Evidence Review Group Report commissioned by the NHS R&D HTA Programme on behalf of NICE

Lapatinib for HER2 over-expressing breast cancer

Produced by Southampton Health Technology Assessments Centre

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Conflicts of Interest:

The authors have no conflicts of interest. Peter Simmonds was the local Principal Investigator for GlaxoSmithKline-funded Study EGF1000151, although no patients were recruited from Southampton.

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LIST OF ABBREVIATIONS

AE	Adverse event
BNF	British National Formulary
CBR	Clinical benefit rate
CEA	Cost-effectiveness analysis
CI	Confidence interval
CIC	Commercial in confidence
CNS	Central nervous system
CR	Complete response
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer therapy evaluation program
CUA	Cost utility analysis
ECOG+PS	Eastern Co-operative Oncology Group Performance Status
EQ-5D	Euro QOL questionnaire
ErbB2	Alternative name for HER2
ERG	Evidence review group
FACT-B	Functional Assessment of Cancer Therapy – Breast
FACT-G	Functional Assessment of Cancer Therapy – General
FISH	Fluorescence *in situ* hybridisation
Grp	Group
GSK	GlaxoSmithKline
HEED	Health Economic Evaluations Database
HER2	Human epidermal growth factor receptor 2
HER2+	HER2 positive
HR	Hazard ratio
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IDMC	Independent Data Monitoring Committee
IHC	Immunohistochemistry
IMS	Intercontinental Marketing Services
IRC	Independent Radiological Review Committee
ITT	Intention to treat
LD	Longest diameter
LOCF	Last observation carried forward
LVEF	Left ventricular ejection fraction
MBC	Metastatic breast cancer
MEIP	Medline in process
MS	Manufacturers submission
N or n	Number
NCI	National Cancer Institute
NEJM	New England Journal of Medicine
NHS	National Health Service
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Clinical Excellence
NRR	National Research Register
ORR	Overall response rate
OS	Overall survival
OTR	Optimally tolerated regimen
PCT	Primary-care Trust

PFS	Progression-free survival
PPE	Palmar-Plantar Erythrodysaesthesia
PR	Partial response
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
Pt	Patient
QALY	Quality adjusted life year
QOL	Quality of life
QUORUM	Quality of reporting of meta-analyses
R&D	Research & Development
RAMOS	Registration and Medication Ordering System
RCT	Randomised controlled trial
RDI	Relative dose intensity
SAE	Serious adverse event
SD	Stable disease
±SD	Standard deviation
SG	Standard gamble
SmPC	Summary of product characteristics
STA	Single technology appraisal
TA	Technology appraisal
TOI	Trial Outcome Index
TTO	Time trade-off
TTP	Time to progression
UK	United Kingdom
US	United States

SUMMARY

Scope of the submission

The manufacturer's submission (MS) generally reflects the scope of the appraisal issued by NICE. The decision problem deviates slightly from the scope in that it specifically requires patients to have had treatment with trastuzumab for metastatic breast cancer, whereas the scope just requires prior trastuzumab. There are also differences in terms of the comparator treatments. The manufacturer did not include any chemotherapy agents other than vinorelbine and capecitabine, and also introduced trastuzumab as a comparator. Lapatinib has not yet received marketing authorisation for the treatment of metastatic breast cancer.

Summary of submitted clinical effectiveness evidence

- The main evidence in the submission comes from a multicentre, multinational open label randomised controlled trial (RCT) named EGF100151. Interim analyses from the trial were published in 2006, but the evidence in the report is from a later time point. This later data is expected to be published in June 2007, but was not available at the time the ERG report was written.
- Median time to progression was longer in the lapatinib+capecitabine arm than in the capecitabine monotherapy arm (27.1 weeks [95% CI 17.4, 49.4] vs. 18.6 weeks [95% CI 9.1, 36.9]), although the confidence intervals overlap. The hazard ratio reported in the MS is 0.57 (95% CI 0.43, 0.77), p=0.00013.
- Median overall survival was very similar between the two groups (67.7 weeks [95% CI 58.9, 91.6] vs. 66.6 weeks [95% CI 49.1, 75.0] for lapatinib+capecitabine vs. capecitabine monotherapy). The hazard ratio was 0.78 (0.55, 1.12), p=0.177.
- Median progression-free survival was statistically significantly longer in the lapatinib+capecitabine group than in the capecitabine monotherapy group (27.1 weeks [95% CI 24.1, 36.9] vs. 17.6 weeks [95% CI 13.3, 20.1]; hazard ratio 0.55 [0.41, 0.74], p=0.000033).

Summary of submitted cost effectiveness evidence

- The cost effectiveness analysis uses survival modelling methodology to estimate progression-free and overall survival for patients with HER2+ advanced/ metastatic breast cancer who have relapsed following treatment with an anthracycline, a taxane and trastuzumab. The incremental costs and consequences of treatment with lapatinib plus capecitabine are estimated relative to each of five different comparator regimes.

- Comparators are capecitabine monotherapy, vinorelbine monotherapy, trastuzumab monotherapy, trastuzumab plus capecitabine and trastuzumab plus vinorelbine.
- The model is generally internally consistent and appropriate to metastatic breast cancer, in terms of structural assumptions, although it uses a different approach from previous economic evaluations of treatments for metastatic breast cancer. The cost-effectiveness analysis (CEA) generally conforms to the NICE Reference Case and the scope/ decision problem.
- Treatment effects for lapatinib plus capecitabine and capecitabine monotherapy are derived from direct clinical trial evidence. In the absence of data on the effectiveness of vinorelbine monotherapy, it was assumed to be identical to capecitabine monotherapy. Effectiveness of trastuzumab-containing regimes was based on pooling of data on time to disease progression, and was used in an unadjusted indirect comparison.
- Utilities for pre-progression survival were based on responses to the EQ-5D in the EGF100151 trial. There was substantial missing data in the quality of life assessment in the trial. The utility reduction following disease progression was based on a published study which reported general population valuations of disease progression and the impact of treatment-related adverse events.
- The base case incremental cost-effectiveness ratios (ICERs) for lapatinib plus capecitabine compared with capecitabine monotherapy or vinorelbine monotherapy are higher than would conventionally be considered cost effective. When compared with trastuzumab-containing regimes, lapatinib plus capecitabine dominates (i.e. gives improved outcome at lower cost).
- Sensitivity analyses reported in the MS and undertaken by the ERG showed that the ICER for lapatinib plus capecitabine compared with capecitabine monotherapy or vinorelbine monotherapy was robust to variation in assumptions. In all sensitivity analyses the ICERs remained higher than would conventionally be considered cost effective. ICERs for trastuzumab-containing regimes were highly sensitive to assumptions over the frequency of treatment (weekly or three-weekly), assumptions over the distribution of weight and body surface area of patients receiving treatment and assumptions over drug wastage for infusional regimes.

Commentary on the robustness of submitted evidence

Strengths

- The MS was well written and presented a clear description of the evidence base.
- The manufacturer conducted a systematic review for this appraisal, and searched all relevant databases using appropriate search strategies.
- The identified RCT EGF100151 appears to be of reasonable methodological quality, although enrolment was terminated before the required sample size had been met.
- The economic model presented with the MS used an appropriate approach for the disease area and given the available data.

Weaknesses

- There is some deviation from the scope issued by NICE in terms of the timing of prior lines of therapy, and of comparator treatments.
- Only one relevant RCT was identified by the manufacturer's systematic review, and the evidence base for lapatinib+capecitabine in the MS is largely based on this one trial. Early termination of enrolment meant that there was insufficient power to detect a statistically significant difference in mean overall survival.
- The trastuzumab studies pooled for an indirect comparison contained a variety of treatment regimens. None of the studies contained a capecitabine monotherapy arm, so it was not possible for the manufacturer to perform an adjusted indirect comparison. The manufacturer therefore used a methodologically weaker unadjusted indirect comparison. The resulting pooled mean of median TTP values for trastuzumab may not be a reliable estimate, and should therefore be treated with caution.
- There is no evidence in the MS of a systematic search for model parameters – in particular cost inputs and utilities.

Areas of uncertainty

- It is possible that there were insufficient progressive disease events to achieve statistical power for the primary outcome measure time to progression (TTP). 266 progressive events were required, but the MS does not appear to state how many took place.

  [redacted]

  Trastuzumab monotherapy has been included as a comparator. Consultation with clinical advisors suggests that trastuzumab is used beyond progression in

combination with chemotherapy agents in some PCTs, but not others. Clinical advisors indicated that trastuzumab monotherapy is unlikely to be continued beyond disease progression.

- The MS included a post-hoc subgroup analysis of patients with brain metastases. It is likely that this is underpowered, and so should be treated with caution.
- There is a lack of robust and reliable evidence on the effectiveness of the majority of comparators included in the economic model (vinorelbine monotherapy and all the trastuzumab-containing regimes).
- There is uncertainty over the pattern of treatment with trastuzumab if it continues beyond disease progression – in particular, whether treatment is weekly or three weekly. This has a large effect on cost effectiveness of lapatinib plus capecitabine.

Key issues

- The included trial was not powered to detect a statistically significant difference in overall survival between lapatinib+capecitabine and capecitabine monotherapy.

  [redacted]

- There is a general lack of evidence on the effectiveness of comparators included in the economic model. A lack of evidence on other key parameters (such as dose adjustments) means that there is a great deal of uncertainty - model outputs need to be interpreted in the light of that uncertainty.

1 Introduction to ERG Report

This report is a critique of the manufacturer's submission (MS) to NICE from GlaxoSmithKline UK (GSK) on the clinical effectiveness and cost effectiveness of lapatinib for the treatment of advanced or metastatic ERbB2- (HER2) over-expressing breast cancer. It identifies the strengths and weakness of the MS. Clinical experts were consulted to advise the Evidence Review Group (ERG) and to help inform this review.

Clarification on some aspects of the MS was requested from the manufacturer by the ERG via NICE on 27th April. A response from the manufacturer via NICE was received by the ERG on 15th May and this has been included in Appendix 1.

2 BACKGROUND

2.1 Critique of manufacturer's description of underlying health problem

The manufacturer provides a clear and accurate overview of the disease, including a short summary of epidemiology and prognosis (MS p.17-18). The MS states that approximately 25-30% of patients with metastatic breast cancer have tumours that over-express HER2, based on figures from the abstract of a French study[2] and from their own market research (MS Appendix 9.4). The ERG's clinical advisor indicated that this is a fairly standard figure for the UK.

2.2 Critique of manufacturer's overview of current service provision

The target patient group for lapatinib will be patients with advanced or metastatic breast cancer that over-expresses the HER2 receptor, who have had prior therapy which includes trastuzumab. The manufacturer outlines current treatment pathways for these patients in figure 4.1 (p.19 of the MS). The percentages in the figure were derived from the Intercontinental Marketing Services (IMS) Oncology Analyzer database, with additional information from studies retrieved in the manufacturer's systematic review. These data and market research conducted by the manufacturer are summarised in Appendix 9.4 of the MS. Continuation of trastuzumab beyond disease progression is not currently recommended by NICE,[3] and its availability depends on individual PCTs' polices. Discussion with clinical experts suggests that continuation of trastuzumab with additional chemotherapy (either capecitabine or vinorelbine) beyond progression is fairly widespread in UK practice. However, continuation of trastuzumab

monotherapy beyond disease progression (i.e. without the addition of a chemotherapy agent) does not appear to be common practice.

The MS contains a summary of the manufacturer's market research to determine current service provision for this patient group (MS appendix 9.4). The ERG's areas of expertise are systematic reviews and health economics. As such, we do not have experience of critically appraising market research data, and are not aware of any standard methodology for this. We have summarised the market research data below and added comment where appropriate.

The breakdown of patients receiving the current treatment options is mainly based on data from the IMS Oncology Analyzer database. Page 34 of the MS describes this database as the largest commercially available patient-record database. The MS reports this to be a syndicated, diary-derived database of patient case history information as reported by hospital clinicians. The manufacturer indicates that case-history reporting should be seen as unbiased and reflective of current practice since it does not disclose the names of the clients that subscribe to the database. However, it is not clear what proportion of hospitals subscribes to this system, so there could be an underlying bias in different regions/ specialist hospitals being over-represented, distorting the view of current practice. The ERG briefly searched the IMS website[i] but could not find any further details on this particular database. Details of data collection for other databases appear to be based on records from hospital pharmacists, but the website does not appear to contain any information on the IMS Oncology Analyzer.

Of the 1,410 metastatic breast cancer patients in the database, 151 had received at least one trastuzumab containing regimen in the metastatic setting. The manufacturer scanned the database to identify patients who had previously received a taxane and an anthracycline, and who then had one or more chemotherapy drugs added to trastuzumab, or who had a chemotherapeutic switch to a trastuzumab-containing regimen. There were only 24 such patients, and the breakdown of treatments used in current practice (MS figure 4.1) broadly reflects the next line of therapy given to these patients. It should be noted that the requirement for patients to have received a taxane and an anthracycline was reflective of the manufacturer's inclusion criteria, rather than the population defined in NICE's scope.

[i] http://research.imshealth.com/default.htm, accessed 23/05/2007

The logic used in searching the IMS database (i.e. looking for patients who had a chemotherapy drug added to trastuzumab) did not allow for trastuzumab monotherapy, so the manufacturer used studies from their systematic review to identify the percentage of patients receiving trastuzumab without chemotherapy. Without further information on the database and methodology used, it is not clear whether it would have been possible for the manufacturer to have simply conducted a second search of the database for trastuzumab monotherapy. The manufacturer incorporated the extra data on monotherapy from their systematic review into the breakdown of treatments experienced by the 24 IMS patients, and calculated the final percentages for table 4.1 in the MS.

2.2.1 Studies from the systematic review and generalisability to the UK

The information on trastuzumab monotherapy came from nine international studies identified in the manufacturer's systematic review. Table 9.4 of MS Appendix 9.4 indicates that the study by Tripathy and colleagues[4] had trial centres in nine countries, including the UK, but it is not clear how many of the study's 93 patients were treated in the UK centres. This trial was an extension study to an earlier RCT, and was designed to allow further collection of safety data. Of the 93 patients, 22 (24%) had treatment with trastuzumab monotherapy beyond progression on treatment with chemotherapy and trastuzumab, and the rest received chemotherapy and trastuzumab. There was quite a range of chemotherapy agents, as shown in Table 1.

The only other study in table 9.4 of MS Appendix 9.4 which might have included UK patients was that by Gelmon and colleagues.[5] The paper only states that there were 13 centres across Canada, Europe and Australia, so it is not possible to determine whether any UK patients were involved. This was an observational study of 105 women, of whom 103 appear to have received a second trastuzumab-containing regimen. Table 9.4 in MS Appendix 9.4 suggests that there were 93 patients in the study, of whom 12% received trastuzumab monotherapy. In the paper by Gelmon and colleagues[5], it appears that 11 of 103 (10.7%) patients received trastuzumab monotherapy. It is not clear why the MS uses figures which are slightly different to those in the cited reference.[5] Table 2 in the paper by Gelmon and colleagues[5] gives the treatment combinations for the second regimens, and these are reproduced in Table 1 of the ERG report.

Table 1 Concomitant therapies for patients in additional UK studies

Therapy in addition to trastuzumab* n(%)	Tripathy et al.[4] (N=93)	Gelmon and colleagues[5] (N=103}
No chemotherapy	22 (24)	11 (10.7)
Taxane (unspecified)		21 (20.3)
Paclitaxel	30 (32)	
Vinorelbine	20 (22)	33 (32.0)
Docetaxel	17 (18)	
Fluorouracil	11 (12)	
Cisplatin	6 (6)	
Cyclophosphamide	7 (8)	
Doxorubicin	8 (9)	
Gemcitabine	7 (7)	
Other chemotherapy agent		38 (36.9)
Hormonal therapy	15 (16)	
Radiation therapy	40 (43)	

* patients may have received more than one therapeutic regimen

The MS uses the data reproduced in Table 1 and further information from seven non-UK studies to estimate that approximately 15% (the mid-point of the data) of patients who receive trastuzumab beyond progression do not receive chemotherapy. The manufacturer does not appear to have used any kind of weighting for study size or quality in determining the estimate of 15%. The MS then indicates that trastuzumab is continued beyond progression in approximately 40-45% of patients, thus reducing the figure for trastuzumab monotherapy to 6.7%. The MS does not appear to incorporate any of the information on other lines of therapy presented in the nine studies shown in Table 9.4 of MS Appendix 9.4. The final breakdown of treatment options shown in MS Fig 4.1 is therefore based on the 24 patients in the IMS, minus the IMS lapatinib+capecitabine group (since this is not a comparator), and adjusted by adding the 6.7% of patients estimated to have trastuzumab monotherapy beyond progression.

2.2.2 Additional market research

The manufacturer sponsored three market research surveys, and these are summarised on pages 37-41 of MS Appendix 9.4. However, none of the data from this market research appears to have been incorporated into the breakdown of current treatment practice shown in MS Figure 4.1. The market research found continuation of trastuzumab beyond progression reported by 41% of 90 UK clinicians in one survey, 31% of 41 in another survey, and 29% of 50 clinicians in the third survey. The market research data therefore give slightly lower values than the 40-45% calculated from the IMS database. Corresponding reports from the three surveys on the use of trastuzumab monotherapy beyond progression are 7%, 12% and 6.0-8.6%.

2.3 Critique of manufacturer's definition of decision problem

2.3.1 Population

The final scope issued by NICE states that the population should be women with advanced, metastatic or recurrent breast cancer that over-expresses the HER2 receptor who have had prior therapy that includes trastuzumab. This suggests that trastuzumab could have been used in the metastatic setting, or earlier in the patient's treatment. The population defined in the draft SPC for lapatinib is: "patients with advanced or metastatic breast cancer whose tumours over-express ErbB2 (HER2) and who have received prior therapy including anthracyclines, taxanes and trastuzumab."

The manufacturer uses a slightly stricter definition in the decision problem, to match the pivotal trial EGF100151. The MS specifies that patients should have "advanced or metastatic breast cancer whose tumours over-express HER2 (ErbB2) and who have received prior therapies, including t*rastuzumab for advanced or metastatic disease* [ERG's emphasis], plus an anthracycline and a taxane in either the adjuvant or metastatic settings" (MS p.4, Statement of Decision Problem). This matches the 'post decision problem' inclusion criteria for the manufacturer's systematic review (MS p.24). The manufacturer's inclusion criteria therefore indicate that only evidence from trials where patients received trastuzumab for advanced or metastatic breast cancer should be included in the review. The decision problem's requirement for pre-treatment with anthracyclines and taxanes is stricter than the population defined in NICE's scope, but page 24 of the MS indicates that this requirement was relaxed for some of the systematic review (see ERG Section 3.1.2 for more details). Without doing a full systematic search for studies including the different populations, only tentative comments can be made regarding the effect the differences in the scope's population and that defined in the decision problem. Patients relapsing after adjuvant trastuzumab may have had no anti-HER2 therapy for some time, unlike patients who received trastuzumab for advanced or metastatic disease. However, the ERG's clinical advisor indicated that this difference is unlikely to have much effect on the current assessment.

The population described in the decision problem appears to be appropriate for the NHS, although only about 10% of the trial's population were UK patients. Consultation with the ERG's clinical advisor suggested that the UK patients might be slightly older than the trial participants, but otherwise patient characteristics are similar. Only small numbers of patients will be eligible

for treatment with lapatinib. For example, Southampton University Hospitals Trust currently sees approximately ten patients per year who would be suitable for lapatinib treatment. It is likely that this will rise to approximately 20 patients per year when an increase in HER2 testing at diagnosis leads to patients receiving trastuzumab at earlier points in the course of their disease, making them eligible for lapatinib at the metastatic stage.

2.3.2 Intervention

At the time of writing, lapatinib had not yet received UK marketing authorisation. It is therefore not possible to say whether or not it is appropriate for use within the NHS. It does not yet appear to be widely used in clinical practice, but our clinical advisor indicated that its use may become more widespread as patients increasingly receive trastuzumab at earlier stages of disease. It is currently available in a limited number of centres under the manufacturer's Expanded Access Programme EGF103659.

2.3.3 Comparators

The NICE scope stated that capecitabine, vinorelbine, taxane regimens and other appropriate chemotherapy regimens in standard practice in England and Wales should be considered as comparators. The comparators described in the decision problem on MS p.5 are: capecitabine monotherapy, vinorelbine monotherapy, trastuzumab monotherapy and trastuzumab in combination with either vinorelbine or capecitabine. The comparators described in the decision problem exclude taxanes, gemcitabine and other chemotherapy agents. The manufacturer justified this exclusion by stating that the majority of patients will have received a taxane at an earlier stage in their disease, and that very few women receive treatments such as gemcitabine. To some extent, this appears to be contradicted by the studies used in the market research data (MS Appendix 9.4), which indicate that taxanes were used by between 20% and up to 50% of patients in the two studies which may have included UK patients (ERG Table 1). However, these data include patients from several other countries, and may not reflect UK practice. The ERG's clinical advisor indicated that it would be unusual to retreat patients with the same class of drug, so on that basis it is entirely reasonable to exclude taxanes from the comparison.

Section 2.2 provides a more detailed discussion of how the comparators relate to current practice in the NHS. Whilst trastuzumab would generally be described as an immunotherapy or biological therapy rather than a chemotherapy, the phrase 'other appropriate chemotherapy regimens' does not explicitly exclude chemotherapy regimens in combination with other types of treatment. The ERG's clinical advisors indicated that trastuzumab is sometimes continued

beyond progression in conjunction with either capecitabine or vinorelbine, but that trastuzumab monotherapy is rarely used beyond disease progression.

On the evidence presented in the MS, it is not likely that the exclusion of taxanes, gemcitabine and other chemotherapy regimens would have affected the evidence base for this review. Table 9.29 in Appendix 9.7 of the MS lists 11 studies which were identified in the original searches but then excluded when the comparators were finalised. These studies are all non-comparative trials, and none used lapatinib-containing treatment regimens. They would not have been suitable for an indirect comparison with the EGF100151 lapatinib trial due to their poor methodological quality and lack of a common comparator. The manufacturer provided a list of studies excluded in the original review. Whilst it has not been possible for the ERG to scan through all of these (n>4000) references, a key word search suggests that there were no studies which would have contributed to the evidence base.

2.3.4 Outcomes

The outcomes specified in the decision problem are: time to progression (primary endpoint); progression-free survival; response rates; overall survival; health related quality of life; adverse effects. These reflect the outcomes specified in the scope for this review. Outcome measures are discussed in more detail in Section 3.1.4 of the ERG report.

3 CLINICAL EFFECTIVENESS

3.1 Critique of manufacturer's approach

The manufacturer's methodology for screening studies is given in MS Appendix 9.2.6, and this appears to have been appropriate. Although it does not state how many reviewers assessed the citations at the title and abstract stage, each retrieved study was screened against the eligibility criteria by two independent reviewers. All included studies were data extracted by two independent reviewers.

3.1.1 Description of manufacturer's search strategy

The manufacturer's search approach appears to have been thorough and systematic, and was appropriate for this review.

3.1.1.1 Clinical effectiveness searches

The manufacturer searched CINAHL, ISI Proceedings and Zetoc in addition to the required databases (Medline, Embase, Medline in Progress and Cochrane) and undertook hand searching of the key oncology meetings. MS Section 9.2.5 states that the NCI clinical trial database, clinical trials.gov and the National Register of Cancer trials were also searched for ongoing trials, together with the manufacturer's in-house databases.

An initial broad search was undertaken on the 24th November 2006 on the databases specified above. The rationale for this is documented as being that the final scope had not been issued and consequently the search included more comparators than were later deemed to be relevant to the submission (for example gemcitabine and docetaxel). This search strategy is clearly tabulated per database line of search strategy, and the number of references retrieved is listed.

An update search was conducted on the 28th February with the comparators limited to capecitabine, vinorelbine and trastuzumab monotherapy or combinations. The date for the main database search was specified as ranging from 1985 to the end of February 2007. Although the details of the approach to the update search were clearly stated in section 5.1, they were not included in the Appendix 9.2. The conference proceedings were recorded in section 5.1 as being searched from 2004-2006, which is an appropriate range. The search terms selected and the documented strategies are appropriate on all the databases. An RCT filter was not applied to the search strategy, on account of the sparseness of data that would result. Only one relevant RCT trial was identified, so non-randomised trials were included in the search.

The tables in Appendix 9.2 appear to be for the initial search rather than for the updated, post-decision problem search. They contain the terms gemcitabine and docetaxel, which are not listed in the restricted comparator list. There is therefore a lack of clarity over the total numbers retrieved from which search strategy, compared against those in the QUOROM diagram in section 5.2.6. However, if the numbers reflect the initial searches, there would not be any additional references once the comparators had been restricted. Studies excluded after the comparator list had been restricted are listed in MS Appendix 9.7, Table 9.29.

3.1.1.2 Cost effectiveness searches

The cost-effectiveness searches run by the manufacturer have exceeded the minimum database criteria set by NICE, searching CINAHL and HTA databases in addition to Medline, Embase, MEIP, NHS EED and HEED. The searches are reproduced in a table in MS Appendix

9.3. The search terms and strategy are appropriate, and an economic search filter has been used in Medline and Embase databases. The search filters have not been used in the others and this is clearly stated to be on account of the low number of hits in the database. This is acceptable practice for searches of this nature.

3.1.2 Statement of the inclusion/exclusion criteria used in the study selection and comment on whether they were appropriate.

The manufacturer initiated the systematic review before the scope was finalised, and consequently there are some discrepancies between the scope, the pre-decision problem criteria and the post-decision problem eligibility criteria. The criteria have been summarised in Table 2.

Table 2 Comparison between Scope and MS systematic review eligibility criteria

	NICE scope	Initial pre-decision problem criteria	Post-decision problem criteria
Population	Women with advanced, metastatic or recurrent breast cancer that over-expresses the HER2 receptor who have had prior therapy that includes trastuzumab	Refractory advanced or metastatic breast cancer with stage IIIB/stage IIIC with T4 lesion, or stage IV disease. HER2+, with prior therapy to have included an anthracycline or a taxane and at least one line of therapy in the metastatic setting.	As for pre-decision problem, but no requirement for prior anthracycline or taxane therapy for retrospective studies*; for any trastuzumab-containing comparator, prior trastuzumab in metastatic setting was required.
Intervention	Lapatinib in combination with capecitabine	At least one of the following: lapatinib; capecitabine; trastuzumab; gemcitabine; vinorelbine; docetaxel; paclitaxel. Comparator treatments to lapatinib could have been placebo, best supportive care or any of the above.	At least one of the following: lapatinib regimens; capecitabine monotherapy; vinorelbine monotherapy; trastuzumab monotherapy; trastuzumab plus capecitabine; trastuzumab plus vinorelbine; trastuzumab plus non-specified or mixed single-agent chemotherapy.
Comparators	Capecitabine, vinorelbine, taxane regimens and other appropriate chemotherapy regimens in standard practice in England and Wales.		
Outcomes	Overall survival; progression free survival; response rate; adverse effects; health-related quality of life	Not specified in eligibility criteria for systematic review	

* no prospective studies were excluded solely on the basis of not meeting the requirement for prior therapy with either an anthracycline or a taxane (as well as prior trastuzumab).

The inclusion and exclusion criteria for the systematic review (p.22) do not distinguish between intervention and comparator treatments, and there is a single list of relevant regimens. Consequently, there are a number of studies which met the inclusion criteria but do not actually

contain evidence on the use of lapatinib. Eleven of these were pooled to allow an indirect comparison with trastuzumab. The inclusion and exclusion criteria in the MS were otherwise clearly stated, and are generally appropriate for this review.

The NICE scope stated that capecitabine, vinorelbine, taxane regimens and other appropriate chemotherapy regimens in standard practice in England and Wales should be considered as comparators. However, for reasons discussed in Section 2.3.3, the manufacturer's inclusion criteria for comparators do not quite match those in the scope.

The ERG's clinical advisor indicated that the selected comparators were appropriate, and that there were no others he would have expected to see. The majority of patients 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 patients. In some UK settings, patients would not be allowed to continue with trastuzumab once the disease had progressed, whereas in others patients would be allowed to continue if there was still some benefit. Initial searches appear to have included gemcitabine and taxanes, and MS Table 9.29 in the Appendix 9.7 lists studies which met the inclusion criteria but had irrelevant interventions.

The patient population considered for the systematic review was people with HER2-positive advanced or metastatic breast cancer and prior treatment including trastuzumab, stated to be in line with the proposed SmPC for lapatinib (MS p.22). This reflects the population defined in the scope, and as such it is appropriate for this review. The manufacturer's initial criteria (MS p.24) also stated that patients were required to have received trastuzumab and either an anthracycline or a taxane, which is a stricter requirement than set out in the scope. However, the post-decision problem criteria relaxed the requirement for an anthracycline or taxane treatment for retrospective studies, and a footnote (MS p.24) states that there were no prospective studies which were excluded for lack of anthracycline/taxane use.

No limits were placed on inclusion relating to the quality of RCTs, and both retrospective and prospective studies were included. Non-randomised and uncontrolled studies were also included. Given that the main section of the MS focuses on RCT data, it would have seemed more appropriate for the inclusion criteria to have stated that only RCTs were to be included.

Setting does not appear to have been used as an inclusion criterion, and no outcomes were specified in the eligibility criteria for the systematic review (MS p.24).

3.1.2.1 Identified studies

The manufacturer's inclusion criteria did not distinguish between interventions and comparators, so two RCTs actually met their inclusion criteria. An RCT by Miller and colleagues[6] met the inclusion criteria as it included a capecitabine monotherapy arm. However, the study was of bevacizumab plus capecitabine vs. capecitabine monotherapy, and did not include a lapatinib arm. It was therefore not included in the clinical effectiveness section of the MS and will not be discussed here.

The only relevant RCT (EGF100151) which met the inclusion criteria provides the main evidence base for the MS, and the characteristics of this trial are presented below in Table 3. Enrolment to EGF100151 was halted early following the recommendations of an Independent Data Monitoring Committee, and women in the capecitabine monotherapy arm were then given the opportunity to cross over to treatment with lapatinib plus capecitabine. The dataset from this point is referred to throughout the MS and ERG report as the 3 April dataset. The manufacturer provided clarification confirming that the 3 April dataset only contains data that precedes the time enrolment was halted, i.e. no data following the crossover were included. The full RCT clinical study report was also provided electronically.

The trial was a comparison of 1250mg/m^2 lapatinib plus 2000mg/m^2 capecitabine vs. 2500mg/m^2 capecitabine monotherapy. The manufacturer justified the lower dose of capecitabine in the combination arm by citing evidence from a phase I study, with reference to two conference abstracts.[7,8] On the basis of the data presented in the conference abstracts, it appears that only eight of the 21 patients included in the optimally tolerated regimen study were patients with breast cancer; the other patients had various other forms of cancer with advanced solid tumours.

Table 3 Characteristics of the included RCT

Study: EGF100151 (3 April 2006 cut off)

Methods	Participants	Outcomes
Design: RCT *Interventions*: Grp1: Lapatinib 1250mg once daily on a continuous basis plus capecitabine 2,000mg/m^2 on days 1-14, of a 21-day treatment cycle Grp2: Capecitabine 2,500mg/m^2 alone on days 1-14, of a 21-day treatment cycle *Number of centres*: not documented in MS (sites in N. America, S. America, S. Africa, Hong Kong, Australia, and Europe, including 12 UK sites which recruited 43 patients) *Length of follow-up:* Follow up to continue to death	*Key Inclusion criteria*: ▪ Histologically confirmed invasive breast cancer with stage IIIb / stage IIIc with T4 lesion, or stage IV disease ▪ Documented HER2 over-expression (IHC 3+ or IHC 2+ with FISH confirmation) ▪ Documented progressive advanced or metastatic breast cancer (defined as appearance of any new lesion not previously identified or increase of > 25% in existent lesions, and must be documented) ▪ Refractory breast cancer, defined as progression in the locally advanced or metastatic setting, or relapse within 6 months of completing adjuvant therapy ▪ Prior therapies must have included, but not been limited to, at least 4 cycles of regimens containing an anthracycline and a taxane (2 cycles if the disease progressed while the women were receiving therapy), administered concurrently or separately in the adjuvant or metastatic setting ▪ Prior treatment must have contained trastuzumab alone or in combination with other chemotherapy for at least 6 weeks in the advanced/metastatic setting ▪ No prior capecitabine ▪ Subjects with hormone-receptor positive tumours must have had disease progression following hormone therapy, unless intolerant to hormonal therapy or hormonal therapy was not considered to be clinically appropriate *Numbers*: ITT n=399; Grp1: n=198; Grp2: n=201. [redacted] *Adverse events:* Grp1 97%; Grp2 93%.	*Primary outcome*: ▪ Time to progression (TTP) assessed by the Independent Radiological review Committee (IRC) *Secondary outcomes*: ▪ Progression-free Survival (PFS) ▪ Overall Response Rate (ORR) ▪ Clinical Benefit Response Rate (CBR) ▪ Median Duration of Response ▪ Investigator Assessed TPP ▪ Investigator Assessed ORR ▪ Investigator Assessed CBR ▪ Overall Survival (OS) ▪ Incidence of Brain Metastases ▪ Response rate by stratification factor ▪ Regression Analyses ▪ Efficacy in sub-groups ▪ Quality of Life ▪ Exposure to Study Medication ▪ Adverse events

Interim analysis from EGF100151 was published in the New England Journal of Medicine (NEJM) in 2006.[9] The published data were from the 15 November 2005 cut-off, whereas the data presented in the MS were from the 3 April 2006 cut-off. There is currently no peer-reviewed publication of the 3 April 2006 dataset.

Although only one RCT met the criteria for inclusion in the MS, the MS also draws on evidence from three non-comparative, phase II trials of lapatinib monotherapy. These met the manufacturer's inclusion criteria for the systematic review, but since they do not contain evidence for the effectiveness of lapatinib in combination with capecitabine they will not be discussed in the ERG report, beyond being summarised in Table 4.

Table 4 Summary of the included non-RCT evidence for lapatinib

Study and design	Participants	Main objective
EGF 20002 Data from CSR Phase II, open-label, multicentre, location: US	Patients with HER2+ stage IIIB or IV breast cancer and who had experienced disease progression whilst treated with trastuzumab.	To evaluate tumour response rate (CR or PR) in patients with advanced or metastatic breast cancer treated with lapatinib who had progressed while receiving trastuzumab-based regimens.
EGF 20008 Data from CSR Phase II, open-label, multicentre, Locations: US, Germany, Belgium, UK, France, Spain, Canada, Japan, Australia, Argentina	Patients with advanced or metastatic breast cancer and who had experienced disease progression on prior treatment with regimens containing anthracyclines, taxanes and capecitabine.	To evaluate tumour response rate (CR or PR) in two cohorts of advanced or metastatic breast cancer patients treated with lapatinib. Cohort A: Subjects with HER2+ tumours who were refractory to taxane-, anthracycline-, capecitabine- and trastuzumab- containing regimens. Cohort B: Subjects with HER2- tumours and who were refractory to taxane-, anthracycline-, and capecitabine-containing regimens.
CTEP 6969 Data from abstracts Investigator-initiated trial (not GSK sponsored) Phase II, open label, single centre, Location: US	Patients with HER2+ breast cancer with new or progressive brain metastases and at least one measurable lesion (LD ≥ 1cm). All patients had received prior trastuzumab. Patients were eligible if they had progressed after radiation therapy.	To evaluate the clinical efficacy and safety of lapatinib in patients with CNS metastases from HER2+ breast cancer.

The manufacturer also identified 12 studies which met their inclusion criteria for relevant treatments, but did not involve lapatinib. Eleven of these involved the use of trastuzumab, and these were used in the indirect comparison discussed in Section 3.1.5 of the ERG report. The studies are summarised in Table 5.

Table 5 Summary of the included evidence for comparators (11 studies used for indirect comparison)

Study and design	Participants	Main objective
H0659g Tripathy[4,10] Multicentre trial extension study; Location: US	Patients with HER2+ metastatic breast cancer. Prior treatment included anthracyclines, and/or taxanes and trastuzumab.	To obtain additional safety information for trastuzumab in combination with chemotherapy following documented disease progression. Prior therapy included chemotherapy with and without trastuzumab.
Bangemann 2000 [11] Single centre trial extension; Location: Germany	Patients with HER2+ metastatic breast cancer. Prior treatment included anthracyclines and/or taxanes.	To evaluate trastuzumab in combination with vinorelbine, capecitabine, and docetaxel. This sequential study concentrates on the population of patients who progressed from the first regimen (weekly trastuzumab, either with no chemotherapy or weekly paclitaxel). The patients who progressed were further

		treated with vinorelbine (n=10), capecitabine (n=17) and docetaxel (n=9).
Suzuki 2003 [12] Phase II, non-comparative, single-centre study; Location: Japan	Patients with HER2+ metastatic breast cancer that had not responded to or had relapsed after treatment with trastuzumab or a combination of trastuzumab and a taxane. Patients had been previously treated with one or two lines of chemotherapy in the metastatic setting.	To determine the response rate and toxicity of vinorelbine/trastuzumab as second or third line therapy for metastatic breast cancer in patients whose tumours did not respond to or relapsed after initial trastuzumab therapy.
Bartsch 2006 [13] Prospective observational single centre study; Location: Austria	Patients had histologically confirmed HER2+ advanced breast cancer. Trastuzumab was administered as first-line therapy in all patients except 14 who had prior treatment with aromatase inhibitors. All patients had received at least two lines of palliative trastuzumab treatment.	The objective of this study was to examine continued trastuzumab treatment beyond disease progression.
HERMINE Extra 2006 [14] Prospective multicentre observational study; Location: France	Women with metastatic breast cancer who had begun trastuzumab treatment for the first time between Jan and Dec 2002 were eligible. 79% of patients had previously been treated with chemotherapy in the adjuvant/ neoadjuvant setting, with 88% of patients having received anthracycline treatment.	To determine whether continuation of trastuzumab treatment after progression was beneficial.
Fountzilas 2003 [15] Retrospective multicentre study; Location: Greece	Patients had HER2+ metastatic breast cancer previously treated with trastuzumab and chemotherapy that was treated with further trastuzumab upon progression.	Retrospectively reviewed the medical records of patients who received trastuzumab monotherapy or combination chemotherapy beyond disease progression in order to register their clinical course.
García-Sáenz 2005 [16] (García-Sáenz 2004)[17] Retrospective study, Single centre; Location: Spain	Patients had HER2+ (IHC3+) metastatic breast cancer treated with at least 1 trastuzumab containing regimen for metastatic disease. 31 patients received a second line of trastuzumab therapy.	To determine the activity of successive trastuzumab-containing regimens in HER2-over-expressing metastatic breast cancer.
Gelmon 2004 [5] Retrospective study, Multicentre; Locations: Canada, Europe Australia	Patients had HER2+ metastatic breast cancer treated with at least 2 lines of trastuzumab-containing therapy.	To evaluate whether there was any evidence of efficacy to support continuation of trastuzumab beyond disease progression and evaluate the feasibility of this approach.
Montemurro 2006[18] Retrospective study, Multicentre;	Patients had HER2+ advanced breast cancer treated with trastuzumab. 40 patients continued trastuzumab treatment after progression on a trastuzumab-	To describe patterns of treatment and clinical outcome in patients with HER2-positive advanced breast cancer progressing on trastuzumab-based therapy.

Location: Italy	containing therapy.	
Stemmler 2005[19] Retrospective study, Multicentre; Location: Germany	Patients with HER2+ (IHC3+) metastatic breast cancer treated with trastuzumab. 23 patients received trastuzumab after progressing on a trastuzumab containing regimen.	To evaluate the impact of trastuzumab-based regimens on the survival of patients with HER2-overexpressing metastatic breast cancer.
Tokajuk 2006[20] Retrospective study; single centre; location not reported but likely to be Poland.	Patients with HER2+ metastatic breast cancer, heavily pre-treated	To assess the activity of trastuzumab-based therapy for metastatic breast cancer patients treated in a single institution outside clinical trials.

3.1.2.2 Details of any irrelevant studies that were included in the submission

The MS has not included any inappropriate RCTs.

3.1.2.3 Ongoing studies

Searches for ongoing studies are described in MS Appendix 9.2.5. The only additional ongoing study identified by the ERG's searches of the National Research Register (NRR) was record N0051189183- 'An open-label expanded access study of lapatinib and capecitabine therapy in subjects with HER2 (ErbB2) over-expressing locally advanced or metastatic breast cancer'. It is likely that this study is part of the EGF103659 expanded access programme, included in MS Table 5.1.

The ERG identified two additional ongoing studies investigating the ongoing use of trastuzumab beyond disease progression which may be of relevance to this review:

- GBG26/TBP – A multicentre randomised phase III study to compare capecitabine alone or in combination with trastuzumab in patients with HER2 positive metastatic breast cancer and progression after previous treatment with trastuzumab (NRR identifier N0256183394). This ongoing RCT is due to end in September 2007. The study is aiming to recruit approximately 100 UK patients plus others overseas. The lead centre is the Royal Free Hampstead NHS Trust, London.
- THOR Study: A study of continued Herceptin (trastuzumab) in combination with second line chemotherapy in patients with HER2 positive metastatic breast cancer (clinical trials identifier NCT00448279). This Italian study is currently recruiting, with a target sample size of 100-500 people.

3.1.2.4 Additional studies

The ERG is not aware of any additional studies which should have been included in the MS. We re-ran searches and identified very similar numbers of references. It would not have been possible to assess all references (n>4000) against the inclusion/exclusion criteria within the timescales/scope of this review, but a keyword search of the excluded studies supplied by the manufacturer suggests that there were no relevant RCTs which should have been included in the review.

3.1.3 Description and critique of manufacturer's approach to validity assessment

The manufacturer applied the quality assessment criteria developed by NICE and presented the information in MS Table 5.3. They do not state whether this was done by a single reviewer or a consensus of multiple reviewers. The quality assessment criteria are discussed below.

- How was allocation concealed?

The study investigators were unaware of the treatment group allocation (after enrolling a patient into the study) until they contacted the Registration and Medication Ordering System (RAMOS) (MS p35) for the computer-generated treatment assignment. Once treatment had been assigned, it was not possible to blind participants to the two different doses of capecitabine, as these were supplied in two tablet strengths with tablets combined to make up the required dose (MS p27).

- What randomisation technique was used?

The MS states that subjects were assigned a unique subject number allocation. This number in combination with stage of disease and sites of disease was entered via RAMOS to obtain a computer generated randomisation number and treatment group assignment. Subjects were randomised in permuted blocks of six within strata defined according to disease stage and the presence or absence of visceral metastases (MS p27 & p35). This was an appropriate randomisation technique.

- Was a justification of the sample size provided?

The MS supplies information about the sample size calculation (MS p33) but this sample size was not achieved because study enrolment was halted after the interim analysis had been carried out (MS p 30). This is discussed further in Section 3.1.4 of the ERG report.

- Was follow-up adequate?

The MS states “Yes” – patients are to be followed up until death (MS p27). The ERG agrees that this is an appropriate follow-up period.

- Were the individuals undertaking the outcomes assessment aware of allocation?

Investigators and study staff were aware of allocation (once treatment groups had been received from RAMOS). A blinded IRC reviewed all objective evidence (e.g. radiological scans and medical photographs from all patients whether or not the investigator had reported progression) to determine response and progression. An independent statistician performed the analysis of the data that was then submitted to IDMC for review. The primary endpoint was based on the independently-assessed TTP.

The MS does not state clearly how the investigator and review committee assessments for the secondary outcomes were used, and in particular notes that the investigator (not blinded) was responsible for the detection and documentation of events meeting the criteria and definition of an AE and an SAE (MS p33). An IDMC reviewed safety and efficacy data to provide an opportunity for early study termination (MS Section 5.3.5.4 p34).

- Was the design parallel-group or crossover? Indicate for each crossover trial whether a carry-over effect is likely.

Design was parallel – however, when study enrolment was halted early after the interim analysis, women in the capecitabine arm alone were offered the option of switching to lapatinib plus capecitabine and continuing in the study after the 3 April cut-off (MS p31). Data in the MS are from the parallel phase of the trial, and no data following the cross-over are included in the analyses.

- Was the RCT conducted in the UK (or were one or more centres of the multinational RCT located in the UK)? If not, where was the RCT conducted, and is clinical practice likely to differ from UK practice?

The MS states that this was a global study with sites in N. America, S. America, S. Africa, Hong Kong, Australia and Europe, including 12 UK sites which recruited 43 patients (approximately 10% of the total study population). The study was carried out to reflect standard therapeutic practice for the management of relapsed metastatic breast cancer across the countries in which

it was conducted. The MS did not state how many centres there were in total, or how many in each study location.

- How do the participants included in the RCT compare with patients who are likely to receive the intervention in the UK? Consider factors known to affect outcomes in the main indication, such as demographics, epidemiology, disease severity, setting.

The MS states that patients are similar. Patients in the RCT were HER2+ and required to have had prior therapy with an anthracycline and a taxane in either the adjuvant or metastatic settings, plus trastuzumab for metastatic disease. This is slightly more restrictive than the patient group described in NICE's scope, which does not stipulate prior trastuzumab in the metastatic setting.

The demographic characteristics of the patients in the RCT were representative of the characteristics expected of this population in the UK. The median age of the total RCT population was 52 years which is similar to that seen in a metastatic breast cancer population progressing on trastuzumab in UK clinical practice (median in range 56-60 years, see Appendix 9.4.1.1) although the clinician consulted by the ERG suggested that UK patients might be slightly older than the trial participants. This observation is not unusual since there is a tendency for RCT participants to be slightly younger and fitter people than those who might be treated in routine clinical practice. The performance status of the RCT and real-life populations is also similar (ECOG PS of 0 or 1).

The ERG found that the table of baseline characteristics (table p29) provided in the MS highlighted a few minor anomalies related to prior trastuzumab. Inclusion criteria for the trial (MS p28) involved prior trastuzumab for at least 6 weeks, [redacted]

- For pharmaceuticals, what dosage regimens were used in the RCT? Are they within those detailed in the Summary of Product Characteristics?

The MS states lapatinib 1250mg daily on a continuous basis plus capecitabine 2000mg/m^2 on days 1-14 of a 21-day cycle, versus capecitabine 2500mg/m^2 on days 1-14 of a 21-day. The dosage in the combination arm was based on the optimally tolerated regimen (OTR) identified in

a phase I study (EGF100051) and is the proposed SmPC recommendation. The dosage in the capecitabine monotherapy arm is consistent with that recommended in the capecitabine SmPC.

- Were the study groups comparable?

The MS says “Yes” but does not state whether or not the company formally looked for statistically significant differences between their groups.

[redacted]

- Were the statistical analyses used appropriate?

The MS says “Yes”, and the ERG agrees that statistical analyses of the EGF100151 data were generally appropriate, although the incidence of brain metastases as a first site of relapse was examined in a post-hoc analysis (MS p32). Section 3.1.4 of the ERG report contains further detail on statistical analyses.

- Was an intention-to-treat analysis undertaken?

The MS says “Yes” and the ERG notes that this is reported in MS Section 5.4.1 Table 5.4. for the April 03 cut-off. Efficacy variables were analysed using the ITT dataset. Non-ITT analyses were carried out for safety data, restricted to only those patients who received at least one dose of the study drugs.

- Were there any confounding factors that may attenuate the interpretation of the results of the RCT(s)?

The MS states “Yes”. The study was powered at 80% to detect a 30% increase in median survival, which required 457 deaths. However, based on the superior TTP findings at the pre-planned interim analysis, the IDMC recommended halting enrolment and allowed patients receiving capecitabine alone to cross-over to lapatinib plus capecitabine.

[redacted] Therefore there is a low likelihood that a statistically significant difference in overall survival between treatment groups will be demonstrated.

[redacted]

[redacted]

3.1.4 Description and critique of manufacturer's outcome selection

The MS states that the primary endpoint of TTP is "considered by clinical oncologists and regulators to be a valid surrogate for overall survival in this setting".[21] Endpoints were assessed by an independent review committee under blinded conditions, which the manufacturer states should be more impartial than those conducted by the investigators (MS p31). The outcome measures appear to be appropriate for a review of this kind.

3.1.5 Description and critique of the statistical approach used

The study did not meet the planned population size determined by the sample size calculation on p.33 of the MS. This was due to the early termination of enrolment when the IDMC found evidence of superior efficacy of lapatinib plus capecitabine. A total of 266 TTP events were required for statistical power of 90% to detect a 50% increase in median TTP. Analysis of overall survival was planned after 457 deaths, giving statistical power of 80% to detect a 30% increase in median survival. The manufacturer states that an enrolment of 528 patients was planned to meet these requirements (MS p.33). The study was underpowered to detect a statistically significant difference between the two treatments in overall survival (MS Table 5.3, p.36).

The NEJM publication states that the final analysis would occur after 266 independently assessed disease-progression events had occurred.[9] Page 30 of the MS states that 146 investigator-identified progression events had been reported by the time of the interim analysis date of 15 November 2005. Data in the MS are from the 3 April cut-off data set, and p.23 of the MS says that "data collection from the study is still ongoing for further analyses." This appears to indicate that the 266 disease-progression events had not occurred by the time of the 3 April cut-off, in which case the analysis of TTP may not be sufficiently statistically powered.

[redacted]

An intention-to-treat population was appropriately defined as comprising all randomised subjects, and this was used for the analysis of efficacy data. Safety data were analysed for all

randomised subjects who received at least one dose of randomised treatment (i.e. not ITT). For patients who had not experienced progressive disease at the time of analyses, TTP, PFS and duration of response were censored at the date of the last independent assessment and before any alternative treatments were introduced. Patients who were still alive when overall survival was analysed were censored at the time of last contact. Data on time to response for people who withdrew with no tumour response were censored at the time of study withdrawal.

Two-sided log-rank tests and Fisher's Exact tests were used to calculate p-values for the main efficacy outcomes. Hazard ratios, odds ratios and 95% CI were also reported as appropriate. A post-hoc analysis was used to explore the incidence of brain metastases as a first site of relapse. Sub-group analyses are frequently underpowered,[22] and post-hoc sub-group analyses can be particularly misleading if the total number of other subgroups analyzed is not reported.[23] Reports of statistical significance for post-hoc subgroup analyses should be treated with caution.[24]

3.1.5.1 Indirect comparison

The manufacturer performed an indirect comparison to calculate the mean of median TTP values for patients treated with trastuzumab beyond progression. They used data from 11 studies which met the inclusion criteria, and these are summarised in Table 5. The studies included in the indirect comparison were not RCTs, two of them were non-comparative studies,[13,12] and some were only published as conference abstracts. Consequently, the evidence base for the studies used in the indirect comparison is rather weak. The MS contains a critical appraisal of their methodological quality in Appendix 9.6.

Only the study by Tripathy and colleagues [4] appears to have included UK patients, although that conducted by Gelmon and colleagues [5] included unspecified centres in Europe. Of the five prospective studies, there were two extension studies,[4,10,11] two observational studies,[13,14] and one non-comparative study.[12] There were six retrospective studies included in the indirect comparison.[5,15,16,18-21] The studies' patient characteristics appear to have been similar, and they are broadly similar to those in the EGF100151 lapatinib RCT. Patients in the studies by Bartsch and colleagues [13] and by Gelmon and colleagues [5] had a considerably younger median age than those in the EGF100151 trial (46 and 47 vs. 52 years). Those in the study by Stemmler and colleagues had a slightly older median age of 57 years. The other trials' patients' mean ages were very similar to those in the EGF100151 lapatinib RCT.

The manufacturer pooled data on TTP, which was the most commonly reported endpoint in the studies. The studies (or selected study arms where applicable) were weighted by the number of people contained in them. This is stated as having been on account of the lack of reporting of variance around TTP within the studies (MS p. 64). The manufacturer then calculated a weighted mean of the pooled median TTP values, its corresponding standard deviation, and the 95% CI.

The recommended approach for an indirect comparison is described in an HTA monograph by Glenny and colleagues.[25] Essentially, this involves adjusting results by their direct comparison with a common control group. In this way, the strength of the randomisation in the pooled studies is partially held. Carrying out an unadjusted comparison, i.e. simply pooling data across the treatment arms and discarding data from the comparison groups, loses the benefits of randomisation in the individual studies. Glenny and colleagues[25] found that the unadjusted method is prone to bias (especially selection bias) and providing over-precise estimates of the treatment effect.

However, it would not have been possible for the manufacturer to undertake an adjusted indirect comparison of the type recommended by Glenny and colleagues.[25] This is owing to the lack of a common comparator group in the included trials and the EGF100151 lapatinib RCT; none of the studies in the indirect comparison had a capecitabine monotherapy arm. Given that the pooled studies were not RCTs, there was no methodological benefit of randomisation to lose by using an unadjusted indirect comparison. The approach taken by the manufacturer, i.e. calculation of a weighted mean of the TTP medians from the 11 pooled studies was probably all that was possible given the lack of good quality data for this comparison. It therefore raises the question of whether such a method can be considered to have provided a sufficiently reliable estimate of TTP for the economic comparison of trastuzumab-containing regimens with lapatinib+capecitabine, in the absence of any appropriate RCTs or direct comparisons. The evidence base was weak due to the poor quality studies, and this will limit the reliability of the indirect comparison.

3.2 Summary statement of manufacturer's approach

The manufacturer's approach identified all relevant studies which met their inclusion criteria. There was one relevant RCT (EGF100151), and in addition there were three non-randomised

studies involving lapatinib monotherapy. The manufacturer's systematic review also included a capecitabine/bevacizumab RCT and 11 studies which involved the use of trastuzumab. Their initial searches included eleven more studies which were later excluded after the manufacturer revised the list of comparators. These studies were summarised in Table 9.29 of MS Appendix 9.7. Given the non-comparative nature of the studies and the fact that they did not involve lapatinib-containing regimens, it is unlikely that they would have contributed reliable data to the evidence base for this review.

The quality assessment performed by the manufacturer used the checklist suggested by NICE, and was adequate for this review. The submitted evidence generally reflects the decision problem defined in the MS, although the comparators defined in the decision problem do not completely reflect the scope issued by NICE.

The manufacturer carried out an appropriate systematic review, which identified only one RCT of relevance. Interim data from the RCT were published in the NEJM in 2006.[9] The published data were from the 15 November 2005 cut-off, whereas the data presented in the MS were from the 3 April 2006 cut-off and differ from those published in the NEJM, as shown in Table 5.15, p.43 of the MS. There is currently no peer-reviewed publication of the data which forms the evidence base for this review.

Study EGF100151 was an open-label RCT, but key efficacy outcomes were assessed by independent assessors, blinded to treatment allocation. Good quality methods of randomisation and concealment of treatment allocation appear to have been used, and efficacy analyses were carried out on the ITT dataset. These factors should minimise bias in the RCT. However, study recruitment was ended early following the IDMC's recommendation and this meant that the target population was never reached. The study was not powered to detect a statistically significant difference in overall survival, and it appears from the evidence that it would only have been powered for TTP if there had been a total of 266 TTP events by the 3 April cut-off.

[redacted]

The poor quality of the comparator studies and the consequent lack of a methodologically rigorous indirect comparison limit the reliability of the pooled estimate of TTP for trastuzumab.

3.3 Summary of submitted evidence

In this section the ERG concentrates on the outcomes of the included RCT. The additional non-RCT evidence of trastuzumab which contributed to the indirect comparison is discussed in Section 3.1.5 of this report.

3.3.1 Summary of results

Study enrolment was terminated on 3 April 2006 after the IDMC had reviewed the findings of the planned interim analysis of the primary endpoint (TTP). A total of 399 patients had been enrolled at this time (lapatinib plus capecitabine N=198; capecitabine alone n=201) and the majority (63%) were still on study drug or being followed up for survival. The results presented in the MS are from an analysis of data at the 3 April 2006 cut-off. The primary outcome and first four secondary outcomes are summarised in Table 6, with further details on other outcomes presented below. The MS also presented data from investigator-assessed outcomes, but the ERG's summary is restricted to the independently-assessed results as the independent assessors were blinded to treatment allocation.

Table 6 Summary of major outcomes

	1250mg/m^2 lapatinib + 2000mg/m^2 capecitabine	**2500mg/m^2 capecitabine monotherapy**	**Hazard or Odds ratios**	**p-value**
Primary Outcome				
Time to Progression (median)	27.1 weeks 95% CI 17.4, 49.4	18.6 weeks 95% CI 9.1, 36.9	Hazard ratio 0.57 95% CI 0.43, 0.77	*p*=0.00013
Selected Secondary Outcomes				
Progression-free Survival (median)	27.1 weeks 95% CI: 24.1, 36.9	17.6 weeks 95% CI: 13.3, 20.1	Hazard ratio 0.55 95% CI: 0.41, 0.74	p=0.000033
Overall tumour response rate	23.7% 95% CI 18.0, 30.3	13.9% 95% CI 9.5, 19.5	Odds ratio 1.9 95% CI 1.1 to 3.4	*p*=0.017
Clinical benefit rate	29.3%	17.4%	Odds ratio 2.0 95% CI: 1.2, 3.3	p=0.008
Duration of response (median)	32.1 weeks	30.6 weeks		not reported

3.3.1.1 Time to Progression

The primary endpoint of TTP is based on the assessments made by the Independent Radiological Review Committee (IRC) who were blinded to both the treatment and the investigator-determined outcome. Time to progression was defined as the interval between the

date of randomisation and the earliest date of either disease progression or death due to breast cancer. For the ITT population, the manufacturer reported a highly statistically significant difference in median TPP (weeks) in favour of the lapatinib plus capecitabine combination in comparison to capecitabine monotherapy (hazard ratio 0.57, 95% CI 0.43 to 0.77, *p*=0.00013). However, the confidence intervals for the two treatments are wide and overlap (27.1 [95% CI 17.4, 49.4] vs. 18.6 [95% CI 9.1, 36.9].

[redacted]

3.3.1.2 Progression-free Survival

PFS is defined as the time from randomisation until the first documented sign of disease progression or death due to any cause. The difference between TTP and PFS was that the latter included death from any cause rather than just breast cancer. A statistically significant difference in PFS between the treatment groups as assessed by independent review of the ITT population was reported by the manufacturer (hazard ratio: 0.55 (95% CI: 0.41, 0.74); two sided p=0.000033). The median PFS (weeks) in the lapatinib plus capecitabine group was 27.1 (95% CI: 24.1, 36.9), compared with 17.6 (95% CI: 13.3, 20.1) in the capecitabine only group.

[redacted]

3.3.1.3 Overall Response Rate

Overall tumour response rate (ORR) is defined as the percentage of subjects achieving either a complete response (CR) or partial response (PR). A CR is defined as the disappearance of all target lesions and a PR requires at least a 30% decrease in the sum of the longest diameter (LD) of the target lesions, taking as a reference the baseline sum LD. A statistically significant difference in ORR (%), as assessed by independent review of the ITT population, was reported by the manufacturer for lapatinib plus capecitabine vs. capecitabine monotherapy (23.7 [95% CI 18.0, 30.3] vs. 13.9 [95% CI 9.5, 19.5]; odds ratio 1.9, 95% CI 1.1 to 3.4, *p*=0.017).

3.3.1.4 Clinical Benefit Response Rate

Clinical benefit rate (CBR) is defined as the percentage of subjects with evidence of CR or PR or stable disease (SD) for at least 6 months (183 days). A statistically significant difference in CBR between the treatment groups as assessed by independent review of the ITT population was reported (CBR (%) in the lapatinib plus capecitabine group 29.3 vs. 17.4 in the capecitabine monotherapy group; odds ratio: 2.0 (95% CI: 1.2, 3.3); two sided p=0.008).

3.3.1.5 Median Duration of Response

Duration of response is defined as the time from first documented evidence of CR or PR until the first documented sign of disease progression or death due to breast cancer. The median duration of response in weeks is reported as assessed by independent review of the ITT population. Median duration of response in the lapatinib plus capecitabine group was 32.1 weeks vs. 30.6 weeks in the capecitabine monotherapy group. The manufacturer did not report 95% confidence intervals for median duration of response or the results of any statistical tests of significance.

3.3.1.6 Overall Survival

Overall survival (OS) is defined as the time from randomisation until death due to any cause. The detection of a survival difference has been impacted by the trial's early termination resulting in both a lower number of patients enrolled as well as the crossover of patients that occurred after recruitment to the trial was terminated at 3 April 2006. Nevertheless the MS reports that a survival effect is present early and persists. There were 55 deaths (28%) in the lapatinib plus capecitabine group and 64 (32%) in the capecitabine monotherapy group. Table 7 indicates a 22% reduction in risk of death for patients receiving lapatinib plus capecitabine relative to capecitabine alone.

[redacted]

Table 7 Overall Survival

Outcome Measure	Lapatinib + Capecitabine (N=198)	Capecitabine (N=201)	Hazard Ratio (95% CI)	Log-rank 2-sided p-value
Censored, follow-up ended Censored, follow-up ongoing	15 (8%) 128 (65%)	20 (10%) 117 (58%)	-	-
Deaths due to disease progression	53 (27%)	59 (29%)	-	-
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

* Immature data. Follow-up still ongoing for further survival analyses.

The MS speculates that had the study accrued to its recruitment target and cross-overs not occurred, a statistically significant survival benefit (expected to be at least as great as the TTP advantage) might have been observed with lapatinib plus capecitabine compared with capecitabine alone. The ERG is not able to comment on whether this speculation is valid, given the lack of data.

3.3.1.7 Incidence of Brain Metastases

A post-hoc analysis was conducted to examine the incidence of brain metastases as site of first progression.

[redacted] As discussed in Section 3.1.5, it is unlikely that there would have been sufficient statistical power for this analysis, and results should be treated with caution.[24]

3.3.1.8 Response rate by stratification factor

The *a priori* stratification factors for stage of disease and site of disease were Stage IIIB or IIIC, with T4 lesion; Stage IV / Visceral; and Stage IV / Non-visceral. Across all strata the independently-assessed response rate in the ITT population was superior in the lapatinib plus capecitabine group when compared to the capecitabine monotherapy group (Table 8).

Table 8 Response by stratification factor

	Lapatinib + capecitabine (N=198)	**Capecitabine alone (N=201)**
Overall response rate (CR or PR)	47/198 (24%)	28/201 (14%)
Stage of disease at screening		
Stage IIIb or IIIc, with T4 lesion	1/7 (14%)	0/7 (0%)
Stage IV	46/191 (24%)	28/193 (15%)
Site of disease at screening		
Visceral	37/148 (25%)	23/158 (15%)
Non-visceral	9/43 (21%)	5/35 (14%)
NA	1/7 (14%)	0/8 (0%)
Stage/site of disease		

Stage IIIb or IIIc with T4 lesion	1/7 (14%)	0/8 (0%)
Stage IV - visceral	37/148 (25%)	23/158 (15%)
Stage IV – non-visceral	9/43 (21%)	5/35 (14%)

3.3.1.9 Regression Analyses

Covariates which were not pre-specified were examined in a proportional hazards model. The covariates examined were: treatment group; number of metastatic sites; stage of disease at screening; site of disease at screening; oestrogen receptor/progesterone receptor status; time from last dose of trastuzumab to randomisation; age; and ECOG performance status. The only covariate tested that had a significant effect on the independently-assessed TTP was treatment group (hazard ratio 0.47 (95% CI: 0.32, 0.68); two sided p value <0.001).

3.3.1.10 Efficacy in sub-groups

No statistical conclusions can be drawn regarding any differences between age groups or racial groups. The number of patients older than 65 years was small, but the data do not appear to indicate any difference between the less than 65 years age group and the over 65 years age group. The majority of participants, about 90% in each group, were white. As noted under 3.3.1.10 Outcome 10, the MS also reports a post-hoc analysis on the incidence of brain metastases and states that the results [redacted]Caution should be exercised when interpreting these results, due to the post-hoc nature of the analysis and the lack of statistical power for the calculation.

3.3.1.11 Quality of Life

Changes in quality of life were assessed relative to baseline using the Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaire and the Euro QOL (EQ-5D) questionnaire. [redacted]

Functional Assessment of Cancer Therapy-Breast (FACT-B)

The FACT-B is a 37-item, self-reporting questionnaire that consists of 5 subscales (physical well-being, social/family well-being, emotional well-being, functional well-being, plus a breast cancer subscale specific to quality of life in breast cancer). The subscale scores are used to generate 3 summary scores – FACT-B total score is the sum of the five subscale scores (range

0-144), FACT-G total score is the sum of four of the five subscale scores (excluding breast cancer subscale) (range 0-108) and Trial Outcome Index (TOI) is the sum of the physical well-being, functional well-being and breast cancer subscale scores (range 0-92). For all scores/scales, a higher score indicates better quality of life.

[redacted]

EuroQOL (EQ-5D)

The EQ-5D questionnaire comprises a visual analogue thermometer (rated 0 to 100) and a multi-attribute health status measure. A UK-specific tariff was applied to data from the latter to attach utilities to health states reported in the study (Dolan 1997). A higher score indicates better quality of life.

[redacted]

3.3.1.12 [redacted]

[redacted]

3.3.1.13 Comparison of results from Geyer paper versus clinical study report

An earlier analysis of the interim results of EGF100151 (15 November 2005, n=324) was published in 2006.[9] A comparison of the results in the NEJM paper and the MS is presented in Table 5.15 of the MS (MS p43). Median TTP was longer in the lapatinib+capecitabine arm in the NEJM paper than in the 3 April 2006 dataset (36.7 weeks vs. 21.7 weeks), but the capecitabine monotherapy arm data remained fairly constant (19.1 vs. 18.6 weeks). Progression-free survival also followed this trend. However, overall survival in the group was reported to be longer in the 03 April data set than in the NEJM paper, with a median of 67.7 weeks compared with 58.9 weeks. Overall survival in the capecitabine monotherapy arm was not presented in the NEJM paper, but is reported to have been 66.6 weeks in the 3 April dataset (i.e. only 1.1 weeks less than that in the lapatinib+capecitabine group). Results for clinical benefit response rate [redacted] were similar between the NEJM publication and the 03 April dataset.

3.3.1.14 Adverse events

A summary of adverse events from the comparative RCT together with further supportive evidence on lapatinib monotherapy which comes from three non-randomised trials is presented in the MS.

RCT evidence: The MS states that overall lapatinib plus capecitabine was well tolerated. In total 97% of patients receiving lapatinib plus capecitabine versus 93% on capecitabine alone experienced an adverse event (AE), of which 87% and 82% respectively were deemed by the investigator to be treatment- related.

Common Adverse Events: The pattern of common adverse events was similar between the treatment groups. The six most common AEs were:

- Diarrhoea: more commonly reported in the lapatinib plus capecitabine arm, 65% vs. 40%. Difference in incidence between the treatment groups primarily due to an increased incidence

of grade 1 severity reports in the combination arm. Most cases of diarrhoea were transient in nature and did not result in discontinuation of treatment.

- Palmar-Plantar Erythrodysaesthesia (PPE): Incidence similar between the two groups at each toxicity grade. There was no increase in PPE incidence or severity with the addition of lapatinib to capecitabine. Most of the events were of grade 1 or 2 severity and resolved while patients were on study. However, median time to onset of PPE (40 vs. 21 days) and median duration of PPE (25.5 vs. 17 days) were both longer in the combination group.
- Nausea
- Fatigue
- Vomiting
- Rash: more commonly reported in the lapatinib plus capecitabine arm (28% vs. 14%) Difference in incidence between the treatment groups primarily due to an increased incidence of grade 1 severity reports in the combination arm. Most rash events resolved without treatment and none led to permanent discontinuation of study medication.

Serious Adverse Events (SAEs): Incidence was similar in the two treatment groups (23-24%). There were no deaths considered related to treatment in the lapatinib plus capecitabine arm. Diarrhoea was the most commonly reported SAE, occurring in 6-7% of patients in both groups. Diarrhoea led to permanent withdrawal of study medication in only 5% and 3% of subject in the combination and capecitabine alone arms respectively.

Discontinuation due to AEs: Overall the proportion of patients with AEs leading to permanent discontinuation of study medication was the same in both treatment groups (14%).

Cardiac Events: A decreased LVEF was experienced by 7 (4%) patients in the lapatinib plus capecitabine arm, and 2 (1%) patients in the capecitabine monotherapy arm. Five of the seven events in the combination group were asymptomatic. None of the events in either group led to study discontinuation.

[redacted]

[redacted]

The manufacturer also provided a summary of adverse events for comparator treatments, taken from other trials. This information is presented in pages 48-52 of the MS.

3.3.2 Critique of submitted evidence syntheses

Since only one RCT was included in the review, there was no meta-analysis. Non-RCT evidence was summarised in tables and discussed in the text, with a critical appraisal of trial quality being provided in Appendix 9.6.

3.4 Summary

On the whole, the MS appears to contain an unbiased estimate of the treatment effect of lapatinib, within the stated scope of the decision problem. The evidence presented in the MS is from a single RCT, which was generally judged to be of reasonable methodological quality using NICE's quality assessment criteria. However, enrolment to the RCT was halted early, and this had the effect of reducing the sample size to below that required by the power calculation. Consequently, the study is unlikely to have sufficient statistical power to detect a difference in overall survival.

[redacted]

Median time to progression was longer in the lapatinib+capecitabine arm than in the capecitabine monotherapy arm (27.1 weeks [95% CI 17.4, 49.4] vs. 18.6 weeks [95% CI 9.1,

36.9]), although the confidence intervals overlap. The hazard ratio reported in the MS is 0.57 (95% CI 0.43, 0.77), p=0.00013. Median overall survival was very similar between the two groups (67.7 weeks vs. 66.6 weeks for lapatinib+capecitabine vs. capecitabine monotherapy).

The comparators listed in the manufacturer's decision problem deviate from the scope issued by NICE. In particular, the manufacturer has attempted to quantify use of trastuzumab beyond progression. This is based on data from a commercial database, supplemented by data from poor quality international trials (which may not be relevant to UK practice). This does not appear to provide a particularly reliable evidence base for the use of trastuzumab beyond progression.

The indirect comparison conducted by the manufacturer uses data from rather poor quality studies, none of which included a capecitabine monotherapy arm. It was therefore not possible for the manufacturer to have conducted an appropriate adjusted indirect comparison, and the resulting unadjusted weighted mean of median TTP values might not be a particularly reliable estimate.

There is also a slight deviation from the scope in terms of the population's previous treatment. The manufacturer's criteria required patients to have received trastuzumab in the metastatic setting, whereas the scope issued by NICE stated that patients should have received prior trastuzumab. From the evidence submitted, it seems unlikely that this will have had any impact on the results of the review.

4 ECONOMIC EVALUATION

4.1 Overview of manufacturer's economic evaluation

The manufacturer's submission to NICE includes:

(i) a systematic review of published economic evaluations of lapatinib for third-line treatment of advanced or metastatic breast cancer. The search strategy to identify published literature is reported in Appendix 9.3 of the MS, and is discussed in section 3.1.1.2 of this report. Studies were included if they reported on cost-effectiveness of lapatinib and their study population related to women with advanced or metastatic or recurrent breast cancer, who have undergone previous treatment. None of the 82 abstracts identified by the searches met the pre-specified inclusion criteria mentioned above.

(ii) a report of an economic evaluation undertaken by the manufacturer, for the NICE STA process. The cost-effectiveness of lapatinib plus capecitabine is estimated relative to five alternative treatment regimes used in patients with HER2+ advanced/metastatic breast cancer who have relapsed following treatment with an anthracycline, a taxane and trastuzumab. The five comparator regimes are: capecitabine monotherapy, vinorelbine monotherapy, trastuzumab plus vinorelbine, trastuzumab plus capecitabine and trastuzumab monotherapy. These are discussed in section 6.2.3, page 73/4 of the MS. The results of the economic evaluation are presented as incremental cost per QALY gained for lapatinib plus capecitabine relative to each of the five comparator treatment regimes.

4.2 CEA Methods

The CEA uses a survival modelling methodology.[26] The structure of the model and the methodology used to evaluate the cost-effectiveness of lapatinib plus capecitabine was based closely on that adopted by Tappenden and colleagues.[27]

The results from the economic evaluation are presented for the base case assumptions of cost-effectiveness for lapatinib plus capecitabine versus capecitabine monotherapy, vinorelbine monotherapy, trastuzumab plus vinorelbine, trastuzumab plus capecitabine and trastuzumab monotherapy (Base-case model results are reported in Section 6.3.1.1, tables 6.10 to 6.14 pages: 105-108 of the MS).

4.2.1 Natural history

The model of disease progression is similar to that used in the recent NICE HTA report of the cost-effectiveness of bevacizumab in the treatment of metastatic colorectal cancer.[27] Three health states are defined in the MS:

(1) Alive prior to disease progression, on therapy
(2) Alive following disease progression, no active therapy
(3) Dead (absorbing health state)

Patients enter the model having already progressed on prior therapy for metastatic disease. In the “alive prior to disease progression health state” patients are assumed to receive one of the six included treatment regimes until they subsequently experience disease progression and/ or death. While the disease progression state is labelled “no active therapy”, the MS acknowledges (page 77) that patients are likely to receive subsequent-line or salvage therapies.

However, they suggest that the use of these therapies would not differ between the treatment groups and they have therefore been excluded from the model. Hence, no active therapy is modelled for patients in the progression state and costs applied here are for supportive care, including pain management and symptom control.

4.2.2 Treatment effectiveness

Direct evidence on the effectiveness of lapatinib plus capecitabine compared with capecitabine monotherapy was taken from the EGF100151 trial. Data reported in Table 6.4, page 81, of the MS shows a [redacted] increase in mean PFS and a [redacted] increase in OS for lapatinib plus capecitabine compared with capecitabine monotherapy. No direct evidence comparing vinorelbine or trastuzumab-containing regimens was reported in the MS. Mean PFS and mean OS with vinorelbine monotherapy was assumed to be the same as for capecitabine monotherapy. As discussed in section 3.1.5.1 of this report, the median time to progression (TTP) for trastuzumab-containing regimens was estimated in the MS by pooling data from eight studies. This value was used to estimate mean PFS, which was applied to each of the trastuzumab-containing regimens. In the base case, post-progression survival for each of the trastuzumab-containing regimens was assumed to be the same as for lapatinib plus capecitabine.

Adverse events are not included explicitly in the base case model. The utility impact of adverse events were assumed to be included in the health state valuation, used for PFS for all regimens, which was derived from patients in the EGF100151 trial (see below and discussion in section 4.4.1.2.3 of this report). The manufacturer rejected the approach of explicit modelling of the occurrence of adverse events, arguing that this would require additional assumptions (see MS section 6.2.6.1, page 85).

4.2.3 Health related quality-of-life

The principal determinant of patients' quality of life, in the model, was assumed to be disease progression. The pre-progression value (0.69) was derived using the EQ-5D in all patients, regardless of treatment arm, in the EGF100151 trial. The value following progression (0.47) was based on the statistical model developed by Lloyd and colleagues.[28] QALYs were estimated by applying these values to the mean progression-free and post-progression survival durations for each regimen. The model assumes 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.

4.2.4 Resources and costs

The MS identified nine groups of resource use to be included in the economic model (see MS, section 6.2.6, pages 86-92, also discussed in section 4.4.1.2.4 of this report). Dose data for capecitabine monotherapy and lapatinib plus capecitabine were taken from the EGF100151 trial. Dose data and frequency of treatment for vinorelbine and trastuzumab were taken from their SmPC's supplemented by assumptions on dose reductions (based on data from EGF100151 trial). Other resource use was based on data from published sources[27,29-33] (see MS, section 6.2.6.1 page 89 and section 6.2.9.2 page 99).

Unit costs were taken from the British National Formulary (BNF),[34] the manufacturers of lapatinib and vinorelbine, NHS Reference Costs (2005/06),[35] published sources[27,31-33] and an NHS Trust (see section 6.2.9.5. page 100 and section 6.2.6.1, pages 85-92 of the MS for more details).

As discussed in section 4.2.1, costs of subsequent-line or salvage chemotherapies following disease progression are not included in the model.

4.2.5 Discounting

An annual discount rate of 3.5% was applied to both costs and outcomes.

4.2.6 Sensitivity analyses

The results of one-way sensitivity analyses for selected variables are reported in Table 6.17 in the MS (section 6.3.3.1, pages 114-116). The results of probabilistic sensitivity analyses are reported in section 6.3.1.1 of the MS, following the base case results (Table 6.16 and Figures 6.7 to 6.16, pages 109-114).

4.2.7 Model validation

Approaches to validating the model are described in MS section 6.2.13, pages 103-104.

The manufacturer commissioned an external consultancy to assess the model's internal consistency – a brief outline is provided in the MS, section 6.2.12, page 104. The ERG requested a copy of the full report mentioned on page 104 of the MS, which was supplied by the manufacturer – this is briefly discussed in section 4.4.1.3 of this report.

In the absence of further clinical trials or economic evaluations of lapatinib plus capecitabine for the treatment of women with HER2+ metastatic breast cancer following progression on trastuzumab, there is limited scope for external validation of the model.

4.2.8 Results

Results from the economic model are presented as incremental cost per life year gained and incremental cost per QALY gained (see MS, section 6.3.1.1, tables 6.10-6.15, pages 105-108). The base case analysis reports an estimated incremental cost per QALY gained of £81,251 for lapatinib plus capecitabine, with capecitabine monotherapy as the comparator, and £67,847 with vinorelbine monotherapy as the comparator. In the base case, lapatinib plus capecitabine dominates each of the trastuzumab-containing regimens (i.e. it is both more effective and less costly).

Table 9 below summarises the results from the base-case scenario and the probabilistic sensitivity analysis.

Table 9 Cost-effectiveness results presented in the MS

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		
Probabilistic analysis[†]					
QALYs gained	0.173 (-0.045 – 0.470)	0.175 (-0.051 – 0.403)	0.140 (-0.097 – 0.383)	0.143 (-0.279 – 0.530)	0.138 (-0.221 – 0.540)
Incremental cost	£ 13,871 (9,178 – 19,219)	£ 11,550 (6,653 – 16,902)	£ -4,668 (-12,265 – 2,350)	£ -2,686 (-16,066 – 8,550)	£ -1,314 (-13,435– 10,174)

[†] Not reported in MS – results from ERG running PSA on models submitted by manufacturer

4.3 Critical appraisal of the manufacturer's submitted economic evaluation

4.3.1 Critical appraisal of economic evaluation methods

The ERG has considered the methods applied in the economic evaluation in the context of the critical appraisal questions listed in Table 10 below, drawn from common checklists for economic evaluation methods (e.g. Drummond and colleagues[36]).

Table 10 Critical appraisal checklist of economic evaluation

Item	Critical Appraisal	Reviewer Comment
Is there a well defined question?	?	To assess the clinical (and cost) effectiveness of lapatinib plus capecitabine compared with other agents used in pts with HER2+ advanced/metastatic breast cancer who had relapsed following treatment with an anthracycline, a taxane and trastuzumab (Section 5.9.1. page 67). • Note: the decision problem is not separately stated in the section for the Cost Effectiveness analysis (Section 6 page 71)
Is there a clear description of alternatives?	Yes	Lapatinib plus Capecitabine versus: (1) Capecitabine monotherapy (2) Vinorelbine monotherapy (3) Trastuzumab plus Vinorelbine (4) Trastuzumab plus Capecitabine (5) Trastuzumab monotherapy Drug dosages reported in Section 6.2.3.
Has the correct patient group / population of interest been clearly stated?	?	Women with advanced or metastatic breast cancer whose tumour over express HER2 and who have received prior therapy with trastuzumab in the advanced/ metastatic setting, as well as an anthacycline and a taxane as either adjuvant treatment or for metastatic disease (Section: 5.3.2.1., page 28.). • Does not exactly match the scope, which only stated that patients will have been previously treated with trastuzumab – does not specify in advanced/ metastatic state. • Patient characteristics in model are those of patients in study EGF100151 (Section 6.2.2.1., page 72). No sub-group identified by MS.
Is the correct comparator used?	?	Comparators in MS do not match those in NICE scope which states: • Standard comparators: capecitabine, vinorelbine, taxane regimes and other appropriate chemotherapy regimes in standard practice in England and Wales. Comparators stated by MS: • Capecitabine monotherapy, vinorelbine monotherapy, trastuzumab either in combination with capecitabine or vinorelbine or as monotherapy. • Note: Regimes including trastuzumab in this setting have not been licensed or proven. Lacking an alternative treatment, trastuzumab as 'rechallenge

		therapy' has been shown to be currently used in this setting (MS, Appendix 9.4 page 38).
Is the study type reasonable?	Yes	Cost-Utility study (see section 2.5. page 7) appropriate - evaluation needs to capture quality of life differences rather than just natural units (progression free time).
Is the perspective of the analysis clearly stated?	Yes	NHS and Personal Social Services (PSS) (See Section 6.2.4., page: 75).
Is the perspective employed appropriate?	Yes	• Costs: Only NHS costs included, no PSS costs included. As major difference between groups expected to relate to monitoring and administration costs incurred in NHS setting, then focus on NHS rather than PSS seems appropriate. • Outcomes: Patient perspective adopted; Progression-free survival, overall survival, quality of life weights based on response to EQ-5D and values from population survey.
Is effectiveness of the intervention established?	Yes ?	vs capecitabine Other comparators • Capecitabine monotherapy vs lapatinib plus capecitabine, direct evidence on progression-free and overall survival from study EGF100151. • For trastuzumab with or without chemotherapy: progression-free time from pooling estimates and unadjusted indirect comparison. Overall survival assumed same as lapatinib plus capecitabine due to lack of evidence. • For vinorelbine assumed same as capecitabine monotherapy due to lack of evidence. Quality adjusted life years: • QALY difference assumed between pre- and post-progression. In base-case utilities do not differ according to treatment received (hence utilities give no account of severity of adverse events or type of drug administration (e.g. IV vs. oral) across treatment regimes). The impact of the latter on health utility is explored within the one-way sensitivity analysis (see Section 6.3.3.).
Has a lifetime horizon been used for analysis (has a shorter horizon been justified)?	Yes	• Life time in the model refers to 5-year time frame. • Weilbull survival modelling used to extrapolate health outcomes of trial EGF100151.
Are the costs and consequences consistent with the perspective employed?	Yes	• Costs consistent with NHS perspective. • Consequences presented as QALYs, consistent with model perspective.
Is differential timing considered?	Yes	Costs and health benefits were discounted at a rate of 3.5% per year.
Is incremental analysis performed?	Yes	Reported in: Table 6.15, page 108.
Is sensitivity analysis undertaken and presented clearly?	Yes	Sensitivity analyses reported in MS : • One-Way Sensitivity analysis results reported in MS,

		section 6.3.3.1, pages 114-116. MS includes justification for choosing variables and explains their plausible ranges see MS, section 6.2.1.1.1, page 101. • Probabilistic Sensitivity analysis results reported in section 6.3.1.1, pages 109-114. List of all variables and their distributions used in probabilistic sensitivity analysis (see Appendix 9.8.). For further details see Ms, section 6.2.11.2., page 103.

NICE reference case

Table 11 NICE reference case requirements

NICE reference case requirements (see detail in NICE report)**:**	Included in Submission
Decision problem: As per the scope developed by NICE	?*
Comparator: Alternative therapies routinely used in the UK NHS	?§
Perspective on costs: NHS and PSS	✓
Perspective on outcomes: All health effects on individuals	✓
Type of economic evaluation: Cost effectiveness analysis	✓(CUA)
Synthesis of evidence on outcomes: Based on a systematic review	?#
Measure of health benefits: QALYs	✓
Description of health states for QALY calculations: Use of a standardised and validated generic instrument	✓
Method of preference elicitation for health state values: Choice based method (e.g. TTO, SG, not rating scale)	✓
Source of preference data: Representative sample of the public	?¶
Discount rate: 3.5% pa for costs and health effects	✓
Notes: * Decision problem is not clearly stated in cost-effectiveness section. § Comparators defined by NICE scope differ to comparators stated in MS. # A systematic review was undertaken for survival outcomes but not for QALY outcomes. ¶ QALY estimates not based on comprehensive systematic review.	

4.4 Modelling methods

An outline critical review of modelling methods has been undertaken. The review has used the framework for good practice in modelling presented by Philips and colleagues[37] as a guide, addressing issues of model structure, structural assumptions, data inputs, consistency, and assessment of uncertainty.

4.4.1 Modelling approach / Model Structure

The basic structure of the model is presented in section 6.2.6.1 of the MS, page 76, and has been discussed briefly in section 4.2.1 of this report.

None of the strategies modelled represents a true natural history of disease progression, with supportive care, but estimate the impact of treatment options on disease progression and overall survival. As discussed in section 4.2.2, PFS and OS with capecitabine monotherapy

were treated as the baseline estimates. OS and PFS for other options were estimated by applying a treatment-specific hazard ratio, estimated by a variety of methods, to the survival models for capecitabine. The model assumes that all patients are eligible for, and would accept, each of the available treatments.

The adoption of a survival modelling approach to estimating cost-effectiveness contrasts with previous economic evaluations of treatment for women with advanced and metastatic breast cancer[38-42] which have typically used Markov models. The MS briefly discusses the similarities between survival models and state transition models. However there is no detailed discussion of the relative merits of alternative modelling strategies or their likely impact on the findings. The discussion is limited to the observation that the survival modelling approach is based on direct modelling of data from clinical trials, without additional assumptions (such as the assumption, common in Markov models of breast cancer chemotherapy, that patients would need to experience disease progression prior to death) that would be required within the Markov framework.

The survival model for each comparator is found on a separate Microsoft Excel worksheet[ii]. These are named *'Trm_CapStg'* for capecitabine monotherapy and *'Trm_LapStg'* for capecitabine + lapatinib in the worksheet named **"1. Final Tyverb model 050407 capecitabine monotherapy.xls"** which includes the cost-effectiveness model for capecitabine plus lapatinib compared with capecitabine monotherapy. Values of gamma and lambda for models of progression-free survival and overall survival reported in the MS (Table 6.2, page 78), entered on the *'Analyze'* worksheet, were used to derive the PFS and OS survival curves. These curves were used to calculate the daily proportion of patients alive and the daily proportion of patients who had not progressed for each comparator up to the model time horizon of five years - the proportion of patients with disease progression was estimated as the difference between these two values. Mean PFS and OS duration were estimated as the sum of these daily proportions.

[ii] Three Excel spreadsheets were submitted to the ERG:
"1. Final Tyverb model 050407 capecitabine monotherapy.xls", reporting the comparison of lapatinib with capecitabine against capecitabine monotherapy
"2. Final Tyverb model 050407 vinorelbine monotherapy.xls", reporting the comparison of lapatinib with capecitabine against vinorelbine monotherapy
"3. Final Tyverb model 050407 trastuzumab plus vinorelbine.xls", reporting the comparison of lapatinib with capecitabine against vinorelbine in combination with trastuzumab.
The ERG derived spreadsheets for the remaining two comparisons by altering input values on the supplied spreadsheets.

Discounted mean survival duration were estimated by applying daily discount rates to the daily proportions and then summing the discounted daily proportions and discounted QALYs derived by applying state-specific utilities to the discounted mean PFS and post-progression survival durations.

The MS describes the model as having a lifetime horizon which was assumed to be five years. Typical estimates of life expectancy for women with advanced or metastatic breast cancer are in the range 18 months[43] to three years,[44,45] though life expectancy may be reduced by as much as 50% for patients with tumours over-expressing HER2.[43] When the model terminates there is less than 1% of the cohort in either of the "alive" states, the vast majority of which are in the post-progression state.

Sources of data used to develop and populate the model structure are clearly specified. These are principally two previous assessments reports on chemotherapy for advanced/ metastatic colorectal cancer[27,31] for the survival modelling methodology and the EGF100151 trial for the survival functions for PFS and OS. The majority of non-drug costs are based on data from the assessment reports[27,31] and from a cancer physician panel estimating costs of managing women with metastatic breast cancer.[33]

4.4.1.1 Structural Assumptions

The MS states that the use of a model structure based on progression-free and post-progression health states was selected as this is consistent with the clinical outcomes used within oncology trials, specifically study EGF100151. As patients typically remain on treatment until their disease progresses, there are clear cost differences for pre-and post-progression health states. In addition, whilst a number of different factors may influence a patient's health-related quality of life, evidence suggests that the presence of disease progression is a key determinant of health utility[28,46].

The MS contains little detail on the development of the model structure and makes no explicit reference to its clinical validation. The model structure is based on an established methodology and has been applied in assessment of metastatic colorectal cancer, but does not appear to have previously been applied in metastatic breast cancer. Review of the modelling approach by clinical experts would offer reassurance that all relevant aspects of the disease and its treatment have been captured. Section 6.2.3 states that the "model structure is intuitively sensible from a

clinical perspective" but it is not clear whether this is statement of belief or whether the model was subjected to clinical review. In discussing the validation of the model and the submission the MS refers to peer review by two academic health economists (though no detail of the review process or criteria used to assess the model or submission is provided). However this would not be adequate to establish the model's clinical relevance and validity

The modelling approach adopted in the submission differs from that used in previous economic evaluations of treatment for women with advanced and metastatic breast cancer[38-42] which have used Markov models. In the MS, the only discussion of the relative merits of alternative modelling strategies is focused on the advantages of the survival modelling method over Markov models. Features of previous models that have been excluded from the current model are explicit modelling of tumour response (which principally affects quality of life, see Table 12 in this report) and adverse events. A review of existing economic studies of treatment for women with advanced and metastatic breast cancer and more detailed discussion of alternative modelling approaches would have provided a more robust justification of the modelling approach adopted.

4.4.1.2 Data Inputs

4.4.1.2.1 Patient Group

The base case analysis uses patients meeting the inclusion criteria for the EGF100151 trial. This broadly corresponds to the final scope issued by NICE and the draft SPC for lapatinib, see section 2.3.1. As discussed in section 3.1.5.1, the MS estimated the median time to progression for trastuzumab-containing regimes using data external to the EGF100151 trial, by pooling median TTP from eight studies. It is difficult to determine how comparable patients in these studies are to those in the EGF100151 trial, since very limited baseline data are available for those studies reported as abstracts (see section 3.1.5.1 for further discussion). The median age of patients in the included studies ranged from 46 to 57 years, which is broadly comparable to the EGF100151 lapatinib trial [redacted].

The model does not have patient characteristics as model inputs, other than mean body surface area (BSA) and mean weight. The use of these inputs in the model to estimate drug dosages and wastage for infusional regimens is discussed more fully in section 4.4.1.2.4. None of the efficacy or health state utility parameters in the model are age-related – age is not explicitly included in the model.

The assessment of clinical effectiveness in the MS did not identify any significant differences between age groups or racial group (section 5.4.6 of MS, page 41, also see section 3.3.1.10 of this report). No sub-groups were included in the economic model.

4.4.1.2.2 Clinical Effectiveness

Direct evidence on the effectiveness of lapatinib plus capecitabine compared with capecitabine monotherapy used in the economic model was derived from the EGF100151 trial. Weibull survival models for overall survival (OS) and progression-free survival (PFS) for capecitabine monotherapy were used to estimate mean OS and mean PFS – equivalent to the area under the curves presented in Figure 6.3 and Figure 6.4 on page 79 of the MS. Hazard ratios for the remaining regimens, relative to capecitabine monotherapy, were applied to these survival models to estimate the mean OS and mean PFS for each regimen. The hazard ratio for lapatinib plus capecitabine was derived for patients in the EGF100151 trial.

In the absence of data on the relative effectiveness of vinorelbine in this patient population, the MS assumed the survival model for capecitabine monotherapy could be applied for vinorelbine monotherapy. Thus mean PFS and mean OS for vinorelbine monotherapy and capecitabine monotherapy were identical, and were estimated using EGF100151 trial data for capecitabine monotherapy. Clinical advice to the ERG suggests that this is a reasonable assumption in the absence of robust evidence.

In the absence of comparative data on trastuzumab-containing regimens the MS reports a pooled estimate of median TTP (discussed in section 3.1.5 of this report). This value is assumed to be a reasonable estimate of PFS – based on an unpublished analysis of the relationship between TTP and PFS. The pooled estimate of median TTP (21.8 weeks, or 153 days, which lies between median PFS for capecitabine monotherapy (122 days) and median PFS for lapatinib plus capecitabine (189 days)) was substituted into the Weibull survival function for progression free survival and solved for the hazard ratio[iii]. This hazard ratio was used to estimate the mean OS and mean PFS for all trastuzumab-containing regimens in the economic

[iii] If median TTP is 21.8 weeks (page 65 of MS) or 152.6 days, then substituting into the model of progression-free survival (for capecitabine lambda = 0.0058 and gamma = 1.3920, MS Table 6.2, page 78) implies $0.5 = \exp(-(0.0058*HR*152.6)^{1.392})$, where HR is the hazard ratio for trastuzumab-containing regimens. This implies a hazard ratio of 0.8653 for trastuzumab-containing regimens, which was applied in the economic model.

model. Mean post-progression survival was assumed to be the same as for lapatinib plus capecitabine giving an estimated mean OS of 487 days or 1.33 life years.

4.4.1.2.3 Patient outcomes

QALYs were estimated by applying state-specific utilities to the mean duration spent in each health state (pre and post-progression) for each of the six included treatment groups. No systematic search of the literature on health state utility values for women receiving treatment for metastatic breast cancer was undertaken for the MS (see MS, section 6.2.8.2, page 98), nor are the sources used to obtain utility data applied in the model critically appraised or assessed for external validity.

The cost-effectiveness model assumed that the principal determinant of patients' quality of life is whether they experience disease progression. This assumption seems reasonable as a lower utility value associated with disease progression has been reported in several studies (Cooper and colleagues,[40] Launois and colleagues,[42] Hutton and colleagues,[41] Brown and Hutton,[38] Brown and colleagues,[39] Lloyd and colleagues.[28] However the extent of the utility loss due to progression assumed in the model, reduction of 68% from pre-progression value, has not been compared with that estimated in other studies with the same patient group, see Table 12. To test the impact of this assumption the MS included a sensitivity analysis where the utility reduction associated with disease progression was set to zero. This had very little impact, slightly increasing the ICER for lapatinib plus capecitabine when compared with capecitabine or vinorelbine as monotherapies. Setting the utility reduction associated with disease progression to zero had no effect on the comparison with trastuzumab-containing regimes, since the MS assumed that post-progression survival duration for these regimes was the same as for lapatinib plus capecitabine.

Table 12 Health state utilities reported in MS and other published economic evaluations

Utility weights	Submission	Lloyd and colleagues[28]	Cooper and colleagues[40]	Launois and colleagues[42]	Hutton and colleagues[41]	Brown and Hutton[38]	Brown and colleagues[39]
Response	0.69	0.791	0.81	0.81	0.81	0.81	0.84
Stable		0.715	0.65	0.75	0.62	0.65	0.62
Progression	0.47	0.444	0.45	0.65[§]	0.41[†]	0.39[†]	0.33[*]

Notes:
[§] utility value of 0.16 for terminal disease (Markov cycle immediately prior to death in progressive state)
[†] utility value of 0.16 for terminal disease (Markov cycle immediately prior to death in progressive state)
[*] utility value of 0.13 for terminal disease (Markov cycle immediately prior to death in progressive state)

Markov models of treatment for metastatic breast cancer have typically included a marked deterioration in utility for the terminal stage. In the examples in Table 12, the reduction was applied in the model cycle immediately prior to death (model cycles were three weeks to correspond with the duration of chemotherapy cycles). Such a utility reduction is difficult to apply when using the survival modelling technique.

[redacted]

The post-progression utility estimate used in the cost-effectiveness model was derived using the statistical model reported by Lloyd and colleagues[28]. This study elicited valuations for 15 health state descriptions relevant to people with metastatic breast cancer, with or without treatment-

related toxicity, using the standard gamble technique. Data from the study suggest that disease progression has the largest impact on utility values (reducing utility values by 0.272, from a value of 0.715 for a patient aged 38.2 with stable disease and no toxicity). The utility reduction associated with disease progression is approximately double the utility loss associated with treatment-related toxicity and over three times the utility gain from response to treatment. The utility loss due to progression was estimated from the statistical model reported by Lloyd and colleagues[28] using the mean age of patients in the EGF100151 trial – see Equation 1, below. It was necessary to re-estimate post-progression utility, rather than use the published value (reported in Table 12, column 3) since Lloyd and colleagues[28] indicated that utility values were positively correlated with age.

Equation 1 Statistical model of utility effect of disease progression in metastatic breast cancer Lloyd and colleagues[28]

$$\frac{\exp(0.008871 + 0.0239 * age - 1.1477)}{1 + \exp(0.008871 + 0.0239 * age - 1.1477)}$$

At the mean age for all patients in the EGF100151 trial the utility reduction following disease progression calculated using Equation 1 is [redacted]. The MS reports that a probabilistic analysis (using 1,000 iterations) was used to determine the mean utility reduction associated with disease progression, and the standard error of the mean. This estimated the mean utility reduction associated with disease progression at 0.319. It is difficult to interpret the slight difference between our estimate of the utility reduction and that reported in the MS, since they do not report the distributions they assumed for the coefficients nor how they were parameterised. These values may over-state the utility reduction due to disease progression since Lloyd and colleagues[28] demonstrated a significant sex-by-progression interaction in their model, with men placing greater disutility on disease progression compared with women. Recalculating the utility reduction, taking account of the sex-by-progression interaction gives a lower utility reduction [redacted] for women than for a mixed sex cohort [redacted].

The MS assumes that pre- and post-progression utility values do not differ according to the type of treatment received. This assumption has been made in previous economic evaluations of chemotherapy for metastatic breast cancer and the appropriateness reviewed by clinical experts. It has generally been accepted that this assumption is reasonable, provided the utility

impact of adverse event profiles for different drugs regimens are captured. The MS assumes that the EQ-5D results for the lapatinib plus capecitabine and capecitabine monotherapy arms of trial EGF100151 have captured the disutility of side effects. Applying a health state valuation that includes disutility due to side effects is likely to be an under-estimate for trastuzumab monotherapy, given the high tolerability of the regimen.

4.4.1.2.4 Resource use

The model distinguishes between the costs of care incurred whilst patients are free from disease progression (and receiving active treatment), and the costs associated with resources consumed following disease progression. The MS does not report whether a systematic search for data on resource use for patients with metastatic breast cancer receiving chemotherapy, having progressed on trastuzumab, was undertaken, nor are the sources for obtaining resource use data discussed. The approach to costing interventions and the categories of resource use identified appear to have been based on the assessment report by Tappenden and colleagues[27]. However this is not acknowledged in the MS. The majority of resource use was estimated using data from sources other than the EGF100151 trial.

Nine groups of resource were identified and costed in the economic model (see MS, section 6.2.6, page 86-92 for details):

1) Drug acquisition;
2) Hospital resources for chemotherapy administration;
3) Pharmacy costs;
4) Management of adverse events;
5) Diagnostic and laboratory tests;
6) Clinical consultations;
7) Radiotherapy;
8) Other special interventions e.g. blood transfusions;
9) Monitoring (due to increased risk of cardiotoxicity) of patients receiving trastuzumab and lapatinib.

This list of identified resource groups seems comprehensive and such resource use elements have been identified previously in the metastatic cancer setting (e.g. see studies included by the MS such as Tappenden and colleagues[27], Remak and Brazil[33]). These agree with the

categories of resource use identified in previous economic studies of treatment for patients with metastatic breast cancer.

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 EGF100151 trial. Drug dosage and frequency of treatment were based on those in the EGF100151 trial for lapatinib plus capecitabine (and which is the proposed SmPC recommendation for this combination), the product label for capecitabine monotherapy, vinorelbine monotherapy (and for the latter two agents in combination with trastuzumab) and for trastuzumab (which was also based on NICE guidance on the use of trastuzumab for the treatment of advanced breast cancer). Relative dose intensity (RDI) adjustments were applied to the drug dosages and frequency of treatment based on data observed in the EGF100151 trial. An RDI for daily dose adjustments was estimated to take account of differences between the planned and actual dose prescribed. Observed daily dose adjustments for lapatinib and capecitabine separately within the combined regimen and for capecitabine monotherapy were derived using data from the EGF100151 trial. The observed dose adjustments for lapatinib plus capecitabine were treated as applicable for all combination therapies. Similarly the observed dose adjustments for capecitabine monotherapy were treated as applicable for all single agent therapies (including trastuzumab monotherapy). The estimated drug acquisition costs per cycle, with and without dose adjustments, are as shown in Table 13.

Table 13 Drug acquisition costs per cycle

	Lapatinib + capecitabine	Capecitabine monotherapy	Vinorelbine monotherapy	Trastuzumab + capecitabine	Trastuzumab + vinorelbine	Trastuzumab monotherapy
Cost per cycle (no RDI adjustment)	£ 1,399	£ 305	£ 143	£ 677	£ 839	£ 455
Cost per cycle (RDI adjustment)	£ 1,082	£ 249	£ 134	£ 537	£ 636	£ 428

For each regimen the costs of drug wastage are also calculated, with different assumptions applied to the infusional (found on *"Dose_Wastage"* worksheet and briefly described on page 88 of MS) and oral regimens (described on page 88 of the MS). To calculate mean number of vials required for trastuzumab, with wastage, a weight distribution was inferred from the mean weight and standard deviation (the standard deviation is presumably taken from trial data, though this

isn't identified in the spreadsheet or in the MS) assuming that weight has a lognormal distribution. The minimum weight was assumed to be two standard deviations below the mean (40.50 kg) and the maximum weight was assumed at 99.99% of cumulative log-normal distribution (144.08 kg). The ERG estimated the mean of this distribution at 71.22 kg. Under these assumptions, around 31% of patients have a body weight requiring greater than one 150 gm vial of trastuzumab, and the weighted mean dose, with wastage, is 196.76 mg. A similar calculation was undertaken to estimate the weighted mean dose for vinorelbine, with wastage, using an inferred distribution for BSA. It is not clear why the weight and BSA distributions from the EGF100151 trial were not used directly, rather than inferring distributions based on the trial mean and standard deviation. Alternatively, a simpler calculation could have been adopted using mean BSA and mean weight for the base case and assessing the effect of variation in these parameters in the sensitivity analysis.

Assumptions concerning the frequency of hospital attendances for infusional treatment regimens (i.e. trastuzumab-containing regimes and vinorelbine monotherapy) in the model were based on SmPCs and NICE guidance, which suggest that treatment should be weekly. Clinical advice to the ERG suggests that this would not be the typical pattern of practice in England and Wales, where trastuzumab would normally be given every three weeks, at a dose of 6mg/m^2. This pattern of treatment was applied in a sensitivity analysis reported in the MS.

The majority of non-drug, or drug administration, resource use elements identified in the model were estimated using a study of the costs of managing women with metastatic breast cancer in the UK.[33] In the study information on resource use and treatment patterns was collected in a survey to a panel of cancer physicians. Twenty one questionnaires were mailed and, of these, 17 (81%) were completed and returned.[33] Use of diagnostic and laboratory tests, clinical consultations and hospital admissions (besides those included in the chemotherapy administration costs), radiotherapy, and other special interventions (e.g. blood transfusions) were assumed to be the same for each treatment regimen (this assumption is adopted from Remak and Brazil[33]). Resource use for those items was not identified, measured and costed separately. Instead the MS adopts average monthly cost per patient from Remak and Brazil[33], separately identifying and costing resource use in the pre- and post- progression period. The generalisability of the Remak and Brazil[33] survey 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.[38-42]

Resource use information on cardiac monitoring, due to increased risk of cardiotoxicity for patients receiving either trastuzumab or lapatinib, in the model was derived from a previous ERG report[32] which was concerned with trastuzumab for early breast cancer. It was assumed in the MS that resources for cardiac monitoring of patients receiving lapatinib would be the same as for trastuzumab.

4.4.1.2.5 Costs

Unit costs for drugs are taken from BNF (no 52)[34] – with the exception of lapatinib which has no UK price and was therefore costed in the MS at the manufacturer's estimate and vinorelbine where sources reported in the MS are inconsistent (see below).

Hospital pharmacy unit costs for supplying oral treatments and for preparing infusions were taken from two previous assessment reports on cancer chemotherapies.[27,31] Unit costs for diagnostic and laboratory tests, clinical consultations and hospital admissions (besides those included in the chemotherapy administration costs), radiotherapy, and other special interventions (e.g. blood transfusions) were taken from Remak and Brazil.[33] Unit costs for cardiac monitoring for patients receiving either trastuzumab or lapatinib were taken from the ERG report by Ward and colleagues on trastuzumab for early breast cancer.[32]

The model adopted an NHS and Personal Social Services perspective. All costs are expressed at 2006 prices - where 2006 prices were not available, these have been uplifted using the Hospital and Community Service Prices Index.[47]

The ERG has noted an inconsistency in the MS between the body of the text and Table 6.9 (see MS, section 6.2.6.1, page 91) giving sources for unit cost estimates. Text on page 86 states that all drug unit costs (except for lapatinib) were obtained from the BNF (no 52)[34] and the unit cost for vinorelbine is stated as £2.80 per mg. However, Table 6.9 (MS section 6.2.6.1, page 91) gives a slightly lower estimate of the unit cost (£2.79 per mg) and gives the source as "Personal communication (Wockhardt UK)". We could not find a full reference to Wockhardt in the MS reference list and no date is given. The cost for a 5-mL vial of vinorelbine, at a concentration of 10mg/mL, in BNF, no 52 is £139.98, not £139.70 as stated in Table 6.6, page 86 of the MS.

However dividing £139.98 by 50 gives a cost per mg of £2.80 as stated in Table 6.6 of MS. The cost differences are very small and this inconsistency will not affect the results reported in the MS.

On page 88 of the MS it is stated that the hospital administration costs for infusional therapies (i.e. trastuzumab and vinorelbine) have been obtained from 2006 NHS Reference Costs. However, Table 6.9 in the MS states that the unit cost for hospital administration of trastuzumab was taken from Ward and colleagues[32]. The ERG checked this source and found a different unit cost for trastuzumab administration (of £117 compared to the £207.22 adopted for the base case of the MS). The ERG report sensitivity and scenario analyses using the trastuzumab administration costs estimated by Ward and colleagues[32], see sections 4.4.1.4.1 and 0.

4.4.1.3 Consistency

Internal consistency

Random checking has been conducted for some of the key equations in the model, for example on sheets *''Trm_CapStg"*, *'Trm_LapStg*' and *'Trm_TrastStg'* which contain the survival models for each regimen. However, the ERG has not undertaken a comprehensive check of all cells in the model. The model is fully executable and inputs changed on the *'Analyze'* sheet or *'ParameterDerivation'* produce immediate changes on the appropriate results sheet (*'Trm_CapStg'* for capecitabine monotherapy, *'Trm_LapStg*' for lapatinib plus capecitabine and *'Trm_TrastStg'* for vinorelbine monotherapy and trastuzumab-containing regimens). Selecting the "Base-Case Results" button on the *'Analyze'* sheet copies the model outputs for the selected comparators to the *'BaseCaseResults'* worksheet. The *'Analyze'* sheet can also be used to replicate some of the univariate sensitivity analyses for the base case model, as reported as scenarios in Table 6.17 of the MS, however some discrepancies were found (detailed below) when using the "one way sensitivity analysis" button on the '*Analyze'* sheet.

The model is generally well presented and user-friendly, with analysis being controlled by buttons on the *'Analyze'* sheet. This sheet also includes drop-down selection boxes for selecting variables for one- and two-way sensitivity analyses, with input boxes to set the initial and final values for selected parameters. The workbook includes separate worksheets that contain the base case results, results from the most recently conducted one- and two-way sensitivity analyses and outputs from the probabilistic sensitivity analysis (also controlled by a button and

input boxes on the *'Analyze'* sheet. There is limited documentation in the workbook and no indication of where the workings of the survival model are found.

The manufacturer commissioned Oxford Outcomes to undertake a validation of the model. The procedure adopted was to produce a new version of the model, referred to as the validation model, according to the original model specification. The results from the validation model were compared with those from the original model, for a range of scenarios and also tested using extreme values. The models were used to perform comparisons of lapatinib plus capecitabine with capecitabine monotherapy and with trastuzumab. The report of the validation exercise – which was made available to the ERG, following a request to the manufacturer – stated that the validation model produced identical results to the original model and that no critical issues were identified. A number of recommendations were made regarding the transparency and usability of the model – including comments on some unnecessary complexity in the model and a heavy reliance on visual basic coding, which the ERG would agree with.

The ERG has discovered an inconsistency when using the "One Way Sensitivity Analysis" button on the *'Analyze'* sheet. Using the One Way Sensitivity Analysis button to test the impact of variation in input parameters does not produce the same results as directly changing values on model input sheets. For example, to check values reported in Table 6.17, page 114-116 of the MS, the ERG entered the reduced price for lapatinib under scenario 1 (£10.45 per tablet rather than £11.00). The One Way Sensitivity Analysis reported an ICER of £78,018 for lapatinib plus capecitabine compared with capecitabine momotherapy, rather than £77,781 as reported in Table 6.17. Similar, slight discrepancies were found in the models for all comparators using the One Way Sensitivity Analysis functionality built into the model. However entering price reductions or increases on the *'ParameterDerivation'* sheet (where the unit cost for lapatinib was stored) returns the ICERs reported in the MS. The ERG has been unable to establish the reason for this discrepancy, due to the model's high reliance on Visual Basic for performing the sensitivity analysis.

External consistency

The MS structures the discussion of the validity of the model in the context of Eddy's four levels of model validation[48] – the second level, internal concurrence, has been discussed in the previous section. In addressing the first level, concurrence of clinical experts, the MS entirely relies on the use of survival models derived from clinical trial data and the adoption of an

established modelling approach to state that the “model structure is intuitively sensible from a clinical perspective”. However, no evidence is presented in the MS that the model structure or the assumptions adopted where evidence was lacking has been subjected to clinical scrutiny. On page 104 the MS states that the model and submission have been subjected to peer review by two academic health economists, but no further detail is given on the scope of this review nor the criteria used to establish the model’s validity.

The third and fourth levels of validation concern the ability of the model to predict non-modelled data sources. Given the absence of further clinical trials or economic evaluations of lapatinib plus capecitabine for the treatment of women with HER2+ metastatic breast cancer following progression on trastuzumab, there is limited scope for validation against external data sources. However the MS includes comparisons of the modelled PFS and OS survival functions and the observed Kaplan-Meier estimates (Figures 6.3 and 6.4 in the MS for capecitabine monotherapy and Figures 6.5 and 6.6 for lapatinib plus capecitabine). Plots of these functions suggest that the modelled survival functions fit the data well and goodness of fit statistics suggest that Weibull functional form is appropriate. An additional validation, reported in Table 6.4 (page 81) in the MS, involves comparison of the mean and median survival durations (PFS and OS) using the Kaplan-Meier curves against the proportional hazards model. The mean survival durations are generally similar. However there are discrepancies in the median survival durations, especially for overall survival.

The method for deriving the PFS hazard ratio for trastuzumab-containing regimes against capecitabine monotherapy is described on page 83 of the MS and outlined in section 4.4.1.2.2 of this report. To examine the validity of this approach to estimating the hazard ratio from median survival, the median PFS for lapatinib plus capecitabine (189 days) was substituted into the PFS survival function and solved for the hazard ratio. This gives a higher PFS hazard ratio (0.6987) for lapatinib plus capecitabine against capecitabine monotherapy than the regression analysis reported in the MS (0.6085). Mean PFS is approximately 33 days lower using the former hazard ratio for lapatinib plus capecitabine.

4.4.1.4 Assessment of Uncertainty

4.4.1.4.1 One-way sensitivity analyses

The MS presents sensitivity analyses for a range of methodological (assumptions in survival model and discount rates) and parameter (drug regimens, efficacy, adverse event costs, health state utility and health state costs) uncertainties in Table 6.17 in the MS. The choice of variables included, and the alternative values applied, in this sensitivity analysis are discussed in section 6.2.11.1 of the MS. These relate to uncertainties over efficacy data (scenarios 11 to 14), dosing regimens, dose adjustments and drug wastage (scenarios 3 to 10), utilities (scenarios 15 to 17) and costs (scenarios 1, 2, 19 and 20) – fuller details in Table 14 below. The majority of these analyses have been conducted by replacing base case values with alternative assumptions – the exceptions are the cost of lapatinib (varied by approximately ± 5%) and health state costs (varied by approximately ± 25%).

The majority of the analyses presented in Table 6.17 in the MS are univariate – applying an alternative assumption for a single model parameter. The exception is scenario 10 which includes alternative assumptions on the dosing of both vinorelbine and trastuzumab.

Table 14 Scenarios included in manufacturer's sensitivity analysis

Parameter type	Scenario	
Costs	1 & 2.	Vary price for lapatinib approximately ± 5%
	18.	Include additional cost of managing adverse events for the lapatinib plus capecitabine groups
	19 & 20.	Vary health state costs ± 25%
Dosing regimens, adjustments and wastage	3.	Assume capecitabine dose of 2000mg/m^2 when combined with trastuzumab
	4.	No dose adjustments (RDI = 100%).
	5:	Exclude wastage.
	6:	Assume patients who continue trastuzumab receive loading dose of 4mg/kg.
	7.	Patients receive vinorelbine on days 1 and 8 of a 21-day cycle.
	8.	As scenario 7, but patients stop vinorelbine after 6 cycles.
	9.	Trastuzumab given every 3 weeks (6mg/kg) rather than weekly (2mg/kg).
	10.	Combination of scenarios 7, 8 and 9.
Efficacy	11.	Progression-free survival duration for trastuzumab-containing regimens is equal to that for capecitabine monotherapy in EGF100151
	12.	Progression-free survival duration for trastuzumab-containing regimens is equal to that for lapatinib plus capecitabine.
	13.	Use independent, rather than proportional, hazards in event rates between treatment groups.
	14.	Use investigator-assessed, rather than independent, progression-free outcomes - using separate statistical analysis of time-to-event data from study EGF100151, including an adjustment of the RDI parameters.
Utility	15.	No utility loss with disease progression.
	16.	Utility for pre-progression (0.715) and post-progression (0.443) health states taken directly from Lloyd and colleagues[28]

	17.	Apply utility decrement of 0.02 for infusional regimens.
Discount rates	21.	Zero discount rate for both costs and health effects
	22.	Differential discount rates - costs (6%) and health effects (1.5%)

The one-way sensitivity analyses presented in the MS suggest that the results for lapatinib plus capecitabine compared with single-agent chemotherapies are robust to variations in assumptions, with all ICERs remaining substantially higher than would conventionally be considered cost-effective - greater than £75,000 per QALY gained when compared with capecitabine and greater than £64,000 per QALY gained when compared with vinorelbine. The greatest impact was shown when adopting an independent, rather than proportional, hazards model where ICERs approximately doubled (to £154,564 and £124,999 per QALY gained, when compared with capecitabine and vinorelbine respectively).

As discussed in section 4.4.1.2.3, using utilities presented in the Lloyd and colleagues[28] paper without adjusting for the difference in mean age (38.2 years in Lloyd and colleagues[28] compared with [redacted] for EGF100151 trial) is not appropriate. The ERG re-ran analysis 16 using the Lloyd and colleagues[28] statistical model, both with and without the sex-by-progression interaction – this is reported in the section ***ERG sensitivity analysis*** below.

The one-way sensitivity analyses showed greater variation in ICER values when compared with trastuzumab-containing regimens. In particular lapatinib plus capecitabine is no longer dominant, in cost-effectiveness terms, compared with at least one of the trastuzumab-containing regimens when changing assumptions over:

- wastage
- frequency of treatment with trastuzumab
- frequency and duration of treatment with vinorelbine
- PFS for trastuzumab-containing regimens
- adverse event costs for lapatinib regimen.

The impact on the cost-effectiveness of lapatinib plus capecitabine of combining some of these assumptions is examined below in section 0 - ***ERG scenario analysis*****.**

ERG sensitivity analysis

The ERG undertook further sensitivity analyses. The first of these involved further analysis of some of the scenarios investigated in the MS. In particular the ERG looked at:

- more extreme variation in the price of lapatinib

- the effect of RDI dose adjustments separately from RDI for progression-free days treated
- the effect of wastage for oral and infusional regimes separately.

The results of these additional sensitivity analyses support the findings of the sensitivity analysis in the MS. The ICERs are higher than would conventionally be considered cost-effective for lapatinib plus capecitabine when compared with capecitabine or vinorelbine as monotherapies. When compared with trastuzumab-containing regimens lapatinib plus capecitabine dominates or has a more acceptable incremental cost effectiveness ratio.

Removing the RDIs for dosages and for progression-free days treated separately indicates that the latter adjustments have greater impact on the cost effectiveness of lapatinib plus capecitabine. Similarly excluding wastage for oral and infusional regimes separately, makes clear that wastage associated with infusional regimes has a far greater impact on the cost effectiveness of lapatinib plus capecitabine in this model.

Of the new sensitivity analyses conducted by ERG the greatest impact on the ICER is associated with poorer progression-free survival 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. Changing the cost of administering chemotherapy infusions to a lower figure, taken from a recent ERG report on the use of trastuzumab in early breast cancer, [32] also has an impact on the ICER. In all these cases, at least one of the trastuzumab-containing regimens is no longer dominated by lapatinib plus capecitabine.

Table 15 ERG sensitivity analyses

	Incremental cost per QALY gained for lapatinib plus capecitabine versus				
Sensitivity analysis	Capecitabine monotherapy	Vinorelbine monotherapy	Trastuzumab + vinorelbine	Trastuzumab +capecitabine	Trastuzumab monotherapy
Reduce lapatinib price 10%	£ 74,311	£ 60,907	Dominant	Dominant	Dominant
Increase lapatinib price 10%	£ 88,190	£ 74,786	Dominant	Dominant	£ 771
Increase lapatinib price 20%	£ 95,129	£ 81,725	Dominant	£ 61	£ 9,074
RDI for doses equal one	£ 81,748	£ 68,302	Dominant	Dominant	Dominant
RDI for days equal one	£ 100,583	£ 86,202	Dominant	Dominant	£ 8,956
Exclude wastage of oral regimes	£ 76,896	£ 61,601	Dominant	Dominant	Dominant
Exclude wastage of infusional regimes	£ 81,251	£ 72,132	Dominant	£ 6,865	£ 14,245
Hazard ratio for lapatinib based on median PFS & OS	£ 92,230	£ 42,008	Dominant	Dominant	Dominant

Cost of chemotherapy administration cost from Ward and colleagues[32]	£ 81,251	£ 70,605	Dominant	Dominant	£ 7,611
Progression utility reduction, Lloyd and colleagues[28] modelled at mean age of patients in EGF100151	£ 70,864	£ 59,174	Dominant	Dominant	Dominant
Use mean BSA/ weight of patients in EGF100151 to estimate drug use, with wastage.	£ 81,251	£ 68,201	Dominant	£ 1,597	£ 517
As above, but weight is one standard deviation greater than mean	£ 81,251	£ 68,201	Dominant	Dominant	£ 517
As above, but BSA is one standard deviation greater than mean	£ 81,316	£ 69,629	Dominant	£ 1,729	£ 2,226
As above, but BSA and weight are both one standard deviation greater than mean	£ 81,316	£ 69,629	Dominant	Dominant	£ 2,226
Hazard ratio for PFS with trastuzumab based on lower median TTP	£ 81,251	£ 67,846	£ 17,371	£ 21,462	£ 24,731
Hazard ratio for PFS with trastuzumab based on lower median TTP	£ 81,251	£ 67,846	Dominant	Dominant	Dominant

4.4.1.4.2 Scenario Analysis

The sensitivity analyses presented in section 6.3.3.1 of the MS are described in the MS as scenarios – since they examine the impact of applying alternative values to model parameters. These are discussed in Section 4.4.1.4.1 above. No further scenario analyses were presented in the MS.

ERG scenario analysis

The assumed frequency of treatment with trastuzumab used in the base case (weekly) was justified in the MS based on the SmPC and existing NICE guidance for metastatic breast cancer. Clinical advice to the ERG indicated that it is more typical in UK practice to administer trastuzumab once every three weeks. Since the dose is tripled when changing from weekly to three weekly administration (from 2mg/m^2 to 6 mg/m^2) changing frequency of dosing has minimal effect on drug costs, but has a large impact on administration cost. Administration cost, over three weeks, of weekly treatment with trastuzumab is £600 compared with costs of £200 for three-weekly dosing. The scenario analysis also examines the 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 16 ERG scenario analyses

	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[†]	£ 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 lower median TTP	£ 81,251	£ 70,960	Dominant	Dominant	Dominant

Notes:
[†] cost for trastuzumab administration was reduced to £117 per visit. Since administration cost 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.

4.4.1.4.3 Probabilistic Sensitivity Analysis

The probabilistic sensitivity analysis can be run by clicking on the 'Probabilistic Sensitivity Analysis' button on the '*Analyze*' Excel spreadsheet. Alongside the table of input values for model parameters, on the '*Analyze*' sheet, are cells containing drop down options to select distributions for variables to be included in the PSA and an associated input cell to hold the standard error (used to parameterise the distribution). The sheet also contains cells that allow the user to specify the number of simulations to run and to control the output of the CEAC.

The PSA takes about 70 minutes to run (on a computer with 2.8 GHz processor) for 2000 simulations. The results of the PSA are presented in Table 6.16, page 114, in the MS. This reports the probability of lapatinib plus capecitabine being cost effective against each comparator separately, using thresholds of £20,000 and £30,000 per QALY gained – these are summarised in Table 17 below. Also reported in Table 6.16 in the MS is the "predominant quadrant" for each comparison – the quadrant of the cost effectiveness plane in which the majority of the simulated ICERs are found - and the proportion of simulated ICERs found in that quadrant. The mean incremental costs and QALYs, their range or other measures of dispersion are not reported for any of the comparisons in the manufacturer's PSA.

Table 17 Probability of lapatinib plus capecitabine being cost effective at willingness to pay thresholds of £20,000 and £30,000, from manufacturer's PSA

	Lapatinib plus capecitabine versus				
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

A scatter-plot of the cost effectiveness results and acceptability curve are also presented for each comparison (Figures 6.7 to 6.16, page 109 to 113, of the MS).

The PSA uses the main variables in the model, but there is limited discussion in the MS of the choice of variables to include, the distributions chosen, or of appropriate ranges for the data. Nevertheless the choice of variables included in the PSA appears reasonable and distributions chosen are generally appropriate (see summary below). The MS refers to section 6.2.6.1 as providing details of the means, standard errors and probability distributions for variable included in the PSA. As this section covers 18 pages, a more concise summary of model variables, their characteristics and whether or not these are included in the PSA is provided in Appendix 9.8 of the MS.

Summary of assumptions for manufacturer's PSA:

- Survival model parameters (lambda and gamma for PFS and OS models for capecitabine, and the hazard ratio for PFS and OS for lapatinib plus capecitabine) were estimated, outside the model, using non-parametric bootstrap techniques and stored in a hidden worksheet *'PH Weibull Param'*. No further detail is provided in the MS on how these bootstrap samples

were generated so no judgement can be made on the appropriateness of techniques used. Ten thousand sets of values are stored in the worksheet and the random number function is used to select values through the list. A single random draw for capecitabine monotherapy and lapatinib plus capecitabine ensures that parameters for the PFS and OS functions and hazard ratios for lapatinib plus capecitabine are selected as a group. This is intended to maintain the correlation between PFS duration and OS. It appears that the hazard ratio for overall survival with trastuzumab is not sampled in the PSA, but is kept at the base case value (0.8344). This departs from the base case assumption that overall survival with trastuzumab-containing regimens is the same as lapatinib plus capecitabine.

- All costs sampled during the PSA are assumed to have log-normal distributions - an alternative distribution would be the gamma, similar to the log-normal distribution, but less apt to produce high extreme values. The distributions are parameterised using the mean values adopted in the base case and estimated standard errors entered on the *'Analyze'* sheet (as described above). The standard errors have been derived by a variety of methods. In cases where the standard error was not known, it was estimated by assuming a 95% confidence interval of plus or minus 25% around the mean value and inferring standard errors based on the interval. In the case of the cost of administration for trastuzumab the MS has used the inter-quartile range for the reference cost as an approximation for a 95% confidence interval.
- Relative dose intensities are all assumed to be normally distributed. This does not seem appropriate as it allows for dose increases (above normal dose) as well as dose reductions, since there is no mechanism to constrain the distribution to the zero to one interval. There do not appear to be any methods in the spreadsheet calculations or the Visual Basic code to ensure that values outside the required interval (less than zero (unlikely, given that all RDIs are greater than 0.75) or more than one) are not used in the analysis. A simulation undertaken by the ERG using the 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. A more appropriate choice for these parameters would seem to be the beta distribution, which is readily implemented in Excel and is naturally constrained to the zero to one interval.
- Utilities were assumed to follow a beta distribution – the parameters of the distribution were calculated using the "Method of Moments" based on mean and standard error for patient in the EGF100151 trial, for pre-progression utility. The mean and standard error for the

simulations using the Lloyd and colleagues[28] statistical model were used to parameterise the distribution for utility reduction due to disease progression.

Drug costs and adverse events, other than costs of monitoring cardiotoxicity in patients receiving lapatinib or trastuzumab, are not included in the PSA.

The hazard ratio for trastuzumab was varied, assuming a lognormal distribution, and based on a standard deviation derived from the 95% confidence interval around the pooled median TTP estimate (see MS section 5.8.3.2, page 64 and section 6.2.6.1, page 83). This does not fully reflect the methodological and parameter uncertainty around the estimate of the relative efficacy of trastuzumab used in the base case analysis. The ERG suggest using a larger standard error in recognition of the greater than two-fold variation in values included in the pooled estimate and the methodological uncertainty involved in this unadjusted indirect comparison.

4.4.1.4.4 ERG probabilistic sensitivity analysis

The ERG conducted a probabilistic analysis after changing the distribution for RDIs to beta rather than normal. Additional assumptions in the ERG probabilistic sensitivity analysis are:

- Changing the cost for administering chemotherapy infusion to the lower value used by Ward and colleagues.[32] A lognormal distribution was used, as in the base case, with a standard error calculated from an estimated 95% that was assumed to be plus or minus 25% of the mean value.
- Greater variation around the mean hazard ratio for PFS with trastuzumab-containing regimes. A lognormal distribution was used, as in the base case, with the standard error increased to 0.08.
- Lapatinib cost was varied by plus or minus 20%, using a uniform distribution.
- Mean BSA and weight were used to estimate drug use rather than the inferred distribution (see discussion on drug wastage in section 4.4.1.2.4 on page 59 of this report). Mean BSA and weight were assumed to have a normal distribution, parameterised using the standard deviations listed on the *'DoseWastage'* sheet and a total sample size of 400.
- Trastuzumab administration occurs every three weeks, rather than weekly.

The cost effectiveness plane and CEACs for each comparison are shown in Figure 1 to Figure 10. The results of the ERG PSA for lapatinib plus capecitabine versus capecitabine monotherapy or vinorelbine monotherapy are very similar to those presented in the MS – they are only affected by variation in the cost of lapatinib and by changing the distribution of RDIs from normal to beta. This has had the effect of shifting the distribution of incremental costs upward for capecitabine monotherapy – from a range between approximately 2,500 to 20,000, in the analysis reported in the MS, to 5,000 to 25,000 in the ERG analysis. The probability of lapatinib plus capecitabine being cost effective compared with capecitabine monotherapy is 0.001 at a willingness to pay threshold of £20,000 and 0.027 at a threshold of £30,000. Equivalent values for the analysis reported in the MS are shown in Table 17 of this report. The difference between the two analyses is less marked for vinorelbine monotherapy - here the upper limit of the incremental costs has increased slightly. However the probability of being cost effective is the same as reported for the analysis in the MS.

Much larger differences between the ERG probabilistic sensitivity analysis and that reported in the MS are seen for the trastuzumab-containing regimes. Given the substantial difference in cost effectiveness estimates associated with reducing treatment frequency from weekly to every three weeks (from lapatinib plus capecitabine being dominant to having ICER between £4,361 and £27,532 when compared with trastuzumab-containing regimes), shown in Table 6.17 in the MS and in Table 16 in this report, it is not surprising that including such a change in the PSA is associated with very different results from those reported in the MS. The mean incremental cost moves from being negative to positive for lapatinib plus capecitabine compared with each of the trastuzumab-containing regimes. The distribution of incremental outcomes is a little wider, but remains centred on a figure of approximately 0.14 QALYs gained. The probability of lapatinib plus capecitabine being cost effective compared with trastuzumab plus vinorelbine is 0.528 at a willingness to pay threshold of £20,000 and 0.632 at a threshold of £30,000. For lapatinib plus capecitabine compared with trastuzumab plus capecitabine the probability of being cost effective at willingness to pay thresholds of £20,000 and £30,000 are 0.395 and 0.525, respectively. For lapatinib plus capecitabine compared with trastuzumab plus capecitabine the probability of being cost effective at willingness to pay thresholds of £20,000 and £30,000 are 0.333 and 0.466, respectively. Equivalent values for the analysis reported in the MS are shown in Table 17 of this report.

Figure 1 Cost effectiveness plane for lapatinib plus capecitabine versus capecitabine monotherapy from ERG's PSA

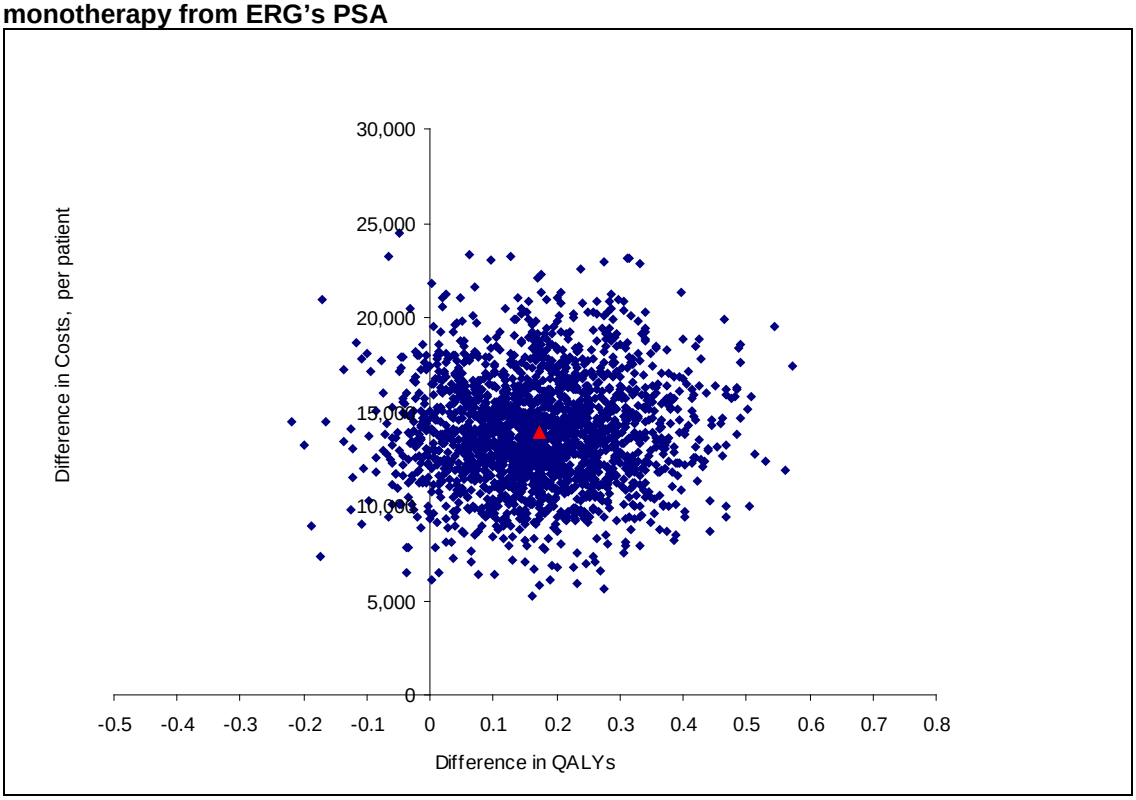


Figure 2 CEACs for capecitabine monotherapy and lapatinib plus capecitabine from ERG's PSA

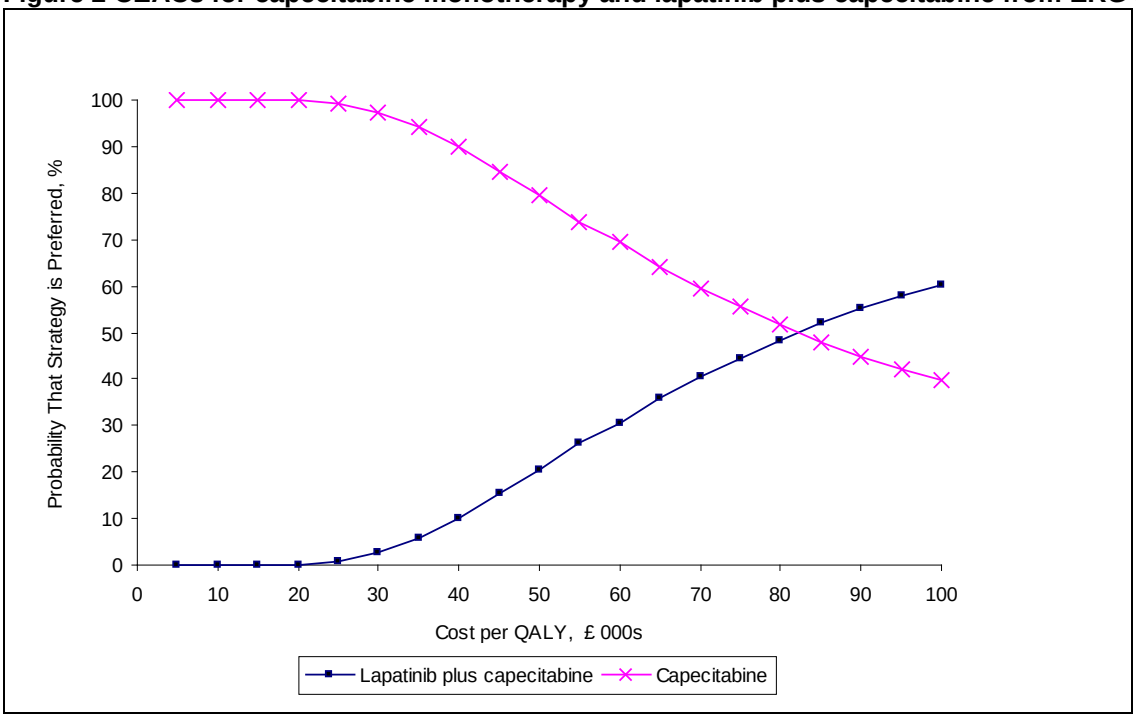


Figure 3 Cost effectiveness plane for vinorelbine monotherapy versus lapatinib plus capecitabine from ERG's PSA

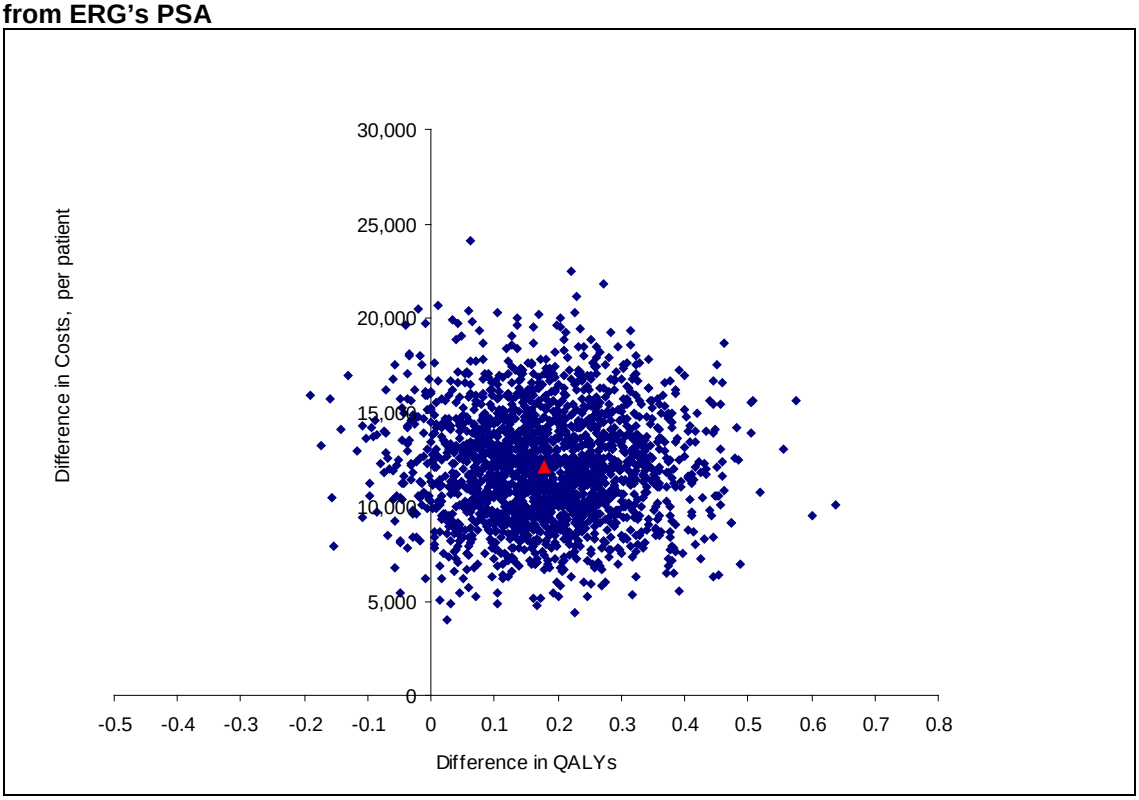


Figure 4 CEACs for vinorelbine monotherapy and lapatinib plus capecitabine from ERG's PSA

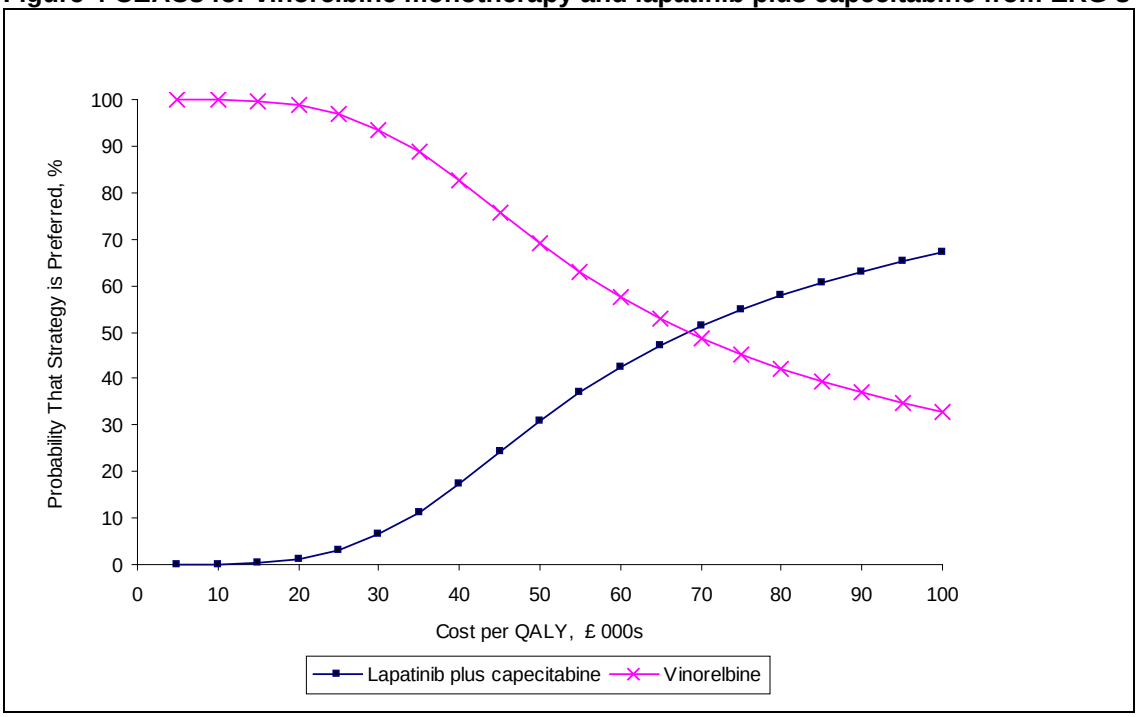


Figure 5 Cost effectiveness plane for trastuzumab plus vinorelbine versus lapatinib plus capecitabine from ERG's PSA

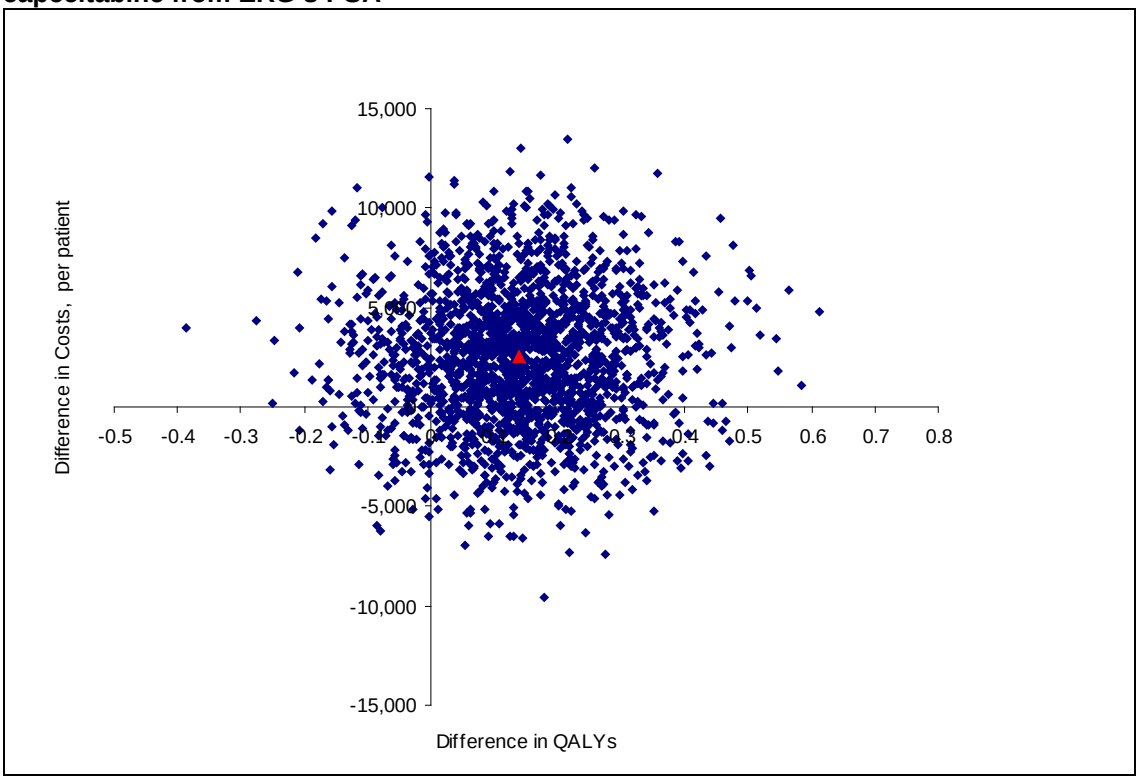


Figure 6 CEACs for trastuzumab plus vinorelbine and lapatinib plus capecitabine from ERG's PSA

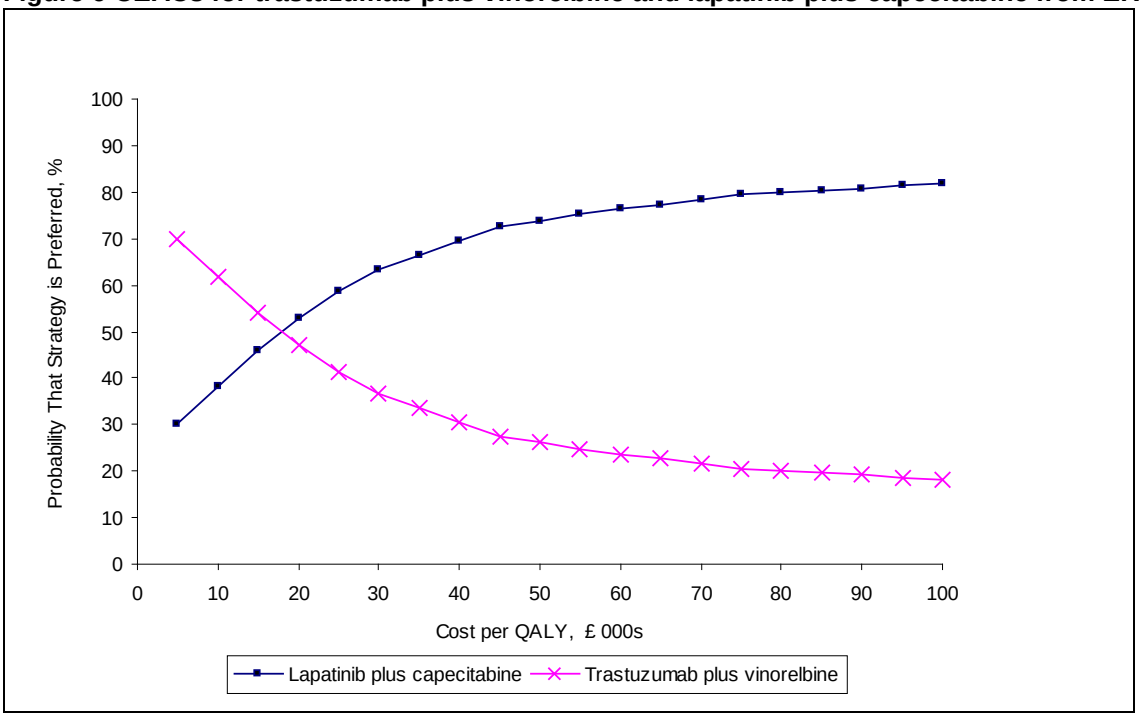


Figure 7 Cost effectiveness plane for trastuzumab plus capecitabine versus lapatinib plus capecitabine from ERG's PSA

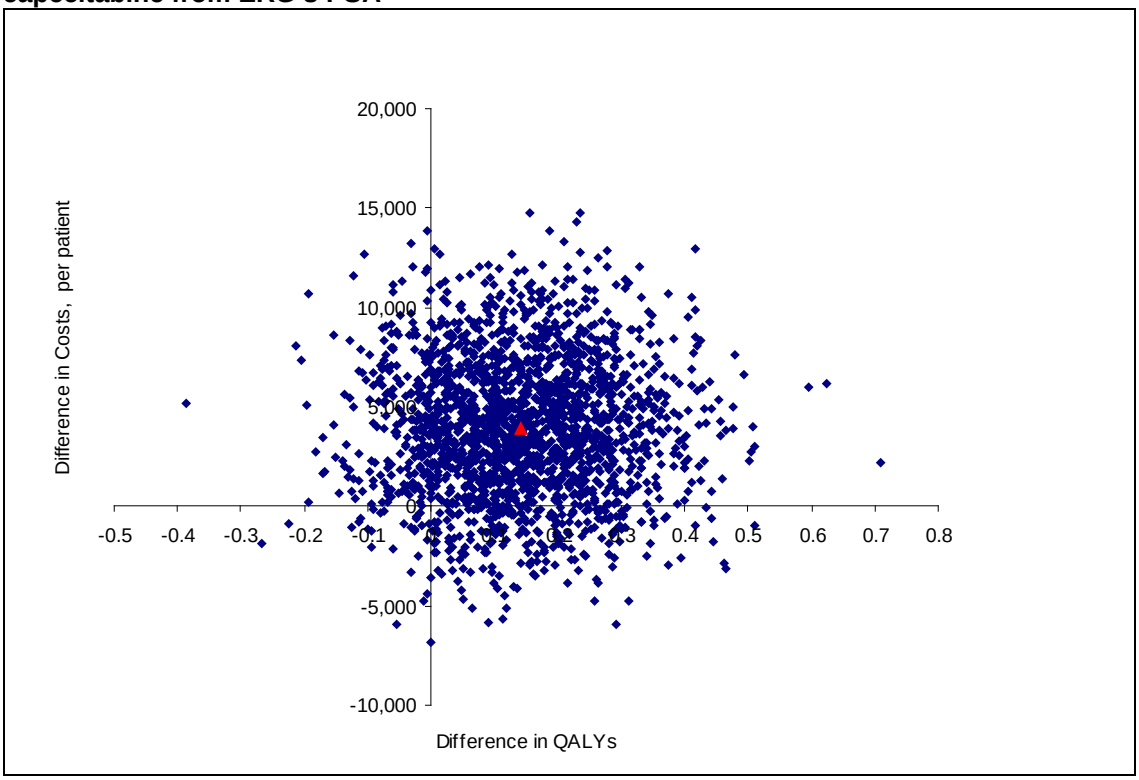


Figure 8 CEACs for trastuzumab plus capecitabine and lapatinib plus capecitabine from ERG's PSA

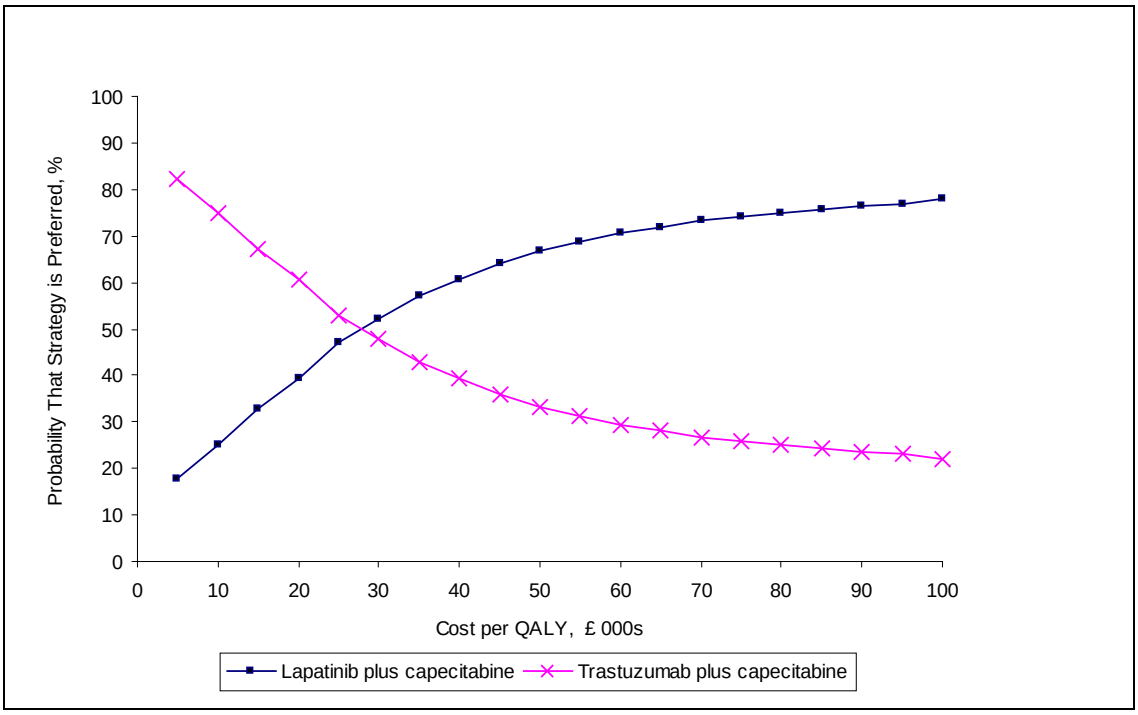


Figure 9 Cost effectiveness plane for trastuzumab monotherapy versus lapatinib plus capecitabine from ERG's PSA

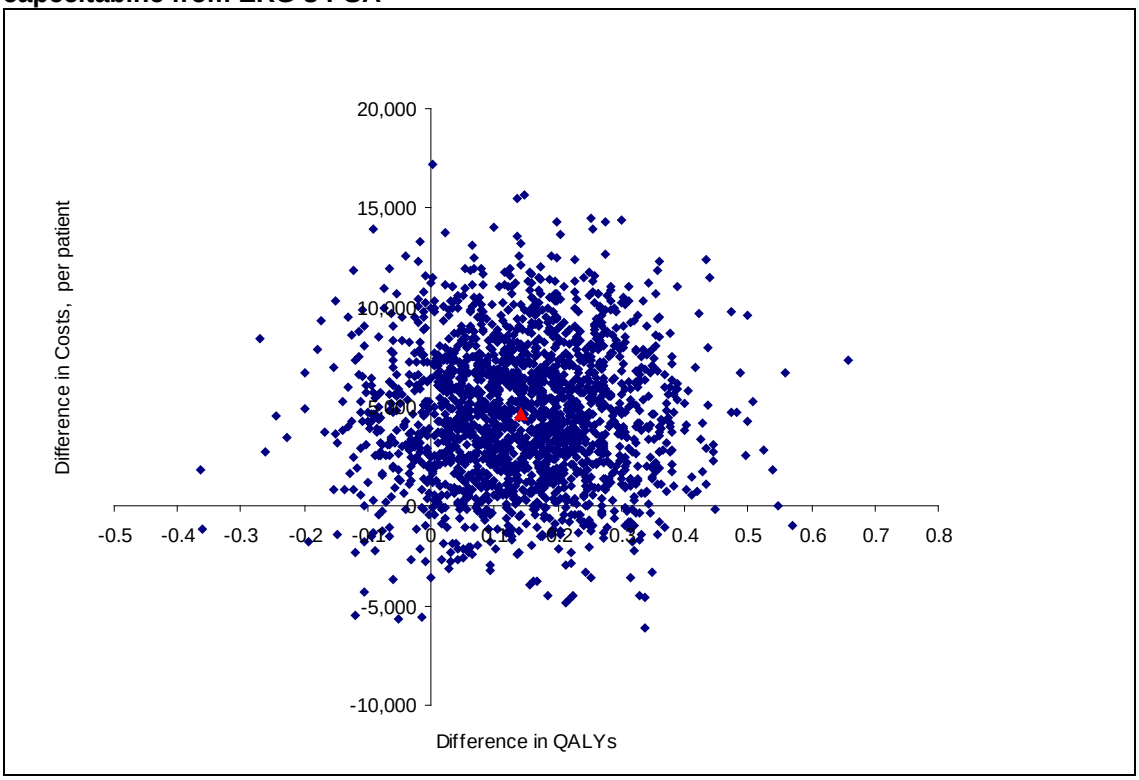
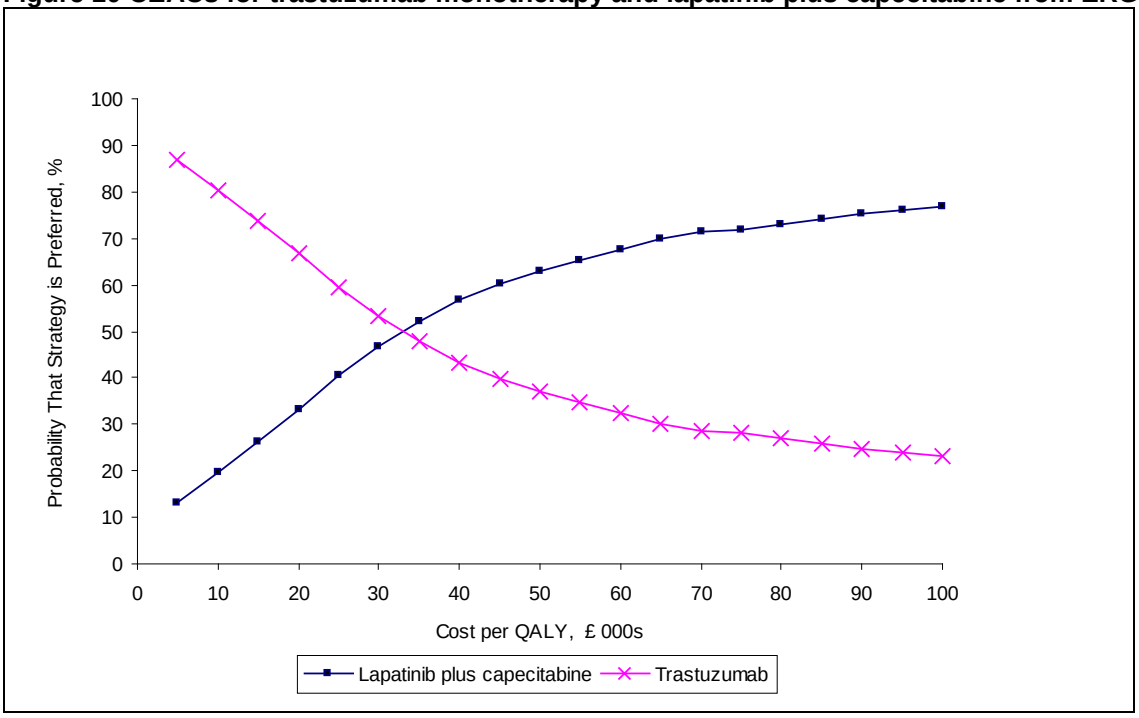


Figure 10 CEACs for trastuzumab monotherapy and lapatinib plus capecitabine from ERG's PSA



4.4.2 Comment on validity of results presented with reference to methodology used

Overall the approach adopted to model cost-effectiveness of treatment for advanced/ metastatic breast cancer seems reasonable. The submission adopted an appropriate technique, given the available data from the clinical trial, using the data from the direct comparison to model survival and cost differences. It should be noted that, while the survival modelling approach is different from that adopted in previous economic evaluations of treatment for metastatic breast cancer, there was little discussion in the MS of alternative modelling strategies.

The main problem with the evaluation is the poor evidence-base for most of the comparisons. There were no data on the relative effectiveness of vinorelbine, so this was assumed to be as effective as capecitabine. The methods for deriving and including evidence of the effectiveness of trastuzumab do not meet the standards for a methodologically sound indirect comparison. However, since the data to perform a methodologically sound analysis do not appear to exist it is unclear what other options were available.

4.4.3 Summary of uncertainties and issues

Overall, the approach taken to modelling cost-effectiveness in this patient group and the model structure adopted seems reasonable. A number of issues have been raised by the ERG during this review.

- There is uncertainty over the effectiveness of the majority of comparators included in the model. In the absence of evidence of the effectiveness of vinorelbine, PFS and OS for capecitabine monotherapy derived from the EGF100151 were used for vinorelbine. Time to progression data from studies reporting a variety of treatment regimens were pooled to provide an estimate of progression free survival for trastuzumab-containing regimens, to be used in an unadjusted indirect comparison.
- The estimate of time to progression for trastuzumab-containing regimens was pooled across all regimens (trastuzumab monotherapy and trastuzumab combined with numerous chemotherapies) assuming they are equally effective. However the range across studies was large (13 – 30 weeks).
- There is uncertainty over the trastuzumab dosing regime. Current guidance is based on weekly dosing for patients with metastatic breast cancer. However clinical advice to the ERG is that 3 weekly dosing is the most common approach in current clinical practice.

- The model takes little account of adverse events. It is assumed that the EQ-5D assessments during the EGF100151 trial captured the quality of life impact of adverse events, and that the pre-progression utility values are equally applicable to all treatments.
- The relative dose adjustments applied in the model were derived only for drugs used in the EGF100151 trial. Values for dose adjustments estimated in the trial are then applied to all comparators in the model – it is not clear from the MS how the decision was made as to which RDI should apply to which drug or combination of drugs.
- The model is sensitive to assumptions about drug wastage for infusional regimes. The calculation of wastage was based on inferred weight and BSA distributions. These were derived using the mean and standard deviations observed in the EGF100151. However, it is not clear why estimated distributions – rather than the real weight and BSA distributions – were used nor how closely the distribution relates to patients who would be seen in normal clinical practice.
- There is uncertainty over utility values used in the analysis. There was substantial missing data in the quality of life assessments in the EGF100151 trial, which were used to estimate pre-progression utility. There was insufficient detail in the MS on the level of completion of EQ-5D to make a judgement on the validity of the valuations used.

5 Discussion

5.1 Summary of clinical effectiveness issues

The clinical evidence for lapatinib comes from a single RCT, whose enrolment was halted early due to the recommendation of an IDMC. It did not reach the population size required to achieve sufficient statistical power to detect a difference in overall survival. There appear to have been fewer TTP events than the 266 required for the power calculation. If the trial was not sufficiently powered for this primary outcome measure, it would reduce the reliability of the evidence base.

The comparators in the decision problem do not quite match those in the scope issued by NICE. Discussion with six expert advisors suggests that some PCTs continue to use trastuzumab beyond progression, in combination with a chemotherapy agent. Other PCTs do not continue trastuzumab, and switch to a chemotherapy agent. It would be of value to investigate UK practice further, to provide an unbiased estimate of the treatments currently used for this patient group in the UK.

The poor evidence base for the use of trastuzumab prevented a more methodologically robust indirect comparison. Without a common capecitabine monotherapy arm, an adjusted indirect comparison was not possible and the weighted mean of median TTP values calculated by the manufacturer might not provide a particularly reliable estimate.

5.2 Summary of cost effectiveness issues

The manufacturer's submission to NICE includes a systematic search for economic evaluations of lapatinib (with no studies identified) and a de novo economic evaluation using a model with a survival modelling approach[27,31]. The model is used to estimate the cost effectiveness of lapatinib in combination with capecitabine against five separate comparators: capecitabine monotherapy, vinorelbine monotherapy, trastuzumab monotherapy, trastuzumab plus vinorelbine and trastuzumab plus capecitabine. Clinical effectiveness data for one of the comparisons in the base case come from the EGF100151 trial. The effectiveness of trastuzumab-containing regimens was estimated by pooling data on time to disease progression, and was used in an unadjusted indirect comparison. In the absence of data on the effectiveness of vinorelbine monotherapy, it was assumed to be identical to capecitabine monotherapy.

In general, the approach taken to modelling cost-effectiveness seems reasonable. However a number of concerns have been identified. There is considerable uncertainty over the estimates of effectiveness for all comparators that were not included in the EGF100151 trial – cost effectiveness estimates based on the unadjusted indirect comparison, for trastuzumab, should be treated with caution. There is also uncertainty over the trastuzumab dosing regime. Whilst current guidance is based on weekly dosing, clinical advice to the ERG suggested that 3 weekly dosing is the most common approach in current clinical practice. Sensitivity and scenario analyses in the MS, and in this report, show that the frequency of treatment with trastuzumab has a substantial impact on the cost effectiveness of lapatinib plus capecitabine.

Other issues raised in this review concern the limited inclusion of adverse events in the model, limited evidence to justify assumptions over dose reductions applied in the model and the impact of alternative assumptions for calculating average drug dosage and wastage (particularly for infusional regimens).

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Appendix 1 – Manufacturer's response to clarification queries

1. ***On page 24 of the submission it states that analysis of health outcomes from the 3rd April data set is available in a separate report (other than CSR ZM2006/00137/00). Please clarify whether this extra report contains any further information of relevance to the submission, if so please provide NICE with a full report.***

We believe that all the health outcomes information of relevance is contained in our evidence submission (pages 41-43), and that the full report does not contain further information which would be of relevance. However, for completeness we have appended the full report.

2. ***Please clarify the date at which women in the capecitabine monotherapy arm were allowed to switch to lapatinib plus capecitabine? Does the 3rd April dataset contain women who switched therapies, and if so how are the data handled in the analysis?***

At the time enrolment was halted on 3 April 06, women in the capecitabine monotherapy arm were allowed to cross over to lapatinib plus capecitabine. Therefore the 3 April dataset contains only data for these women while they were receiving capecitabine, and no data following any crossover.

In our submission we stated that due to the premature termination of enrolment to the study, as well as the crossover of patients from the capecitabine only arm to lapatinib plus capecitabine, it is unlikely that there will be sufficient power to confirm a significant difference in overall survival (page 35, section 5.3.5.10). For clarity we would like to point out that only the premature termination and resultant lower number of patients will impact on the April 06 data quoted in the submission; any impact of switching therapy would be realised in updated analyses from data cuts subsequent to that date.

An updated analysis of overall survival will be performed when 75% of the patients in the study have died. At the time of the April 06 cut 119/399 patients had died i.e. 30%. The patients who crossed over to lapatinib plus capecitabine after 3 April 06 will be included in the capecitabine arm for the intent-to-treat analysis. In addition, there were 8 subjects who were in the screening phase at the time study was halted on April 3, 2006 who were not randomized but were offered lapatinib plus capecitabine. These subjects will also be included in subsequent updated analysis of overall survival.

3. ***Please provide NICE with the full report mentioned on page 104 of the submission. This report refers to validation of internal concurrence - "review by an external economics agency to ensure internal validity of the economic model.... (report available on request, but summarised below)."***

The full validation report is appended.