NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Final appraisal document

Lapatinib or trastuzumab in combination with an aromatase inhibitor for the first-line treatment of metastatic hormone-receptor-positive breast cancer that overexpresses HER2

1 Guidance

1.1 Lapatinib in combination with an aromatase inhibitor is not recommended for first-line treatment in postmenopausal women with metastatic hormone-receptor-positive breast cancer that overexpresses human epidermal growth factor receptor 2 (HER2).

1.2 Trastuzumab in combination with an aromatase inhibitor is not recommended for first-line treatment in postmenopausal women with metastatic hormone-receptor-positive breast cancer that overexpresses HER2.

1.3 Postmenopausal women currently receiving lapatinib or trastuzumab in combination with an aromatase inhibitor that is not recommended according to 1.1 or 1.2 should have the option to continue treatment until they and their clinicians consider it appropriate to stop.

2 Clinical need and practice

2.1 Breast cancer is the most common type of cancer among women in the UK. Women have a one in nine lifetime risk of developing breast cancer. The incidence of breast cancer increases with age, doubling every 10 years until menopause, after which the rate of

increase slows down. In the UK, 45,972 people were diagnosed with breast cancer in 2007, of whom over 99% were women.

2.2 Metastatic breast cancer is an advanced stage of the disease when it has spread to other organs. An estimated 5% of patients present with metastatic breast cancer, and approximately 30% of people who present with localised breast cancer will later develop metastatic breast cancer. Common sites of metastasis include bone, liver, lung and brain.

2.3 When clinicians manage breast cancer they consider various prognostic factors, including hormone receptor status and HER2 status. Hormone receptors include oestrogen receptors and progesterone receptors. Tumours that express either oestrogen receptors or progesterone receptors are commonly referred to as being hormone receptor positive. It is estimated that 60% and 80% of all breast cancers in premenopausal and postmenopausal women respectively are hormone receptor positive. People with hormone-receptor-positive breast cancer generally have a better prognosis than those with hormone-receptor-negative breast cancer.

2.4 Tumours that overexpress the HER2 protein (HER2+) grow and divide more quickly, so women with HER2+ tumours generally have a worse prognosis than women with HER2 negative tumours. Approximately 20–30% of people with metastatic breast cancer have HER2+ tumours, of which about 50% will also be hormone receptor positive. In this appraisal, estimates from consultees and clinical specialists for the number of women per year with newly diagnosed metastatic breast cancer who have tumours that are HER2+ and hormone receptor positive ranged from 50 to 2000.

2.5 The aim of treatment in metastatic breast cancer is to palliate symptoms, prolong survival and maintain a good quality of life with

minimal adverse events. Choice of treatment depends on previous therapy, hormone receptor status, HER2 status and the extent of the disease. 'Advanced breast cancer: diagnosis and treatment' (NICE clinical guideline 81) recommends that if the disease is not imminently life threatening, or does not need early relief of symptoms because of significant visceral organ involvement, women who are postmenopausal and have hormone-receptor-positive breast cancer should be offered an aromatase inhibitor such as anastrozole or letrozole. There is variation in clinical practice for people with tumours that are both HER2+ and hormone receptor positive.

3 The technologies

3.1 Lapatinib (Tyverb, GlaxoSmithKline) is a protein kinase inhibitor that blocks the tyrosine kinase components of the epidermal growth factor receptors (ErbB1 and ErbB2), which are implicated in the growth of various tumours. Lapatinib has conditional marketing authorisation (that is, further evidence on this medicinal product is being awaited) in the UK. Lapatinib is 'indicated for the treatment of patients with breast cancer, whose tumours overexpress HER2 (ErbB2); in combination with an aromatase inhibitor for postmenopausal women with hormone receptor positive metastatic disease, not currently intended for chemotherapy'. The summary of product characteristics (SPC) states that 'patients in the registration study were not previously treated with trastuzumab or an aromatase inhibitor'.

3.2 The SPC states that the most common adverse reactions during therapy with lapatinib are diarrhoea, nausea, vomiting and rash. For full details of adverse reactions and contraindications, see the SPC.

3.3 Lapatinib is administered orally at a dosage of 1500 mg (six tablets) per day. The net price per pack of 84 tablets is £965.16 (excluding VAT; British national formulary [BNF], edition 62). The acquisition cost for a lifetime of treatment with lapatinib plus the aromatase inhibitor letrozole is £28,212 (£27,024 for lapatinib and £1188 for letrozole), assuming a mean treatment duration of 55.2 weeks and excluding administration costs. Costs may vary in different settings because of negotiated procurement discounts.

3.4 Trastuzumab (Herceptin, Roche Products) is a recombinant humanised IgG1 monoclonal antibody directed against HER2. Trastuzumab is indicated for the treatment of patients with HER2+ metastatic breast cancer 'in combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone-receptor positive metastatic breast cancer, not previously treated with trastuzumab'.

3.5 The SPC states that the most common adverse reactions associated with trastuzumab in combination with chemotherapy are cardiotoxicity, infusion-related reactions, haematotoxicity (in particular neutropenia) and pulmonary events. In the clinical trials, patients receiving trastuzumab had to have a left ventricular ejection fraction of at least 55% and to have cardiac monitoring every 4 months. For full details of adverse reactions and contraindications, see the SPC.

3.6 The recommended dosage of trastuzumab is either a loading dose of 4 mg/kg by intravenous infusion followed by a weekly maintenance dose of 2 mg/kg until disease progression, or a loading dose of 8 mg/kg by intravenous infusion followed by 3-weekly maintenance doses of 6 mg/kg until disease progression. The net price per 150 mg vial is £407.40 (excluding VAT; BNF 62). Assuming an average patient weight of 67 kg, a mean treatment period of 15 months and excluding administration, monitoring and

wastage costs, the acquisition cost for a lifetime of treatment with trastuzumab plus anastrozole is £26,018 (£24,852 for trastuzumab and £1166 for anastrozole) for a weekly schedule and £26,832 (£25,666 for trastuzumab and £1166 for anastrozole) for a 3-weekly schedule. Costs may vary in different settings because of negotiated procurement discounts.

4 Evidence and interpretation

The Appraisal Committee (appendix A) considered evidence from a number of sources (appendix B).

4.1 Clinical effectiveness

4.1.1 Three randomised controlled trials were identified that considered lapatinib or trastuzumab used within their licensed indications. The studies compared:

- lapatinib plus letrozole with letrozole alone (the EGF30008 trial)
- trastuzumab plus anastrozole with anastrozole alone (the TAnDEM trial)
- trastuzumab plus letrozole with letrozole alone (the eLEcTRA trial).

All three trials were multicentre, multinational trials that included postmenopausal women receiving first-line treatment for metastatic breast cancer. In all three trials, patients received treatment until disease progression.

Lapatinib

4.1.2 The EGF30008 trial compared lapatinib plus letrozole with letrozole alone. All patients in the trial (n = 1286, the intention-to-treat population [ITT]) had hormone-receptor-positive metastatic breast cancer but only 219 out of 1286 had HER2+ breast cancer. The trial excluded patients considered by the investigators to have

rapidly progressing or life-threatening disease. The median age of patients in the ITT population was 62 years for the lapatinib plus letrozole group and 63 years for the letrozole group (the ages were 60 years and 59 years respectively for patients with HER2+ breast cancer). The two treatment groups were broadly similar in Eastern Cooperative Oncology Group (ECOG) performance status. In the lapatinib plus letrozole group, 58% had an ECOG performance status of 0, compared with 54% in the letrozole alone group; the proportions were 53% and 47% respectively for patients with HER2+ breast cancer. The median number of metastatic sites was two in both treatment groups, including patients with HER2+ breast cancer. The proportion of patients with metastases only to bone was 15% in the lapatinib plus letrozole group and 13% in the letrozole alone group (14% and 17% respectively in patients with HER2+ breast cancer). The remainder had visceral or soft tissue metastases. Patients were randomised to either lapatinib plus letrozole (n = 642, which included 111 patients with HER2+ breast cancer) or to letrozole alone (n = 644, which included 108 patients with HER2+ breast cancer).

4.1.3 The primary outcome was progression-free survival, and secondary outcomes included overall survival, time to progression and overall response rate. For patients with hormone-receptor-positive and HER2+ breast cancer, median progression-free survival was 8.2 months for the lapatinib plus letrozole group and 3.0 months for the letrozole alone group (hazard ratio [HR] for progression 0.71, 95% confidence interval [CI] 0.53 to 0.96, p = 0.019). A Cox regression analysis was performed to adjust for known baseline prognostic factors. These factors included treatment group, site of disease, previous adjuvant endocrine therapy, performance status, number of metastatic sites and serum HER2 extracellular domain levels at baseline. From this analysis, the hazard ratio for progression was 0.65 (95% CI 0.47 to 0.89, p = 0.008). For the ITT

population, progression-free survival was 11.9 months for the lapatinib plus letrozole group and 10.8 months for the letrozole alone group (HR for progression 0.86; 95% CI 0.76 to 0.98; p = 0.026).

4.1.4 Median overall survival for patients with hormone-receptor-positive and HER2+ breast cancer was 33.3 months for the lapatinib plus letrozole group and 32.3 months for the letrozole alone group (HR for death 0.74, 95% CI 0.49 to 1.12, p = 0.113). Overall survival results for the ITT population were not reported. The overall response rate for patients with hormone-receptor-positive and HER2+ breast cancer was 28% for the lapatinib plus letrozole group and 15% for the letrozole alone group (odds ratio [OR] 0.4, 95% CI 0.2 to 0.9, p = 0.021). The overall response rate for the ITT population was 33% in the lapatinib plus letrozole group and 32% in the letrozole alone group (OR not reported, p = 0.726).

4.1.5 Quality of life was assessed using the Functional Assessment of Cancer Therapy – Breast (FACT-B) questionnaire. Quality of life scores for patients with HER2+ breast cancer were reported to be generally constant over time in both treatment groups. The difference between the two groups was not statistically significant.

4.1.6 Patients who received lapatinib pus letrozole were more likely to experience adverse events, although serious adverse events were rare in both treatment groups. In the ITT population, the incidence of diarrhoea, rash and nausea was statistically significantly greater in the lapatinib plus letrozole group (64%, 45% and 31% respectively) compared with the letrozole alone group (20%, 13% and 21% respectively, p < 0.05).

Trastuzumab

4.1.7 The TAnDEM trial (n = 207) compared trastuzumab plus anastrozole with anastrozole alone. Patients included in the trial

were postmenopausal women with hormone-receptor-positive and HER2+ metastatic breast cancer with an ECOG performance status of 0 or 1. The median age of patients was 56 years in the trastuzumab plus anastrozole group and 54 years in the anastrozole alone group. The median number of metastatic sites was two and 56% of patients had bone metastases. Patients were randomised to either trastuzumab plus anastrozole (n = 103) or to anastrozole alone (n = 104). At disease progression, 73 patients in the anastrozole alone group received second-line therapy including trastuzumab.

4.1.8 The primary outcome was progression-free survival. The secondary outcomes included overall survival, time to progression and overall response rate. Progression-free survival results were presented according to the ITT population, and in a subgroup in whom hormone-receptor positivity was centrally confirmed and updated results were provided at a later cut-off point (April 2008). For the ITT population, median progression-free survival was 4.8 months (95% CI 3.7 to 7.0) for the trastuzumab plus anastrozole group and 2.4 months (95% CI 2.0 to 4.6) for the anastrozole alone group (HR for progression 0.63, 95% CI 0.47 to 0.84, p = 0.002). For the centrally confirmed results, median progression-free survival was 5.6 months (95% CI 3.8 to 8.3) for the trastuzumab plus anastrozole group and 3.8 months (95% CI 2.0 to 6.3) for the anastrozole alone group (HR for progression 0.62, 95% CI not reported, p = 0.006). For the updated results, the median progression-free survival was 5.8 months (95% CI 4.6 to 8.3) for the trastuzumab plus anastrozole group and 2.9 months (95% CI 2.1 to 4.5) for the anastrozole alone group (HR for progression 0.55, 95% CI 0.41 to 0.74, p < 0.001).

4.1.9 Overall survival results were presented according to the ITT population and the centrally confirmed hormone-receptor-positive

population, and results were adjusted for patients who had crossed over from the aromatase inhibitor group to receive trastuzumab. For the ITT population, the median overall survival was 28.5 months (95% CI 22.8 to 42.4) for the trastuzumab plus anastrozole group and 23.9 months (95% CI 18.2 to 37.4) for the anastrozole alone group (HR for death 0.84, 95% CI 0.59 to 1.20, p = 0.33). For the centrally confirmed results, the median overall survival was 34.1 months (95% CI 23.9 to 52.0) for the trastuzumab plus anastrozole group and 28.6 months (95% CI 17.4 to 40.0) for the anastrozole alone group (HR for death 0.85, 95% CI not reported, p = 0.45).

4.1.10 The manufacturer attempted to account for crossover by conducting a post-hoc analysis of overall survival. The 'rank preserving structural failure time' approach was used to account for crossover (70% of the patients randomised to anastrozole alone subsequently received trastuzumab). In this analysis, the manufacturer reported that the overall survival was 28.52 months (95% CI not reported) for the trastuzumab plus anastrozole group and 21.98 months (95% CI not reported) for the anastrozole alone group (HR for death 0.73, 95% CI 0.51 to 1.04, p value not reported). The Assessment Group commented that no pre-planned statistical methods were described to address the issue of crossover and there was no agreement about the best method to use. It stated that the 'rank preserving structural failure time' approach might not be appropriate when imbalances occur after randomisation, such as when there is an unequal distribution of patients receiving second-line treatment across the groups. The Assessment Group noted that in the TAnDEM trial, the proportion of patients who crossed over was relatively high, and this increased the likelihood of bias. The Assessment Group stated that, ideally, different methods for accounting for crossover should have been tested.

4.1.11 Patient utility data were not collected in the TAnDEM trial. Patients who received trastuzumab plus anastrozole were more likely to experience adverse events compared with patients who received anastrozole alone (87% compared with 65%), including serious adverse events (23% compared with 6%). Fatigue, diarrhoea and vomiting were among the most common adverse events (21%, 20% and 21% respectively in the trastuzumab plus anastrozole group compared with 10%, 8% and 5% in the anastrozole alone group).

4.1.12 The eLEcTRA trial aimed to compare trastuzumab plus letrozole with letrozole alone. However, only 92 patients with hormone-receptor-positive metastatic breast cancer were enrolled (out of a planned 370 patients) before the study was stopped early because of slow recruitment.

Indirect comparisons

4.1.13 The manufacturer of lapatinib (GlaxoSmithKline) performed adjusted indirect comparisons in which data from five studies were incorporated: EGF30008, TAnDEM, one study comparing letrozole with tamoxifen and two studies comparing anastrozole with tamoxifen. The eLEcTRA study was not included because only an abstract had been published. Overall survival data suggested that the hazard ratio for death with lapatinib plus letrozole was 0.85 (95% CI 0.47 to 1.54) when compared with trastuzumab plus anastrozole, 0.77 (95% CI 0.52 to 1.14) when compared with letrozole alone, 0.71 (95% CI 0.45 to 1.14) when compared with anastrozole alone and 0.74 (95% CI 0.49 to 1.12) when compared with tamoxifen.

4.1.14 GlaxoSmithKline reported that the hazard ratio for progression with lapatinib plus letrozole was 0.89 (95% CI 0.54 to 1.47) when compared with trastuzumab plus anastrozole, 0.65 (95% CI 0.47 to 0.89) when compared with letrozole alone, 0.53 (95% CI 0.36 to

0.80) when compared with anastrozole alone and 0.45 (95% CI 0.32 to 0.65) when compared with tamoxifen.

4.1.15 The manufacturer of trastuzumab (Roche) performed an indirect network meta-analysis with a number of different analyses for overall survival (12 trials) and progression-free survival (seven trials). Roche used the overall survival findings from the TAnDEM trial, adjusting for crossover and assuming that aromatase inhibitors have a 'class effect' (that is, letrozole is equivalent to anastrozole). In the base case, Roche reported that the hazard ratio for death with trastuzumab plus aromatase inhibitors was 0.98 (95% CI 0.58 to 1.67) when compared with lapatinib plus aromatase inhibitors and 0.73 (95% CI 0.51 to 1.04) when compared with aromatase inhibitors. The hazard ratio for death with lapatinib plus aromatase inhibitors compared with aromatase inhibitors was 0.74 (95% CI 0.50 to 1.10). When the results were not adjusted for crossover, the hazard ratio for death with trastuzumab plus aromatase inhibitors was 1.13 (95% CI 0.67 to 1.92) compared with lapatinib plus aromatase inhibitors and 0.84 (95% CI 0.59 to 1.19) compared with aromatase inhibitors. The hazard ratio for death with lapatinib plus aromatase inhibitors compared with aromatase inhibitors was 0.74 (95% CI 0.50 to 1.10).

4.1.16 The hazard ratio for progression of trastuzumab plus aromatase inhibitors was 0.78 (95% CI 0.52 to 1.18) when compared with lapatinib plus aromatase inhibitors and 0.55 (95% CI 0.42 to 0.74) when compared with aromatase inhibitors. The hazard ratio for progression of lapatinib plus aromatase inhibitors compared with aromatase inhibitors was 0.71 (95% CI 0.53 to 0.95).

4.1.17 The Assessment Group considered that the findings of the indirect comparisons presented by the two manufacturers should be treated with caution. It stated that the populations in the EGF30008 and

TAnDEM trials differed substantially and that neither of the manufacturers' indirect comparisons met the basic requirement for indirect comparisons – that is, exchangeability of relative treatment effect between trials could not be assumed. The Assessment Group noted that the proportion of patients with hormone-receptor positive and HER2+ metastatic breast cancer included in the other trials in the indirect comparisons was unclear. It also noted that the length of follow-up and the proportion of patients receiving first-line treatment differed between trials.

4.2 Cost effectiveness

4.2.1 The Assessment Group did not identify any published economic analyses that were considered relevant to the appraisal. The manufacturer of trastuzumab identified one study that it considered to be relevant. This was a poster by Hastings et al. presented in June 2010 at the annual meeting of the American Society of Clinical Oncology. The poster described analysis of an indirect comparison of the cost effectiveness of lapatinib plus letrozole and trastuzumab plus anastrozole in postmenopausal women with hormone-receptor positive and HER2+ metastatic breast cancer who had not received previous treatment. The Assessment Group considered that the studies that made up the evidence network addressed different populations and the analysis could not provide a reliable estimate of relative cost effectiveness.

4.2.2 Both manufacturers provided economic analyses to support their submissions in which the technologies under assessment were compared with each other and with letrozole and anastrozole as monotherapies.

GlaxoSmithKline (lapatinib plus an aromatase inhibitor)

4.2.3 The manufacturer's economic model had three states: alive and no disease progression, alive with progression, and dead. The model

had a time horizon of 10 years and both costs and benefits were discounted at 3.5% per year. The analysis was carried out from the perspective of the NHS and personal social services. The key clinical data comparing lapatinib plus letrozole with letrozole alone came from the EGF30008 trial. To compare lapatinib plus letrozole with other technologies, the manufacturer used the results of the indirect comparison. The manufacturer's model generated 431 and 269 progression-free survival days with lapatinib and an aromatase inhibitor respectively. This gave a gain of 162 pre-progression survival days with lapatinib. The model generated 810 and 759 post-progression survival days with lapatinib and an aromatase inhibitor respectively; a gain of 51 post-progression days with lapatinib. The manufacturer estimated 1241 overall survival days with lapatinib and 1028 overall survival days with an aromatase inhibitor, a gain of 213 overall survival days with lapatinib treatment.

4.2.4 The utility value for the 'alive and no disease progression' state was estimated using data from the FACT-B questionnaire administered during the EGF30008 trial. The utility value for the 'alive with progression' state was taken from the results of a study by Lloyd et al. (2006) of societal preferences for different stages of metastatic breast cancer in the UK. The utility value used for the 'alive and no disease progression' state was 0.86 and the value for 'alive with progression' was 0.62. The utility decrements applied in the economic model included: nausea (0.1); vomiting (0.1); diarrhoea (0.1); alopecia (0.11); asthenia, fatigue or lethargy (0.12); skin and nail disorders (0.15).

4.2.5 In the base case, the incremental cost of lapatinib plus letrozole compared with letrozole alone was £34,737 and the incremental quality-adjusted life year (QALY) gain was 0.467. This generated an incremental cost-effectiveness ratio (ICER) of £74,448 per

QALY gained. The ICER for lapatinib plus letrozole compared with trastuzumab plus anastrozole was £21,836 per QALY gained (incremental cost of £5513 and incremental QALY gain of 0.252) while the ICER for lapatinib plus letrozole compared with anastrozole alone was £59,895 per QALY gained (incremental cost of £35,995 and incremental QALY gain of 0.601).

4.2.6 The manufacturer examined 51 scenarios in deterministic sensitivity analyses. The analyses showed that the ICERs were most sensitive to the utility value for the 'alive and no disease progression' health state, the discount rate for costs and outcomes and the time horizon. Using different assumptions, the ICER for lapatinib plus letrozole compared with letrozole alone ranged from £41,877 per QALY gained to lapatinib plus letrozole being dominated by letrozole alone (that is, letrozole alone was more effective and less costly). The ICER for lapatinib plus letrozole compared with anastrozole alone ranged from £38,170 to £378,674 per QALY gained. The ICER for lapatinib plus letrozole compared with trastuzumab plus anastrozole ranged from lapatinib plus letrozole dominating the comparator to £45,106 per QALY gained. The manufacturer also performed a probabilistic sensitivity analysis. The results showed that at £30,000 for an additional QALY, the probability of lapatinib plus letrozole being cost effective was less than 25% when compared with any aromatase inhibitor, and about 50% when compared with trastuzumab plus anastrozole.

Roche (trastuzumab plus an aromatase inhibitor)

4.2.7 The manufacturer's economic model had three states: progression-free survival, progressive disease and death. The model had a time horizon of 15 years and discounted both costs and benefits at 3.5% per year. The key clinical data used for trastuzumab plus anastrozole compared with anastrozole alone were taken from the TAnDEM trial. All model inputs were from the latest data available,

with an April 2008 cut-off point. Based on the results from the indirect comparison it was assumed that letrozole and anastrozole have a 'class effect' and therefore the progression-free survival and overall survival curves for anastrozole were used for letrozole. The clinical estimates for lapatinib plus letrozole came from the EGF30008 trial. The manufacturer's model generated 434 and 190 progression-free survival days with trastuzumab and an aromatase inhibitor respectively. This gave a gain of 244 pre-progression survival days with trastuzumab. The model generated 810 and 737 post-progression survival days with trastuzumab and an aromatase inhibitor respectively. This gave a gain of 73 post-progression days with trastuzumab. The manufacturer estimated 1245 overall survival days with trastuzumab and 931 overall survival days with an aromatase inhibitor, giving a gain of 314 overall survival days with trastuzumab treatment.

4.2.8 The manufacturer used utility values reported by Cooper et al. (2003) that assigned a utility of 0.73 to progression-free survival and 0.45 to progressive disease. Only grade 3 or 4 adverse events were considered in the model and disutilities resulting from adverse events were not modelled.

4.2.9 The manufacturer presented the results based on an incremental analysis. In the base case, it was reported that trastuzumab plus anastrozole compared with anastrozole alone gave an incremental QALY gain of 0.58 at an incremental cost of £31,408, giving an ICER of £54,312 per QALY gained. The manufacturer also reported the results of a pairwise analysis with the remaining two comparisons. In comparison with letrozole alone the ICER was £54,336 per QALY gained (an incremental QALY gain of 0.58 and an incremental cost of £31,422). In comparison with lapatinib plus letrozole the ICER was £18,347 per QALY gained (an incremental QALY gain of 0.16 and an incremental cost of £2866).

4.2.10 A univariate sensitivity analysis showed that the ICERs were most sensitive to the utility value for progression-free survival. When the base-case utility value of 0.73 was varied between 0.803 and 0.657 the ICER ranged from £50,099 to £59,355 per QALY gained for trastuzumab plus anastrozole compared with anastrozole alone. The manufacturer also described three multivariate scenario analyses. In these analyses, when the hazard ratios for progression and for death from the indirect comparisons were used in the model, anastrozole represented a cost-effective treatment option up to £3594 for an additional QALY; letrozole was the most cost-effective treatment option from £3594 to £57,773 per QALY gained; and trastuzumab plus anastrozole was the most cost-effective treatment option above £57,773 per QALY gained.

4.2.11 The manufacturer conducted a probabilistic sensitivity analysis. This analysis showed that at £30,000 for an additional QALY, the combination therapies were not cost effective. At £55,000 for an additional QALY, trastuzumab plus anastrozole was cost effective in approximately 35% of simulations.

4.2.12 Following consultation, the manufacturer updated the base case to include the utility values used by the Assessment Group. The manufacturer also removed the indirect comparison and only used the comparison of trastuzumab plus anastrozole compared with anastrozole alone. The effect of this was to decrease the ICER to £50,975 per QALY gained (incremental cost £31,400 and incremental QALY gain 0.62) for trastuzumab. The manufacturer noted that they had not accounted for the effects of second-line therapy in this analysis.

Independent economic assessment by the Assessment Group

4.2.13 Because of potential differences between the EGF30008 and TAnDEM trials in the baseline characteristics of patients, the Assessment Group performed two separate cost-effectiveness

analyses. These analyses used directly observed progression-free survival and post-progression survival data from the trials to generate expected overall survival. The analyses had common parameter values, but took effectiveness data from a single randomised controlled trial (either TAnDEM or EGF30008). Days spent in 'progression-free survival' and 'progressive disease' from the trials were used to calculate health service costs and expected QALY gains. Costs and outcomes were discounted at 3.5% per year.

Assessment Group model for lapatinib plus letrozole compared with letrozole alone

4.2.14 The Assessment Group calculated the mean progression-free survival by applying the difference between the Kaplan–Meier area under the curve estimates up to the time of convergence (505 days) and then applying a single exponential model of progression-free survival to both the intervention and the comparator. This generated 266 progression-free survival days for lapatinib plus letrozole and 199 progression-free survival days for letrozole alone, giving a progression-free survival gain of 67 days per patient attributable to lapatinib. The Assessment Group reported that, following disease progression, patients in both groups of the trial were at the same risk of death, which appeared to be constant over time. The model generated 765 days post-progression survival for both groups. Overall survival was calculated as progression-free survival plus post-progression survival. After adjusting post-progression survival to exclude patients who died at or before disease progression, the overall survival was 983 days for lapatinib plus letrozole and 928 days for letrozole alone, resulting in an overall survival gain of 55 days per patient attributable to lapatinib.

4.2.15 Based on a study by Lloyd et al. (2006), slightly different utility values for the 'progression-free survival' state were assigned to the

lapatinib plus letrozole group (0.766) and to the letrozole alone group (0.762). A utility of 0.496 was assigned to the 'post-progression survival' state. Disutility of adverse events was not included in the base case but was examined in a sensitivity analysis.

4.2.16 In the base case, the Assessment Group stated that lapatinib plus letrozole provided less than 0.12 additional QALYs at an additional cost of more than £26,150 per patient compared with letrozole alone, resulting in an ICER in excess of £220,000 per QALY gained. The results from deterministic sensitivity analysis showed that the ICER is most sensitive to the health state utility values, and to the cost of lapatinib. The Assessment Group conducted a probabilistic sensitivity analysis, which estimated the ICER to be in excess of £2,000,000 per QALY gained.

4.2.17 In response to consultation comments, the Assessment Group in its deterministic sensitivity analysis revised the estimates of survival and the ICER for lapatinib. The revised estimates of pre-progression survival were 343 days and 255 days for lapatinib and an aromatase inhibitor respectively, giving a gain of 89 days of pre-progression survival with lapatinib treatment. The revised estimates of post-progression survival were 717 days and 742 days for lapatinib and an aromatase inhibitor respectively, giving a loss of 25 days of pre-progression survival with lapatinib treatment. Overall survival was estimated to be 1061 days with lapatinib and 997 days with an aromatase inhibitor, giving an increase of 64 days with lapatinib treatment. The corresponding ICER remained in excess of £225,000 per QALY gained. Also in response to consultation comments, the Assessment Group corrected its model for all the issues raised by the manufacturer of lapatinib. The revised probabilistic ICER was £228,913 per QALY gained.

Assessment Group model for trastuzumab plus anastrozole compared with anastrozole alone

4.2.18 The mean progression-free survival was calculated using the Kaplan–Meier area under the curve estimate up to the last recorded event in each group, and then adding the area under the projected long-term Weibull curve. The number of days in progression-free survival and post-progression survival were reported in the Assessment Group report but were corrected following consultation on the model. The corrected values for progression-free survival were 515 days for trastuzumab plus anastrozole and 190 days for anastrozole alone, giving a gain of 325 progression-free survival days attributable to trastuzumab. Mean post-progression survival was calculated using the Kaplan–Meier area under the curve estimate up to the last recorded event in each group, and then adding the area under the projected long-term Weibull model as applied for progression-free survival. The corrected values for post-progression survival were 810 days for trastuzumab plus anastrozole and 870 days for anastrozole alone, making a loss of 60 post-progression survival days attributable to trastuzumab. The estimate for overall survival was obtained by combining estimates of mean progression-free survival and mean post-progression survival in each group, and adjusting for the patients who died at or before progression. This generated 1030 overall survival days for trastuzumab plus anastrozole and 810 overall survival days for anastrozole alone, with a gain of 220 overall survival days attributable to trastuzumab.

4.2.19 Based on the study by Lloyd et al. (2006), slightly different utility values for progression-free survival were assigned to the trastuzumab plus anastrozole group (0.769 [standard error 0.113]) and to the anastrozole alone group (0.764 [standard error 0.114]). A health state utility value of 0.496 (standard error 0.160) was assigned to the post-progression survival state. Disutility of adverse

events was not included in the base case, but was examined in a sensitivity analysis.

4.2.20 In the base case, the Assessment Group reported that there was a mean health gain per patient of 0.51 QALYs at an additional cost of about £37,500 per patient. The resulting ICER exceeded £73,000 per QALY gained for trastuzumab plus anastrozole compared with anastrozole alone. A sensitivity analysis showed that the ICER is most sensitive to the utility values for the different states, the cost of trastuzumab and discounting rates. A probabilistic sensitivity analysis was undertaken using the base-case scenario over a 20-year time horizon. This showed no measurable probability of trastuzumab plus anastrozole being cost effective at £40,000 for an additional QALY, and a 3.2% probability of being cost effective at £50,000 for an additional QALY.

4.2.21 In response to consultation comments, the Assessment Group revised the estimates of survival and the ICER for trastuzumab, correcting for an error in the number of patients who died at or before progression in the trastuzumab group. The revised estimates of pre-progression survival were 510 days and 194 days for trastuzumab and an aromatase inhibitor respectively, giving a gain of 316 days pre-progression survival with trastuzumab treatment. The revised estimates of post-progression survival were 612 days and 672 days for trastuzumab and an aromatase inhibitor respectively, giving a loss of 60 days pre-progression survival with trastuzumab treatment. Overall survival was estimated to be 1122 days with trastuzumab and 866 days with an aromatase inhibitor, giving an increase of 256 days with trastuzumab treatment. The corresponding ICER was £69,514 per QALY gained.

4.3 Consideration of the evidence

4.3.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of lapatinib and trastuzumab, having considered evidence on the nature of metastatic hormone-receptor-positive and HER2+ breast cancer and the value placed on the benefits of lapatinib and trastuzumab by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

4.3.2 The Committee considered the population for whom the two combination technologies would be used. It discussed current clinical practice in the UK in the treatment of metastatic hormone-receptor-positive and HER2+ breast cancer and the position of lapatinib and trastuzumab in the treatment pathway. The Committee heard from clinical specialists that in current UK clinical practice, women with metastatic HER2+ breast cancer are more likely to receive trastuzumab plus chemotherapy than an aromatase inhibitor. Aromatase inhibitors alone are currently offered to women who prefer not to receive chemotherapy, who are not fit enough to receive chemotherapy or in whom it is contraindicated. The clinical specialists stated that the combination of lapatinib or trastuzumab plus an aromatase inhibitor would therefore be likely to be offered to these women. The clinical specialists stated that lapatinib or trastuzumab plus an aromatase inhibitor might be preferred for some women in whom chemotherapy would currently be offered because these combinations have a better adverse reaction profile than chemotherapy. The Committee heard from patient experts that for some women, chemotherapy was particularly difficult to cope with and treatment with lapatinib or trastuzumab in combination with an aromatase inhibitor may make carrying on with their lives easier. The Committee also noted comments from patient experts that

women wish to have access to the newer therapies because these may increase progression-free survival, and that this benefit outweighed concerns about potential adverse reactions associated with adding these agents to aromatase inhibitor monotherapy. The Committee therefore concluded that lapatinib or trastuzumab plus an aromatase inhibitor are likely to be used in women who, in consultation with their clinicians, consider that chemotherapy is not the best option for first-line treatment of metastatic disease.

4.3.3 The Committee considered the clinical trial evidence for the two technologies under consideration. It noted that the trial results suggested a greater difference between treatment and comparators in median progression-free survival in the lapatinib trial than in the trastuzumab trial (that is, a difference of 5.2 months in EGF30008, compared with 2.4 months in the TAnDEM trial). However, the results over the duration of the trials suggested a greater gain in median overall survival with trastuzumab than with lapatinib. In EGF30008, the percentage of people alive without progression was the same between the treatment and comparator arms at 16 months, and remained the same for the remainder of the trial, indicating no gain in progression-free survival with lapatinib after 16 months. However, in TAnDEM the percentage of people alive without progression in the treatment arm remained higher than that in the comparator arm throughout the duration of the trial. The Committee noted that the curves showing the percentages of people alive without progression for the treatment arms were similar to each other between the trials. It understood from clinical specialists that this would be expected in clinical practice (that is, that there would be no difference in the clinical effectiveness of lapatinib and trastuzumab). The Committee noted the comments received during consultation on the post-appeal appraisal consultation document and discussed the difficulties with comparing the trials. The Committee discussed the inclusion

criteria of the trials (the baseline characteristics including hormone receptor status, the number and location of metastatic sites, and time from diagnosis to inclusion in the trials) and whether the two trial populations were comparable. The Committee also discussed crossover, differences in post-progression treatments, randomisation, the size of the trial populations, and whether the use of different aromatase inhibitors in the trials was relevant. Taking all these factors into consideration, the Committee was uncertain to what extent the trials could be compared. The Committee heard from the clinical specialist that the trials did not provide robust evidence for or against a real difference between the two agents.

4.3.4 The Committee noted the mixed treatment comparisons presented by the manufacturers. It heard that the Assessment Group believed it was not possible to combine the EGF30008 and TAnDEM trials in a meta-analysis because of the different populations included in the trials, and that the results of the manufacturer's meta-analyses should be interpreted with caution. The Committee noted that the Assessment Group had not compared the clinical and cost effectiveness of lapatinib plus an aromatase inhibitor with trastuzumab plus an aromatase inhibitor in one model. The Committee accepted that it would need to consider the clinical and cost effectiveness of lapatinib plus an aromatase inhibitor and trastuzumab plus an aromatase inhibitor independently, at least in the first instance.

Lapatinib plus an aromatase inhibitor

4.3.5 The Committee considered the clinical effectiveness of treatment with lapatinib plus an aromatase inhibitor. It first considered the progression-free survival outcomes from EGF30008. It noted a statistically significant difference of 5.2 months in median progression-free survival with lapatinib plus letrozole when

compared with letrozole alone. The Committee considered the overall survival outcomes. In the subgroup of HER2+ patients there was a non-statistically significant median increase of 1 month in overall survival for patients receiving lapatinib plus an aromatase inhibitor. The Committee concluded that lapatinib plus an aromatase inhibitor offered a benefit in progression-free survival but only a small and uncertain overall survival gain.

4.3.6 The Committee considered the manufacturer's and Assessment Group's economic models for lapatinib plus an aromatase inhibitor. The Committee understood that the manufacturer had estimated overall survival as a single entity using projective modelling from the trial data whereas the Assessment Group had projected progression-free survival and post-progression survival separately and combined these to obtain an estimate of overall survival. The Committee noted that there were some differences between the Assessment Group's and the manufacturer's estimates of progression-free survival and post-progression survival.

4.3.7 The Committee considered the estimates of progression-free survival in the manufacturer and Assessment Group's models. It noted that for the lapatinib plus an aromatase inhibitor treatment group, the manufacturer's estimate of progression-free survival was 431 days and the Assessment Group's estimate was 343 days. The Committee heard from the Assessment Group that its (the Assessment Group's) model may have underestimated the longer term progression-free survival gain with lapatinib plus an aromatase inhibitor. The Committee therefore concluded that the manufacturer's estimate of progression-free survival was acceptable. The Committee accepted the manufacturer's estimate of progression-free survival for the aromatase inhibitor arm, because the estimates of the manufacturer's model (269 days) and the Assessment Group's model (255 days) were similar.

4.3.8 The Committee then considered the modelled estimates of post-progression survival. The Committee understood that patients would have stopped treatment with lapatinib plus an aromatase inhibitor at this stage. It noted that the Assessment Group's model resulted in a lower estimate for lapatinib plus an aromatase inhibitor (717 days) than for the aromatase inhibitor alone (742 days). This resulted in a negative number of days gain in post-progression survival (−25 days) with lapatinib plus an aromatase inhibitor treatment. The Committee further noted that the manufacturer's model resulted in a higher estimate of post-progression survival for lapatinib plus an aromatase inhibitor (810 days) than for an aromatase inhibitor alone (759 days). This resulted in a positive number of days gained during post-progression survival following lapatinib plus an aromatase inhibitor treatment (51 days). The Committee heard from clinical specialists that there is no reason why the addition of lapatinib to an aromatase inhibitor before progression should result in either a shorter or longer duration of post-progression survival. The Committee concluded that it was possible that a longer time in progression-free survival might reduce the time in post-progression survival, but that uncertainty remained around this.

4.3.9 The Committee considered the ICERs for lapatinib plus an aromatase inhibitor. It noted that the manufacturer presented an ICER of £74,400 per QALY gained (representing incremental costs of £34,700 and incremental QALYs gained of 0.47). The Assessment Group presented a deterministic ICER in excess of £225,000 per QALY gained (incremental costs of £26,200 and incremental QALYs gained of less than 0.12). After consultation the Committee noted the Assessment Group's revised estimate of £228,900 per QALY gained for the mean probabilistic ICER. The Committee considered that the Assessment Group's estimates were likely to be an overestimate of the most plausible ICER for

lapatinib plus an aromatase inhibitor on the basis of previous discussions in which the Committee had agreed that the progression-free survival had been underestimated (section 4.3.7) by the Assessment Group. The Committee discussed the manufacturer's estimate of the ICER. On the basis of previous discussions regarding post-progression survival (section 4.3.8) the Committee concluded that the most plausible ICER would be nearer £74,000 per QALY gained.

Trastuzumab plus an aromatase inhibitor

4.3.10 The Committee considered the clinical effectiveness of treatment with trastuzumab plus an aromatase inhibitor. It first considered the progression-free survival outcomes from TAnDEM. It noted a statistically significant difference of 2.4 months in median survival with trastuzumab plus anastrozole compared with anastrozole alone. The Committee then considered the overall survival outcomes. The Committee was aware that the manufacturer of trastuzumab had presented an analysis that adjusted for patients who had crossed over from the aromatase inhibitor group to receive trastuzumab plus an aromatase inhibitor, which it considered to be the most appropriate analysis. It noted that this gave a non-statistically significant gain of 6.5 months in overall survival. The Committee concluded that trastuzumab plus an aromatase inhibitor is associated with a statistically significant increase in median progression-free survival but that the trial did not demonstrate a statistically significant increase in overall survival.

4.3.11 The Committee considered the estimates of progression-free survival in the manufacturer and Assessment Group's models. It noted that the manufacturer's estimate of progression-free survival with trastuzumab treatment was 434 days and the Assessment Group's estimate was 510 days. The Committee accepted the

manufacturer's estimate of progression-free survival for trastuzumab because it was based on a complete dataset.

4.3.12 The Committee considered the modelled estimates of post-progression survival. It noted the large differences in the estimates produced by the manufacturer and the Assessment Group's models. In particular it noted that the Assessment Group's model resulted in a negative value of −60 days in post-progression survival for trastuzumab plus an aromatase inhibitor compared with an aromatase inhibitor. The Committee noted comments from the manufacturer of trastuzumab that it would seem wrong that treatment with trastuzumab causes a shortened life expectancy following disease progression. The Committee heard from clinical specialists that there is no reason why the addition of trastuzumab to an aromatase inhibitor before progression should result in either a shorter or longer duration of post-progression survival. The Committee concluded that it was unable to fully explain this finding. It noted the Assessment Group's opinion that the finding relates to data in the control arm of the trial and the manufacturer's view that other pivotal trials of trastuzumab all showed prolonged post-progression survival. The Committee concluded that there was a considerable lack of clarity around the relationship between progression-free survival and post-progression survival.

4.3.13 The Committee considered the ICERs for trastuzumab plus anastrozole compared with anastrozole alone. It understood that the manufacturer's revised base-case ICER (£51,000 per QALY) gained was based on the Assessment Group's original estimate (£73,100 per QALY gained), adjusted to correct the number of patients who died at or before progression, minus £6500 (the difference in drug costs between the manufacturer's and the Assessment Group's model) and using the higher utility values used in the Assessment Group's model. The Committee also noted

that the Assessment Group's revised estimate of the ICER was £69,500 per QALY gained. The Committee concluded that the most plausible ICER for trastuzumab plus an aromatase inhibitor would be at least £51,000 per QALY gained.

Supplementary advice to the Committee for end-of-life conditions

4.3.14 The Committee considered the supplementary advice from NICE that should be taken into account when appraising treatments that may extend the life of patients with a short life expectancy and that are licensed for indications that affect small numbers of people with incurable illnesses. For this advice to be applied, all the following criteria must be met:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months.
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.
- The treatment is licensed or otherwise indicated for small patient populations.

In addition, when taking these criteria into account, the Committee must be persuaded that:

- the estimates of the extension to life are robust and can be shown or reasonably inferred from either progression-free survival or overall survival (taking account of trials in which crossover has occurred and has been accounted for in the effectiveness review) and
- the assumptions used in the reference case of the economic modelling are plausible, objective and robust.

Trastuzumab plus an aromatase inhibitor

4.3.15 The Committee considered whether trastuzumab met the criterion for a small population. The Committee examined the estimates provided by the manufacturer of the number of patients diagnosed annually with conditions for which trastuzumab is indicated. It noted that the total number (7158) had previously been accepted as fulfilling the criterion for a small population by another Committee. It also noted that on that occasion, the other Committee had accepted that patients in clinical trials could be excluded from the calculation of population size. The Committee was not persuaded that a population of over 7000 was small, or that it was valid to exclude patients in clinical trials from the calculation of population size. The Committee recognised that these different conclusions from those of a previous Committee were matters of judgement. However in the interest of fairness to this patient population, the Committee agreed not to differ from the other Committee's conclusion on this occasion. On this basis the Committee accepted that trastuzumab plus an aromatase inhibitor fulfilled the small population criterion.

4.3.16 The Committee considered the criterion for short life expectancy. The Committee reviewed all the evidence for life expectancy in this group of patients, including historical published data and estimates of overall survival in the aromatase inhibitor arms of the trials. It considered that the best estimate of expected survival using current standard NHS treatment was demonstrated in the control arms of the trials. The Committee noted that a range of overall survival estimates were presented, from the median survival in the ITT population of 23.9 months, median survival in the centrally confirmed population of 28.6 months and the Assessment Group and manufacturer's estimates of mean survival of 29 and 31 months respectively. The Committee was aware that, in distributions of survival times that are asymmetrical and skewed to

the right (that is, most patients are alive in the first few months and then a few patients survive for much longer), the median would always underestimate the mean. The Committee noted that when an attempt was made to remove the effect of crossover (rank preserving structural failure time analysis) the median survival was 22 months, but considered that in clinical practice patients may be offered further treatment on progression. The Committee also noted that additional information on survival with standard NHS treatment was available from the aromatase inhibitor arm of the EGF30008 trial in which median overall survival was 32 months. The Committee concluded that, taken together, the balance of evidence on survival indicated that patients receiving current standard NHS treatment would have an expected survival of greater than 24 months. The Committee therefore concluded that the life expectancy of patients exceeded 24 months and that trastuzumab plus an aromatase inhibitor did not fulfil the criterion for short life expectancy.

4.3.17 The Committee discussed the extension to life criterion. The Committee discussed whether a 3 month survival gain could be reasonably inferred from the data provided and it decided that as trastuzumab did not meet the end-of-life criterion for life expectancy it was not necessary to make a decision about the extension to life criterion.

4.3.18 On the basis of these discussions (sections 4.3.15–4.3.17) the Committee concluded that treatment with trastuzumab plus an aromatase inhibitor did not fulfil all of the criteria for special consideration under the supplementary advice from NICE. The Committee also considered that even if all the criteria had been satisfied, the ICERs were too high to consider trastuzumab plus an aromatase inhibitor a cost-effective use of NHS resources.

Lapatinib plus an aromatase inhibitor

4.3.19 The Committee considered whether lapatinib plus an aromatase inhibitor for the treatment of metastatic hormone-receptor-positive and HER2+ metastatic breast cancer fulfilled the criteria for consideration as a life-extending, end-of-life treatment. The Committee discussed the first criterion and noted that the evidence for life expectancy in this group of patients exceeded 24 months (see section 4.3.16). The Committee concluded that lapatinib plus an aromatase inhibitor did not fulfil the criterion for short life expectancy.

4.3.20 The Committee considered the second criterion. The Committee considered that no robust evidence had been presented to indicate that lapatinib plus an aromatase inhibitor compared with an aromatase inhibitor alone offered a 3-month survival gain and concluded that lapatinib plus an aromatase inhibitor did not meet this criterion.

4.3.21 The Committee considered that the potential population covered by the marketing authorisation for lapatinib would not be as large as for trastuzumab (see 4.3.15) because lapatinib does not have a marketing authorisation for early breast cancer or for gastric cancer. The Committee concluded that lapatinib did fulfil the small population criterion.

4.3.22 On the basis of these discussions (sections 4.3.19 -4.3.21) the Committee concluded that lapatinib did not fulfil all the criteria for special consideration under the supplementary advice from NICE. The Committee also concluded that even if all the criteria had been satisfied, the ICERs were too high to consider lapatinib plus an aromatase inhibitor a cost-effective use of NHS resources.

4.3.23 The Committee considered the clinical and cost effectiveness of lapatinib plus an aromatase inhibitor and trastuzumab plus an

aromatase inhibitor in light of the submitted evidence and the comments of the clinical specialists, the commissioning expert and the patient experts. The Committee agreed that the cost-effectiveness estimates for both technologies were high and subject to uncertainties which would increase, rather than decrease, the manufacturers' ICERs. The Committee concluded that neither lapatinib nor trastuzumab would be a cost-effective use of NHS resources when combined with an aromatase inhibitor for the first-line treatment of metastatic hormone-receptor-positive breast cancer that overexpresses HER2 compared with an aromatase inhibitor alone.

4.3.24 The Committee considered whether NICE's duties under the equalities legislation required it to alter or to add to its recommendations. The Committee discussed comments from consultees indicating that a small population of older patients who are not fit enough to receive chemotherapy may not have access to an alternative treatment and so may be disadvantaged. The Committee agreed that this was not an issue of age discrimination because other factors can also affect whether people are fit enough to receive chemotherapy, such as comorbidities. The Committee also noted that the cost-effectiveness estimates had been based on the comparison with an aromatase inhibitor alone and not with chemotherapy, and that neither lapatinib nor trastuzumab plus an aromatase inhibitor were cost effective relative to an aromatase inhibitor alone. The Committee concluded that there was no need to change or add to its recommendations.

Summary of Appraisal Committee's key conclusions

TAXXX	**Appraisal title:** Lapatinib or trastuzumab in combination with an aromatase inhibitor for the first-line treatment of metastatic hormone-receptor-positive breast cancer that overexpresses HER2	**Section**
Key conclusion		
Lapatinib in combination with an aromatase inhibitor is not recommended for first-line treatment in postmenopausal women with metastatic hormone-receptor-positive breast cancer that overexpresses human epidermal growth factor receptor 2 (HER2). Trastuzumab in combination with an aromatase inhibitor is not recommended for first-line treatment in postmenopausal women with metastatic hormone-receptor-positive breast cancer that overexpresses HER2. The end-of-life supplementary advice was not accepted for either technology.		1.1 1.2 4.3.15–4.3.22
Current practice		
Clinical need of patients, including the availability of alternative treatments	The Committee heard from clinical specialists that in current UK clinical practice, women with metastatic HER2+ breast cancer are more likely to receive trastuzumab plus chemotherapy than an aromatase inhibitor. The Committee concluded that lapatinib or trastuzumab plus an aromatase inhibitor would be most likely to be used in women who, in consultation with their clinicians, consider that chemotherapy is not the best option for first-line treatment of metastatic disease.	4.3.2
The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	Clinical specialists stated that lapatinib or trastuzumab plus an aromatase inhibitor might be preferred for some women in whom chemotherapy would currently be offered because the combination has a better adverse reaction profile than chemotherapy. The Committee heard from patient experts that for some women, chemotherapy was particularly difficult to cope with and treatment with lapatinib or trastuzumab in combination with an aromatase inhibitor may make carrying on with their lives easier.	4.3.2
What is the position of the treatment in the pathway of care for the condition?	The Committee concluded that lapatinib or trastuzumab plus an aromatase inhibitor are likely to be used in women who, in consultation with their clinicians, consider that chemotherapy is not the best option for first-line treatment of metastatic disease.	4.3.2

Adverse reactions	Clinical specialists stated that that lapatinib or trastuzumab plus an aromatase inhibitor might be preferred for some women in whom chemotherapy would currently be offered because the combination has a better adverse reaction profile than chemotherapy.	4.3.2
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The Committee heard from the Assessment Group that it was not possible to combine the EGF30008 and TAnDEM trials in a meta-analysis because of the different populations included in the trials, and that the results of the manufacturer's meta-analyses should be interpreted with caution. The Committee accepted that it would need to consider the clinical effectiveness of lapatinib plus an aromatase inhibitor and trastuzumab plus an aromatase inhibitor independently, at least in the first instance.	4.3.4
Relevance to general clinical practice in the NHS	The Committee understood from the clinical specialists that no difference in the clinical effectiveness of lapatinib and trastuzumab plus an aromatase inhibitor would be expected in clinical practice. It also heard that the trials did not provide robust evidence for or against a real difference between the two agents.	4.3.3
Uncertainties generated by the evidence	The Committee concluded that lapatinib plus an aromatase inhibitor offered a benefit in progression-free survival but only a small and uncertain overall survival gain. The Committee concluded that trastuzumab plus an aromatase inhibitor is associated with a statistically significant increase in median progression-free survival but that the evidence did not demonstrate a statistically significant increase in overall survival.	4.3.5 4.3.10
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	No subgroups were identified in this appraisal.	–
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The Committee noted that the trial results suggested a greater difference between treatment and comparators in median progression-free survival in the lapatinib and trastuzumab trials (that is, a difference of 5.2 months in EGF30008, compared with 2.4 months in the TAnDEM trial). Evidence of an overall survival gain was not demonstrated conclusively for either drug.	4.3.3 4.3.5, 4.3.10

Evidence for cost effectiveness		
Availability and nature of evidence	The Assessment Group did not identify any published economic analyses that were considered relevant to the appraisal. The manufacturer of trastuzumab identified one study that it considered to be relevant. This was a poster by Hastings et al. presented in June 2010 at the annual meeting of the American Society of Clinical Oncology.	4.2.1
Uncertainties around and plausibility of assumptions and inputs in the economic model	In the Assessment Group's models, the estimates of additional post-progression survival with treatment with either lapatinib or trastuzumab plus an aromatase inhibitor were negative. Conversely, in both the manufacturer's models, the gain was a positive number. The Committee heard from clinical specialists that there is no reason why the addition of lapatinib or trastuzumab to an aromatase inhibitor before progression should result in either a shorter or longer duration of post-progression survival.	4.3.8, 4.3.12
Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	The Committee did not discuss the incorporation of health-related quality-of-life benefits or utility values.	–
Are there specific groups of people for whom the technology is particularly cost effective?	No subgroups were identified in this appraisal.	–
What are the key drivers of cost effectiveness?	The Committee considered that the differences in the ICERs were mainly because of different incremental QALYs that resulted from the different progression-free and post-progression survival estimates.	4.3.9 and 4.3.13
Most likely cost-effectiveness estimate (given as an ICER)	The Committee concluded that the most plausible ICER for lapatinib plus an aromatase inhibitor would be near to £74,000 per QALY gained. The Committee concluded that the most plausible	4.3.9

	ICER for trastuzumab plus an aromatase inhibitor would be at least £51,000 per QALY gained.	4.3.13
Additional factors taken into account		
Patient access schemes (PPRS)	Not applicable to this appraisal.	–
End-of-life considerations	**Trastuzumab** The Committee noted that the total number (7158) of patients diagnosed annually with conditions for which trastuzumab is indicated had been accepted by another Committee. The Committee was not persuaded that a population of over 7000 was small, or that it was valid to exclude patients in clinical trials from the calculation of population size. The Committee recognised that these different conclusions from that of a previous Committee were matters of judgement. However in the interest of fairness to this patient population, the Committee agreed not to differ from the other Committee's conclusion on this occasion. It therefore concluded that trastuzumab plus an aromatase inhibitor fulfilled the small population criterion.	4.3.15
	The Committee noted that a range of survival estimates were presented and that all the evidence indicated that patients receiving current standard NHS treatment would have an expected survival greater than 24 months. The Committee concluded that trastuzumab did not fulfil the criterion for short life expectancy.	4.3.16
	The Committee discussed whether a 3 month survival gain could be reasonably inferred from the data provided and it decided that as trastuzumab did not meet the end-of-life criteria for life expectancy it was not required to make a decision for the extension to life criterion. The Committee concluded that treatment with trastuzumab plus an aromatase inhibitor did not fulfil all of the criteria for special consideration under the supplementary advice from NICE.	4.3.17, 4.3.18
	Lapatinib The Committee noted that the mean overall survival in the aromatase inhibitor monotherapy arm of the EGF30008 trial and in the ITT population of the TAnDEM trial exceeded 24 months. The Committee concluded that	4.3.19

	lapatinib plus an aromatase inhibitor did not fulfil the criterion for short life expectancy. The Committee considered that no robust evidence had been presented to indicate that lapatinib plus an aromatase inhibitor compared with an aromatase inhibitor alone offered a 3-month survival gain and concluded that lapatinib plus an aromatase inhibitor did not meet this criterion. The Committee concluded that lapatinib did fulfil the small population criterion. However, because lapatinib had failed to meet the first and second criteria for consideration as a life-extending end-of-life treatment, the Committee concluded that lapatinib did not fulfil all the criteria for special consideration under the supplementary advice from NICE.	4.3.20 4.3.21, 4.3.22
Equalities considerations and social value judgements	Comments from consultees indicated that a small population of older patients who are not fit enough to receive chemotherapy may not have access to an alternative treatment and so may be disadvantaged. The Committee agreed that this was not an issue of age discrimination because other factors can also affect whether people are fit enough to receive chemotherapy, such as comorbidities. The Committee concluded that there was no need to change or add to its recommendations.	4.3.24

5 Implementation

5.1 The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS in England and Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must usually provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website. When there is no NICE technology appraisal guidance on

a drug, treatment or other technology, decisions on funding should be made locally.

5.2 NICE has developed tools to help organisations put this guidance into practice (listed below). These are available on our website (www.nice.org.uk/guidance/TAXXX). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.
- Costing template and report to estimate the national and local savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

6 Related NICE guidance

Published

- Advanced breast cancer: diagnosis and treatment. NICE clinical guideline 81 (2009). Available from www.nice.org.uk/guidance/CG81
- Familial breast cancer: the classification and care of women at risk of familial breast cancer in primary, secondary and tertiary care. NICE clinical guideline 41 (2006). Available from www.nice.org.uk/guidance/CG41
- Guidance on the use of trastuzumab for the treatment of advanced breast cancer. NICE technology appraisal guidance 34 (2002). Available from www.nice.org.uk/guidance/TA34

Under development

NICE is developing the following guidance (details available from www.nice.org.uk):

- Eribulin for the treatment of locally advanced or metastatic breast cancer. NICE technology appraisal guidance (publication date to be confirmed).

7 Review of guidance

7.1 The guidance on this technology will be considered for review by the Guidance Executive in June 2015. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Jane Adam and Philip Home
Chairs, Appraisal Committee
March 2012

Appendix A: Appraisal Committee members and NICE project team

A Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are four Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Jane Adam (Chair)
Department of Diagnostic Radiology, St George's Hospital

Professor Philip Home (Vice Chair) – until October 2011

Professor of Diabetes Medicine, Newcastle University

Professor Iain Squire (Vice-Chair)
Consultant Physician, University Hospitals of Leicester

Professor A E Ades

Professor of Public Health Science, Department of Community Based Medicine, University of Bristol

Dr Gerardine Bryant

General Practitioner, Heartwood Medical Centre, Derbyshire

Dr Fiona Duncan

Clinical Nurse Specialist, Anaesthetic Department, Blackpool Victoria Hospital, Blackpool

Mr Christopher Earl – until March 2011

Surgical Care Practitioner, Renal Transplant Unit, Manchester Royal Infirmary

Mr Adrian Griffin

Vice President, HTA & International Policy, Johnson & Johnson

Dr Sharon Saint Lamont

Head of Quality and Innovation, North East Strategic Health Authority

Dr Ian Lewin

Consultant Endocrinologist, North Devon District Hospital

Dr Louise Longworth

Reader in Health Economics, HERG, Brunel University

Dr Anne McCune

Consultant Hepatologist, University Hospitals Bristol NHS Foundation Trust

Professor John McMurray

Professor of Medical Cardiology, University of Glasgow

Dr Alec Miners

Lecturer in Health Economics, London School of Hygiene and Tropical Medicine

Ms Pamela Rees

Lay Member

Dr Ann Richardson

Lay Member

Dr Paul Robinson

Medical Director, Merck Sharp & Dohme

Mr Stephen Sharp

Senior Statistician, MRC Epidemiology Unit

Dr Peter Sims

General Practitioner, Devon

Dr Eldon Spackman

Research Fellow, Centre for Health Economics, University of York

Ms Amelia Stecher

Associate Director of Individual Funding Requests and Clinical Effectiveness, NHS Kent and Medway

Mr David Thomson

Lay Member

Mr William Turner

Consultant Urologist, Addenbrooke's Hospital

Dr John Watkins

Clinical Senior Lecturer/Consultant in Public Health Medicine, Cardiff University and National Public Health Service Wales

Dr Anthony S Wierzbicki

Consultant in Metabolic Medicine/Chemical Pathology, Guy's and St Thomas' Hospitals NHS Trust

Dr Olivia Wu

Reader in Health Economics, University of Glasgow

B NICE project team

Each technology appraisal is assigned to a team consisting of one or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Raphael Yugi (until March 2011) and Sally Doss

Technical Leads

Joanne Holden (until October 2011) and Joanna Richardson

Technical Adviser

Bijal Joshi

Project Manager

Appendix B: Sources of evidence considered by the Committee

A The assessment report for this appraisal was prepared by Liverpool Reviews and Implementation Group (LRiG):

- Fleeman N, Bagust A, Boland A, et al. Lapatinib and trastuzumab in combination with an aromatase inhibitor for the first-line treatment of metastatic hormone receptor positive breast cancer which over-expresses HER2, September 2010

B The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were also invited to comment on the draft scope, assessment report and the appraisal consultation document (ACD). Organisations listed in I, II and III were also invited to make written submissions and have the opportunity to appeal against the final appraisal determination.

I Manufacturers/sponsors:

- GlaxoSmithKline
- Roche Products

II Professional/specialist and patient/carer groups:

- Breast Cancer Campaign
- Breast Cancer Care
- Breast Cancer UK
- Cancer Networks Pharmacists Forum
- Cancer Research UK
- Macmillan Cancer Support
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians, Medical Oncology Joint Special Committee
- United Kingdom Oncology Nursing Society

III Other consultees:

- Betsi Cadwalader University
- Department of Health
- Welsh Assembly Government

IV Commentator organisations (without the right of appeal):

- AstraZeneca (anastrozole, tamoxifen)
- Commissioning Support Appraisals Unit
- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- Liverpool Reviews and Implementation Group, University of Liverpool
- Medicines and Healthcare Products Regulatory Agency
- National Collaborating Centre for Cancer
- National Institute for Health Research Health Technology Assessment Programme
- Pfizer (exemestane)

C The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer/sponsor consultees and commentators. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on lapatinib and trastuzumab in combination with an aromatase inhibitor for the first-line treatment of metastatic hormone-receptor-positive breast cancer that overexpresses HER2 by attending the Committee discussions and/or providing written evidence to the Committee. They were also invited to comment on the ACD.

- Professor David Cameron, nominated by organisation representing Healthcare Improvement Scotland – clinical specialist
- Dr Rob Stein, nominated by organisation representing Royal College of Physicians (NCRI/RCP/RCR/ACP/JCCO) – clinical specialist
- Mrs Emma Freeborn nominated by organisation representing Breast Cancer Care – patient expert
- Mrs Jackie Harris nominated by organisation representing Breast Cancer Care – patient expert
- Ms Maria Leadbeater nominated by organisation representing Breast Cancer Care – patient expert

D Representatives from the following manufacturers/sponsors attended Committee meetings. They contributed only when asked by the

Committee chair to clarify specific issues and comment on factual accuracy.

- GlaxoSmithKline
- Roche Products