Royal College of Physicians
Setting higher medical standards

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Dear [redacted]

**Re: Lapatanib for the treatment of previously treated women with advanced metastic or recurrent breast cancer - ACD**

I write on behalf of the NCRI Breast Clinical Studies Group/RCP/RCR/ACP/JCCO with relation to the above. We are grateful for the opportunity to comment and would like to make the following joint response.

There would seem to me to be some incontrovertible conclusions from the available data:

(a) there is clear evidence of the efficacy for the addition of Lapatinib to Capecitabine in patients with advanced, HER2-overexpressing breast cancer previously treated with Herceptin and chemotherapy [n=399]. The demonstrated efficacy is in terms of an improvement in time to progression and response rate. The trial was not primarily designed to measure either the overall survival benefit, nor the cost-effectiveness of the intervention, so that data on these two aspects are necessarily much less certain

(b) there is also further evidence from randomised trials to support the use of continued anti-HER2 therapy after progression on Trastuzumab (when Trastuzumab is combined with Capecitabine: GBG-26 trial [n=156]; and when combining Lapatinib and Trastuzumab as compared to using Lapatinib monotherapy – EGF104900 trial, [n=296]

(c) there is a clear unmet need for this patient population with generally poor outcomes, as demonstrated by the median survivals of patients in both the pivotal Lapatinib trial and the German GBG trial not given further anti-HER2 therapy being less than 24 months from time of entry into the study. The unmet need is because there are no randomised trials of which I am aware that demonstrate superiority for any other intervention in this subgroup of breast cancer patients.

Patients enrolled in these studies were of good performance status, and are similar to many candidate patients treated in the NHS at present: living independent and fully functional lives including full-time employment, caring for relatives etc. Thus their burden on the state health care (and social care systems) will significantly increase when their disease is less well controlled.

Thus it would seem that the two questions that NICE has had to address are:

(a) what is the best estimate of the cost/QALY for adding Lapatinib to Capecitabine in patients progressing after chemotherapy and Trastuzumab

(b) is that cost something that the NHS should bear, given the resource constraints, noting that NICE is NOT asked to consider this in stead of any other medical intervention for breast cancer or any other condition.

This NICE STA is not structured to draw any conclusions about the cost-effectiveness of either continued anti-HER2 therapy beyond progression on Trastuzumab, nor in particular for the use of Trastuzumab in that setting. However, there were statements in the FAD about the latter for which the evidence base is thin (only 156 patients in the trial) and no modelling data were made available to those of us accessing the draft FAD.

The UK population eligible for using Lapatinib fall into three groups in my view, based on current clinical practice and the trial data:

(a) patients progressing for the second+ time after anti-HER2 therapy (usually Trastuzumab). These patients were represented by only 1/3 of the patients in the Lapatinib trial but none of those in the GBG trial. In these patients the addition of Lapatinib resulted in smaller improvements in PFS (HR = 0.64, p = 0.09) but no evidence for any difference in overall survival

(b) patients progressing/relapsing for the first time on Trastuzumab who would in the NHS get further Trastuzumab. Survey data produced by NHS clinicians independently of any pharmaceutical company (previously supplied to NICE) suggests that as much as 50% of the population of patients progressing on Trastuzumab in the NHS may be offered further Trastuzumab. In these patients the best estimates suggest little difference in either efficacy (cross-trial comparison) OR cost-effectivenesss (NICE's own calculations) between these two strategies. There are practical advantages for each: there may be compliance problems with oral Lapatinib, and for some patients the continued administration of Trastuzumab intravenously requires significant travel to a hospital and/or insertion of a semi-permanent indwelling intravenous cather with associated risks and health care costs.

(c) patients progressing/relapsing for the first time on Trastuzumab who would in the NHS get NO further anti-HER2 therapy – these patients make up 2/3 of those women enrolled into the Lapatinib study and 100% of those enrolled into the GBG study. Survey data suggest they may represent at least ½ of patients in the NHS progressing on Trastuzumab. In both studies, this group demonstrated statistically significant benefits for further anti-HER2 therapy, with HRs for PFS of 0.5 for the addition of Lapatinib to Capecitabine and 0.69 for the administration of continued Trastuzumab in combination with Capecitabine. There were also statistically significant improvements in response rates (for which there are data from other studies demonstrating that this usually results in improvements in Quality of Life), and clinically significant improvements in Overall Survival in this population (medians improving from 51 to 74 weeks, p = 0.08 for Lapatinib and from 20 to 25 months with Trastuzumab, p = 0.26). Thus whilst neither trial is significant for survival gains alone, neither trial was designed to address this question, and *any* estimates of the cost/QALY gained are therefore necessarily only crude approximates. Given the observed differences in median survival in a group of patients half of whom will have died within 2 years, these data would seem to be eligible for the new "end-of-life" approach by NICE.

There would seem to be little or NO evidence to support access to Lapatinib for patients in group (a). However, for patients in group (b), the data presented by NICE find no significant efficacy or cost differences, so it would seem logical that for patients in this group, in the NHS, access to Lapatinib is as reasonable as access to Trastuzumab, in that there are very few if any cost implications for the NHS when choosing between anti-HER2 therapy. NICE might argue that continued Trastuzumab is not Licensed, and neither is the use of Lapatinib in only a sub-group of patients: but as we all know, there are many unlicensed treatments given in the NHS which may have LESS robust supporting evidence than the use of continued anti-HER2 therapy, for which question over ***800*** patients worldwide have been enrolled into randomised phase II/III clinical trials.

For patients in group (c), the available data strongly suggest clinical efficacy in terms of response rate, progression-free and overall survival, in a patient group that meets the revised criteria for "end-of-life" drugs in the NHS:

- median survival less than 2 years
- improvements in survival of the order of 3-4 months
- no other proven therapies given that there are no other randomised trials demonstrating superior efficacy for one therapy or another in this sub-group of HER2 positive, Trastuzumab-exposed patients.

The creation of this "route" for NICE recommendation for NHS use was created in response to recognition that the UK public is prepared to spend more to help these patients than some other patient groups. I am not aware of any evidence that the public is less prepared to spend the increased cost/QALY in this particular patient group just because, having breast cancer, they have already benefited from active therapies in contrast to patients with other cancers that have less effective therapies.

It might be argued that this conclusion is based on a hypothesis-generating subgroup analysis of patients in the Lapatinib trial, but it needs to be recalled that this patient group is not only larger than the GBG026 trial, but is also larger than the number of patients in the subgroup which formed the basis of the first registration of Trastuzumab in metastatic breast cancer, an analysis that was also an unplanned, subgroup analysis (using only HER2 3+ and taxol treated patients)! Furthermore, since even the full dataset of patients in the Lapatinib trial was inadequately powered to demonstrate the likely differences in overall survival, drawing conclusions about differences in Overall Survival from either this large subset, or the full trial dataset, are similarly unreliable.

We therefore find NICE's rejection of the use of Lapatinib in patients progressing for the first time on Trastuzumab inconsistent with its own "end-of-life" criteria, and deprives some (but not all) eligible patients in the NHS of the option of further effective therapy that is very likely to make a difference to their overall quality of life, contribution to society and survival.

I trust these comments will be of use.

Yours sincerely

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