# 1 Executive Summary

## 1.1 Introduction

Breast cancer is the most common cancer affecting women in the UK (Cancer Research UK, 2010). Between 16 and 20% of new cases of breast cancer are advanced/metastatic stage cancers where the tumour has spread beyond a localised area within the breast to other organs of the body; around 50% of patients presenting with early or localised breast cancer will eventually develop metastatic disease (NICE 2002). HER2 positive tumours are associated with a worse prognosis and reduced overall survival compared to HER2 negative tumours. Up to a third of women with metastatic breast cancer have tumours which over-express HER2 (human epidermal growth factor) receptors and of these approximately 50% are also hormone receptor positive (HR+) (NICE, 2002, Penault-Llorca 2005).

The patients under consideration in this NICE appraisal are:

> *'postmenopausal women with HER2 positive metastatic breast cancer which is oestrogen receptor and/or progesterone receptor positive, who have not previously received treatment for metastatic disease and for whom treatment with an aromatase inhibitor is suitable.' (NICE 2010)*

Current estimates in the UK suggest that there are approximately 500 post-menopausal women per year with HR+ tumours that over express HER2, (IMS Oncology Analyzer 2008) of which less than 100 fall within the remit of this appraisal.

As metastatic breast cancer is generally incurable, the goals of treatment are to control the disease, prolong time to progression and survival, and to relieve symptoms whilst maintaining a reasonable quality of life. The two main classes of agents used to treat post-menopausal women with metastatic breast cancer are chemotherapy and hormone therapy; treatment choice is influenced by multiple factors. For HR+/HER2+ patients not intended for chemotherapy, HER2 over expression is associated with resistance to hormonal therapy (Benz 1992, Pietras 1995 and Shou 2004) and the aggressive nature of the tumours may warrant the use of the combination treatment of an anti-HER2 therapy and an endocrine (hormonal) agent rather than single-agent hormonal therapy (Cortes 2009). The poor outcomes of patients in the control arms of trials with endocrine therapy alone for HR+/HER2+ patients suggest that endocrine monotherapy should no longer be accepted as the standard of care for these patients (Cortes, 2009; Kaufman, 2009). Therefore there is a high unmet need for more effective and less toxic treatment options for post-menopausal HER2+/HR+ metastatic breast patients.

## 1.2 Overview of Lapatinib

Lapatinib (Tyverb®) is an orally administered tyrosine kinase inhibitor that selectively targets both the ErbB1 (EGFR) and ErbB2 (HER2) receptor. Clinical evidence suggests that lapatinib, administered alone or in combination with chemotherapy (capecitabine) or an aromatase inhibitor has activity in HER2-positive breast cancer. Lapatinib in combination with capecitabine is currently licensed for the treatment of HER2+ patients with advanced or metastatic breast cancer who have progressed on trastuzumab in the metastatic setting. Lapatinib in combination with an aromatase inhibitor has had a CHMP positive opinion and is awaiting full marketing authorisation for the first- line treatment of postmenopausal patients with HR+/HER2+ metastatic breast cancer not currently intended for chemotherapy (European Medicines Agency, 2010).

As an all-oral regimen, lapatinib plus an aromatase inhibitor offers the convenience of self-administration at home.

## 1.3 Comparators

The comparators for this appraisal are aromatase inhibitors (letrozole, anastrazole and exemestane) and trastuzumab (Herceptin®) plus an aromatase inhibitor (AI). Based on clinical evidence (Kleijnen Systematic Reviews 2010) the assumption in the context of this submission, is that the individual AIs are of comparable clinical efficacy.

Trastuzumab is the only anti-HER2 agent other than lapatinib that is licensed for the treatment of metastatic breast cancer in the patient population under consideration.

Market research data (IMS Oncology Analyzer 2009) indicates that trastuzumab plus AI is prescribed in approximately 54% and AI monotherapy in 46% of the patient population under consideration.

## 1.4 Clinical Evidence

A comprehensive systematic review was undertaken to identify studies of lapatinib and relevant comparator therapies for the first-line treatment of hormone sensitive advanced or metastatic breast cancer, in post-menopausal women who had not received prior therapy for advanced or metastatic disease. The search results identified eighteen randomised controlled trials including one Phase III lapatinib study (study EGF30008, Johnston 2009) comparing lapatinib plus letrozole with letrozole plus placebo. Seventeen other studies were identified and included a Phase III study comparing trastuzumab plus anastrozole with anastrozole monotherapy (TAnDEM Kaufman 2009).

*The EGF30008 trial*

EGF30008 was a double-blind, placebo-controlled, phase III trial conducted to evaluate the safety and efficacy of lapatinib plus letrozole and letrozole monotherapy in post-menopausal women with HR+ metastatic breast cancer. The primary endpoint was investigator-evaluated progression-free survival (PFS) in the subgroup of HER2+ patients; PFS in the intent-to-treat population was one of the secondary endpoints. The results for the HER2+ population showed that progression-free survival was significantly increased from 3.0 months in the letrozole plus placebo group to 8.2 months in the lapatinib plus letrozole group (hazard ratio 0.71 [95% CI: 0.53 to 0.96] p=0.019]) (Johnston 2009). The median overall survival (OS) for the HER2+ population was 33.3 months in the lapatinib plus letrozole group and 32.3 months in the letrozole plus placebo group. This difference was not statistically significant.

*The TAnDEM trial*

The direct comparison of trastuzumab plus anastrozole and anastrozole plus placebo (the TAnDEM trial) shows that anastrozole plus trastuzumab is more efficacious in slowing disease progression than anastrozole alone in HR+/ HER2+ metastatic breast cancer patients (Kaufman 2009). Progression-free survival was significantly increased from 2.4 months in the anastrozole plus placebo group to 4.8 months in the anastrozole plus trastuzumab group (hazard ratio 0.63 [95% CI: 0.47 to 0.84]; log rank P=0.0016). Median OS was higher for patients treated with anastrozole plus trastuzumab (28.5 months) than those treated with anastrozole plus placebo (23.9 months) but the difference was not statistically significant.

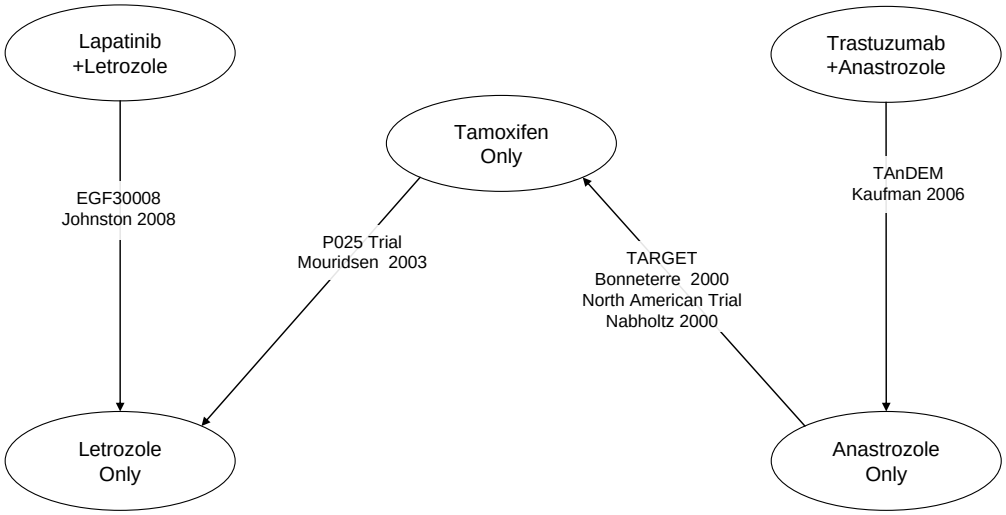
The lack of significance in the overall survival data for both the EGF30008 and TAnDEM trials may be explained by patients usually receiving other therapies at the end of the study period thus confounding the OS data.

*Indirect comparison*

No studies were identified that directly compared the efficacy of lapatinib plus AI with that of trastuzumab plus AI. An indirect comparison was therefore conducted using a network meta-analysis approach (Kleijnen Systematic Reviews 2009a). The network was comprised of five studies identified in the systematic review and is illustrated in Figure 1 below.

The results of the indirect comparison suggest that lapatinib plus AI is at least as effective as trastuzumab plus AI as measured by PFS and OS.

**Figure 1: Indirect comparison of lapatinib plus an aromatase inhibitor and trastuzumab plus an aromatase inhibitor (Kleijnen Systematic Reviews 2009a)**




## 1.5 Cost-effectiveness of lapatinib

A cost-utility analysis was undertaken to assess the cost-effectiveness of lapatinib in combination with an aromatase inhibitor in the treatment of post-menopausal women with HR+/ HER2+, metastatic breast cancer. In the absence of a trial directly comparing lapatinib and trastuzumab plus an AI, an indirect comparison was performed in which survival curves for PFS and OS for letrozole were estimated directly from EGF30008 patient-level data (Johnston 2009). PFS and OS for the other therapies were obtained by applying to these curves the hazard ratios for PFS and OS for the other therapies versus letrozole. The indirect comparison generated a number of PFS and OS hazard ratios based on the use of different mathematical models, the use of investigator or independent reviewer assessment data and the inclusion or exclusion of women of unknown hormone receptor status (Kleijnen Systematic Reviews 2009a). Those sets of hazard ratios that were not used in the base case analysis were incorporated into the deterministic sensitivity analyses.

The results of the economic evaluation show that when lapatinib plus letrozole is compared with letrozole monotherapy, the incremental cost per QALY estimate is £74,448 and when compared with anastrozole monotherapy the incremental cost per QALY estimate is £59,895. The results of the analysis for lapatinib plus letrozole versus trastuzumab plus anastrozole indicate that lapatinib combined with an AI is a cost-effective alternative to trastuzumab plus AI with an incremental cost per QALY of £21,836.

A range of deterministic sensitivity analyses indicates that for the comparison with letrozole monotherapy the incremental cost per QALY is in the range of £41,877 to lapatinib plus letrozole being dominated by letrozole monotherapy (i.e. lapatinib plus letrozole less effective and more costly). The cost per QALY gained versus anastrozole monotherapy ranges from £38,170 to £378,674 and for the comparison with trastuzumab plus anastrozole the range is lapatinib plus letrozole dominating the comparator to a cost per QALY estimate of £45,106. The key assumptions driving the uncertainty are the OS and PFS hazard ratios. In the comparison with trastuzumab plus anastrozole the cost-effectiveness of lapatinib plus letrozole was also sensitive to wastage of study medication and assumptions regarding the trastuzumab dosage regimen. In the base case analysis trastuzumab is administered on a three weekly dosage regimen but if a weekly dosage regimen is assumed, lapatinib plus letrozole dominates trastuzumab plus anastrozole.

A probabilistic sensitivity analysis shows that a high percentage of the sample estimates of the incremental costs and QALYs for lapatinib plus AI fall in the North-East quadrant of the cost-effectiveness plane which means that this intervention is more effective and more costly than AI monotherapy and trastuzumab plus AI. In approximately 75% to 80% of the simulations comparing lapatinib plus an AI with AI monotherapy, the lapatinib combination produced more QALYs at a greater cost than AI monotherapy. In approximately 49% of the simulations comparing lapatinib plus AI with trastuzumab plus AI the lapatinib intervention produced more QALYs at a greater cost than trastuzumab plus AI.

## 1.6 Resource implications for the NHS

In England and Wales the estimated current NHS cost is approximately £1.3 million for the first-line treatment of postmenopausal patients with HR+/HER2+ metastatic breast cancer not currently intended for chemotherapy. The budget impact of introducing lapatinib plus letrozole and displacing trastuzumab plus and AI and AI monotherapy is an additional cost of approximately £1.3 to 1.4 million per year. This assumes a 100% uptake in the eligible population, and includes drug acquisition and resource costs. Displacement of trastuzumab plus AI therapy only, would result in an additional annual expenditure of approximately £142,000 to £147,000.

## 1.7 Conclusions

Approximately 46% of postmenopausal patients with HR+/HER2+ metastatic breast not currently intended for chemotherapy receive first-line treatment with an aromatase inhibitor alone. Recent data from clinical studies (TAnDEM and EGF30008) have shown that the combination of an anti-HER2 agent and an AI is significantly superior to an AI alone in prolonging progression free survival in postmenopausal women with HR+ /HER2+ metastatic breast cancer. This suggests that the combination of an anti-HER2 and AI could delay disease progression in patients who overexpress HER2 and who would otherwise progress rapidly on single agent AI therapy.

Post-menopausal women with HR+/HER2 positive metastatic breast cancer, have a high unmet clinical need for more effective, less toxic treatment options that are convenient. The combination therapy of lapatinib and an aromatase inhibitor provides an effective, less toxic, all-oral treatment option for patients for whom chemotherapy is not currently intended.

The results of the indirect comparison indicate that lapatinib plus AI is at least as effective as trastuzumab plus AI. The economic evaluation shows that lapatinib in combination with an AI is a cost-effective alternative to trastuzumab plus AI with similar lifetime costs. As an all-oral regimen lapatinib plus an aromatase inhibitor is particularly beneficial for patients for whom intravenous drug administration is unsuitable. It is also more convenient for patients in terms of allowing drug administration at home, thus reducing visits to hospital and potentially enhancing the quality of life of patients and their carers. Lapatinib thus represents an effective, orally administered and clinically valuable alternative to intravenous trastuzumab when combined with an aromatase inhibitor in the treatment of post-menopausal women with HR+/HER2+ metastatic breast cancer not intended for chemotherapy.