LRiG

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Dear Jeremy

LRiG has considered the new data presented by Merck in respect of cetuximab for the treatment of squamous cell carcinoma of the head and neck. Our comments are attached.

Please let me know if you need anything further.

Yours sincerely

[redacted]

Cetuximab for the treatment of Squamous Cell Carcinoma of the Head and Neck

ERG comments on Additional Evidence submitted by Merck Serono in response to ACD - February 2009

New Target Subgroup

Manufacturer is now proposing a new subgroup not previously considered in their submission or economic model: patients aged under 65 years and with a Karnofsky Performance Score (KPS) of 90 or 100.

Insufficient information has been provided in the Appendix to allow the ERG to incorporate the new subgroup into the company model and verify the economic results reported by the manufacturer.

No new survival charts were provided by the manufacturer, so it is not possible to assess the appropriateness of the new models of overall survival and progression-free survival as a basis for projecting outcomes beyond the trial period. Therefore, the ERG is not able to comment on the validity of the modelled overall survival gain of 3.77 months.

As a result, the ERG is unable to re-estimate economic results for this subgroup after incorporation of the ERG recommended amendments to the model, and assess the robustness of the incremental cost-utility ratio (£92,804/QALY gained) claimed for this subgroup, except to point out that the amendments to the model previously identified by the ERG would increase the cost-effectiveness ratio considerably (by 20% or more).

No mention is made of the absence of cetuximab efficacy for patients suffering metastatic disease. It is noteworthy that in the Cox step-wise regression analysis reported in the Clinical Study Report (Table 14.2-1.2) to identify factors influential on overall survival, four variables were included in the final model: KPS and previous chemotherapy were forced into the final model, trial medication was included as the (automatic) final step, and only metastatic disease features by virtue of meeting the inclusion criteria. It is therefore remarkable that the manufacturer did not also include this factor when constructing their new subgroup.

No information has been provided concerning the number of patients included in each treatment arm of this new subgroup in the EXTREME trial. This is important for assessment of the robustness of survival modelling estimates, which become very uncertain where only small numbers of patients are involved.

In the absence of patient numbers from the trial data, we can estimate the number of patients in each arm if we assume that all factors are uncorrelated. For the group of patients under 65 years old and with KPS of 90 or 100, the totals are 87 receiving cetuximab+platinum and 82 platinum only (38% of the trial population), whereas if only the subset of these patients with non-metastatic disease are considered the totals reduce to 41 and 38 respectively (18% of the trial population). It may be appropriate to consider whether these numbers are sufficient to provide reliable evidence of effectiveness and cost-effectiveness, since the trial was not powered for pre-specified subgroup analyses, let alone a new smaller compound subgroup ("Further analyses, such as subgroup analyses, were purely exploratory. All subgroup analyses were stipulated in the protocol." Vermorken 2008 NEJM).

Utility Weighting for End-of-Life

The manufacturer presents evidence for calculating a weighting factor to apply to model estimates of cost-effectiveness to recognise a priority for End-of-Life benefits. A study by Petrou (2005 Health Economics) using population EQ-5D values obtained from the Health Survey for England 1996, is cited as the basis for attributing 'normal' utility values to survival gains for SCCHN patients. Comparing the weighted average EQ-5D score for adults under 65 (0.821 - not 0.789 as used by the manufacturer) to the mean utility score of additional life years in the submitted model (0.678), indicates

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that on this basis a utility weighting of x 1.21 would be appropriate. If instead a more generous assumption is made that survival gains be weighted as 'perfect health' (1.0), the utility weighting rises to 1.475. However, the required weighting necessary to correspond to an ICER of £30,000/QALY is estimated by the manufacturer as x 2.65 using the original model. If the ERG recommended model amendments were to be applied, the required weighting to establish acceptability would most likely fall into the range x 3.0 - x 4.0.

Summary

- The manufacturer has proposed a new patient sub-group as the basis for use of cetuximab in treating recurrent/metastatic SCCHN

- The manufacturer has not provided sufficient detailed information to allow the ERG to replicate their economic results, or to assess the robustness of evidence for this subgroup.

- The ERG expects that when previously identified amendments to the model are applied, the economic results for this subgroup will worsen markedly.

- The ERG questions whether the number of patients included in this subgroup is sufficient to yield robust evidence of efficacy, especially for the magnitude of any life extension.

- The ERG questions the absence of an additional criterion, excluding patients with metastatic disease from the new subgroup, in view of the strength of evidence that in metastatic disease there is little or no benefit to patients.

- The ERG notes that estimates of 'End-of-Life' utility weighting based on imputing utility values for additional life either from the general population, or assuming 'perfect health' would not be sufficient to satisfy the maximum acceptability threshold of cost-effectiveness. Indeed a weighting more than double those proposed would probably be required.