG *de novo* model. Importantly, we assume the same mean times as Merck Serono for PFS and OS for cetuximab and for BSC. Nonetheless, Merck Serono estimates a far lower ICER for cetuximab vs BSC than us: £47,000 vs £98,000 per QALY

gained. This is explained almost entirely by Merck Serono's estimation of the total mean costs of cetuximab acquisition and administration, which are far lower than our estimates. These differences in turn are due almost entirely to Merck Sorono's far lower estimation of the mean time on cetuximab treatment than us: 2.6 vs 4.8 months. Merck Serono's derivation of their estimate is based on their imposition of an artificial maximum time on cetuximab treatment. When we use Merck Serono's model, and lift their cap on the time on cetuximab treatment, their ICER increases from £47,000 to £75,000 per QALY gained.

We are aware of only one other fully published cost-effectiveness analysis of any of the treatments in this appraisal for KRAS WT people, that of Mittmann and colleagues (2009).(8) They perform a trial-based economic analysis to consider cost effectiveness from the health care payer perspective in Canada. After we adjust their result for the cost per mg of cetuximab appropriate in the UK in 2011, and other costs for inflation to the year 2011, we estimate their ICER is approximately equivalent to £101,000 per QALY gained. This is very close to our estimate of £98,000 per QALY gained, and much higher than Merck Serono's £48,000 per QALY gained.

Cost-effectiveness of cetuximab+irinotecan vs BSC: Again there are many similarities between Merck Sorono's model for cetuximab+irinotecan vs BSC and the PenTAG *de novo* model. Importantly, we assume similar mean times as Merck Serono for PFS and OS for cetuximab+irinotecan and for BSC. Merck Serono estimates a far lower ICER for cetuximab+irinotecan vs BSC: £44,000 vs £88,000 per QALY gained. Similar to the case of cetuximab vs BSC, this is explained almost entirely by Merck Serono's estimation of the total mean costs of cetuximab+irinotecan acquisition and administration, which are far lower than our estimates. These differences, in turn, are due almost entirely to Merck Serono's far lower estimation of the mean time on cetuximab+irinotecan treatment than us: 4.4 vs 8.8 months. Merck Serono's derivation of their estimate is based on their imposition of an artificial maximum time on cetuximab+irinotecan treatment. When we use Merck Serono's model, and lift their cap on the time on treatment, their ICER increases from £44,000 to £67,000 per QALY.

Cost effectiveness of panitumumab vs BSC: The estimate of cost-effectiveness from the PenTAG *de novo* model is £150,000 per QALY gained with no alternative estimate being offered by the manufacturer.

9. Conclusions

9.1. Implications

On balance we conclude that used third- and subsequent-line treatment relative to BSC, cetuximab+BSC, cetuximab+irinotecan+BSC and panitumumab+BSC are not cost-effective if decision thresholds of £20,000 per QALY or £30,000 per QALY are used.

There is no additional evidence on the effectiveness and cost-effectiveness of cetuximab used in second-line treatment relative to that informing the guidance on second-line use provided by TA118.

In common with the manufacturer, we were not able to estimate the cost-effectiveness of bevacizumab in combination with non-oxaliplatin chemotherapy second-line or beyond due to the absence of RCT evidence.

9.2. Suggested research priorities

- Given the lack of clinical data for patients with KRAS WT status taking cetuximab+irinotecan, it would be useful to conduct a RCT for these patients, compared with cetuximab+BSC, or panitumumab+BSC. It would be helpful to collect HRQoL in such a trial.
- We cannot model the cost-effectiveness of bevacizumab in combination with non-oxaliplatin chemotherapy, due to the absence of relevant clinical evidence. Ideally an RCT should be conducted if this was thought to be a potentially important use of the agent by the wider clinical community.
- Given that the mean treatment durations of cetuximab and cetuximab+irinotecan treatment strongly influence cost-effectiveness, and that they are not known with certainty, further data on these parameters from the RCTs of cetuximab vs BSC and cetuximab+irinotecan vs cetuximab would be helpful.
- Given that the medical management cost data come from a study of women with breast cancer over 10 years ago, collecting data on the medical management of mCRC would be useful.

Ongoing trials identified in the course of this appraisal indicate that some of the gaps in knowledge may already be being addressed.

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