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Dr Carole Longson
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Dear Dr Longson

Re: Appraisal consultation document on erlotinib monotherapy for the maintenance treatment of non-small-cell lung cancer

We welcome the opportunity to review and comment on the appraisal consultation document (ACD) for erlotinib monotherapy in maintenance treatment of non-small-cell lung cancer (NSCLC).

The Appraisal Committee has noted that the manufacturer submitted data analyses for a number of subgroups prior to the marketing authorisation being finalised and as a result of this some of the analyses and subgroups originally presented are no longer relevant for this appraisal.

As per the final marketing authorisation granted for erlotinib maintenance treatment in patients with stable disease after four cycles of platinum-based chemotherapy, and in response to the requests from the Committee, Lilly anticipates that the manufacturer will be submitting new evidence that has not been previously presented or appraised within this current ACD. We are concerned that if substantial new evidence relevant to the marketing authorisation is submitted by the manufacturer at the ACD consultation stage, in particular any comparisons with pemetrexed, we would have no opportunity to comment on the new evidence which may form the basis of the final NICE recommendation.

In light of the above, we would like to request that consultees and commentators are given an opportunity to review and comment on any new evidence provided during the ACD consultation for the licensed patient population.

In addition, we would like to highlight the following comments in relation to questions posed by the Committee relating to the ACD and the Evaluation Report.

Comments on the ACD

Has all the relevant evidence been taken into account?

Evaluation of overall survival benefit

In this appraisal, the Committee discussed the clinical effectiveness evidence for maintenance treatment with erlotinib in the subgroup of patients with stable disease and noted that the only evidence for these patients came from one randomised-controlled trial, SATURN. The Committee also noted that the manufacturer's submission only reported hazard ratios for the difference in progression-free survival (PFS) and overall survival (OS) between the erlotinib and placebo groups. The duration of PFS and OS and the response rates were not provided however we note that these are available in the European Public Assessment Report (EPAR) and Summary of Product Characteristics (SPC) for erlotinib. The values from the EPAR and SPC are shown below:

The SPC for erlotinib reports the following results for patients with stable disease after chemotherapy: Patients with stable disease (n= 487) had:

- PFS HR of 0.68 (95% CI, 0.56 to 0.83; p<0.0001; median 12.1 weeks in the erlotinib group and 11.3 weeks in the placebo group)
- OS HR of 0.72 (95% CI, 0.59 to 0.89; p= 0.0019; median 11.9 months in the erlotinib group and 9.6 months in the placebo group).

As stated in the EPAR the difference in **median** OS between erlotinib and placebo translates into a survival difference of **2.3 months**.

Based on the above and given the marketing authorisation for erlotinib, we do not believe that all the relevant evidence has been taken into account by the Committee to make an informed decision on this appraisal.

Application of the End of Life Criteria

In previous appraisals, as stated in the Update Report on the Application of the "End of Life" Supplementary Advice, the incremental median overall survival from the pivotal trial as well as the incremental mean OS from the economic model have been taken into account. In general, the median and mean results reported were similar giving more certainty around the most plausible value of OS and the subsequent cost-effectiveness ratios. In this appraisal the manufacturer submitted an incremental mean OS for patients with stable disease of 3.3 months based on their economic model while only hazard ratios for OS from SATURN were available for the Committee to assess the life extension criterion of >3 months of erlotinib in the stable disease group. Both median and mean values should be available to enable the Committee to evaluate the evidence consistently.

NICE's supplementary advice to the Appraisal Committees on appraising treatments which may extend life states that the Committee will take into account the cumulative population for each licensed indication when considering whether or not a treatment meets the criteria. We note that the Committee has applied this advice consistently for both the current appraisal and the recent appraisal of pemetrexed (TA190).

Manufacturer's indirect analysis of erlotinib and pemetrexed

The manufacturer conducted an indirect analysis of erlotinib and pemetrexed in patients with non-squamous disease using data from the SATURN and JMEN studies. Lilly is disappointed that this analysis has been marked as commercial-in-confidence, which prevents us from commenting on the accuracy of the results of the analysis conducted. Since the manufacturer's submission, erlotinib has been granted a licence for patients with stable disease only. The pemetrexed license includes patients who responded (partial or complete response) as well as patients with stable disease and this has been recognised by the Committee as an inappropriate comparison for the sub-group of patients under consideration for this appraisal. We agree with the Committee that the indirect comparison performed by the manufacturer is not appropriate for this appraisal.

Erlotinib maintenance treatment in patients receiving pemetrexed /cisplatin first-line

The Appraisal Committee and the ERG have both commented upon the uncertainty about the clinical benefit of erlotinib in patients receiving first-line treatment with pemetrexed/cisplatin, since no patients in the SATURN trial received pemetrexed/cisplatin first-line. This is particularly significant given the fact that pemetrexed/cisplatin was recently recommended for first-line treatment of patients with adenocarcinoma and large cell carcinoma and is likely to become the standard of care for first-line non-squamous NSCLC.

In an effort to address the issue of how patients should be treated after first-line pemetrexed/cisplatin and to provide clinical evidence to form the basis for recommendations, Lilly is currently conducting a randomised controlled trial of pemetrexed maintenance treatment following first-line pemetrexed/cisplatin (study S124).

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

Given that the manufacturer submitted data analyses for a number of subgroups prior to the marketing authorisation being finalised and that some of the evidence originally presented is no longer relevant for this appraisal we believe that it is premature to comment on the suitability of the provisional recommendations at this stage.

We therefore reiterate our request to have a further opportunity to review and comment on any new evidence provided for the licensed patient population during the ACD consultation.

Comments on the evaluation report

Administration costs for pemetrexed and erlotinib

Lilly is pleased to note that the ERG identified issues relating to the costs of pemetrexed.

The manufacturer's submission states that since erlotinib is prescribed at monthly routine monitoring visits, no extra administration cost is incurred to the NHS, only a pharmacy cost. However, in the costing statement for the NICE STA for the second-line treatment of NSCLC with erlotinib (TA162), the NHS reference cost SB11Z for delivering exclusively oral chemotherapy on an outpatient basis has been applied for monitoring erlotinib each month. Lilly considers, in the interests of fairness and consistency, that it would also be appropriate to apply the same NHS reference cost in the current appraisal.

Utility values for erlotinib vs placebo/best supportive care (BSC)

The ERG deemed the utility values used by the manufacturer as unsatisfactory and instead employed utility values from the Nafees study, also used in the recent appraisal of pemetrexed in maintenance NSCLC (TA190), for the sake of consistency between appraisals. The values used were 0.6732 for erlotinib, 0.6568 for pemetrexed and 0.6628 for placebo/BSC.

The higher utility value for erlotinib compared to placebo/BSC implies that no disutility has been assigned to erlotinib to account for toxicities such as rash and diarrhoea and that patients experienced greater symptom reduction on erlotinib (for which no data are presented, only a delay in worsening). In the appraisal of pemetrexed in maintenance treatment, the ERG, commenting on the utilities submitted in Lilly's initial economic model, stated that the use of higher utility values for pemetrexed compared to the BSC arm (0.66 vs 0.58) was counterintuitive since the rate of adverse events (e.g., fatigue) was noticeable higher in the pemetrexed arm than in the placebo arm (3.66% vs 0.64%). Since the SATURN trial showed a higher incidence of grade 3/4 rash (6% vs 0%) and diarrhoea (2% vs 0%) in the erlotinib arm vs the placebo arm, we believe that in line with the approach adopted in the pemetrexed appraisal, toxicities should also be considered in the estimation of utilities for erlotinib.

It should be noted that the utility values used by the ERG are based on patients who had either stable disease or who were responding. Consistent with the erlotinib license, a lower base utility value should be used when evaluating a patient population of those with only stable disease (e.g., 0.6532 for placebo/BSC).

Yours sincerely

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Lilly UK

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