LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Erlotinib monotherapy for the maintenance treatment of non-small cell lung cancer after previous platinum containing chemotherapy

(ERG comments on manufacturer's response to 2nd ACD)

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DOES NOT CONTAIN IN CONFIDENCE DATA

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INTRODUCTION

The ERG has been requested by NICE to comments on the following issues raised during consultation on the second ACD:

- Overall survival estimate
- Generalisability of the SATURN stable disease results (squamous and non-squamous) in the UK
- Overall stable disease model

Where these ERG comments relate specifically to sections of the manufacturer's response to the second ACD (MR), the relevant sections of the MR have been inserted in *italics*.'

Section .1.1: *Overall survival estimate*

The overall survival (OS) figure of 4.2 months quoted in the MR is the figure calculated by the ERG for the initial ERG report. Given the submission of new data from the manufacturer between the first two Appraisal Committee (AC) meetings, the ERG provided a revised estimate of OS.

The ERG considers that their revised estimated gain in OS for patients with squamous lung cancer and stable disease following chemotherapy is the most defensible estimate available from the trial data, since it addresses the whole life expectancy of patients in both arms and avoids any potential bias from truncating data at different stages of maturity. It should be noted that the ERG estimated OS gain is 3.36 months with 95% confidence intervals of 1.45 and 5.26 months.

Section 1.2 of MR(see individual points)

"Section 1.2.1: *The proportion of squamous histology stable disease patients with EGFR mutation*

> *In SATURN itself only 1 of the 190 squamous histology stable disease patients randomized had an EGFR mutation. This equates to an EGFR mutation incidence of 0.005%. Given this extremely small incidence the notion that the OS advantage observed in SATURN would not hold in UK clinical practice due to the exclusion of patients with EGFR mutations is unreasonable."(MR pg 4)*

The demographics provided for the squamous cell SD group in the submitted model did not provide information on EGFR mutations. Table 10 of the CSR shows 69.9% of patients with IHC positive EGFR status, 13.6% negative and 16.5% indeterminate/missing.

On the basis of the available information it was reasonable for the committee to assume that a similar proportion of SD squamous patients would also be EGFR positive, much greater than the proportion usually seen in European populations. The new information presented by the manufacturer appears to be so different from expectation that it suggests a very strong interaction effect, which should have been presented to the committee in the manufacturer's submission of clinical evidence.

"Section 1.2.2: *The proportion of squamous histology stable disease patients who were 'never smokers'*

> *In fact, in SATURN only 13 or the 190 squamous histology stable disease patients (6.86%) in the study were never smokers, this is not unusually high for lung cancer patients under treatment in the UK.*
>
> *In any case, the reason that the proportion of 'never-smokers' in SATURN would be of interest to the Committee when discussing the reproducibility of the SATURN results is that it represents a surrogate for patients with a high rate of EGFR mutations which as noted above is an invalid concern in the squamous histology group.*
>
> *Given the small magnitude of the percentage of squamous patients who were never smokers in SATURN and the contents of section 1.1.1 the Committee's concerns on the validity of the survival gain observed in SATURN due to the study containing too many 'never-smokers' appear unfounded. (MR pg 4)"*

The manufacturer did not provide separate demographic analyses for the histology subgroups within the stable disease population in their second submission. Appendix 1 of the second manufacturer's submission provided comparative demographic and EGFR results for the whole stable disease population to demonstrate apparent balance between trial arms, but did not provide these results separately for squamous and non-squamous subgroups so that there was no indication that the combined proportions of patients with specific smoking histories (about 20% 'never smokers') would be any different based on histology. Each of the three new models submitted included a demographics table, but all three were identical and therefore for at least two of the models these data were not based on the relevant trial population for the specific model. Due to the short time available to the ERG to review the new submission and the three models, it was not possible to investigate this discrepancy before the second AC meeting, or to obtain and validate the correct figures for each subgroup.

"Section 1.2.3: *The proportion of squamous histology stable disease patients who were 'Asian'*

In the squamous histology group of SATURN only 7.9% patients were Asian and over 92% were White. This percentage is considerably less than the proportions of Asian patients in studies that have recently been accepted by NICE in support of other positive appraisals (notably the IPASS study in the appraisal of gefitinib in mNSCLC (TA192) and the ToGA study in the appraisal of trastuzumab in mGC (TA208)).

If the Committee's concerns on this proportion are due to the increased likelihood of Asian patients having tumours harboring activating EGFR mutations, the 0.005% EGFR mutation incidence noted above should allay that concern.

Overall it is unreasonable to suppose that the percentage of Asian patients in the squamous SD group in SATURN will have any appreciable impact on the efficacy seen relative to what might be achieved in clinical practice in England and Wales."(MR pg 4)

The same considerations apply to racial differences as to EGFR status and smoking history as described above. Full disclosure of demographic statistics for each subgroup would have allowed the ERG to comment with confidence on differences.

Section 1.2.4: *Performance status*

The ERG has no comment to make.

"Section 1.2.5: *The second-line treatments received by squamous histology stable disease patients in SATURN*

In the ACD the Committee note their concerns that overall survival advantage offered by erlotinib as observed in SATURN may not hold in clinical practice due to the utilization of 2nd line therapies not typically seen in the United Kingdom within the study. Such concerns are not new in NICE appraisals and are the product of the divide between the decision problem as defined by typical practice in the NHS and that in the rest of the world.

.....

In the case of the squamous histology stable disease population of SATURN the second line treatments are indeed balanced and so the Committee's logic that the overall survival gain seen in SATURN would not hold in UK in practice appears unreasonable."(MR pg5)

On the basis of the analysis of second-line treatments in the whole trial, there appears to be no bias in types of treatment given. However, no similar analysis was available for stable disease squamous patients, so this assertion could not be validated. However, the ERG considers that this is unlikely to have made more than a very minor impact on the model results.

Section 1.2.6: *Pemetrexed first-line treatment*

The ERG agrees that this issue is not relevant to the squamous subgroup.

"Section 1.2.7: *The utilisation of a post-hoc defined subgroup for the purposes of economic modelling*

> *In the ACD the Committee express their concern that the squamous histology stable disease group was post-hoc defined. Given the prime reason for presenting this group was because in first ACD it was noted that the decision problem was different for the stable disease group split by histology it appears unreasonable this is raised as an issue within the 2nd ACD." (MR pg5-6)*

The ERG considers that this comment confuses two distinct issues:

- in general placing reliance on subgroup results when the trial was not powered nor designed for this purpose opens the possibility of finding accidental differences arising from random events. For this reason it is important to exercise increasing caution over clinical effectiveness claims based on small post-hoc subgroups.

- in this particular case the decision problem depends on the existing comparators consistent with current NICE guidance. Since pemetrexed is recommended for maintenance therapy only in non-squamous patients for whom it is the comparator, the comparator for squamous patients is necessarily different, i.e. best supportive care/placebo.

The evidence of clinical effectiveness in the case of stable disease squamous patients is based on a very small subgroup and so it must be considered that, though suggestive of benefit, the evidence may not be sufficiently robust to allow reliable quantification of that benefit to address the squamous stable disease decision problem.

Section 1.5: *The generalisability of the SATURN non-squamous histology stable disease results to UK clinical practice*

The manufacturer cites differences in baseline characteristics in the stable disease non-squamous subgroup as a likely cause of bias against erlotinib in the SATURN trial. Unfortunately, these baseline data were not provided in the evidence submitted or in the manufacturer's non-squamous model, so the ERG is not able to verify these differences directly. However, simple calculations suggest that the differences in ECOG status and smoking history involve small patient numbers and are not statistically significant (p=0.16 and 0.26 respectively from the chi-square test). Moreover, no mention is made of other important prognostic factors (such as gender and disease stage) which could show different results. The ERG would need access to detailed patient level data on baseline characteristics and patient outcomes to be able to give a definitive comment on this issue.

A more important source of uncertainty concerns the mode by which patient benefit is produced when pemetrexed+cisplatin is used rather than other third-generation chemotherapy regimens for first-line treatment of advanced NSCLC. In previous trials the modest gains in survival were generally the result of improved response to treatment leading to extended progression-free survival (PFS) times, with post-progression survival (PPS) largely unaffected. By contrast, the results of the JMDB trial indicated that for patients with non-squamous disease, the additional gain in OS for pemetrexed+platinum compared to gemcitabine+platinum was mainly the result of extended PPS, the PFS results being very similar. This suggests that the pemetrexed combination therapy may be producing a qualitatively different effectiveness benefit in addition to the gains already available from other third generation treatments.

In the light of these findings it is unclear whether erlotinib used as maintenance therapy is delivering benefit through a similar or different pathway to pemetrexed, and therefore whether the gains seen in the SATURN trial from maintenance therapy will supplement or merely duplicate the extended advantage seen in JMDB when patients receive pemetrexed+cisplatin as first-line chemotherapy. This question can only be resolved by a clinical trial similar to SATURN involving patients who are pre-treated with pemetrexed+cisplatin.

Section 1.6: *Overall stable disease model*

Relevance to the decision problem

There are potentially four distinct decision problems covered by this appraisal:

1) Patients receiving pemetrexed+cisplatin as first-line chemotherapy and achieving 'stable disease' as their best response.

As discussed above in relation to 1.5, the ERG considers that this problem cannot be addressed by the use of SATURN trial results since none of the trial patients received pemetrexed+cisplatin as first-line chemotherapy. Moreover there is sufficient empirical evidence from the JMDB trial to suggest that an interaction (of unknown type) between pemetrexed and erlotinib in a sequential treatment strategy is a distinct possibility and would invalidate the use of SATURN results in this appraisal.

2) Patients with predominantly squamous disease receiving NICE recommended platinum-based first-line chemotherapy other than pemetrexed and achieving 'stable disease' as their best response.

In this case the SATURN trial results provide appropriate evidence of clinical effectiveness to allow comparison of erlotinib maintenance therapy with a 'no maintenance treatment' comparator.

3) Patients with non-squamous disease receiving NICE recommended platinum-based first-line chemotherapy other than pemetrexed and achieving 'stable disease' as their best response, for whom pemetrexed maintenance therapy is considered suitable.

In this case a combination of results from the SATURN and JMDB trials provides appropriate evidence of clinical effectiveness to allow comparison with a 'no maintenance treatment' comparator.

4) Patients with non-squamous disease receiving NICE recommended platinum-based first-line chemotherapy other than pemetrexed and achieving 'stable disease' as their best response, for whom pemetrexed maintenance therapy is **not** considered suitable.

This comparison is addressed through the version of the manufacturer's model calibrated specifically for the non-squamous subgroup. The manufacturer of erlotinib has not chosen to submit a revised version of this model. The ERG's revised analysis indicated an ICER for erlotinib vs 'no maintenance treatment' of £68,120 per QALY gained.

In response to the second ACD, the manufacturer has submitted a revised model for all stable disease patients, which suggests erlotinib maintenance treatment is cost-effective if no distinction is made by histology, essentially encompassing both decision problems (3) and (4).

Importance of histology in projecting clinical effectiveness

Combining all stable disease patients in a single model without differentiating by histology assumes that patients with squamous and non-squamous histology are broadly similar in terms of known prognostic factors, and that the available clinical trial evidence shows no evidence of heterogeneity attributable to histological differences.

Baseline characteristics

As previously noted, the manufacturer has not provided full and directly comparable baseline statistics for the two histological stable disease subgroups. However, it has been possible for the ERG to derive comparable SATURN data in respect of three important variables:

a) Gender balance – 12.1% of squamous stable disease patients were female, compared to 34.3% of non-squamous stable disease patients, a highly significant difference (χ^2 = 8.8, p=0.003)

b) ECOG performance status – 24.2% of squamous stable disease patients had a score of 0, compared to 34.0% of non-squamous stable disease patients, a significant difference (χ^2 = 5.3, p=0.022)

c) Smoking history – of squamous stable disease patients 6.8% had never smoked and 44.2% were current smokers, compared to 27.6% of non-squamous stable disease patients who had never smoked and 58.2% who were current smokers. These differences in smoking history are highly significant (χ^2 = 80.6, p<0.0001).

Trial evidence

Comparing SATURN results for PFS between the squamous and non-squamous subgroups indicates that there is no evidence of any difference based on histology (log-rank test p=0.54 in erlotinib arm, p = 0.63 in placebo arm; Cox regression shows strong treatment effect (p<0.001) but no histology effect (p=0.51)).

By contrast, analysis of the SATURN PPS data indicates that although histology has no influence for patients in the erlotinib arm (log-rank test p=0.43), there is a strong histology influence on PPS in the placebo arm in which squamous patients had a significantly worse long-term prognosis than non-squamous patients (p=0.004 on log-rank test, p=0.01 in Cox regression).

The ERG remains of the opinion that the squamous and non-squamous subgroups represent quite different populations in terms of important prognostic factors evident from baseline characteristics and also that the results of the SATURN trial suggest that following disease progression long-term survival differs in patients not receiving maintenance therapy by histology. Taken together it appears to be inappropriate to combine these groups in a single analysis of OS, especially as a basis for long-term projection of OS which may lead to unpredictable under or over-estimation of survival benefits.

Section 2 *Summaries of clinical and cost effectiveness interpretations*

In Table 5 (MR pg 14) the manufacturer shows an ERG estimate of OS gain for the stable disease population as a whole alongside separate estimates for the squamous and non-squamous subgroups. This is misleading, since the combined estimate was prepared for the ERG's first report to the AC, when only aggregate data were available for analysis. As noted earlier, this result was superseded when additional data were provided for the separate subgroups allowing more accurate results to be obtained. This comparison confirms the risks of projecting OS on the basis of undifferentiated data when the underlying population is essentially heterogeneous as detailed above in response to section 1.6 of the manufacturer's response to the second ACD.