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Reference Erlotinib for the first line treatment of locally advanced or metastatic EGFR-TK mutation positive non-small-cell lung cancer: Appraisal Consultation Document

9th March 2012

Dear Kate

Thank you for the opportunity to comment on the appraisal consultation document for erlotinib for the first line treatment of locally advanced or metastatic EGFR-TK mutation positive non-small-cell lung cancer. In line with wishes of NICE, we have separated our comments into those on the ACD and those on the evaluation report

Appraisal Consultation Document

1. Addressing the ACD's statement '...that the patient access scheme for gefitinib is not straightforward and that hospitals may find the patient access scheme for erlotinib easier to administer" (section 4.5) and in section 4.14 where "The Committee considered the administration costs associated with implementing the gefitinib patient access scheme used in the model and concluded that they were reasonable.." we wish to challenge this view and believe that a more robust analysis of the administration costs of the Single Payment Access scheme is required.

   Our experience with the implementation of the scheme within the NHS has shown that:
   - Research conducted by AstraZeneca demonstrated that in 25% of NHS centres, Pharmacy Technicians implement the scheme
   - It does not take 90 minutes to register a new patient on SPA scheme and the sunsequent re-ordering process. Feedback from a recent survey of NHS centres that use the SPA scheme shows that this takes no more than 30 minutes to register a new patient with the majority of respondents stating it takes 6-10 minutes.

   This significantly reduces the costs per patient managed through the AZ SPA scheme. This feedback is also backed up by survey of NHS centres that currently use the SPA scheme and insight gained from focus groups and advisory boards.
   We have concerns that Roche seem to have to obtained these costs from Expert Opinion but give no further background to how these values were derived. From the Manufacturer's Submission (MS), the cost effectiveness model is very sensitive to the administration costs of the Single Payment Access (SPA) scheme and we believe that a more rigorous assessment of the costs is required to ensure that the Committee can truly assess whether erlotinib is value for money based on a transparent and robust evidence base

In addition based on ongoing dialogue between AstraZeneca and the NHS, a number of enhancements have been made to improve the NHS' experience of the scheme. These include:

- Multiple deliveries (including extended service to now include Saturday delivery
- Multiple patient ordering
- Changes to the administration process (reducing burden on the NHS)
- Web-based ordering & reporting (providing both convenient ordering & transparent audit of Gefitinib patients)

1. In the absence of Phase III randomised trials in which gefitinib and erlotinib have been directly compared, AstraZeneca do not feel that it is appropriate to draw conclusions about the relative rate of adverse event reporting for these 2 compounds. Therefore AstraZeneca would like to request that the following statements are withdrawn from the Appraisal Consultation Document for erlotinib:

   The clinical specialists highlighted that having the choice of two similar treatments enables better management of adverse reactions. The Committee also heard from the clinical specialists that the adverse reactions associated with both these treatments are much less than those associated with chemotherapy but vary (for example, rash is more common with erlotinib and interstitial lung disease with gefitinib). The adverse reactions associated with erlotinib and gefitinib were modest but slightly different.

   and

   The Committee concluded ..... that from a clinical perspective there may be some advantage to having a choice of tyrosine kinase inhibitors for this patient group to improve the management of the rare but more severe adverse reactions.

   In addition to the fact that it may not be appropriate to draw conclusions in the absence of Phase III randomised comparative data, the non comparative data does not support the statement that ILD is more common with gefitinib than with erlotinib, and seems to show that in the first line setting in EGFR mutation positive patients the rates of rash may be similar.

   There have been 6 phase III randomised trials of EGFR-TKIs (erlotinib or gefitinib) used as first-line treatment for advanced NSCLC. Four of the 6 studies were conducted in EGFR mutation-positive patients only (NEJ002, WJTOG3405, OPTIMAL and EURTAC) and 2 were conducted in clinically selected patients (IPASS and First-SIGNAL). Patients in IPASS and First-SIGNAL were Asian, never- or light ex-smokers with adenocarcinoma and thus these study populations had higher EGFR mutation rates than unselected patients. It should be noted that none of these were head to head studies of erlotinib vs gefitinib, therefore all comparisons of rates of adverse events are indirect.

   The ILD and rash reporting rates in these studies are tabulated below:

Study	EGFR-TKI	Rash (all grades)	Rash (grades 3 or 4)	ILD
IPASS (Asian)* (n=1217)	Gefitinib	66%	3.1%	2.6%
First-SIGNAL (Korean)* (n=313)	Gefitinib	72%	29.3%	1.3%
NEJ002 (Japanese) (n=228)	Gefitinib	81%	5.3%	5.3%
WJTOG3405 (Japanese) (n=172)	Gefitinib	74%	2.3%	2.3%
OPTIMAL (Chinese) (n=165)	Erlotinib	75%	2%	0%
EURTAC (European) (n=174)	Erlotinib	80%	13%	1%

**please note that these studies were conducted in a clinically selected population, not EGFR mutation-positive only populations*

Based on the data presented above, the rates of rash in EGFR mutation-positive patients appear similar for 1st-line gefitinib and erlotinib.

On considering the figures for ILD it might appear that the reporting rates for gefitinib are slightly higher than those for erlotinib, however the patient numbers in most of these studies are small and therefore it is difficult to determine whether these percentage values are truly different.

In addition, a large proportion of the gefitinib data has been generated in a Japanese population. It is acknowledged that ILD reporting rates for all treatments are higher in this population, and this is demonstrated specifically for gefitinib by the AstraZeneca cumulative reporting rates for ILD in patients receiving IRESSA. The reporting rates of ILD are expressed in number of patients who experienced ILD per 100 patient-years of IRESSA patient exposure.

	Cumulative reporting rates for ILD-type events as of 05 January 2012[a]		
	No. of patients reporting ILD	**Total patient exposure (patient-years)**	**No. of patients per 100 patient-years**
Japan	2286	62012	3.69
EU	142	7555	1.88
Rest of World (RoW) excluding Japan[b]	597	82626	0.72
South-East (SE) Asia[c]	154	46514	0.33
Total (Global)	**2883**	**144638**	**1.99**

[a] These estimates of reporting rates include all reports of ILD-type events in IRESSA-treated and treatment-blinded patients, regardless of reported causality

[b] Including SE Asia, US and EU data.

[c] SE Asia comprises data from China, Hong Kong, Korea, Philippines, Malaysia, Indonesia, Singapore, Thailand and Taiwan

Recently data has become available for erlotinib in the Japanese patient population from the Japanese Post Marketing Surveillance (PMS) Study (Scrip 10 February 2012). Detailed safety data is available for 3488 patients treated with erlotinib. These patients were mainly pre-treated. The reporting rate for ILD events was 5%, higher than the rate seen non-Japanese patients in the OPTIMAL and EURTAC studies, but similar to the gefitinib Japanese PMS study (also mainly pre-treated patients) where the incidence of ILD was 5.8%.

We believe that the Committee should request similar data from Roche to enable an informed and balanced conclusion is reached on ILD and EGFR-TKIs.

2. We would like to challenge the Appraisal Committee's conclusion that erlotinib offers an advantage regarding the dose variation available. We believe that the dose variation is only an advantage when the erlotinib's rash is taken into account. The Appraisal Committee does not take into account the increased cost of nursing time, drug wastage and outpatient visits when adjusting the erlotinib dose due to rash.

Evaluation Report

1. We believe that the ERG's recommendation of pooling EURTAC and OPTIMAL is inappropriate. We believe their recommendation was based on an incorrect assumption that Roche assessed the similarity of the studies using median PFS (see section 3.23 of the Appraisal consultation document) when in fact it was

the hazard ratios they compared in their assessment of heterogeneity (see figures 22 and 23 of the manufacturer submission where the forest plots with the fixed- and random-effects HRs are displayed). Given the negligible overlap of the confidence intervals for the treatment effect (measured using the hazard ratio) in the two studies, it is not appropriate to pool these heterogeneous effects together to estimate the overall efficacy of erlotinib; quoting an average value for the intervention effect when the magnitude of the treatment effect observed in each study is not consistent and is likely to be misleading and unreliable.

We hope you have found our response to the consultation on the Appraisal Consultation Document useful and informative. Please don't hesitate to contact me if further clarification required

Yours sincerely

[redacted]

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