

The clinical effectiveness and cost-effectiveness of cetuximab (review of technology appraisal no. 176) and panitumumab (partial review of technology appraisal no. 240) for previously untreated metastatic colorectal cancer: a systematic review and economic evaluation

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Scientific summary

Effectiveness of cetuximab and panitumumab for previously untreated mCRC

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Scientific summary

Background

Colorectal cancer (CRC) is the fourth most common cancer in the UK. In 2011, 34,000 people were diagnosed with CRC in England. Approximately 25% of people with CRC have metastatic disease (mCRC).

Cetuximab (Erbix[®], Merck Serono UK Ltd, Feltham, UK) and panitumumab (Vectibix[®], Amgen UK Ltd, Cambridge, UK) are inhibitors of epidermal growth factor receptor (EGFR) that can be used in combination with chemotherapy regimens for the treatment of CRC. The European Medicines Agency marketing authorisations for cetuximab and panitumumab are licensed for a targeted population based on *RAS* wild-type (WT) status.

Objective

The key objectives of this report were to estimate the clinical effectiveness and cost-effectiveness of cetuximab and panitumumab for the first-line treatment of *RAS* WT mCRC.

Methods

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

Clinical effectiveness systematic review

A systematic review of published research evidence was undertaken following principles published by the Centre for Reviews and Dissemination (CRD).

The population of interest was defined as adults with *RAS* WT mCRC. The interventions of interest were cetuximab in combination with FOLFOX (folinic acid + 5-fluorouracil + oxaliplatin or irinotecan-based chemotherapy) and panitumumab in combination with 5-fluorouracil-containing regimens. Comparators identified in the scope were FOLFOX, XELOX (capecitabine + oxaliplatin), FOLFIRI (folinic acid + 5-fluorouracil + irinotecan), capecitabine, tegafur (UFToral[®], Merck Serono, Feltham, UK; no longer produced in the UK), folinic acid and 5-fluorouracil, and bevacizumab (Avastin[®], Roche Products Ltd), in combination with oxaliplatin- or irinotecan-based chemotherapy. Evidence on the following outcome measures was considered: overall survival (OS), progression-free survival (PFS), response rate, adverse events (AEs) related to treatment and health-related quality of life (HRQoL).

Searches were conducted in January 2015 and updated on 27 April 2015. After the reviewers had identified studies for inclusion, the quality of the clinical effectiveness data was assessed according to recommendations provided by the CRD. The bibliographies of included papers were scrutinised for further potentially relevant studies. Manufacturers' submissions were assessed for unpublished data.

The extracted data and quality assessment for each study were presented in structured tables and as a narrative summary. Network meta-analyses (NMAs) were undertaken within a Bayesian framework in WinBUGS version 1.4.3 (MRC Biostatistics Unit, Cambridge, UK).

Cost-effectiveness systematic review

The inclusion criteria for the cost-effectiveness systematic review were the same as for the clinical effectiveness systematic review, except that the relevant study design was full cost-effectiveness studies. Cost studies were considered only if they were UK based.

Studies were critiqued using summary tables and narrative synthesis, and full papers were quality appraised using published guidelines.

Peninsula Technology Assessment Group de novo cost-utility model

Two treatment networks were considered, based on the results of the clinical effectiveness review and the treatments that were considered to be widely used in the NHS:

1. FOLFOX network –

- cetuximab plus FOLFOX
- panitumumab plus FOLFOX
- FOLFOX

2. FOLFIRI network –

- cetuximab plus FOLFIRI
- FOLFIRI.

Scenario analyses considered bevacizumab and XELOX as comparators.

Other comparators were not considered as patients eligible for combination chemotherapies were unlikely to receive these treatments.

The patient population considered was first-line patients with *RAS* WT mCRC. A subgroup analysis was also presented for patients with metastases confined to the liver.

The Peninsula Technology Assessment Group (PenTAG) cost-effectiveness model, implemented in Microsoft Excel® (2010; Microsoft Corporation, Redmond, WA, USA), simulated a cohort of people with *RAS* WT mCRC starting on first-line treatment. Health states for unresected patients included first-line PFS, second-line treatment with FOLFOX or FOLFIRI and third-line best supportive care. A post-resection state was modelled for the proportion of patients who become suitable for resection of liver metastases.

Survival after first-line progression was assumed to be independent of first-line treatment. A scenario analysis explored OS as a product of the responses to both first-line treatment and subsequent lines of treatment, as experienced in the randomised controlled trials (RCTs).

Clinical effectiveness data for first-line treatment was taken from the relevant trials. OS and post-resection PFS were taken from published literature.

The PRIME (Panitumumab Randomized trial In combination with chemotherapy for Metastatic colorectal cancer to determine Efficacy) and CRYSTAL (Cetuximab Combined with Irinotecan in First-Line Therapy for Metastatic Colorectal Cancer) trials were chosen as the baseline RCTs for the two model networks. Treatment duration was estimated through direct and indirect comparisons and capped to mean PFS.

Difference in test accuracy of *RAS* mutation testing between trials and clinical practice was not incorporated into the model because of a lack of evidence.

In the absence of *RAS* WT data, EuroQol 5-Dimensions data from two trials with Kirsten rat sarcoma (*KRAS*) WT populations was used to inform first- and second-line utility values (0.767 and 0.762, respectively). Third-line utility (0.641) was taken from published literature.

Utilities post resection were calculated as an age-related population utility in PFS (0.831) and a disutility based on a weighted average of second- and third-line utilities (0.142).

In the base case, the monthly costs of drug acquisition were calculated using list prices for cetuximab (£3859) and panitumumab (£4109).

The monthly costs of drug acquisition for FOLFOX (£86) and FOLFIRI (£128) were estimated using the Commercial Medicines Unit Electronic Market Information Tool (CMU eMit).

In line with common clinical practice in the NHS, cetuximab was assumed to be administered fortnightly. Panitumumab was modelled on a fortnightly basis, in line with its marketing authorisation.

Administration costs included the costs of chemotherapy delivery, pharmacy costs and the costs of infusion pumps and line maintenance. The total monthly drug administration costs were:

- cetuximab/panitumumab plus FOLFOX – £1563
- FOLFOX – £1544
- cetuximab plus FOLFIRI – £849
- FOLFIRI – £830.

Other costs, including the costs of resection surgery, medical management and AE treatment, were based on NHS reference costs, published literature and previous economic assessments.

Results

Clinical effectiveness systematic review

Five *RAS* WT subgroup analyses from RCTs met the inclusion criteria for the clinical effectiveness systematic review.

The risk of bias in the studies was high but was generally similar between studies. Because the analyses were of subgroup data, all comparisons were made without protection by stratification/randomisation, but no major differences in baseline characteristics were observed, minimising the potential for selection bias. Because of the retrospective nature of the *RAS* analysis, the low number of samples reduced the power of the studies to show statistically significant differences between the treatments.

All subgroup analyses contributed to NMAs. No studies were identified comparing FOLFOX with FOLFIRI in the *RAS* WT population and so two discrete networks were generated, one evaluating FOLFOX-containing chemotherapy regimens and one evaluating FOLFIRI-containing chemotherapy regimens.

Cetuximab

Two trials [OPUS (Oxaliplatin and Cetuximab in First-line Treatment of Metastatic Colorectal Cancer) and CRYSTAL] provided evidence for the effectiveness of cetuximab plus chemotherapy compared with chemotherapy alone. The evidence consistently suggested a treatment effect in favour of cetuximab plus chemotherapy compared with chemotherapy alone, including a reduction in the risk of progression [cetuximab + FOLFOX vs. FOLFOX: hazard ratio (HR) 0.53, 95% confidence interval (CI) 0.27 to 1.04; cetuximab + FOLFIRI vs. FOLFIRI: HR 0.56, 95% CI 0.41 to 0.76] and an improvement in OS (cetuximab + FOLFIRI vs. FOLFIRI: HR 0.69, 95% CI 0.54 to 0.88). Tumour response rates in the experimental arm ranged from 58% to 66% across studies, and in the control arm ranged from 29% to 60% across studies. In people with liver

metastases at baseline, improvement in OS and PFS was consistent with the results for the whole *RAS* WT population. Overall, in all of the trials the clinical safety results were consistent with the results for the *KRAS* WT population.

One trial [FIRE-3; 5-FU, Folinic Acid and Irinotecan (FOLFIRI) Plus Cetuximab versus FOLFIRI Plus Bevacizumab in First Line Treatment of Colorectal Cancer] provided evidence for the effectiveness of cetuximab plus FOLFIRI compared with bevacizumab plus FOLFIRI. Cetuximab plus FOLFIRI showed an improvement in OS compared with bevacizumab plus FOLFIRI (HR 0.70, 95% CI 0.53 to 0.92), but other results were similar across the arms.

Panitumumab

One trial (PRIME) provided evidence for the effectiveness of panitumumab plus FOLFOX compared with FOLFOX. No studies were identified that compared panitumumab plus FOLFIRI with FOLFIRI. The evidence suggested a treatment effect in favour of panitumumab plus FOLFOX compared with FOLFOX. For PFS the HR was 0.72 (95% CI 0.58 to 0.9) and for OS the HR was 0.77 (95% CI 0.64 to 0.94), favouring panitumumab + FOLFOX. The clinical safety results were consistent with the results for the *KRAS* WT population. The liver metastases subgroup results for OS and PFS were consistent with the results for the total *RAS* WT population.

One trial [PEAK; Panitumumab Plus mFOLFOX6 vs. Bevacizumab Plus mFOLFOX6 for First Line Treatment of Metastatic Colorectal Cancer (mCRC) Patients With Wild-Type Kirsten Rat Sarcoma-2 Virus (*KRAS*) Tumors] provided evidence for the effectiveness of panitumumab plus FOLFOX compared with bevacizumab plus FOLFOX. For PFS, panitumumab plus FOLFOX was associated with a 35% reduction in the risk of progression compared with bevacizumab plus FOLFOX. Little OS benefit with panitumumab plus FOLFOX was observed (HR 0.63, 95% CI 0.39 to 1.02). Overall response rates were similar in both arms.

Network meta-analysis: FOLFOX network

The NMA provided no statistically significant evidence to suggest that cetuximab plus FOLFOX was any more effective than FOLFOX, bevacizumab plus FOLFOX or panitumumab plus FOLFOX at increasing PFS or OS.

Direct evidence suggested that panitumumab plus FOLFOX was more effective at increasing PFS than FOLFOX and bevacizumab plus FOLFOX. Panitumumab plus FOLFOX was also estimated to be more effective at increasing survival than FOLFOX.

There was little evidence to suggest that cetuximab plus FOLFOX was more effective at improving the objective response rate (ORR) or reducing the incidence of AEs than panitumumab plus FOLFOX.

Network meta-analysis: FOLFIRI network

Evidence from the NMA suggested that cetuximab plus FOLFIRI and bevacizumab plus FOLFIRI were more effective than FOLFIRI at increasing time to progression or death and improving the ORR.

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

Cost-effectiveness

Published economic evaluations

Four studies were identified in the cost-effectiveness systematic review, only one of which was a full paper. No study completely answered the decision problem in this health technology assessment.

Appraisal of Merck Serono's economic analysis

Merck Serono's cost-effectiveness review was generally appropriate but was restricted to cetuximab studies and not *RAS* WT populations. This accounted for all of the differences between the PenTAG review and Merck Serono's review.

The Merck Serono model was generally poorly reported. The general structure of the model was similar to that of the PenTAG model.

In the base case, Merck Serono assumed fortnightly administration of cetuximab. The estimated incremental cost-effectiveness ratios (ICERs) for the two key comparisons were as follows:

1. cetuximab plus FOLFOX compared with FOLFOX – £47,000 per quality-adjusted life-year (QALY)
2. cetuximab plus FOLFIRI compared with FOLFIRI – £56,000 per QALY.

The most important difference between the models was that the Merck Serono model used lower mean treatment durations. This had the effect that the Merck Serono model estimated far lower ICERs than the PenTAG model.

Peninsula Technology Assessment Group model

Our base-case results were as follows:

- FOLFOX network:
 - discounted QALYs – FOLFOX 1.26, panitumumab plus FOLFOX 1.41, cetuximab plus FOLFOX 1.61
 - discounted total costs – FOLFOX £30,585, panitumumab plus FOLFOX £61,225, cetuximab plus FOLFOX £67,057
 - ICERs per QALY gained compared with FOLFOX – cetuximab plus FOLFOX £104,205, panitumumab plus FOLFOX £204,103.
- FOLFIRI network:
 - discounted QALYs – FOLFIRI 1.23, cetuximab plus FOLFIRI 1.53
 - discounted total costs – FOLFIRI £28,250, cetuximab plus FOLFIRI £65,380
 - ICER per QALY gained compared with FOLFIRI – cetuximab plus FOLFIRI £122,554.

For cetuximab plus FOLFOX compared with FOLFOX, most incremental QALYs came from PFS post resection. This is largely because of the high expected resection rate for cetuximab plus FOLFOX compared with FOLFOX. Total incremental QALYs for panitumumab plus FOLFOX compared with FOLFOX were lower than for cetuximab plus FOLFOX compared with FOLFOX because a lower resection rate was predicted.

For cetuximab plus FOLFIRI compared with FOLFIRI, post-resection QALYs were less important than for cetuximab plus FOLFOX compared with FOLFOX because of low rates of resection estimated for cetuximab plus FOLFIRI and FOLFIRI.

First-line drug acquisition costs were the largest cost items.

Probabilistic sensitivity analyses predicted that, at a willingness-to-pay threshold of £30,000 per QALY, the probability that FOLFOX was most cost-effective was 80% (cetuximab plus FOLFOX 20%, panitumumab plus FOLFOX 0%) and the probability that FOLFIRI was most cost-effective was 100% (cetuximab plus FOLFIRI 0%) in the two networks.

For the liver metastases subgroup, the ICERs compared with FOLFOX were £95,514 per QALY gained for cetuximab plus FOLFOX and £86,875 per QALY gained for panitumumab plus FOLFOX. The ICER for

cetuximab plus FOLFIRI was £76,298 per QALY gained compared with FOLFIRI. There was greater uncertainty in the results for this subgroup as estimates for PFS for unresected patients required additional assumptions.

When OS was modelled directly from the RCTs, with treatment duration uncapped and second-line drug costs altered to match those in the RCTs, the ICER for cetuximab plus FOLFOX compared with FOLFOX increased to £219,952 per QALY, the ICER for panitumumab plus FOLFOX compared with FOLFOX reduced to £92,585 per QALY and the ICER for cetuximab plus FOLFIRI compared with FOLFIRI reduced to £84,523 per QALY.

Deterministic sensitivity analyses showed that the cost-effectiveness results were very sensitive to resection rates, PFS and OS post resection, PFS for unresected patients and treatment duration.

Comparison between the Peninsula Technology Assessment Group cost-effectiveness results and the Merck Serono cost-effectiveness results

Items that differed between the PenTAG and Merck Serono models and had an important impact on cost-effectiveness included treatment duration, rates of resection, PFS and progressive disease, and costs of treatment.

Comparison between the current multiple technology appraisal and previous single technology appraisals (TA176 and TA240)

The current scope specified people with *RAS* WT mCRC, whereas previous single technology appraisals specified EGFR-expressing mCRC [technology appraisal (TA) no. 176] and *KRAS* WT mCRC (TA240).

No comparison can be made between TA240 and the current assessment as TA240 was terminated. TA176 assessed the clinical effectiveness and cost-effectiveness of first-line cetuximab in combination with chemotherapy for mCRC patients. When comparisons could be made, effect estimates for cetuximab were generally similar between the two reviews.

Both TA176 and the current assessment include a de novo economic analysis provided by Merck Serono. As we do not have the original model for TA176, it is not possible to confirm which parameters differed, but the main differences appeared to be around first-line treatment costs.

Discussion

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

Strengths and limitations of the systematic review of effectiveness studies

A strength of this report is the use of a systematic review and a NMA to evaluate the relative efficacy of cetuximab and panitumumab in people with mCRC with *RAS* WT tumours.

There are some important sources of uncertainty that may impact on the conclusions, including the use of subgroup analyses of intention-to-treat trial populations; the lack of evidence to estimate the effectiveness of panitumumab plus FOLFIRI; the lack of direct evidence to compare cetuximab + FOLFOX with panitumumab plus FOLFOX or FOLFOX-containing regimens with FOLFIRI-containing regimens; unclear time points at which ORR was measured in the trials; and the lack of reported HRQoL estimates for the *RAS* WT population.

The study arm populations were younger and fitter than the UK population of people with mCRC and the extent to which the results can be generalised to the UK NHS mCRC population is unclear.

Strengths and limitations of the de novo economic analysis

A strength of the PenTAG model is that it was independently produced. It uses up-to-date clinical effectiveness data, acquired through the systematic review. Drug acquisition costs were obtained, when possible, from the CMU eMit database, reflecting the true cost to the NHS.

Areas of uncertainty were explored through scenario analyses and sensitivity analyses.

The model is subject to the same limitations as the clinical effectiveness review as data from the clinical effectiveness review were carried through into the modelling. Additional assumptions were also made in the model when evidence was not available.

Conclusions

Clinical effectiveness evidence in this review suggests that there is some clinical benefit from anti-EGFR therapies in comparison with standard chemotherapy treatments. Estimates of cost-effectiveness currently suggest that these therapies are likely to represent poor value for money at willingness-to-pay thresholds of £20,000 per QALY.

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

Study registration

This study is registered as PROSPERO CRD42015016111.

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