NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Lapatinib for the treatment of previously treated women with advanced, metastatic or recurrent breast cancer

Premeeting briefing

This briefing presents major issues arising from the manufacturer's submission (MS), Evidence Review Group (ERG) report and statements made by consultees and their nominated clinical specialists and patient experts. Please note that although condensed summary information is included for ease of reference, this briefing should be read in conjunction with the full supporting documents.

The manufacturer was asked to clarify the date of crossover of patients from the control to the treatment group in the pivotal trial when it was halted and to provide a list of excluded studies from their systematic review. The manufacturer also provided, on request, a copy of the model validation report and a report containing analyses of all health outcomes, although these were fully reported in the MS.

Abbreviations

BSA	Body surface area
CI	Confidence interval
CR	Complete response
EMEA	European Medicines Agency
ERG	Evidence Review Group
FACT-B questionnaire	Functional Assessment of Breast Cancer Therapy- Breast
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IDMC	Independent Data Monitoring Committee
ITT	Intention-to-treat
LVEF	Left ventricular ejection fraction
MS	Manufacturer's submission
OS	Overall survival
PCT	Primary care trust
PFS	Progression-free survival
PR	Partial response
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RDI	Relative dose intensity
SD	Standard deviation
SPC	Summary of product characteristics
TTP	Time to progression
WTP	Willingness to pay

Status of marketing authorisation

Lapatinib currently has a positive opinion from the European Medicines Agency (EMEA). Subject to formal approval, the marketing authorisation will have specific conditions. These conditions include a requirement of the manufacturer to perform and submit an updated analysis of survival data for study EGF100151 and to conduct a randomised controlled trial (RCT) to evaluate the incidence of brain metastases.

The indication in the draft SPC is 'Lapatinib (Tyverb, GlaxoSmithKline) in combination with capecitabine is indicated for the treatment of patients with advanced or metastatic breast cancer whose tumours overexpress ErbB2 (HER2). Patients should have progressive disease following prior therapy which must include anthracyclines and taxanes and therapy with trastuzumab in the metastatic setting.

Key issues for consideration

- Is current UK practice to continue prescribing trastuzumab after disease progression in women with metastatic breast cancer?
- What conclusions can be drawn regarding the effect of lapatinib on overall survival (OS) given that the trial was not sufficiently powered to detect a difference in this outcome measure?
- How reliable are the cost-effectiveness results for lapatinib plus capecitabine versus trastuzumab regimens given that the effectiveness estimates were derived through unadjusted indirect comparisons?
- How reliable are the pooled mean estimates of median time to progression (TTP) for trastuzumab? These estimates were obtained by pooling median TTPs from eight studies, but the similarity of patient characteristics in these studies with those of participants in the lapatinib trial are unknown.
- Is there uncertainty in cost-effectiveness results because of the use of inferred weight and body surface area (BSA) distributions in the manufacturer's model instead of actual values from the main trial?
- How reliable are the methods used to derive the hazard ratio for progression-free survival (PFS) for trastuzumab-containing regimens applied to the economic model?

1 Decision problem

1.1 Decision problem approach in the manufacturer's submission

Population	Women with advanced or metastatic breast cancer whose tumours overexpress HER2 (ErbB2) and who have already received therapies such as an anthracycline and a taxane in either the adjuvant or metastatic settings, and trastuzumab for advanced or metastatic disease.
Intervention	Lapatinib in combination with capecitabine.
Comparators	Capecitabine monotherapy, vinorelbine monotherapy and trastuzumab (either in combination with capecitabine or vinorelbine, or as monotherapy).
Outcomes	The outcome measures considered, as in the original scope, were: OS, PFS, response rates (overall response rate, clinical benefit rate), adverse effects possibly related to study treatment and health-related quality of life (HRQoL). Refer to pages 35 to 36 of the Evidence Review Group (ERG) report for an explanation of outcomes. An additional outcome considered was TTP. This was the primary endpoint considered by the manufacturer. The incidence of brain metastases as the site of first relapse in both treatment groups was examined as a post-hoc analysis.

1.2 Evidence Review Group comments

1.2.1 Population

The final scope issued by NICE states that the population should be women with advanced, metastatic or recurrent breast cancer that overexpresses the HER2 receptor who have had prior therapy that includes trastuzumab. The MS notes that women who are most likely to continue receiving trastuzumab are those in whom the drug still appears to be having some effect, despite progression (for example, women with stable disease at most sites but with progression at an isolated site, including those with brain metastases, those with few metastases in the soft tissues or bone, and those with a good response to an initial trastuzumab regimen).

1.2.2 Comparators

The MS includes comparison of lapatinib plus capecitabine against capecitabine and vinorelbine as in the scope. The MS also includes comparison of lapatinib plus capecitabine against trastuzumab either in combination with capecitabine or vinorelbine, or used as monotherapy. The ERG highlighted a discussion with six expert advisers. This suggested that some primary care trusts (PCTs) continue to use trastuzumab beyond progression, in combination with chemotherapy, while others do not continue trastuzumab and switch to a chemotherapy agent. Therefore, continuation of trastuzumab monotherapy beyond disease progression may not be routine practice.

The MS states that the majority of women will have received a taxane at an earlier point in their treatment, and so would not be offered another taxane for advanced/metastatic disease. Trastuzumab with either capecitabine or vinorelbine would be the most likely treatment for these women. The MS also excludes gemcitabine and other chemotherapy regimens in the decision problem. The ERG states that clinical advice suggests that the manufacturer's exclusion of these comparators was appropriate.

1.2.3 Outcomes

The ERG states that the outcomes specified in the decision problem reflect the outcomes specified in the scope for this appraisal.

1.3 Statements from professional/patient groups and nominated experts

Experts stated that the role of continuation of trastuzumab with chemotherapy after disease progression as an alternative to the technology under review is unknown. However, despite the lack of evidence, many clinicians do continue to use trastuzumab beyond progression and simply change the associated chemotherapeutic agent, for example, vinorelbine or capecitabine. This variation in practice is based on clinical opinion and the availability of funding

to continue trastuzumab, and thus varies widely. Clinical advice to the ERG similarly suggested that alternative combinations with trastuzumab may sometimes be continued beyond disease progression but that trastuzumab monotherapy is rarely used in this circumstance.

Experts stated that women whose breast cancer has reached this stage are not considered to have curable disease, and so the toxicity of any treatment is particularly important. Some experts also mentioned that lapatinib may be suitable only for a small minority of women who have a limited life expectancy.

2 Clinical-effectiveness evidence

2.1 Clinical effectiveness in the manufacturer's submission

The manufacturer reported one main trial: a phase III, randomised, open-label, multi-centre, parallel-group study. Women with HER2-overexpressing advanced or metastatic breast cancer, who had already received therapy with trastuzumab in the advanced/metastatic setting, were assigned to lapatinib plus capecitabine or capecitabine alone. The trial was designed to detect a statistically significant difference in OS between treatment groups, but because a pre-planned interim analysis showed a statistically significant result in the primary endpoint (TTP), enrolment was halted early after a recommendation from the Independent Data Monitoring Committee (IDMC). The manufacturer noted that there may be lack of sufficient power to confirm a significant difference in OS when the data become mature. The MS also reported that women receiving capecitabine alone were offered the option of switching to lapatinib plus capecitabine, which was taken up [redacted] capecitabine therapy, and stated that this may further confound the opportunity to demonstrate a significant difference in OS.

The clinical-effectiveness results are based on one main RCT. Two sets of analyses were conducted: one set by an independent review committee under blinded conditions (see tables 1 and 2) and the other set by the investigator (see table 3). A summary of the results for the primary and secondary outcomes is given below. An updated analysis was also reported in the summary of product characteristics (SPC; see table 4).

Table 1 Primary endpoint – TTP (as assessed by independent review, ITT population, 03 April 2006 cut-off)

Outcome measure	Lapatinib + capecitabine (N = 198)	Capecitabine (N = 201)	Hazard ratio (95% CI)	Log-rank two-sided p value
Median TTP (weeks) (95% CI)	27.1 (17.4, 49.4)	18.6 (9.1, 36.9)	0.57 (0.43, 0.77)	<0.001

CI, confidence interval; ITT, intention-to-treat; TTP, time to progression.

Table 2 Secondary endpoint results (as assessed by independent review, ITT population, 03 April 2006 cut-off)

Outcome measure	Lapatinib + capecitabine (N = 198)	Capecitabine (N = 201)	Hazard ratio (95% CI)	Odds ratio (95% CI)	Two-sided p value
Median PFS (weeks) (95% CI)	27.1 (24.1, 36.9)	17.6 (13.3, 20.1)	0.55 (0.41, 0.74)	–	<0.001*
Overall response rate (CR or PR) (%) (95% CI)	23.7 (18.0, 30.3)	13.9 (9.5, 19.5)	–	1.9 (1.1, 3.4)	0.017†
Clinical benefit response rate (CR or PR or SD > 6 months) (%)	29.3	17.4	–	2.0 (1.2, 3.3)	0.008†
Median duration of response (weeks)	32.1	30.6	–	–	Not analysed
Median overall survival (weeks) (95% CI)**	67.7 (58.9,91.6)	66.6 (49.1, 75.0)	0.78 (0.55, 1.12)	–	0.177

* Log rank two-sided p value

† Exact test two-sided p value

CI, confidence interval; CR, complete response; ITT, intention-to-treat; PFS, progression-free survival; PR, partial response; SD, standard deviation.

Table 3 Results as assessed by investigator, ITT population, 03 April 2006 cut-off

Outcome measure	Lapatinib + capecitabine (N = 198)	Capecitabine (N = 201)	Hazard ratio (95% CI)	Odds ratio (95% CI)	Two-sided p value
Median TTP (weeks) (95% CI)	23.9 (12.0, 44.0)	18.3 (6.9, 35.7)	0.72 (0.56, 0.92)	–	0.007[a]
Overall response rate (CR or PR) (%) (95% CI)	31.8 (25.4, 38.8)	17.4 (12.4, 23.4)	–	2.2 (1.3, 3.6)	0.002[c]
Clinical benefit response rate (CR or PR or SD > 6 months) (%)	36.9	21.4	–	2.1 (1.3, 3.4)	0.001[c]

[a] Log-rank two-sided p value.

[c] Exact test two-sided p value.

CI, confidence interval; CR, complete response; ITT, intention-to-treat; PR, partial response; SD, standard deviation; TTP, time to progression.

Table 4 Results reported in the summary of product characteristics of an updated analysis of the overall survival data to 28 September 2007

	Lapatinib (1250 mg/m^2/day) + capecitabine (2000 mg/m^2/day)	Capecitabine (2500 mg/m^2/day)
	(N = 207)	(N = 201)
Number of participants who died	148	154
Median overall survival, weeks	74.0	65.9
Hazard ratio 0.9 (95% CI) (0.71, 1.12) p value 0.3		

CI, confidence interval.

The MS also reported the incidence of brain metastases by post-hoc analysis. [redacted] in the lapatinib plus capecitabine group had [redacted] than in the capecitabine alone group.

The MS reports that the difference between the independently assessed and investigator assessed results was due to the [redacted].

The manufacturer cites a study that suggests that the activity of lapatinib may have been enhanced by the persistence of trastuzumab in the body owing to its long half-life (28.5 days). However, efficacy results split by the time interval from last dose of trastuzumab to randomisation (≤ 8 weeks versus > 8 weeks) showed that the presence of any residual trastuzumab had a minimal influence on the response to lapatinib.

2.1.1 Adverse effects of treatment

Diarrhoea and rash were more commonly reported adverse events in the lapatinib plus capecitabine group (65% of women). The MS reports that the incidence of serious adverse events was similar between the two treatment groups (23−24%). Diarrhoea was the most commonly reported serious adverse event, occurring in 6−7% of women in both groups. In addition, approximately 4% of women in the lapatinib plus capecitabine group and 1% of women in the capecitabine group experienced a decreased left ventricular ejection fraction (LVEF) and five of the seven women receiving combination therapy were asymptomatic of LVEF. The SPC for lapatinib states that LVEF decreases resolved or improved in more than 60% of cases on discontinuation of treatment with lapatinib. Rash occurred in approximately 28% of women who received lapatinib in combination with capecitabine, but was generally low grade and did not result in discontinuation of treatment with lapatinib. For more details on the issues discussed above, refer to pages 44 to 51 of the MS.

2.1.2 Quality of life

Quality of life scores in the trial were obtained using the EQ-5D and FACT-B instruments. Missing post-baseline data were estimated using a last

observation carried forward method. Nearly [redacted] who completed questionnaires [redacted] Because [redacted] completed questionnaires [redacted] the results reported in the MS relate to only treatment visits up to week 24. The quality of life scores were also based only on those women who completed baseline questionnaires because the objective was to measure changes from baseline. For more details on the quality of life scores, refer to tables 5.11 to 5.13 in the MS.

2.1.3 Indirect comparison for trastuzumab regimens

The MS presented results of an indirect comparison using non-randomised, non-comparative data sources such as single-treatment group studies and observational data. The MS reported that it was not possible to link randomised studies for lapatinib plus capecitabine versus trastuzumab from the available trial data because the trastuzumab studies did not contain the specific relevant comparisons. In addition, there were limited data available on patient characteristics after their first progression on trastuzumab. Therefore, unadjusted comparisons of the efficacy data for trastuzumab beyond progression with data obtained for the treatment groups in the EGF100151 were used. The efficacy of vinorelbine was assumed to be similar to that of capecitabine. Table 5 summarises the key results from the relevant non-RCT evidence.

Table 5 Summary of key results from pooled studies

Interventions	Median TTP (in weeks)	Overall survival	Median PFS
Trastuzumab with or without chemotherapy beyond progression	21.8[a]	–	–
Trastuzumab beyond progression	–	62.4	–
Multiple lines of trastuzumab beyond progression	–	21.3	–
Capecitabine monotherapy	–	58	16.68

[a] Pooled estimates of median TTP in studies of trastuzumab beyond progression.

PFS, progression-free survival; TTP, time to progression.

2.2 Evidence Review Group comments

The ERG reported that the MS described the treatment effect of lapatinib plus capecitabine in a balanced manner and that the evidence from the single RCT was of reasonable methodological quality. The ERG's concern was that the evidence on the effectiveness of lapatinib was mainly based on a single trial.

In addition, the ERG noted that the main RCT forming the evidence base was stopped early owing to the recommendation of an IDMC. As a result of this, the trial did not reach the necessary population size required to achieve sufficient statistical power to detect a difference in OS (266 TTP events were required for the power calculation).

The ERG was concerned about the weakness of the unadjusted indirect comparison methodology that was used by the manufacturer. However, the ERG agreed that the poor evidence base for trastuzumab prevented a more methodologically robust indirect comparison and so a methodologically weaker unadjusted indirect comparison was used.

2.3 Statements from professional/patient groups and nominated experts

Experts and patient groups noted that lapatinib is also well tolerated with very few grade 3 or 4 toxicities as well as very low, if any, cardiotoxicity. It has

been found that among women with metastatic HER2 positive breast cancer on treatment with trastuzumab, a significant number (about 11%) experience grade 3 cardiac toxicity, with a small risk (2-4%) of severe congestive cardiac failure. The experts noted however that lapatinib appears to have very low cardiotoxicity. Therefore, they believed that the majority of women would consider the potential benefits of lapatinib to outweigh any increase in toxicity. However, others suggested that careful assessment of the effects of lapatinib on cardiac function should continue and the monitoring of LVEF during treatment was recommended.

Furthermore, patient experts considered that patients taking lapatinib were less likely to develop brain metastases than those taking comparator treatments. Patient experts stated that the clinical effects of brain metastases, such as unsteadiness of gait, speech difficulties, visual disturbances, headaches or confusion, can significantly impact on quality of life.

Some experts suggested that an advantage of lapatinib over existing treatments is its potential to be effective in people who have relapsed on or have not had a complete response to trastuzumab. It was also noted that lapatinib is administered orally as a tablet which is preferential for many patients as it reduces the number of hospital visits required.

3 Cost effectiveness

3.1 Cost effectiveness in the manufacturer's submission

3.1.1 The economic model

The health economic model submitted by the manufacturer used a survival modelling methodology to estimate the expected time to disease progression and death. All outcomes and costs were evaluated over a lifetime horizon beginning with the start of treatment.

The manufacturer stated that use of a Markov model was problematic because of the nature of the available data and considered that a survival model was more appropriate. Time spent in each state was estimated by calculating the area under the curves for OS and PFS. The trial data were extrapolated using a Weibull model for the 5-year time horizon of the model. For further details on the structure of the model and related issues, refer to pages 71 to 105 of the MS.

3.1.2 Health-related quality of life

In the manufacturer's model, the principal determinant of patients' quality of life was assumed to be disease progression. In the main trial (EGF100151), the pre-progression value (0.69) was obtained using the EQ-5D in all patients, regardless of treatment group. The value following disease progression (0.47) was based on a separate study that obtained valuation of descriptions of metastatic breast cancer from 100 members of the general public. The ERG reports that quality-adjusted life years (QALYs) were estimated by applying these values to the mean progression-free and post-progression survival durations for each regimen. The manufacturer's model assumes that health utilities do not differ according to treatments received and does not explicitly include the impact of treatment-related adverse events on quality of life. The MS also mentions that there may be a benefit in HRQoL for women receiving oral as opposed to infusional regimens. However, these were not included in the model.

3.1.3 Costs and resource use

The cost-effectiveness model distinguishes between the costs of care incurred while patients are free from disease progression (and are receiving active treatment), and the costs associated with those resources consumed after disease progression. The model also includes relative dose adjustment factors to account for differences between planned dose and actual dose prescribed in the main RCT, and to account for differences between independent and investigator-led analyses of PFS. For the indirect

comparisons with trastuzumab-containing therapy, the model assumes the relative dose adjustments for trastuzumab would be the same as that for lapatinib in the lapatinib plus capecitabine comparison, while that for adjunctive chemotherapy would be the same as that for capecitabine in the lapatinib plus capecitabine comparison. The model assumes a mean body mass of 68.9 kg and a mean BSA of 1.77 m^2 based on the characteristics of the study population included in main trial.

The model calculated the costs of wastage for those patients who discontinue therapy before completing their last prescription for such therapy.

Other types of resource-use included hospital resources for chemotherapy administration, pharmacy costs, management of adverse events, diagnostic and laboratory tests, clinical consultation, radiotherapy, other special interventions (for example, blood transfusions) and monitoring of patients receiving trastuzumab and lapatinib, which are all described in detail in the MS. The model was also evaluated for internal and external consistency. For more details on the modelling, refer to chapter 6, pages 71 to 105 of the MS.

3.1.4 Base-case results

The model evaluated the following treatment comparisons: lapatinib plus capecitabine versus (i) capecitabine monotherapy; (ii) vinorelbine monotherapy; (iii) trastuzumab plus vinorelbine; (iv) trastuzumab plus capecitabine; and (iv) trastuzumab monotherapy. Table 6 summarises the results.

Table 6 Manufacturer's submission cost-effectiveness results

Incremental	Lapatinib plus capecitabine versus				
	Capecitabine monotherapy	Vinorelbine monotherapy	Trastuzumab plus vinorelbine	Trastuzumab plus capecitabine	Trastuzumab monotherapy
Base case					
QALYs gained	0.171		0.143		
Incremental cost	£13,873	£11,584	–£4,452	–£2,186	–£1,075
Cost per QALY gained	£81,251	£67,847	Lapatinib plus capecitabine dominates		

QALY, quality-adjusted life year.

3.1.5 Sensitivity analysis

A summary of the scenarios that had the most impact on the incremental cost-effectiveness ratios (ICERs) is given in table 7. For more details on the sensitivity analysis, refer to pages 114 to 116 of the MS.

Table 7 Results of the deterministic sensitivity analyses

Scenario number and description	Incremental cost per QALY gained for lapatinib plus capecitabine versus				
	Capecitabine	Vinorelbine	Trastuzumab plus vinorelbine	Trastuzumab plus capecitabine	Trastuzumab monotherapy
Base-case scenario	£81,251	£67,847	Dominant (QALYs = +0.14, costs = –£4,452)	Dominant (QALYs= +0.14, costs = –£2,186)	Dominant (QALYs = +0.14, costs = –£1,075)
Scenario 5: Wastage excluded for all medicines	£76,896	£65,887	Dominant (QALYs = +0.14, costs = –£1,539)	£1,650	£6,772
Scenario 9: 3-weekly (6 mg/kg) rather than 1-weekly (2 mg/kg) trastuzumab regimen			£4,361	£20,248	£27,532
Scenario 11: PFS for trastuzumab-containing regimens = PFS for capecitabine			Dominant (QALYs = +0.17, costs = –£1,733)	£1,428	£7,099
Scenario 18: Inclusion of additional adverse event costs associated with lapatinib regimen	£83,003	£69,861	Dominant (QALYs = +0.14, costs = –£3,024)	Dominant (QALY s= +0.14, costs = –£1,866)	£2,470

PFS, progression-free survival; QALY, quality-adjusted life year.

3.2 Evidence Review Group comments

3.2.1 The modelling approach and structure

The ERG reports that they considered the overall approach used in the MS to model the cost effectiveness of lapatinib to be reasonable and that the submission adopted an appropriate technique, given the available data from the clinical trial. According to the ERG, the main problem with the economic analysis is the poor evidence base for most of the comparisons. Vinorelbine was assumed to be as effective as capecitabine because vinorelbine had no relative effectiveness data. The ERG stated that the methods used for including evidence of the effectiveness of trastuzumab do not meet the standards of a methodologically sound indirect comparison, but noted that this was due to a lack of appropriate data.

The ERG noted that dose adjustments were applied for all therapies and the ERG estimated drug acquisition costs without dose adjustments (see table 13, page 60, of the ERG report for drug acquisition costs per cycle).

To calculate the mean number of vials required for trastuzumab, with wastage, a weight distribution was inferred from the mean weight and standard deviation assuming that weight has a lognormal distribution. A similar calculation was undertaken to estimate the weighted mean dose for vinorelbine, with wastage, using an inferred distribution for BSA. The ERG notes that it is not clear why the weight and BSA distributions from the main trial were not used directly, rather than inferring distributions based on the trial mean and standard deviation and conducted an exploratory analysis on this issue.

3.2.2 Health-related quality of life

The ERG also highlighted several concerns with the health-related utilities used in the manufacturer's model. The ERG noted that summary patient data or calculations used to derive the pre-progression utility of 0.69 were not reported. The utility associated with post progression was derived using a

published study reporting valuations of descriptions of health states relevant to women with metastatic breast cancer (reducing utility by 0.272 from a value of 0.715 for a patient aged 38 years with stable disease and no toxicity). The MS assumed that the EQ-5D results from the main trial captured the disutility of side effects. Applying a health state valuation that includes disutility due to side effects is likely to be an underestimate for trastuzumab monotherapy, given the high tolerability of the regimen.

3.2.3 Resource use and costs

The ERG reported that the list of identified resource groups seems comprehensive and such resource use elements have been identified previously in the metastatic cancer setting.

The ERG noted that the generalisability of some of the cost data was not addressed in the MS. The resources identified in the survey and the costs applied to these resources have not been compared with those identified and costed in published economic evaluations of treatment for this patient group.

Drug acquisition costs in the base-case model were calculated using the mean BSA (for lapatinib plus capecitabine, capecitabine monotherapy, vinorelbine monotherapy and for the latter two agents in combination with trastuzumab) or mean weight (for trastuzumab) for patients in the main trial. Assumptions concerning the frequency of hospital attendances for infusional treatment regimens (that is, trastuzumab-containing regimens and vinorelbine monotherapy) in the model were based on SPCs, which suggest that treatment should be weekly. Clinical advice to the ERG suggested that weekly infusional treatment regimens would not be the typical pattern of practice in England and Wales, where trastuzumab would normally be given every 3 weeks at a dose of 6 mg/kg.

3.2.4 Internal and external consistency and exploratory analyses

The ERG reported that a validation exercise comparing the modelled survival functions against the Kaplan-Meier curves showed that the mean survival durations (PFS and OS) were similar. When the median PFS for lapatinib plus capecitabine was substituted into the PFS survival function, a higher PFS hazard ratio for lapatinib plus capecitabine compared with capecitabine monotherapy was obtained (0.6987) in comparison with that from the regression analysis reported in the MS (0.6085). The resulting mean PFS is lower using the former hazard ratio for lapatinib plus capecitabine.

The ERG also noted some inconsistencies in the unit cost estimates and the working of the model, but these only had a minor effect on the results.

The ERG re-ran sensitivity analysis around various parameters and realised that there was greater ICER variation when lapatinib plus capecitabine was compared with trastuzumab-containing regimens. The following assumptions were changed: wastage, frequency of treatment with trastuzumab, frequency and duration of treatment with vinorelbine, PFS for trastuzumab-containing regimens, and adverse-event costs for lapatinib regimens. The ERG noted that only one of these changed parameters resulted in an ICER above £20,000 but below £30,000 per QALY gained. The rest had ICERs below £20,000 per QALY gained. For more details refer to table 15 in the ERG report.

The MS assumed a weekly treatment frequency with trastuzumab in the base case. Changing frequency of dosing had minimal effect on drug costs, but had a large impact on administration costs. Table 8 shows the ERG's cumulative impact of assuming lower administration costs, and of estimating dosages at mean weight and BSA, on the cost effectiveness of lapatinib and capecitabine.

Table 8 ERG scenario analysis

	Incremental cost per QALY gained for lapatinib plus capecitabine versus				
Scenario analysis	**Capecitabine monotherapy**	**Vinorelbine monotherapy**	**Trastuzumab +vinorelbine**	**Trastuzumab +capecitabine**	**Trastuzumab monotherapy**
Trastuzumab every 3 weeks	£81,251	£67,846	£4,361	£19,019	£27,532
Trastuzumab every 3 weeks & lower administration cost[a]	£81,251	£70,605	£11,759	£23,315	£32,580
Trastuzumab every 3 weeks & lower administration cost & mean weight/BSA	£81,251	£70,960	£18,089	£29,247	£33,005
Hazard ratio for PFS with trastuzumab based on lower median TTP	£81,251	£70,960	£32,698	£35,700	£37,336
Hazard ratio for PFS with trastuzumab based on higher median TTP	£81,251	£70,960	Dominant	Dominant	Dominant

[a] Cost for trastuzumab administration was reduced to £117 per visit. Because administration costs for vinorelbine in the model is calculated as a proportion of the cost for trastuzumab, reducing the cost for trastuzumab automatically reduces the administration cost for vinorelbine.

BSA, body surface area; ERG, Evidence Review Group; PFS, progression-free survival; QALY, quality-adjusted life year; TTP, time to progression.

Table 8 shows that the greatest impact on the ICER was associated with poorer PFS with trastuzumab-containing regimens and using mean BSA or weight to estimate drug usage, rather than the inferred BSA and weight distributions used in the base case in the MS.

3.2.5 Probabilistic sensitivity analysis

The ERG reported several concerns about the assumptions used in the manufacturer's probabilistic sensitivity analysis (PSA). The first concern was that the hazard ratio for OS with trastuzumab was not sampled in the PSA, but was kept at the base-case value (0.8344). This departs from the base-case assumption that OS with trastuzumab-containing regimens is the same as lapatinib plus capecitabine.

The ERG's second concern was that the relative dose intensities are all assumed to be normally distributed. The ERG concludes that this does not seem appropriate because it allows for dose increases (above normal dose) as well as dose reductions, and there is no mechanism to constrain the distribution to the zero to one interval. A simulation undertaken by the ERG using the relative dose intensity (RDI) for progression-free days treated applied to capecitabine monotherapy (mean 0.94, standard error 0.072) produced 20% of sampled values greater than one. The PSA did not include drug costs and adverse events.

The ERG conducted a PSA after adjusting for the following.

- Changing the cost for administering chemotherapy infusion to the lower value based on a published assessment report for a previous appraisal (Trastuzumab for the adjuvant treatment of early-stage HER2-positive breast cancer [NICE technology appraisal 107]).
- Greater variation around the mean hazard ratio for PFS with trastuzumab-containing regimens with the standard error increased to 0.08.
- Lapatinib cost varied by plus or minus 20%, using a uniform distribution.
- Mean BSA and weight used to estimate drug use rather than the inferred BSA and weight.
- Trastuzumab administration occurs every 3 weeks, rather than weekly.

Table 9 presents the PSA results from the MS and the ERG report after the above modifications.

Table 9 Probability of lapatinib plus capecitabine being cost effective at thresholds of £20,000 and £30,000

	Lapatinib plus capecitabine versus the comparators below)				
Manufacturer PSA					
Threshold	**Capecitabine monotherapy**	**Vinorelbine monotherapy**	**Trastuzumab plus vinorelbine**	**Trastuzumab plus capecitabine**	**Trastuzumab monotherapy**
£20,000 per QALY gained	0.01	0.01	0.95	0.88	0.83
£30,000 per QALY gained	0.05	0.07	0.95	0.89	0.85
ERG PSA					
£20,000 per QALY gained	0.001	0.01	0.528	0.395	0.333
£30,000 per QALY gained	0.027	0.07	0.632	0.525	0.466

ERG, Evidence Review Group; MS, manufacturer's submission; PSA, probabilistic sensitivity analysis, QALY, quality-adjusted life year.

4 Authors

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Appendix Sources of evidence considered in the preparation of the premeeting briefing

A Single Technology Appraisal of Lapatinib for the treatment of women with previously treated advanced or metastatic ErbB2 (HER2) overexpressing breast cancer. Manufacturer submission (GlaxoSmithKline UK), 2007

B The evidence review group (ERG) report for this appraisal was prepared by

- J Jones, Takeda A, Picot J, von Keyserlingk C, Clegg A (Southampton Health Technology Assessment Centre), University of Southampton. Single Technology Appraisal of Lapatinib for HER2 over-expressing breast cancer, 2007.