NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Cetuximab and panitumumab for previously untreated metastatic colorectal cancer

This guidance includes a review of TA176 and a partial review of TA240, and was developed using the multiple technology appraisal (MTA) process.

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using cetuximab and panitumumab in the NHS in England. The Appraisal Committee has considered the evidence submitted and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the Committee. NICE invites comments from the consultees and commentators for this appraisal (see section 8) and the public. This document should be read along with the evidence base (the Committee papers).

The Appraisal Committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on these technologies. The recommendations in section 1 may change after consultation.

After consultation:

- The Appraisal Committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the Committee will also consider comments made by people who are not consultees.
- After considering these comments, the Committee will prepare the final appraisal determination.
- Subject to any appeal by consultees, the final appraisal determination may be used as the basis for NICE's guidance on using cetuximab and panitumumab in the NHS in England.

For further details, see the Guides to the technology appraisal process.

The key dates for this appraisal are:

Closing date for comments: 8 December 2015

Second Appraisal Committee meeting: 6 January 2016

Details of membership of the Appraisal Committee are given in section 7, and a list of the sources of evidence used in the preparation of this document is given in section 8.

Note that this document is not NICE's final guidance on these technologies. The recommendations in section 1 may change after consultation.

1 Appraisal Committee's preliminary recommendations

1.1 Cetuximab and panitumumab are not recommended within their marketing authorisations for previously untreated RAS wild-type metastatic colorectal cancer, that is, in combination with 5-fluorouracil, folinic acid and oxaliplatin (FOLFOX) or 5-fluorouracil, folinic acid and irinotecan (FOLFIRI).

1.2 People whose treatment with cetuximab or panitumumab was started within the NHS before this guidance was published should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

2 Clinical need and practice

2.1 Colorectal cancer usually develops slowly over 10–15 years. Metastatic colorectal cancer is a disease that has spread beyond the large intestine and nearby lymph nodes. It most often spreads first to the liver, but metastases may also occur in other parts of the body including the peritoneum, lungs, brain and bones. About 25% of people present with metastases at initial diagnosis and almost 50% of people with colorectal cancer will develop metastases. The 1-year survival rate in England and Wales is about 75%, and the 5-year survival rate is under 60%.

2.2 Treatment of metastatic colorectal cancer may involve a combination of surgery, biological agents, cytotoxic chemotherapy (hereafter 'chemotherapy'), radiotherapy and supportive care.

When possible, surgically removing (resecting) the primary tumour and metastases is considered, but usually only when there are no metastases outside of the liver. Therapy, including monoclonal antibodies and chemotherapy, may be recommended before surgery, to shrink the tumour(s) and make it suitable for resection. For people with metastases only in their liver, complete resection appears to offer the best chance of long-term survival.

2.3 NICE's clinical guideline on colorectal cancer: diagnosis and management recommends chemotherapy options including:

- folinic acid and fluorouracil plus oxaliplatin (FOLFOX)
- tegafur plus fluorouracil and folinic acid
- capecitabine plus oxaliplatin (XELOX)
- capecitabine alone.

There are different FOLFOX dosing schedules, depending on how the fluorouracil is given; both regimens involve 2-hour intravenous infusions of folinic acid and oxaliplatin on day 1:

- FOLFOX4: on day 1, an intravenous injection of fluorouracil and an intravenous infusion of fluorouracil over 22 hours is given. On day 2, another injection of fluorouracil is given with an intravenous infusion of folinic acid, followed by another 22-hour infusion of fluorouracil.
- FOLFOX6: on day 1, an intravenous injection of fluorouracil is given, followed by fluorouracil infused over 48 hours.

2.4 Chemotherapy may be combined with biological agents such as cetuximab (for 16 weeks only) or panitumumab (currently available through the Cancer Drugs Fund). In NICE's technology appraisal on cetuximab for the first-line treatment of metastatic colorectal cancer (which this guidance replaces), cetuximab is recommended only when all the following 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 person is fit enough to have surgery to resect the primary colorectal tumour and to have liver surgery if the metastases become resectable after treatment with cetuximab.

3 The technologies

3.1 Cetuximab (Erbitux, Merck Serono) and panitumumab (Vectibix, Amgen) appear to be more effective for treating tumours without mutations (known as 'wild-type') in genes in the rat sarcoma (RAS) family (specifically Kirsten [KRAS] and neuroblastoma [NRAS]) than those with mutations. Since previous NICE technology appraisals of cetuximab and panitumumab, the European Medicines Agency has updated the marketing authorisations of both drugs to reflect a newer stricter definition of RAS wild-type status. The result is that the drugs are now licensed for a smaller population. The original marketing authorisations applied only to people with metastatic colorectal cancer who did not have mutations in a single part (exon 2) of the KRAS gene. The current, updated marking authorisations are restricted to people without any mutations in any of the RAS genes (known as RAS wild-type status). About half of people with metastatic colorectal cancer have RAS wild-type tumours, according to the current definition.

Cetuximab

3.2 Cetuximab has a marketing authorisation in the UK for treating "patients with epidermal growth factor receptor-expressing (EGFR), RAS wild-type metastatic colorectal cancer:

- in combination with irinotecan-based chemotherapy,

- in first-line in combination with FOLFOX [fluorouracil, folinic acid and oxaliplatin],
- as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan."

Cetuximab is given via intravenous infusion once a week. The initial dose is cetuximab 400 mg/m^2 body surface area. All subsequent weekly doses are 250 mg/m^2 cetuximab.

3.3 The summary of product characteristics states that the most frequently reported adverse reactions associated with the use of cetuximab are: skin reactions, which occur in more than 80% of people; hypomagnesaemia, which occurs in more than 10% of people; and infusion-related reactions, which occur with mild-to-moderate symptoms in more than 10% of people and with severe symptoms in more than 1% of people. For full details of adverse reactions and contraindications, see the summary of product characteristics.

3.4 Cetuximab costs £178.10 per 20 ml vial and £890.50 per 100 ml vial (excluding VAT, British national formulary [BNF] online October 2015). The company has agreed a patient access scheme with the Department of Health. If cetuximab had been recommended, this scheme would provide a simple discount of 35.6% to the list price of cetuximab, with the discount applied at the point of purchase or invoice. The Department of Health considered that this patient access scheme would not constitute an excessive administrative burden on the NHS.

Panitumumab

3.5 Panitumumab has a marketing authorisation in the UK for treating "adult patients with wild-type RAS metastatic colorectal cancer (mCRC):

- in first-line in combination with FOLFOX or FOLFIRI [folinic acid, fluorouracil and irinotecan].
- in second-line in combination with FOLFIRI for patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan).
- as monotherapy after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens."

Panitumumab at a dose of 6 mg/kg of bodyweight is given via intravenous infusion once every 2 weeks.

3.6 The summary of product characteristics states that the most frequently reported adverse reactions associated with the use of panitumumab are skin reactions, which occur in 93% of people. Most of these reactions are mild to moderate in nature, 25% are severe and less than 1% are life threatening. For full details of adverse reactions and contraindications, see the summary of product characteristics.

3.7 Panitumumab costs £379.29 per 5 ml vial and £1517.16 per 20 ml vial (excluding VAT, BNF online October 2015). The company has agreed a patient access scheme with the Department of Health. If panitumumab had been recommended, this scheme would provide a simple discount to the list price of panitumumab with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme would not constitute an excessive administrative burden on the NHS.

4 Evidence and interpretation

The Appraisal Committee (section 7) considered evidence from a number of sources (section 8).

Clinical effectiveness

4.1 The Assessment Group included 3 key clinical trials of cetuximab and panitumumab in its base-case model: OPUS, CRYSTAL, and PRIME (see Table 1).

Table 1 Summary of clinical trials included in Assessment Group base-case model

	Trial	Intention-to-treat population	People with RAS wild-type	Intervention	Comparator
CET	OPUS[1]	337	87	CET+FOLFOX	FOLFOX
	CRYSTAL	1198	367	CET+FOLFIRI	FOLFIRI
PAN	PRIME[1]	1183	512	PAN+FOLFOX	FOLFOX

[1]The Assessment Group used PRIME as the baseline trial for the FOLFOX network in their base-case cost-effectiveness model because PRIME was larger than OPUS.
Abbreviations: CET, cetuximab; FOLFIRI, folinic acid+fluorouracil+irinotecan; FOLFOX, folinic acid+fluorouracil+oxaliplatin; PAN, panitumumab; RAS, rat sarcoma.

4.2 The Assessment Group did a network meta-analysis to compare:

- cetuximab plus chemotherapy with chemotherapy alone
- panitumumab plus chemotherapy with chemotherapy alone
- cetuximab plus chemotherapy with panitumumab plus chemotherapy (see Table 2).

The Assessment Group could not construct a complete network based on the trials it identified, so instead it generated 2 discrete networks: 1 evaluating chemotherapy regimens containing fluorouracil, folinic acid and oxaliplatin (FOLFOX; known as the FOLFOX network); the other comparing chemotherapy regimens containing folinic acid, fluorouracil and irinotecan (FOLFIRI; known as the FOLFIRI network). Merck Serono, the manufacturer of cetuximab, constructed a complete network using the CALGB-80405 trial, which compared cetuximab plus FOLFOX or

FOLFIRI with bevacizumab plus FOLFOX or FOLFIRI. The Assessment Group excluded this trial because it did not randomly allocate patients to FOLFOX or FOLFIRI, and the trial is available only as an abstract. Results from the Assessment Group's 2 discrete networks are not directly comparable (see Table 2). The Assessment Group concluded from the results that:

- there was no evidence to suggest that cetuximab plus FOLFOX is any more effective than either FOLFOX alone or than panitumumab plus FOLFOX at improving overall survival or progression-free survival
- there was little evidence to show that cetuximab plus FOLFOX improves overall response rate compared with panitumumab plus FOLFOX
- there was some evidence to show that cetuximab plus FOLFOX is associated with fewer adverse events compared with panitumumab plus FOLFOX
- cetuximab plus FOLFIRI is more effective than FOLFIRI at improving overall survival, progression-free survival and overall response rate
- panitumumab plus FOLFOX is more effective than FOLFOX at improving overall survival and progression-free survival.

4.3 The Assessment Group stated that the clinical evidence was limited because it reflected subgroup analyses. The trials were analysed post-hoc after re-evaluating tumour samples from people with KRAS wild-type exon 2 tumours, and reclassifying them by RAS wild-type status as currently defined. The Assessment Group noted that there were few samples available for re-analysis and missing data further reduced the power of some studies. The Assessment Group stated that the trial populations were generally balanced with respect to baseline characteristics, which lessened confounding bias.

Table 2 Summary of results from Assessment Group's network meta-analysis (fixed-effect model)

	PFS, HR (95%CrI)	OS, HR (95% CrI)	Complete resection rate, OR (95% CrI)
RAS wild-type			
CET+FOLFOX versus FOLFOX	0.53 (0.27, 1.04)[1]	0.94 (0.56, 1.56)[1]	NE
CET+FOLFOX versus PAN+FOLFOX	0.74 (0.36, 1.49)	1.22 (0.71, 2.11)	NE
PAN+FOLFOX versus FOLFOX	0.72 (0.58, 0.90)[2]	0.77 (0.64, 0.93)[2]	Data academic in confidence
CET+FOLFIRI versus FOLFIRI	0.56 (0.41, 0.76)[3]	0.69 (0.54, 0.88)[3]	NE
RAS wild-type with metastases confined to the liver			
CET+FOLFOX versus FOLFOX	0.35 (0.06, 1.96)[1]	0.90 (0.33, 2.43)[1]	4.63 (0.20, 104.60)[1]
CET+FOLFOX versus PAN+FOLFOX	0.44 (0.07, 2.66)	1.29 (0.42 3.94)	2.09 (0.08, 56.28)
PAN+FOLFOX versus FOLFOX	0.79 (0.49, 1.27)[2]	0.69 (0.42, 1.15)[2]	2.20 (0.80, 6.07)[2]

[1]Direct evidence from OPUS; [2]direct evidence from PRIME; [3]direct evidence from CRYSTAL
Abbreviations: CET, cetuximab; CrI, credible interval; FOLFIRI, folinic acid+fluorouracil+irinotecan; FOLFOX, folinic acid+fluorouracil+oxaliplatin; HR, hazard ratio; NE, not evaluable (no data available); OR, odds ratio; OS, overall survival; PAN, panitumumab; PFS, progression-free survival; RAS, rat sarcoma.

Cost effectiveness

4.4 Both cetuximab and panitumumab had a patient access scheme (price discount) agreed with the Department of Health. Only the panitumumab patient access scheme is commercial in confidence. To protect the confidentiality of this patient access scheme, NICE requested that the companies provide the results of their base-case, cost-effectiveness and sensitivity analyses using the list prices of cetuximab and panitumumab. NICE requested that the Assessment Group provide the results of its own model including the list prices and, separately in a confidential appendix, incorporating both discounts.

Company submissions

4.5 Amgen, the manufacturer of panitumumab, did not submit an economic model. Merck Serono, the manufacturer of cetuximab, did submit an economic model.

4.6 Merck Serono's model had 5 health states: first-line progression-free survival; second-line progressive disease; third-line progressive disease; post-resection; and dead. People remained in first-line progression-free survival until they moved to either post-resection or to further lines of treatment. Merck Serono used head-to-head trial data in its economic model. It stated that this was because there was significant uncertainty in the results of its network meta-analysis. The model had a cycle length of 1 month and a time horizon of 10 years. The Assessment Group considered that the time horizon was too short because Merck Serono estimated that 12% of people are still alive 10 years after resection.

4.7 Merck Serono submitted 2 models: 1 for the overall RAS wild-type population and 1 for a subgroup with metastases confined to the liver. Merck Serono stated that parameter values that were unique to the subgroup model were the proportion of people who have surgical resection and the duration of progression-free survival for people who do not have surgical resection. The Assessment Group received the subgroup model late in the review period and were unable to reconcile the subgroup analysis with the overall population model, so did not critique the subgroup analysis.

4.8 In Merck Serono's base case, it compared:

- cetuximab plus FOLFOX4 with FOLFOX4
- cetuximab plus FOLFIRI with FOLFIRI
- cetuximab plus FOLFIRI with bevacizumab plus FOLFIRI.

Merck Serono provided results based on weekly dosing of cetuximab, the dosage recommended in the marketing authorisation, and also for fortnightly dosing of cetuximab, which is not specified in the marketing authorisation. NICE can issue guidance only within the marketing authorisation, so only results based on weekly dosing of cetuximab are relevant. The results in this document are based on weekly dosing of cetuximab unless otherwise stated. Merck Serono compared cetuximab plus FOLFOX with XELOX in a scenario analysis.

4.9 In Merck Serono's deterministic base case of all patients, using the list price for cetuximab, the incremental cost-effectiveness ratios (ICERs) were £61,894 per quality-adjusted life year (QALY) gained for cetuximab plus FOLFOX and £74,212 per QALY gained for cetuximab plus FOLFIRI, compared with chemotherapy alone. Cetuximab plus chemotherapy produced approximately 0.3 extra QALYs compared with chemotherapy alone. Merck Serono did not provide estimates of cost effectiveness for the subgroup of people with metastases confined to the liver who have cetuximab weekly.

4.10 The company did one way sensitivity analyses around its base case using list prices for cetuximab. For comparisons with either FOLFOX or FOLFIRI, the 5 parameters that had the largest effect on the ICERs were:

- costs of treatment as a function of treatment duration and body surface area
- duration of progression-free survival
- utility associated with progression-free survival
- proportion of people who have liver resection.

Assessment Group's model

4.11 The Assessment Group model simulated a cohort of people with RAS wild-type metastatic colorectal cancer starting on first-line

treatment. It used a cycle length of 1 month and a time horizon of 30 years; the model predicted that most people had died by 20 years from start of treatment. In its base case, the Assessment Group used the results of its network meta-analysis to compare:

- cetuximab plus FOLFOX4 with FOLFOX4
- cetuximab plus FOLFIRI with FOLFIRI
- panitumumab plus FOLFOX4 with FOLFOX4.

The Assessment Group assessed other comparators in scenario analyses: FOLFOX6; bevacizumab plus FOLFOX or FOLFIRI; and XELOX.

4.12 The Assessment Group assumed that a proportion of people having first-line treatment then have surgery to resect liver metastases; the Assessment Group calculated this separately for each treatment arm. For people who do not have resection despite first-line treatment, the Assessment Group modelled: first-line progression-free survival for each therapy; second-line treatment with FOLFOX or FOLFIRI; and third-line treatment with best supportive care. For people who have resection, the Assessment Group did not model further treatments; instead, it modelled progression-free survival and progressed disease post-resection. In the model, people who had resections lived longer than people who did not have resections.

4.13 As in the Merck Serono model, differences in clinical effectiveness between first-line drug treatments were represented by the differences between:

- duration of progression-free survival on first-line treatments
- proportion of people who have surgical resection
- incidence of adverse events.

The Assessment Group derived utility values from trial-based EQ-5D data from the KRAS wild-type population.

4.14 The Assessment Group assumed in its base-case analysis that the duration of survival after first-line treatment was independent of first-line treatment (that is, any treatment effect from first-line drugs stopped when disease progressed). By contrast, in the randomised controlled trials, overall survival reflected response to both first and subsequent lines of treatment. However, the Assessment Group considered it inappropriate to assume this in its model because the trials included second-line drugs that are not commonly used in the NHS (including second-line panitumumab, cetuximab and bevacizumab) and may prolong survival. It also noted that second-line treatments were imbalanced across the trial arms. In addition, it considered that the survival data from trials were not mature enough. Therefore the Assessment Group modelled only progression-free survival from the randomised controlled trials, not overall survival. Merck Serono used the same approach to calculating overall survival in its economic model.

4.15 For the subgroup analysis of people with metastases confined to the liver, the Assessment Group assumed that the following parameters had the same values in this subgroup as for the full population:

- how long after starting first-line treatment people have resection of liver metastases
- how long people live who have not had surgical resection
- how long people live after resection
- how long people remain progression-free after resection
- utilities
- costs
- adverse events.

Parameter values that were unique to the subgroup of people with metastases confined to the liver were:

- proportion of people who have surgical resection
- duration of progression-free survival for people who have not had surgical resection
- duration of first-line treatment.

4.16 The Assessment Group predicted slightly longer life expectancy in the liver metastases subgroup (1.8–3.0 years) compared with all patients (1.7–2.4 years) because it predicted that a higher proportion of patients would have resection of liver metastases in this subgroup compared with all patients.

4.17 Although Merck Serono and the Assessment Group used the same overall model structure, the Assessment Group noted 8 key differences between the 2 models, which resulted in different ICERs for cetuximab plus chemotherapy compared with chemotherapy alone:

- **Duration of first-line treatment.** The Assessment Group considered that Merck Serono underestimated the mean duration of treatments. This resulted in lower drug acquisition costs and lower ICERs than the Assessment Group's estimates. The Assessment Group noted that treatment duration was the most important issue explaining the difference between the results of the Merck Serono model and the Assessment Group's model.
- **Proportion of patients who have resection.** Although Merck Serono and the Assessment Group both estimated resection rates using data from randomised controlled trials, the company assumed a lower proportion of patients have resection after treatment with cetuximab plus FOLFOX than did the Assessment Group (7.3% compared with 20.7%). On this basis,

the Assessment Group estimated lower ICERs than Merck Serono. The company also estimated lower resection rates with FOLFOX treatment than the Assessment Group:

- **Duration of progression-free survival in patients who have not had resection of liver metastases.** The Assessment Group considered that the Merck Serono model overestimated this parameter by using data from all patients (those who had their tumours resected and those whose tumours were not resected), which resulted in lower ICERs than the Assessment Group.
- **Post-resection progression-free survival and progressive disease.** Merck Serono assumed shorter durations, and therefore estimated higher ICERs, than the Assessment Group.
- **Drug administration unit costs.** Merck Serono assumed lower costs, which reduced the ICERs, compared with the Assessment Group. During consultation of the assessment report, Merck Serono suggested that the Assessment Group's estimates included double-counting.
- **Drug acquisition costs per month.** Merck Serono assumed lower costs for cetuximab, and therefore lower ICERs, than the Assessment Group. Merck Serono used higher costs for FOLFOX and FOLFIRI than the Assessment Group, which does not impact cost effectiveness because both treatment arms are affected similarly.
- **Cost of a resection operation**. Merck Serono assumed a lower cost, which resulted in lower ICERs, compared with the Assessment Group.
- **Monthly cost of post-resection progressive disease**. Merck Serono assumed lower costs, which resulted in lower ICERs, compared with the Assessment Group.

When the Assessment Group applied its preferred assumptions to Merck Serono's model, the results were similar to the results of its own model.

4.18 The Assessment Group highlighted a number of uncertainties in its own model:

- **Estimates of progression-free survival.**
  - The evidence for cetuximab was not as strong as the evidence for panitumumab because the OPUS trial of cetuximab had fewer patients with RAS wild-type cancer (n=87) than the PRIME trial of panitumumab (n=512).
  - Because the Assessment Group did not have access to individual patient data, it could only approximate how progression-free survival differs between patients who do or do not have resection.
  - The Assessment Group used a study by Adam et al. (2004) to estimate the duration of progression-free survival and overall survival, but acknowledged that these data are several years old, and that no patients in the study had had either cetuximab or panitumumab.
  - The Assessment Group noted that the analysis of the subgroup with metastases only in the liver is subject to more uncertainty than analyses of the overall population because Assessment Group had to make additional assumptions to estimate progression-free survival in these patients.
- **Treatment effect (overall survival).** The Assessment Group did not model overall survival directly from the randomised controlled trials; it estimated overall survival by adding up the duration on first-, second- and third-line treatments for patients who had not had resection, and from the life expectancy of patients who had had resection. It acknowledged that this introduced uncertainty in the model, and explored the impact of

using survival data directly from randomised controlled trials in a scenario analysis.

- **Proportion of patients who have resection.** The Assessment Group stated that its estimated proportion of patients who have resection with cetuximab plus FOLFOX (20.7%) was uncertain because it was based on an indirect comparison.

4.19 In the Assessment Group's base-case analysis of all patients, both cetuximab plus chemotherapy and panitumumab plus chemotherapy generated more QALYs than for chemotherapy alone: 0.15–0.35 more QALYs compared with FOLFOX and 0.30 QALYs compared with FOLFIRI. However, the additional costs using list prices were substantial: up to about £69,000 for cetuximab or panitumumab compared with FOLFOX or FOLFIRI. When the Assessment Group used the list prices for panitumumab and cetuximab, the ICERs compared with chemotherapy alone were £239,007 per QALY gained for panitumumab plus FOLFOX, £165,491 per QALY gained for cetuximab plus FOLFOX, and £227,381 per QALY gained for cetuximab plus FOLFIRI. When the Assessment Group used the discounted price for panitumumab (discount commercial in confidence), the ICER was substantially above £30,000 per QALY gained compared with FOLFOX. When the Assessment Group used the discounted price for cetuximab, the ICERs were about £135,000 per QALY gained for cetuximab plus FOLFOX and £183,000 per QALY gained for cetuximab plus FOLFIRI, both compared with chemotherapy alone.

4.20 In the Assessment Group's base-case analysis of the subgroup of people with metastases confined to the liver, cetuximab and panitumumab produced more incremental QALYs than chemotherapy alone (0.40–0.57) and the ICERs were lower than for the full population. The ICERs for cetuximab (using the discounted price) plus chemotherapy were about £130,000 per

QALY gained compared with chemotherapy alone. The ICER for panitumumab (using the confidential discounted price) plus chemotherapy was substantially above £30,000 per QALY gained compared with chemotherapy alone. NICE cannot report the exact ICERs for panitumumab because the patient access scheme is confidential.

4.21 The Assessment Group explored the impact of using survival data directly from randomised controlled trials in a scenario analysis of all patients (it did not report results for people with metastases confined to the liver). After consultation, the Assessment Group updated the scenario analysis to adjust for drugs used second-line in the randomised controlled trials that are also not commonly used in the NHS. The ICER for cetuximab plus FOLFOX (using the discounted price for cetuximab) compared with FOLFOX, increased above the £135,000 per QALY gained in the Assessment Group's base case. The ICER for cetuximab (using the discounted price) plus FOLFIRI decreased from £183,000 to £123,000 per QALY gained. The ICER for panitumumab (using the discounted price) plus FOLFOX also decreased from the base case, but remained substantially above £30,000 per QALY gained.

4.22 In the Assessment Group's deterministic sensitivity analysis, the ICERs were very sensitive to the:

- proportion of patients who have resection
- length of progression-free survival after resection
- life expectancy (overall survival) after resection
- duration of progression-free survival for patients who have not had resection
- treatment duration.

4.23 The Assessment Group presented data for the NICE end-of-life criteria for cetuximab and panitumumab, for all patients (see Table 3). The NICE technical team extracted data from the assessment report relevant to the subgroup of people with metastases confined to the liver (Table 4).

Table 3 End-of-life considerations: all patients with RAS wild-type metastatic colorectal cancer

	CET+FOLFOX compared with FOLFOX	**CET+FOLFIRI compared with FOLFIRI**	**PAN+FOLFOX compared with FOLFOX**
Short life expectancy, normally <24 months	Months, mean: 22.3 (AG model) 26.7 (PRIME)	Months, mean: 21.0 (AG model) 24.9 (CRYSTAL)	Months, mean: 22.3 (AG model) 26.7 (PRIME)
Extension to life, normally ≥3 months	Months, mean: 6.6 (AG model) 0.5 (OPUS)	Months, mean: 5.5 (AG model) 8.8 (CRYSTAL)	Months, mean: 2.6 (AG model) 5.7 (PRIME)
Licensed for <7000 people in England (all indications)	• 8,807 (data in TA176, incl other indications and updated to reflect RAS wt subgroup) • 7,567 (Merck Serono data, updated to reflect England only and incl all indications) • 11,349 (data cited in assessment report)		• 5,968 (data in TA176, updated to reflect RAS wt subgroup) • 4,728 (Merck Serono data, updated to England only) • 8,511 (data cited in assessment report)
Note that the indications for cetuximab and panitumumab differ; cetuximab is also approved for treating squamous cell cancer of the head and neck. Abbreviations: AG, Assessment Group; CET, cetuximab; FOLFIRI, folinic acid+fluorouracil+irinotecan; FOLFOX, folinic acid+fluorouracil+oxaliplatin; incl, including; PAN, panitumumab; TA, NICE technology appraisal guidance; wt, wild-type.			

Table 4 End-of-life considerations: subgroup of patients with RAS wild-type metastatic colorectal cancer; metastases confined to the liver

	CET+FOLFOX compared with FOLFOX	CET+FOLFIRI compared with FOLFIRI	PAN+FOLFOX compared with FOLFOX
Short life expectancy, normally <24 months	Months: 26.5 (AG model, mean) 33.4 (PRIME, median)	Months: 22.0 (AG model, mean) 29.5 (CRYSTAL, median)	Months: 26.5 (AG model, mean) 33.4 (PRIME, median)
Extension to life, normally ≥3 months	Months: 9.2 (AG model, mean) −0.9 (OPUS, median)	Months: 10.3 (AG model, mean) 0.3 (CRYSTAL, median)	Months: 7.8 (AG model, mean) 7.3 (PRIME, median)
Licensed for <7000 people in England (all indications)	See table 3		
Note that the indications for cetuximab and panitumumab differ; cetuximab is also approved for treating squamous cell cancer of the head and neck. Abbreviations: AG, Assessment Group; CET, cetuximab; FOLFIRI, folinic acid+fluorouracil+irinotecan; FOLFOX, folinic acid+fluorouracil+oxaliplatin; PAN, panitumumab.			

Consideration of the evidence

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of cetuximab and panitumumab, having considered evidence on the nature of RAS wild-type metastatic colorectal cancer and the value placed on the benefits of cetuximab and panitumumab by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

4.24 The Committee heard that the population under consideration in this technology appraisal guidance differed from the population in the original appraisal on cetuximab for the first-line treatment of metastatic colorectal cancer. It understood that the current appraisal is restricted to people with metastatic colorectal cancer whose tumours do not have any mutations in any of the RAS genes

(known as RAS wild-type status). The Committee noted that cetuximab and panitumumab are licensed for treating RAS wild-type metastatic colorectal cancer, which responds better to cetuximab and panitumumab than tumours with RAS mutations. The Committee heard that testing for RAS wild-type status is routinely available in clinical practice, and that about half of people with metastatic colorectal cancer have RAS wild-type tumours. The Committee understood the rationale for reviewing the previous technology appraisal.

Clinical practice

4.25 The Committee discussed the current management of metastatic colorectal cancer and considered who would be eligible for surgical resection of metastases. It heard that resection improves prognosis. The Committee heard from clinical experts that surgical resection would not be considered for people with widespread metastases (that is, tumours in many parts of the body); it heard that these people would be given up to 3 lines of chemotherapy treatment. Clinical experts noted that resection is usually only done if metastases are confined to the liver but, in people with a low number of resectable metastases outside the liver (for example, in the lung), resection of liver metastases may be considered. The Committee heard that patients with small numbers of resectable metastases confined to the liver (about 1–3 metastases) may proceed to surgery without any chemotherapy. The Committee heard that, if there are more than 4 or 5 metastases in the liver or if resecting them would remove too much of the liver, chemotherapy can be given before surgery to shrink the liver metastases and make them resectable. Clinical experts explained that they use first-line chemotherapy for 8–12 weeks, at which point they assess whether the patient is eligible for resection. People who, at that point, are not eligible for resection would be offered up to 3 lines of different chemotherapy treatments. The clinical experts suggested

that resection is successful in about 90% of people. The Committee heard that, of patients who have successful resection, about half experience disease progression, at which point they may be offered repeat surgery followed by more chemotherapy. The Committee concluded that the aim of chemotherapy is to shrink tumours to make them resectable, and that chemotherapy is also given to people for whom surgery is not appropriate because of widespread metastases.

4.26 The Committee considered the chemotherapy regimens used in clinical practice in England. It heard from clinical experts that combinations including oxaliplatin (FOLFOX) and irinotecan (FOLFIRI) are used to treat RAS wild-type tumours. The Committee understood that there are 2 types of FOLFOX treatment: FOLFOX4 and FOLFOX6, and heard from experts that FOLFOX6 is more commonly used in clinical practice in England. The Committee heard that FOLFOX4 and FOLFOX6 are equally effective, but that FOLFOX6 costs more than FOLFOX4. Clinical experts noted that single-agent chemotherapies such as capecitabine may be used in a few people with small tumours (known as low volume) and no symptoms. The Committee heard that the Assessment Group excluded capecitabine from its analysis because capecitabine is usually offered to people if combination chemotherapy is unsuitable; therefore, capecitabine is not relevant when considering cetuximab and panitumumab because their marketing authorisations recommend that they are taken with combination chemotherapy. The Committee concluded that the Assessment Group had included the appropriate comparators in its base case, and noted that a scenario analysis provided results for FOLFOX6.

4.27 The Committee discussed the place of cetuximab and panitumumab in the treatment pathway. It understood that these drugs are combined with chemotherapy with the aim of making

initially unresectable tumours resectable. It heard from clinical experts that not all patients with unresectable tumours would be offered cetuximab or panitumumab. The clinical experts stated that cetuximab and panitumumab would be reserved for people with high volume, symptomatic disease where the treatment objective is to slow disease progression as soon as possible. The Committee heard that cetuximab is usually given with FOLFIRI and that panitumumab is usually given with FOLFOX, because there is a stronger evidence base for these combinations than for cetuximab plus FOLFOX or panitumumab plus FOLFIRI. The clinical experts suggested that cetuximab is more commonly used than panitumumab in England, because cetuximab is recommended by NICE. The Committee concluded that cetuximab and panitumumab would be offered as first-line treatments with chemotherapy to a subgroup of people with metastatic colorectal cancer: people who have symptomatic disease and high volume metastases, either inside or outside the liver, which are not initially resectable.

4.28 The Committee considered how long people would have cetuximab or panitumumab. It heard that clinicians use cetuximab for up to 16 weeks, based on NICE's technology appraisal guidance on cetuximab for the first-line treatment of metastatic colorectal cancer, and assess whether the patient's disease responds and is appropriate for resection at about 8 weeks. If the disease has progressed, treatment with cetuximab stops, but chemotherapy continues. The Committee heard that, where possible, treatment with cetuximab continues for longer than 16 weeks as long as the cancer is responding to treatment, even if resection is not possible. The Committee understood that, in clinical trials, first-line cetuximab or panitumumab is given until disease progression. But, it heard from clinical experts that clinical practice in the UK includes treatment holidays and so patients are not treated continuously until disease progression. The Committee concluded that treatment

duration with cetuximab or panitumumab in clinical trials may not reflect clinical practice in England.

Clinical effectiveness

4.29 The Committee discussed the clinical trial evidence for cetuximab and panitumumab in people with RAS wild-type metastatic colorectal cancer. It heard that the Assessment Group considered that survival data were not sufficiently mature, and that the size of the effect was confounded by the use of different second and subsequent lines of treatment across the trial arms. These treatments are associated with prolonged survival and are also not widely available in the NHS. The Committee heard from clinical experts that the trial populations were younger than patients seen in clinical practice. The Committee concluded that the populations in the clinical trials of cetuximab and panitumumab differed from patients in clinical practice in England, and that this difference was a source of uncertainty in the clinical- and cost-effectiveness results.

4.30 The Committee heard that the evidence for cetuximab and panitumumab in people with RAS wild-type colorectal cancer is based on post-hoc subgroup analyses of clinical trial data. The Committee understood that analyses were based on small data sets with missing data, which reduced the chance that these analyses would uncover true differences between treatments. The Committee concluded that, although the current data are more mature than in NICE's technology appraisal guidance on cetuximab for the first-line treatment of metastatic colorectal cancer, there is more uncertainty in the evidence base because it involved smaller populations.

4.31 The Committee heard from a patient expert about their treatment with cetuximab, noting that they had had 52 doses of cetuximab.

The patient expert explained that the key benefit of cetuximab treatment was that the adverse reactions (such as skin reactions) were much more manageable than the adverse reactions they had previously experienced with chemotherapy alone (including debilitating fatigue and neuropathy). The patient expert stated that they believed that cetuximab had extended their life, which they valued because it has enabled them to see their children grow up, to lead an active life and to improve their quality of life. The Committee considered that the benefits of cetuximab for the patient expert may not be fully generalisable to the patients covered in this appraisal because the patient expert had received cetuximab after, rather than before, resection of his liver metastases. The Committee heard from clinical experts that, although cetuximab plus chemotherapy is associated with more adverse events than chemotherapy alone, people rarely stop cetuximab because of adverse events whereas many stop FOLFOX and FOLFIRI for this reason. The Committee recalled that people treated in practice are older than those in the clinical trials, but heard from clinical experts that they would not expect to see more adverse events in practice than those reported in the clinical trials. The Committee concluded that adding cetuximab to chemotherapy provides benefits to patients with RAS wild-type metastatic colorectal cancer.

4.32 The Committee discussed the results of the Assessment Group's network meta-analysis. It heard that there was no evidence that cetuximab plus FOLFOX was more effective than FOLFOX alone, but understood from the clinical experts that cetuximab would be given with FOLFIRI, not FOLFOX, in clinical practice (see section 4.27). The Committee heard that the results of the network meta-analysis suggested that cetuximab plus FOLFIRI and panitumumab plus FOLFOX were more effective than chemotherapy alone. The Committee heard that the evidence for panitumumab plus FOLFOX compared with cetuximab plus FOLFOX was mixed, and it was

unclear whether 1 treatment was more effective than the other. It heard from clinical experts that cetuximab and panitumumab probably had similar efficacy, and panitumumab may be associated with a lower risk of hypersensitivity, although the Committee understood that the experts had limited experience using panitumumab in clinical practice in England. The Committee noted that the results of the network meta-analysis were subject to substantial uncertainties, and recognised that the credible intervals around the odds ratios were extremely large. It recalled the uncertainty associated with the individual clinical trials. The Committee would have preferred to see a complete network rather than 2 separate networks for FOLFOX- and FOLFIRI-containing regimens, but it understood that this was difficult with the evidence available. The Committee concluded that the clinical evidence surrounding the degree to which cetuximab and panitumumab are effective in RAS wild-type metastatic colorectal cancer was subject to considerable uncertainty.

Cost effectiveness

4.33 The Committee compared the economic model submitted by Merck Serono with the Assessment Group's model and understood that the models shared the same overall structure. It heard that neither Merck Serono nor the Assessment Group modelled overall survival from the clinical trials and that the ICERs were sensitive to different methods for estimating survival. The Committee understood that the Assessment Group used a French study by Adam et al. (2004), in which patients had resection for primarily unresectable colorectal liver metastases downstaged by chemotherapy, to estimate overall survival and progression-free survival in its model. The Committee had some concerns that these data are several years old, and that no patients in the Adam et al. study had either cetuximab or panitumumab. The Committee would have preferred to see a model based on survival data from trials, but understood that the

trial data for cetuximab and panitumumab may have been confounded by second-line drugs that are not commonly used in the NHS. The Committee noted that the Assessment Group had adjusted for subsequent treatments in a scenario analysis incorporating trial data, but heard that the Assessment Group had concerns about the robustness of the methods used, and the reliability of the results. The Committee concluded that, in general, it would prefer to see trial-based survival modelled, but it recognised the limitations associated with using trial data in this instance.

4.34 The Committee considered whether the Assessment Group's model reflected clinical practice. It understood from clinical experts that people who develop progressive disease after successful resection of liver metastases have chemotherapy, but noted that the model did not allow for this. The Committee also recalled that resection is not successful in about 10% of people, and noted that the Assessment Group included an estimate of 5%. The Committee heard that the Assessment Group had modelled an average of 1.6 resection operations per patients, which the clinical experts noted reflected clinical practice. The Committee concluded that the model included uncertainties, but was an adequate basis for its decision-making.

4.35 The Committee noted that the estimates of the duration of first-line treatment differed in the models from Merck Serono and the Assessment Group. It understood from clinical experts that, in England, first-line treatment does not continue uninterrupted until disease progression. The clinical experts stated that people who have resection generally have treatment for between 8 and 12 weeks. For those who cannot have resection, treatment holidays are part of standard practice (see section 4.28). The clinical experts therefore considered that the Assessment Group had

overestimated treatment duration in its model. The Committee heard from the Assessment Group that it preferred to use the treatment durations from clinical trials because the effectiveness estimates in the model use trial data. The Assessment Group noted that, because the estimates of effectiveness in the trials followed directly from the duration of treatment in the trials, modellers should not source these estimates separately. The clinical experts advised that Merck Serono's estimates of treatment duration better reflected clinical practice in England than the Assessment Group's. However, the Committee heard that the Assessment Group was unable to validate Merck Serono's estimates of treatment duration because the company did not provide the underlying data. The Committee considered that more realistic estimates of treatment duration in England would come from a real-world database such as the one set up by the Cancer Drugs Fund. The Committee concluded that the Assessment Group's estimates of treatment duration may not reflect clinical practice, and would have preferred to see the model validated with observational data.

4.36 The Committee discussed the Assessment Group's estimates of the proportion of people who have resection of liver metastases after first-line treatment. It heard from clinical experts that, for patients whose tumours are initially unresectable, chemotherapy with or without cetuximab or panitumumab could shrink the metastases enough to be resected in about 15% of people. The clinical experts explained that resection rates would be higher in the subgroup of people with metastases confined to the liver. The clinical experts advised that the resection rates for cetuximab and panitumumab chosen by the Assessment Group in its model were too high in both the overall population (in which, after first-line treatment, up to 20.7% of people had resection) and the subgroup of people with metastases confined to the liver (in which, after first-line treatment, up to 31.3% of people had resection). The

Committee concluded that the Assessment Group had overestimated resection rates associated with cetuximab and panitumumab.

4.37 The Committee discussed other key differences between the Assessment Group's model and Merck Serono's model. It concluded:

- Merck Serono overestimated the duration of progression-free survival for patients whose tumours had not been resected; the Assessment Group's estimates were more plausible.
- The Assessment Group estimated drug administration costs appropriately; double-counting of costs was unlikely and would not substantially affect the ICERs.
- The Assessment Group's estimate for average body surface area (1.85m^2) was plausible.
- The Assessment Group's estimate for the cost of resection surgery (£10,440) was more plausible than Merck Serono's estimates of £2707 in its original submission.

4.38 Having noted that the population considered in this technology appraisal guidance differed from the population in the original appraisal on cetuximab for the first-line treatment of metastatic colorectal cancer (see section 4.24), the Committee compared the economic model submitted for the original appraisal of cetuximab with the model in the current appraisal. It noted the following key differences:

- Duration of treatment with cetuximab was shorter in the original appraisal when the company applied a 16-week stopping rule. In the current appraisal, treatment duration ranged from 38–46 weeks in the Assessment Group's model and 25 weeks in the Merck Serono model, which the Committee had concluded were overestimates (see section 4.35). The Committee noted that a

stopping rule had not been explored as part of the current modelling.

- Resection rates were higher in the original appraisal, ranging from 30–43% compared with about 7–31% in the current appraisal. These were based on clinical expert opinion and the results of an open-label phase II trial comparing cetuximab plus FOLFOX with cetuximab plus FOLFIRI (the CELIM trial). The Committee heard that the CELIM trial studied a specific subgroup of people with KRAS wild-type metastatic colorectal cancer who had metastases confined to the liver, good performance status and who were fit for surgery. It considered that the population in the CELIM trial was narrower than the population relevant to the current appraisal.

4.39 The Committee discussed the Assessment Group's base-case results for cetuximab and panitumumab, with the discounts applied.

- In the overall population, the ICER for cetuximab was about £135,000 per QALY gained when it was combined with FOLFOX and £183,000 per QALY gained when combined with FOLFIRI, both compared with chemotherapy alone. The Committee noted that the ICER for panitumumab plus FOLFOX was also substantially above £30,000 per QALY gained compared with FOLFOX.
- The ICERs for cetuximab and panitumumab were lower in the subgroup of people with metastases confined to the liver. The ICER for cetuximab was about £127,000 per QALY gained when it was combined with FOLFOX and £129,000 per QALY gained when combined with FOLFIRI, both compared with chemotherapy alone. The ICER for panitumumab plus FOLFOX remained substantially above £30,000 per QALY gained compared with FOLFOX. NICE cannot report the exact ICERs

for panitumumab because the patient access scheme is confidential.

- The Committee considered its preferred assumptions and how each affected the ICERs for cetuximab and panitumumab:
  - **FOLFOX6 instead of FOLFOX4:** the Committee heard that the ICERs did not change substantially in the Assessment Group's scenario analysis using the higher-cost FOLFOX6 instead of FOLFOX4.
  - **Modelling overall survival using trial data**: the Committee heard that modelling overall survival using trial data reduced the ICERs for cetuximab plus FOLFIRI and for panitumumab plus FOLFOX. However, the Committee noted that the ICERs remained substantially higher than £30,000 per QALY compared with chemotherapy alone.
  - **Proportion of people who have resection**: the Committee understood from the clinical experts that the Assessment Group had overestimated resection rates. The Assessment Group had not presented ICERs using lower resection rates, but informed the Committee that lower resection rates would increase the ICERs and worsen cost effectiveness.
  - **Treatment duration:** the Committee understood from the clinical experts that the Assessment Group had overestimated treatment duration. The Assessment Group did not present ICERs using shorter treatment durations, but informed the Committee that reducing treatment duration would decrease the ICERs.

The Committee acknowledged that the clinical experts had advised that cetuximab and panitumumab would be used only in a small subgroup of people with metastatic colorectal cancer (even smaller than the population in the marketing authorisation), but noted that it had not seen evidence in this group. It noted that the model was

associated with many uncertainties: the clinical trials were subject to bias from post-hoc analysis and may or may not be generalisable to clinical practice in England; the effectiveness estimates from the network meta-analysis were uncertain; and the model structure did not wholly reflect current disease management. The Committee concluded that the ICERs presented were associated with considerable uncertainty, and were all substantially higher than what is normally considered to be an appropriate use of NHS resources.

4.40 The Committee considered supplementary advice from NICE that Committees should take into account when appraising treatments that may extend the life of patients with a short life expectancy and that are licensed for indications affecting small numbers of people with incurable illnesses. For this advice to be applied, all the following criteria must be met:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months.
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.
- The treatment is licensed or otherwise indicated for small patient populations (normally less than 7000 people).

In addition, the Committee must be persuaded that the estimates of the extension to life are robust, and that the assumptions used in the reference case of the economic modelling are plausible, objective and robust.

4.41 The Committee was presented with the Assessment Group's assessment of cetuximab and panitumumab against the NICE end-of-life criteria (see Table 3 and Table 4).

- The Committee first considered the licensed populations for cetuximab and panitumumab. It heard 3 estimates of population size based on the marketing authorisation of cetuximab; all exceeded 7000. Of the 3 estimates for panitumumab, 1 was above 7000 and 2 were lower than 7000. The Committee considered that cetuximab did not meet the criterion of small population size, and that there was uncertainty about whether panitumumab met the criteria.
- The Committee then considered the life expectancy of people with RAS wild-type metastatic colorectal cancer, using estimates from the Assessment Group's model. It noted that mean life expectancy estimates were below 24 months in the overall patient population. It therefore accepted the criterion of short life expectancy. It heard from clinical experts that life expectancy is longer for the subgroup of people with metastases confined to the liver, and noted that the mean estimates from the Assessment Group model exceeded 24 months. The Committee did not accept that the criterion of short life expectancy was met for the subgroup with metastases confined to the liver.
- The Committee considered the extension to life with cetuximab and panitumumab in all patients, based on the estimates in the Assessment Group model. It noted that estimates were above a mean of 3 months for cetuximab, but not for panitumumab. However, because clinical experts considered that cetuximab and panitumumab were probably equally effective, the Committee concluded that both cetuximab and panitumumab met the criterion of extension to life when considering all patients. The Committee noted that, based on the Assessment Group's model, the estimates for the time that cetuximab and panitumumab extended life were higher for the subgroup of people with metastases confined to the liver compared with the overall population. It had concerns about whether these

estimates were robust because the clinical trial estimates were much lower and, in one instance, suggested that patients live longer with chemotherapy alone (see Table 4) than with biological therapy. The Committee recalled hearing from the clinical experts that patients in the clinical trials of cetuximab and panitumumab were younger and fitter than patients in clinical practice in England, so patients in clinical practice may not achieve the level of survival benefit estimated. The Committee considered that these estimates were not sufficiently robust.

The Committee concluded that neither cetuximab plus chemotherapy nor panitumumab plus chemotherapy fulfilled the NICE supplementary advice criteria to be considered as life-extending, end-of-life treatments. Its decisions are summarised in Table 5. The Committee also concluded that, even if the end-of-life criteria were met, an unacceptably large weighting would need to be put on the QALY to bring the ICERs for cetuximab and panitumumab into the range representing a cost-effective treatment.

Table 5 Summary of the Committee's conclusions about each end-of-life criterion

	Cetuximab plus FOLFOX/FOLFIRI	Panitumumab plus FOLFOX
All patients		
Short life expectancy, normally <24 months average	Criterion met	Criterion met
Extension to life, normally ≥3 months average	Criterion met	Criterion met
Licensed for <7000 people in England (all indications)	Criterion not met	Criterion probably not met
Patients with metastases confined to the liver		
Short life expectancy, normally <24 months average	Criterion not met	Criterion not met
Extension to life, normally ≥3 months average	Criterion probably met, estimates not robust	Criterion probably met, estimates not robust
Licensed for <7000 people in England (all indications)	Criterion not met	Criterion probably not met
Abbreviations: FOLFIRI, folinic acid+fluorouracil+irinotecan; FOLFOX, folinic acid+fluorouracil+oxaliplatin.		

4.42 The Committee considered whether it should take into account the consequences of the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism, when appraising cetuximab and panitumumab. The Appraisal Committee noted NICE's position statement in this regard, and accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The Committee heard nothing to suggest that there is any basis for taking a different view with regard to the relevance of the PPRS to this appraisal of cetuximab and panitumumab. It therefore concluded that the PPRS payment mechanism was not applicable for considering the cost effectiveness of cetuximab and panitumumab.

Summary of Appraisal Committee's key conclusions

TAXXX	Appraisal title:	Section
Key conclusion		
Cetuximab and panitumumab are not recommended within their marketing authorisations for previously untreated RAS wild-type metastatic colorectal cancer, that is, with 5-fluorouracil, folinic acid and oxaliplatin (FOLFOX) or with 5-fluorouracil, folinic acid and irinotecan (FOLFIRI). The incremental cost-effectiveness ratios (ICERs) presented were associated with considerable uncertainty, and were all substantially higher than what is normally considered to be an appropriate use of NHS resources.		1.1 4.39
Current practice		
Clinical need of patients, including the availability of alternative treatments	About 25% of people with colorectal cancer have metastases at diagnosis and almost 50% of people will develop metastases. When possible, surgically removing (resecting) the primary tumour and metastases is considered, but usually only when there are no metastases outside of the liver. Chemotherapy regimens such as FOLFOX or FOLFIRI may be used before surgery, to shrink the metastases and make them suitable for resection.	2.1, 2.2, 2.3
The technology		
Proposed benefits	Cetuximab and panitumumab appear to	3.1

of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	be more effective for treating tumours without mutations (known as 'wild-type') in genes in the rat sarcoma (RAS) family than those with mutations. Since previous NICE technology appraisals of cetuximab and panitumumab, the European Medicines Agency has updated the marketing authorisations of both drugs to reflect a newer stricter definition of RAS wild-type status.	
What is the position of the treatment in the pathway of care for the condition?	Cetuximab and panitumumab may be combined with chemotherapy before surgery, to shrink metastases and make them suitable for resection. Cetuximab is recommended by NICE for 16 weeks for metastases confined to the liver, when certain conditions are met.	2.4, 4.27
Adverse reactions	The most frequently reported adverse reactions associated with the use of cetuximab and panitumumab are skin reactions.	3.3, 3.6
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The clinical evidence for cetuximab came from 2 key clinical trials: OPUS and CRYSTAL. The clinical evidence for panitumumab came from 1 key clinical trial: PRIME. Both trials compare cetuximab or panitumumab with combination treatments that do not	4.1, 4.30

	include these drugs. The evidence for cetuximab and panitumumab in people with RAS wild-type colorectal cancer is based on post-hoc subgroup analyses of clinical trial data.	
Relevance to general clinical practice in the NHS	The populations in the clinical trials differed from patients in clinical practice in England. For example, the trial populations were younger than patients seen in clinical practice, and the second and subsequent lines of treatment used in the trials are not widely available in the NHS.	4.29
Uncertainties generated by the evidence	Survival data from the clinical trials were not sufficiently mature, and the size of the effect was confounded by the use of different second and subsequent lines of treatment across the trial arms. These treatments are associated with prolonged survival. The effect of cetuximab and panitumumab was also potentially confounded by relying on post-hoc analyses. The difference between trial populations and real-world practice, and the true magnitude of benefit, was a source of uncertainty in the clinical- and cost-effectiveness results because the evidence for cetuximab and panitumumab was based on small data sets with missing data. This reduced the chance that these	4.29, 4.30

	analyses would uncover true differences between treatments.	
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The Committee discussed the clinical and cost effectiveness of cetuximab and panitumumab in a subgroup of people with metastases confined to the liver. It heard from clinical experts that people with metastases confined to the liver are more likely to have surgical resection, which it heard improves their prognosis.	4.36
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The Assessment Group's network meta-analysis showed that there was no evidence that cetuximab plus FOLFOX was more effective than FOLFOX alone, but the Committee understood from the clinical experts that cetuximab would be given with FOLFIRI, not FOLFOX, in clinical practice. The network meta-analysis suggested that cetuximab plus FOLFIRI and panitumumab plus FOLFOX were more effective than chemotherapy alone. It was unclear whether cetuximab or panitumumab was more effective than the other. Clinical experts suggested that cetuximab and panitumumab probably had similar efficacy. The results of the network meta-analysis were subject to considerable uncertainties, and the credible intervals around the odds ratios	4.32

	were extremely large.	
How has the new clinical evidence that has emerged since the original appraisal (TA176) influenced the current (preliminary) recommendations?	Although the current data are more mature than in NICE's technology appraisal guidance on cetuximab for the first-line treatment of metastatic colorectal cancer, there is more uncertainty in the evidence base because it involved smaller populations (based on the stricter definition of wild-type status in the new marketing authorisations).	3.1, 4.30
Evidence for cost effectiveness		
Availability and nature of evidence	The economic models submitted by Merck Serono and the Assessment Group shared the same overall structure, but differed in a number of parameter estimates.	4.33
Uncertainties around and plausibility of assumptions and inputs in the economic model	**Relevance to clinical practice:** the Assessment group's model did not allow for people who develop progressive disease after successful resection to have chemotherapy (which they would have in clinical practice). The Assessment Group may have underestimated the number of people in whom resection is not successful. **Overall survival and progression-free survival:** neither Merck Serono nor the Assessment Group modelled overall	4.18, 4.33, 4.34, 4.35, 4.36

	survival from the clinical trials, and the ICERs were sensitive to different methods for estimating survival; the Committee had concerns around this. Progression-free survival estimates were also subject to uncertainty. Because the Assessment Group did not have access to individual patient data, it could only approximate how progression-free survival differs between patients who do or do not have resection. **Treatment duration:** the Assessment Group may have overestimated treatment duration and therefore overestimated the ICERs; the Committee would have preferred to see the model validated with observational data. **Resection rates:** the Assessment Group overestimated the resection rates associated with cetuximab and panitumumab, and therefore underestimated the ICERs.	
Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-	Utility values were derived from trial based EQ-5D data. No benefits were identified that were not already included in the economic model.	4.13

related benefits been identified that were not included in the economic model, and how have they been considered?		
Are there specific groups of people for whom the technology is particularly cost effective?	The estimated ICERs for cetuximab and panitumumab were lower in people with metastases confined to the liver than in the overall population of people with RAS wild-type metastatic colorectal cancer.	4.39
What are the key drivers of cost effectiveness?	The duration of first-line treatment was the most important issue explaining the difference between the results of the Merck Serono model and the Assessment Group's model. The proportion of people who have resection of liver metastases was also a key driver. There were substantial uncertainties in the estimates for both parameters, and the Committee considered that the Assessment Group's estimates did not reflect clinical practice.	4.17, 4.35, 4.36, 4.39
Most likely cost-effectiveness estimate (given as an ICER)	The Committee noted the base-case ICERs, and further noted that the model was associated with many uncertainties: the clinical trials were subject to bias from post-hoc analysis, and may or may	4.39

	not be generalisable to clinical practice in England; the estimates of effectiveness from the network meta-analysis were uncertain; and the model structure did not wholly reflect current disease management. The Committee concluded that the ICERs presented were associated with considerable uncertainty, and were all substantially higher than what is normally considered to be an appropriate use of NHS resources.	
How has the new cost-effectiveness evidence that has emerged since the original appraisal (TA176) influenced the current (preliminary) recommendations?	Although the current data are more mature than in NICE's technology appraisal guidance on cetuximab for the first-line treatment of metastatic colorectal cancer, there is more uncertainty in the evidence base because it involved post-hoc analyses and smaller populations (based on the stricter definition of wild-type status in the new marketing authorisations).	3.1, 4.30
Additional factors taken into account		
Patient access schemes (PPRS)	Not applicable	4.42
End-of-life considerations	The Committee concluded that neither cetuximab plus chemotherapy nor panitumumab plus chemotherapy fulfilled the NICE supplementary advice criteria to be considered as life-extending, end-	4.41

	of-life treatments. The Committee also concluded that, even if the end-of-life criteria had been met, an unacceptably large weighting would need to be put on the quality-adjusted life year (QALY) to bring the ICERs for cetuximab and panitumumab into the range representative of a cost-effective treatment.	
Equalities considerations and social value judgements	Not applicable	-

5 Related NICE guidance

Details are correct at the time of consultation and will be removed when the final guidance is published. Further information is available on the NICE website.

Published

- Cetuximab, bevacizumab and panitumumab for the treatment of metastatic colorectal cancer after first-line chemotherapy (review of TA150 and part review of TA118). NICE technology appraisal guidance 242 (2012).
- The diagnosis and management of colorectal cancer. NICE clinical guideline 131 (2011).
- Panitumumab in combination with chemotherapy for the treatment of metastatic colorectal cancer (terminated appraisal). NICE technology appraisal guidance 240 (2011).

- Selective internal radiation therapy for non-resectable colorectal metastases in the liver. NICE interventional procedure guidance 401 (2011).
- Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for the treatment of metastatic colorectal cancer. NICE technology appraisal guidance 212 (2010).
- Cetuximab for the first-line treatment of metastatic colorectal cancer. NICE technology appraisal guidance 176 (2009).
- Radiofrequency ablation for colorectal liver metastases. NICE interventional procedure guidance 327 (2009).
- Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer. NICE technology appraisal guidance 118 (2007).
- Preoperative high dose rate brachytherapy for rectal cancer. NICE interventional procedure guidance 201 (2006).

6 Proposed date for review of guidance

6.1 NICE proposes that the guidance on this technology is considered for review by the Guidance Executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Amanda Adler

Chair, Appraisal Committee

November 2015

7 Appraisal Committee members, guideline representatives and NICE project team

Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. 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. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

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.

Dr Amanda Adler (Chair)
Consultant Physician, Addenbrooke's Hospital

Professor Ken Stein (Vice Chair)
Professor of Public Health, University of Exeter Medical School

Dr Ray Armstrong
Consultant Rheumatologist, Southampton General Hospital

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

Mr David Chandler
Lay member

Mr Mark Chapman

Health Economics and Market Access Manager, Medtronic UK

Dr Peter Crome

Honorary Professor, University College London and Honorary Consultant at Royal Free Hospital

Mrs Anne Joshua

NHS 111 Pharmacy Lead, Patients and Information, NHS England

Dr Miriam McCarthy

Consultant, Public Health, Public Health Agency, Northern Ireland

Mr Christopher O'Regan

Head of Health Technology Assessment and Outcomes Research, Merck Sharp & Dohme

Professor Stephen Palmer

Professor of Health Economics, Centre for Health Economics, University of York

Dr John Pounsford

Consultant Physician, Frenchay Hospital, Bristol

Dr Danielle Preedy

Lay Member

Ms Pamela Rees

Lay Member

Dr Nicky Welton

Senior Lecturer in Biostatistics/Health Technology Assessment, University of Bristol

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Sophie Laurenson
Technical Lead

Raisa Sidhu
Technical Adviser

Jeremy Powell
Project Manager

8 Sources of evidence considered by the Committee

A. The assessment report for this appraisal was prepared by the Peninsula Technology Assessment Group (PenTAG):

- Huxley N, Crathorne L, Varley-Campbell J et al., The clinical effectiveness and cost-effectiveness of cetuximab (review of TA176) and panitumumab (partial review of TA240) for previously untreated metastatic colorectal cancer: a systematic review and economic evaluation, August 2015

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, assessment report and the appraisal consultation document (ACD). Organisations listed in I, II and III were also invited to make written submissions and have the opportunity to appeal against the final appraisal determination.

I. Companies:

- Amgen

- Merck Serono

II. Professional/expert and patient/carer groups:

- Beating Bowel Cancer
- Bowel Cancer UK
- Cancer Research UK
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians

III. Other consultees:

- Department of Health
- NHS England
- Welsh Government

IV. Commentator organisations (without the right of appeal):

- Healthcare Improvement Scotland
- Roche
- Sysmex

C. The following individuals were selected from clinical expert and patient expert nominations from the consultees and commentators. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on cetuximab and panitumumab by attending the initial Committee discussion and/or providing a written statement to the Committee. They are invited to comment on the ACD.

- Dr Saifee Mullamitha, Consultant in Medical Oncology, nominated by Roche – clinical expert
- Dr Vanessa Potter, Consultant Gastrointestinal Medical Oncologist, nominated by National Cancer Research Institute (NCRI)/Royal College of

Physicians (RCP)/Royal College of Radiologists (RCR)/Association of Cancer Physicians (ACP) – clinical expert

- Ben Ashworth, nominated by Beating Bowel Cancer – patient expert
- Stuart Barber, nominated by Beating Bowel Cancer – patient expert

D. Representatives from the following companies attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Amgen
- Merck Serono