NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Overview

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

This document is a summary of the evidence and views submitted by consultees and the Assessment Group. It highlights key issues for discussion at the first Appraisal Committee meeting. NICE prepares the overview before it receives consultees' comments on the assessment report. The sources of evidence used in the preparation of this document are given in appendix A.

1 Background

1.1 The condition

Breast cancer is the uncontrolled, abnormal growth of malignant breast tissue. It is the most common type of cancer among women in the UK, and women have a 1 in 9 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. In the UK 45,972 people were diagnosed with breast cancer in 2007, of whom 99% were women. Metastatic breast cancer is an advanced stage of the disease when the disease has spread to other organs. Common sites of metastasis include bone, liver, lung and brain. It is estimated that approximately 5% of people present with metastatic breast cancer, and that approximately 30% of people who present with early breast cancer will later develop metastatic breast cancer.

A number of prognostic factors are taken into account by clinicians when deciding on treatment options and making a clinical prognosis. Two of these are hormone receptor status and human epidermal growth factor receptor 2 (HER2) status. Hormone receptors include oestrogen receptors (ERs) and progesterone receptors (PgRs). Tumours that express either ER (ER+) or

PgR (PgR+) are commonly referred to as being hormone-receptor-positive (HR+). It is estimated that 60% and 80% of all breast cancers in premenopausal and postmenopausal women respectively are HR+. Patients with HR+ breast cancer generally have an improved prognosis compared with those who are HR−.

HER2 is involved in mediating the growth, differentiation and survival of cells. Overexpression of ErbB2 (the HER2 protein) and/or amplification of the *HER2* gene results in cancer cells growing and dividing more quickly. HER2+ breast cancer may be more aggressive than HER2− disease, and the prognosis of patients with HER2+ breast cancer is generally poor, whether the cancer is HR− or HR+. Approximately 30% of people with metastatic breast cancer have tumours that overexpress HER2, of which about 50% will also be HR+. It is estimated that 350 to 500 women with newly diagnosed metastatic breast cancer will have tumours that overexpress HER2 and are HR+.

Following a diagnosis of metastatic breast cancer, the average length of survival has been reported to be 12 months for people receiving no treatment, compared with 18–24 months for those receiving chemotherapy. Survival is reduced by up to 50% for people whose cancer is HER2+.

1.2 Current management

Metastatic breast cancer is usually incurable. The aim of treatment is to palliate symptoms, prolong survival and maintain a good quality of life with minimal adverse events. Choice of treatment depends on previous therapy, ER status, HER2 status and the extent of the disease.

NICE clinical guideline 80 (’Early and locally advanced breast cancer’) recommends that all invasive breast cancers are tested for ER status using immunohistochemistry. It also recommends that PgR status is not routinely assessed, noting that PgR status does not appear to add useful information when tumours are ER+. The guideline further recommends that HER2 status is tested for all invasive breast cancers. HER2+ tumours are usually identified by immunohistochemistry. Fluorescent *in situ* hybridisation (FISH) can also be

used to measure HER2 expression, but is usually used only when the immunohistochemistry results are judged to be borderline. In the UK, tumours scoring 3+ using immunohistochemistry, or 2+ and amplified by *in situ* hybridisation, are defined as HER2+.

NICE clinical guideline 81 (’Advanced breast cancer’) recommends that if the disease is not imminently life-threatening or does not require early relief of symptoms because of significant visceral organ involvement, patients who are postmenopausal and HR+ should be given an aromatase inhibitor such as anastrozole or letrozole. NICE clinical guideline 81 does not make recommendations specifically for tumours that are both HER2+ and HR+. In clinical practice, for most people with breast cancer that is HER2+ and HR+, trastuzumab is given in combination with chemotherapy such as taxanes. The number of patients estimated to be suitable for treatment with either lapatinib or trastuzumab in combination with an aromatase inhibitor is around 50 per year.

2 The technologies

Two interventions are considered in this appraisal: trastuzumab in combination with an aromatase inhibitor, and lapatinib in combination with an aromatase inhibitor. Summary information can be found in table 1.

Table 1 Summary description of technologies

Non-proprietary name	Lapatinib	Trastuzumab
Proprietary name	Tyverb	Herceptin
Manufacturer	GlaxoSmithKline	Roche
Dose	1500 mg (six tablets) daily	4 mg/kg intravenous infusion over a 90-minute period, followed by 2 mg/kg 1 week later and repeated at weekly intervals until disease progression. Alternatively, 8 mg/kg on day 1, followed by 6 mg/kg 3 weeks later and repeated at 3-weekly intervals until disease progression. If the initial dose is well tolerated, subsequent doses can be administered as a 30-minute infusion.
Acquisition cost excluding VAT ('British national formulary' edition 59)	Net price for a pack of 70 tablets = £804.30	Net price for a 150-mg vial = £407.40

Lapatinib is a protein kinase inhibitor that blocks the tyrosine kinase components of the epidermal growth factor receptors (ErbB1 and ErbB2), implicated in the growth of various tumours. It therefore helps to control division of cancer cells. Lapatinib has conditional approval for use in combination with an aromatase inhibitor for the first-line treatment of postmenopausal women with HR+ and HER2+ metastatic breast cancer who are not currently intended for chemotherapy. The conditional marketing authorisation states that patients in the registration study were not previously treated with trastuzumab or an aromatase inhibitor. The most common side effects of lapatinib are loss of appetite, diarrhoea, nausea, vomiting, rash and fatigue.

Trastuzumab is a recombinant humanised IgG1 monoclonal antibody directed against HER2. Trastuzumab is licensed in combination with an aromatase inhibitor for the treatment of postmenopausal women with HER2+ and HR+ metastatic breast cancer who have not been treated previously with

trastuzumab. The most common side effects of trastuzumab are cardio toxicity, fatigue and diarrhoea. In the clinical trials, patients on treatment with trastuzumab had a left ventricular ejection fraction (LVEF) of 55% and above and cardiac monitoring was undertaken every four months.

Aromatase inhibitors act by inhibiting the action of the enzyme aromatase, thereby blocking the conversion of androgens to oestrogens. They are classified into irreversible steroidal inhibitors (such as exemestane) and irreversible non-steroidal inhibitors (such as anastrozole and letrozole)

3 The evidence

3.1 Clinical effectiveness

Three studies were identified by the Assessment Group as meeting the criteria for inclusion in the systematic review. All the studies were randomised controlled trials (RCTs) that compared an aromatase inhibitor alone with either lapatinib or trastuzumab in combination with an aromatase inhibitor (table 2). Both Roche and GlaxoSmithKline identified additional studies which they utilised for indirect evidence. However, the Assessment Group excluded these studies because they were not limited to the HR+/HER2+ population and did not include subgroup analysis on the HR+/HER2+ population.

Table 2 Summary of the RCTs in the systematic review (page 33 of the assessment report)

Study and principal citation	Type of study and years of recruitment	Population	Interventions, dose and duration
EGF30008 (Johnson et al. 2009)	Double-blind multicentre trial conducted internationally; 212 sites in 29 countries, 2003–2006	1st-line postmenopausal HR+/HER2+ MBC (n = 219)	LAP + LET (n = 111) vs LET + placebo (n = 108) LAP = 1500 mg/day (oral) LET = 2.5 mg/day (oral) Placebo = pill (oral)
TAnDEM (Kaufman et al. 2009)	Open-label multicentre trial conducted internationally: 77 sites in 22 countries, 2001–2004	1st-line postmenopausal HR+/HER2+ MBC (n=208)	TRA + ANA (n=103) vs ANA (n=104) TRA = 4 mg/kg loading dose (IV) followed by 2 mg/kg/week (IV); or 8 mg/kg on day 1 followed by 6 mg/kg every 3 weeks ANA = 1 mg/day (oral)
eLEcTRA (Huober et al. 2009)	Open-label multicentre trial conducted internationally: 32 sites in 7 countries, 2003–2007	1st-line postmenopausal HR+/HER2+ MBC (n=57)	TRA + LET (n = 26) vs LET (n = 31) TRA = 4 mg/kg loading dose (IV) followed by 2 mg/kg/week (IV); or 8 mg/kg on day 1 followed by 6 mg/kg every 3 weeks ANA = 1 mg/day (oral)
ANA=anastrozole; IV=intravenous; LAP=lapatinib; LET=letrozole; MBC=metastatic breast cancer; TRA=trastuzumab.			

All three trials (EGF30008, TAnDEM and eLEcTRA) were multicentre, multinational trials enrolling postmenopausal patients receiving first-line treatment for metastatic breast cancer, and included patients who had HR+/HER2+ metastatic breast cancer. In all trials, treatment was administered until disease progression, at which point patients in the TAnDEM and eLEcTRA trials received second-line therapy, which included trastuzumab

plus anastrozole for patients in the anastrozole group in the TAnDEM trial. It was not stated whether patients in EGF30008 received any second-line therapy. Although clinical endpoints including overall survival (OS), progression-free survival (PFS) and time to progression (TTP) were utilised in at least one of the three trials, the only common efficacy endpoints were complete benefit rate and overall response rate. All three trials reported on adverse events. Only EGF30008 reported on quality of life.

3.1.1 Lapatinib in combination with an aromatase inhibitor

The EGF30008 trial compared lapatinib plus letrozole with letrozole alone. All patients in the trial had HR+ metastatic breast cancer but only 219 out of 1286 in the intention to treat (ITT) population had HER2+ breast cancer. The primary endpoint was PFS, and the HR+/HER2+ population was defined as the primary population of interest. The trial excluded patients in whom the disease was considered by the investigator to be rapidly progressing or life threatening.

The results were analysed separately for the HR+/HER2+ and ITT populations, and are summarised in table 3. No significant differences in OS were reported between the groups. For the HR+/HER2+ population, the trial reported significant improvements in PFS in the lapatinib plus letrozole group when compared with the letrozole group. Quality of life was assessed using the 'functional assessment of cancer therapy-breast' (FACT-B) questionnaire. Within the HR+/HER2+ population, quality of life scores were reported to be generally stable over time.

The results also showed that patients who received lapatinib pus letrozole were more likely to experience adverse events although serious adverse events were rare in both groups. Incidences of diarrhoea, rash and nausea were significantly greater in patients receiving lapatinib plus letrozole (68%, 46% and 27% compared to 8% and 18% respectively). The Assessment Group therefore concluded that there were no new safety issues and that the safety profile of lapatinib plus letrozole was consistent with the safety profiles of both drugs when given as single agents.

Table 3 Key results from the EGF30008 trial (page 38 of assessment report)

	HR+/HER2+ population[a]			All patients, i.e. including those who are HR+/HER2−[b] (ITT analysis)		
	LAP + LET (n=111)	LET (n=108)	HR (95% CI) OR (95% CI) p-value	LAP + LET (n=644)	LET (n=642)	HR (95% CI) OR (95% CI) p-value
OS (months)[c]	33.3	32.3	HR=0.74 (0.5 to 1.1) p=0.113	not reported	not reported	not reported
PFS (months)[c]	8.2	3.0	HR=0.71 (0.53 to 0.96) p=0.019 Cox regression analysis (adjusting for known baseline prognostic factors): HR=0.65 (0.47 to 0.89) p=0.008	11.9	10.8	HR=0.86 (0.76 to 0.98) p=026
TTP (months)[c]	8.2[d]	3.0[d]	HR=0.71 (0.53 to 0.96) p=0.019	not reported	not reported	not reported
ORR[e]	28%	15%	OR=0.4 (0.2 to 0.9) p=0 .021	33%	32%	OR not reported p=0.726
– CR	5%	4%		5%	4%	
– PR	23%	11%		28%	27%	
Stable disease ≥ 6 months[e]	20%	14%	not reported	26%	25%	not reported
CBR[f]	48%	29%	OR=0.4 (0.2 to 0.8) p=0.003	58%	56%	OR not reported p=0.761

CBR=clinical benefit rate; CI=confidence interval; CR=complete response; HR=hazard ratio; LAP=lapatinib; LET=letrozole; ORR=overall response rate; OR=odds ratio; OS=overall survival; PFS=progression-free survival; PR=partial response; TTP=time to progression.

[a] median follow-up of 1.8 years

[b] median follow-up of 2 years

[c] median (95% CIs were not presented)

[d] TTP data only presented in the GlaxoSmithKline submission

[e] data only presented as percentages

[f] CBR=CR, PR or stable disease ≥ 6 months

3.1.2 Trastuzumab in combination with an aromatase inhibitor

The TAnDEM trial compared trastuzumab plus anastrozole with anastrozole alone. Postmenopausal women with HR+/HER2+ metastatic breast cancer with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 were included in the trial. There were three amendments to the protocol, one of which allowed for crossover of patients from anastrozole alone to trastuzumab plus anastrozole following disease progression.

A significant difference in favour of the trastuzumab plus anastrozole group was reported for PFS (the primary outcome) for the ITT population. A non-significant benefit in OS was reported for the trastuzumab plus anastrozole group for the ITT population. In addition, results were presented of an unplanned exploratory post-hoc analysis of OS based on those patients who had not crossed over. The manufacturer reported that the difference between the groups was not statistically significant using log rank testing, but was statistically significant using the Wilcoxon test. A further post-hoc analysis of OS was provided by the manufacturer in which the rank preserving structural failure time (RPSFT) approach was used to account for crossover (70% of the patients randomised to anastrozole alone subsequently received trastuzumab plus anastrozole). No statistical methods were described to address this issue of crossover *a priori*. The key results of the TAnDEM trial are summarised in table 4. The manufacturer also reported that around one-third (31%) of patients on anastrozole alone received chemotherapy post-progression, compared with 8% of patients who received trastuzumab plus anastrozole. The manufacturer suggested that this could have an impact on the size of the OS estimates.

Patients who received trastuzumab plus anastrozole were more likely to experience adverse events compared with patients who received anastrozole alone (87% compared with 65%). Serious adverse events were also more common in the trastuzumab plus anastrozole group (23% compared with 6%). The Assessment Group noted that the safety profile of trastuzumab plus anastrozole was consistent with the safety profiles of both drugs when given

as single agents. For more information on TAnDEM, see pages 44–48 of the assessment report.

Table 4 Key results from TAnDEM study (page 44 of assessment report)

	TRA+ANA (n=103)	ANA (n=104)	HR (95% CI) p-value
OS (months)[a] unadjusted ITT population[b]	28.5 (22.8 to 42.4)	23.9 (18.2 to 37.4)	HR =0.84 (0.59 to 1.20) p=0.325
OS (months)[a] centrally confirmed HR status[b]	34.1 (23.9 to 52.0)	28.6 (17.4 to 40.0)	HR=0.85 (no CI) p=0.451
OS (months)[a] adjusted for crossover by RPSFT (ITT population?)	28.52[c]	21.98[c]	HR =0.73 (0.51 to 1.04) p=not reported
OS (months)[d] PP analysis (patients who did not cross over)	28.5 (22.8 to 42.4)	17.2[e]	p=0.218[f] p=0.048[g]
PFS (months)[a] ITT population[b]	4.8 (3.7 to 7.0)	2.4 (2.0 to 4.6)	HR=0.63 (0.47 to 0.84) p=0.0016
PFS (months)[a] centrally confirmed HR status[b]	5.6 (3.8 to 8.3)	3.8 (2.0 to 6.3)	HR=0.62 (no CI) p=0.006
PFS (months)[a] updated[d]	5.8 (4.6 to 8.3)	2.9 (2.1 to 4.5)	HR= 0.55 (0.41 to 0.74) p<0.0001
TTP (months)[a] ITT population[b]	4.8 (3.7 to 7.7)	2.4 (2.0 to 4.6)	HR not reported p=0.0007
TTP (months)[a] centrally confirmed HR status[b]	5.6 (3.8 to 8.3)	3.9 (2.1 to 6.3)	HR=0.62 (no CI) p=0.0007

ANA= anastrozole; CBR=clinical benefit rate; CI=confidence interval; CR=complete response; HR=hazard ratio; OR=odds ratio; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PP= per protocol; PR=partial response; RPSFT= rank preserving structural failure time; TRA= trastuzumab; TTP=time to progression.

[a] median (95% CI)

[b] the ITT data constituted data from local investigator assessments; the centrally confirmed data were that confirmed by a blinded Response Evaluation Committee

[c] The RPSFT adjustment was made only in the submission by Roche;[39] No CIs were presented for median OS

[d] The updated PFS was from a later cut-off point; it is unclear whether this was centrally confirmed

[e] n=31; no CIs presented for OS

[f] Log-rank Test

[g] Wilcoxon test

In the manufacturer's submission, the crossover adjustment employed was based on an RPSFT approach. The manufacturer stated that RPSFT approach has been used for two other NICE appraisals: sunitinib for the

treatment of gastrointestinal stromal tumours (TA179) and everolimus for the second-line treatment of advanced renal cell carcinoma (in development). The Assessment Group commented that there is no agreement about the best method for adjusting for crossover. It stated that RPSFT might not be appropriate when imbalances occur post-randomisation, such as when there is an unequal distribution of patients receiving second-line treatment across the arms. The Assessment Group noted that in the TAnDEM trial, the proportion of patients who crossed over was relatively high (around 70%), which increased the likelihood of bias. Although the Assessment Group agreed that attempts to adjust for crossover were justifiable, it stated that, ideally, different randomisation-based methods should be used. The Assessment Group therefore utilised other methods to adjust for crossover in its economic analysis.

Trastuzumab in combination with letrozole was compared with letrozole alone in the eLEcTRA trial. Only 92 patients out of the planned 370 patients with HR+ metastatic breast cancer were enrolled because the study was halted because of slow recruitment. For more information, see pages 48–50 of the assessment report.

3.1.3 Indirect comparisons

GlaxoSmithKline

The manufacturer of lapatinib performed adjusted indirect comparisons analyses using the methods and principles described by Bucher et al (1997). 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 as it was only published as an abstract. The findings for both OS (table 5) and PFS/TTP (table 6) are summarised below. The manufacturer reported no significant differences between any of the interventions for OS. Improvements in PFS and TTP were reported to be statistically significant for lapatinib plus letrozole and trastuzumab plus letrozole when compared with anastrozole, letrozole and tamoxifen alone.

Table 5 Adjusted indirect comparisons analysis conducted by GlaxoSmithKline: median OS (table 35 in appendix 4 of the assessment report)

	TRA+ANA	LET	ANA	TAM
LAP+LET	0.85 (0.47, 1.54)	0.77 (0.52, 1.14)	0.71 (0.45, 1.14)	0.74 (0.49, 1.12)
TRA+ANA		0.90 (0.60, 1.36)	0.84 (0.59, 1.19)	0.87 (0.59, 1.27)
LET			0.93 (0.76,1.15)	0.96 (0.84, 1.09)
ANA				1.03 (0.88, 1.22)

ANA=anastrozole; LAP=lapatinib; LET=letrozole;TAM=tamoxifen; TRA=trastuzumab.

Values are hazard ratio (95% confidence interval). Hazard ratio < 1 indicates greater likelihood of better response on treatment versus comparator

Table 6 Adjusted indirect comparisons analysis conducted by GlaxoSmithKline: median PFS and TTP (table 36 appendix 4 of the assessment report)

	TRA+ANA	LET	ANA	TAM
LAP+LET	0.89 (0.54,1.47)	0.65 (0.47, 0.89)	0.53 (0.36, 0.80)	0.45 (0.32, 0.65)
TRA+ANA		0.73 (0.50, 1.07)	0.60 (0.45, 0.81)	0.51 (0.36, 0.71)
LET			0.82 (0.65,1.04)	0.70 (0.60, 0.82)
ANA				0.85 (0.71, 1.01)

ANA=anastrozole; LAP=lapatinib; LET=letrozole;TAM=tamoxifen; TRA=trastuzumab.

Values are hazard ratio (95% confidence interval). Bold = significant difference in terms of TTP/PFS Hazard ratio < 1 indicates greater likelihood of better response on treatment versus comparator.

Roche

The manufacturer performed an indirect network meta-analysis based on a Bayesian approach in which a number of different analyses were performed for OS (12 trials) and PFS (seven trials). Three of the included trials reported HER2 status. The manufacturer assumed that PFS is equivalent to TTP and that OS findings from the TAnDEM trial based on the RPSFT adjustment should be used as the base case. The manufacturer reported that the aromatase inhibitors had similar efficacy and could be considered as a class.

On this basis, two studies (EGF30008 and TAnDEM) were used in a network meta-analysis to establish the hazard ratios (HR) for OS and PFS for lapatinib in combination with an aromatase inhibitor, trastuzumab in combination with an aromatase inhibitor and aromatase inhibitors alone. Based on the results of this analysis (see table 7) the manufacturer reported that there were no significant differences between lapatinib plus letrozole and trastuzumab plus anastrozole for OS. For PFS the manufacturer reported that the difference between the two combination treatments was not significant but the estimated hazard ratio was in favour of trastuzumab in combination with an aromatase inhibitor. For additional analysis, see pages 51–56 and tables 37–44 of appendix 4 in the assessment report.

Table 7 Network analysis conducted by Roche

	LAP+AI	AI
Median OS – aromatase inhibitors as a class (crossover adjustment for TAnDEM applied)		
TRA+AI	0.98 [0.58;1.67]	0.73 [0.51;1.04]
LAP+AI		0.74 [0.50;1.10]
Median OS (sensitivity analysis without crossover adjustment); AIs as a class		
TRA+AI	1.13 [0.67;1.92]	0.84 [0.59;1.19]
LAP+AI		0.74 [0.50;1.10]
Median PFS; AIs as a class		
TRA+AI	0.78 [0.52;1.18]	0.55 [0.42;0.74]
LAP+AI		0.71 [0.53;0.95]
AI=aromatase inhibitor; LAP=lapatinib; TRA=trastuzumab. Values are hazard ratio [95% confidence interval]. Hazard ratio < 1 indicates greater likelihood of better response on treatment versus comparator.		

The Assessment Group considered that the findings of the indirect comparisons presented by the manufacturers of lapatinib and trastuzumab should be treated with caution. It stated that the populations in the EGF30008 and TAnDEM trials differed substantially and that both the manufacturers'

indirect comparisons analyses did not meet 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 HR+/HER2+ metastatic breast cancer included in each of the trials was unclear. It also noted that length of follow-up and the proportion of patients receiving first-line treatment differed between trials.

3.2 Cost effectiveness

3.2.1 Published literature

The manufacturers conducted literature reviews to identify cost-effectiveness analyses relevant to the decision problem. One study identified by the manufacturer of trastuzumab was found to be relevant. This was a poster presented in June 2010 at the American Society of Clinical Oncology by Hastings et al. The poster describes an indirect comparison of the cost effectiveness of lapatinib plus letrozole versus trastuzumab plus anastrozole in postmenopausal women with HR+/HER2+ metastatic breast cancer who have not received prior treatment. The evidence network used to estimate treatment effectiveness included both EGF30008 and TAnDEM. The conclusion of the poster presentation is that lapatinib plus letrozole is cheaper and more clinically effective than trastuzumab plus anastrozole and is therefore dominant. The Assessment Group considered that the results of this analysis are unreliable because the studies which made up the evidence network considered different populations. In addition, the Assessment Group noted that without access to more detailed information on costs, it was difficult to comment on the reliability of the cost-effectiveness results. The Assessment Group concluded that there is no relevant, currently available, published cost-effectiveness evidence to describe the use of lapatinib plus letrozole or trastuzumab plus anastrozole in women who have HR+/HER2+ metastatic breast cancer.

3.2.2 Manufacturers' submissions

Both manufacturers provided economic analyses to support their submissions in which the technologies under assessment were compared with each other

and with the aromatase inhibitors letrozole and anastrozole as monotherapies. Both submissions were based on cost–utility analyses run over a lifetime horizon and from the perspective of the NHS and Personal Social Services (PSS).

GlaxoSmithKline (lapatinib in combination with an aromatase inhibitor)
GlaxoSmithKline developed a decision analytic model to estimate PFS, OS, lifetime costs of treatment of metastatic breast cancer and quality-adjusted life years (QALYs). The model featured three health states: progression-free, post-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 key clinical data comparing lapatinib plus letrozole with letrozole monotherapy came from the EGF30008 trial. PFS and OS estimates for patients receiving lapatinib plus letrozole were obtained by applying the HRs for lapatinib plus letrozole compared with letrozole to the the PFS and OS curves for letrozole for the HR+/HER2+ subgroup. PFS and OS for patients receiving letrozole were estimated by fitting Weibull survival functions to patient-level data for the subgroup of patients with HR+/HER2+ disease. The clinical effectiveness estimates for the other technologies was taken from the indirect comparison (see section 3.1).The estimates in the model are given in table 39 on page 110 of the manufacturer's submission.

Utility values for PFS (without adverse events) were estimated using data from EGF30008 from the FACT-B questionnaire. The pre-progression utility value used in the model was 0.86. Post-progression utility values were largely unavailable because FACT assessments were only routinely completed by patients until withdrawal of study medications. In order to identify a utility decrement for progressive disease, the manufacturer used the results of a study by Lloyd et al. (2006) of societal preferences for different stages of metastatic breast cancer in the UK. The absolute reduction in utility for progressive disease used in the model was 0.23, resulting in a utility of about 0.62. Disutility values from grade 3+ adverse events were obtained from published and unpublished sources, and assumptions were made if no data

were available. The utility decrements employed in the economic model included: nausea (0.1); vomiting (0.1); diarrhoea (0.1); alopecia (0.11); asthenia/fatigue/lethargy (0.12); skin and nail disorders (0.15).

The results are summarised in table 8. The incremental cost effectiveness ratio (ICER) was £74,448 per QALY gained for lapatinib plus letrozole compared with letrozole monotherapy. Compared with trastuzumab plus anastrozole the ICER was £21,836 per QALY gained. For more information, see pages 59–67 of the assessment report.

Table 8 Base case cost effectiveness results - GlaxoSmithKline (adapted from page 65 of the assessment report)

					Incremental comparisons: LAP+LET vs		
	LAP+ LET	LET	TRA+ ANA	ANA	LET	TRA+ ANA	ANA
Life years	3.399	2.817	3.045	2.657	0.582	0.354	0.742
QALYs	2.389	1.923	2.137	1.788	0.467	0.252	0.601
Total costs	£60,614	£25,878	£55,101	£24,620	£34,737	£5,513	£35,995
Cost per QALY gained	-	-	-	-	£74,448	£21,836	£59,895
ANA=anastrozole; LAP=lapatinib; LET=letrozole; QALY= quality-adjusted life year; TRA=trastuzumab.							

The manufacturer examined 51 scenarios in deterministic sensitivity analyses. The analyses showed that the incremental cost-effectiveness ratio (ICER) was most sensitive to the utility of PFS, the discounting rate and the time horizon. The ICER for lapatinib plus letrozole compared with letrozole monotherapy ranged from £41,877 per QALY gained to lapatinib plus letrozole being dominated by letrozole monotherapy. Compared with anastrozole monotherapy, the ICER for lapatinib plus letrozole ranged from £38,170 to £378,674 per QALY gained. For the comparison with trastuzumab plus anastrozole, the ICER ranged from lapatinib plus letrozole dominating the comparator to £45,106 per QALY gained. The manufacturer also performed a probabilistic sensitivity analysis. The results of this analysis showed that at a cost-effectiveness threshold of £30,000 per QALY gained, the probability of

lapatinib plus letrozole being cost effective is less than 25% when compared with any aromatase inhibitor, and about 50% when compared with trastuzumab plus anastrozole.

Roche (trastuzumab in combination with an aromatase inhibitor)
Roche utilised an area under curve model to calculate the present value of the health outcomes and costs. The model featured three health states (PFS, progressive disease and death) and had a cycle length of 1 month. The model had a time horizon of 15 years and discounted both costs and benefits at 3.5% per year (implemented monthly).

The key clinical data (PFS and OS) used were taken directly from the TAnDEM trial for trastuzumab plus anastrozole compared with anastrozole monotherapy. All model inputs were taken from the latest data available (some of which were unpublished), from an April 2008 data cut (for further details, see page 218 of the manufacturer's submission). Kaplan–Meier PFS curves for the two regimens were used directly to model the majority of disease progression of patients within the economic model and were extrapolated beyond the follow-up period by parametric fitting of the curves. The manufacturer concluded that the exponential distribution most accurately portrayed the OS curves of the two regimens. On the basis of the results from the systematic review it was assumed that letrozole and anastrozole have a 'class effect' and therefore the PFS and OS curves for anastrozole were used for letrozole. The clinical estimates for lapatinib plus letrozole came from the EGF30008 trial.

In order to estimate utility values for patients with HR+/HER2+ breast cancer, the manufacturer underook a review of the literature and presented utility values from six of the published studies identified (see pages 247–249 of the manufacturer's submission). However, because no studies were identified that were relevant specifically to patients with HR+/HER2+ disease, the manufacturer applied utilities identified by Cooper et al (2003). The Cooper et al. paper pooled utilities from many different sources (all derived from

oncology nurses using the standard gamble technique) and was used in the NICE Clinical Guideline for Advanced Breast Cancer (CG81).

The costs of grade 3 or 4 adverse events were considered in the model; disutilities resulting from adverse events were not modelled. It was assumed that the adverse events recorded for trastuzumab plus anastrozole are the same for lapatinib plus letrozole and that the adverse events recorded for anastrozole can be applied to letrozole.

In an incremental analysis trastuzumab plus anastrozole and letrozole monotherapy were the two regimens which formed an efficiency frontier. Trastuzumab plus anastrozole resulted in an incremental cost of £31,421 and 0.58 incremental QALYs gained compared with letrozole monotherapy. The ICER for this comparison was £54,336 per QALY gained. Results were also presented for pairwise comparisons and are summarised in table 9.

Table 9 Base case cost effectiveness results - Roche

	TRA+ANA	LAP+LET	ANA	LET
Total costs	£54,748.92	£51,882.53	£23,340.88	£23,327.52
Total QALYs	1.87	1.71	1.29	1.29
ICER: Trastuzumab plus anastrozole vs...				
Lapatinib plus letrozole			£18,347/QALY gained	
Anastrozole			£54,312/QALY gained	
Letrozole			£54,336/QALY gained	

Twenty-three different parameters were modified in a univariate sensitivity analysis. The base-case ICER was most sensitive to variation in the utility values for PFS, with the ICER ranging from £50,099 to £59,355 per QALY gained for trastuzumab plus anastrozole compared with anastrozole. The ICER was also sensitive to the discount rate for health outcomes, with values ranging from £48,664 to £58,400 per QALY gained for trastuzumab plus anastrozole compared with anastrozole. The manufacturer also described three multivariate scenario analyses. In these analyses, when the PFS and OS HRs of the indirect comparisons analysis were used in the model, anastrozole represented a cost-effective option up to a threshold of £3594 per QALY gained; letrozole was the most cost-effective option from £3594 to

£57,773 per QALY gained; and trastuzumab plus anastrozole represented the most cost-effective treatment above £57,773 per QALY gained.

The manufacturer stated that the base case may be subject to a confounding influence from an imbalance in second-line chemotherapy between groups in the TAnDEM trial. When a range of detriments were applied to the aromatase inhibitor baseline OS curve to account for this, the base-case ICER for trastuzumab plus anastrozole decreased to around £49,426 per QALY gained. However the manufacturer stated that this was subject to some uncertainty because of the difficulty in determining the detriment to account for the imbalance. The manufacturer also conducted a probabilistic sensitivity analysis. This showed that at a threshold of £30,000 per QALY gained, the combination therapies were not cost effective. At a threshold of £55,000 per QALY gained, trastuzumab plus anastrozole was shown to be cost effective in approximately 35% of simulations.

End-of-life considerations

The manufacturer made a case for trastuzumab to be considered under end-of-life criteria. The manufacturer cited data from the comparator (anastrozole) group of the TAnDEM trial to support the view that patients with metastatic breast cancer that is HER2+/HR+ have a very poor prognosis. The median OS of this group was shown to range between 17.2 months (excluding all patients who crossed over) to 32.1 months (excluding all patients with liver metastases). The manufacturer stated that there is sufficient evidence from the TAnDEM trial to indicate that trastuzumab plus anastrozole offers an extension to life of at least an additional 3 months, compared with current NHS treatment. In the TAnDEM trial, the estimated unadjusted median increase in OS was 4.6 months and the estimated RPFST-adjusted median increase in OS was 6.5 months. The manufacturer reported that in England and Wales, across all the indications, 7158 patients are eligible to receive trastuzumab each year (2333 with metastatic breast cancer, 506 with metastatic gastric cancer and 4319 with early breast cancer). For more information, see pages 76–77 of the assessment report.

3.2.3 Independent economic assessment by the Assessment Group

The Assessment Group reiterated that the baseline characteristics of patients in the EGF30008 and TAnDEM trials were too dissimilar for data to be combined in one economic evaluation. The EGF30008 trial excluded patients with extensive symptomatic visceral disease or disease that was considered by the investigator to be rapidly progressing or life threatening, and so the patients in this trial may have been fitter and with better prognoses than those recruited into the TAnDEM trial. Differences in how measures of patient characteristics were defined and/or reported in the two trials also made a comparison difficult. The ECOG status was presented with numerical frequencies in one trial but not in the other; and the number and location of metastatic lesions at baseline were defined differently in the two trials. There was also a significant difference in the mean ages of the populations (60.9 years in EGF30008 and 56.4 years in TAnDEM; $p < 0.0001$) and a greater incidence of soft tissue metastases in patients in the TAnDEM trial compared with patients in EGF30008 (43.5% versus 30.14%; $p = 0.004$). The frequency of metastatic sites affected per patient (1.77 in EGF30008 versus 2.40 in TAnDEM) suggested more severe advanced disease in patients in the TAnDEM trial, but the Assessment Group noted that this too could have been a result of different reporting techniques. Because of these uncertainties, the Assessment Group undertook two separate cost-effectiveness analyses using a common modelling framework and common parameter values, but employing effectiveness data drawn only from a single RCT (either TAnDEM or EGF30008).

Model design

The Assessment Group model employed outcomes data derived from the relevant clinical trials in the form of Kaplan–Meier estimated survival values augmented by projected survival estimates. Estimates of PFS and post-progression survival (PPS) were used directly as the basis for calculating expected OS. PFS and PPS values from the trials were used to calculate health service costs and expected future patient utility. The survival estimates were calculated separately for each date on which a resource is expected to

be used (for example, when prescriptions are dispensed, or when a hospital visit or test takes place) such that model cycle corrections were not applied. Costs and outcomes were discounted at 3.5% per year and deterministic results were generated for up to 30 years. A probabilistic sensitivity analysis and a range of univariate sensitivity analyses were performed. For more information, see pages 79–82 of the assessment report.

Patient utilities

The Assessment Group conducted an exploratory search which failed to find any additional utility data to those identified by the manufacturers. Patient utilities from the study reported by Lloyd et al. (2006) were found to be the best available option. The study collected data from a sample of 100 UK residents broadly similar to the general population in age and sex, and considered health states and treatment-related adverse events specific to metastatic breast cancer. For patients who were pre-progression a weighted average was calculated from stable disease and treatment response. A common health state utility value was obtained for post-progression patients of 0.496 (standard error [SE] 0.160).

Assessment Group model for lapatinib plus letrozole versus letrozole

Outcomes and utilities

For mean PFS, the Assessment Group applied the difference between the Kaplan–Meier area under the curve estimates up to the time of convergence (505 days). Thereafter a single exponential model of PFS was applied to both the intervention and the comparator. This generated 266.2 PFS days (SE 16.1 days) for lapatinib plus letrozole and 198.5 PFS days (SE 17.6 days) for letrozole only, giving a PFS gain of 67.6 days (SE 16.9 days) attributable to the use of lapatinib. The mean duration of survival for patients in PPS was 764.8 days (SE 5.0 days). OS was obtained by summing PFS and PPS, after adjusting PPS to exclude patients who died at or before disease progression. This generated values of 982.8 OS days (SE 16.8 days) for lapatinib plus letrozole and 928 OS days (SE 18.2 days) for letrozole only, resulting in an OS gain of 54.8 days (SE 24.8 days) attributable to lapatinib.

The health state utility values for patients in PFS in the two trial groups differed slightly because of differential treatment response rates. A utility of 0.7663 (SE 0.1136) was assigned to the lapatinib plus letrozole group and one of 0.7623 (SE 0.1141) to the letrozole group. For adverse events, the Assessment Group stated that the absolute difference in estimated utility per patient was very small (less than 0.01) and the disutility of adverse events was not included in the base case, but was examined in a sensitivity analysis.

Costs

An acquisition cost of £804.30 per pack of 70 tablets was assigned to lapatinib and a dose of six tablets per day was used. It was assumed that lapatinib is prescribed to patients without disease progression every 28 days. Taking into account unused tablets from previous prescriptions, it was assumed that two or three packs are prescribed at each visit. An average wastage of 14 days' supply is automatically included in this calculation as the dispensed tablets are unused at the time of progression and no mid-cycle correction is applied. It was assumed that prescriptions would be dispensed by a hospital pharmacist.

An acquisition cost of £66.50 per pack of 28 tablets was assigned to letrozole, assuming that one pack was dispensed every 28 days to all patients remaining in the PFS health state. Wastage was limited to an average of 14 days of treatment per patient. It was assumed that prescriptions would be dispensed by a community pharmacist, except for the first prescription which would be provided in the hospital.

For more information on costs, see pages 85 of the assessment report.

Cost-effectiveness results: lapatinib plus letrozole versus letrozole

The base-case cost-effectiveness results from the Assessment Group model are summarised in table 10. The expected mean health gain per patient is an extension to life of less than 2 months, and less than 0.12 additional QALYs. The additional cost is more than £25,000 per patient, most of which is incurred in the first 5 years. This results in an ICER in excess of £220,000 per QALY

gained. Results from a sensitivity analysis showed that the ICER is most sensitive to the health state utility parameter values, and to the cost of lapatinib.

Table 10 Cost-effectiveness results for the base-case analysis of lapatinib plus letrozole versus letrozole (discounted) using the Assessment Group model (page 94 of the assessment report)

Treatment	Cost per patient						Outcomes per patient		ICER
Time horizon (years)	Drugs	Monitoring	Adverse events	Best supportive care	Terminal care	Total costs	Life years	QALYs	£ / QALY gained
Letrozole									
10	£718	£757	-	£12,266	£1,622	£15,362	2.526	1.444	
20	£718	£757	-	£12,407	£1,643	£15,524	2.549	1.455	
30	£718	£757	-	£12,408	£1,643	£15,525	2.549	1.455	
Lapatinib plus letrozole									
10	£25,082	£1,397	£98	£12,374	£1,622	£40,573	2.670	1.558	
20	£25,082	£1,397	£98	£12,513	£1,643	£40,733	2.693	1.570	
30	£25,082	£1,397	£98	£12,514	£1,643	£40,734	2.693	1.570	
Incremental									
10	£24,364	£640	£98	£108	£0	£25,211	0.145	0.114	£220,252
20	£24,365	£640	£98	£106	£0	£25,209	0.144	0.114	£220,626
30	£24,365	£640	£98	£106	£0	£25,209	0.144	0.114	£220,628

The results of a probabilistic sensitivity analysis conducted by the Assessment Group showed that there is no measurable probability of the combination therapy being cost effective at a threshold of £40,000 per QALY gained, and the probability does not reach 50% until a threshold of nearly £3,000,000 per QALY gained. This is attributable to the uncertainty around whether the combination treatment delivers any real benefit to patients in the long term. A comparison of deterministic versus probabilistic results is shown in table 11. For more information, see pages 93–96 of the assessment report.

Table 11 Comparison of deterministic and probabilistic (PSA) cost-effectiveness results for lapatinib plus letrozole versus letrozole (base case with 20-year horizon) (page 96 of assessment report)

	Incremental cost	Incremental QALYs	ICER (£ per QALY gained)
Deterministic	£25,209	0.114	£220,628
PSA	£24,878	0.009	£2,895,994

Assessment Group model for trastuzumab plus anastrozole versus anastrozole

Outcomes and utilities

The mean PFS was obtained by 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. This generated 514.8 PFS days (SE 64.1 days) for trastuzumab plus anastrozole and 189.6 PFS days (SE 21.4 days) for anastrozole only, a gain of 325.1 PFS days (SE 67.6 days) attributable to trastuzumab. Mean PPS was estimated by 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 PFS. This generated 649.6 PPS days (SE 63.1 days) for trastuzumab plus anastrozole and 869.6 PPS days (SE 46.3 days) for anastrozole only, a loss of 220.0 PPS days (SE 78.3 days) attributable to trastuzumab.

The estimate for OS was obtained by combining estimates of mean PFS and mean PPS in each group, and adjusting for the minority of patients who die at

or before progression (5.8% in the anastrozole group and 9.3% in the trastuzumab plus anastrozole group). This generated 1101.3 OS days (SE 85.6 days) for trastuzumab plus anastrozole and 1009.0 OS days (SE 50.5 days) for anastrozole only, with a gain of 92.2 OS days (SE 99.4 days) attributable to use of trastuzumab.

Adjusting for crossover and second-line chemotherapy

The Assessment Group noted that the separate Kaplan–Meier analyses of patients in the anastrozole group of the TAnDEM trial demonstrated an advantage for patients who crossed over to the trastuzumab plus anastrozole group after disease progression, although this advantage diminished after about 6 months and disappeared altogether after about 3 years. The Assessment Group therefore fitted two separate exponential models from which mean survival gain attributable to crossover for patients in the post-progression phase was estimated. The net benefit of crossover (the area between the two modelled PPS lines) was estimated as 150.5 days. This advantage only accrued to patients who did not die at or before progression (91% of the total), so that the actual mean PPS adjustment was 137.5 days (SE 11.7 days).

The Assessment Group compared all patients receiving second-line chemotherapy with all patients who did not, although it is stated in the assessment report that a detailed analysis was hindered by the small numbers of patients in each stratum. Estimated exponential survival parameters suggested a HR of 0.83 and a gain in PPS of 145.2 days (SE 31.1 days) in favour of those receiving second-line chemotherapy. This figure was then adjusted for the difference in use of second-line chemotherapy between the trial groups (32% in the anastrozole group compared with 8% in the trastuzumab plus anastrozole group); the percentage of patients receiving chemotherapy who also benefited from crossover to trastuzumab (82%) and the absolute difference in PPS was only applied to patients who did not die at or before disease progression. The net effect of these adjustments resulted in

an estimated additional gain in PPS in the comparator group of 5.9 days (SE 1.2 days) for patients who received second-line chemotherapy.

Combining the adjustments for crossover and second-line chemotherapy generated 1101.3 OS days (SE 85.6 days) for trastuzumab plus anastrozole and 861.2 OS days (SE 52.1 days) for anastrozole only, with a gain of 240.1 OS days (SE 100.2 days) attributable to use of trastuzumab.

Patient utilities

The health state utility values for patients in PFS in the two trial groups differed slightly because of differential treatment response rates. A utility of 0.7687 (SE 0.1133) was assigned to the trastuzumab plus anastrozole group and one of 0.7639 (SE 0.1139) to the anastrozole group.

The Assessment Group stated that the difference in the incidence of grade 3 and 4 adverse events between groups featured in the Lloyd et al. (2006) study was not significant. The disutility of adverse events was not modelled in the base case but was considered in a sensitivity analysis.

Costs

The cost of treatment with trastuzumab was estimated using the distribution of body weight recorded at baseline in the TAnDEM trial. Parameters were estimated by a weighted average of the individual doses and vials of trastuzumab used, assuming no vial sharing. This calculation incorporated drug wastage. For the initial loading dose (8 mg/kg) the cost per dose was estimated as £1657.86, and for a regular dose (6 mg/kg) the cost per dose was estimated as £1292.88. These costs were applied to all patients remaining in PFS at the beginning of each cycle. The costs of administering trastuzumab were derived from the NHS Reference Costs 2008–09, using average day case and outpatient costs weighted by national activity levels. The unit costs per treatment were £284.66 (loading dose) and £198.63 (regular doses).

An acquisition cost of £68.56 per pack of 28 tablets was assigned to anastrozole. It was assumed that one pack is dispensed every 28 days to all patients remaining in PFS and that wastage was limited to an average of 14 days of treatment per patient. It was assumed that prescriptions would be dispensed by a community pharmacist, except for the first prescription which would be provided in the hospital.

For more information on the model, see pages 86–92 of the assessment report.

Cost-effectiveness results: trastuzumab plus anastrozole versus anastrozole

The base-case cost-effectiveness results from the Assessment Group model are summarised in table 12. During consultation on the Assessment Report, an error was identified in the results of the model. Only the amended results are reported here. A mean health gain per patient of about 0.5 QALYs is attained at an additional cost of more than £35,000 per patient, most of which is incurred in the first 5 years. The resulting ICER exceeds £70,000 per QALY gained. Results from a sensitivity analysis showed that the ICER is most sensitive to the health state utility parameter values, the cost of trastuzumab and discounting rates.

Table 12 Cost-effectiveness results for the base-case analysis of trastuzumab plus anastrozole versus anastrozole (discounted) using the Assessment Group model (see erratum)

Treatment	Cost per patient						Outcomes per patient		ICER
Time horizon (years)	Drugs	Monitoring	Adverse events	BSC	Terminal care	Total costs	Life years	QALYs	£ / QALY gained
ANA									
10	£549	£602	-	£11,101	£1,632	£13,884	2.204	1.235	
20	£549	£602	-	£11,194	£1,647	£13,992	2.220	1.243	
30	£549	£602	-	£11,194	£1,648	£13,993	2.220	1.243	
TRA+ANA									
10	£35,197	£1,843	£90	£11,471	£1,695	£50,296	2.783	1.725	
20	£36,251	£1,898	£92	£11,549	£1,696	£51,487	2.823	1.755	
30	£36,370	£1,905	£93	£11,557	£1,696	£51,621	2.827	1.759	
Incremental									
10	£34,648	£1,241	£90	£370	£63	£36,412	0.579	0.490	£74,312
20	£35,702	£1,297	£92	£355	£49	£37,495	0.603	0.513	£73,135
30	£35,821	£1,303	£93	£363	£49	£37,628	0.607	0.516	£72,919

A probabilistic sensitivity analysis was undertaken using the base-case scenario over a 20-year horizon. This showed that there is no measurable probability of the combination therapy being cost effective at a willingness-to-pay threshold of £40,000 per QALY gained, and only a 3.2% probability at a threshold of £50,000 per QALY gained. A comparison of probabilistic versus deterministic results is shown on table 13.

Table 13 Comparison of deterministic and probabilistic (PSA) cost-effectiveness results for trastuzumab plus anastrozole versus anastrozole (base case with 20-year horizon) (see erratum)

	Incremental cost	Incremental QALYs	ICER (£ per QALY gained)
Deterministic	£37,495	0.448	£73,135
PSA	£33,085	0.463	£71,470

3.2.4 End-of-life treatment criteria

NICE's supplementary advice on end-of-life treatment has three key criteria:

- 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, the estimates of the extension to life must be robust and the assumptions used in the reference case economic modelling plausible, objective and robust.

Life expectancy of less than 24 months

The Assessment Group noted that published literature on prognosis after a diagnosis of metastatic breast cancer confirms that patient life expectancy is short. It cites the scope issued by NICE on Lapatinib for the treatment of previously treated women with advanced, metastatic or recurrent breast cancer, which indicated that the average life expectancy after diagnosis of

metastatic breast cancer is 18–24 months, and that this is reduced by up to 50% for patients with HER+ tumours. The Assessment Group therefore concluded that the life expectancy of people with HER2+ metastatic breast cancer is less than 24 months.

Extension to life of at least 3 months

The Assessment Group noted that in the TAnDEM trial, unadjusted median OS gain and RPFST-adjusted median OS gain were estimated to be 4.6 and 6.54 months respectively. The Assessment Group concurred that trastuzumab in combination with anastrozole compared with anastrozole alone offers an extension to life of at least 3 months for patients who have HER+/HR+ metastatic breast cancer for which they have had no prior treatment

Licensed for a small patient population

The Assessment Group highlighted the ongoing single technology appraisal (STA) of trastuzumab for the treatment of HER2+ metastatic adenocarcinoma of the stomach or gastro-oesophageal junction. It noted that the Appraisal Committee for that STA considered the size of the eligible patient population and was not satisfied that the population for which trastuzumab is licensed met the criterion of a small patient population. The population in that ongoing STA was estimated by the manufacturer to be 7144 people who have HER2+ metastatic gastric cancer, HER2+ early and locally advanced breast cancer or HER2+ metastatic breast cancer. The Assessment Group therefore considered that trastuzumab does not meet the criterion of a small patient population.

4 Equalities issues

No equality and diversity issues have been identified in the scoping of this appraisal

5 Issues for consideration

5.1 Clinical effectiveness

5.1.1 Appropriate comparisons

The manufacturers of trastuzumab and of lapatinib compared the respective technologies (in combination with anastrozole and letrozole respectively) with each other and with anastrozole and letrozole monotherapy respectively using indirect treatment comparisons. The Assessment Group considered the populations in the TAnDEM and the EGF30008 studies to be too dissimilar and stated that they (and therefore trastuzumab and lapatinib) cannot be compared with each other.

- Does the Committee consider that the populations in the trials are comparable?
- Is it appropriate to combine the technologies in an incremental analysis?

5.1.2 Class effect for aromatase inhibitors

The manufacturer of trastuzumab presents the results of a network meta-analysis to suggest that aromatase inhibitors hold a 'class effect' (that is, letrozole and anastrozole are equivalent in efficacy). The same assumption was used in NICE technology appraisal guidance 112 ('Hormonal therapies for the adjuvant treatment of early oestrogen-receptor-positive breast cancer').

- Can the aromatase inhibitors be considered as a group with the same or similar clinical effectiveness?

5.1.3 Adjustment for crossover

The manufacturer of trastuzumab stated that patients in the TAnDEM study who were randomised to receive anastrozole and subsequently crossed over to receive trastuzumab plus anastrozole after disease progression demonstrated a significant survival benefit compared with those who did not cross over. The manufacturer therefore adjusted the OS results to take this into account.

- Does the Committee agree with the approaches taken by the manufacturer, and is the resulting estimate of OS robust?

5.2 Cost effectiveness

5.1.4 Effectiveness estimates

Different methods are used to derive clinical effectiveness parameters for the economic models. Methods include the use of indirect comparisons, network meta-analysis and the use of data from single trials.

- Given the available clinical effectiveness data, what does the Committee consider to be the most appropriate method of incorporating this into the economic models?

5.1.5 End-of-life considerations

The manufacturer of trastuzumab makes a case for the technology to be considered under end-of-life criteria. The Assessment Group highlights that in the ongoing NICE technology appraisal of trastuzumab for metastatic gastric cancer, the population size was estimated to be 7144 by the manufacturer. The manufacturer's estimate of the population including the indication for trastuzumab plus an aromatase inhibitor is 7158.

- Does the Committee consider that treatment with trastuzumab plus an aromatase inhibitor meets the criteria for consideration under NICE's supplementary advice on end of life?

6 Authors

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Appendix A: Sources of evidence considered in the preparation of the overview

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 Submissions or statements were received from the following organisations:

I Manufacturers/sponsors

- GlaxoSmithKline
- Roche

II Professional/specialist, patient/carer and other groups:

- Royal College of Physicians
- Breast Cancer Care
- Breakthrough Breast Cancer
- Breast Cancer Campaign
- Macmillan Cancer Support