Submission for NICE Single Technology Appraisal

Lapatinib for women with previously treated advanced or metastatic breast cancer: Whether, and how, lapatinib meets NICE end of life criteria

25th August 2009

Thank you very much for the opportunity to comment on this next stage of the lapatinib appraisal.

The question of whether and how lapatinib meets the "end of life" supplementary criteria relating to life extension poses some challenges in this instance as the specific evidence submitted by the manufacturer of lapatinib on this topic is not in the public domain. We therefore consider in turn the ITT population which formed the basis of the original appraisal and licence for lapatinib, followed by commentary on the few details we are aware of regarding the subgroup analysis submitted to NICE at a late stage during the appraisal process and discussed further in the appeal hearing itself.

Despite the recent adjustment to the "end of life" criteria, the pre-planned analysis of data from the pivotal trial (EGF100151) using the ITT population still does not meet the 'life extension' criteria as it fails to achieve at least a 3 month median overall survival gain. We therefore assume that the submission from the manufacturer must refer to a different unplanned analysis of the data from the pivotal trial.

Section 4.21 of the FAD describes a subgroup of patients enrolled in the pivotal trial EGF100151 that received less than three prior treatment regimens. The Committee expressed understandable concerns regarding the clinical plausibility of a different response to lapatinib in this subgroup, the very small number of patients observed and the lack of exploration regarding the possibility that the differences in efficacy in this subgroup occurred by chance.[1] The subsequent appeal hearing described in point 38 of the findings of the appeal panel that the subgroup consisted of a total of 66 patients (16.5% of the study population) with a prolonged median overall survival of approximately seven months.[2]

Roche agrees with the concerns of the Appraisal Committee regarding the issues with relying on a post hoc unadjusted subgroup analyses and would like to highlight two additional points:

1.) In-licence versus out of licence patient population

The inclusion criteria in the EGF100151 trial required that patients had progressed after treatment with regimens that included an anthracycline, taxane and trastuzumab. It did not specify whether trastuzumab should have been provided in the *adjuvant* or *metastatic* setting. The lapatinib licence differs in that it states that the patient should have had prior therapy that must include an anthracycline, taxane and therapy with trastuzumab ***in the metastatic setting***. Therefore, the subgroup of patients that had received less than three

prior treatment regimens (i.e. only one or two prior treatments) may include some for whom lapatinib is not licenced. These patients may have received lapatinib as a 1st line metastatic treatment. The possibility that this does in fact represent the population included in the unplanned post hoc analysis is supported by a recent publication on the EGF100151 trial which shows that 16 patients included in the trial only received trastuzumab in the *adjuvant* setting.[3] Hence, it will be important to understand what proportion of the 66 patients in this subgroup analysis reflect the actual licenced population.

2.) Evidence of potential bias in the post-hoc analysis

Reflecting the Appraisal Committee's concerns regarding the post-hoc analysis of such a very small sub-group, there is evidence to suggest that inconsistencies exist within this data set. This is observed in the Poster presentation of a cost-effectiveness analysis presented at the ISPOR Conference earlier this year which we assume is based on the same/similar subgroup analysis described above.[4] In the ITT population, median overall survival was 15.3 months in the control (capecitabine monotherapy) arm. In the subgroup containing patients who had received less than 3 prior treatments, the median overall survival in the control arm was 12.7 months. This would imply that those patients in the control arm who received three or more prior treatments have a median overall survival of greater than 15.3 months. This is clearly counterintuitive as those patients who have received more lines of previous treatments are likely to have a shorter life expectancy. This lends credence to the possibility that these results may have occurred by chance or reflect a bias in such a small patient population.

Roche therefore feels strongly that the data supporting claims around the life extension criteria should be treated with caution (a comment in made in fact by GSK in their own presentation at ISPOR[3]) and we look forward to being able to comment directly on further data submitted to NICE once this is placed into the public domain. .

References:

[1] NICE Final Appraisal Determination. Lapatinib for the treatment of women with previously treated advanced or metastatic breast cancer.
http://www.nice.org.uk/nicemedia/pdf/BreastCancerLapatinibFAD.pdf

[2] NICE HTA Appeal Hearing. Advice on lapatinib for the treatment of women with previously treated advanced or metastic breast cancer. Decision of the Panel.
http://www.nice.org.uk/nicemedia/pdf/AppealDecision230609.pdf

[3] Cameron, D. et al. A phase III randomized comparison of lapatinib plus capecitabine versus capecitabine alone in women with advanced breast cancer that has progressed on trastuzumab: updated efficacy and biomarker analyses. Breast Cancer Res Treat (2008) 112: 533-543.

[4] Delea, T. et al. Cost-Effectiveness Analyses of ErbB2 (HER2)-Targeted Therapies in Women with Trastuzumab-Refractory HER2+ Metastatic Breast Cancer and Limited Prior Exposure to Chemotherapy for Metastatic Disease. Presented at ISPOR 14th Annual Meeting. Orlando, FL, USA, May 18, 2009.