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

1 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)

2 Name of TAR team and project 'lead'

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3 Plain English Summary

This project will review and update the evidence presented to the National Institute of Health and Clinical Excellence 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.

4 Decision problem

4.1 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.

4.2 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.

4.3 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.

4.4 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.

4.5 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.

4.6 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.

5 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:

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

6 Methods for synthesising evidence of cost-effectiveness

6.1 Review question

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

6.2 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.

6.3 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.

6.4 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]

6.5 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.

6.6 Synthesis of extracted evidence

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

7 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.

8 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 underlined and highlighted in the assessment

9 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)
Anoop Sivasankaran	PenTAG, Peninsula Medical School, University of Exeter	Economic modelling
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

TAR Centre

About PenTAG:

The Peninsula Technology Assessment Group (PenTAG) is part of the Institute of Health Service Research (IHSR) at the Peninsula Medical School. PenTAG was

established in 2000 and carries out independent Health Technology Assessments HTAs) for the UK HTA Programme, systematic reviews and economic analyses for the NICE (Technology Appraisal and Centre for Public Health Excellence) and systematic reviews as part of the Cochrane Collaboration Heart Group, as well as for other local and national decision-makers. The group is multi-disciplinary and draws on individuals' backgrounds in public health, health services research, computing and decision analysis, systematic reviewing, statistics and health economics. The Peninsula Medical School is a school within the Universities of Plymouth and Exeter. The IHSR is made up of discrete but methodologically related research groups, among which HTA is a strong and recurring theme.

Recent projects include:

- Systematic review of the effectiveness and cost-effectiveness of weight management schemes for the under fives (2009).
- Barriers to and facilitators for the effectiveness of multiple risk factor programmes aimed at reducing cardiovascular disease within a given population: a systematic review of qualitative research (2009).
- Population and community programmes addressing multiple risk factors to prevent cardiovascular disease: a qualitative study into how and why some programmes are more successful than others (2009)
- Barriers to and facilitators of conveying information to prevent first occurrence of skin cancer: a systematic review of qualitative research (2009)
- The Effectiveness and Cost-Effectiveness of Cochlear Implants for Severe to Profound Deafness in Children and Adults: A Systematic Review and Economic Model (2008)
- The Effectiveness and Cost-Effectiveness of Methods of Storing Donated Kidneys from deceased donors: A Systematic Review and Economic Model (2009)
- Bevacizumab, sorafenib tosylate, sunitinib and temsirolimus for renal cell carcinoma: A systematic review and economic model (2008)
- The Effectiveness and Cost-Effectiveness of Cinacalcet for Secondary Hyperparathyroidism in end stage renal disease patients on dialysis. Systematic Review And Economic Evaluation (2007)

- The effectiveness and cost-effectiveness of Carmustine Implants and Temozolomide for the treatment of newly-diagnosed High Grade Glioma. Systematic Review And Economic Evaluation (2007)
- The Effectiveness and Cost-Effectiveness of Cardiac Resynchronisation Therapy for Heart Failure. Systematic Review and Economic Evaluation (2007)
- Inhaled Corticosteroids and Long-Acting Beta2-Agonists for The Treatment of Chronic Asthma in Adults and Children Aged 12 Years and Over: a Systematic Review and Economic Analysis (2007)
- Inhaled Corticosteroids and Long-Acting Beta2-Agonists for The Treatment of Chronic Asthma an Children Under the Age of 12 Years: a Systematic Review and Economic Analysis (2007)
- The Cost-Effectiveness of testing for hepatitis C (HCV) in former injecting drug users. Systematic Review And Economic Evaluation. (2006)

10 Competing interests of authors

None

11 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

12 Appendix A

As previously discussed 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 below).[7]

Search strategy for clinical effectiveness[7]

Database: Ovid MEDLINE 1966 to April Week 2 2005

1 (bevacizumab or avastin).af.

2 216974-75-3.rn.

3 Recombinant humanised monoclonal antibody

to VEGF.af.

4 (cetuximab or erbitux).af.

5 or/1-4

6 exp Colorectal Neoplasms/

7 NEOPLASMS/

8 CARCINOMA/

9 ADENOCARCINOMA/

10 or/7-9 (260268)

11 Colonic Diseases/

12 Rectal Diseases/

13 exp COLON/

14 exp RECTUM/

15 or/11-14

16 10 and 15

17 (carcinoma adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.

18 (neoplasia adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.

19 (neoplasm$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.

20 (adenocarcinoma adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.

21 (cancer$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.

22 (tumor$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.

23 (tumour$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.

24 (malignan$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.

25 or/17-24

26 6 or 16 or 25

27 randomized controlled trial.pt.

28 controlled clinical trial.pt.

29 Randomized Controlled Trials/

30 Random Allocation/

31 Double-Blind Method/

32 Single-Blind Method/

33 or/27-32

34 clinical trial.pt.

35 exp Clinical Trials/

36 (clin$ adj25 trial$).ti,ab.

37 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.

38 PLACEBOS/

39 placebos.ti,ab.

40 random.ti,ab.

41 Research Design/

42 or/34-41

43 33 or 42

44 5 and 26 and 43

45 from 44 keep 1-100

Search strategy for cost-effectiveness[7]

Database: Ovid MEDLINE 1966 to April Week 3 2005

1 (bevacizumab or avastin).af.

2 216974-75-3.rn.

3 Recombinant humanised monoclonal antibody

to VEGF.af.

4 (cetuximab or erbitux).af.

5 or/1-4

6 exp Colorectal Neoplasms/

7 NEOPLASMS/

8 CARCINOMA/

9 ADENOCARCINOMA/

10 or/7-9

11 Colonic Diseases/

12 Rectal Diseases/

13 exp COLON/

14 exp RECTUM/

15 or/11-14

16 10 and 15

17 (carcinoma adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.

18 (neoplasia adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.

19 (neoplasm$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.

20 (adenocarcinoma adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.

21 (cancer$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.

22 (tumor$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.

23 (tumour$ adj3 (colorectal or colon$ or rect$ or

intestin$ or bowel)).tw.

24 (malignan$ adj3 (colorectal or colon$ or rect$

or intestin$ or bowel)).tw.

25 or/17-24

26 6 or 16 or 25

27 ECONOMICS/

28 exp "Costs and Cost Analysis"/

29 "Value of Life"/

30 exp Economics, Hospital/

31 exp Economics, Medical/

32 Economics, Nursing/

33 Economics, Pharmaceutical/

34 exp Models, Economic/

35 exp "Fees and Charges"/

36 exp BUDGETS/

37 ec.fs.

38 (Costs or cost or costed or costly or costing$).tw.

39 (economic$ or pharmacoeconomic$ or price$ or pricing).tw.

40 Quality-Adjusted Life Years/

41 economic burden.tw.

42 "Cost of Illness"/

43 exp quality of life/

44 Quality of Life.tw.

45 life quality.tw.

46 hql.tw.

47 (Sf36 or sf36 or sf thirtysix or sf thirty six or short form 36 or short term thirty six or short form thirtysix or shortform 36).tw.

48 Qol.tw.

49 (Euroqol or eq5d or eq 5d).tw.

50 Qaly$.tw.

51 Quality adjusted life year$.tw.

52 Hye$.tw.

53 Health$ year$ equivalent$.tw.

54 Health utilit$.tw.

55 HUI.tw.

56 Quality of wellbeing$.tw.

57 Qwb.tw.

58 Quality of well being.tw.

59 (Qald$ or qale$ or qtime$).tw.

60 or/27-59

61 5 and 26 and 60

62 from 61 keep 1-10

Search strategy for literature on

quality of life in patients with

colorectal cancer

Search strategy for literature in quality of life on patients with colorectal cancer[7]

Database: Ovid MEDLINE 1966 to April Week 3 2005

1 exp Colorectal Neoplasms/

2 Neoplasms/

3 Carcinoma/

4 Adenocarcinoma/

5 or/2-4

6 Colonic Diseases/

7 Rectal Diseases/

8 exp Colon/

9 exp Rectum/

10 or/6-9

11 5 and 10

12 (carcinoma adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.

13 (neoplasia adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.

14 (neoplasm$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.

15 (adenocarcinoma adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.

16 (cancer$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.

17 (tumor$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.

18 (tumour$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.

19 (malignan$ adj3 (colorectal or colon$ or rect$ or intestin$ or bowel)).tw.

20 or/12-19

21 1 or 11 or 20

22 health related quality of life.tw.

23 hrql.tw.

24 hrqol.tw.

25 hql.tw.

26 sf 36.tw.

27 sf thirtysix.tw.

28 sf thirty six.tw.

29 short form 36.tw.

30 short form thirty six.tw.

31 short form thirtysix.tw.

32 shortform 36.tw.

33 shortform thirty six.tw.

34 shortform thirty six.tw.

35 sf36.tw.

36 medical outcomes survey.tw.

37 mos.tw.

38 euroqol.tw.

39 eq 5d.tw.

40 eq5d.tw.

41 qaly$.tw.

42 quality adjusted life years/

43 quality adjusted life year$.tw.

44 hye$.tw.

45 health$ year$ equivalent$.tw.

46 psychological general well being index.tw.

47 psychological general wellbeing index.tw.

48 pgwb$.tw.

49 health utilit$.tw.

50 hui.tw.

51 quality of wellbeing$.tw.

52 quality of well being.tw.

53 qwb$.tw.

54 rosser.tw.

55 trade off$.tw.

56 standard gamble.tw.

57 tto.tw.

58 "Quality of Life"/

59 "Outcome Assessment (Health Care)"/

60 (preference$ or utilit$).tw. and (58 or 59)

61 ((preference$ or utilit$) and quality of life).tw.

62 (preference$ adj2 (elicit$ or patient$ or population$ or measure$ or based or cost$)).tw.

63 (utilit$ adj2 (elicit$ or patient$ or population$ or measure$ or based or cost$)).tw.

64 or/22-57,60-63

65 21 and 64

Search strategy to identify studies which included patients with metastatic CRC receiving active/best supportive care following one or more lines of active chemotherapy[7]

Database: MEDLINE

Date undertaken: 19 October and 7 November 2005

Scope of search: survival following second-, third or fourth-line treatment for colorectal cancer. Search technique: browsing or ‘berrypicking’.

1 (3rd line or third line or 4th line or fourth line).tw.

2 Colorectal Neoplasms/

3 1 and 2

4 supportive care.ti.

5 survival.tw.

6 2 and 4 and 5

7 Drug Resistance, Neoplasm/

8 2 and 5 and 7

9 from 3 keep 2,4-7,10-12,23,25

10 salvage.tw.

11 2 and 10

12 from 11 keep 4,6-7,19,22,45

13 from 8 keep 1-2,8

14 compassionate.tw.

15 2 and 14

16 from 15 keep 1

17 survival.ti.

18 refractory.tw.

19 2 and 5 and 18

20 from 19 keep 4,6,8,14,21,54

21 or/9,12-13,16,20

22 from 21 keep 1

23 (2nd line or second line).ti.

24 2 and 23

25 limit 24 to clinical trial

26 (2nd line or second line).tw.

27 2 and 26

28 limit 27 to clinical trial

29 28 not 25

30 22 or 28

13 References

1. NICE. Irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer: Technology Appraisal 93 (review of Technology Appraisal 33). London: National Institute of Health and Clinical Excellence, 2005.

2. NICE. Guidance on the use of capecitabine and tegafur with uracil for metastatic colorectal cancer: Technology Appraisal 61. London: National Institute of Health and Clinical Excellence, 2003.
3. NICE. Cetuximab for the first-line treatment of metastatic colorectal cancer: Technology Appraisal 176. London: National Institute for Health and Clinical Excellence, 2009.
4. NICE. Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer: Technology Appraisal 118. London: National Institute for Health and Clinical Excellence, 2007.
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