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24th August 2009

Dear Mr Boysen

Re: Single Technology Appraisal - Lapatinib for women with previously treated advanced or metastatic breast cancer

I write on behalf of the NCRI (Breast CSG)/RCP/RCR/ACP/JCCO to thank you for the opportunity to submit further comments on this appraisal. We would like to make the following response which has been coordinated across the expert members of the above organisations by Professor Rob Coleman, Chair NCRI Breast CSG.

In addition to previous comments and feedback, we are aware of additional analyses and new data that further support the use of lapatinib in HER2+ advanced breast cancer. Detailed information will be provided within the GSK re-submission. However there are a couple of aspects that we wish to highlight.

The ability of the EGF100151 study to show a statistically significant survival advantage to the addition of lapatinib to capecitabine was severely compromised by the crossover of patients on the monotherapy arm following the interim planned analysis for progression free survival. However, we are aware that recent updated analyses have indicated an approximate 3-month survival advantage that would appear to meet the criteria set out in the Supplementary Advice. Indeed, in some subsets of patients, a survival advantage in excess of 6 months has been reported. As a community of breast cancer clinicians, we believe this is a clinically important and worthwhile treatment benefit for this far advanced population of patients with very limited treatment options

EGF100151 was a global study and the relevance to UK practice may be questioned. However there is positive experience of lapatinib in the UK through the Global Lapatinib Expanded Access Program (LEAP). This compassionate use protocol provided access to lapatinib combined with capecitabine for women with HER2+ve metastatic breast cancer who had previously received an anthracycline, taxane and trastuzumab, including patients with central nervous system (CNS) disease that had progressed following prior loco-regional treatment for who limited other treatment options existed.

356 patients were recruited into LEAP from the UK, and the overall progression free survival (PFS) for these patients was 21 weeks (95%CI 17.6-24.7 weeks) which was comparable to the phase III EGF100151 trial. A more detailed analysis of efficacy was assessed in 162 patients from five lead recruiting centres within the UK LEAP study, including 34 patients with CNS metastases. In the 162 patients assessable for response, the overall response rate (ORR) was 21% (95% CI 15-27%), with a median time to progression (TTP) of 5 months (95% CI 4-6 months), again demonstrating similar efficacy in a UK setting to that reported in the original phase III EGF100151 trial. For the 34 patients

with CNS metastases, the ORR was 21% (95% CI 9-39%) with evidence of improvement in neurological symptoms. The median TTP for patients with CNS metastases was 5 months (95% CI 4-6 months).

These data show the utility of this combination in HER2+ve refractory metastatic breast cancer in the UK setting, and in particular demonstrate the useful clinical benefit for patients with progressive CNS metastases following prior radiotherapy, for whom treatment options are very limited and life expectancy is short (<3months).

In summary, we believe there is a strong case for lapatinib to be accepted as an end of life treatment option for patients with trastuzumab refractory HER2+ metastatic breast cancer.

I trust these comments will be of use.

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