National Institute for Health and Clinical Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Erlotinib monotherapy for the maintenance treatment of advanced or metastatic non-small cell lung cancer

Please find enclosed the ERG report prepared for this appraisal.

You are asked to check the ERG report from Liverpool Reviews and Implementation Group to ensure there are no factual inaccuracies contained within it. If you do identify any factual inaccuracies you must inform NICE by **5pm, Wednesday 31st March 2010** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The attached proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

29th October 2009

Issue 1 Regulatory status

Description of problem	Description of proposed amendment	Justification for amendment	LRiG comments
Page 6 License announcement. Details of the CHMPs opinion on the Roche application for an extension to the Marketing Authorisation (MA) does not represent “licensining”. The EMEA are likely (though not obligated) to act on this opinion and grant the suggested extension to the Marketing Authorisation within 90 days	The current regulatory status of erlotinib maintenance should be made clear	Until final marketing authorisation is extended and wording of change confirmed, Erlotinib remains unlicensed as a maintenance therapy	Thank you for pointing out the inaccuracy. Wording changed to indicate CHMP opinion only

Issue 2 End of life considerations

Description of problem	Description of proposed amendment	Justification for amendment	LRiG comments
Section 1.5 States that the ERG does not think that Roche has met the end of life criteria for patients with non-squamous histology. Given the likely license for Tarceva as a maintenance treatment only for patients with stable disease (SD) after first-line chemotherapy, all patients with non-squamous histology may now be an irrelevant population. Additionally, the reason given for non-squamous patients not being eligible for EoL consideration is that their overall survival (OS gain) is less than	Remove this statement or correct it and indicate that it is now irrelevant	For patients with both non-squamous and squamous tumours with SD after chemotherapy erlotinib maintenance extends OS by 3 months or more, satisfying this criterion for application of end of life considerations	Wording from Section 7.2.2 added to clarify that additional analysis did not substantiate the analysis presented in the MS

3 months This is inconsistent with the information on median OS gain supplied by the manufacturer and reported in Section 4.3.3 (**p34)** of the ERG report			

Issue 3 Range of second-line treatments available to UK NSCLC patients

Description of problem	Description of proposed amendment	Justification for amendment	LRiG comment
In section 4.3 **(final para p. 28)** it is stated that the treatments received by SATURN patients at progression are not typical of those in the UK because NICE recommends only erlotinib and docetaxel, the implication being that these are the only treatments used. A similar issue arises in Section 5.5.5 which states *"a wide range of licensed and experimental treatments are included which are not recommended for use in UK, where only erlotinib and docetaxel are approved by NICE"*	Rewording is required to clarify that treatments other than erlotinib and docetaxel are used in the UK these include (but are not limited to) platinum doublets, pemetrexed (despite NICE guidance) vinorelbine and experimental treatments	Since the ERG raise the possible disparity between second-line treatments in SATURN and those used in UK clinical practice as an issue, it is important for the reader to understand that the range of follow-on treatments in the UK is not as restricted as the ERG imply with only pemetrexed and gefitinib specifically not recommended for second-line use.	The statement is correct as it stands – these are the treatments recommended by NICE

Issue 4 In appropriate linking of medians and Hazard Ratios (HR)

Description of problem	Description of proposed amendment	Justification for amendment	LRiG comment
Section 4.3. 1 **(second para, p29)** states: "*As can be seen from Table 4-7 using the FAS, the median PFS is 12.3 weeks for the erlotinib group and 11.1 weeks for the placebo group. Although this difference of 1.2 weeks between the groups is reported as being statistically significantly different with a HR of 0.71 and a 95% CI of 0.62, 0.82, it represents a small clinical difference".* Given the shape of the survival curves in SATURN, median values substantially underestimate the progression-free survival benefit conferred by erlotinib, which is more accurately reflected in the HR, which describes the full separation of the survival curves. Reduction in the risk of progression as described by the HR and not median survival gain was the primary end-point in this study. The statements on median OS and HR that follow this statement have similar issues to those described here	Reword along the following lines "As can be seen from Table 4-7 using the FAS, the median PFS is 12.3 weeks for the erlotinib group and 11.1 weeks for the placebo group. Although this difference of 1.2 weeks between the groups is small because of the shape of the PFS curves which approach each other at this point, overall the HR for PFS is 0.71 with a 95% CI of 0.62, 0.82, representing a significant 29% reduction in the risk of progression"	Summarising the magnitude of the clinical difference according to the difference in the medians is misleading and not factually accurate in light of the availability of the hazard ratio and given it is the primary end-point of the study.	The data as presented are accurate and no change has been made

Issue 5 Lack of clarity around statistical methodology

Description of problem	Description of proposed amendment	Justification for amendment	LRiG comment
Section 4.3.1 states *"In Table 4-7 non-stratified analysis reported in the MS shows statistically significant results in the erlotinib group for PFS and OS. However, when the results of the Log rank stratified analysis were received with the clarification response, the ERG noted that the statistically significant OS benefit was no longer apparent. In the clarification response, the manufacturer explained that a multiple Cox regression analysis was also carried out and that erlotinib generated a statistically significant OS benefit compared with placebo using this method."* This casts doubt both on the survival advantage of erlotinib and also on the appropriate statistical methods utilised.	It seems only fair to explain, as was reported in the Manufacturer's response to clarification question A4 from the ERG why the Cox analysis was preferred to the log rank test for stratified analysis of OS	The summary leaves the reader unclear as to whether the survival benefit is statistically significant or not – a fundamental when evaluating the trial results.	The document is factually correct and does not need to be changed.

Issue 6 Representation of manufacturer's views on generalisability of study results

Description of problem	Description of proposed amendment	Justification for amendment	LRiG comment
Section 4.7.2 contains the statement (**p 40**, **penultimate bullet**) *"first-line chemotherapy treatments are not representative of UK treatments"* The manufacturer believes this to be incorrect – all patients were treated with a range of	This statement should be removed or if not an evidence based justification provided as to why they are not representative and the likely impact of this inconsistency	The current wording diminishes confidence in the SATURN study for reasons that do not appear based upon facts – patients entering the study had to	The statement is valid but has been reworded.

platinum doublets that would be allowed following current NICE guidance which also reflects the widely-held view that (with the new exception of pemetrexed for non-squamous tumours) all platinum doublets have similar efficacy and differ only to some degree in the details of their toxicity profile. Under these circumstances the first-line treatments used are completely representative of UK treatments.		have received a combination of cisplatin and carboplatin and a contemporary non-platinum drug –this is entirely consistent with UK practice in this area.	

Issue 7 Commercial in Confidence (CIC)

Description of problem	Description of proposed amendment	Justification for amendment	LRiG comment
Some "commercial in confidence" data for the non-squamous subgroup is not highlighted in red as CIC within the ERG report.	The following text in the ERG report should be highlighted as CIC, as highlighted within the manufacturer's submission. Data on the last paragraphs of point 1.2 (page 11) " As pemetrexed is also under consideration by NICE as maintenance therapy for patients with NSCLC, the manufacturer appropriately carried out an indirect comparison of pemetrexed vs erlotinib using data from the JMEN trial. The indirect comparison shows that pemetrexed vs erlotinib in patients with non-squamous histology yields a	Commercial in confidence (CIC) status on results were requested on the non-squamous sub-population pending NICE recommendation on pemetrexed 1LM. The ERG report should be subject to the same CIC status.	You are absolutely correct and thank you for pointing this out – we endeavoured to mark all CIC but these sections were obviously missed – data has now been marked CIC Table 6.3 has been imported and it is not possible to colour it all in. So NICE will have to remove the table prior to putting this on the web if the CIC status is not removed

	statistically significant PFS benefit for patients on pemetrexed compared with erlotinib [redacted] there is no statistically significant benefit shown for pemetrexed compared with erlotinib in patients with non-squamous histology in terms of OS [redacted] The “Indirect evidence” part of Table 4-10 on section 4.6. (page 42) Table 6-3 on section 6 (page 74)		NOTE to Roche –can the CIC status be lifted once the decision pemetrexed is in the public domain?

Issue 8 Cost of second-line chemotherapy

Description of problem	Description of proposed amendment	Justification for amendment	LRiG comment
The ERG states in page 68 (section 5.5.5) “Cost of second-line chemotherapy” that the manufacturer model includes cost of palliative radiotherapy already included in the BSC figure This statement is incorrect, as the radiotherapy palliative cost has not been included in the manufacturer’s model (only in the BSC calculations).	Please remove the following bullet point in page 68 (section 5.5.5), as follows: “ – various types of palliative radiotherapy are included, which are already included within the BSC figure”	This statement is an incorrect statement given the actual model inputs.	Bullet point removed