STA ERRATUM

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Pertuzumab in combination with trastuzumab and docetaxel for the treatment of HER2 positive metastatic or locally recurrent unresectable breast cancer: A Single Technology Appraisal

This report was commissioned by the NIHR HTA Programme as project number 11/139/01

Erratum completed 24 June 2013

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

The manufacturer identified four issues in relation to factual errors in the original ERG report. This resulted in minor changes to the ERG report. The pages of the report affected are presented here. Text that remains unaltered is greyed out.

5.3 Critique of manufacturer's decision model

The submitted economic model has been developed as a Microsoft Excel application. It is logically structured and implemented competently. There is adequate annotation provided to allow most features to be readily understood, with key variables, range names and data sources identified throughout. Standard principles of cost-effectiveness modelling (such as correct use of discounting and mid-interval correction) have been followed throughout. In this section we comment only on areas of concern, grouped into major issues, and minor issues.

5.3.1 Major issues

Response to clarification questions

The manufacturer did not provide the information requested by the ERG in their priority questions B1 and B2, which concern alternative survival analyses from the CLEOPATRA[18] trial data (see Appendix 2). In addition, the manufacturer stated that these are not clarification questions, implying that the ERG was thereby exceeding their brief. The manufacturer claims that the method of analysis (alternative censoring definition) is 'significantly flawed', and also that consideration by the ERG of the impact of specified subgroups on modelled estimates of cost-effectiveness is 'not legitimate.

It is important to respond to these statements to demonstrate:

- that these matters fall within the scope of the ERG's role in the STA process
- that the analyses requested are relevant to the Appraisal Committee's consideration of the available evidence for this STA
- that failure to provide the requested analyses has seriously impeded the ERG's assessment of the accuracy and robustness of the cost-effectiveness results presented by the manufacturer.

ERG's role

Unlike the NICE Multiple Technology Appraisal (MTA) process, the STA process does not involve the independent academic group (ERG) in developing their own decision model. However, it does require the ERG to comment on the robustness and accuracy of the submitted model and the data used to populate the model, and where possible to carry out sensitivity analyses using the manufacturer's submitted model to indicate what they consider to be the most reliable estimate of cost-effectiveness. Both survival and patient subgroups are explicitly included in the STA evidence submission template, and the ERG is required to consider these matters alongside all other issues on which the manufacturer is asked to submit evidence.

arms of the trial follow separate long-term trends which are approximately linear. However from about 1000 days onwards both trial cohorts show the same sudden increase in hazard (upward 'kink') so that the placebo arm crosses the stable trend line of the Munich Registry data.[46] This provides a strong indication that the informative censoring has caused bias in the final section of the analysis of CLEOPATRA[18] data,[18] and should not be used as the basis for projective modelling of survival. Similar anomalies were detected in the PFS and TTOT Kaplan-Meier analyses. These problems can only be resolved by rerunning the Kaplan-Meier analyses using the alternate censoring method requested by the ERG.

Figure 8 Comparison of CLEOPATRA[18] overall survival cumulative hazard data (censoring at last observation date) with Munich registry data[46]

5.3.3 Exploration of subgroups

The EMA[34] observed that patients with only non-visceral disease in the CLEOPATRA[18] trial (n=178) appeared to gain much less benefit from use of pertuzumab, than did the larger visceral disease group (n=630). Despite additional multivariate Cox regression analyses this difference persisted, and no potential biological explanations have been offered. The manufacturer has suggested that the discrepancy may be attributable to the smaller number of non-visceral patients and some differences between treatment arms in baseline characteristics.

5.3.4 Modelling and projection of progression-free survival data

In the manufacturer's base-case decision analysis, Kaplan-Meier analysis results are used directly up to 35 months (pertuzumab) and 27 months (control) post-randomisation. A common long-term exponential projection is applied to both arms from 32 months (pertuzumab) or 35 months (control). A separate exponential trend is used in the pertuzumab arm in the period between 27 and 32 months. This approach leads to mean undiscounted PFS estimates of [redacted] months (pertuzumab) vs [redacted] months (control), a gain of [redacted] months favouring pertuzumab.

Although the ERG considers that the Kaplan-Meier data available are subject to serious bias, an exploratory projective modelling exercise was undertaken to assess the sensitivity of the manufacturer's method of curve-fitting to alternative assumptions. [redacted], the ERG considered that long-term hazard trends should only be estimated based on the segment of the trial data after 600 days. Moreover, it was observed that if the final data points showing evidence of serious bias (sudden upward rise) are ignored, then the long-term trends appeared to follow simple near-linear trajectories. On this basis the ERG fitted linear trend lines to estimate long-term linear hazard trends to each trial arm and applied these to project PFS from day 600 onwards.

This approach yielded ERG exploratory PFS mean undiscounted estimates of [redacted] months (pertuzumab) and [redacted] months (control), indicating a PFS gain of [redacted] months favouring pertuzumab. Thus the ERG confirms that addition of pertuzumab to trastuzumab and docetaxel results in a clear improvement in PFS, though the size of that improvement is subject to considerable uncertainty.

5.3.5 Modelling and projection of overall survival data

In the manufacturer's base-case decision analysis [redacted] of the estimated life extension occurs in the post-progression health state, and [redacted] of the discounted QALY gain occurs after disease progression. However, it is clear from the Kaplan-Meier analysis of post-progression survival data from CLEOPATRA[18] (Figure 10) [redacted]