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)

Appraisal Committee Meeting 4 August 2011

PenTAG response to consultee and commentator comments on the commercial-in-confidence redacted assessment report

Table of contents

1. PenTAG response to comments from Amgen

Cross reference to PenTAG report	Company Comment	PenTAG Response
AMGEN		
Section 4.2.1.4.3. Panitumumab+BSC vs BSC, page 51 and 52 ***"Patients were randomly assigned 1:1 to receive panitumumab+BSC or BSC alone, however, details of the randomisation procedure are not given."*** ***"Of the 463 patients originally enrolled, 427 were included in the KRAS analysis, although the assessable sample size was 380 due to unavailable or poor quality samples. The primary outcome was PFS between KRAS mutant and KRAS WT status, with secondary outcomes."***	We would like to provide clarification that randomisation was performed centrally through an interactive voice response system (IVRS) and subjects were randomly assigned in a 1:1 ratio to receive panitumumab plus BSC or BSC alone. Randomization was stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1 versus 2) and geographic region (Western Europe versus Central and Eastern Europe versus the rest of the world, including Canada, Australia, and New Zealand). We would like to provide clarification on the statement with respect to the ascertainment of KRAS status as it appears to be incorrect. The study by Amado et al reported that KRAS status was ascertained in 427 (92%) of 463 patients (208 panitumumab, 219 BSC).(1)	Thank you for the clarification regarding randomisation. The statement: *'although the assessable sample size was 380…'* was included in error and can be removed from the final report.
Section 4.2.1.7., Indirect Comparison of Cetuximab and Panitumumab, Page 71 ***"In Amgen's submission analyses were undertaken to address the cross-over (see Section 6, page 98), but the results are not presented in terms of HRs and so are not included in the indirect comparisons described here."***	The Assessment Group undertook indirect comparisons and report that there is no statistically significant difference in the hazard for progression free survival (PFS) between those receiving cetuximab+BSC (best supportive care) and those receiving panitumumab+BSC. They note that there is a statistically significant difference in hazard for overall survival (OS) between cetuximab+BSC and panitumumab+BSC, with patients receiving cetuximab+BSC having longer OS but state that the panitumumab study is subject to a large cross-over, potentially biasing the results against panitumumab. The Assessment Report concludes that the HR for OS is therefore subject to confounding. It is noteworthy that the Assessment Report states that	We thank Amgen for this further description and justification of their analyses to adjust for confounding. We acknowledge that calculation of HRs for these analyses was not appropriate here.

Cross reference to PenTAG report	Company Comment	PenTAG Response
AMGEN		
	Amgen presented reasonable analyses to adjust for cross-over in the study by Amado et al,(1) leading to an estimate of OS advantage of 2.74 or 3.13 months, depending on the method of adjustment used (overall survival estimated by splitting response rates and fitting parametric models, or overall survival estimated by aggregating survival across response rates and calculating the area under the Kaplan Meier curves), for panitumumab compared to BSC. However, the Assessment Report 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 included in the indirect comparisons described in section 4.2.1.7 of the Assessment Report, although we recognize that our estimates adjusted for crossover are used later in the Assessment Group's economic analysis. For the method (to overcome the confounding associated with treatment 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. <u>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 6.78 in the BSC arm and 9.91 in the panitumumab arm yielding an average survival gain of 3.13 months. The accompanying HR using this</u>	

Cross reference to PenTAG report	Company Comment	PenTAG Response
AMGEN		
	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. 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.	
Section 6.2.6.1. Drug Acquisition Costs and Dose Intensity: Cetuximab, page 103 ***"Merck Serono assumes a guaranteed NHS price of £136.50 for 20 ml (100 mg) vial for cetuximab. We believe that this price is that which would be available nationally."***	The NICE Methods Guide states that the reference case analysis should be based on the list price with the discounted price included as sensitivity analysis (instead of being used as the reference case).(2) *"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*	We took advice from NICE regarding which price of cetuximab to use in the assessment report; i.e. £136.50 for 20 ml (100 mg) vial.

Cross reference to PenTAG report	Company Comment	PenTAG Response
AMGEN		
	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. The review date for the appraisal will be informed by the period of time over which any such agreements can be guaranteed." We would like to seek clarification as the approach undertaken in the Assessment Report may not be consistent with the NICE Methods Guide.(2)	
Section 7.1.3.1.3.3. OS for Panitumumab+BSC, Page 147 ***"First, we fitted a Weibull curve to OS for the panitumumab+BSC group corresponding to the panitumumab+BSC vs BSC RCT, by minimising the sums of squares of differences between the actual and estimated survival probabilities, using survival probabilities at four-weekly intervals. This gives a mean OS of 9.9 months based on analysis of the underlying IPD (see page 37, Amgen's submission)."*** ***"Amgen's analysis of the IPD suggested that, after adjusting for cross-over, the mean OS in the BSC group is 2.7 months less than for the panitumumab+BSC group."*** ***"We therefore estimate the mean OS for the BSC group as the mean OS for the panitumumab+BSC group minus***	The Assessment Report uses a common comparator, BSC from the cetuximab plus BSC vs BSC trial, for its indirect comparison analysis. A key assumption underlying the choice of BSC from the cetuximab trial as a common comparator is that the baseline patient characteristics between the cetuximab and panitumumab trials are similar (consequently there should be no/minimal bias in the indirect comparison results). It is noteworthy that 100% of patients in the panitumumab trial received two lines of prior chemotherapy compared to around 20% in the cetuximab trial.(3, 4) Therefore, it appears that panitumumab monotherapy was not studied in the same population as cetuximab monotherapy given that panitumumab was studied in a patient population that had failed more, i.e. at least two, prior therapies compared to the cetuximab patient population. The Assessment Report estimated the mean OS for BSC (based upon the cetuximab trial) as 6.2 months. The OS for panitumumab and BSC from the panitumumab trial, relative to the OS estimated for BSC in the cetuximab trial was estimated by fitting a Weibull curve to the summary data (that is, the published data), which resulted in a mean OS of 9.9 months. The analysis undertaken by Amgen to estimate OS in the BSC arm accounting for treatment crossover was deemed reasonable by the	We agree that patient populations should be reasonably similar in order to justify conducting an indirect comparison. However, we believe that the patient populations in the cetuximab vs best supportive care (BSC) randomized controlled trial (RCT), and the panitumumab vs BSC RCT are indeed reasonably similar. We agree that 100% of patients in the panitumumab RCT received at least two lines of prior chemotherapy, but according to the reference cited by Merck Serono (Jonker et al, 2007(3)), more than 82% of people in the cetuximab RCT received at least two lines of prior chemotherapy, not 20% as claimed by Amgen. It is impossible to say exactly how many people received at least two prior lines of chemotherapy, because Jonker et al (2007) only state the number of people who received one and two prior lines of treatment combined. We agree with the information in the second paragraph. Concerning Amgen's first point in their third paragraph, this changes the estimate of mean OS for panitumumab and BSC only incrementally. Further, the ICER for panitumumab vs BSC decreases only incrementally, from £150,000 to £148,000 per QALY.

Cross reference to PenTAG report	Company Comment	PenTAG Response
AMGEN		
the 2.7 months = 9.9 – 2.7 = 7.2 months."	Assessment Group and was used to estimate the mean OS for the BSC group in the panitumumab trial by subtracting 2.7 months from the panitumumab mean OS. We believe that the analysis in the Assessment Report is suboptimal for three reasons. First, although the Assessment Group deemed the analysis undertaken by Amgen to account for crossover as reasonable and used the mean survival difference of 2.74 months (based on the method of estimating overall survival by splitting response rates) between panitumumab and BSC, the corresponding estimates of mean survival for panitumumab of 9.74 months and for BSC of 7.00 months – based upon patient-level data and reported in the Amgen submission data – were not used. Given that these figures were estimated using actual patient level data, rather than an approximation (as used by the Assessment Group), they are likely to be more accurate. If these estimates for OS had been used (assuming a mean difference of 2.74 months between panitumumab and BSC), the OS estimate for panitumumab using the Bucher technique would have been higher at 8.6 months (9.74*(6.2/7.00)=8.6) instead of 8.5 months, and the incremental gain for panitumumab compared to BSC would have been higher at 2.4 months compared to 2.3 months leading to more favourable cost-effectiveness results for panitumumab. Second and more importantly, given that the cost-effectiveness model developed by the Assessment Group does not split survival by response rates, using the estimates of mean survival for panitumumab and BSC of 9.91 and 6.78 respectively and the corresponding mean survival difference of 3.13 months (based on the method of estimating overall survival by aggregating survival across response rates) presented in the Amgen submission would have been more appropriate. In this instance, using the Bucher technique, the OS estimate for panitumumab would have been higher at	Concerning Amgen's second point in their third paragraph, while their argument is plausible, the impact on the ICER for panitumumab vs BSC is small: from £150,000 to £134,000 per QALY. Concerning Amgen's third point in their last paragraph; first, we repeat that the patient baseline characteristics are sufficiently similar to justify an indirect comparison. Furthermore, it is only possible to compare the clinical and cost-effectiveness of panitumumab vs cetuximab and cetuximab+irinotecan using an indirect comparison. Therefore, we defend our multi-treatment comparison. Having said this, we agree that it would be informative to perform a direct comparison of the cost-effectiveness of panitumumab vs BSC using the clinical data from the RCT of panitumumab vs BSC. As suggested by Amgen, when we set: • the mean OS for panitumumab to 9.91 (and assuming parameter gamma of Weibull is unchanged from our base case analysis), and setting the mean OS for BSC to 6.78 (assuming gamma of Weibull is unchanged from our base case analysis), and assuming a mean of 10 doses of panitumumab (as in the panitumumab RCT); i.e. not adjusted for the indirect comparison • and setting the mean PFS for panitumumab to four months and the mean PFS for BSC to 2.15 months (i.e. unadjusted, directly from the panitumumab RCT) • the ICER for panitumumab vs BSC decreases from £150,000 to £109,000 per QALY. Also as suggested by Amgen, when we repeat the above, but set OS for BSC to 7.2, rather than 6.8, the ICER for panitumumab vs BSC decreases from £150,000 to £119,000 per QALY. We would like to repeat that these analyses rely on

Cross reference to PenTAG report	Company Comment	PenTAG Response
AMGEN		
	9.1 months (9.91*(6.2/6.78)=9.1) instead of 8.5 months with a higher incremental gain of 2.9 months again leading to more favourable cost-effectiveness results for panitumumab. Third, the use of a common comparator, BSC from the cetuximab plus BSC vs BSC trial may be questionable given the differences in baseline characteristics. The differences in the estimates of PFS and OS in the BSC arm of the two trials lead to problems with the indirect comparison that could bias against panitumumab. For example, PFS (in the BSC arm) was shorter in the panitumumab trial than in the cetuximab plus BSC vs BSC trial (2.2 months compared to 2.7 months, according to the Assessment Group analysis). Hence, in the indirect comparison, PFS for panitumumab is 'uprated' from 4.0 months in the actual panitumumab trial (according to the Assessment Group analysis) to 5.1 months in the indirect analysis. Given that the Assessment Group relate PFS to time on treatment, the amount of panitumumab treatment assumed to be given is also uprated, from 10 doses to 12.7 doses. However, OS in the BSC arm of the panitumumab trial was longer than that in the cetuximab plus BSC vs BSC trial even when treatment crossover is controlled for (7.2 months compared to 6.2 months, according to the Assessment Group analysis). Hence in the indirect comparison, OS for panitumumab is 'down-graded' from 9.9 months to 8.5 months, which results in a lower OS gain for panitumumab compared to that observed in the trial (after adjusting for crossover). The net result of the Assessment Group's indirect analysis significantly increases the costs associated with panitumumab whilst reducing the survival advantage associated with panitumumab. This is likely to lead to an unreasonable and unfavourable increase in the ICER associated with panitumumab. Given the uncertainties with performing an indirect comparison, a direct analysis using the survival gain	the accuracy of Amgen's broad-brush assumption for adjustment to OS for BSC for cross-over to panitumumab treatment to yield an OS of panitumumab vs BSC of either 2.7 or 3.1 months.

Cross reference to PenTAG report	Company Comment	PenTAG Response
AMGEN		
	for panitumumab reported in the Amgen submission should be preferred. The table below summarises the results of using alternative estimates and methods to estimate the mean OS gain with panitumumab (see Table 1).	
Section 7.2.3. Cost-Effectiveness Results, Table 52 Page 179 ***"Probability that panitumumab provides extension to life expectancy compared to current standard care of >3 months is low."***	Tables 52 assesses panitumumab against all of NICE's End of Life (EoL) criteria. The Assessment Report concludes that panitumumab does not qualify for consideration as EoL treatment based on failing to meet the condition that 'treatment provides extension to life expectancy compared to current standard care of >3 months'. Specifically, the Assessment report states that the probability that panitumumab provides extension to life expectancy compared to BSC of over 3 months is low. It is noteworthy that using the method that is in line with the cost-effectiveness model developed by the Assessment Group, i.e. not splitting survival by response rates, the mean survival difference (presented in the Amgen submission) for panitumumab compared to BSC is 3.13 months based on observed Kaplan Meier curves for the panitumumab WT KRAS group and the BSC mutant KRAS group. The accompanying HR using this method is 0.657 (95% CI 0.497 to 0.868). It is also noteworthy that this is in line with that observed for cetuximab, which meets the criterion that 'treatment provides extension to life expectancy compared to current standard care of >3 months' with mean extension to life expectancy of 3.9 months. It is therefore highly plausible that panitumumab could qualify for consideration as EoL treatment based on NICE criteria should the method adjusting for crossover that is in line with the modelling approach undertaken by the Assessment Group be used.	To recap: Amgen present two possible estimates for the OS benefit of panitumumab vs BSC: 2.7 months and 3.1 months. If it is considered that 2.7 months is most likely, then panitumumab would not qualify for end of life (EoL) because this is less than the required three months. If it is considered that 3.1 months is most likely, then panitumumab would qualify for EoL. We are not able to say which estimate is more likely. However, clearly, regardless of which estimate is more appropriate, panitumumab is borderline on this particular EoL criteria. However, Amgen do not mention another relevant EoL criteria, that the 'estimates of extension to life are robust'. We believe that this is very doubtful given that Amgen's estimate of the extension to life result from their crude method for adjusting for cross-over in the panitumumab vs BSC RCT.
Section 1.3.2. Summary of benefits and risks, Page 19 ***"The rapid cross-over of 76% of patients originally allocated to***	The above should read: "The rapid cross-over of 76% of patients originally allocated to BSC to treatment with panitumumab (median time to cross-over 7.1 weeks) is ~~less~~ likely to have had an extensive confounding effect."	This sentence should be amended as proposed i.e.: *The rapid cross-over of 76% of patients originally allocated to BSC to treatment with panitumumab (median time to cross-over 7.1 weeks) is likely to have had an extensive confounding effect.*

Cross reference to PenTAG report	Company Comment	PenTAG Response
AMGEN		
BSC to treatment with panitumumab (median time to cross-over 7.1 weeks) is less likely to have had an extensive confounding effect."		
Section 2.5.3. Panitumumab (Amgen®, Vectibix), Page 38 ***"Skin toxicities, hypomagnesaemia, and diarrhoea were the most common treatment-related toxicities observed."*** ***"The most common AEs (incidence ≥20%) are skin toxicities (i.e. erythema, dermatitis acneiform, pruritus, exfoliation, rash and fissures), paronychia, hypomagnesemia, fatigue, abdominal pain, nausea, diarrhoea and constipation."***	The paper by Van Cutsem et al (reference 5 of MTA assessment report) states that AEs (incidence ≥20%) are skin toxicities (i.e. erythema, dermatitis acneiform, pruritus, exfoliation, rash and fissures), paronychia, fatigue, abdominal pain, anorexia, nausea and diarrhoea.	Section 2.5.3, page 38: The last two paragraphs should be amended in line with the SmPC to read as follows: *Panitumumab is contraindicated in patients with a history of severe or life-threatening hypersensitivity reactions to the active substance or to any of the excipients.(5)* *Commonly reported adverse reactions occurring in ≥20% of patients were gastrointestinal disorders (nausea, diarrhea and vomiting), fatigue, paronychia; and skin toxicities (pruritus, erythema, dermatitis acneiform, exfoliation, rash and fissures).(5)*
Section 4.2.1.4.3. Panitumumab+ BSC vs BSC, Page 52 ***"The median time to cross-over was seven weeks (range 6.6–7.3) and the median follow-up after cross-over was 61 weeks (range 1–103). Median duration of treatment and dose intensity was not reported."***	This should read "The median time to cross-over was seven weeks (range 6.6-7.3) and the median follow-up after cross-over was 61 weeks (range 18-103). Median duration of treatment and dose intensity was not reported".	The sentence should be amended as proposed; i.e.: *The median time to cross-over was seven weeks (range 6.6-7.3) and the median follow-up after cross-over was 61 weeks (range 18-103). Median duration of treatment and dose intensity was not reported.*
Section 4.2.1.6.2.3. Panitumumab+BSC vs BSC, Table 12 Page 64	The median PFS for PAN+BSC vs BSC in Table 12 should read as 'Median PFS (months)' instead of 'Median PFS (weeks)'.	Table 12 (page 64); Row 6, Column 4 heading should be corrected as proposed; i.e.: *Median PFS (months)*
Section 4.2.1.7. Indirect comparison of cetuximab and panitumumab, Page 71 ***"However, the study by Amado***	This should read "However, the study by Amado and colleagues is subject to a large number of patients randomised to receive BSC actually receiving panitumumab+BSC during the progressed disease stage, potentially biasing the results against	This sentence should be corrected as proposed: *However, the study by Amado and colleagues is subject to a large number of patients randomised to receive BSC actually receiving panitumumab+BSC during the progressed disease stage, potentially*

Cross reference to PenTAG report	Company Comment	PenTAG Response
AMGEN		
and colleagues is subject to a large number of patients randomised to receive BSC actually receiving panitumumab+BSC during the progressed disease stage, potentially biasing the results against cetuximab."	~~cetuximab~~ panitumumab."	*biasing the results against panitumumab.*
Section 6.4.3. Safety data: panitumumab, Table 40 Page 132	The title of Table 40 should read "Table 40. AEs experienced by patients with KRAS WT status receiving PAN in ~~Van Cutsem~~ Amado et al."	Table 40 (page 133) caption should be corrected as proposed: *Table 40. AEs experienced by patients with KRAS WT status receiving PAN in Amado et al.*

2. PenTAG response to comments from Merck Serono

Cross reference to PenTAG report	Company Comment	PenTAG Response
MERCK SERONO		
–	Merck Serono believes that cetuximab plus BSC or in combination with irinotecan qualifies for consideration of the end-of-life criteria in the third line treatment of metastatic colorectal cancer for the following reasons: • Cetuximab plus BSC or in combination with irinotecan offers an extension of life of more than three months. Effectively, the Karapetis et al. study shows statistically significant improvement of median overall survival for cetuximab plus BSC (9.5 months) versus BSC (4.8 months). • Life expectancy of patients in third line treatment is less than 24 months. • The patient population targeted by cetuximab plus BSC in third line treatment ranges from 260 to 390 patients. We understand that NICE considers the "small population" criteria per indication in this instance; we believe that this patient range could be considered as small for England and Wales. • Additionally, no other treatments offering comparative benefits are available on the NHS in	We do indeed suggest in our report (p177) that cetuximab meets all EoL criteria, subject to patient numbers. However, we believe that it is necessary to consider patient numbers across all indications for cetuximab, not just for colorectal cancer. Merck Serono does not mention this. We state (p178) that cetuximab+irinotecan meets some of the EoL criteria, but in addition to the size of the patient population, we also question whether the estimate of the extension to OS is robust. Merck Serono does not mention this.

Cross reference to PenTAG report	Company Comment	PenTAG Response
MERCK SERONO		
	terms of improving life expectancy associated with an improvement in quality of life compared to BSC(6, 7) PenTAG agrees that cetuximab plus BSC reaches the end-of-life criteria, subject to patient numbers. As noted above we confirmed that in this indication patient numbers will be below 400 per annum.	
–	PenTAG's main disagreement with Merck Serono economic modelling is related to the input of mean treatment duration. We understand that mean duration of treatment is one of the key drivers of the economic case along with time in the progression-free and progressive disease health states. In the PenTAG report the mean time on cetuximab plus BSC treatment is 4.8 months compared to 2.6 months in the company submission. Similarly a figure of 8.8 months was used by Pen TAG for cetuximab plus irinotecan compared to 4.4 months in the company submission. To help resolve this difference, Merck Serono will endeavour to collect real life estimate of the treatment duration in current UK clinical practice.	We note that Merck Serono will try to collect estimates of cetuximab treatment duration in current UK clinical practice. However, we caution that if Merck Serono produce such information, there would then follow a range of methodological problems with the use of such data. For example, if treatment duration is taken from current practice, then so too should all clinical effectiveness; e.g. OS and PFS, in order to ensure consistency of evidence. This would then sadly result in the loss of randomization of the clinical effectiveness evidence.
–	In the cetuximab submission, Merck Serono reported the regression parameter for the Weibull function modelling the PFS and OS Kaplan-Meier curves of BSC and cetuximab plus BSC. The Assessment Report comments in this relation that: *"We did not use precisely the same PFS curve as Merck Serono, because this function is commercial in confidence (CiC). We specified that PFS follows a Weibull distribution, as this is a flexible function, widely used in cancer survival analysis."* This has resulted in the BSC PFS curve presented by PenTAG (page 139) fitting the Kaplan Meier curve less well than that presented in the original submission by Merck Serono. This has the effect of artificially inflating the efficacy of best supportive care and subsequently skewing the ICER calculation in favour of BSC.	This is a minor point. First, it is the mean PFS that determines the ICER, not the exact shape of PFS. We deliberately set the mean PFS in our model to equal the corrected mean PFS in Merck Serono's model of 2.72 months. Note that Merck Serono's model, before the logical corrections discussed in our report, was 2.61 months. This explains the very slight discrepancy in modelled PFS between the PenTAG and Merck Serono models. Second, if we had modelled PFS for BSC with the same (incorrect) mean of 2.61 months as Merck Serono, then the ICER of cetuximab vs BSC would decrease only incrementally, from £98,000 to £97,000 per QALY.

Cross reference to PenTAG report	Company Comment	PenTAG Response
MERCK SERONO		
–	In the cost comparison of bevacizumab plus FOLFIRI against cetuximab plus FOLFIRI, clinicians in the second line setting would generally use bevacizumab at 10mg/kg plus FOLFIRI rather than 5mg/kg. Taking this dose into account, cetuximab plus FOLFIRI would save the NHS more than £9,000 per patient compared to the use of bevacizumab plus FOLFIRI which is in contrast to the data presented by the manufacturer of bevacizumab.	We agree that the recommended dosage for bevacizumab in addition to FOLFIRI is 5mg/kg or 10mg/kg for colorectal cancer,(8) whereas Roche have only assumed 5mg/kg. However, since there is no effectiveness evidence for bevacizumab in this setting, the cost calculations undertaken by Roche (regardless of the dose assumed) do not help with decision-making.
–	Since April 2011, KRAS testing is provided for free by Merck Serono ensuring that the best diagnostic test (PCR) is performed and accurately identifying patients suitable for cetuximab treatment. Merck Serono would like to inform the Assessment Group and NICE that the KRAS testing is using the TheraScreen PCR assay (CE marked for In Vitro Diagnostics). In terms of sensitivity TheraScreen PCR will detect 1% mutant allele in a background of wild type in samples with 20% tumour.	We thank Merck Serono for this information.

3. PenTAG response to comments from Roche

Cross reference to PenTAG report	Company Comment	PenTAG Response
ROCHE		
Page 24	*'There is an absence of RCT evidence of bevacizumab combined with non-oxaliplatin chemotherapy'* should be amended. This statement is not factually correct. It should be amended to reflect the fact that there is evidence demonstrating the efficacy of bevacizumab in combination with non-oxaliplatin based chemotherapy in previously untreated mCRC but not in subsequent lines of treatment. This comment similarly applies to page 207.	This sentence should be amended to: *There is an absence of RCT evidence of bevacizumab combined with non-oxaliplatin chemotherapy in the context of this appraisal'*
Page 36	Here it is noted that bevacizumab is '*contraindicated in patients who … have untreated central nervous system metastases'*. This is not factually correct.	SmPC checked. Please amend as proposed; i.e. remove comment to read: *It is contraindicated in patients who are pregnant, and have hypersensitivity*

Cross reference to PenTAG report	Company Comment	PenTAG Response
ROCHE		
	Whilst this was previously a contraindication for bevacizumab this is no longer the case and section 4.3 of the bevacizumab's SPC ('contrainidications') contains nothing on CNS metastases. This comment should therefore be removed.	*to products derived from…*

4. PenTAG response to commentator comments

Cross reference to PenTAG report	Commentator Comment(s)	PenTAG Response
Royal College of Nursing		
–	*There are no comments to make on this document at this stage on behalf of the Royal College of Nursing (RCN). The RCN will participate in the next stage of this appraisal. …'*	–

Cross reference to PenTAG report	Commentator Comment(s)	PenTAG Response
Royal College of Pathologists		
–	The cost effectiveness figures submitted by Merck-Serono for Cetuximab were different from those calculated by PenTAG. It seems that the majority of this difference arose from differences in the length of treatment assumed by each party. The PenTAG calculations were based on an assumption of continuous treatment until disease progression (which was the protocol adopted in the two trials which provide most of the evidence). I wonder whether this would fit with activity in the "real world" – the study cited in this document by Annemans et al. suggests that the treatments may be more cost effective they are stopped when there is no evidence of cost effectiveness.	This analysis is correct, although we're not entirely sure about the meaning of the last sentence. Assuming this is suggesting that prompt stopping of treatments in case of non-response is likely to increase cost-effectiveness we would in general agree, with the very strong proviso that while it is clear that cost would fall with early stopping, it is also possible that effectiveness will fall too because categorization of non-response is not totally objective. We also note that the estimates of overall survival with early stopping used by Annemans et al required several assumptions which reduce the certainty we can have about their conclusions
–	Mutation analysis for Kras was done retrospectively in both trials and there was some concern about the sensitivity of the laboratory test. Only the codon12/13 hotspot was tested whilst mutations in Kras can occur in codons 64 and 146 and this may be an	Thank you for this useful additional information. This raises the possibility that the sub-group effect associated with KRAS WT/mutant status may be underestimated in the trials. If performed using current gold standard methods of analysis it may be

Cross reference to PenTAG report	Commentator Comment(s)	PenTAG Response
Royal College of Pathologists		
	important confounder. More importantly, there was no mention in document of mutational analysis of Braf. This gene lies downstream of Kras and is mutated in approximately 10% of all colorectal cancers. Braf and Kras mutations ares mutually exclusive and thus a proportion of the Kras WT tumours may harbour Braf mutation. Furthermore, Braf is reported to be a poor prognostic factor and it is possible that the metastatic CRCs may thus be comparatively enriched for these mutations. It is reported that Braf mutations may confer resistance to anti-EGFR therapies and thus the proposed studies delineated in the research recommendations should include an analysis of Braf mutation (as well as the other Kras mutation hotspots and mutational analysis of PIK3CA).	that the number of missed KRAS mutated individuals would fall, so reducing the number of individuals who receive EGFR inhibitors inappropriately. However, without knowing the extent of this reduction it is impossible to speculate on what the effect on effectiveness and cost-effectiveness might be. The interesting information about Braf might have similar implications but again without quantification the impact on effectiveness and cost-effectiveness is highly speculative. The point about need to ensure gold standard measurement of mutation status in any future research is well made.

Cross reference to PenTAG report	Commentator Comment(s)	PenTAG Response
Royal College of Physicians		
–	*'I write on behalf of the NCRI/RCP/RCR/ACP/JCCO who are grateful for the opportunity to jointly respond to this consultation. Our experts found the report to both comprehensive and objective and have not raised any areas of concern. However, as this is a substantial document, we feel that steps could be taken to add to its utility by making it more reader-friendly. This could be achieved by producing an abbreviated version with the key points highlighted.'*	We agree that the report is a challenging read but are constrained by the requirements of the process and the template.

Cross reference to PenTAG report	Commentator Comment(s)	PenTAG Response
NICE Sponsor Team, Department of Health		
–	*'Thank you for the opportunity to comment on the technical content of the assessment report for the above multiple technology appraisal.* *I wish to confirm that the Department of Health has no substantive comments to make regarding this consultation.'*	–

Figures and tables

Table 1. Summary results of using alternative estimates and methods to estimate the mean OS gain with panitumumab (Amgen)

	Results adjusted using Bucher (using different estimates of Panitumumab OS)			**Anticipated results if Assessment Group had performed a direct analysis**	
	Assessment Group's analysis (OS 9.9)	Amgen analysis (OS 9.74)	Amgen analysis (OS 9.91)	Using appropriate survival gain of 3.13 months	Using survival gain of 2.74 months
OS PAN	8.5	8.6	9.1	9.9	9.9
OS BSC	6.2	6.2	6.2	6.8	7.2
Mean OS gain (mths)	**2.3**	**2.4**	**2.9**	**3.1**	**2.7**
BSC, best supportive care; OS, overall survival; PAN, panitumumab					
NB: Table taken from Amgen's comments on the CiC redacted assessment report					

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