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Cetuximab for the first-line treatment of metastatic colorectal cancer

**This guidance was developed using the
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NICE technology appraisal guidance 176 Cetuximab for the first-line treatment of metastatic colorectal cancer

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1 Guidance

- 1.1 Cetuximab in combination with 5-fluorouracil (5-FU), folinic acid and oxaliplatin (FOLFOX), within its licensed indication, is recommended for the first-line treatment of metastatic colorectal cancer only when all of the following criteria are met:
- The primary colorectal tumour has been resected or is potentially operable.
 - The metastatic disease is confined to the liver and is unresectable.
 - The patient is fit enough to undergo surgery to resect the primary colorectal tumour and to undergo liver surgery if the metastases become resectable after treatment with cetuximab.
 - The manufacturer rebates 16% of the amount of cetuximab used on a per patient basis.
- 1.2 Cetuximab in combination with 5-FU, folinic acid and irinotecan (FOLFIRI), within its licensed indication, is recommended for the first-line treatment of metastatic colorectal cancer only when all of the following criteria are met:
- The primary colorectal tumour has been resected or is potentially operable.
 - The metastatic disease is confined to the liver and is unresectable.
 - The patient is fit enough to undergo surgery to resect the primary colorectal tumour and to undergo liver surgery if the metastases become resectable after treatment with cetuximab.
 - The patient is unable to tolerate or has contraindications to oxaliplatin.
- 1.3 Patients who meet the criteria in 1.1 and 1.2 should receive treatment with cetuximab for no more than 16 weeks. At 16 weeks,

treatment with cetuximab should stop and the patient should be assessed for resection of liver metastases.

- 1.4 People with metastatic colorectal cancer with metastatic disease confined to the liver who receive cetuximab should have their treatment managed only by multidisciplinary teams that involve highly specialised liver surgical services.

2 The technology

- 2.1 Cetuximab (Erbix, Merck Serono) is a recombinant monoclonal antibody that blocks the human epidermal growth factor receptor (EGFR) and therefore inhibits the proliferation of cells that depend on EGFR activation for growth. Cetuximab is indicated for the treatment of patients with EGFR-expressing, Kirsten rat sarcoma (KRAS) wild-type metastatic colorectal cancer:

- in combination with chemotherapy
- as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan.

- 2.2 One common adverse effect of cetuximab treatment is the development of skin reactions, which occur in more than 80% of patients and mainly present as an acne-like rash or, less frequently, as pruritus, dry skin, desquamation, hypertrichosis or nail disorders (for example, paronychia). The majority of skin reactions develop within the first 3 weeks of treatment. The summary of product characteristics (SPC) notes that if a patient experiences a grade 3 or 4 skin reaction, cetuximab treatment must be stopped, with treatment being resumed only if the reaction resolves to grade 2. Other common adverse effects of cetuximab include mild or moderate infusion-related reactions such as fever, chills, nausea, vomiting, headache, dizziness or dyspnoea that occur soon after the first cetuximab infusion. For full details of adverse effects and contraindications, see the SPC.

- 2.3 The acquisition cost of cetuximab is £159.02 for a 5-mg/ml, 20-ml vial (excluding VAT; 'British national formulary' [BNF] edition 57). The manufacturer has agreed with the Department of Health that the NHS price will be £136.50 for a 20-ml vial (the previous list price) until NICE next reviews the guidance on cetuximab for this indication. All calculations are based on this price. The initial dose is 400 mg/m² body surface area. Subsequent weekly doses are 250 mg/m² each. The SPC states that cetuximab treatment is recommended until there is progression of the underlying disease. A person with a body surface area of 1.75 m² would receive seven vials per loading dose and five vials per maintenance dose, equating to a cost of £955.50 for the loading dose and £682.50 for each maintenance dose. Patients in the key clinical trials received cetuximab for approximately 8 months, equating to an average total cost of £22,796 per patient. Costs may vary in different settings because of negotiated procurement discounts.

3 The manufacturer's submission

The Appraisal Committee (appendix A) considered evidence submitted by the manufacturer of cetuximab and a review of this submission by the Evidence Review Group and the Decision Support Unit (ERG and DSU; appendix B).

Clinical effectiveness

- 3.1 In the submission, the manufacturer compared a regimen of cetuximab in combination with FOLFIRI with the FOLFIRI chemotherapy regimen alone, and a regimen of cetuximab in combination with FOLFOX with the FOLFOX chemotherapy regimen alone.
- 3.2 The main evidence on the efficacy of cetuximab in the manufacturer's submission was derived from two randomised controlled trials:

- CRYSTAL (n = 1198), a phase III, multicentre, open-label randomised controlled trial, which compared cetuximab in combination with FOLFIRI with FOLFIRI alone, and examined progression-free survival as the primary outcome.
- OPUS (n = 336), a phase II, multicentre, open-label randomised controlled trial, which compared cetuximab in combination with FOLFOX with FOLFOX alone, and examined response rate as the primary outcome.

The participants in both trials were patients with previously untreated metastatic colorectal cancer with non-resectable metastases and an Eastern Cooperative Oncology Group (ECOG) performance status of less than or equal to 2 at study entry. The planned treatment duration in both trials was until demonstration of progressive disease by computed tomography (CT) or magnetic resonance imaging (MRI), withdrawal of consent, or occurrence of unacceptable adverse events (CRYSTAL only) or toxicity (OPUS only).

- 3.3 In the submission, the manufacturer presented data for the full analysis set (people with KRAS wild-type metastatic colorectal cancer and KRAS mutations) for both trials. However, the main data in the submission focused on the post hoc analysis of the KRAS wild-type subgroup (n = 348 for the CRYSTAL trial; n = 134 for the OPUS trial), which was requested by the regulatory agencies and reflects the licensed indication.
- 3.4 In response to ACD consultation, the manufacturer submitted updated overall survival data from the CRYSTAL trial (described in sections 3.5 and 3.7) and additional clinical evidence on the rates of liver resection (described in sections 3.12 and 3.13).
- 3.5 The results of the full analysis set for the CRYSTAL study showed an improved progression-free survival for cetuximab in combination with FOLFIRI compared with FOLFIRI alone (p = 0.0479) with a

hazard ratio (HR) of 0.85 (95% confidence interval [CI] 0.726 to 0.998). In the manufacturer's additional evidence, the overall survival (median follow-up 30 months) was 19.9 months (95% CI 18.5 to 21.3) for cetuximab in combination with FOLFIRI compared with 18.6 months (95% CI 16.6 to 19.8) for FOLFIRI alone (HR = 0.93, 95% CI 0.81 to 1.07). This was not statistically significant ($p = 0.30$).

- 3.6 In the OPUS study, for the full analysis set, the best overall response rate for cetuximab in combination with FOLFOX was 45.6% compared with 36.0% for FOLFOX alone. The chance for a best overall response of either complete response or partial response increased by 50% in the cetuximab in combination with FOLFOX group, which was not statistically significant ($p = 0.064$).
- 3.7 The results of the CRYSTAL trial for the KRAS wild-type subgroup showed a statistically significant increase in progression-free survival with a median progression-free survival of 9.9 months (95% CI 8.7 to 14.6) for cetuximab in combination with FOLFIRI compared with 8.7 months (95% CI 7.4 to 9.9) for FOLFIRI alone (HR = 0.684, $p = 0.0167$). Cetuximab in combination with FOLFIRI was also associated with a statistically significant increase in response rate compared with FOLFIRI alone (59.3%, 95% CI 51.6 to 66.7 versus 43.2%, 95% CI 35.8 to 50.9, respectively; $p = 0.0028$). The rate of potentially curative liver metastases resection for cetuximab in combination with FOLFIRI was 3.5% ($n = 6$) compared with 2.3% ($n = 4$) for FOLFIRI alone (statistical significance was not reported for this outcome). In the additional evidence, the overall survival (median follow-up 30 months) was 24.9 months (95% CI 22.2 to 27.8) for cetuximab in combination with FOLFIRI compared with 21.0 months (95% CI 19.2 to 25.7) for FOLFIRI alone (HR = 0.84, 95% CI 0.64 to 1.11). This was not statistically significant ($p = 0.22$).

- 3.8 The OPUS trial results for the KRAS wild-type subgroup also showed a statistically significant increase in progression-free survival, with a median progression-free survival of 7.7 months (95% CI 7.1 to 12.0) for cetuximab in combination with FOLFOX compared with 7.2 months (95% CI 5.6 to 7.4) for FOLFOX alone (HR = 0.570, p = 0.0163). Cetuximab in combination with FOLFOX was also associated with a statistically significant increase in response rate compared with FOLFOX alone (60.7%, 95% CI 47.3 to 72.9 versus 37.0%, 95% CI 26.0 to 49.1, p = 0.011). The rate of potentially curative liver metastases resection for cetuximab in combination with FOLFOX was 11.5% (n = 7) compared with 4.1% (n = 3) for FOLFOX alone (statistical significance was not reported for this outcome).
- 3.9 The CRYSTAL trial also reported results for people in the KRAS wild-type subgroup who had metastatic disease confined to the liver (n = 67). The addition of cetuximab to FOLFIRI increased the median progression-free survival from 9.5 months to 14.6 months. However, this difference was not statistically significant (HR = 0.724, p = 0.437). Cetuximab in combination with FOLFIRI was associated with a statistically significant increase in response rate compared with FOLFIRI alone (77.1%, 95% CI 59.9 to 89.6 versus 50.0%, 95% CI 31.9 to 68.1, p = 0.0246).
- 3.10 Quality of life was assessed in the CRYSTAL study using the QLQ-C30 and the EuroQol (EQ-5D) questionnaires. In the KRAS wild-type subgroup, some measures of the QLQ-C30 showed statistically significant differences between the two treatment groups in favour of the FOLFIRI-only group (mean change from baseline to worst physical functioning score, and dyspnoea scores). Only 37 patients completed evaluable baseline EQ-5D questionnaires; therefore, no formal statistical analyses were performed. A summary utility value was calculated for all patients, pooling all values at each visit. This provided a utility value

representative of patients receiving first-line chemotherapy of 0.77 (standard deviation 0.22, n = 128). The OPUS study did not collect any quality of life data.

- 3.11 The majority of adverse events in the KRAS wild-type subgroup were in line with the existing SPC for cetuximab or 5-FU with folinic acid in combination with irinotecan or oxaliplatin. In the CRYSTAL trial, the adverse events that occurred more frequently with cetuximab in combination with FOLFIRI compared with FOLFIRI alone (a difference of 5% or more between groups) were neutropenia, constipation, dyspepsia, dyspnoea, dysgeusia, injection site reaction, erythema, hypotension, hypertrichosis and cheilitis. In the KRAS wild-type population of both the CRYSTAL and OPUS trials, the frequency of palmar-plantar erythrodysesthesia syndrome was higher with cetuximab in combination with FOLFIRI compared with FOLFIRI alone (16.2% versus 2.8% [28 versus 5 patients]) and with cetuximab in combination with FOLFOX compared with FOLFOX alone (13.1% versus 4.1% [8 versus 3 patients]).
- 3.12 The manufacturer submitted data from the CELIM trial (n = 114), a phase II, multicentre, open-label, randomised trial that compared cetuximab in combination with FOLFOX with cetuximab in combination with FOLFIRI, and examined tumour response as the primary outcome. Secondary endpoints included liver resection rates, progression-free survival, disease-free survival and overall survival. The participants in the trial were patients with non-resectable colorectal liver metastases (defined as patients with five or more liver metastases, or patients with liver metastases that are technically non-resectable) and a Karnofsky performance status score of 80 or more. Patients received 8 cycles (approximately 4 months) of treatment.
- 3.13 The results of the interim analysis of the data from the CELIM trial showed that the liver resection rate for cetuximab in combination

with FOLFIRI (n = 53) was 43% compared with 40% for cetuximab in combination with FOLFOX (n = 52). For all patients in the trial (n = 105) the liver resection rate was 42%, and for the KRAS wild-type subgroup (n = 67) it was 43%. For those patients who had technically non-resectable liver metastases at baseline (n = 57) the liver resection rate was 40%.

3.14 The ERG considered that there were a number of limitations with the evidence in the manufacturer's submission. It noted that the KRAS wild-type analysis was carried out post hoc and was likely to have been underpowered. It also noted that the differences in progression-free survival of 1.2 months and 0.5 months for the CRYSTAL and OPUS trials' KRAS wild-type populations, respectively, were statistically significant in favour of cetuximab but not clinically meaningful. The ERG was also uncertain of the accuracy of the KRAS test in clinical practice.

3.15 The ERG identified a number of limitations with the evidence from the CELIM study. It was concerned that the study was not a randomised assessment of cetuximab compared with no cetuximab. Therefore the ERG was uncertain whether the higher rates of resection were because of cetuximab treatment or other factors in the study such as those associated with patient care, surgical practice and patient characteristics. The ERG noted that inclusion criteria for the study specified patients with non-resectable liver metastases, with 55% of patients having technically non-resectable metastases at baseline and 45% having five or more liver metastases. In addition, the ERG commented that the sample size in the trial was relatively small, with approximately 55 patients in each arm.

Cost effectiveness

3.16 The manufacturer developed a semi-Markov model to simulate the disease progression and survival of a cohort of patients with EGFR-expressing, KRAS wild-type metastatic colorectal cancer

throughout first and subsequent lines of treatment (second- and third-line) including longer-term survival after successful curative surgery. The model had a cycle length of 1 week and estimated costs and benefits over a lifetime horizon (approximately 23 years).

- 3.17 The analysis looked at two treatment strategies: cetuximab in combination with FOLFIRI compared with FOLFIRI alone, and cetuximab in combination with FOLFOX compared with FOLFOX alone. The economic evaluation focused on a population with the following characteristics:
- Good performance status (the majority of KRAS wild-type patients in the CRYSTAL and OPUS trials [96% and 90%, respectively] had an ECOG performance status of 0 or 1, so this was reflected in the modelled cohort).
 - Suitable for irinotecan- or oxaliplatin-containing chemotherapy.
 - Metastatic disease confined to the liver, excluding people whose liver metastases were resectable at presentation.
- 3.18 The analysis assessed the impact of cetuximab in combination with FOLFIRI or FOLFOX on the rates of potentially curative resection among people whose tumours became resectable during first-line treatment. The first-line treatment regimens were as set out in the CRYSTAL and OPUS trial protocols and administered as recorded in the trial data sets. The second-line treatment regimens of FOLFIRI or FOLFOX were taken from the published evidence, dependent on first-line treatment. If FOLFIRI was used in the first line, then FOLFOX was used in the second line, and vice versa. In the third-line setting, people received best supportive care. In the model, people were considered to be tumour-free following successful curative resection. Based on other published evidence, people were assumed to have an increase in their estimated mean life expectancy of 4.76 years, with an observed median survival time of 3.23 years. Following a successful curative liver resection, people did not receive any further treatment with cetuximab.

However, people who had an unsuccessful curative liver resection or did not undergo a liver resection were treated with cetuximab until disease progression.

- 3.19 Subsequent lines of treatment were modelled because neither clinical trial had generated mature overall survival data at the time of the manufacturer's original submission. Extrapolation techniques were used in the economic model to estimate survival benefits in the base case. These were varied in the scenario analyses.
- 3.20 The manufacturer considered the liver resection rates from the CRYSTAL and OPUS trials (3.5% [n = 6] for cetuximab in combination with FOLFIRI versus 2.3% [n = 4] for FOLFIRI alone; 11.5% [n = 7] for cetuximab in combination with FOLFOX versus 4.1% [n = 3] for FOLFOX alone) to be low compared with current clinical practice in the NHS. Data from a published study were therefore used to estimate possible resection rates for patients with metastatic disease confined to the liver from the response rates. The correlation observed between response rates and resection rates was used to model resection rates in the base case and different scenarios in the model. The value for the failure rate of liver resection used in the model was 27.8%, which was taken from the full analysis set from the CRYSTAL trial. This rate was applied to all arms in the model.
- 3.21 The cost data were taken from the BNF edition 55 (2008) and the NHS National Tariff (2006). The cost of the KRAS test included in the model was £300 per test. This was provided verbally by a manufacturer of the test to the manufacturer of cetuximab, based on ad hoc patient testing. The analysis took into account testing of the whole patient population. The model used a weighted average cost per liver resection surgery of £2271 calculated from four liver healthcare resource groups: G02 (liver – complex procedures), G03 (liver – very major procedures), G04 (liver – major procedures, patient aged over 69 years with complications and/or comorbidities)

and G05 (liver – major procedures, patient aged under 70 years without complications and/or comorbidities). This cost was assumed to occur only once, at 16 weeks.

- 3.22 Health-related utility weights were applied to the time lived with disease at different stages of disease progression in the Markov model. Health-related utilities were taken from clinical trials in the first- and third-line settings and estimated for the second-line setting. The utility in the period following curative resection took into account utility in patients free of disease and patients with recurrent disease. It was assumed that patients free of disease had health-related utility equal to that of the general population. In patients with progressive disease, the utility was estimated as the weighted average of utilities in the second- and third-line setting.
- 3.23 The economic analysis results included in the manufacturer's original submission have since been superseded by updated analyses (see sections 3.29, 3.31 and 3.32).
- 3.24 The ERG identified a number of limitations with the manufacturer's economic model. It was concerned that the model focused on a much smaller patient population (people with KRAS wild-type metastatic colorectal cancer who had metastases confined to the liver and had a good performance status) than the population defined in the appraisal scope (people with untreated metastatic colorectal cancer) and was therefore concerned about the applicability of the results to clinical practice. The ERG was also concerned that no evidence was provided by the manufacturer to support the assumptions in the model that all patients who are suitable for cetuximab treatment are identified and treated with cetuximab (those who are KRAS wild-type) and that patients who are not suitable for cetuximab treatment (those with KRAS mutations) are not treated with cetuximab. Given the importance of estimating the outcomes for those treated incorrectly in reaching a

conclusion on the cost effectiveness of the treatment, the ERG considered that this omission was a flaw in the model design.

- 3.25 The ERG was uncertain how accurate the effectiveness estimates used within the economic model were, given that they were derived from small post hoc subgroup analyses of trial results, and whether all relevant costs had been included within the model.

Revised economic analyses

- 3.26 In response to ACD consultation, revised economic analyses were provided amending the following parameters: the time at which patients were referred for liver resection, liver resection rates and failure rates of liver resection. The manufacturer also submitted revised analyses for cetuximab in combination with FOLFOX compared with FOLFOX alone that incorporated a patient access scheme, a 16-week stopping rule for cetuximab and revised costs of liver resection.

Liver resection rates

- 3.27 The revised economic analysis used a 43% liver resection rate for both cetuximab in combination with FOLFIRI and cetuximab in combination with FOLFOX, taken from the CELIM trial (KRAS wild-type subgroup). The CELIM trial did not include FOLFIRI or FOLFOX alone as a direct comparator. Therefore, in the revised economic analysis the manufacturer assumed a liver resection rate of 9% for FOLFIRI alone and 22% for FOLFOX alone (taken from published evidence [GERCOR study]), based on the recommendation of clinical specialists as being the most robust data for resection rates for FOLFIRI and FOLFOX. The model was also adjusted so that patients were referred for curative liver resection surgery at 16 weeks rather than 12 weeks, to reflect the data from the CELIM trial.

Failure rates of liver resection

- 3.28 In addition, the manufacturer obtained clinical opinion on the 27.8% liver resection failure rate used in the original analysis. Clinical advice suggested that this rate was high for patients who have a liver resection in a specialist centre, and suggested that this rate was more likely to be 5%. The manufacturer used the revised value of 5% for the revised economic analyses.
- 3.29 The results of the revised analysis (updated liver resection rates, 5% failure rate of liver resection and lifetime horizon) for cetuximab in combination with FOLFIRI compared with FOLFIRI alone gave an ICER of £23,456 per QALY gained. The results for cetuximab in combination with FOLFOX compared with FOLFOX alone gave an ICER of £29,891.

Patient access scheme

- 3.30 Details of a patient access scheme were provided by the manufacturer based on a 16% rebate of the amount of cetuximab used when given in combination with FOLFOX for people with KRAS wild-type metastatic colorectal cancer who have metastases confined to the liver. The scheme requires that patients are treated according to the final NICE guidance and that data should be provided to the manufacturer to show that the NICE guidance has been followed. Cetuximab would normally be rebated in the form of free stock at a rate of 16% for all patients in the scheme on a per patient basis, with an option for rebate via credit note or cash. The patient access scheme was incorporated into the economic analysis for the comparison of cetuximab in combination with FOLFOX compared with FOLFOX alone.

Stopping rule

- 3.31 The manufacturer incorporated a stopping rule for treatment with cetuximab when analysing cetuximab in combination with FOLFOX compared with FOLFOX alone. A scenario was explored in which

the cost of treatment with cetuximab was stopped at 16 weeks (the point at which people were assessed for curative resection) for all people in the analysis. No amendments were made to the progression-free survival of cetuximab after stopping treatment with cetuximab at 16 weeks. The result of this 16-week analysis incorporating the patient access scheme, liver resection rates of 43% for cetuximab in combination with FOLFOX and 22% for FOLFOX alone, and a 5% failure rate of liver resection, gave an ICER for cetuximab in combination with FOLFOX compared with FOLFOX alone of £18,660 per QALY gained. The manufacturer performed a sensitivity analysis around the liver resection rate for cetuximab in combination with FOLFOX, and when the rate was varied to 35% and 30%, the ICER for cetuximab in combination with FOLFOX compared with FOLFOX alone increased to £24,610 and £31,006 per QALY gained, respectively.

Cost of liver resection

- 3.32 The manufacturer also revised the costs of liver resection by calculating a new weighted average cost of £8929, based on the proportion of people receiving different surgical techniques from a published study and assigning the healthcare resource groups G02 (liver – complex procedures) and G03 (liver – very major procedures). Incorporating this revised cost of liver resection in the 16-week analysis gave an ICER for cetuximab in combination with FOLFOX compared with FOLFOX alone of £21,056 per QALY gained. Varying the liver resection rate for cetuximab in combination with FOLFOX to 35% and 30%, the ICER for cetuximab in combination with FOLFOX compared with FOLFOX alone increased to £26,662 and £32,688 per QALY gained, respectively.

Decision Support Unit report

- 3.33 The Decision Support Unit (DSU) commented that although the manufacturer had removed the direct costs of cetuximab after

16 weeks in the 16-week analysis, it had not altered the progression-free survival and therefore the probabilities of progression after 16 weeks of treatment with cetuximab. The DSU considered this to be the most optimistic method of implementing a stopping rule. The DSU conducted an exploratory analysis implementing a more conservative stopping rule in which the patients in the cetuximab in combination with FOLFOX arm followed the cetuximab progression-free survival curve for 16 weeks, after which they then switched to follow the progression-free survival curve for the FOLFOX-alone arm. Incorporating the DSU's 16-week stopping rule (in addition to the patient access scheme, the £8929 revised cost of liver resection, 43% liver resection rate for cetuximab in combination with FOLFOX, 22% liver resection rate for FOLFOX alone and a 5% failure rate of liver resection), the ICER for cetuximab in combination with FOLFOX compared with FOLFOX alone increased from £21,056 (estimated by the manufacturer) to £24,022 per QALY gained. When varying the liver resection rate for cetuximab in combination with FOLFOX to 35% and 30%, the ICER increased from £26,662 to £33,291 and from £32,688 to £45,604, respectively.

- 3.34 Full details of all the evidence are in the manufacturer's submissions, the ERG reports and the DSU report, which are available from www.nice.org.uk/TA176

4 Consideration of the evidence

- 4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of cetuximab for the first-line treatment of metastatic colorectal cancer, having considered evidence on the nature of the condition and the value placed on the benefits of cetuximab by people with metastatic colorectal cancer, those who represent them, and clinical specialists. It was also mindful of the need to take account of the effective use of NHS resources.

- 4.2 The Committee noted that the marketing authorisation for cetuximab limits its use to people with KRAS wild-type metastatic colorectal cancer, a narrower indication than outlined in the scope. The Committee acknowledged that the scope pre-dated the marketing authorisation for cetuximab, which placed this restriction on use. It heard from the clinical specialists that the marketing authorisation for cetuximab reflects increasing evidence that KRAS mutation status is predictive of response to treatment and that people whose tumours have KRAS mutations are unlikely to respond to treatment with cetuximab. The Committee also heard from the clinical specialists that KRAS testing accurately identifies people with wild-type KRAS status. The test can be carried out on 95% of tissue samples and is currently only conducted in two NHS centres (Leeds and Cardiff), although the tests are becoming more widely available through the NHS for people with metastatic colorectal cancer. Commercial companies offer KRAS testing, but these are understood to be more expensive than the tests carried out within the NHS.
- 4.3 The Committee reviewed the clinical-effectiveness results from the two clinical trials; one that compared cetuximab in combination with FOLFIRI with FOLFIRI alone and another that compared cetuximab in combination with FOLFOX with FOLFOX alone in the KRAS wild-type subgroup. It noted the statistically significant improvements in progression-free survival and response rates associated with cetuximab. However, it was aware that the improvement in median progression-free survival was 1.2 months and 0.5 months respectively in the two trials and concluded that the effectiveness of cetuximab at improving progression-free survival was therefore limited. In addition, the Committee noted that the difference in the overall survival of 3.9 months from the CRYSTAL trial was not statistically significant. The Committee was also concerned that the KRAS wild-type subgroup analysis was based on small sample sizes and was carried out post hoc (at the request of the European

Medicines Agency; EMEA). However, the Committee was reassured by the clinical specialists that differential response based on KRAS status had biological plausibility given current understanding of the pathology of metastatic colorectal cancer.

4.4 The Committee heard from the clinical specialists that cetuximab combined with chemotherapy had an important potential role in shrinking secondary liver metastases, to enable potentially curative resection in people with KRAS wild-type metastatic colorectal cancer. The clinical specialists reported that, of people whose disease responds sufficiently to cetuximab to enable resection of liver metastases, approximately 90% would do so within 12 weeks of treatment with cetuximab. The duration of treatment with cetuximab in clinical practice for KRAS wild-type metastatic colorectal cancer patients with liver-only metastases would not normally exceed 16 weeks. Patients for whom liver resection was not possible (for example, because of the distribution of liver metastases) or who were not well enough to undergo potentially curative liver resection would not be treated with cetuximab, and would receive standard chemotherapy only. The Committee noted that in people who have undergone primary colorectal surgery with curative intent and whose liver metastases are rendered resectable following a successful response to chemotherapy, the 5- and 10-year survival rate is approximately 30% and 20% respectively.

4.5 The Committee considered the evidence for the effect of treatment with cetuximab on the rate of potentially curative resection of liver metastases. The results of the clinical trials showed that very few patients with KRAS wild-type metastatic colorectal cancer went on to receive potentially curative resection (cetuximab in combination with FOLFIRI 3.5%, FOLFIRI alone 2.3%; cetuximab in combination with FOLFOX 11.5%, FOLFOX alone 4.1%) and the Committee noted that no statistical significance was reported for these differences. It heard from the clinical specialists that the

number of patients receiving potentially curative liver resection in the CRYSTAL and OPUS trials was lower than that seen in UK clinical practice, which is based on management by multidisciplinary teams involving highly specialised liver surgical services. The clinical specialists stated that a more realistic rate for potentially curative resection with chemotherapy in general was approximately 12–15%, which could rise to approximately 30–35% with the addition of cetuximab. The Committee also heard from the clinical specialists that the current UK standard chemotherapy approach for shrinking liver metastases was to use the FOLFOX regimen, which in practice enables a resection rate of approximately 20%. The Committee acknowledged the importance of liver resection rates as an endpoint in assessing the effectiveness of cetuximab.

- 4.6 The Committee reviewed the additional clinical data submitted by the manufacturer on the liver resection rates. It noted that the CELIM trial was not a randomised assessment of cetuximab in combination with chemotherapy compared with chemotherapy alone, had a relatively small sample size and had not been peer-reviewed. The Committee was initially concerned that only 55% of patients were described as having technically non-resectable liver metastases at baseline; however, the Committee then noted that the remaining 45% had at least five or more liver metastases at baseline, and were therefore also non-resectable. It noted that the subgroup analysis for these two groups of patients indicated a liver resection rate of 40% and 44% respectively, but that this subgroup analysis was for all patients and not just those with KRAS wild-type metastatic colorectal cancer. The Committee heard from the clinical specialists that the 43% liver resection rate for patients with KRAS wild-type metastatic colorectal cancer who were treated with cetuximab was an encouraging result, but it also noted that this was higher than the 30–35% rate originally considered likely by the clinical specialists (see section 4.5). The Committee was

concerned that the 22% liver resection rate for FOLFOX was taken from an older study (GERCOR, Tournigand et al. 2004), but noted that the clinical specialists suggested that a liver resection rate of approximately 20% for FOLFOX was appropriate for current UK clinical practice (see section 4.5).

- 4.7 The Committee discussed the failure rate of liver resection. It noted that the 27.8% failure rate used in the original analysis appeared high for current practice. The Committee heard from the clinical specialists that a 5% failure rate of liver resection was a more appropriate reflection of current practice in UK specialist centres. The Committee agreed that this low rate reflected improvements in preoperative assessment and surgical technique and was appropriate to be used in the model.
- 4.8 The Committee discussed the adverse effects related to cetuximab. The clinical specialists advised the Committee that cetuximab is associated with an increase in an acne-like rash affecting a person's upper trunk, gastrointestinal adverse effects such as diarrhoea, and fatigue. The clinical specialists and patient experts explained that the acne-like rash may be indicative of response to cetuximab treatment and would not usually cause admission to hospital. Therefore, it is often interpreted by people as a positive effect because it suggests that the drug is working, outweighing any negative effects of the rash.
- 4.9 The Committee considered the results of the economic analysis submitted by the manufacturer. The Committee noted that the manufacturer had not provided an economic analysis that included the entire population for which cetuximab is licensed. The economic model focused on a subgroup of patients with a good performance status and metastatic disease confined to the liver. The Committee was persuaded that, in this group of patients, the aim of treatment with cetuximab was to reduce the size of metastases so they were resectable. Therefore the most

appropriate comparator was FOLFOX (see section 4.5), considered over a lifetime horizon. The Committee heard from the clinical specialists that in current UK clinical practice, all patients would normally stop receiving treatment with cetuximab at the time of the assessment for possible liver resection (that is, after approximately 12–16 weeks), and noted the impact of incorporating a 16-week stopping rule for cetuximab on the economic analysis. In addition, the Committee was aware of the patient access scheme details provided by the manufacturer for cetuximab in combination with FOLFOX, and the impact of the scheme on the results of the economic analysis. The Committee concluded that the most appropriate analysis for consideration was that which incorporated the 16-week stopping rule for cetuximab and the patient access scheme.

- 4.10 The Committee was aware that in the manufacturer's new 16-week analysis (incorporating a 5% failure rate of liver resection, 43% liver resection rate, lifetime horizon and the patient access scheme), the ICER for cetuximab in combination with FOLFOX compared with FOLFOX alone was £18,700 per QALY gained (see section 3.31). The Committee was concerned about the limited methodology used for estimating the resection rates in the model, in that single arms from two separate studies were used to provide the data for the two groups in the model; the CELIM study for cetuximab in combination with FOLFOX and the GERCOR study for FOLFOX alone. The Committee considered that exploration of the different populations and evaluation of possible selection biases between the trials had not been done to a satisfactory level. Therefore, the Committee expressed caution about the results produced by the new analysis using a 43% resection rate for cetuximab in combination with FOLFOX, as the relative difference in resection rates was assumed from unrelated studies without any adjustments. It noted the sensitivity analysis requested from the manufacturer, which used resection rates of 35% and 30% for cetuximab in combination with

FOLFOX (assuming a 22% resection rate for FOLFOX alone), resulted in ICERs of £24,600 and £31,000 per QALY gained, respectively. The Committee agreed that a 35% liver resection rate for cetuximab in combination with FOLFOX compared with the 22% for FOLFOX alone more closely reflected the 10–15% relative difference in resection rates for these two comparators considered to be realistic by the clinical specialists and was a more appropriate value to use in the economic analysis.

- 4.11 The Committee discussed the cost of liver resection included in the economic analysis. It noted that the manufacturer had originally used a weighted average of a range of healthcare resource groups for all liver procedures giving an average cost of £2300 for liver resection surgery, and that this only occurred once in the model. The Committee considered that this cost could be low compared with current UK clinical practice because a proportion of patients may undergo more than one operation to achieve complete resection of metastases. In addition, the Committee heard from the clinical specialists that liver resection costs £7000 per case. The Committee discussed the additional analysis requested from the manufacturer, which used a new weighted average based on the surgical technique employed by Adam et al. (2004) giving an average cost of £8900 for liver resection surgery. The Committee agreed that this weighted cost was a more accurate reflection of current UK clinical practice. Using this liver resection cost, the ICER for cetuximab in combination with FOLFOX compared with FOLFOX alone increased from £18,700 to £21,100 per QALY gained for the scenario with a liver resection rate of 43%. Varying the resection rate to 35% (considered by the Committee to be more likely than 43%) increased the ICER from £24,600 to £26,700 per QALY gained. Using a resection rate of 30% (considered by the Committee to be a conservative estimate) increased the ICER from £31,000 to £32,700 per QALY gained.

- 4.12 The Committee noted that the 16-week analysis provided by the manufacturer only explored stopping the costs of cetuximab treatment at 16 weeks. The manufacturer made no amendments to the efficacy of cetuximab in terms of progression-free survival after the decision to resect the liver metastases and stop cetuximab treatment, due to the lack of evidence for progression-free survival following 16 weeks of treatment. The Committee considered this to be the most optimistic scenario. The Committee then discussed the alternative 16-week analysis provided by the DSU which took a more conservative view and also changed the efficacy of cetuximab after 16 weeks to equal that of the FOLFOX-alone arm. It noted that incorporating the revised cost of liver resection (£8900) and a 43% resection rate, the ICER for cetuximab in combination with FOLFOX compared with FOLFOX alone increased from £21,100 to £24,000 per QALY gained. The result of the sensitivity analysis which used the Committee's preferred resection rate of 35% showed an increase in the ICER from £26,700 to £33,300 per QALY gained.
- 4.13 The Committee agreed that the most likely ICER for cetuximab in combination with FOLFOX compared with FOLFOX alone was between £26,700 (estimated by the manufacturer) and £33,300 per QALY gained (estimated by the DSU), and that this was within a range that could be considered a cost-effective use of NHS resources. The Committee was mindful that people with liver-only metastases form a subgroup of the population within the marketing authorisation, and that the manufacturer had submitted economic evidence only for this subgroup. On the basis of its considerations of the clinical evidence, the Committee thought that the QALYs gained for the whole population would be substantially lower than that of the subgroup, while the incremental costs would not be any lower. Therefore, the Committee felt that the cost effectiveness for the whole population had not been demonstrated. The Committee noted that for patients who are not well enough to have surgery to

remove liver metastases, adding cetuximab to their chemotherapy would not help in enabling a curative operation. It therefore concluded that the addition of cetuximab is only appropriate for patients who have had the primary colorectal tumour resected, or if that is not the case, where the primary colorectal tumour is potentially operable and the patient is fit enough to undergo colorectal surgery. The patient also needs to be fit enough to undergo liver surgery if their metastases become resectable after treatment with cetuximab. The Committee noted that the suitability for undergoing such surgery was determined in different ways in the clinical trials underpinning the evidence base. Therefore the Committee considered it appropriate that fitness for surgery be decided on an individual basis following discussion between patients and their clinicians. The Committee concluded that cetuximab in combination with FOLFOX should be recommended for the first-line treatment of metastatic colorectal cancer when the following criteria are met:

- The primary colorectal tumour has been resected or is potentially operable.
- The metastatic disease is confined to the liver and is unresectable.
- The patient is fit enough to undergo surgery to resect the primary colorectal tumour and to undergo liver surgery if the metastases become resectable after treatment with cetuximab.
- The manufacturer rebates 16% of the amount of cetuximab used on a per patient basis.
- The duration of treatment with cetuximab is restricted to 16 weeks.

4.14 The Committee then discussed cetuximab in combination with FOLFIRI as a first-line treatment option for patients with metastatic colorectal cancer. The Committee had earlier noted that the most appropriate comparator for patients with liver-only metastases was

FOLFOX (see section 4.9); therefore adding cetuximab to this chemotherapy regimen with the intention of reducing the size of liver metastases would be the combination of choice for this population. However, the Committee was aware that there may be some patients who are unable to tolerate, or have a contraindication to oxaliplatin, and it agreed that for these patients, the most appropriate comparator would be FOLFIRI. The Committee discussed the analysis presented by the manufacturer for cetuximab in combination with FOLFIRI compared with FOLFIRI alone. It noted that this analysis did not include the 16-week stopping rule and the revised cost of liver resection. Assuming resection rates of 43% for cetuximab in combination with FOLFIRI and 9% for FOLFIRI alone, and a liver resection cost of £2300, the ICER for cetuximab in combination with FOLFIRI compared with FOLFIRI alone was £23,500 per QALY gained. Although the precise value of the ICER that incorporated the 16-week stopping rule for cetuximab, the revised cost of liver resection (£8900) and the preferred 35% resection rate for cetuximab was not known, the Committee accepted that the ICER would likely be within a range considered to be a cost-effective use of NHS resources. The Committee therefore concluded that cetuximab in combination with FOLFIRI should be recommended for first-line treatment of metastatic colorectal cancer when the following criteria are met:

- The primary colorectal tumour has been resected or is potentially operable.
- The metastatic disease is confined to the liver and is unresectable.
- The patient is fit enough to undergo surgery to resect the primary colorectal tumour and to undergo liver surgery if the metastases become resectable after treatment with cetuximab.
- The patient is unable to tolerate or has contraindications to oxaliplatin.

- The duration of treatment with cetuximab is restricted to 16 weeks.

4.15 The Committee was aware that, in current UK clinical practice, the treatment of patients with metastatic colorectal cancer receiving potentially curative resection of metastases confined to the liver is managed by multidisciplinary teams involving highly specialised liver surgical services. The Committee concluded that current practice for this population was the most appropriate approach, and that patients should continue to be managed in this way.

5 Implementation

5.1 The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website. The NHS is not required to fund treatments that are not recommended by NICE.

5.2 NICE has developed tools to help organisations implement this guidance (listed below). These are available on our website (www.nice.org.uk/TA176).

- Costing report and costing template to estimate the savings and costs associated with implementation.
- Audit support for monitoring local practice.

6 Recommendations for further research

6.1 The Committee noted the following ongoing clinical trial related to this appraisal:

- NCT00182715 is a phase III randomised controlled trial evaluating first-line use of cetuximab for metastatic colorectal cancer (COIN trial). It aims to determine whether the addition of cetuximab to continuous oxaliplatin plus fluoropyrimidine chemotherapy improves overall survival when compared with either continuous or intermittent oxaliplatin plus fluoropyrimidine chemotherapy.

7 Related NICE guidance

Published

- Cetuximab for the treatment of metastatic colorectal cancer following failure of oxaliplatin-containing chemotherapy (terminated appraisal). NICE technology appraisal 150 (2008). Available from www.nice.org.uk/TA150
- Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer. NICE technology appraisal guidance 118 (2007). Available from www.nice.org.uk/TA118
- Capecitabine and oxaliplatin in the adjuvant treatment of stage III (Dukes' C) colon cancer. NICE technology appraisal guidance 100 (2006). Available from www.nice.org.uk/TA100
- Irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer (review of technology appraisal 33). NICE technology appraisal guidance 93 (2005). Available from www.nice.org.uk/TA93
- Improving outcomes in colorectal cancers – manual update. NICE cancer service guidance (2004). Available from www.nice.org.uk/csgcc
- Guidance on the use of capecitabine and tegafur with uracil for metastatic colorectal cancer. NICE technology appraisal guidance 61 (2003). Available from www.nice.org.uk/TA61

Under development

NICE is developing the following guidance (details available from www.nice.org.uk):

- Bevacizumab in combination with oxaliplatin and either 5-FU or capecitabine for the treatment of metastatic colorectal cancer. NICE technology appraisal (publication date to be confirmed).
- Diagnosis and management of colorectal cancer. NICE clinical guideline (publication expected July 2011).

8 Review of guidance

8.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider whether the technology should be reviewed. This decision will be taken in the light of information gathered by the Institute, and in consultation with consultees and commentators.

8.2 The guidance on this technology will be considered for review in August 2012.

Andrew Dillon
Chief Executive
August 2009

Appendix A: Appraisal Committee members and NICE project team

A *Appraisal Committee members*

The Appraisal Committee is a standing advisory committee of the Institute. Its members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. The Appraisal Committee meets three times a month except in December, when there are no meetings. The Committee membership is split into three branches, each with a chair and vice chair. Each branch considers its own list of technologies, and ongoing topics are not moved between the branches.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Professor Keith Abrams

Professor of Medical Statistics, University of Leicester

Dr Ray Armstrong

Consultant Rheumatologist, Southampton General Hospital

Dr Jeff Aronson

Reader in Clinical Pharmacology, University Department of Primary Health Care, University of Oxford

Dr Darren Ashcroft

Reader in Medicines Usage and Safety, School of Pharmacy and Pharmaceutical Sciences, University of Manchester

Professor David Barnett (Chair)

Professor of Clinical Pharmacology, University of Leicester

Dr Peter Barry

Consultant in Paediatric Intensive Care, Leicester Royal Infirmary

Professor John Cairns

Public Health and Policy, London School of Hygiene and Tropical Medicine

Dr Mark Chakravarty

External Relations Director – Pharmaceuticals & Personal Health, Oral Care Europe

Professor Jack Dowie

Health Economist, London School of Hygiene and Tropical Medicine

Dr Martin Duerden

Medical Director, Conwy Local Health Board

Ms Lynn Field

Nurse Director, Pan Birmingham Cancer Network

Dr Fergus Gleeson

Consultant Radiologist, Churchill Hospital, Oxford

Ms Sally Gooch

Independent Nursing and Healthcare Consultant

Mrs Eleanor Grey

Lay Member

Mr Sanjay Gupta

Former Service Manager in Stroke, Gastroenterology, Diabetes and Endocrinology, Basildon and Thurrock University Hospitals Foundation NHS Trust

Mr Terence Lewis

Lay Member, Mental Health Consultant, National Institute for Mental Health in England

Professor Gary McVeigh

Professor of Cardiovascular Medicine, Queens University, Belfast

Dr Ruairidh Milne

Senior Lecturer in Public Health, National Coordinating Centre for Health Technology

Dr Neil Milner

General Practitioner, Tramways Medical Centre, Sheffield

Dr Rubin Minhas

General Practitioner, CHD Clinical Lead, Medway PCT

Dr John Pounsford

Consultant Physician, Frenchay Hospital, Bristol

Dr Rosalind Ramsay

Consultant Psychiatrist, Adult Mental Health Services, Maudsley Hospital

Dr Stephen Saltissi

Consultant Cardiologist, Royal Liverpool University Hospital

Dr Lindsay Smith

General Practitioner, East Somerset Research Consortium

Mr Roderick Smith

Finance Director, West Kent Primary Care Trust

Mr Cliff Snelling

Lay Member

Professor Ken Stein

Professor of Public Health, Peninsula Technology Assessment Group (PenTAG), University of Exeter

Professor Andrew Stevens

Professor of Public Health, Department of Public Health and Epidemiology, University of Birmingham

Dr Rod Taylor

Associate Professor in Health Services Research, Peninsula Medical School, Universities of Exeter and Plymouth

Ms Nathalie Verin

Health Economics Manager, Boston Scientific UK and Ireland

Dr Colin Watts

Consultant Neurosurgeon, Addenbrookes Hospital

Mr Tom Wilson

Director of Contracts and Information Management and Technology, Milton Keynes PCT

B ***NICE project team***

Each technology appraisal is assigned to a team consisting of one or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Helen Knight

Technical Lead

Helen Chung

Technical Adviser

Jeremy Powell

Project Manager

Appendix B: Sources of evidence considered by the Committee

- A The Evidence Review Group (ERG) report for this appraisal was prepared by West Midlands Health Technology Assessment Collaboration – University of Birmingham:
- Meads C, Round J, Tubeuf S, et al. Cetuximab for the first-line treatment of metastatic colorectal cancer, July 2008
- B Additional evidence for this appraisal was prepared by West Midlands Health Technology Assessment Collaboration – University of Birmingham:
- Critical appraisal of additional material on the CELIM randomised controlled trial submitted by Merck Serono for the Cetuximab STA
 - Comment on additional material submitted by Merck Serono in relation to cetuximab for metastatic colorectal cancer
 - Cetuximab CRC STA – Additional briefing document required for third committee meeting
- C Additional evidence for this appraisal was also prepared by the Decision Support Unit, School of Health and Related Research – University of Sheffield:
- Cetuximab for the first line treatment of metastatic colorectal cancer – report by the Decision Support Unit
- D The following organisations accepted the invitation to participate in this appraisal. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to give their expert views. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

- I Manufacturer/sponsor:
- Merck Serono
- II Professional/specialist and patient/carer groups:
- Association of Coloproctology of Great Britain and Ireland
 - Beating Bowel Cancer
 - Bowel Cancer UK
 - British Association of Surgical Oncology
 - Cancer Research UK
 - Macmillan Cancer Relief
 - Royal College of Nursing
 - Royal College of Pathologists
 - Royal College of Physicians, Medical Oncology Joint Special Committee
 - UK Oncology Nursing Society
- III Other consultees:
- Department of Health
 - Islington PCT
 - Nottinghamshire County PCT
 - Welsh Assembly Government
- IV Commentator organisations (did not provide written evidence and without the right of appeal):
- Department of Health, Social Services and Public Safety for Northern Ireland
 - Institute of Cancer Research
 - National Collaborating Centre for Cancer
 - NHS Quality Improvement Scotland
 - Pfizer
 - Roche Diagnostics
 - Roche Products
 - Sanofi-Aventis

E The following individuals were selected from clinical specialist and patient advocate nominations from the non-manufacturer/sponsor consultees and commentators. They gave their expert personal view on cetuximab by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Mr Ian Beaumont, nominated by Bowel Cancer UK – patient expert
- Dr Rob Glynne-Jones, Clinical Oncologist, Mount Vernon Hospital, nominated by Bowel Cancer UK – clinical specialist
- Professor Timothy Maughan, Consultant Clinical Oncologist and Professor of Cancer Studies, Cardiff University, nominated by the Royal College of Physicians – clinical specialist
- Mr Goff Norrington, nominated by Beating Bowel Cancer – patient expert
- Mr Graeme Poston, nominated by the British Association of Surgical Oncology – clinical specialist