

Cetuximab and panitumumab for previously untreated metastatic colorectal cancer

Technology appraisal guidance

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Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

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This guidance replaces TA176.

This guidance partially replaces TA240.

1 Recommendations

- 1.1 Cetuximab is recommended, within its marketing authorisation, as an option for previously untreated epidermal growth factor receptor (EGFR)-expressing, RAS wild-type metastatic colorectal cancer in adults in combination with:
- 5-fluorouracil, folinic acid and oxaliplatin (FOLFOX) or
 - 5-fluorouracil, folinic acid and irinotecan (FOLFIRI).
- 1.2 Panitumumab is recommended, within its marketing authorisation, as an option for previously untreated RAS wild-type metastatic colorectal cancer in adults in combination with:
- FOLFOX or
 - FOLFIRI.
- 1.3 The drugs are recommended only when the companies provide them with the discount agreed in the patient access scheme (for panitumumab) or commercial access agreement (for cetuximab).

2 The technologies

	Cetuximab	Panitumumab
Description of the technologies	Cetuximab (Erbix, Merck Serono) is a chimeric monoclonal IgG1 antibody that is specifically directed against epidermal growth factor receptor (EGFR).	Panitumumab (Vectibix, Amgen) is a recombinant, fully human IgG2 monoclonal antibody that binds with high affinity and specificity to human EGFR.
Marketing authorisations	<p>Cetuximab has a marketing authorisation in the UK for treating 'patients with epidermal growth factor receptor (EGFR)-expressing, RAS wild-type metastatic colorectal cancer:</p> <ul style="list-style-type: none"> • in combination with irinotecan-based chemotherapy, • in first-line in combination with FOLFOX, • as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan'. 	<p>Panitumumab has a marketing authorisation in the UK for treating 'adult patients with wild-type RAS metastatic colorectal cancer (mCRC):</p> <ul style="list-style-type: none"> • 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'.
	<p>Please note this appraisal considered the previously untreated population only.</p> <p>Monotherapy for previously treated mCRC was not within the scope of the appraisal.</p>	

Adverse reactions	The most frequently reported adverse reactions are skin reactions, hypomagnesaemia and infusion-related reactions. For full details of adverse reactions and contraindications, see the summary of product characteristics.	The most frequently reported adverse reactions are skin reactions and gastrointestinal disorders. For full details of adverse reactions and contraindications, see the summary of product characteristics.
Recommended doses and schedules	Cetuximab is given by intravenous infusion once a week. The first dose of cetuximab is 400 mg/m ² body surface area. All further doses are 250 mg/m ² of cetuximab given weekly.	Panitumumab is given by intravenous infusion once every 2 weeks at a dose of 6 mg/kg of body weight.
Prices	<p>Cetuximab costs £178.10 per 20-ml vial and £890.50 per 100-ml vial (excluding VAT, 'British national formulary' [BNF] online, October 2015).</p> <p>The pricing arrangement considered during guidance development was that Merck had agreed a patient access scheme with the Department of Health. This scheme provided a simple discount to the list price of cetuximab with the discount applied at the point of purchase or invoice. After guidance publication in March 2017, the company agreed a commercial access agreement with NHS England that replaces the patient access scheme on equivalent terms. The financial terms of the agreement are commercial in confidence.</p>	<p>Panitumumab costs £379.29 per 5-ml vial and £1,517.16 per 20-ml vial (excluding VAT, BNF online, October 2015).</p> <p>The company has agreed a patient access scheme with the Department of Health, providing 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.</p>

3 Evidence

The appraisal committee ([section 6](#)) considered evidence from a number of sources, including from the companies and from the assessment group, an independent group which evaluated each company's submission, reviewed the clinical evidence, and developed a cost-effectiveness model. See the [committee papers](#) for full details of the evidence.

4 Committee discussion

Review objectives

4.1 The appraisal committee recognised that this appraisal reviewed the NICE technology appraisal guidance on:

- Cetuximab for the first-line treatment of metastatic colorectal cancer, which before this review recommended up to 16 weeks of treatment with cetuximab only in a subgroup of people with metastases confined to the liver.
- Panitumumab in combination with chemotherapy for the treatment of metastatic colorectal cancer, which did not recommend treatment with panitumumab because the company did not submit evidence.

The committee understood that the guidance was being reviewed because the marketing authorisations for cetuximab and panitumumab had changed since the previous appraisal. The change narrows the marketing authorisation to exclude a genotype that responds poorly to cetuximab and panitumumab. The committee also understood that cetuximab and panitumumab had been available on the Cancer Drugs Fund. The committee reviewed the data available on the clinical and cost effectiveness of cetuximab and panitumumab, having considered evidence on the nature of previously untreated 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.

Clinical practice

4.2 The committee discussed the current management of metastatic colorectal cancer and considered the population relevant for this appraisal. The committee heard from NHS England at the fourth appraisal committee meeting that managing colorectal cancer with liver-only metastases has evolved over the course of this appraisal. It heard that clinicians continue to offer surgical resection, which may improve prognosis, to people with metastases confined to the liver and that treatment with cetuximab or panitumumab makes it easier for surgeons to resect tumours. The committee heard from the clinical experts, that if the metastases are not resectable after treatment, the person would be offered up to 3 lines of chemotherapy. It heard that few people have successful resection, meaning that there is a greater emphasis on using cetuximab and

panitumumab palliatively for people with liver-only metastases. The committee noted that this was in line with palliative use of these treatments in people with widespread metastases, who have a biological treatment (such as cetuximab or panitumumab) with chemotherapy and then up to 2 further lines of chemotherapy alone. It heard that the aim of palliative treatment is to slow disease progression early, and to prolong life. The committee concluded that there are 2 purposes of treatment: to shrink tumour tissue for surgical resection and to palliate.

- 4.3 The committee was aware that previous guidance recommended cetuximab only in a subgroup of patients with metastases confined to the liver and included a stopping rule at 16 weeks (see section 4.1). During this appraisal, commentators and consultees, including NHS England, stated that people with metastases confined to the liver no longer represent a distinct subgroup in clinical practice and that resection was likely to be done after the best response to treatment, rather than at 16 weeks as with the stopping rule. The committee also heard that the stopping rule is difficult to implement in practice, because it can mean withdrawing a palliative treatment from people. The committee concluded that people with metastases confined to the liver were no longer a distinct subgroup in current clinical practice and did not further consider this subgroup separately from the overall population. In addition, it concluded that it was inappropriate to implement a stopping rule in people with metastatic colorectal cancer.
- 4.4 The committee considered the most appropriate comparators for cetuximab and panitumumab for treating RAS wild-type tumours in people with metastatic disease. It heard from the clinical experts that they use combinations including oxaliplatin (for example, FOLFOX) and irinotecan (for example, FOLFIRI). The committee understood that there are 2 different delivery schedules for FOLFOX treatment, FOLFOX4 and FOLFOX6, and heard from the clinical experts that FOLFOX6 is more commonly used in clinical practice in England. 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 committee was aware that other chemotherapy regimens, such as XELOX (oxaliplatin and capecitabine), were listed among the comparators in the scope but heard from the clinical experts and the assessment group that these drugs were not routinely offered in clinical

practice in the NHS. The committee concluded that the appropriate comparators for this appraisal were FOLFOX and FOLFIRI for both cetuximab and panitumumab.

4.5 The committee considered how frequently cetuximab is administered in clinical practice. It was aware the summary of product characteristics for cetuximab recommends a weekly dose of 250 mg/m² body surface area. However, the committee heard from the clinical experts and from NHS England that in practice a dose of 500 mg/m² body surface area is given every 2 weeks, which reduces administration costs. The committee was concerned that cetuximab given every 2 weeks may not have the same effectiveness as cetuximab given weekly, as done in the trials. At the fourth appraisal committee meeting, the committee heard from the company that a study (CECOG/CORE2) in a similar population showed that the effectiveness of cetuximab given every 2 weeks or weekly may be the same and that the Cancer Drugs Fund chose to offer cetuximab every 2 weeks on the basis of this evidence. The committee was aware that NICE's [guide to the methods of technology appraisal](#) states that the committee 'does not normally make recommendations regarding the use of a drug outside the terms of its marketing authorisation'. It noted that the guide also states that evidence relating to using the technology under appraisal outside the terms of its marketing authorisation may inform deliberations. The committee concluded that it would take into account the lower costs of administration in clinical practice.

Clinical effectiveness

4.6 The committee discussed the clinical trial evidence for cetuximab and panitumumab in people with RAS wild-type metastatic colorectal cancer. The assessment group included 3 main randomised clinical trials of cetuximab and panitumumab in its base-case model: OPUS (cetuximab plus FOLFOX compared with FOLFOX alone), CRYSTAL (cetuximab plus FOLFIRI compared with FOLFIRI alone), and PRIME (panitumumab plus FOLFOX compared with FOLFOX alone).

- The committee heard that the evidence for cetuximab and panitumumab in patients with RAS wild-type colorectal cancer was based on post-hoc subgroup analyses. Although based on small data sets, it understood from the clinical experts that knowledge about metastatic colorectal cancer and biomarkers has changed. The

- committee agreed that it was appropriate to use data from post-hoc subgroup analyses for its decision-making.
- The committee heard from the assessment group that the survival data were likely confounded by different second and further lines of treatment across the trial arms. These treatments are associated with prolonged survival and are not widely available in the NHS. The committee noted that, in response to the appraisal consultation document, the assessment group adjusted for subsequent treatments (see [section 4.12](#)).

The committee concluded that, for the purpose of this appraisal, the populations in the clinical trials of cetuximab and panitumumab were broadly generalisable to clinical practice in the NHS.

Network meta-analysis results: previously untreated RAS wild-type metastatic colorectal cancer

Cetuximab

- 4.7 Cetuximab plus FOLFIRI increased progression-free survival (hazard ratio [HR] 0.56; 95% credible interval [CrI] 0.41 to 0.76) and overall survival (HR 0.69; 95% CrI 0.54 to 0.88) compared with FOLFIRI alone.
- 4.8 Cetuximab plus FOLFOX increased progression-free survival (HR 0.53; 95% CrI 0.27 to 1.04) and might have increased overall survival (HR 0.94; 95% CrI 0.56 to 1.57) compared with FOLFOX alone. The committee noted that large credible intervals surrounded the estimated hazard ratios and that this evidence was based on a very small clinical trial (OPUS). The committee heard that the clinical experts consider FOLFOX and FOLFIRI to be broadly equivalent. The committee concluded that cetuximab plus either FOLFOX or FOLFIRI increased progression-free survival and overall survival in people with previously untreated RAS wild-type metastatic colorectal cancer.

Panitumumab

- 4.9 Panitumumab plus FOLFOX increased progression-free survival (HR 0.72; 95% CrI 0.58 to 0.90) and overall survival (HR 0.77; 95% CrI 0.64 to 0.93) compared with FOLFOX alone. There was no estimate for panitumumab plus FOLFIRI compared with FOLFIRI alone because the assessment group could not identify any eligible studies. In its response to the assessment group's additional

work, Amgen stated that there were results presented in its submission. The committee noted that these studies were either not carried out in people with previously untreated metastatic colorectal cancer or were single-arm studies and so it was not possible to use these in the network meta-analysis. It noted that panitumumab was licensed for use with either FOLFOX or FOLFIRI and recalled the advice from the clinical experts that FOLFOX and FOLFIRI had similar effectiveness (see section 4.8). The committee agreed that although it would have preferred to see evidence for the clinical effectiveness of panitumumab plus FOLFIRI, the clinical effectiveness of panitumumab plus FOLFIRI was likely to be similar to that of panitumumab plus FOLFOX in people with previously untreated RAS wild-type metastatic colorectal cancer. The committee concluded that panitumumab plus either FOLFOX or FOLFIRI increased progression-free survival and overall survival in people with previously untreated RAS wild-type metastatic colorectal cancer.

Panitumumab and cetuximab compared with each other

- 4.10 There was no statistically significant difference in progression-free survival (HR 0.74; 95% CrI 0.36 to 1.49) or overall survival (HR 1.22; 95% CrI 0.71 to 2.11) when comparing cetuximab plus FOLFOX with panitumumab plus FOLFOX. The committee noted that the evidence for panitumumab plus FOLFOX compared with cetuximab plus FOLFOX was mixed, and it was unclear whether one treatment was more effective than the other. It heard from the clinical experts that they considered cetuximab and panitumumab to have equal effectiveness (see section 4.8) and that it is helpful to be able to choose between them. The committee concluded that cetuximab and panitumumab were likely to have similar effectiveness in treating RAS wild-type metastatic colorectal cancer.

Resection rates for cetuximab and panitumumab

- 4.11 The committee heard from the clinical experts that they estimate that, for metastases which are unresectable before treatment, chemotherapy with or without cetuximab or panitumumab will shrink them enough to allow resection in about 15% of all people. The committee noted that the assessment group used trial data in its model, in which the resection rate in the overall population was up to around 20%. The committee heard from the clinical experts that it was implausible for there to be such discrepancies in the rates from the clinical trials, given the similarity in effectiveness of cetuximab and panitumumab. The

committee heard from Amgen that PRIME was not powered to look at resection rates as an outcome. The committee acknowledged the uncertainty in the resection rates, but concluded that it was appropriate to use the trial data for the resection rates.

Cost effectiveness

Structure of the model

4.12 The committee considered whether the assessment group's model reflected clinical practice. The committee noted that, in its base-case model, the assessment group simulated a cohort of people with RAS wild-type metastatic colorectal cancer starting on first-line treatment, assumed that a proportion of them then have surgery to resect liver metastases, and 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
- third-line treatment with best supportive care.

For people who have resection of liver metastases, the assessment group did not model further treatments; instead, it modelled progression-free survival and progressed-disease after resection. In the model, people who had resection of liver metastases lived longer than people who did not have resections. The assessment group derived utility values from trial-based EQ-5D data. The committee concluded that the assessment group's model reflected clinical practice.

Modelling of second-line drugs

4.13 The assessment group stated that data on mortality for cetuximab and panitumumab from trials may have been confounded by second-line drugs that are not commonly used in the NHS and which prolong survival (see [section 4.6](#)). The companies and the assessment group investigated methods to correct for imbalances in subsequent treatments. The committee noted that the companies had provided adjusted measures of effectiveness; Amgen used the inverse probability of censoring weighted method for panitumumab, whereas Merck Serono used the rank-preserving structural failure time method for cetuximab.

These methods provided adjusted estimates of overall survival, which were then used in the model instead of overall-survival data from the clinical trials. The committee noted that, although the adjusted overall survival changed the incremental cost-effectiveness ratios (ICERs), the size of the effect was small. The assessment group explained that the small number of patients progressing to further treatments in the clinical trials meant that the adjustments were unlikely to have a large effect. The committee concluded that, although the effect of these adjustments on survival were small, they were more plausible than the unadjusted estimates.

Proportion of people who have resection of liver metastases

4.14 The committee discussed the assessment group's estimates of the proportion of people in the overall population who have their liver metastases resected after first-line treatment. It recalled that resection may improve progression-free survival and overall survival (see [section 4.2](#)), which would increase the effectiveness of cetuximab or panitumumab in the model. The committee was aware that the resection rates in NICE's previous appraisal for cetuximab were higher (30% to 43%) than in the current appraisal (about 7% to 20%). It recognised that the rates in the previous appraisal 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 population in CELIM was people with KRAS wild-type metastatic colorectal cancer who had liver-limited metastases. The committee agreed that the population in CELIM was narrower than the population relevant to the current appraisal. In this appraisal, the committee was aware that, because of the improved prognosis after resection, the cost-effectiveness results were sensitive to the resection rates. The committee agreed that it was unlikely that there would be a large difference in resection rates between treatments (see [section 4.11](#)), but noted that the rates used in the model were directly from the clinical trials. The committee concluded that the resection rates used in the model were more appropriate than those used in the previous appraisal.

Treatment costs

4.15 The committee was aware that the treatment costs for cetuximab were partly based on the weight of the patient. The committee heard from Merck Serono that, rather than using a single mean weight of around 85 kg, the assessment group should have accounted for a distribution of weights when calculating

treatment dose and cost. It noted that cetuximab dosing is based on body surface area, which the assessment group estimated from body weight, and that panitumumab dosing is based directly on body weight. The committee concluded that using a distribution of body weight was more appropriate than using only the mean and so it took into account the assessment group's ICERs using the distribution of weights for both cetuximab and panitumumab.

Cost-effectiveness results and conclusions

- 4.16 The committee considered the cost-effectiveness results for cetuximab and panitumumab in all patients. The committee recalled its preferred assumptions to consider cetuximab given 2-weekly and to adjust survival for subsequent treatments (see section 4.13). The committee noted that the assessment group's ICERs for cetuximab plus FOLFIRI compared with FOLFIRI alone and panitumumab plus FOLFOX compared with FOLFOX alone were all below £50,000 per quality-adjusted life year (QALY) gained. The exact ICERs are not reported to prevent calculation of the discount associated with the patient access scheme and commercial access agreement.
- 4.17 The committee noted that it had not been presented with ICERs consistent with its preferred assumptions for some comparisons:
- Cetuximab plus FOLFOX compared with FOLFOX alone: It noted that ICERs adjusted for subsequent treatments were not presented because of limited data. It recalled hearing that the clinical experts considered FOLFOX and FOLFIRI to be broadly equivalent (see [section 4.8](#)). The committee concluded that the ICER for cetuximab plus FOLFOX compared with FOLFOX alone was likely to be similar to that for cetuximab plus FOLFIRI compared with FOLFIRI alone (see section 4.16).
 - Panitumumab plus FOLFIRI compared with FOLFIRI alone: It noted that ICERs were not presented because of a lack of relevant clinical evidence (see section 4.9). It recalled its earlier conclusion that the effectiveness of panitumumab plus FOLFIRI was likely to be similar to that of panitumumab plus FOLFOX. The committee concluded that the ICER for panitumumab plus FOLFIRI compared with FOLFIRI alone was likely to be similar to that for panitumumab plus FOLFOX compared with FOLFOX alone (see section 4.16).

End-of-life considerations

4.18 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's [final Cancer Drugs Fund technology appraisal process and methods](#). Having previously concluded that the end-of-life criteria were met for the overall population, but not for the subgroup of people with metastases confined to the liver, the committee limited its discussion to the overall population at the fourth appraisal committee meeting. The committee concluded that the end-of-life criteria were met in the overall population based on the following discussions:

- The committee considered the life expectancy of people with RAS wild-type metastatic colorectal cancer with either FOLFOX or FOLFIRI, using estimates from the assessment group's model. For the overall population, it noted that mean life-expectancy estimates were below 24 months for FOLFIRI when adjusted for subsequent treatments. The committee noted that the estimates for FOLFOX were slightly above 24 months. It recalled its earlier conclusion that FOLFOX and FOLFIRI were likely to be broadly equivalent (see [section 4.8](#)) and was aware that there was uncertainty about the estimates. The committee concluded that the criterion for short life expectancy was met.
- The committee considered how long, on average, cetuximab and panitumumab extended life in the whole population, based on the estimates in the assessment group's model. It noted that estimates were above a mean of 3 months for both cetuximab with FOLFIRI and panitumumab with FOLFOX when adjusted for subsequent treatments. The committee was aware that estimates adjusted for subsequent treatments were not available for cetuximab with FOLFOX but recalled its earlier conclusion that FOLFOX and FOLFIRI were likely to be broadly equivalent (see [section 4.8](#)). The committee concluded that both cetuximab and panitumumab met the criterion of extension to life when considering the whole population.

Conclusion

4.19 The committee concluded that panitumumab and cetuximab plus either FOLFOX or FOLFIRI could be considered a cost-effective use of NHS resources for previously untreated RAS wild-type metastatic colorectal cancer in adults.

Innovation

4.20 The committee heard from the companies that they consider cetuximab and panitumumab to be innovative treatments and a step-change in managing metastatic colorectal cancer, because their targeted mechanisms of action mean that those people with colorectal cancer that is most likely to respond (that is, RAS wild-type) have treatment. The committee concluded that it had not been presented with any additional evidence of benefits that were not captured in the measurement of QALYs.

Pharmaceutical Price Regulation Scheme (PPRS) 2014

4.21 The committee was aware of NICE's position statement on the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism. It 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 about the relevance of the PPRS to this appraisal. It therefore concluded that the PPRS payment mechanism was not relevant in considering the cost effectiveness of any of the technologies in this appraisal.

Summary of appraisal committee's key conclusions

TA439	Appraisal title:	Section
Key conclusions		

<p>Cetuximab is recommended, within its marketing authorisation, as an option for previously untreated epidermal growth factor receptor (EGFR)-expressing, RAS wild-type metastatic colorectal cancer in adults in combination with:</p> <ul style="list-style-type: none"> • 5-fluorouracil, folinic acid and oxaliplatin (FOLFOX) or • 5-fluorouracil, folinic acid and irinotecan (FOLFIRI). <p>Panitumumab is recommended, within its marketing authorisation, as an option for previously untreated RAS wild-type metastatic colorectal cancer in adults in combination with:</p> <ul style="list-style-type: none"> • FOLFOX or • FOLFIRI. <p>The committee concluded that people with metastases confined to the liver no longer represent a clinically relevant subgroup of people with metastatic colorectal cancer.</p> <p>The committee heard that cetuximab is given every 2 weeks in practice and agreed to consider the reduced administration costs.</p>		<p>1.1, 1.2, 4.3, 4.5</p>
<p>Current practice</p>		
<p>Clinical need of patients, including the availability of alternative treatments</p>	<p>The prognosis of people with metastatic colorectal cancer may be improved by resection of metastases. When possible, resecting the primary tumour and metastases is carried out. Chemotherapy regimens may be used before surgery to shrink the metastases and make them suitable for resection.</p>	<p>4.2</p>
<p>The technologies</p>		

Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The committee heard from the companies that they consider cetuximab and panitumumab to be innovative treatments and a step-change in managing metastatic colorectal cancer, because their targeted mechanisms of action mean that those people with colorectal cancer that is most likely to respond (that is, RAS wild-type) have treatment.	4.20
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 and panitumumab may also be offered to people with widespread disease as a palliative treatment when the objective is to slow disease progression as soon as possible.	4.2
Adverse reactions	The most frequently reported adverse reactions associated with the use of cetuximab and panitumumab are skin reactions.	2
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. The trials compared cetuximab or panitumumab with combination treatments that did not include these drugs. The evidence for cetuximab and panitumumab in people with RAS wild-type colorectal cancer was based on post-hoc subgroup analyses of clinical trial data.	4.6
Relevance to general clinical practice in the NHS	The populations in the clinical trials differed from patients in clinical practice in England. For example, second and further lines of treatment used in the trials are not widely available in the NHS.	4.6

Uncertainties generated by the evidence	Survival data from the clinical trials were confounded by the use of different second and further 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 true size of the 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.	4.6
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	A subgroup of people with metastases confined to the liver was considered, but after advice from NHS England, this was no longer deemed a clinically relevant subgroup.	4.3
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The assessment group's network meta-analysis showed that cetuximab plus FOLFIRI and panitumumab plus FOLFOX were more effective than chemotherapy alone. The evidence for cetuximab plus FOLFOX was less conclusive. This evidence was based on a very small clinical trial, OPUS. Clinical experts stated that cetuximab and panitumumab probably had similar effectiveness. There were uncertainties about the results of the network meta-analysis and the credible intervals around the hazard ratios were large.	4.7–4.10
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).	4.1, 4.6
Evidence for cost effectiveness		
Availability and nature of evidence	The committee concluded that the assessment group's model reflected clinical practice.	4.12

<p>Uncertainties around and plausibility of assumptions and inputs in the economic model</p>	<p>The adjustment for further treatments was a source of uncertainty. The committee concluded that, although the effect of these adjustments on survival were small, they were more plausible than the unadjusted estimates.</p> <p>The difference in resection rates between treatment arms was a source of uncertainty. Although it was appropriate to source these from the clinical trials, the discrepancies between them were considered clinically implausible.</p>	<p>4.13, 4.11</p>
<p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?</p>	<p>Utility values were derived from trial-based EQ-5D data. The committee concluded that it had not been presented with any additional evidence of benefits that were not captured in the measurement of quality-adjusted life years.</p>	<p>4.12, 4.20</p>
<p>Are there specific groups of people for whom the technology is particularly cost effective?</p>	<p>Not applicable.</p>	<p>–</p>
<p>What are the key drivers of cost effectiveness?</p>	<p>Giving cetuximab every 2 weeks was the most important driver of cost effectiveness.</p>	<p>4.5</p>

Most likely cost-effectiveness estimate (given as an ICER)	The committee noted the base-case incremental cost-effectiveness ratios (ICERs), and further noted that the model was associated with uncertainties about the estimates of cost effectiveness from the network meta-analysis and the estimates of resection rates. Despite this, it concluded that they were within the range normally considered to be a cost-effective use of NHS resources for the whole population with previously untreated RAS wild-type metastatic colorectal cancer.	4.16, 4.17, 4.19
How has the new cost-effectiveness evidence that has emerged since the original appraisal (TA176) influenced the current (preliminary) recommendations?	Resection rates were higher in the original appraisal, ranging from 30% to 43% compared with about 7% to 20% in the current appraisal. This is likely to influence cost effectiveness.	4.14
Additional factors taken into account		
Patient access schemes (PPRS)	Not applicable.	-
End-of-life considerations	The committee concluded that both cetuximab plus chemotherapy and panitumumab plus chemotherapy fulfilled NICE's final Cancer Drugs Fund technology appraisal process and methods advice to be considered as life-extending, end-of-life treatments in the overall population of people with RAS wild-type metastatic colorectal cancer.	4.18
Equalities considerations and social value judgements	Not applicable.	-

5 Implementation

- 5.1 Section 7(6) of the [National Institute for Health and Care Excellence \(Constitution and Functions\)](#) and the [Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- 5.2 The Welsh Assembly Minister for Health and Social Services has issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 3 months of the guidance being published.
- 5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has previously untreated RAS wild-type metastatic colorectal cancer and the doctor responsible for their care thinks that cetuximab or panitumumab is the right treatment, it should be available for use, in line with NICE's recommendations.
- 5.4 The Department of Health and Amgen have agreed that panitumumab will be available to the NHS with a patient access scheme which makes it available with a discount. The size of the discount is commercial in confidence. It is the responsibility of the company to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to commercial-team@amgen.com.
- 5.5 NHS England and Merck have agreed that cetuximab will be available to the NHS with a commercial access agreement. The details of this commercial access agreement are confidential. Any enquiries from NHS organisations about the commercial access agreement should be directed to clara.loveman@merckgroup.com.

6 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by [committee B](#).

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.

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 Cooper, Caroline Hall, Thomas Palmer

Technical Leads

Raisa Sidhu, Jasdeep Hayre

Technical Advisers

Jeremy Powell

Project Manager

Update information

September 2017: Reference to a patient access scheme for cetuximab in recommendation 1.3 has been replaced with details of a commercial access agreement. Sections 2 and 5.5 have been updated with the same information.

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Accreditation

