Gefitinib for the first-line treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC)

LRiG comments on additional information provided by the manufacturer-post 2\textsuperscript{nd} AC meeting held March 4, 2010

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1 BACKGROUND

This document provides feedback to NICE regarding this appraisal and communication following the 2nd Appraisal Committee (AC) meeting that was held March 4, 2010. Since that meeting NICE have been in communication with AstraZeneca. AstraZeneca have provided written feedback regarding the modelling errors identified just prior to that meeting. The ERG (LRiG) provide here their initial preliminary impressions regarding that explanation. For clarity Appendix 1 includes the LRiG identification of the modelling errors in the documentation presented for the 2nd AC meeting.

It is worth noting that to adhere to NICE timelines the manufacturer was given a very short period of time in which to respond to the Appraisal Consultation Document (ACD). Equally, LRiG was allowed only four days to examine that response and provide a report to the AC. As has been mentioned in both the manufacturer and LRiG responses, this has limited their ability to address all relevant issues in an adequate manner.

2 INITIAL ERG COMMENTS

Below are the preliminary initial comments provided by the ERG on AstraZeneca’s letter of response regarding the identified model errors. The actual response is included in Appendix 2 of this document.

AstraZeneca have acknowledged a problem with the information provided within their submitted model regarding Progression-Free Survival (PFS). They believe that this error has no material effect on the cost-effectiveness results for gefitinib when compared to existing chemotherapy regimens.

The ERG have considered their argument, noting particularly the Kaplan-Meier analysis output included as an appendix to their letter. The following points arise from a very preliminary examination of these data and their possible implications for the economic results generated by the model. A full critique would require considerably more time to ensure that all relevant components of the model have been explored.

1) The ERG confirms the transcription error identified by the manufacturer.

2) The ERG does not agree that adjusting the analysis for this factor fully explains the discrepancy reported by the ERG at the ACD meeting.
3) Comparison of the Kaplan-Meier output and the PFS estimates produced by the PFS estimation equation within the manufacturer’s model for gefitinib shows an accumulated bias of 0.72 months overstating the estimated PFS per patient up to the end of data collection. It is estimated that this difference will continue to grow when the model is projected to the time horizon to a final level of about 1.0 month. Taken together with the previously identified under-estimation of PFS in the comparator arm of IPASS, it appears that a substantial discrepancy remains uncorrected by the problem mentioned by AstraZeneca.

4) It is not possible to be definitive about the impact of such an uncorrected bias on the estimated ICERs, but it seems likely to be substantial and must be added to the increases arising from other model problems previously described in the ERG report. Several days further analysis would be required to provide these results.

5) In the note provided by the ERG following the ACD meeting two potential causes of the PFS problem were suggested - either the type of unstratified statistical analysis used by the manufacturer was responsible, or there were implementational issues with the Excel model. We now believe that both these suggestions are probably true. If so, then a reliable set of economic results cannot be provided to the Appraisal Committee until the manufacturer accedes to the request made in the ACD to carry out independent (i.e. stratified) modelling of the arms of the IPASS trial, to allow the Committee to assess the uncertainty associated with the choice of analytical approach. Alternatively, the manufacturer could accede to the request made originally by the ERG to make a limited extract of the trial IPD available for independent analysis.

3 CONCLUSION

It is the opinion of the ERG that it would require 3-5 days for full examination of the currently available data to provide a clearer perspective of the impact of uncorrected bias on the estimated ICERs. In addition the provision of the additional requested unstratified analysis would allow for a more accurate estimate of the parameters that remain uncertain. The ERG is not able in the first instance to provide this additional analysis prior to the AC meeting that has been scheduled for April 6, 2010. As noted earlier the manufacturer has not provided the data or unstratified analysis to allow exploration of the causes of differences in PFS within the model. Therefore it is not possible, with currently available time and information for the ERG to provide the AC with accurate estimates on which to base their decision in this appraisal.
Appendix 1 LRiG comments on identified errors

Document sent to NICE March 9, 2010 following the 2nd AC meeting held March 4, 2010

Modelling problem identified in AZ Gefitinib STA submitted model

Shortly before the NICE Appraisal committee meeting on 4th March 2010, in which responses to the ACD issued for gefitinib as first-line therapy for advanced non-small cell carcinoma, an anomaly was detected in the results generated by the economic model submitted by the manufacturer, which has an important impact on the cost-effectiveness estimates for gefitinib.

This relates specifically to the estimation of the mean progression-free survival (PFS) for EGFR mutation positive patients receiving treatment with gefitinib. Examination of the summary outcomes produced by the model (see below), indicates an unusually high PFS estimate (10.22 months) leading to apparently substantial increases in PFS relative to the gain in overall survival (OS), amounting to about double the OS gain compared to treatment with a gemcitabine doublet. In the comparison with pemetrexed the anomaly is even more extreme, since the model suggests a substantial PFS gain at the same time as a reduction in OS. In the light of experience with several previous appraisals of chemotherapy for NSCLC, these results appear to be unlikely; in previous Appraisal Committee meetings discussions have focussed on the likely proportion of observed PFS gains which might reasonably be expected to translate into OS gains in the range of 0% - 100%, but has not previously been presented with evidence suggesting >200% ratio of effects.

Markov model results

<table>
<thead>
<tr>
<th></th>
<th>Mean PFS (mths)</th>
<th>Mean PPS (mths)</th>
<th>Mean OS (mths)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gefitinib EGFR M+</td>
<td>10.22</td>
<td>13.87</td>
<td>24.08</td>
</tr>
<tr>
<td>Gem/carb EGFR M+</td>
<td>5.98</td>
<td>14.88</td>
<td>22.11</td>
</tr>
<tr>
<td>Gem/cis EGFR M+</td>
<td>7.09</td>
<td>15.51</td>
<td>22.60</td>
</tr>
<tr>
<td>Pem/cis EGFR M+</td>
<td>7.77</td>
<td>16.83</td>
<td>24.60</td>
</tr>
</tbody>
</table>

PFS = Progression Free Survival, PPS = post progression survival, OS = Overall survival
Since all these unexpected results would be explained if the estimate of mean PFS in the gefitinib were found to be faulty, the ERG examined the information made available by the manufacturer from the IPASS trial. Using the output from the Kaplan-Meier analysis of PFS in the two treatment arms, the area under the survival curve (AUC) was calculated. This is a very close approximation to the true value of PFS since the trial is very mature, with less than 4% of patients still unprogressed at the end of data collection. This was then compared with the mean PFS estimated by the ERG’s own PFS model, and the output from the manufacturer’s model.

<table>
<thead>
<tr>
<th>Mean PFS (months)</th>
<th>Gemcitabine/carboplatin</th>
<th>Gefitinib</th>
<th>Gain in mean PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC estimate</td>
<td>6.84</td>
<td>8.81</td>
<td>+1.97</td>
</tr>
<tr>
<td>ERG model estimate</td>
<td>6.85</td>
<td>8.76</td>
<td>+1.91</td>
</tr>
<tr>
<td>Manufacturer’s model</td>
<td>5.98</td>
<td>10.22</td>
<td>+4.24</td>
</tr>
</tbody>
</table>

Although the manufacturer’s model gives a rather low estimate of PFS in the comparator arm, the major anomaly is clearly the larger overestimation of PFS in the gefitinib arm, leading directly to more than doubling of the gain attributable to gefitinib shown by the IPASS data.

This discrepancy is readily revealed in the chart below. The minor under-estimation in the comparator arm arises in the period 100-200 days where the Weibull model (dashed blue line) is noticeably lower than the observed trial data (blue diamonds). The larger over-estimation in the gefitinib arm is due to a consistent mismatch between Weibull model used by the manufacturer (dashed gold line) and the trial data (yellow/red triangles), which is in favour of gefitinib across the whole trial period. The solid lines show the much closer correspondence of the ERG’s own models to the observed data.
There are two possible explanations for these discrepancies: either the imposition of joint estimation of Weibull models (unstratified analysis) has generated these effects directly, or the statistical model has been incorrectly implemented in the Excel decision model. The ERG has not had available the necessary time and resources to determine which explanation are correct.
Dear Dr George

RE: Gefitinib for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC)

Thank you for giving AstraZeneca the opportunity to clarify the situation regarding the anomaly the Evidence Review Group (ERG) detected in the revised economic model, developed in response to the Appraisal Committee's request for further information.

The root cause of the anomaly is a typographical error in the gefitinib EGFR M+ progression-free survival (PFS) Kaplan Meier (KM) data that was included in the background worksheets of the revised economic model.

The AstraZeneca statistician who worked on the issues relating to model selection and fit had identified and corrected this error. The statistical analyses and models presented in the response to the Appraisal Committee meeting are therefore correct and based on the right PFS KM curve data (see page 5 Figure 2).

It is regrettable that, due to an oversight and time pressures, this error was not also corrected in the PFS background worksheet that was supplied with the revised economic model. However, the Appraisal Committee should note the PFS KM data played no part in the cost-effectiveness calculations.

A copy of the SAS PFS output for the EGFR mutation positive treatment arms of IPASS has been included as an Appendix to this letter. To correct the gefitinib EGFR M+ PFS data in the model a value of 1 should be inserted between cells F69 and F70 in the “Eqns PFS” worksheet and a value of 0.037 should be inserted at the end of the data column in cell F91. The effect of the missing value was to shift the gefitinib PFS KM
data to the left by 30 days. This error contributed to the reduction in the PFS advantage for gefitinib reported by the ERG.

You will note that the mean PFS for gefitinib EGFR mutation positive of 10.22 months (310.9 days) estimated using the revised economic model is consistent with the mean of 9.83 months (299.0 days) reported in the SAS KM PFS output (Appendix).

AstraZeneca would like to apologise to NICE, the Appraisal Committee and the ERG for the confusion and additional work this typographical error has caused.

It is unfortunate that time constraints limited the opportunity for the ERG to corroborate the gefitinib PFS KM data in the revised economic model before the additional analyses were conducted and presented to the Appraisal Committee. This could have been done by either contacting AstraZeneca directly, reviewing the PFS KM curves in the NEJM IPASS publication or comparing the spline models fitted to these data to those fitted to the PFS data in the original ERG report.

I look forward to contacting you on Monday to discuss the way forward.

Yours faithfully

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