AMGEN RESPONSE TO ASSESSMENT REPORT

We have reviewed the Assessment Report and the analyses undertaken by the Assessment Group 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 Assessment Report, and in our response, we have addressed points of clarification, key analyses undertaken in the Assessment Report and identified factual inaccuracies.

1. 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].

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 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. 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 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.

2. <u>Section 6.2.6.1. Drug Acquisition Costs and Dose Intensity: Cetuximab, Page 103</u>

"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 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].

3. 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 2.7 months = 9.9 – 2.7 = 7.2 months."

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 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 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 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.

	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 Panitumumab	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 (Months)	**2.3**	**2.4**	**2.9**	**3.1**	**2.7**

4. <u>Section 7.2.3. Cost-Effectiveness Results, Table 52 Page 179</u>

"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.

5. Factual Inaccuracies

- **Section 1.3.2. Summary of benefits and risks, Page 19**

  "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."

  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."*

- **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[4].

- **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".*

- **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)'.

- **Section 4.2.1.7. Indirect comparison of cetuximab and panitumumab, Page 71**

  "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 cetuximab."

  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 ~~cetuximab~~ panitumumab."*

- **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."

References

[1] Amado RG, Wolf M, Peeters M, Van Cutsem E, Siena S, Freeman D, et al. Wild-Type KRAS Is Required for Panitumumab Efficacy in Patients With Metastatic Colorectal Cancer. Journal of Clinical Oncology. 2008;26(10):1626-34.

[2] National Institute for H, Clinical E. Guide to the Methods of Technology Appraisal. London: NICE; 2008.

[3] Jonker DJ , O'Callaghan CJ , Karapetis CS , et al . Cetuximab for the treatment of colorectal cancer . N Engl J Med . 2007 ; 357 (20): 2040-2048.

[4] Van Cutsem E, Peeters M, Siena S, etal. Open-label phase III trial of panitumumab plus best supportive care with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. J Clin Oncol 2007;25: 1658-64.