AMGEN RESPONSE TO APPRAISAL CONSULTATION DOCUMENT (ACD)

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.

1. 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[1].

"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."

Consequently, the approach undertaken in this appraisal is not consistent with the NICE Methods Guide[1]. 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.

2. 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 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.

3. Factual Inaccuracies

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."*

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)[2]. 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."*

References

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

[2] 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.