National Institute for Health and Care Excellence

MultipleTechnology Appraisal (MTA)

Cetuximab (review of TA176) and panitumumab (partial review of TA240) for the first line treatment of metastatic colorectal cancer

Response to consultee and commentator comments on the draft scope

Section	Consultee/ Commentator	Comments	Action
Background information	Amgen	The background information describes metastatic colorectal cancer and treatment options including chemotherapy and biological agents. We recommend no changes to this section.	Comment noted. No action required.
	Merck Serono	In addition to stating that 35%-40% have mutations in KRAS, it worth mentioning that 50% have mutations in both NRAS and KRAS (RAS) according to the latest clinical studies.	Comment noted. The scope has been updated to state that “Approximately 50% of people with advanced colorectal cancer have mutations in the KRAS or NRAS genes.”
The technology/ intervention	Amgen	Panitumumab and cetuximab are described. We recommend no changes to this section.	Comment noted. No action required.
	Merck Serono	**Is the description of the technologies accurate?** No. It is correct to state that cetuximab marketing authorisation includes the use of cetuximab in combination with FOLFOX only in first line treatment of metastatic colorectal cancer (mCRC). However, the use of cetuximab in combination with Irinotecan-based chemotherapy applies to all lines of treatment, not just first line treatment, i.e. for treating previously untreated patients. In addition, the UK marketing authorisation	Comment noted. The scope lists the indications in the marketing authorisation that fall within the remit of the appraisal. The remit specifies previously untreated patients.

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		includes use of cetuximab as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan. It is important to differentiate between the UK marketing authorisation and the scope of the MTA as a review of TA 176 which only assess cetuximab as a the first line treatment of RAS wild type mCRC patients.	Accordingly, the relevant indications are those stated in the draft scope. No action required.
Population	Amgen	We agree that the population is patients with previously untreated wild-type RAS metastatic colorectal cancer.	Comment noted. No action required.
	Merck Serono	Yes	Comment noted. No action required.
Comparators	Amgen	FOLFOX; XELOX; FOLFIRI; capecitabine; tegafur folinic acid, and fluorouracil; and bevacizumab in combination with oxaliplatin or irinotecan based chemotherapy are listed as comparators.	Comment noted. No action required.
	Amgen	Market research data indicate that bevacizumab in combination with chemotherapy is used in the majority of this patient population in the NHS due to availability through the Cancer Drugs Fund. Therefore, we recommend that bevacizumab is considered the primary comparator and described as best alternative care.	Comment noted. The scope contains an inclusive list of all potentially relevant comparators. At the scoping stage, NICE does not identify 'primary' comparators. No action required.
	Amgen	Conversely, capecitabine monotherapy and tegafur/folinic acid/fluorouracil are not considered standard treatments and not routinely used in the NHS. Therefore, we recommend these comparators are removed from the scope.	Comment noted. The scope contains an inclusive list of all potentially relevant comparators. NICE clinical guideline 131 recommends

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			treatment options including tegafur in combination with fluorouracil and folinic acid, and capecitabine alone. The marketing authorisations for capecitabine, cetuximab and panitumumab cover a similar population. If a company has evidence that a comparator is not part of established NHS practice in England, it is invited to include this evidence in its submission. No action required.
	Merck Serono	FOLFOX, FOLFIRI, CAPOX and Bevacizumab + FOLFOX can be considered as established clinical practice in the NHS for previously untreated patients.	Comment noted. No action required.
	Merck Serono	Not all treatments in the list can be considered as standard treatments. The following treatments should be excluded from the scope of the proposed MTA: • Tegafur in combination with folinic acid and fluorouracil is no longer licenced in the UK for the treatment of colorectal cancer. Therefore it should not be included as a comparator treatment. • Capecitabine monotherapy is usually reserved for patients with poor performance status who cannot tolerate combination chemotherapy. These patients are usually excluded from clinical trials and tend to have worse outcomes than fitter patients.	Comment noted. The scope contains an inclusive list of all potentially relevant comparators. The Appraisal Committee can consider as comparators technologies that do not have a marketing authorisation for the indication defined in the scope, when they are considered to be part of

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		Therefore it would not be appropriate to compare these patients to relatively fitter patients who can tolerate combination chemotherapy with biological agents; the type of patients enrolled in cetuximab clinical trials. None of these treatments can be described as “best alternative care”.	established clinical practice in the NHS, and if there is evidence for its effectiveness. NICE clinical guideline 131 recommends treatment options including tegafur in combination with fluorouracil and folinic acid, and capecitabine alone. The marketing authorisations for capecitabine, cetuximab and panitumumab cover a similar population. If a company has evidence that a comparator is not part of established NHS practice in England, it is invited to include this evidence in its submission. No action required.
Outcomes	Amgen	We recommend no changes to this section.	No action required.
	Merck Serono	Yes	No action required.
Economic analysis	Amgen	Bevacizumab is available through the Cancer Drugs Fund. As such, we (sponsor manufacturer of panitumumab) will not have information regarding the actual cost incurred by NHS England (Cancer Drug Fund) for the basis of the economic analyses given the potential confidential circumstances of such arrangements. We propose to present analyses at NHS list-price and also model a range of potential costs of the	Comment noted. No action required.

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		comparator. This approach would be consistent with the Institute's current Guide to the processes of technology appraisal with regards handling confidential information and patient access schemes.	
	Merck Serono	No comments	No action required.
Equality and Diversity	Amgen	No comments	No action required.
	Merck Serono	No issues noted	No action required.
Innovation	Amgen	Panitumumab is an innovative therapeutic for patients with wild-type RAS metastatic colorectal cancer. It is the only fully human IgG2 monoclonal antibody with high affinity for EGFR, and is the first targeted therapy to gain approval from the EMA for the treatment of patients with wild-type RAS metastatic colorectal cancer. Through its innovative, targeted mechanism of action, panitumumab offers a significant scientific advance, with an associated medical step-change in the treatment of patients with metastatic colorectal cancer. Because use of panitumumab to patients with wild-type RAS, it is targeted to those patients most likely to benefit from treatment and spares those unlikely to respond from unnecessary drug exposure.	Comment noted. The company is invited to provide evidence of the innovative nature of the technology in its submission. No action required.
	Merck Serono	In the cetuximab pivotal trials (i.e. CRYSTAL and OPUS) of RAS wild type patients, cetuximab plus chemotherapy demonstrates a significant increase in median overall survival (mOS), of up to 8.2 months compared to chemotherapy alone, and median progression free survival (PFS) of up to 6.2 months compared to chemotherapy alone. This is a major advancement over currently available chemotherapy options in the NHS and demonstrates innovation for an end-of-life medicine. In addition, RAS biomarker testing ensures that patients who are more likely to benefit from cetuximab treatment are identified, while those who	Comments noted. The company is invited to provide evidence of the innovative nature of the technology in its submission. No action required.

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		will not benefit from treatment are prescribe alternative treatments than cetuximab. This represents innovation as a targeted treatment. It is also in line with NHS England's expectation and drive to make the NHS a world leader in stratified medicine and maximise the potential of patient treatments.	
Other considerations	Amgen	No comments	No action required.
	Merck Serono	No comments	No action required.
NICE Pathways	Amgen	We consider panitumumab (combined with FOLFOX chemotherapy) will fit into the current NICE pathway as an option for first-line treatment of wild-type RAS metastatic colorectal cancer.	Comment noted. No action required.
	Merck Serono	Cetuximab's optimal position in the existing NICE pathway for colorectal cancer is in first line treatment due the following reasons: 1. The best available evidence for cetuximab benefit was demonstrated in first line treatment. 2. Patients in 1st line treatment are likely to be healthier than in subsequent lines upon disease progression which tends to be more aggressive than the pre progression phase. Therefore, they have a higher chance of survival and should be treated with the most effective therapy. 3. Patients who require resection of liver metastasis require cetuximab treatment as it was proven to reduce the size of the tumor to a size allowing resection more than other available treatments. 4. Clinicians should have the option of prescribing anti EGFR treatments in combination with either FOLFOX or irinotecan	Comment noted. No action required.

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		chemotherapy in first line treatment. Cetuximab can be prescribed with either chemotherapy treatments in first line while Panitumumab can only be used with FOLFOX in first line and with Irinotecan based chemotherapy in second line treatment in accordance to its licence.	
Questions for consultation	Amgen	**Have all relevant comparators for cetuximab and panitumumab been included in the scope?** Partially, please see our comments under Comparators. **Are the outcomes suggested in the scope appropriate?** Yes, please see our comments under Outcomes. **Are the subgroups suggested in 'other considerations' appropriate?** Yes, we believe that consistent with previous appraisals, patients with unresectable liver only metastatic disease are an appropriate subgroup. **Are there any other subgroups of people in whom cetuximab and panitumumab are expected to be more clinically effective and cost effective or other groups that should be examined separately?** No, we believe that the subgroups identified are sufficient. **Should the appraisal consider subgroups based on clinical characteristics of the cancer (for example, whether the primary tumour or metastases have been, or may be, resected)?** Yes, please refer to the response above regarding appropriate subgroups.	Comments noted. No action required.
	Amgen	**Should the appraisal consider any other genetic markers (for example, EGFR or BRAF mutation status)?** No, panitumumab is licensed in all wild-type RAS patients regardless of EGFR expression status. There is no evidence to suggest EGFR expression status as determined by currently available methods relates	Comment noted. No action required.

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		to clinical efficacy hence we suggest EGFR expression status is not considered as a subgroup. Panitumumab is licensed in wild-type RAS patients with or without BRAF mutations. As there are no specific studies in BRAF mutants receiving EGFR antagonists we suggest these patients are not considered as a separate subgroup.	
	Merck Serono	**Should the appraisal consider any other genetic markers (for example, EGFR or BRAF mutation status)?** RAS biomarker testing is the standard test performed in clinical practice to identify patients who are more likely to benefit from anti EGFR treatment and exclude those who will not benefit from this treatment. Other biomarker tests (EGFR and BRAF) are not conducted in clinical practice. Therefore should not be considered in the scope of the MTA.	Comment noted. No action required.
	Amgen	**Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?** See above, we will provide further evidence in our evidence submission of other benefits that are unlikely to be captured in the QALY calculation. **Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.** See above	Comment noted. No action required.
	Merck Serono	**Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?** Merck Serono anticipates that all health related benefits of cetuximab treatment will be included in the QALY calculation.	Comments noted. No action required.

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		Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits Evidence demonstrating clinical outcomes of cetuximab treatment stems from Phase III and Phase II randomised controlled trials. However, these clinical trials were not originally designed or powered to capture outcomes in RAS wild type patients. The efficacy analyses were performed post-hoc on a subset of the initially conceived population for these studies (RAS wt population) as a result of emerging scientific evidence of the role of biomarkers in metastatic colorectal cancer and following dialogue with regulatory agencies. Despite the nature of this data, most clinical trials demonstrated statistically significant outcomes from cetuximab treatment in combination with chemotherapy.	
Additional comments on the draft scope		None.	

The following consultees/commentators indicated that they had no comments on the draft scope:

Bowmed Ibisqis, Roche Products