NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Cetuximab (monotherapy or combination chemotherapy), bevacizumab (in combination with non-oxaliplatin chemotherapy) and panitumumab (monotherapy) for the treatment of metastatic colorectal cancer after first-line chemotherapy (review of technology appraisal 150 and part review of technology appraisal guidance 118)

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees	Comment	Response
Amgen	We have reviewed the Appraisal Consultation Document (ACD) for the Multiple Technology Appraisal of "Cetuximab, bevacizumab and panitumumab monotherapy for the treatment of metastatic colorectal cancer that has progressed after first line chemotherapy (review of technology appraisal 150 and part-review of technology appraisal 118)". We welcome the opportunity to respond to the ACD, and in our response, we have addressed points of clarification and identified factual inaccuracies.	Comment noted
Amgen	**ACD Section 3.6, The Technologies** "The list price of a 20-ml vial (100mg) is £178.10, and a 100-ml vial (500mg) is £890.50 (excluding VAT; BNF edition 61). The manufacturer of cetuximab has agreed with the Department of Health that the NHS price will be £136.50 for a 20-ml vial and £682.50 for a 100-ml vial, and all calculations in the economic modelling are based on these prices." The ACD clarifies that the price of cetuximab used in the economic modeling for the reference case analysis is based on the discounted NHS price instead of the list price. This contradicts the NICE Methods Guide which states that the reference case analysis should be based on the list price with the discounted price included as sensitivity analysis[i]. "5.5.2 When the acquisition price paid for a resource differs from the public list price (for example, pharmaceuticals and medical devices sold at reduced prices to NHS institutions), the public list price should be used in the reference-case analysis. Sensitivity analysis should assess the implications of variations from this price. Analyses based on price reductions for the NHS will only be considered when the reduced prices are transparent and can be consistently available across the NHS, and if the period for which the specified price is available is guaranteed. In these circumstances, advice will be taken from institutions such as the NHS Purchasing and Supply Agency (PASA) or Welsh Health Supplies. (Cont…)	Comment noted. The wording has been amended for the FAD (See FAD section 3.6) to explain why the discounted NHS price has been considered by the Committee in this appraisal.

Comments received from consultees	Comment	Response
	The review date for the appraisal will be informed by the period of time over which any such agreements can be (guaranteed." Consequently, the approach undertaken in this appraisal is not consistent with the NICE Methods Guide. We consider it most important that NICE appraisals adhere to the published methods as failure to do so, as is the case for this appraisal, has the potential to set an unintended precedent for future appraisals. Further, it is of paramount importance to the integrity of the Institute's technology appraisals process that the Institute adheres with all elements of their published methods. We kindly request that the Institute adheres with the published methods by presenting the cost-effectiveness of cetuximab using the list price in the reference case analysis and the NHS price in sensitivity analysis.	See above response
Amgen	**ACD Section 4.2.18, Assessment Group's Mixed Treatment Comparison** "The Assessment Group could not use HRs that were adjusted for this crossover effect to generate its mixed treatment comparison because HRs were not provided by the manufacturer. The Assessment Group reported an overall survival estimate of 16.2 months for cetuximab plus irinotecan in an appendix to the assessment report." The ACD notes that in Amgen's analyses to address the impact of cross-over on OS, the results are not presented in terms of Hazard Ratios (HRs) and thus could not be used by the Assessment Group to generate its mixed treatment comparisons. We would like to clarify that we provided the HR in our response to the Assessment Report and that the information we had provided can be used to generate mixed treatment comparisons. For ease of reference, we have outlined below our response to the Assessment Report that was submitted to the Institute on 20 July 2011. For the method (to overcome the confounding associated with treatment	Comment noted. The wording has been amended for the FAD (See FAD section 4.2.18)

Comments received from consultees	Comment	Response
	crossover) of estimating overall survival by aggregating survival across response rates, i.e. based on the aggregated OS Kaplan Meier (KM) curves for the BSC mutant KRAS group (n=100) and the panitumumab WT KRAS group (n=124), it is possible to estimate an HR based upon a Cox proportional hazards model. This method of estimating overall survival gain by aggregating survival across response rates is in line with the structure of the cost-effectiveness model developed by the Assessment Group and is therefore a more appropriate estimate of overall survival gain for panitumumab compared to the approach of splitting the data by response rates. Further, it is noteworthy that the data from the trial was relatively complete as 92% (based on all KRAS evaluable patients N=427) of patients died by the end of the follow-up period. The method of aggregating response rates results in estimates of mean survival of [redacted] in the BSC arm and [redacted] in the panitumumab arm yielding an average survival gain of 3.13 months. The accompanying HR using this method is 0.657 (95% CI 0.497 to 0.868). For the method (to overcome the confounding associated with treatment crossover) of estimating overall survival by splitting response rates, we did not present HRs as models were fitted individually for each response category and for each treatment in our base case analysis. The best fitting models were log-normal and log-logistic models, which are accelerated failure time models rather than proportional hazards models and do not involve a constant HR (fitting models in this way avoids the requirement of making the proportional hazards assumption for the treatment effect). We could have fitted proportional hazards models to the response categories - stable disease (SD), progressive disease (PD), and not done, unevaluated, or other (ND/UE) - which would have given us HRs comparing survival by treatment group in each of these categories, but this would not have been possible in the partial response (PR) category, since no BSC patients achieved a PR. Consequently, we are not able to present a HR using this method of adjustment. (Cont…)	See above response

Comments received from consultees	Comment	Response
	Hence, HRs would not have been an appropriate measure of the treatment effect using the response rate disaggregation survival analysis technique, whereas the estimated mean survival gain is informative.	Comment noted. The wording has been amended for the FAD (See FAD section 4.2.18)
Amgen	**Section 4.2.10, Panitumumab** "The manufacturer and the Assessment Group identified one RCT (the 'Amgen' trial) that compared panitumumab plus best supportive care with best supportive care alone in 463 people with metastatic colorectal cancer that had progressed after standard first and second-line chemotherapy (a fluoropyrimidine, irinotecan and oxaliplatin). The primary endpoint of the trial was overall survival." The primary end point of the panitumumab trial was progression-free survival (PFS). Overall survival was analysed as a secondary end point (other secondary end points included objective response and safety). Therefore, the above should read *"The primary endpoint of the trial was progression free ~~overall~~ survival."*	Comment noted. The wording has been amended for the FAD (See FAD section 4.2.11)
Amgen	**Section 4.2.11, Panitumumab** *"Tumour samples from 427 (92%) people in the Amgen trial were retrospectively tested for KRAS mutation status after the end of the trial."* We would like to provide clarification on this statement with respect to KRAS mutation status in the panitumumab trial. The study by Amado et al reported that KRAS status was ascertained in 427 (92%) of 463 patients (208 panitumumab, 219 BSC). However, 445 (96%) patients in the Amgen trial were retrospectively tested before KRAS status was obtained in 427 (92%) of people. It would be more accurate to state that, *"Tumour samples from 427 (92%) people in the Amgen trial were retrospectively ~~tested~~ obtained for KRAS mutation status after the end of the trial".*	Comment noted. The wording has been amended for the FAD (See FAD section 4.2.12)
Merck Serono	Merck Serono has reviewed the Appraisal Consultation Document (ACD) for cetuximab, bevacizumab and panitumumab in colorectal cancer (metastatic)	Comments noted.

Comments received from consultees	Comment	Response
	in the pre-treated setting. According to the ACD report, cetuximab is the technology offering the greatest chance of survival in terms of life extension compared to the other available technologies in this setting. Cetuximab plus best supportive care prolonged life by 4.7 months in the third line or later setting relative to best supportive care alone while the second best technology (panitumumab) can offer between 2.7 to 3.2 months only. As noted in the ACD, we understand from the Assessment Group's (AG) mixed treatment comparison that "the results showed that patients who received cetuximab plus best supportive care would be expected to have significantly longer overall survival than those receiving panitumumab plus best supportive care (unadjusted HR 0.56, 95%CI 0.37 to 0.83; adjusted HR 0.63, 95%CI 0.41 to 0.97)". We understand that the AG highlighted that the HR for overall survival for panitumumab from the Amgen trial may have underestimated the effectiveness. The ERG critique highlights that the economic case developed for the use of cetuximab shows it is not cost-effective use of NHS resource. We agree that the technology is not cost-effective under the usual threshold range for acceptability.	
Merck Serono	Additionally, we applied for the Supplementary Advice of the End of Life (EoL) to be coherent with our evidence (i.e. CO17 study comparing cetuximab plus best supportive care versus best supportive care in the third line setting, a clinical study carried out following advice from the NICE TA118 guidance). NICE is considering that cetuximab meets two out of the three End-of-Life criteria (i.e. population life expectancy less than 24 months and life extension beyond 3 months) (Cont…) Small population" is the third criterion reported as not met. According to our	Comments noted. The Committee understood that it should take into account all populations with a marketing authorisation for a given technology when considering the size of the patient populationThe Committee concluded that the true size of the cumulative population covered by the marketing authorisation for cetuximab was likely to be over 10,000 patients and was not small, and that cetuximab does not meet all of the criteria for a life-

Comments received from consultees	Comment	Response
	computation the eligible population for the third line setting is 260 to 390 patients as outlined in our submission.	extending, end-of-life treatment. (See FAD section 4.4.2.1).
Merck Serono	1. **Has all of the relevant evidence been taken into account?** We believe all relevant evidence have been considered for this appraisal.	Comment noted
Merck Serono	2. **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Merck Serono trusts the summaries of clinical and cost effectiveness are reasonable interpretations in light of the available evidence.	Comment noted
Merck Serono	3. **Are the provisional recommendations sound and a suitable basis for guidance to the NHS**? In relation to our application to the End of Life criteria, we acknowledge that the Committee agreed that cetuximab meet the following: • "For metastatic colorectal cancer that has progressed after first line treatment, the Committee agreed that the technologies fulfilled the first criterion related to life expectancy" • "Cetuximab plus best supportive care prolonged life by 4.7 months in the third line or later setting relative to best supportive care alone and therefore met the second criterion" • The Committee concluded that "the cumulative population covered by the marketing authorisation for cetuximab was not small". However, the population outlined in the submission is 390 and therefore could be considered small and these patients will be disadvantaged by this recommendation. Beside, all our licensed indications (see Appendix 1) have been appraised by NICE (see Appendix 2: TA118, TA145, TA150, TA172, TA176), and only 1670 patients can currently benefit from cetuximab across England and Wales with NICE TA 176 (population obtained from TA176 costing template). Adding these 390 patients, cetuximab cumulative population for recommended use would still be small approximately 2,100 patients. (Cont…) Does that imply that technology licensed for a wide population should not	Comments noted. The Committee concluded that the true size of the cumulative population covered by the marketing authorisation for cetuximab was likely to be over 10,000 patients and was not small, and that cetuximab does not meet all of the criteria for a life-extending, end-of-life treatment.(See FAD section 4.4.2.1)

Comments received from consultees	Comment	Response
	explore efficacy in small population and seek potential NICE recommendation using the EoL?	See above response.
Merck Serono	4. **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 gender, race, disability, age, sexual orientation, religion or belief?** No.	Comment noted
Roche Products	Section 4.4.5 of the ACD states that: 'the Committee was not provided with any observational data documenting survival times in people who received bevacizumab as a second or third-line treatment in clinical practice.' This is factually inaccurate. Appendix 2 of our submissions contains details of observational data in which 'survival times in people who received bevacizumab as a second or third-line treatment in clinical practice' were documented (i.e. the BRiTE registry and the ARIES registry). This evidence has not been taken into account by the Committee. The results of BRiTE and ARIES are summarized briefly below (with further detail provided in our original submission). BRiTE In BRiTE the median survival beyond first progression for patients treated with bevacizumab + chemotherapy as a second line treatment was 19.2 months compared to 9.5 months for patients who received chemotherapy alone ($p<0.05$). ARIES The ARIES registry showed a trend towards superior overall survival for bevacizumab based second line therapy compared to chemotherapy alone (median OS for bevacizumab plus chemotherapy was (Cont…) 21.7 months, 95% CI 17.8-27.0 compared to 17.5 months, 95% CI 15.9-21.5 for chemotherapy alone).	Comment noted. At the second committee meeting, the Committee discussed the results of the two registry-based observational studies, BRiTE and ARIES (See FAD Sections 4.2.5 and 4.4.6). The Committee heard from the Roche Products that these registries were unlikely to inform the Committee's decision regarding the use of bevacizumab as second-line or subsequent therapy in combination with non-oxaliplatin chemotherapy.

Comments received from consultees	Comment	Response
	Relevance of this evidence to the current decision problem This data indicates that, in the real world, patients who receive bevacizumab in combination with chemotherapy after first line therapy appear to have longer progression-free and overall survival than those that are treated with chemotherapy alone (significantly so in the case of the BRiTE registry). However as this data is not available limited to solely those patients who received non-oxaliplatin based chemotherapy and is not randomized (and so potentially subject to selection bias) it's relevance to the current decision problem is unclear. Nevertheless, despite these limitations, observational data was submitted and has not been considered, or acknowledged, by the Committee. Both BRiTE and ARIES are supportive of the findings of the randomized evidence available, and are aligned with the EMA's opinion that bevacizumab in combination with chemotherapy is efficacious and safe in the treatment of 2nd line mCRC.	Comment noted. The Committee understood that the BRiTE registry only included people with previously untreated metastatic colorectal cancer, who then received bevacizumab as first-line treatment, and therefore the BRiTE registry did not provide data in line with the appraisal scope. Data from the ARIES registry were also noted to be outside of the appraisal scope. The Committee was also aware that Roche Products could not provide data from these registries specifically for bevacizumab in combination with non-oxaliplatin-based chemotherapy. (See FAD Section 4.4.6).
Roche Products	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Section 4.3.1. of the ACD states: 'The treatment cost for cetuximab plus FOLFIRI was estimated to exceed that for bevacizumab plus FOLFIRI by £5408, with costs for KRAS testing of £462, drugs costs of £3357 and administration costs of £1589. '(Cont…) Given its current wording the following section of the sentence 'with costs for KRAS testing of £462, drugs costs of £3357 and administration costs of £1589' may be misinterpreted. These values were incremental rather than absolute costs yet currently it is plausible that these may be interpreted as being absolute.	Comment noted. The wording has been amended for the FAD (See FAD section 4.4.3) Comment noted. The wording has been amended for the FAD (See FAD section 4.4.3)

Comments received from consultees	Comment	Response
	We suggest the wording should be amended to reflect this. Perhaps ‘‘The treatment cost for cetuximab plus FOLFIRI was estimated to exceed that for bevacizumab plus FOLFIRI by £5408, with an incremental KRAS testing cost of £462, additional drug costs of £3357 and additional administration costs of £1589’	
Roche Products	**Are the provisional recommendations a sound and suitable basis for guidance to the NHS?** We have no issues to raise under this heading	Comment noted
Roche Products	**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 gender, race, disability, age, sexual orientation, religion or belief?** We are not aware of any such issues.	Comment noted
Royal College of Nursing	We would ask that the summaries of the clinical and cost effectiveness of this appraisal should be aligned to the clinical pathway followed by patients with metastatic colorectal cancer. The preliminary views on resource impact and implications should be in line with established standard clinical practice.	Comments noted
Royal College of Nursing	We are not aware of any specific issue *[relating to equality]* at this stage. However, it would be helpful to know if NICE will publish the equality analysis for this appraisal. We would also ask that any guidance issued should show that an analysis of equality impact has been considered and that the guidance demonstrates an understanding of issues relating to all the protected characteristics where appropriate.	Comments noted. The Committee discussed the issues relating to equality for this appraisal (See FAD section 4.4.4). The Committee heard that patients with colorectal cancer in England are becoming increasingly worried about what they perceive to be unequal access to treatment with biological drugs, which are currently only provided to some patients through the Cancer Drugs Fund.

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
Royal College of Pathologists	One of the interesting things to emerge is the apparent superiority of Cetuximab over Panitumumab in treating metastatic colorectal cancer. It is stated that "panitumumab provided a survival benefit relative to best supportive care, but that the magnitude of this benefit was uncertain". However it may be worth considering whether the effectiveness of Panitumumab has been overestimated since, in the "Amgen" trial, it seems that patients with mutant Kras who were crossed over receive Panitumumab were regarded as the equivalent of best supportive care since they would not benefit from the biological therapy. However this assumes that there is no toxicity from Panitumumab which could possibly reduce survival and artefactually lower the outcome of the best supportive care group.	Comment noted
Royal College of Pathologists	Page 40 of the ACD states "the identification of further *KRAS* mutations will allow for an even better identification of people who are likely to benefit from therapy"; it would be more accurate to also include *BRAF* i.e. "further *KRAS* and *BRAF* mutations".	Comment noted. The wording has been amended for the FAD (See FAD section 4.4.2.3)
Royal College of Pathologists	Page 27 of the ACD states "that KRAS testing is now routinely offered in the NHS"; this is not strictly speaking true as not all NHS hospitals (including teaching hospitals) have this test locally available. A more accurate statement would be "that KRAS testing is now routinely offered in some parts of the NHS"	Comment noted. The wording has been amended for the FAD (See FAD section 4.3.1)