NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

Single Technology Appraisal (STA)

Afatinib for treating epidermal growth factor receptor mutation positive locally advanced or metastatic non-small cell lung cancer

Dear [redacted],

The Evidence Review Group, Liverpool Reviews and Implementation Group, and the technical team at NICE have now had an opportunity to take a look at the submission received on the 30 September 2013 by Boehringer Ingelheim. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **5pm on Thursday 7th November 2013**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please fully complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be emailed to us separately as attachments or sent on a CD.

If you have any further queries on the technical issues raised in this letter then please contact Melinda Goodall Technical Lead (melinda.goodall@nice.org.uk). Any procedural questions should be addressed to Kate Moore Project Manager (kate.moore@nice.org.uk) in the first instance.

Yours sincerely

Helen Knight
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

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Section A: Clarification on clinical effectiveness data

Mixed treatment comparison

The mixed treatment comparison (MTC) presented uses studies of patients with mixed EGFR status. For progression-free survival (PFS), where both independent and local investigator assessments are available, PFS measured by independent assessment has been used. Updated overall survival (OS) data for Mok et al. 2009 and Maemondo et al. 2010 are available in Fukuoka et al. 2011 and Inoue et al 2012 respectively but have not been incorporated. In order to complete the network, the hazard ratio for erlotinib vs. chemotherapy (which can be one of any four combinations of treatment) is replicated four times for the following comparators: (i) erlotinib vs. docetaxel/cisplatin, (ii) erlotinib vs. docetaxel/carboplatin, (iii) erlotinib vs. gemcitabine/cisplatin, (iv) erlotinib vs. gemcitabine/carboplatin.

A1. **Priority Question:** Please clarify the impact of using the hazard ratio derived from the same study (EURTAC) four times within the same network on the results from the MTC.

A2. **Priority Question(s):** Please conduct the following sensitivity analyses for the MTC (using updated OS data, where available):

A3. :

i. Using only data from the population of patients with EGFR mutations (see Table below for full list of studies to be included and excluded) for both PFS and OS.
ii. Excluding EURTAC even if this precludes a comparison with erlotinib. This analysis should be conducted for the current MTC and as in (i).

Non-priority question: Conduct (i) and (ii) using local investigator assessments (where available) instead of independent assessment for PFS

Table of studies to be included and excluded in modified MTC for A2 (iii)

Included	Excluded
LUX-Lung 3	Chang et al. 2001
LUX-Lung 6	Comella et al. 2000
Han et al. 2012 (First SIGNAL)	Fossella et al. 2003
Mitsudomi et al. 2010	Gridelli et al. 2002
Mok et al. 2009 and Fukuoka et al. 2011	Mazzanti et al. 2003
Maemondo et al. 2010 and Inoue et al. 2012	Melo et al. 2002
Rosell et al. 2012 (EURTAC)	Rosell et al. 2002
	Scagliotti et al. 2002
	Scagliotti et al. 2008*
	Schiller et al. 2002
	Smit et al. 2003
	Thomas et al. 2006
	Zatloukal et al. 2003

* This study is referred to as Scagliotti et al. 2009 in the MS but the ERG believe the study being referred to is actually Scagliotti et al. 2008 (Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naïve patients with advanced-stage non–small-cell lung cancer. JCO 26 (21): 3543-3549). Scagliotti et al. 2009 is a retrospective analysis and includes no relevant data,hence Scagliotti et al. 2009 should also be excluded from the MTC

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LUX-Lung 3 and LUX-Lung 6 trials

A4. **Priority Question:** In LUX-Lung 3, for each arm of the trial (afatinib and pemetrexed/cisplatin), please provide a breakdown of the baseline characteristics and findings for OS, local investigator assessed PFS, tumour response and adverse events (AEs) for the following two subgroups: (i) Asian and (ii) non-Asian. For AEs, please provide the data in the same format as Table 56 and 57 of the manufacturer's submission.

A5. For each of the LUX-Lung 3 and LUX-Lung 6 subgroup analyses presented on pages 78 and 87 of the manufacturer's submission, please provide an overall test for interaction.

A6. Page 82 and page 90 of the manufacturer's submission present forest plots for the time to deterioration in coughing, dyspnoea, and pain related items of QLQ-C30 and QLQ-L13 in LUX-Lung 3 and LUX-Lung 6. Here the n value for all analyses is 345 and 364 respectively. Please clarify if this implies a 100% response to these questions.

A7. Page 142 of the manufacturer's submission states the median number of cycles in LUX-Lung 3 was 16 (336 days) but on page 144 this is not reported for LUX-Lung 6 (it just states median 398 days). Please provide the median number of cycles.

Systematic review and mixed treatment comparison

A8. Page 93 of the manufacturer's submission states: "*The systematic review was designed to capture randomized controlled trials, meta-analyses and systematic reviews comparing any licensed chemotherapy and targeted therapies for locally advanced or metastatic NSCLC for either 1st line or 3rd/4th line therapy.*" Please clarify why second line was not included.

A9. Page 96 of the manufacturer's submission states that "of the 66 first line studies identified in the systematic literature review, only 8 were conducted in an EGFR mutation positive population" and implies this is why the other 58 studies were excluded. However, the manufacturer later includes further studies which were not conducted in an EGFR mutation positive population in its MTC. Please list the 58 studies and provide the reasons why they were not considered for the MTC.

A10. Page 95 of the manufacturer's submission states: "*The three additional records identified through other sources mentioned in the PRISMA diagram, were relevant articles that were published after the systematic search was completed Rosell et al. (2012), Han et al. (2012), and Miller et al. (2012).*" Please clarify how these were identified.

A11. Page 234 of the manufacturer's submission states: "*As the systematic literature review was undertaken in March 2012, a literature search was done using the same databases as before. The terms searched for were "EGFR mutation NSCLC," the reference sections for each paper identified were checked to ensure that no articles were missed. The search aimed to identify systematic reviews that had taken place on EGFR mutation positive patients after March 2012*" Please clarify when the additional search was carried out.

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Section B: Clarification on cost-effectiveness data

Kaplan Meier analysis results

In order to allow a full validation of the model's accuracy in replicating the trial data, please provide the following:

B1. **Priority Question:** Full Kaplan-Meier analysis results (see example overleaf) showing K-M survival estimates at each event time, for each treatment arm in the LUX-Lung 3 trial for Overall Survival (OS), Progression-Free Survival (PFS) and Post-Progression Survival (PPS). These analyses should use the most recent data cut, be based on local assessment of disease progression, and any patient still at risk at the date of data cut should be censored at the date of data cut, not date of last contact/assessment. These data should be presented separately for the following populations: (i) Asian (ii) non-Asian (iii) All patients.

B2. **Priority Question:** Full Kaplan-Meier analysis results (see example overleaf) showing K-M survival estimates at each event time, for each treatment arm in the LUX-Lung 6 trial for Overall Survival (OS), Progression-Free Survival (PFS) and Post-Progression Survival (PPS). These analyses should use the most recent data cut, be based on local assessment of disease progression, and any patient still at risk at the date of data cut should be censored at the date of data cut, not date of last contact/assessment.

Utility values

B3. **Priority Question**: Please provide PFS utility values (mean and standard error) from the LUX-lung 3 trial for two groups of patients: (i) Asian and (ii)) non-Asian. Two sets of figures should be produced (i) figures including all AEs, and (ii) figures excluding key AEs.

B4. **Priority Question**: Please provide details of compliance with EQ-5D assessments in the LUX-lung 3 trial. Two tables, similar to Table A4 (p119) in the BI HE LUX-Lung 3 report, should be produced: (i) Asian and (ii) non-Asian

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Example from SAS of typical output requested from analyses specified above (B1 and B2)

Product-Limit Survival Estimates						
SURVIVAL		Survival	Failure	Survival Standard Error	Number Failed	Number Left
0.000		1.0000	0	0	0	62
1.000		.	.	.	1	61
1.000		0.9677	0.0323	0.0224	2	60
3.000		0.9516	0.0484	0.0273	3	59
7.000		0.9355	0.0645	0.0312	4	58
8.000		.	.	.	5	57
8.000		.	.	.	6	56
8.000		0.8871	0.1129	0.0402	7	55
10.000		0.8710	0.1290	0.0426	8	54
SKIP...		0.8548	0.1452	0.0447	9	53
389.000		0.1010	0.8990	0.0417	52	5
411.000		0.0808	0.9192	0.0379	53	4
467.000		0.0606	0.9394	0.0334	54	3
587.000		0.0404	0.9596	0.0277	55	2
991.000		0.0202	0.9798	0.0199	56	1
999.000		0	1.0000	0	57	0

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Section C: Data marked as in confidence

C1. On page 55 of the manufacturer's submission, it is unclear why smoking status and ECOG performance status are highlighted in green; is this intended to be marked as data in confidence? It should also be noted that if so, the values can be determined from the data that is not highlighted.

C2. The PFS data for common mutations presented in Table 15 and marked as being academic in confidence are presented elsewhere in the manufacturer's submission un-marked (PFS events on page 87 and the hazard ratio and confidence intervals in Table 25 on page 106). Please clarify whether these data are academic in confidence.

C3. On page 172 and 173 of the manufacturer's submission, the name of the expert clinician with whom the manufacturer consulted is not always marked as being commercial in confidence. Please clarify if the clinician's name should always be marked as in confidence.

Section D: References

D1. Page 30 of the manufacturer's submission states: "*Afatinib would provide … access to an EGFR TKI with the longest median PFS reported in a 1st line registration study.*" Please provide a reference for this study and ideally also the full document (e.g. PDF) if this has not already been provided.

D2. As highlighted above, the MTC refers to Scagliotti et al 2009. Please clarify if this is the correct citation.