Royal College of Physicians
Setting higher medical standards

[redacted]
Regent's Park, London NW1 4LE

Telephone +44(0) [redacted]
Textphone +44(0) [redacted]
Facsimile +44(0) [redacted]

www.rcplondon.ac.uk

From [redacted]
[redacted] MD FRCP

Telephone extension [redacted]
Direct facsimile +44(0) [redacted]
[redacted]@rcplondon.ac.uk

Eloise Saile
Project Manager: Technology Appraisals
National Institute for Health and Clinical Excellence (NICE)
MidCity Place
71 High Holborn
London
WC1V 6NA

24 July 2008

Dear Ms Saile

Re: Lapatinib for breast cancer (for use in women with previously treated advanced or metastatic breast cancer) ACD

The oncology community as represented by the Royal College of Physicians, the Royal College of Radiologists, the Joint Collegiate Council for Clinical Oncology, the Association of Cancer Physicians and the NCRI Breast Group (who coordinated this response) are grateful for the opportunity to consider the ACD for the above subject. We would like to make the following comments:

Lapatinib is licensed in Europe for the treatment of metastatic breast cancer expressing the growth factor receptor HER2 following progression during or after treatment with trastuzumab. Significantly improved time to progression (the pre-specified primary endpoint) was reported, with minimal excess toxicity over and above capecitabine alone. The trial was underpowered to determine any difference in overall survival and the survival analysis is confounded by crossover to lapatinib in the capecitabine arm alone, a treatment recommendation that was made by the Independent Data Monitoring Committee due to the very clear effects of the study drug on the underlying disease.

At the time the study was conducted the standard of care was chemotherapy alone, and the choice of single agent capecitabine as the comparator was appropriate and consistent with UK practice. However, the standard of care is changing as data emerges to show that continued inhibition of HER2 with trastuzumab is also superior to chemotherapy with capecitabine alone (von Minckwitz et al. GBG-26 study, ASCO Proceedings 2008). Although there is not regulatory approval for trastuzumab beyond progression, it is frequently and increasingly used in many centres throughout the UK.

We believe that capecitabine plus lapatinib provides an approved **alternative** to current clinical practice of trastuzumab beyond progression for minimal additional cost to the NHS (admittedly manufacturers estimate of £1650 per QALY). It is true that if the 'comparator' of capecitabine with continued trastuzumab is chosen then the incremental benefit of capecitabine plus lapatinib may be degraded.Estimates have to be made with data from indirect comparisons and interpolations across trials. This presents a difficult modelling exercise but one that should

happen to provide a more realistic estimate of the cost benefit effect of lapatinib in the context of modern practice.

We agree with the recommendation that further research is required to compare chemotherapy with trastuzumab to chemotherapy with lapatinib, and would welcome the opportunity to work with NICE and the manufacturers to achieve this. Pending results from such a study however, we would urge the appraisal panel to reconsider their proposed recommendation which is based largely on the cost per QALY associated with adding lapatinib to capecitabine, as this does not reflect the actual cost to the health care system within the UK. Patients with HER2+ breast cancer derive considerable benefit from a second treatment targeted to the HER2 receptor (trastuzumab or lapatinib). A recommendation to allow lapatinib plus capecitabine as an alternative to trastuzumab would significantly reduce the current inequality in access to trastuzumab beyond progression that exists across the NHS.

With best wishes.

Yours sincerely