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

Produced by Peninsula Technology Assessment Group (PenTAG), Peninsula College of Medicine and Dentistry, University of Exeter

APPENDICES

Appendix 1: Literature search strategies

Database searching was conducted on Wednesday, November 17th (2010) with the database results being uploaded first into Endnote X4 (Thomson Reuters) for conversion into RIS format and second, into Eppi Reviewer (Version 4) for de-duplication and screening.

Tappenden's 2007 search strategy was employed as the initial basis for syntax development.[2] Early includable studies/trials from testing the search syntax were used to benchmark the development of the strategy and the final result was checked again on this basis. The final strategy was quality controlled by our clinical expert, Dr Mark Napier.

No study design filters were added to the searches in order to retrieve a range of study designs and to locate results of mixed methodological focus, including: randomised controlled trials (RCTs), clinically controlled trials (CCTs) and systematic reviews, in addition to economic evaluations and any adverse event literature relating to the interventions.

Significant duplication between the resources was anticipated, giving a reasonable N for screening.

Database: Medline

Host: Ovid

Resource Parameters: 1950 to November Week 1 2010 - Current

Date searched: Wednesday, November 17th (2010)

Date Limits Applied: 2005 - Current

Searcher: C. Cooper

Hits: 1472

1. (Cetuximab or IMC C225 or MAb C225 or C225 or Erbitux).mp.
2. (Bevacizumab or Avastin or nsc 704865 or nsc704865).mp.
3. (Panitumumab or ABX-EGF* or Vectibix).mp.
4. or/1-3
5. Neoplasms/

6. Carcinoma/
7. Adenocarcinoma/
8. Or/5-7
9. Colonic Diseases/
10. Rectal Diseases/
11. Exp Colon/
12. Exp rectum/
13. Or/9-12
14. 8 AND 13
15. exp Colorectal Neoplasms/
16. (neoplasm$ or neoplasia adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).ti,ab.
17. (carcinoma adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).ti,ab.
18. (adenocarcinoma adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).ti,ab.
19. (cancer$ or CRC adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).ti,ab.
20. (tumour$ or tumor$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).ti,ab.
21. (malignan$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).ti,ab.
22. (metasta$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).ti,ab.
23. ((First line or second line or first-line or second-line or 1st line or 2nd line) and (chemo$) adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).ti,ab.
24. (Epidermal Growth Factor Receptor or EGFR or KRAS or VEGF adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).ti,ab.
25. or/15-24

26. 14 or 25

27. 4 AND 26

28. limit 27 to yr="2005 -Current"

Database: Embase

Host: Ovid

Resource Parameters: 1980 to 2010 Week 45

Date searched: Wednesday, November 17th (2010)

Date Limits Applied: 2005 - Current

Searcher: C. Cooper

Hits: 3417

1. (Cetuximab or IMC C225 or MAb C225 or C225 or Erbitux).mp. or cetuximab/
2. (Bevacizumab or Avastin or nsc 704865 or nsc704865).mp. or Bevacizumab/
3. (Panitumumab or ABX-EGF* or Vectibix).mp. or Panitumumab/
4. Or/1-3
5. *neoplasm/
6. *Carcinoma/
7. *Adenocarcinoma/
8. Or/5-7
9. exp colon disease/
10. exp rectum disease/
11. Exp Colon/

12. Exp rectum/
13. Or/9-12
14. 8 AND 13
15. exp colorectal tumor/
16. (neoplasm$ or neoplasia adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).ti,ab.
17. (carcinoma adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).ti,ab.
18. (adenocarcinoma adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).ti,ab.
19. (cancer$ or CRC adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).ti,ab.
20. (tumour$ or tumor$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).ti,ab.
21. (malignan$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).ti,ab.
22. (metasta$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).ti,ab.
23. ((first line or second line or first-line or second-line or 1st line or 2nd line) and (chemo$) adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).ti,ab.
24. (Epidermal Growth Factor Receptor or EGFR or KRAS or VEGF adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).ti,ab.
25. or/15-24
26. 14 or 25
27. 4 AND 26
28. limit 27 to yr="2005 -Current"

Database: Cochrane Library

Host: http://onlinelibrary.wiley.com/o/cochrane/cochrane_search_fs.html?newSearch=true

Resource Parameters: Issue 11 of 12, Nov 2010

Date searched: Wednesday, November 17th (2010)

Date Limits Applied: 2005 - Current

Searcher: C. Cooper

Hits: 269

1. **("Cetuximab" or "IMC C225" or "MAb C225" or "C225" or "Erbitux")**
2. **("Bevacizumab" or "Avastin" or "nsc 704865" or "nsc704865")**
3. **("Panitumumab" or "ABX-EGF*" or "Vectibix")**
4. **#1 or #2 or #3**
5. MeSH descriptor **Neoplasms**, this term only
6. MeSH descriptor **Carcinoma**, this term only
7. MeSH descriptor **Adenocarcinoma**, this term only
8. #5 or #6 or #7
9. MeSH descriptor **Colonic Diseases**, this term only
10. MeSH descriptor **Rectal Diseases**, this term only
11. MeSH descriptor **Colon** explode all trees
12. MeSH descriptor **Rectum** explode all trees
13. #9 or #10 or #11 or #12
14. #8 AND #13
15. MeSH descriptor **Colorectal Neoplasms** explode all trees
16. (neoplasm* or neoplasia near/3 (colorectal or colon* or rect* or intestine* or bowel))

17. (carcinoma near/3 (colorectal or colon* or rect* or intestine* or bowel))
18. (adenocarcinoma near/3 (colorectal or colon* or rect* or intestine* or bowel))
19. (cancer* or CRC near/3 (colorectal or colon* or rect* or intestine* or bowel))
20. (tumour* or tumor near/3 (colorectal or colon* or rect* or intestine* or bowel))
21. (malignan* near/3 (colorectal or colon* or rect* or intestine* or bowel))
22. (metasta* near/3 (colorectal or colon* or rect* or intestine* or bowel))
23. ((First line or second line or first-line or second-line or 1st line or 2nd line) and (chemo*) near/3 (colorectal or colon* or rect* or intestine* or bowel))
24. (Epidermal Growth Factor Receptor or EGFR or KRAS or VEGF near/3 (colorectal or colon* or rect* or intestine* or bowel))
25. (#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24)
26. (#14 OR #25)
27. (#4 AND #26), from 2005 to 2010

Database: Web of Science

Host: ISI

Resource Parameters: 1900-Current

Date searched: Wednesday, November 17th (2010)

Date Limits Applied: 2005 - Current

Searcher: C. Cooper

Hits: 2481

1. TS=((Cetuximab or Erbitux OR Bevacizumab or Avastin OR Panitumumab or Vectibix))

2. TS=((colorectal) SAME (neoplasm* or neoplasia or carcinoma or adenocarcionoma or cancer* or tumour* or tumor* or malignan* or metastasi*))
3. TS=((bowel) SAME (neoplasm* or neoplasia or carcinoma or adenocarcionoma or cancer* or tumour* or tumor* or malignan* or metastasi*))
4. TS=((colon*) SAME (neoplasm* or neoplasia or carcinoma or adenocarcionoma or cancer* or tumour* or tumor* or malignan* or metastasi*))
5. TS=((animal* or mice or rat or rats or dog* or cat* or rabbit* or pig))
6. #2 OR #3 OR #4
7. #1 AND #6
8. #6 NOT #5
9. Timespan=2005-2010

Database: Econlit

Host: Ebsco host

Resource Parameters:

Date searched: Wednesday, November 17th (2010)

Date Limits Applied: 2005 - Current

Searcher: C. Cooper

Hits: 0

(Cetuximab OR Erbitux OR Bevacizumab OR Avastin OR Panitumumab OR Vectibix)

Appendix 2: Protocol

Technology Assessment Report commissioned by the NETSCC HTA Programme on behalf of the National Institute for Health and Clinical Excellence

HTA 10/11/01

FINAL PROTOCOL

November 2010

Title of the project:

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)

Name of TAR team and project 'lead'

PenTAG, Peninsula College of Medicine and Dentistry, University of Exeter

Name: Chris Hyde

Post held: Prof of Public Health & Clinical Epidemiology

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Plain English Summary

This project will review and update the evidence presented to the National Institute of Health and Clinical Excellence (NICE) in 2007 on how good a number of drugs (cetuximab, bevacizumab and panitumumab) are for treating metastatic colorectal cancer (cancer that has spread beyond the bowel) and stopped responding to initial chemotherapy. The assessment will also assess whether the reviewed drugs are likely to be considered good value for money for the NHS.

Decision problem

Purpose

Colorectal cancer is a malignant neoplasm arising from the lining of the large intestine (colon and

rectum). Approximately 34,000 new cases of colorectal cancer were diagnosed in England and Wales in 2007, and approximately 14,000 deaths registered in 2008. The median age of patients at diagnosis is over 70 years.

In metastatic colorectal cancer 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 Dukes' classification. Between 20% and 55% of people first diagnosed with colorectal cancer have metastatic disease. In addition, approximately 50% to 60% of patients who have undergone surgery for early stage colorectal cancer with apparently complete excision will eventually develop advanced disease and distant metastases (typically presenting within two years of initial diagnosis). The five-year survival rate for metastatic colorectal disease is 12%.

The management of metastatic colorectal cancer is mainly palliative and involves a combination of specialist treatments (such as palliative surgery, chemotherapy and radiation), symptom control and psychosocial support. NICE have examined several chemotherapy agents used at various points in the care of metastatic CRC (see Section 4.3). This appraisal continues this examination.

Interventions

This technology assessment report (TAR) will consider three pharmaceutical interventions:

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

Cetuximab (Erbitux, Merck Serono) is a recombinant monoclonal antibody that blocks the human epidermal growth factor receptor (EGFR), inhibiting the growth of tumours expressing EGFR. Cetuximab has a UK marketing authorisation for the treatment of patients with EGFR-expressing, KRAS wild-type metastatic colorectal cancer 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.

Bevacizumab (Avastin®, Roche Products) is a recombinant monoclonal antibody that acts as an angiogenesis inhibitor by targeting the biologic activity of human vascular endothelial growth factor (VEGF), which stimulates new blood vessel formation in the tumour. It has a UK marketing authorisation in combination with fluoropyrimidine-based chemotherapy for the treatment of patients with metastatic carcinoma of the colon or rectum.

Panitumumab (Vectibix®, Amgen) is a recombinant monoclonal antibody that blocks the EGFR, inhibiting the growth of tumours expressing EGFR. It has a UK marketing authorisation as monotherapy for the treatment of EGFR expressing metastatic colorectal cancer with non-mutated (wild-type) KRAS after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.

Place of the interventions in the treatment pathway

NICE currently recommends oxaliplatin in combination with infusional 5-fluorouracil plus folinic acid (FOLFOX) and irinotecan in combination with infusional 5-fluorouracil plus folinic acid (FOLFIRI) as first-line treatment options for advanced colorectal cancer. FOLFOX or irinotecan alone are recommended as subsequent therapy options (Technology Appraisal 93).[1] The oral analogues of 5-fluorouracil, capecitabine and tegafur, in combination with uracil (and folinic acid) are also recommended as first-line treatment options for metastatic colorectal cancer (Technology Appraisal 61).[2]

Cetuximab in combination with FOLFOX, or in combination with FOLFIRI, is recommended as an option for the first-line treatment of metastatic colorectal cancer where the metastatic disease is confined to the liver and the aim of treatment is to make the metastases resectable (Technology Appraisal 176).[3]

In Technology Appraisal 118, bevacizumab in combination with 5-fluorouracil plus folinic acid, with or without irinotecan, as a first-line treatment and cetuximab in combination with irinotecan, as a second and subsequent line treatment were not recommended for metastatic colorectal cancer.[4]

In Technology Appraisal 150, NICE was unable to recommend the use of cetuximab for the treatment of colorectal cancer following failure of oxaliplatin-containing chemotherapy because no evidence submission was received from the manufacturer of the technology (terminated appraisal).[5]

There is also an on-going STA on bevacizumab in combination with oxaliplatin and either 5FU or capecitabine for the treatment of metastatic colorectal cancer.

Relevant comparators

The main comparators of interest are:

- Irinotecan- or oxaliplatin-based chemotherapy regimens
- The interventions will be compared with each other (where appropriate)

- Best supportive care: pain control, anti-emetics, appetite stimulants (steroids) and, in some cases, radiotherapy.

Population and relevant sub-groups

This will depend on the particular drug under consideration:

- People with EGFR-expressing and KRAS wild-type metastatic colorectal cancer that has progressed after first-line chemotherapy (cetuximab and panitumumab population).
- People with metastatic colorectal cancer that has progressed after first-line chemotherapy (bevacizumab population).

Subgroup: Variation in outcome depending on whether tumour response has occurred will be assessed if evidence is available. This will help inform any deliberations concerning continuation rules.

Outcomes to be addressed

The following outcomes will be measured:

- Overall survival (OS)
- Progression-free survival (PFS)
- Response rate
- Adverse effects of treatment
- Health-related quality of life (HRQL)
- Liver resection rates will also be considered if evidence is available.

Methods for synthesis of evidence of clinical effectiveness

The assessment report will include a systematic review of the evidence for clinical effectiveness of cetuximab monotherapy and in combination with chemotherapy; bevacizumab in combination with non-oxaliplatin based chemotherapy; and, panitumumab monotherapy. The review will be undertaken following the general principles published by the NHS Centre for Reviews and Dissemination.[6] The components of the review question will be:

Population: Adults with metastatic colorectal cancer – this will be further restricted to EGFR-expressing and KRAS wild-type metastatic colorectal cancer for cetuximab and panitumumab in line with the marketing authorisations for these treatments. Adults will in addition have had to fail first-line chemotherapy.

Interventions: This technology assessment report (TAR) 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 the previous paragraph.

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

- Irinotecan- or oxaliplatin-based chemotherapy regimens.
- One of the other interventions under consideration.
- Best supportive care: pain control, anti-emetics, appetite stimulants (steroids);and, in some cases, radiotherapy.

Outcomes: The following kinds of outcomes will be measured in a variety of scales reflecting the included studies:

- Overall survival
- Progression-free survival
- Response rate
- Adverse effects of treatment
- Health-related quality of life
- Liver resection rates (if available).

Search strategy

The search strategy will comprise the following main elements:

- Searching of electronic databases
- Contact with experts in the field
- Scrutiny of bibliographies of retrieved papers and manufacturer submissions
- Follow-up on mentions of potentially relevant on-going trials noted in NICE guidance on colorectal cancer.

The main electronic databases of interest will be:

MEDLINE (Ovid); PubMed; EMBASE; The Cochrane Library including the Cochrane Systematic Reviews Database, Cochrane Controlled Trials Register, DARE, NHS EED and HTA databases; NRR (National Research Register); Web of Science Proceedings; Current Controlled Trials; Clinical Trials.gov; FDA website; EMEA website. These will be searched from search end-date of the last MTA[7] on this topic April 2005. Although panitumumab was not covered in this report, we believe that relevant interventional research is highly unlikely to have been published on this drug prior to this date.

The searches will be developed and implemented by a trained information specialist using the search strategy detailed in the MTA by Tappenden *et al* as the starting point (see Appendix A for more information).[7]

Inclusion criteria

For the review of clinical effectiveness, in the first instance, only systematic reviews of randomised controlled trials (RCTs) and RCTs will be considered. However, if key outcomes of interest are not measured at all in the included RCTs we will discuss whether extending the range of included study designs ie to controlled clinical trials could be of value and feasible in the time available with NICE. The systematic reviews will be used as a source for finding further included studies and to compare with our systematic review. Systematic reviews provided as part of manufacturer's submissions will be treated in a similar manner. These criteria may be relaxed for consideration of adverse events, for which observational studies may be included.

Titles and abstracts will be examined for inclusion by two reviewers independently. Disagreement will be resolved by consensus.

Exclusion criteria

Studies will be excluded if they do not match the inclusion criteria, particularly:

- Non-randomised studies (except if agreed, in the absence of RCTs)
- Animal models
- Preclinical and biological studies
- Narrative reviews, editorials, opinions
- Non-English language papers
- Reports published as meeting abstracts only, where insufficient methodological

details are reported to allow critical appraisal of study quality.

Data extraction strategy

Data will be extracted independently by one reviewer using a standardised data extraction form and checked by another. Discrepancies will be resolved by discussion, with involvement of a third reviewer if necessary.

Quality assessment strategy

Consideration of study quality will be based on the guidelines set out by the NHS Centre for Reviews and Dissemination[6] and include the following factors for RCTs:

- Timing, duration and location of the study
- Method of randomisation
- Allocation concealment
- Blinding
- Numbers of participants randomized, excluded and lost to follow up.
- Whether intent to treat analysis is performed
- Methods for handling missing data
- Appropriateness of statistical analysis.

This framework will be adapted should other study designs subsequently be included.

Methods of analysis/synthesis

Data will be tabulated and discussed in a narrative review. Where appropriate, meta-analysis will be employed to estimate a summary measure of effect on relevant outcomes based on intention to treat analyses.

Meta-analysis will be carried out using fixed and random effects models, using RevMAN supplemented with STATA or equivalent software as required. Heterogeneity will be explored through consideration of the study populations, methods and interventions, by visualisation of results and, in statistical terms, by the χ^2 test for homogeneity and the I^2 statistic.

Sub-group analyses by completeness of tumour response will be undertaken if appropriate data are available.

Methods for synthesising evidence of cost-effectiveness

Review question

For the interventions and populations indicated above, the existing evidence on cost-effectiveness will be systematically reviewed.

Search strategy

The searches will again be developed and implemented by a trained information specialist using the search strategy detailed in the MTA by Tappenden *et al*[7] as the starting point.[7] The range of sources searched will include those for clinical effectiveness and extend to include NHS EED and Econlit. April 2005 will again be the starting point.

Study selection criteria and procedures

The inclusion and exclusion criteria for the systematic review of economic evaluations will be identical to those for the systematic review of clinical effectiveness, except:

Non-randomised studies will be included (e.g. decision model based analyses, or analyses of patient-level cost and effectiveness data alongside observational studies).

Full cost-effectiveness analyses, cost-utility analyses, cost-benefit analyses and cost consequence analyses will be included. (Economic evaluations which only report average cost-effectiveness ratios will only be included if the incremental ratios can be easily calculated from the published data.)

Stand alone cost analyses based in the UK NHS will also be sought and appraised.

Based on the above inclusion/exclusion criteria, study selection will be made by one reviewer.

Study quality assessment

The methodological quality of the economic evaluations will be assessed by one reviewer according to internationally accepted criteria such as the Consensus on Health Economic Checklist (CHEC) questions developed by Evers *et al*.[8] Any studies based on decision models will also be assessed against the International Society for Pharmacoecnomics and Outcomes Research (ISPOR) guidelines for good practice in decision analytic modelling.[9]

Data extraction strategy

Data will be extracted by one researcher into two summary tables: one to describe the study

design of each economic evaluation and the other to describe the main results.

In study design table: author and year; model type or trial based; study design (e.g. cost-effectiveness analysis [CEA], cost utility analysis [CUA] or cost-analysis); service setting/country; study population; comparators; research question; perspective, time horizon, and discounting; main costs included; main outcomes included; sensitivity analyses conducted; and other notable design features.

For modelling-based economic evaluations a supplementary Study Design table will record further descriptions of: model structure (and note its consistency with the study perspective, and knowledge of disease/treatment processes; sources of transition and chance node probabilities; sources of utility values; sources of resource use and unit costs; handling of heterogeneity in populations; evidence of validation (e.g. debugging, calibration against external data, comparison with other models).

In the results table for each comparator we will show; incremental cost; incremental effectiveness/utility and incremental cost-effectiveness ratio(s). Excluded comparators on the basis of dominance or extended dominance will also be noted. The original authors' conclusions will be noted, and also any issues they raise concerning the generalisability of results. Finally the reviewers' comments on study quality and generalisability (in relation to the TAR scope) of their results will be recorded.

Synthesis of extracted evidence

Narrative synthesis, supported by the data extraction tables, will be used to summarise the evidence base.

Economic Modelling

The general approach will be consistent with the NICE reference standard.[10] A new cost-effectiveness analysis will be carried out from the perspective of the UK NHS and Personal Social Services (PSS) using a decision analytic model. This will build on the modelling approach used in the original MTA[7] and be informed by modelling approaches used in subsequent NICE appraisals and published cost-effectiveness literature reviewed (see Section 6).

Model structure will be determined on the basis of available research evidence and clinical expert opinion.

The sources of parameter values that determine the effectiveness of the interventions being compared will be obtained from our own systematic review of clinical effectiveness or other

relevant research literature. Where required parameters are not available from good quality published studies in the relevant patient group we may use data from manufacturer submissions to NICE.

Cost data will be identified from NHS and PSS reference costs or, where these are not relevant, will be extracted from published work and/or sponsor submissions to NICE. If insufficient data are retrieved from published sources, costs may be derived from individual NHS Trusts or groups of Trusts.

To reflect health related quality of life, utility values will be sought either directly from relevant research literature or indirectly from quality of life studies.

Analysis of uncertainty will focus on costs and utilities, assuming cost per QALY can be estimated. Uncertainty will be explored through one way sensitivity analysis and, if the data and modelling approach permit, probabilistic sensitivity analysis (PSA). The outputs of PSA will be presented using plots on the cost-effectiveness plane and cost-effectiveness acceptability curves.

A life-time time horizon will be taken for our analysis and both cost and outcomes (QALYs) will be discounted at 3.5%.[10]

We will collate the available relevant material necessary to inform an assessment of the applicability of the End of Life Criteria.

The TAR team cannot guarantee to consider any data or information relating to the technologies if received after 21 February 2011.

Handling the company submissions

All data submitted by the manufacturers will be considered if received by the TAR team no later than 21 February 2011. Data arriving after this date will not be considered.

If the data meet the inclusion criteria for the review they will be extracted and quality assessed in accordance with the procedures outlined in this protocol. Any economic evaluations included in the company submission will be assessed against NICE's guidance on the Methods of Technology Appraisal2 and will also be assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used. Where the TAR team have undertaken further analyses, using models submitted by manufacturers or via de novo modelling and cost effectiveness analysis, a comparison will be made of the alternative models used for the analysis.

Any „commercial in confidence' data taken from a company submission will be

[redacted] in the assessment

Expertise in this TAR team

Name	Institution	Expertise
Louise Crathorne	PenTAG, Peninsula Medical School, University of Exeter	Systematic reviewing and project management
Tracey Jones-Hughes	PenTAG, Peninsula Medical School, University of Exeter	Systematic reviewing
Martin Hoyle	PenTAG, Peninsula Medical School, University of Exeter	Health economics and economic modelling (lead)
Paul Tappenden	ScHARR, University of Sheffield	Economic modelling (liaison with previous MTA)
Jaime Peters	PenTAG, Peninsula Medical School, University of Exeter	Economic modelling
Chris Cooper	PenTAG, Peninsula Medical School, University of Exeter	Information science
Mark Napier	Royal Devon and Exeter Foundation Trust	Clinical expert
Chris Hyde	PenTAG, Peninsula Medical School, University of Exeter	Systematic reviewing and economic evaluation. Project guarantor

Competing interests of authors

None

Timetable/milestones

Event	Expected due date
Draft scope	29/07/10
Team to comment on draft scope	26/08/10
Early sight of final scope	20/09/10

Final scope	25/10/10
Final protocol due	01/11/10
Consultee information meeting (CIM) (if applicable)	13/12/10
Manufacturers' submission	21/02/11
ERG Appraisal Report due	02/06/11
1st Appraisal Committee meeting	04/08/11
2nd Appraisal Committee meeting	05/10/11

Appendix 3: Clinical effectiveness: data extraction forms

These are available in separate PDF files.

Appendix 4: Method of indirect comparison

To calculate the indirect comparison for cetuximab+BSC vs panitumuab+BSC, the formulae reported in the Appendix of the paper by Bucher and colleagues was used (see below).{Bucher, 1997 #76}

Let $HR_{(CvB)}$ be the HR for the direct comparison of cetuximab+BSC vs BSC (from Karapetis and colleagues), and let $HR_{(PvB)}$ be the HR for the direct comparison of panitumumab+BSC vs BSC (from Amado and colleagues). Then the HR for the indirect comparison of cetuximab+BSC vs panitumumab+BSC $HR_{(CvP)}$ can be calculated by:

$$\ln(HR_{(CvP)}) = \ln(HR_{(CvB)}) - \ln(HR_{(PvB)}) .$$

The corresponding variance for $HR_{(CvP)}$ is calculated by:

$$\mathrm{var}(\ln HR_{(CvP)}) = \mathrm{var}(\ln HR_{(CvB)}) + \mathrm{var}(\ln HR_{(PvB)}) .$$

Appendix 5: Critique of manufacturer's search strategy

Randomised controlled trials (RCTs)

Merck Serono

Searches by Merck Serono were performed in the following databases on 5th October, 2009 and updated on 2nd November 2010:

- Ovid EMBASE
- Ovid MEDLINE®
- Ovid MEDLINE® In-Process
- The COCHRANE Central Register of Controlled Trials (CENTRAL)

Hand searches were also undertaken on several internet resources to identify relevant conference proceedings:

- ASCO (American Society of Clinical Oncology – www.asco.org)
- ESCO and ESMO (European Cancer Conference and European Society for Medical Oncology – www.esmo.org and www.ecco.org)
- ACCR (American Association of Cancer Research – www.aacr.org)

Separate search strategies were provided for EMBASE, Medline®, Medline® In-Process and Cochrane CENTRAL by the manufacturer. EMBASE, Medline, Medline in-process database searches were based on a conjunction of terms identifying the mCRC population with known KRAS status and terms identifying cetuximab, panitumumab and bevacizumab as interventions. For each term, a combination of thesaurus headings (where possible) and free-text search-words was used. No outcomes were specified to limit the searches in any of these databases.

The EMBASE, Medline and Medline in-process searches included a study design filter to limit results to clinical trials. No additional filters were applied in any databases.

The combination of terms within the search strategies to define the mCRC population and/or the intervention were appropriate and were replicable. Overall, we found the syntax to be highly focused, which has the potential to impinge on the sensitivity of the search. The choice of RCT filter was good and highly sensitive. The internet searches appear vague in their recording of findings and limited in their depth, and the Cochrane search was considered poor due to some

uncertainty regarding the use of the interface. That said, we found no additional trials.

Amgen

Searches by Amgen were performed in the following databases on 24th to 29th September, 2010 and updated in January 2011:

- EMBASE
- MEDLINE®
- MEDLINE® In-Process
- The COCHRANE Central Register of Controlled Trials (CENTRAL)
- Cumulative Index to Nursing and Allied Health Literature (CINAHL)
- Web of Science (WoS)

Conference abstracts were also searched:

- Conference proceedings Citation Index – Science (CPCI-S)
- Conference Proceedings Citation Index – Social Sciences & Humanities (CPCI-SSH)

To identify recently completed trials:

- National Research Register (www.nihr.ac.uk/Pages/NRRArchiveSearch)
- Current Controlled Trial (www.controlled-trials.com/mrct/)

A search strategy was only provided for Medline® by the manufacturer, which we considered to be an acceptable bare minimum: it would have been preferable to have records of all of the database searches. The search employed terms identifying the mCRC population and terms identifying cetuximab, panitumumab and bevacizumab as interventions, although CAS registry numbers were not included. Free text terms and medical subject heading (MESH) terms were used in the searches. No outcomes were specified to limit the search, however a study design filter was in place to limit hits to clinical trials.

The combination of terms within the search strategies to define the mCRC population and/or the intervention were appropriate and were replicable. The search was considered satisfactory but not particularly sensitive. We found no additional trials.

Roche

The following databases were searched in January 2011:

- The Cochrane Library
- MEDLINE®
- MEDLINE® In-Process
- EMBASE
- EMBASE In-Process
- BIOSIS

Searches were restricted to English Language publications. Roche report that the search strategy was modified to account for differences in syntax and thesaurus headings between databases. Searches included terms for free text and the relevant MESH/EMTREE index terms.

Hand searches were also undertaken on the following resources:

- ASCO (American Society of Clinical Oncology – www.asco.org)
- ESMO (European Society for Medical Oncology – www.esmo.org)
- ESMO/ECCO Joint meeting 2009 (European Cancer Conference)
- Reference lists of previous trials and systematic reviews

A full search strategy, with terms listed by numeric lines, was not included in the search report. Consequently, it is difficult to comment on the precession of retrieval.

Non-RCTs

Merck Serono

Manufacturer searches were performed in the following databases on 2nd July, 2010:

- Ovid EMBASE
- Ovid MEDLINE®

- Ovid MEDLINE® In-Process

Separate search strategies were provided for EMBASE, Medline® and Medline® In-Process, by the manufacturer. EMBASE, Medline, Medline in-process database searches were based on a conjunction of terms identifying the mCRC population and terms identifying cetuximab as an intervention, although the CAS registry numbers was not included. For each term, a combination of thesaurus headings (where possible) and free-text search-words was used. No study filter was used and no outcomes were specified to limit the searches in any of these databases. The search was limited to English and human only populations.

Amgen

Non-RCTs not searched for.

Roche

Non-RCTS, other than meta-analysis or systematic reviews, which were encompassed in the RCT search, were included.

Inclusion/exclusion criteria used in study selection

Merck Serono

The submission included RCTs in which the population had advanced or metastatic CRC after first line treatment, without specification of outcomes. We consider these inclusion and exclusion criteria are appropriate.

Amgen

The inclusion criteria comprised of RCTs in which the population had metastatic CRC after first line treatment, which compared panitumumab monotherapy with either placebo, BSC, cetuximab monotherapy, bevacizumab monotherapy or irinotecan/oxaliplatin based chemotherapy. Outcomes were specified. Studies not available in English were excluded. We consider these inclusion exclusion criteria to be appropriate.

Roche

The submission included RCTs in which the population had mCRC requiring treatment after failure of first line therapy. All therapies other than bevacizumab with non-oxaliplatin therapy were excluded. We consider these inclusion exclusion criteria to be appropriate.

Details of relevant studies not included in the manufacturers' submissions

Despite the variability in search strategies between manufacturers, we were unable to identify any additional studies.

Appendix 6: Clinical effectiveness: excluded studies

Papers excluded	Reason for exclusion
Ades (2009)	Not a relevant intervention or population
Alberts (2005)	Not a relevant population
Allegra (2009)	Not a relevant intervention
An Mao (2010)	Results mixed for different populations
Anonymous (2006)	Not a relevant intervention
Anonymous (2007)	Not a clinical trial or SR
Cao (2009)	Not a relevant intervention or population
Clinical Trials. gov	Not an RCT or CCT
Cunningham (2004)	Not a relevant population
Folprecht (2010)	Not a relevant population
Frieze (2006)	Not a relevant population
Galal (2008)	Not a relevant intervention
Galal (2009)	Not a relevant intervention
Galfrascoli (2009)	Not a relevant intervention or population
Galfrascoli (2010)	Not a relevant intervention or population
Gao (2009)	Not in English
Giantonio (2007)	Not a relevant intervention
Gibson (2006)	Not a relevant population
Golfinopoulos (2007)	Results mixed for different populations
Hapani (2009)	Results mixed for different populations
Hecht (2008)	Not a relevant intervention
Hoy (2006)	Not a relevant population
Hurwitz (2009)	Not a relevant population

Liu (2010)	Not a relevant population
Liu (2010)	Results mixed for different populations
Lordick (2010)	Not a relevant intervention
Mross (2009)	Not in English
Nie (2009)	Results mixed for different populations
Pander (2010)	Not a relevant population
Pfieffer (2007)	Not an RCT or CCT
Ranpura (2010)	Results mixed for different populations
Saltz (2007)	Not a relevant intervention
Sargent (2005)	Not a relevant intervention
Simkens (2008)	Not a relevant population
Sorbrero (2008)	Not a relevant population
Su (2009)	Results mixed for different populations
Taieb (2008)	Not a relevant population
Tol (2008)	Not a relevant population
Tol (2010)	Results mixed for different populations
Tol (2010)	Not a relevant population
Welch (2010)	Not a relevant population
Wilke (2008)	Not an RCT or CCT
Wu (2008)	Not a clinical trial or SR
Zhu (2007)	Not a relevant population

Appendix 7: Ongoing trials

Trial	Sponsor	ID	Intervention
ASPECCT: A study of panitumumab efficacy and safety compared to cetuximab in subjects with KRAS wild-type metatstaic colorectal cancer	Amgen	NCT01001377	Experimental: panitumumab Comparator: cetuximab
Bevacizumab maintenance versus no maintenance after stop of first-line chemotherapy in patients with metastatic colorectal cancer. A randomized multicenter phase III non-inferiority trial	Swiss Group for Clinical Cancer Research	NCT00544700	Experimental: bevacizumab maintenance therapy Comparator: no maintenance therapy
A prospective randomised open label trial of oxaliplatin/fluoropyrimidine versus oxaliplatin/fluoropyrimidine plus cetuximab pre and post operatively in patients with resectable colorectal liver metastasis requiring chemotherapy	Southampton University Hospitals NHS Trust	NCT00482222	Experimental: oxaliplatin/fluoropyrimidine plus cetuximab Comparator: oxaliplatin/fluoropyrimidine
Phase III trial of irinotecan-based chemotherapy plus cetuximab (NSC-714682) with or without bevacizumab (NSC-704965) as second-line therapy for patients with metastatic colorectal cancer who have progressed on bevacizumab with either FOLFOX, OPTIMOX or XELOX	Southwest Oncology Group	NCT00499369	Experimental: irinotecan or FOLFIRI and cetuximab plus bevacizumab Comparator: irinotecan or FOLFIRI plus cetuximab
SPIRITT - Multi-center, open-label, randomized, phase 2 clinical trial evaluating safety and efficacy of FOLFIRI with either panitumumab or bevacizumab as second-line treatment in subjects with metastatic colorectal cancer with wild-type KRAS tumors	Amgen	NCT00418938	Experimental: FOLFIRI plus panitumumab Comparator: FOLFIRI plus bevacizumab
PICCOLO - A randomised clinical trial of treatment for	University of	NCT00389870	1. Irinotecan

Trial	Sponsor	ID	Intervention
fluorouracil-resistant advanced colorectal cancer comparing standard single-agent irinotecan versus irinotecan plus panitumumab and versus irinotecan plus cyclosporin	Leeds CTAAC (UK) 2. Amgen Ltd (UK)		2. Irinotecan with cyclosporin 3. Irinotecan plus panitumumab 4. Irinotecan with cyclosporin plus panitumumab
Study of irinotecan and cetuximab versus irinotecan as second-line treatment in patients with metastatic, EGFR-positive colorectal cancer	ImClone LLC Bristol-Myers Squibb	NCT00063141	Experimental - cetuximab plus irinotecan Comparator - irinotecan
A study of RO5083945 in combination with FOLFIRI versus FOLFIRI plus cetuximab or FOLFIRI alone as second-line treatment in patients With metastatic colorectal cancer	Hoffmann-La Roche	NCT01326000	*KRAS WT A* Experimental: RO5083945 plus FOLFIRI *KRAS WT B* Comparator: FOLFIRI plus cetuximab *KRAS mutant A*: Experimental: RO5083945 plus FOLFIRI *KRAS mutant B*: Comparator: FOLFIRI

CTAAC, Trials Advisory and Awards Committee; EGFR, epidermal growth factor receptor; FOLFIRI, irinotecan plus infusional 5-fluorouracil and folinic acid; FOLFOX, oxaliplatin plus infusional 5-fluorouracil and folinic acid; NCT, National Clinical Trials; NHS, National Health Service

Appendix 8: Clinical effectiveness – supplementary tables

Study	Jonker et al (2007)[8]	Van Cutsem et al (2007)[13]	Van Cutsem et al (2008)[17]
Participants	**Inclusion criteria:** Advanced colorectal cancer expressing EGFR detectable by immunohistochemical methods. Previous treatment with either fluoropyrimidine, irinotecan or oxaliplatin with no response to treatment or contraindications to treatment with these drugs Disease that could be measured or evaluated An ECOG of 0 to 2 with adequate bone marrow, kidney and liver function; and no serious concurrent illness. **Exclusion criteria:** Patients were ineligible if they had received any agent that targets the EGFR pathway or treatment with a murine monoclonal antibody. Previous bevacizumab was permitted but not required.	**Inclusion criteria:** Age ≥18 years Pathological diagnosis of metastatic colorectal adenocarcinoma and radiologic documentation of disease progression during or within 6 months following the last administration of fluoropyrimidine, irinotecan and oxaliplatin. Dose intensity of irinotecan > or = 65mg/m2 per week and oxaliplatin > or = 30 mg/m2 per week. ECOG 0 to 2 Two or three prior chemo regimens for mCRC 1% EGFR-positive membrane staining in primary or metastaic tumour cells **Exclusion criteria:** Symptomatic brain metastases, interstitial pneumonitis or pulmonary fibrosis, systematic chemotherapy or radiotherapy within 30 days before	**Inclusion criteria:** As for reference [13] **Exclusion criteria:** As for reference [13]

Study	Jonker et al (2007)[8]	Van Cutsem et al (2007)[13]	Van Cutsem et al (2008)[17]
		random assignment and prior anti-EFGR agents.	

Study	Jonker et al (2007)[8]	Van Cutsem et al (2007)[13]	Van Cutsem et al (2008)[17]
Interventions	**Cetuximab + BSC**. Given IV as an initial dose of 400 mg per square meter of body-surface area, administered over 120 minutes, followed by a weekly maintenance infusion of 250 mg per square meter, administered over 60 minutes. **BSC** Measures designed to provide palliation of symptoms and improve quality of life.	**Panitumumab plus BSC** Administered by a 60 minute IV infusion at 6 mg/kg once every two weeks until patients progressed or developed unacceptable toxicity developed. Pre-medication was not required. **BSC** Defined as the best palliative care per investigator excluding antineoplastic agents.	**Panitumumab plus BSC** As for reference 12
Study objectives	To demonstrate the effect of cetuximab on survival or quality of life in patients with advanced colorectal cancer	To evaluate the effect of panitumumab monotherapy in patients with chemorefactory metastatic colorectal cancer	To demonstrate the efficacy and safety of cetuximab on survival or quality of life in patients with advanced colorectal cancer
Outcomes	**Primary**: Overall survival, defined as time from randmisation until death from any cause. **Secondary**: Progression free survival, defined as time from randomisation until the first objective observation of disease progression or death from any cause	**Primary**: Progression free survival by blinded central radiology assessment, calculated from day of random assignment until radiologic progression or death. **Secondary**: Objective response, overall survival and safety. Best objective response by blinded central review and overall survival time. OS was calculated from the day of random assignment until death, censoring patients at the last day known to be alive. All patients were followed up for survival every three months up to 2 years after	**Primary**: Safety, including incidence of grade 3/4 adverse and treatment-related events, skin related events and antibody formation. **Secondary**: Although no secondary endpoints were prespecified in the protocol, the efficacy of panitumumab monotherapy was explored by assessing PFS, ORR, time to and duration of response, duration of stable disease (SD) and survival using the local investigators' assessment of radiographic images.

Study	Jonker et al (2007)[8]	Van Cutsem et al (2007)[13]	Van Cutsem et al (2008)[17]
		random assignment.	
Analysis	All patients who underwent randomisation were included in the efficacy analyses on the basis of the group to which they were assigned. Time to event variables were summarised with the use of Kaplan-Meier plots. Primary comparisons were made using the stratified log-rank test. Hazard ratios with 95% CI were calculated from stratified Cox regression models with treatment group as the single factor. Deterioration in quality of life scores was defined a priori as a decline of 10 points or more from baseline. It was estimated a priori that 445 deaths would provide a statistical power of 90% and a two sided alpha of 5% to detect an absolute increase of 9.6% in the 1 year overall survival from the predicted 1-year overall survival of 14.1% in the group assigned to supportive care alone (HR 0.74). Safety analysis was conducted on an on-treatment basis, contrasting patients who had at least one dose of cetuximab	The primary analysis included all patients randomly assigned. PFS was analysed at the 5% significance level using a log-rank test stratified by baseline ECOG performance status and region. A 1% test of objective response at the primary analysis and 4% test of OS were prespecified conditional on a significant PFS difference. The analysis of OS and an update of objective response rates and duration of response were conducted after a minimum of 12 months follow up. Kaplan-Meier methodology was used to estimate PFS, OS and time to and duration of the response, including 95% CI for event-free rates and difference in rates. The 65% CI for time-to-event quartiles were calculated per Brookmeye and Crowley. HRs for PFS and OS were estimated with a Cox proportional hazards regression model adjusted for the randomisation factors. The study had 90% power for a two-sided 1% significance level test given a	The primary analyses of safety and efficacy outcomes included all enrolled patients who received at least one dose of panitumumab. Time to response was calculated as period from enrolment date to the first objective response. Duration of response was calculated only for the responders as the period from the first objective response to the first observation of disease progression or death due to disease progression. Duration of SD was calculated as the period from enrolment date to the first observation of disease progression or death due to disease progression; only patients who had at least one scan of SD as their best response were included. PFS time was calculated as the period from enrollment date to the first observed disease progression or death. Overall survival time was calculated as the time period from enrolment to death.

Study	Jonker et al (2007)[8]	Van Cutsem et al (2007)[13]	Van Cutsem et al (2008)[17]
	(including those who crossed over) with patients assigned to supportive care alone, and omitting patients who withdrew consent before any intervention.	hazard ratio (panitumumab relative to BSC) of 0.67. The sample size goal was 430 patients, with an event goal of 362 patients with progressive disease by central review or death.	Descriptive statistics were calculated for the incidence of objective response (with two sided 95% confidence intervals), adverse events, laboratory values, changes in vital signs and antibody measurements. Time-to-event outcomes were analysed by Kaplan-Meier methods. For the analyses on OS, a minimum of 12 months of follow up were included. Among patients with skin toxicity, the relationship between severity of skin toxicity and OS was evaluated using a Cox regression model adjusted for the pahse 3 randomisation factors, ECOG score and geographic region. Patients were included in the analysis if they were progression free for at least 28 days to allow the worst severity of skin toxicity to manifest. The sample size was limited to the patients enrolled in the BSC arm of the phase 3 study who met the eligibility criteria (planned n = 200). Assuming a true event rate of 1%, the probability of at least one patient experiencing a given adverse event was 87% for a sample size of 200.

Appendix 9: Cost-effectiveness: quality appraisal

Table 1. Summary of quality assessment: Norum and colleagues{Norum, 2006 #25} using critical appraisal checklist from Evers and colleagues{Evers, 2005 #1681}

	Item	Yes / No
1	Is the study population clearly described?	Yes. Patients with mCRC having received two lines of treatment.
2	Are competing alternatives clearly described?	Yes. The comparator is no third-line therapy.
3	Is a well-defined research question posed in answerable form?	Yes. The cost per LYG from changing policy from no third-line therapy to cetuximab+irinotecan in the treatment of mCRC.
4	Is the economic study design appropriate to the stated objective?	Yes. A model-based CEA is used reporting cost per LYG.
5	Is the chosen time horizon appropriate to include relevant costs and consequences?	Unclear. Time horizon is not reported, but Norum states that *„All costs occurred within one year and were not discounted*' (p533)
6	Is the actual perspective chosen appropriate?	Yes. The CEA is conducted from a third-party payer in Norway.
7	Are all important and relevant costs for each alternative identified?	Yes. Total costs include drug, administration, hospitalisations, out-patient therapy and EGFR analysis, and family costs (travelling).
8	Are all costs measured appropriately in physical units?	Yes. All costs were calculated according to Norwegian unit costs and converted to Euros.
9	Are costs valued appropriately?	Yes.
10	Are all important and relevant outcomes for each alternative identified?	Yes. LYG is the outcome used.
11	Are all outcomes measured appropriately?	Yes. Treatment benefit is defined as LYG and is based upon data in BOND (Cunningham et al) and Saltz et al.
12	Are outcomes valued appropriately?	Yes.
13	Is an incremental analysis of costs and outcomes of alternatives performed?	Yes and subjected to sensitivity analyses.

14	Are all future costs and outcomes discounted appropriately?	No. No discounting was applied.
15	Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	Yes. One-way sensitivity analyses on all health care costs (EGFR analysis cost, cetuximab and irinotecan drug costs, outpatient clinic cost, drug administration cost) and treatment impact on OS. The impact of travelling costs was not assessed in sensitivity analyses.
16	Do the conclusions follow from the data reported?	Yes. Third-line therapy with cetuximab+irinotecan was acknowledged to be promising, but very expensive. Lower drug costs and/or improved survival could change these findings. This conclusion reflects the high base case ICERs reported and the lower ICERs from assuming reduced drug costs and improved survival.
17	Does the study discuss the generalisability of the results to other settings and patient/ client groups?	To some extent. The author discusses differences in cetuximab acquisition cost between countries and also the willingness to pay thresholds in different countries.
18	Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	The author acknowledges a research grant from the Norwegian Cancer Union for this work. There is no indication that this would represent a conflict of interest.
19	Are ethical and distributional issues discussed appropriately?	No.

Table 2. Summary of quality assessment: Starling and colleagues{Starling, 2007 #26} using critical appraisal checklist from Evers and colleagues{Evers, 2005 #1681}

	Item	Yes / No
1	Is the study population clearly described?	Yes. Patients with mCRC who have failed previous chemotherapy treatment.
2	Are competing alternatives clearly described?	Yes. Active/best supportive care, where active supportive care is the best care available and may include chemotherapy.
3	Is a well-defined research question posed in answerable form?	Yes. To compare the cost-effectiveness of cetuximab+irinotecan with active/best supportive care.

4	Is the economic study design appropriate to the stated objective?	Yes. A trial-based CEA of Cunningham et al.
5	Is the chosen time horizon appropriate to include relevant costs and consequences?	Yes. A lifetime horizon extrapolating beyond the end of follow-up in Cunningham et al.
6	Is the actual perspective chosen appropriate?	Yes. The study was calculated from a third-payer perspective: NHS.
7	Are all important and relevant costs for each alternative identified?	Yes. Drug acquisition and administration, in-patient hospitalisation, out-patient consultations, laboratory tests (including EGFR testing) and imaging.
8	Are all costs measured appropriately in physical units?	Yes.
9	Are costs valued appropriately?	In GBP, but source if unit costs not reported.
10	Are all important and relevant outcomes for each alternative identified?	Yes. The primary health outcome is LYG, with the secondary outcome of QALY using utility values form the MABEL study.
11	Are all outcomes measured appropriately?	Yes. EQ-5D utility values from the MABEL study.
12	Are outcomes valued appropriately?	Unclear. Although utility values are reported to have been measured directly from Cunningham et al, the mean utility reported by MABEL „*was applied to all patients at all time points in the economic model*'' p209
13	Is an incremental analysis of costs and outcomes of alternatives performed?	Yes and subject to sensitivity analyses.
14	Are all future costs and outcomes discounted appropriately?	Unclear. Discounting is not reported.
15	Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	Yes. In one-way sensitivity analyses the following were assessed: proportion of active/best supportive care patients receiving chemotherapy, OS, cetuximab acquisition costs, chemotherapy administration costs and best supportive care costs.
16	Do the conclusions follow from the data reported?	The conclusion does not reflect on any of the results reported.

17	Does the study discuss the generalisability of the results to other settings and patient/ client groups?	Yes. The authors comment that use of one RCT for the basis of the CEA *‚may lead to a partial and limited analyses to inform decision making*', p211.
18	Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	The CEA was undertaken by the authors on behalf of the Merck KGaA, Darmstadt. One author has received research findings from Merck and participated in advisory boards for Merck and Pfizer.
19	Are ethical and distributional issues discussed appropriately?	No.

Table 3. Summary of quality assessment: Annemans and colleagues{Annemans, 2007 #22} using critical appraisal checklist from Evers and colleagues{Evers, 2005 #1681}

	Item	Yes / No
1	Is the study population clearly described?	Yes. Patients from the BOND study and patients receiving current care. Details on age, gender, body surface area and the number of previous chemotherapy regimes are reported.
2	Are competing alternatives clearly described?	Yes. Current care received by patients in three major oncology centres, with 80% of patients receiving chemotherapy third-line.
3	Is a well-defined research question posed in answerable form?	Yes. Comparison of the cost-effectiveness in Belgium of cetuximab+irinotecan with current care in EGFR expressing mCRC patients who have failed irinotecan-containing therapy.
4	Is the economic study design appropriate to the stated objective?	Yes. Retrospective CEA based on BOND and a matched population of patients, reporting cost per LYG.
5	Is the chosen time horizon appropriate to include relevant costs and consequences?	Unclear. Time horizon is not reported.
6	Is the actual perspective chosen appropriate?	Yes. From the perspective of the health care system in Belgium.
7	Are all important and relevant costs for each alternative identified?	Yes. Cetuximab and irinotecan acquisition costs and the cost of drugs for treating AEs. Additional costs included were for laboratory tests, imaging, consultations, hospitalisations and any subsequent chemotherapy.

8	Are all costs measured appropriately in physical units?	Yes. Costs are reported in Euros. Resource use data were derived directly from patient records.
9	Are costs valued appropriately?	Yes. Costs were derived from Belgian unit costs.
10	Are all important and relevant outcomes for each alternative identified?	Yes. LYG is the outcome used.
11	Are all outcomes measured appropriately?	Yes. Treatment benefit is defined by OS based on data from the BOND study.
12	Are outcomes valued appropriately?	Yes.
13	Is an incremental analysis of costs and outcomes of alternatives performed?	Yes, with two scenarios presented as base case analyses (6- and 12-week treatment continuation rule).
14	Are all future costs and outcomes discounted appropriately?	Unclear. Discounting is not reported.
15	Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	Yes. The impact of changing survival and cost data in the current care arm is described.
16	Do the conclusions follow from the data reported?	Yes. The conclusion states that cetuximab+irinotecan is rather is „rather cost-effective in Belgium' (p424) and this reflects the ICERs of €17,000 and €40,000 per LYG reported.
17	Does the study discuss the generalisability of the results to other settings and patient/ client groups?	To some extent. The authors state that current care in the major oncology centres may not reflect that in smaller centres.
18	Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	Unclear. There are no acknowledgements to a funding source. All authors are affiliated either with a university or hospital.
19	Are ethical and distributional issues discussed appropriately?	No.

Table 4. Summary of quality assessment: Wong and colleagues{Wong, 2009 #28} using critical appraisal checklist from Evers and colleagues{Evers, 2005 #1681}

	Item	Yes / No
1	Is the study population clearly described?	Yes. Hypothetical cohort of 1,000 patients with newly diagnosed mCRC. Patients supposedly received up to three lines of treatment before supportive care and death.
2	Are competing alternatives clearly described?	Yes. In total nine possible treatment strategies are modelled. Five of these involve cetuximab third-line.
3	Is a well-defined research question posed in answerable form?	Yes. To measure the cost implications of treatment with sequential regimens that include chemotherapy and/or monoclonal antibodies.
4	Is the economic study design appropriate to the stated objective?	Yes. Model-based CEA reported as cost per discounted LY.
5	Is the chosen time horizon appropriate to include relevant costs and consequences?	Unclear. Time horizon is not reported.
6	Is the actual perspective chosen appropriate?	Yes. Third party payer.
7	Are all important and relevant costs for each alternative identified?	No. Only costs related to drug acquisition and administration were modelled. Costs associated with supportive care medications, toxicity management, radiographic assessments or physician visits were not modelled.
8	Are all costs measured appropriately in physical units?	Yes. Drug costs measured in US$ based on average patient weight of 75kg and body surface area of 1.9m^2.
9	Are costs valued appropriately?	Yes. Drug costs are based on average sales price.
10	Are all important and relevant outcomes for each alternative identified?	Yes. Drug toxicity and discounted LY.
11	Are all outcomes measured appropriately?	Yes. Treatment benefit is defined by OS, and for cetuximab treatments it is based on data from Cunningham et al.
12	Are outcomes valued appropriately?	Yes.
13	Is an incremental analysis of costs and outcomes of alternatives performed?	Yes, and with a cost-effectiveness frontier presented.

14	Are all future costs and outcomes discounted appropriately?	Yes. Life expectancy and costs are discounted at 3% per year.
15	Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	Yes. One-way sensitivity analyses were performed for changes in toxicity, progression, drug costs, time on supportive care and cost of supportive care.
16	Do the conclusions follow from the data reported?	Yes. The authors report that the most effective regimens came at very high incremental costs, reflecting the large ICERs reported.
17	Does the study discuss the generalisability of the results to other settings and patient/ client groups?	To some extent. The authors comment that changes in drug costs in the future will impact on the cost-effectiveness of these drugs.
18	Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	Conflicts of interest are declared: One author has received funding from Bristol Myers Squibb, while the other three authors have acted as consultants and/or received honoraria from Amgen, Genentech, Pfizer, Sanofi-Aventis, Roche and/or Bristol Myers Squibb.
19	Are ethical and distributional issues discussed appropriately?	No.

Appendix 10: Cost-effectiveness: excluded studies

Papers excluded	Reason for exclusion
1. Amado (2008)	Not a cost effectiveness analysis
2. Arocho (2009)	Not in English
3. Blank (2010)	Abstract only (no additional information received)
4. Borovicka (2010)	Not a relevant population
5. Carlson (2010)	Abstract only (no additional information received)
6. Darba (2008)	Not a relevant intervention
7. Ducournau (2008)	Not a relevant intervention
8. Ducournau (2008)	Not a relevant intervention
9. Eggington (2009)	Not a relevant population
10. Ferro (2008)	Not a relevant population
11. Foley (2009)	Not a relevant population
12. Folprecht (2009)	Not a relevant population
13. Garrell (2008)	Not a relevant population
14. Garrison (2007)	Not a relevant population
15. Garrison (2007)	Not a relevant intervention
16. Graham (2008)	Abstract only (no additional information received)
17. Griebsch (2010)	Not a relevant population
18. Gyldmark (2009)	Not a relevant population
19. Holmberg (2009)	Not a relevant population
20. Jonker (2007)	Not a cost effectiveness analysis
21. Kim (2009)	Not a relevant intervention
22. Labianca (2007)	Unobtainable
23. Lamarque (2008)	Not a relevant population (non-UK)
24. Lewis (2008)	Not a relevant intervention
25. Odom (2008)	Not a cost-effectiveness analysis
26. Papagiannopoulou (2008)	Not a relevant population (non-UK)
27. Papagiannopoulou (2008)	Not a relevant population (non-UK)
28. Peeters (2006)	Not a cost-effectiveness analysis
29. Rubio (2005)	Not a relevant population (non-UK)
30. Ruhmann (2007)	Unobtainable

31. Salazar (2008)	Not a relevant intervention
32. Scheithauer (2007)	Not a relevant population
33. Shah (2009)	Unobtainable
34. Siena (2007)	Not a cost effectiveness analysis
35. Tebbutt (2010)	Not a relevant population
36. Thuss-Patience (2006)	Not in English
37. Tigue (2007)	Not a cost effectiveness analysis
38. Tilden (2005)	No additional information received
39. Tonon (2009)	Not in English
40. Torrecillas (2008)	Not a relevant population
41. Tran (2009)	Not a relevant population (non-UK)
42. Uyl-de Groot (2005)	Not a cost-effectiveness analysis
43. Villa (2010)	Not a relevant population
44. Wei (2010)	Abstract only (no additional information received)
45. Wils (2007)	Not a cost effectiveness analysis
46. Wong (2008)	Unobtainable
47. Yunger (2009)	Not a cost effectiveness analysis
48. Zafar (2009)	Not a cost effectiveness analysis
49. Zazaa (2009)	Not a relevant intervention

Appendix 11: Requests for clarification – Merck Serono

Page #	PenTAG's query	Merck Serono's response
Page 111	Please clarify the equation for dose intensity. We assume that dose intensity cetuximab = total cumulative dose over all patients actually received / total cumulative dose over all patients if all patients had received intended dosage.	The equation as stated in the submission (see page 111) excludes the first loading dose from the calculation (as all patients received this loading dose), hence the mention of „cumulative dose from ***1st infusion***' and „***second*** (weekly) cetuximab dosing date'.
Page 110	What is the source of the assumption of 100% dose intensity of panitumumab?	Dose intensity is a parameter that enables adjustment of the dose independently of the "standard" dose. Another place where the total dose can be adjusted is the maximum number of model cycles. This enables the user to adjust the model to make sure the mean dose in the base case represents the best reflection of the treatment. Additionally, there is no dose intensity reported in the Amado et al. publication, we therefore assume that all patients received their chemotherapy cycles.
Page 110	Please can Merck confirm that the dose intensity of irinotecan when used in combination with cetuximab is 90%.	The 90% dose intensity of cetuximab in combination with irinotecan has been measured from the BOND clinical trial.
Page 110	Are the dose intensities means or medians?	The mean dose intensities are used throughout the economic analyses.
General	What is the probability that a KRAS mutant patients is incorrectly tested as being KRAS wild-type using the standard KRAS test?	A review paper by van Krieken et al noted the following regarding KRAS mutations: The most frequent alterations in the KRAS oncogene are detected in codons 12 (approx 82% of all reported KRAS mutations) and 13 (approx 17%) in the KRAS oncogene. Mutations in other positions, such as codons 61 and 146, have also been reported. KRAS mutations in codons 12 and 13 appear to play a major role in

Page #	PenTAG's query	Merck Serono's response
		the progression of colorectal cancer. KRAS mutations are also associated with a lack of response to anti-EGFR therapies. As a company it is our aim to ensure that patients are treated appropriately with Erbitux and therefore should not be given Erbitux if they are unlikely to respond to the treatment. Therefore we recommend the use of central commercial laboratories as they have expertise with the testing method and also give advice regarding sampling. To this end we recommend KRAS testing in central laboratories for all patients and will pay for testing in these central laboratories when the cost of the test is not funded by other means. In the central laboratories KRAS testing is typically carried out using the TheraScreen PCR assay (CE marked for In Vitro Diagnostics) or a pyrosequencing technique. Both techniques assay for mutations in codons 12 and 13 as a minimum. Sample quality and assay sensitivity are key to minimising the risk of a KRAS mutant tumour sample being incorrectly tested as KRAS wild-type. We have information from the two major central testing laboratories regarding Sample quality and Assay sensitivity. **Sample quality** Sample quality is key to obtaining a good result. It is imperative that good quality sample with adequate tumour material is provided by histopathology. One of the most frequently used central KRAS testing laboratories, use the TheraScreen PCR assay which requires at least 20% tumour in the sample.

Page #	PenTAG's query	Merck Serono's response
		Another major central laboratory, follows European guidelines by enriching the sample to ensure a tumour burden of at least 70%. By this means, they should have sufficient tumour cell DNA to be detected against a background of normal (wild-type) DNA, irrespective of which of the current methods they use; PCR or pyrosequencing. If insufficient tumour sample is available for testing then the test result is reported as not available. The Erbitux Summary of Product Characteristics (SmPC) would then direct clinicians not to use Erbitux in this instance as the tumour has not been identified as KRAS wild-type. The SmPC states the following "Cetuximab should not be used in the treatment of colorectal cancer patients for whom KRAS tumour status is unknown." **Assay sensitivity** TheraScreen PCR will detect 1% mutant allele in a background of wild type in samples with 20% tumour. Using pyrosequencing the laboratories routinely report mutations in codons 12, 13 and 61. The probability of the assay misreading a base is highly unlikely for pyrosequencing. **Conclusion** The probability of reporting a mutant sample as wild type is slim but can be minimised by good assay sensitivity and good sample quality.
Page 98	Can Merck please confirm whether there was consideration of cross-over in the analysis of the CO17 or De	Merck Serono took a conservative approach in this regard and did

Page #	PenTAG's query	Merck Serono's response
onwards	Roock/BOND trial.	not adjust for potential crossover in the CO17 or BOND study.
Page 72	There is no report on how the OS HR from De Roock in Table 46 was obtained – please can Merck clarify how this estimated was calculated.	Data comparing Cetuximab+Irinotecan to Cetuximab in patients with wild type KRAS are available as Kaplan-Meier curves in the DeRook paper (Figure 2B and 2C). Values of the Kaplan-Meier product-limit estimator at different time points were read off the graphs for each treatment arm, and the number of patients at risk and the number of deaths during each time interval were calculated by using the formula defining the product-limit estimator backwards. The publication reported that only one patient was censored, in the Cetuximab+Irinotecan group, and that this happened at the end of the observation period. Therefore, the pattern of censoring was completely known and there was no need to rely on assumptions to perform the calculations. Once these data had been generated, the HR and its variance were calculated from the numbers of events observed and expected in each arm using the standard formulas shown below. $HR= (O_{bsc}-E_{bsc})/(O_c-E_c)$ $Var(ln(HR))=(1/E_{bsc}) – (1/E_c)$ where: ▪ O_{bsc} represents the number of events observed in the BSC group ▪ E_{bsc} represents the number of events expected in the BSC group

Page #	PenTAG's query	Merck Serono's response
		▪ O_c represents the number of events observed in the Cetuximab group ▪ E_c represents the number of events expected in the Cetuximab group These numbers were obtained with the 'sts test' command in Stata SE version 8.2.
Page 74	There is no report on how the PFS HR from De Roock in Table 47 was obtained – please can Merck clarify how this estimated was calculated.	The same principles are applied to determine the HR for PFS from the De Roock study (Table 47).
Page 73	Please could you clarify how the De Roock 2010 data were used to adjust the indirect comparison OS HR for CET + IRIN vs BSC.	De Roock et al were able to provide to Merck Serono a survival KM curves for KRAS wild-type patients (364 patients as reported in submission page 73) receiving cetuximab in combination with irinotecan. We then use that survival curve to parameterise the overall survival of cetuximab plus irinotecan and obtain the HR by comparison to the placebo survival of the initial De Roock study 2007. The detailed technique is incorporated in the modelling.
Page 110	Could Merck clarify whether the HUI estimates calculated for PF and PD from CO17 are for KRAS wild type participants only, or for all participants.	We confirm that the HUI estimates reported for PF and PD from the CO.17 study (Page 110) are from KRAS wild-type patients only.
Page 110	For the calculation of the utilities in Table 80, what was the maximum follow up time ? Are we correct to assume that HRQoL questionnaires were filled in by patients who had been in progressive disease for a longer time, on average, in the BSC group than patients in the panitumumab group? This is due to the fairly short data cut-off time, and the fact	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.

Page #	PenTAG's query	Merck Serono's response
	that patients in the BSC group progress faster than those in the panitumumab group.	
	What proportion of patients stopped taking cetuximab due to serious adverse events, and what was their average duration of treatment before stopping treatment?	In the CO17 study 11 patients discontinued cetuximab therapy among the 287 treated subjects, and only 3 patients amongst the 117 KRAS wild-type patients taking cetuximab stopped the therapy due to adverse events. We don't have the data of the average duration of treatment before stopping however we feel that it is unlikely that 3 patients would have a significant effect on the average duration of treatment for cetuximab. In addition, these 3 patients are already accounted for in the in the mean cohort dose per patient.
	The mean number of doses of panitumumab for wild-type patients is quoted as 10 in Amado et al. What was mean number of doses of cetuximab in the cetuximab vs. BSC RCT for wild-type patients, and what was the mean number of doses of cetuximab monotherapy and cetuximab + irinotecan combination therapy in the BOND RCT wild-type patients ? Can Merck also provide the corresponding standard deviations across all patients (alternatively, the standard errors of the mean)?	**Cetuximab monotherapy** The mean number of infusions for cetuximab plus BSC was not reported in the CO.17 either for the full population or for the KRAS wild-type patients. In the Jonker et al (2007) publication the median duration of cetuximab treatment was quoted as 8.1 weeks. As the Assessment Group correctly stated, the mean number of infusions for panitumumab in the KRAS wild type population was 10 (Amado et al, 2008). In addition the ITT population was 7. Given the lack of relevant data for the mean number of infusions for cetuximab monotherapy in the KRAS wild type an estimation was undertaken using the median number of weeks and the relative difference in the mean number of infusions of panitumumab monotherapy between the ITT and KRAS wild type populations as a proxy i.e. 8.1*10/7= 11.57.

Page #	PenTAG's query	Merck Serono's response
		This was described to some extent in table 59 on page 97 of the submission, and was thought to be an appropriate approach for cetuximab monotherapy. The model is constructed by setting a cap for the maximum number of infusions, which then calculates the average number of infusions. The maximum number of infusion is set to estimate a mean as close as possible to 11.57. **Cetuximab irinotecan** The BOND study compared cetuximab plus irinotecan versus 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 wild-type 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 latter figure highlights that 8.1 infusions discussed above may be a conservative estimate for those on monotherapy. The mean number of cetuximab and irinotecan combination therapy infusions within the model for the KRAS wild type population was not increased proportionately as per cetuximab monotherapy. The increasing side effects with combination therapy are likely to limit the treatment duration.
Page 74	Log rank HR from the CO17 study is reported for PFS (Table 47). What is the log rank HR for OS (Table 46)?	The reported HR for OS (Table 46) is also determined using a log rank test method to allow consistency in the statistics developed to determine the HR for PFS and OS and subsequently used in the indirect treatment comparisons. In the submission (page 74) we eluded that we are using a similar statistics (i.e. Log rank test) to

Page #	PenTAG's query	Merck Serono's response
		perform the indirect treatment comparisons.
Page 111	Please could Merck clarify the value taken from Remak and Brazil for the monthly cost of BSC	The study by Remak and Brazil was on end of life cost in women with metastatic breast cancer. This publication is often used as a source of data for monthly cost of BSC in mCRC (Tappenden et al). This value by nature is uncertain as BSC is difficult to quantify, and having average monthly cost of BSC is acceptable. In order to recognise the uncertain nature of such data a broad confidence interval is assumed. The sum of the supportive care phase cost as reported by the authors is £672.73, we then inflated this monthly cost to 2009/2010 value giving a £785.

Appendix 12: Estimation of difference in utility

Estimation of difference in utility for patients taking panitumumab vs BSC while in PFS

Here, we use the utilities measured in the RCT of panitumumab vs BSC, published by Odom et al (2011)(Odom, Barber et al. 2011), to estimate that the utility for people in PFS taking panitumumab is 0.12 higher than for people in PFS for on BSC.

Define $PFS_{pan}(t)$ and $PFS_{BSC}(t)$ as the PFS probabilities as a function of time t for panitumumab and BSC respectively. Also define $\Delta U_{pan}(t)$ and $\Delta U_{BSC}(t)$ as the changes in utility from baseline over time for panitumumab and BSC respectively, and U_B as the baseline utility. Then the total QALYs in PFS for panitumumab and BSC are:

$$U_B \int_0^\infty PFS_{pan}(t)dt + \int_0^\infty \Delta U_{pan}(t) PFS_{pan}(t)dt$$

$$U_B \int_0^\infty PFS_{BSC}(t)dt + \int_0^\infty \Delta U_{BSC}(t) PFS_{BSC}(t)dt$$

Expressed differently, suppose we assume a time independent utilities in PFS of U_{pan} and U_{BSC} for panitumumab and BSC, then the total QALYs for panitumumab and BSC are:

$$U_{pan} \int_0^\infty PFS_{pan}(t)dt$$

$$U_{BSC} \int_0^\infty PFS_{BSC}(t)dt$$

Solving these two pairs of equations gives;

$$U_{pan} = U_B + \frac{\int_0^\infty \Delta U_{pan}(t) PFS_{pan}(t)dt}{\int_0^\infty PFS_{pan}(t)dt}$$

$$U_{BSC} = U_B + \frac{\int_0^{\infty} \Delta U_{BSC}(t) PFS_{BSC}(t) dt}{\int_0^{\infty} PFS_{BSC}(t) dt}$$

and the quantity we require, the difference between the mean PFS utilities for panitumumab and BSC is:

$$U_{pan} - U_{BSC} = \frac{\int_0^{\infty} \Delta U_{pan}(t) PFS_{pan}(t) dt}{\int_0^{\infty} PFS_{pan}(t) dt} - \frac{\int_0^{\infty} \Delta U_{BSC}(t) PFS_{BSC}(t) dt}{\int_0^{\infty} PFS_{BSC}(t) dt}$$

We calculate this quantity in our model as 0.12, using discrete time intervals. By necessity, we have assumed that for time periods after 17 weeks, the same decrements in utility from baseline at time 17 weeks applies.

Appendix 13: Estimation of mean dosage of cetuximab, irinotecan and panitumumab

Estimation of mean dosage of cetuximab, irinotecan and panitumumab, including wastage, for patients of varying body surface areas and weights

To calculate the cost of cetuximab+irinotecan, we need to estimate people's body surface areas (BSAs). Sacco and colleagues (2010),{Sacco, 2010 #55} calculated the body surface areas of 3,613 patients receiving chemotherapy for various cancers in the UK in 2005. They calculated BSA from the height and weight, using the Dubois and Dubois method: BSA (m^2) = 0.007184 X weight (kg)$^{0.425}$ X height (cm)$^{0.725}$.

Appendix S3 of Sacco and colleagues (2010)(Sacco, Botten et al. 2010), freely available online, gives the BSAs of 291 males receiving palliative chemotherapy for colon cancer. We calculate the mean and standard deviation of these as 1.93 and 0.19. Similarly, we calculate the mean and standard deviation of the body surface areas of 151 females receiving palliative chemotherapy for colon cancer as 1.68 and 0.18. Next, we follow the methodology described in the example calculations in Appendix S1 for Sacco and colleagues (2010)(Sacco, Botten et al. 2010) to calculate the mean dosage of males and independently for females, allowing for wastage of drugs due to fixed vial sizes. The mean dose, over all patients, assuming 66% males and 34% females is calculated as the average of the male and females doses, weighted by the 66% and 34%.

Next, to calculate the cost of panitumumab, we need to estimate people's weights. Appendix S3 of Sacco and colleagues (2010)(Sacco, Botten et al. 2010), does not give the weights of people. Sacco provided us with the weights data which were used to calculate the BSA. We calculate the mean and standard deviation of the weights of the 291 males as 79.8 kg and 15.0kg respectively. Similarly, we calculate the mean and standard deviation of the weights of the 151 females receiving palliative chemotherapy for colon cancer as 65.3kg and 14.0kg. Next, we again follow the methodology described in the example calculations in Appendix S1 for Sacco and colleagues (2010)(Sacco, Botten et al. 2010) to calculate the mean dosage of males and independently for females, allowing for wastage of drugs due to fixed vial sizes. The mean dose, over all patients, assuming 66% males and 34% females is calculated as the average of the male and females doses, weighted by the 66% and 34%.

Pharmacy drug preparation costs

All drugs require preparation by a hospital pharmacist. Kate Copland, a hospital pharmacist from the Royal Devon & Exeter Hospital (Exeter, Devon), cited in personal communication the preparation times per infusion of bevacizumab, irinotecan and cetuximab as being equal (see Table 5).{Copland, 2011 #1667} We assume the same schedule applies to panitumumab.

Table 5. Hospital pharmacy preparation tasks per infusion of bevacizumab, irinotecan and cetuximab

	Task	Time	Staff grade	Average annual salary[a]
1	Clinical check of prescription	10 mins	Band 7	£36,000
2	Producing batch sheets and labels	5 mins	Band 4	£20,000
3	Assembly of ingredients	5 mins	Band 4	£20,000
4	Checking in of batch	5 mins	Band 4 to 8c	£38,071
5	Decontamination of ingredients	5 mins	Band 2 to 4	£17,333
6	Drug reconstitution and labelling of product	15 mins	Band 2 to 4	£17,333
7	Final check of batch	5 mins	Band 6 to 8c	£44,400
8	Documentation control	10 mins	Band 2 to 4	£17,333

[a]Taken from NHS terms and conditions of service handbook Annex C Table 13 *****ref*****

Using the information in Table 5, the length of the average working week (37.5) and number of days holiday per year (38 days)*****ref*****, we calculate the total cost of the preparation of one infusion as £15.

Appendix 14: Requests for clarification – Amgen

Page #	PenTAG's query	Amgen response
General	What was the dose intensity of panitumumab for wild-type patients in the main RCT of panitumumab vs. BSC? If not available for wild-type patients, then for wild-type and mutants combined.	The average weight-adjusted dose delivered in mg/kg is [mean (SD)]: [redacted]
General	What is the probability that a KRAS mutant patients is incorrectly tested as being KRAS wild-type using the standard KRAS test?	The probability that a KRAS mutant patient is incorrectly tested as being KRAS wild-type using the standard KRAS test assured by is negligible.

General	What proportion of patients stopped taking panitumumab due to serious adverse events, and what was their average duration of treatment before stopping treatment?	[redacted]
General	Amado says that the mean number of treatment cycles of panitumumab in the panitumumab vs. BSC RCT was 10 across all wild-type patients. Can Amgen provide the corresponding standard deviation	The mean and the corresponding standard deviation, mean (SD), for the mean number of treatment cycles (i.e. the mean number of • [redacted]

	across all patients (alternatively, the standard error of the mean)?	

Appendix 15: Calculating PFS for cetuximab+irinotecan

PFS for cetuximab+irinotecan: Stage (1)

We suggest four possible methods of estimating median PFS for patients with KRAS WT status on cetuximab+irinotecan in the BOND RCT. All methods split out the median PFS of 4.1 months for all people combined (KRAS WT and KRAS mutant status) on cetuximab+irinotecan in the BOND RCT to get the corresponding figure for patients with KRAS WTstatus only.

Method A: We first estimate the median PFS for patients with KRAS WT status on cetuximab+BSC in the BOND RCT as:

median PFS of 3.7 months for KRAS WT people taking cetuximab+BSC in the RCT of cetuximab+BSC vs BSC[2]

x median PFS of 1.5 months for all people (KRAS WT and KRAS mutant status) taking cetuximab+BSC in the BOND RCT[53]

/ median PFS of 1.9 months for all people (KRAS WT and KRAS mutant status) taking cetuximab+BSC in the RCT of cetuximab+BSC vs BSC[5]

= 2.9 months.

Next, we estimate the median PFS in the BOND RCT for patients with KRAS WT status taking cetuximab+irinotecan as:

median PFS of 4.1 months for all patients (KRAS WT and KRAS mutant status) taking cetuximab+irinotecan in the BOND RCT

x (estimated median PFS of 2.9 months for patients with KRAS WT status taking cetuximab+BSC in the BOND RCT

/ median PFS of 1.5 months for all patients (KRAS WT and KRAS mutant status) taking cetuximab+BSC in the BOND RCT)[53]

= 8.0 months.

Method B: Alternatively, we can estimate the median PFS in the BOND RCT for patients with KRAS WT people taking cetuximab+irinotecan, denoted by M, as follows. First, we note that the median PFS for patients with KRAS mutant status taking

cetuximab+irinotecan is approximately 12 weeks, and the median PFS for patients with KRAS WT status taking cetuximab+irinotecan is approximately 34 weeks from the study by De Roock and colleagues (2008).[12] Then, given that 59.3% of patients were KRAS WT status (the rest KRAS mutant status) in De Roock and colleagues (2008):

$59.3\%M + (100\% - 59.3\%)\frac{12}{34}M$ = median PFS of 4.1 months for all patients (KRAS WT and KRAS mutant status) taking cetuximab+irinotecan in the BOND RCT

Solving, we find M = 5.6 months.

This is considerably lower than the 8.0 months estimated by Method A.

Method C: This method is identical to Method B, except we use data from Lievre and colleagues (2008),[77] instead of De Roock and colleagues (2008). In Lievre and colleagues (2008) the median PFS for patients with KRAS mutant status taking cetuximab+irinotecan is approximately nine weeks, the median PFS for patients with KRAS WT status taking cetuximab+irinotecan is approximately 32 weeks, and 68% of patients with KRAS WT status. Solving again for M, the estimated median PFS in the BOND RCT for patients with KRAS WT status taking cetuximab+irinotecan is 5.3 months.

Method D: This method is identical to Methods B and C, except we use data from De Roock and colleagues (2010).[78] In this study, the median PFS for patients with KRAS mutant status taking cetuximab+irinotecan is approximately 12 weeks, the median PFS for patients with KRAS WT status is approximately 24 weeks; 58% of patients were KRAS WT status. Solving for M, the estimated median PFS in the BOND RCT for patients with KRAS WT status taking cetuximab+irinotecan is 5.2 months. One possible problem with the data from De Roock and colleagues (2010) is that patients were treated with cetuximab+chemotherapy, where „chemotherapy' is not specified. We require the chemotherapy to be irinotecan, but this is not clear. However, the data set has the advantage that it covers many patients.

It is very difficult to choose a preferred method for estimating the median PFS in the BOND RCT for patients with KRAS WT status taking cetuximab+irinotecan, since all methods rely on assumptions, and all have strengths and weaknesses. Method A assumes that the proportionate difference in PFS for patients on cetuximab+irinotecan between patients with KRAS mutant and KRAS WT status is similar to the proportionate difference in PFS for patients on cetuximab between patients with KRAS mutant and

KRAS WT status. However, it has the advantage that it relies solely on randomised data. Methods B to D assume similarity in the baseline characteristics of the people on cetuximab+irinotecan between patients with KRAS mutant and KRAS WT status, given that the De Roock and colleagues (2008), De Roock and colleagues (2010) and Lievre and colleagues (2008) studies were observational, not randomised. However, Methods B to D give very similar estimates of the median PFS (5.6, 5.3, 5.2 months), and these are different to the 8.0 months from Method A. Given the consistency in estimates of Methods B-C, we take the average of these values, and hence estimate the median PFS in the BOND RCT for patients with KRAS WT status taking cetuximab+irinotecan as 5.4 months.

PFS for cetuximab+irinotecan: (Stage 2)

Next, we adjust our estimate of the median PFS of 5.4 months in the BOND RCT for patients with KRAS WT status taking cetuximab+irinotecan for the purposes of the indirect comparison with other treatments, as follows:

Estimated modelled median PFS for patients with KRAS WT status taking cetuximab+irinotecan

= estimated median PFS of 5.4 months in the BOND RCT for patients with KRAS WT status taking cetuximab+irinotecan (calculated in Stage (1))

x modelled median PFS of 3.9 months for patients with KRAS WT status taking cetuximab+BSC (estimated from lambda and gamma of Weibull)

/ estimated median PFS of 2.9 months in the BOND RCT for patients with KRAS WT status taking cetuximab+BSC (estimated in Method A above)

= 7.1 months.

PFS for cetuximab+irinotecan: Stage (3)

Finally, given that we have specified the PFS median for cetuximab+irinotecan (7.1 months), and that we assume the same Weibull shape parameter γ for cetuximab+irinotecan as for cetuximab+BSC, this then specifies the scale parameter, λ, of the Weibull for cetuximab+irinotecan, given that the median t* of the Weibull is given by $0.5 = \exp\left(-\lambda t^{*\gamma}\right)$ This then gives the estimated mean PFS for cetuximab+irinotecan of 8.8 months. This is similar to Merck Serono's estimated mean of 7.8 months.

Appendix 16: Calculating OS for cetuximab+irinotecan

OS for cetuximab+irinotecan: Stage (1)

We have identified four methods to estimate OS for cetuximab+irinotecan: Methods A to D, each of which has strengths and weaknesses.

Method A This method is very similar to Method A in the estimation of PFS above. We first estimate the median OS for patients with KRAS WT status on cetuximab monotherapy in the BOND RCT as:

median OS of 9.5 months for patients with KRAS WT status taking cetuximab+BSC in the RCT of cetuximab+BSC vs BSC[2]

x median OS of 6.9 months for all people (KRAS WT and KRAS mutant status) taking cetuximab+BSC in the BOND RCT[53]

/ median OS of 6.1 months for all people (KRAS WT and KRAS mutant status) taking cetuximab+BSC in the RCT of cetuximab+BSC vs BSC [5]

= 10.7 months.

Next, we estimate the median OS in the BOND RCT for patients with KRAS WT status taking cetuximab+irinotecan as:

median OS of 8.6 months for all patients (KRAS WT and KRAS mutant status) taking cetuximab+irinotecan in the BOND RCT[53]

x (estimated median OS of 10.7 months for patients with KRAS WT status taking cetuximab+BSC in the BOND RCT

/ median OS of 6.9 months for all patients (KRAS WT and KRAS mutant status) taking cetuximab+BSC in the BOND RCT)[53]

= 13.4 months.

Next, we adjust this, our estimate of the median OS of 13.4 months in the BOND RCT for patients with KRAS WT status taking cetuximab+irinotecan for the purposes of the indirect comparison as follows;

Estimated modelled median OS for patients with KRAS WT status taking cetuximab+irinotecan

= estimated median OS of 13.4 months in the BOND RCT for patients with KRAS WT status taking cetuximab+irinotecan

x (modelled median OS of 9.0 months for KRAS WT people taking cetuximab+BSC

/ estimated median OS of10.7 months in the BOND RCT for patients with KRAS WT status taking cetuximab+BSC)

= 11.3 months.

However, the problem with this step in the calculation is that there was extensive cross over: approximately 50% of people randomised to cetuximab+BSC crossed over to cetuximab+irinotecan treatment on disease progression in the BOND RCT. This then unfairly dilutes the OS advantage of cetuximab+irinotecan relative to cetuximab+BSC. Therefore, 11.3 months is probably an underestimate of the median OS of patients with KRAS WT status on cetuximab+irinotecan.

Method B This is very similar to the method used by Merck Serono. Merck Serono estimated OS for patients with KRAS WT status for people on cetuximab+irinotecan by adjusting OS for patients with KRAS WT status on cetuximab+BSC (taken from the cetuximab+BSC vs BSC RCT) by the HR for OS for patients with KRAS WT status between people on cetuximab+irinotecan and cetuximab+BSC taken from other sources. Merck Serono quote the HR as [redacted] between cetuximab+irinotecan vs BSC for patients with KRAS WT status, which they say they obtained via personal communications from the authors of the De Roock (2010) paper,[78] which corresponds to a HR of [redacted] (where 1.82 is HR for cetuximab+BSC vs BSC) = [redacted] between cetuximab+irinotecan and cetuximab+BSC for patients with KRAS WT status. Alternatively, Merck Serono quote a HR of 0.53 for patients with KRAS WT status between cetuximab+irinotecan and cetuximab+BSC from De Roock and colleagues (2008) (page 72, Merck Serono's submission). The assumption in using HRs from De Roock and colleagues (2008) is that very few of the patients on cetuximab+BSC later received cetuximab+irinotecan on disease progression. Unfortunately, such information is not reported, but Merck Serono state that they estimated the HR by reading off survival data from the OS curves published in De Roock and colleagues (2008) (see @Appendix 11).

In Method A, we use a very similar method as Merck Serono to estimate OS for cetuximab+irinotecan for patients with KRAS WT status for the purposes of the indirect comparison. We estimate the median OS for patients with KRAS WT status for cetuximab+irinotecan as:

median OS for cetuximab+BSC from our model

x (median OS for patients with KRAS WT status on cetuximab+irinotecan from de Roock and colleagues (2008)[12]

/ median OS for patients with KRAS WT status for cetuximab+BSC from de Roock and colleagues (2008))

= 9.0 x (10.3 / 6.2) = 15.0 months

This method uses the median OS for patients with KRAS WT status for cetuximab+BSC from Roock and colleagues (2008), which is uncertain due to the very same sample size, 18 patients. Also, this method relies on similarity in baseline characteristics between treatments in Roock and colleagues (2008), given that that the data is retrospective, not randomised. The method also assumes little cross-over from cetuximab+BSC to cetuximab+irinotecan. The estimate of the median OS for KRAS WT people for cetuximab+irinotecan of 15.0 months is therefore very uncertain.

Method C Here, we estimate that the modelled median OS for patients with KRAS WT status taking cetuximab+irinotecan:

= estimated median OS of 13.4 months in the BOND RCT for patients with KRAS WT status taking cetuximab+irinotecan (see Method A)

x (modelled median PFS of 7.1 months for patients with KRAS WT status taking cetuximab+irinotecan (see Stage (2) calculations for PFS above)

/ estimated median PFS of 5.4 months in the BOND RCT for patients with KRAS WT status taking cetuximab+irinotecan) (see Stage (1) calculations for PFS above)

= 17.7 months.

This method has the advantage that it does not rely on the highly uncertain data from de Roock and colleagues (2008). However, the disadvantage is that all three quantities in

the calculation above are themselves estimates.

Method D Here, 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, which we estimate in Method A as 13.4 months. This has the advantage of simplicity, and the estimate is not affected by confounding due to cross-over. However, it has the disadvantage that randomisation is broken, and no adjustment is made for the indirect comparison with other treatments.

In summary the median OS for patients with KRAS WT status on cetuximab+irinotecan for our model is:

- greater than 11.3 months from Method A
- 15.0 months from Method B
- 17.7 months from Method C
- 13.4 months from Method D

Considering all methods we chose Method B because it is most consistent with the estimates from all methods, and because it gives a similar mean OS for patients with KRAS WT status on cetuximab+irinotecan (see Section 0, below) as estimated by Merck Serono, who used a slightly different method.

OS for cetuximab+irinotecan: Stage (2)

This stage is identical to Stage (3) in the estimation of PFS above (see @Appendix 15). Given that we have specified the median OS for cetuximab+irinotecan and we assume the same shape parameter γ for cetuximab+irinotecan as for cetuximab+BSC, this then specifies the scale parameter, λ, of the Weibull. This then gives the estimated mean OS for cetuximab+irinotecan of 16.6 months. This is very similar to Merck Serono's estimate of 16.3 months.