NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Trastuzumab emtansine for treating HER2-positive, unresectable locally advanced or metastatic breast cancer after treatment with trastuzumab and a taxane

This premeeting briefing is a summary of:

- the evidence and views submitted by the manufacturer, the consultees and their nominated clinical specialists and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Key issues for consideration

Clinical effectiveness evidence

- Treatment pathway
  - The manufacturer stated that, in clinical practice, trastuzumab emtansine is likely to be used as a second-line treatment for HER2-positive, unresectable locally advanced or metastatic breast cancer. Where in the treatment pathway of the disease does the Committee consider trastuzumab emtansine is likely to be used?
  - Most patients in the clinical trials of trastuzumab emtansine received treatment as third or subsequent line. Does the Committee consider the data from these trials appropriate for the place in therapy in which trastuzumab emtansine is likely to be used?
  - What would be the key comparators for trastuzumab emtansine in clinical practice?
- Generalisability of the trials for trastuzumab emtansine
  - The ERG indicated that, in EMILIA and TH3RESA, not all patients received prior treatment according to UK practice, and 0% and 6.2% of patients,

respectively, had an ECOG performance status of 2, while in clinical practice around one third of patients would have an ECOG performance status of 2. Does the Committee consider the results from EMILIA and TH3RESA generalisable to UK clinical practice?

  - Some patients may now receive pertuzumab in combination with trastuzumab and a taxane for the first-line treatment of metastatic disease. Are the trial data equally applicable to these patients?
- Mixed treatment comparison
  - The ERG noted that the clinical trials used in the mixed treatment comparison differed for: prior taxane therapy, whether or not the outcome assessors were blinded to the intervention the patient had received, the criteria used to assess disease progression, and the sites of disease metastases in patients. Does the Committee consider the trials comparable for the purpose of performing a mixed treatment comparison?
  - The manufacturer performed the mixed treatment comparison using a fixed-effect model, which assumed no between-trial heterogeneity. The ERG considered that between-trial heterogeneity was likely to exist and repeated the analysis using a random-effect model. Which analysis does the Committee prefer?
- In its cost-effectiveness analysis, the manufacturer assumed that vinorelbine and trastuzumab plus vinorelbine were clinically equivalent to capecitabine and trastuzumab plus capecitabine, respectively. Does the Committee consider this assumption clinically plausible?

Cost-effectiveness evidence

- The clinical evidence from EMILIA (on which the cost-effectiveness analysis was based) included patients receiving treatment as first (12%), second (36%), or third or subsequent (52%) line for their metastatic disease. Is this evidence appropriate to answer the cost-effectiveness question?
- The manufacturer explored a range of methods to extrapolate progression-free survival and overall survival in the model. These included fitting parametric functions to the entire survival curves, and using Kaplan-Meier data directly

combined with parametric functions fitted to parts of the curves. What is the Committee's view on the most appropriate method of extrapolation?

- The manufacturer calculated drug doses based on the average body weight of patients in EMILIA (this assumed that all patients receive the same dose of the treatment). The ERG stated that drug doses should be based on a distribution of body weight rather than an average because patients' weight varies, and so does the combination of vial sizes patients would receive to administer the drug efficiently. What is the Committee's view on the appropriate assumptions to model drug doses?
- The ERG did not consider the manufacturer's sensitivity analyses to have adequately characterised the uncertainty in the model. What is the Committee's view on the robustness of the manufacturer's model?
- What does the Committee consider to be the most relevant and plausible ICER?
- Does trastuzumab emtansine fulfil the end-of-life criteria?

1 Background: clinical need and practice

1.1 Breast cancer is a common malignant disease accounting for approximately 30% of all new cancers in women. A breast lump is often the first symptom of breast cancer. In locally advanced breast cancer, the cancer has not spread to other parts of the body but may be bigger than 5 cm across, growing into the skin or muscle of the chest, or may be present in proximate lymph nodes. Metastatic breast cancer (also called secondary breast cancer) describes a cancer that has spread to other parts of the body, such as the liver or bones.

1.2 A number of prognostic factors are taken into account when deciding on treatment options. One of these is the human epidermal growth factor receptor 2 (HER2) status. Human epidermal growth factor occurs naturally in the body, and it can stimulate the breast cancer cells to divide and grow when it attaches itself to the HER2 on breast cancer cells. The HER2 level of the cancer cells is scored from 0 to 3+. Breast cancers that have a HER2 score of 3+ are termed 'HER2-positive' and tend to be more

aggressive than other types of breast cancers. Approximately 20% of all breast cancers are HER2 positive.

1.3 In 2010, 41,259 women in England were diagnosed with breast cancer. Approximately 5% of women initially presenting with breast cancer have locally advanced or metastatic disease. The risk of developing breast cancer increases with age, with over 80% of newly diagnosed women being older than 50 years. It is expected that 85% and 77% of women with breast cancer will survive their disease for 5 and 10 years from the time of diagnosis respectively.

1.4 The aim of treatment for locally advanced or metastatic breast cancer is to prolong survival and maintain a good quality of life. Advanced breast cancer: diagnosis and treatment (NICE clinical guideline 81) recommends first-line treatment with an anthracycline-based chemotherapy regimen. If anthracyclines are unsuitable, docetaxel monotherapy should be considered according to the guideline. Trastuzumab in combination with paclitaxel is recommended as an option for people with tumours expressing HER2 scored at levels of 3+ who have not received chemotherapy for metastatic breast cancer and in whom anthracycline treatment is inappropriate (NICE technology appraisal guidance 34). After disease has progressed on trastuzumab, patients may receive non-targeted therapies such as capecitabine or vinorelbine, which can be combined with continued trastuzumab therapy if disease progression is within the central nervous system alone (NICE clinical guideline 81). Lapatinib is a HER2-targeted treatment, which is licensed in combination with capecitabine for use at this stage in the treatment pathway.

2 The technology

2.1 Trastuzumab emtansine (Kadcyla, Roche) is an antibody-drug conjugate consisting of trastuzumab linked to maytansine, which is a cytotoxic agent. Because the antibody targets HER2, and HER2 is overexpressed in breast cancer cells, the conjugate delivers the toxin directly to the

cancer cells. Trastuzumab emtansine, as a single agent, has a UK marketing authorisation 'for the treatment of adult patients with HER2-positive, unresectable locally advanced or metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either:

- received prior therapy for locally advanced or metastatic disease, or
- developed disease recurrence during or within 6 months of completing adjuvant therapy.'

Trastuzumab emtansine is administered intravenously. The recommended dose of trastuzumab emtansine is 3.6 mg/kg body weight administered every 3 weeks (21-day cycle). Patients should be treated until the disease progresses or unacceptable toxicity occurs.

2.2 The summary of product characteristics lists the following adverse reactions for trastuzumab emtansine: increase in serum transaminases, left ventricular dysfunction, infusion-related reactions, hypersensitivity reactions, decreased platelet counts, an immune response to trastuzumab emtansine, and reactions secondary to the accidental administration of trastuzumab emtansine around infusion sites. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 Trastuzumab emtansine costs £1641.01 per 100 mg vial and £2625.62 per 160 mg vial (excluding VAT; manufacturer's submission). The manufacturer estimated an average cost of a course of treatment with trastuzumab emtansine of £90,831 (excluding administration costs). Costs may vary in different settings because of negotiated procurement discounts.

3 Remit and decision problem(s)

3.1 The remit from the Department of Health for this appraisal was: to appraise the clinical and cost effectiveness of trastuzumab emtansine

within its licensed indication for the treatment of unresectable locally advanced or metastatic HER2-positive breast cancer after treatment with trastuzumab and a taxane.

	Final scope issued by NICE	**Decision problem addressed in the submission**
Population	People with HER2-positive, unresectable advanced or metastatic breast cancer whose disease has progressed after treatment with trastuzumab and a taxane.	
Intervention	Trastuzumab emtansine	
Comparators	• lapatinib in combination with capecitabine • capecitabine • vinorelbine • trastuzumab in combination with capecitabine • trastuzumab in combination with vinorelbine	
Outcomes	The outcome measures to be considered include: • progression free survival • overall survival • adverse effects of treatment • health-related quality of life.	

3.2 The manufacturer indicated that, courtesy of the Cancer Drugs Fund, patients with HER2-positive, unresectable locally advanced or metastatic breast cancer in England may receive pertuzumab plus trastuzumab plus docetaxel as first-line treatment, lapatinib plus capecitabine as second-line treatment, and capecitabine or vinorelbine as third-line treatment. The manufacturer noted that this differs from the treatment pathway recommended by NICE in which patients receive trastuzumab plus paclitaxel first line, and capecitabine or vinorelbine (with or without trastuzumab) second and third line. Of patients who receive second-line treatment in clinical practice, the manufacturer estimated that 41% receive lapatinib plus capecitabine and 13% receive trastuzumab plus capecitabine. In the third-line setting, the manufacturer considered that lapatinib plus capecitabine is also the most routinely used regimen (27% of patients) followed by vinorelbine. The manufacturer envisaged that trastuzumab emtansine would be used in patients with HER2-positive

metastatic breast cancer who received 1 treatment for their disease (that is, second line), or whose disease relapsed during, or within 6 months after completing, adjuvant therapy, thus principally displacing lapatinib plus capecitabine.

4 Clinical-effectiveness evidence

4.1 The manufacturer's systematic review of clinical evidence identified 2 relevant randomised controlled trials (RCTs) for inclusion in its submission: EMILIA and TH3RESA. Both trials were international, phase III, randomised, open-label trials evaluating the safety and efficacy of trastuzumab emtansine (3.6 mg/kg every 3 weeks) for HER2-positive, unresectable, locally advanced or metastatic breast cancer (table 1). EMILIA compared trastuzumab emtansine with lapatinib plus capecitabine, and TH3RESA compared it with treatment of physician's choice (defined in section 4.3). At the time of the manufacturer's submission to NICE, both trials were ongoing. The manufacturer used 4 additional RCTs, together with EMILIA, to perform a mixed treatment comparison between trastuzumab emtansine and the other comparators listed in the scope (that is, an analysis combining direct and indirect evidence for particular pairwise comparisons).

Table 1 Summary of the methodology of EMILIA and TH3RESA

	EMILIA (n=991)	TH3RESA (n=602)
Location	213 sites worldwide	250 sites worldwide
Design	Phase III, randomised, open-label	
Status	Ongoing	
Expected duration of follow-up	51 months	26 months
Population	Patients with unresectable, locally advanced or metastatic HER2-positive breast cancer that has progressed after trastuzumab and a taxane.	Patients with HER2-positive unresectable, locally advanced or metastatic breast cancer whose disease progressed after at least 2 HER2-targeted regimens, including trastuzumab and lapatinib, and a taxane.
Intervention	Trastuzumab emtansine (n=495)	Trastuzumab emtansine (n=404)
Comparator	Lapatinib plus capecitabine (n=496)	Treatment of physician's choice (n=198): • single-agent chemotherapy • hormonal therapy **or** • HER2-targeted therapy. A maximum of 2 agents was allowed.
Primary outcomes	• PFS (assessed by independent review • OS	• PFS (assessed by study investigators) • OS
Analyses in MS		
PFS	1 primary analysis	1 primary analysis
OS	2 interim analyses	1 interim analysis
Key differences between inclusion criteria		
Baseline ECOG PS	0 to 1	0 to 2
Prior therapies for LABC or MBC	None: 12%, 1 therapy: 36%, 2 or more therapies: 52%	2 therapies: 35%, 3 therapies: 36%, 4 or more therapies: 29%
PFS, progression-free survival; OS, overall survival; MS, manufacturer's submission; ECOG PS, Eastern Cooperative Oncology Group performance status; LABC, locally advanced breast cancer; MBC, metastatic breast cancer		

Source: Manufacturer's submission

4.2 Eligible patients in EMILIA had documented progression of unresectable, locally advanced or metastatic HER2-positive breast cancer previously treated with trastuzumab, alone or in combination with another agent, and

a taxane, alone or in combination with another agent. The trial's inclusion criteria stipulated that disease progression must have occurred:

- during or after at least 1 line of therapy for locally advanced or metastatic disease, or
- within 6 months after completing adjuvant therapy for early-stage disease.

Patients were randomised in a 1:1 ratio to trastuzumab emtansine (n=495) or lapatinib plus capecitabine (n=496). More than 50 patients were randomised from the UK. Stratification factors were geographical region (United States, Western Europe, or other), the number of prior chemotherapy regimens for unresectable, locally advanced or metastatic disease (0 or 1 versus more than 1), and disease involvement (visceral versus non-visceral). Dose delays, reductions, and discontinuations were allowed when toxic effects occurred, as defined in the study protocol. The study investigators and an independent review committee assessed the tumour at baseline and every 6 weeks thereafter until disease progressed according to the investigators' assessment. Patients continued to receive study treatment until investigators established disease progression or unmanageable toxic effects developed.

4.3 TH3RESA enrolled patients with HER2-positive unresectable, locally advanced or metastatic breast cancer whose disease progressed after at least 2 HER2-targeted regimens, including trastuzumab and lapatinib, and a taxane. Disease progression must have occurred on both trastuzumab- and lapatinib-containing regimens (unless the patient was intolerant to lapatinib). Patients were randomised 2:1 to trastuzumab emtansine (n=404) or treatment of physician's choice (n=198), which could be any of the following:

- single-agent chemotherapy

- hormonal therapy as a single agent (for example, tamoxifen or an aromatase inhibitor) or a dual agent (for example, an aromatase inhibitor plus a luteinizing hormone-releasing hormone agonist)
- HER2-targeted therapy alone (for example, trastuzumab or lapatinib) or in combination with 1 of the following:
  - another HER2-targeted therapy (for example, trastuzumab plus lapatinib)
  - single-agent chemotherapy (for example, lapatinib plus capecitabine)
  - single-agent hormonal therapy (for example, lapatinib plus letrozole).

Patients randomised to treatment of physician's choice could switch to trastuzumab emtansine when their disease progressed. This was allowed after results from EMILIA were published.

4.4 The co-primary efficacy end points in both EMILIA and TH3RESA were progression-free survival and overall survival. In EMILIA, progression-free survival was assessed by independent review (progression-free survival assessed by study investigators was a secondary end point), and in TH3RESA, it was assessed by study investigators. Progression-free survival was defined as the time from randomisation to disease progression or death from any cause. The independent review committee in EMILIA and the study investigators in TH3RESA assessed disease progression based on Response Evaluation Criteria in Solid Tumours (RECIST). Overall survival was defined as the time from randomisation to death from any cause. Pre-specified secondary end points in both trials included objective response rate, duration of response, and time to symptom progression, which in EMILIA, was used as a proxy for health-related quality of life. TH3RESA collected EQ-5D utility data.

4.5 Patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 were eligible for inclusion in EMILIA. TH3RESA enrolled patients with an ECOG performance status of 0, 1 or 2 (6.2% of the trial's population had an ECOG performance status of 2). For

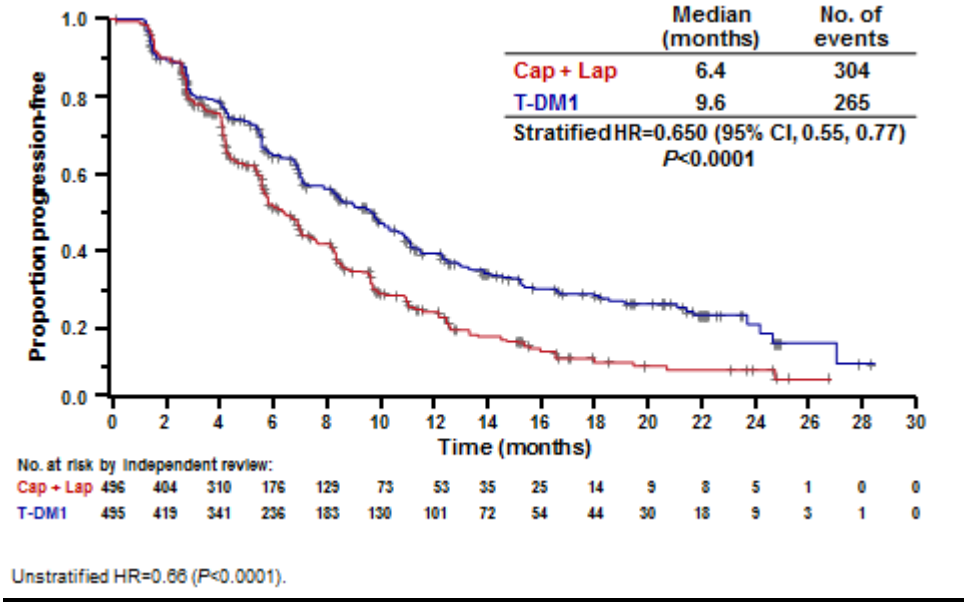
patients randomised to trastuzumab emtansine in EMILIA, the median age was 53 years, 99.8% were female, and 57% had oestrogen- or progesterone-receptor-positive disease. Approximately 70% of patients in EMILIA and TH3RESA had visceral disease. EMILIA included patients whose disease progressed on trastuzumab and a taxane in any breast cancer setting. Because of this, patients received study treatment either as first (12%), second (36%), or third or subsequent (52%) line for locally advanced or metastatic disease. In contrast, patients in TH3RESA had previously received, on average, 4 lines of therapy for locally advanced or metastatic disease. The manufacturer stated that, overall, patient and disease characteristics at baseline were well balanced between study groups in EMILIA and TH3RESA.

4.6 The primary analysis of progression-free survival and the first interim analysis of overall survival were performed after 508 patients had had independently assessed disease progression (14 January 2012), as specified in EMILIA's study protocol. A second interim analysis of overall survival was performed 6 months later at the request of regulatory authorities (31 July 2012). The final analysis of overall survival is to be performed when 632 patients have died (not yet reached). For TH3RESA, the manufacturer presented the primary analysis of progression-free survival and 1 interim analysis of overall survival, which were performed at the same time (data cut-off date: 11 February 2013). All efficacy end points in EMILIA and TH3RESA were assessed in the intention-to-treat population (that is, in all patients randomised at baseline). Patients in TH3RESA who initially received treatment of physician's choice but then switched to trastuzumab emtansine were included in the analyses as originally randomised.

4.7 In EMILIA, the median duration of follow-up was 13 months at the time of the primary analysis of progression-free survival and the first interim analysis of overall survival (14 January 2012). Of patients randomised to trastuzumab emtansine and lapatinib plus capecitabine, 265 (54%) and

304 (61%) had disease that progressed, respectively (figure 1). Treatment with trastuzumab emtansine improved median progression-free survival as assessed by independent review by 3.2 months (trastuzumab emtansine: 9.6 months, lapatinib–capecitabine: 6.4 months), with a hazard ratio stratified on randomisation factors of 0.65 (95% confidence interval [CI] 0.55 to 0.77, p<0.001). Investigator-assessed progression-free survival was similar (difference in median progression-free survival 3.6 months; hazard ratio [HR] 0.66, 95% CI 0.56 to 0.78).

Figure 1 Progression-free survival by independent review in EMILIA

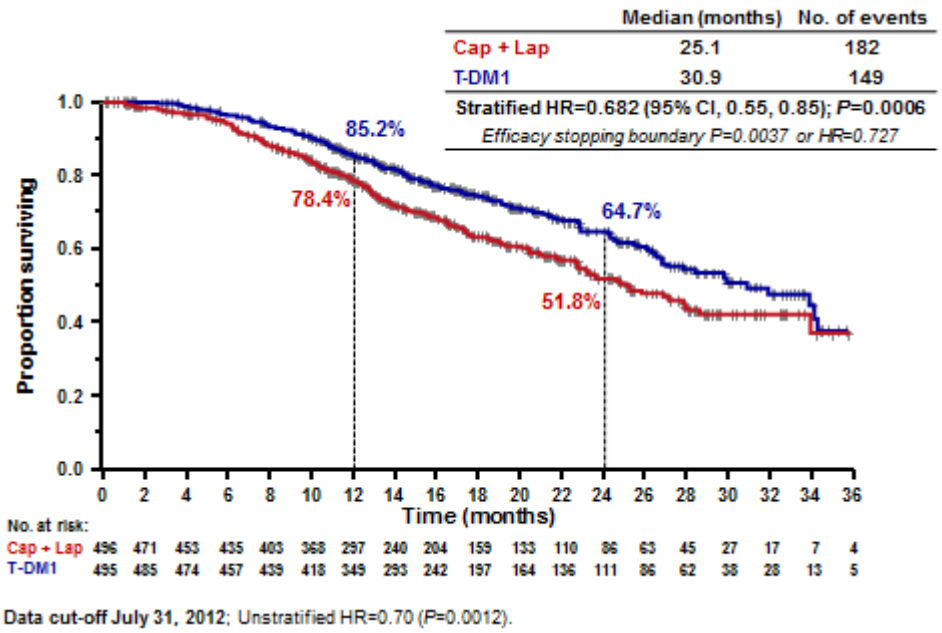


Source: Manufacturer's submission, figure 5, page 94

4.8 When the second interim analysis of overall survival was performed (31 July 2012), the median duration of follow-up was 19 months. At that time, 149 (30%) and 182 (37%) patients randomised to trastuzumab emtansine and lapatinib plus capecitabine respectively had died (figure 2). Trastuzumab emtansine increased median overall survival by 5.8 months (trastuzumab emtansine: 30.9 months, lapatinib–capecitabine: 25.1 months). The hazard ratio for overall survival was 0.68 (95% CI 0.55 to 0.85, p<0.001). Estimated 1-year survival rates were 85.2% in the trastuzumab emtansine group compared with 78.4% in the lapatinib–

capecitabine group, and rates at 2 years were 64.7% and 51.8% for the trastuzumab emtansine group compared with the lapatinib–capecitabine group respectively.

Figure 2 Second interim analysis of overall survival in EMILIA

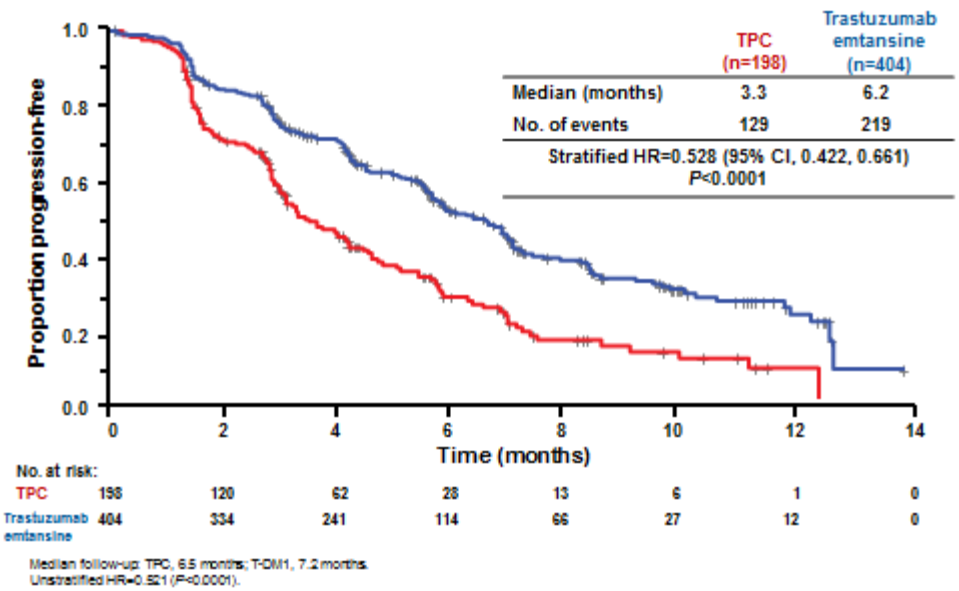


Source: Manufacturer's submission, figure 8, page 97

4.9 In TH3RESA, a total of 44 patients (22.2%) had switched from treatment of physician's choice to trastuzumab emtansine after their disease progressed. Of patients randomised to treatment of physician's choice, 68.5% received chemotherapy plus trastuzumab, 10.3% received lapatinib plus trastuzumab, 1.6% received hormonal therapy plus trastuzumab, 2.7% received chemotherapy plus lapatinib, and 16.8% received single-agent chemotherapy. After 16 months of follow-up and 348 events (trastuzumab emtansine: 219, treatment of physician's choice: 129) of investigator-assessed disease progression, median progression-free survival was 6.2 months with trastuzumab emtansine and 3.3 months with treatment of physician's choice, a difference of 2.9 months (figure 3). This was consistent with a hazard ratio of 0.53 (95% CI 0.42 to 0.66, p<0.0001). The manufacturer also presented an analysis comparing trastuzumab emtansine with trastuzumab-containing treatment of

physician's choice (that is, excluding treatments that did not contain trastuzumab). This showed an increase in median progression-free survival by 3.2 months with trastuzumab emtansine (HR 0.56, 95% CI 0.44 to 0.71).

Figure 3 Progression-free survival in TH3RESA



Source: Manufacturer's submission, figure 11, page 99

4.10 Median overall survival in the trastuzumab emtansine group of TH3RESA had not been established by the time of the interim analysis (less than 50% of patients had died). The hazard ratio for overall survival (which accounted for patients who switched treatment) was 0.55 (95% CI 0.37 to 0.83, p=0.0034), but the manufacturer did not consider it statistically significant because it had not crossed the stopping boundary (that is, the number of deaths that had accumulated at that time was not enough to come to a conclusion about overall survival). For the Kaplan–Meier curve for overall survival, see figure 15 on page 101 of the manufacturer's submission. A summary of the key results of EMILIA and TH3RESA is presented in table 2.

Table 2 Summary of the key results of EMILIA and TH3RESA

	EMILIA		TH3RESA	
	Trastuzumab emtansine	Lapatinib + capecitabine	Trastuzumab emtansine	Treatment of physician's choice
PFS (months)	9.6	6.4	6.2	3.3
	Difference: 3.2		Difference: 2.9	
	HR (95% CI) 0.65 (0.55 to 0.77)		HR (95% CI) 0.52 (0.42 to 0.66)	
OS (months)	30.9	25.1	Not reached	14.9
	Difference: 5.8		Difference: -	
	HR (95% CI) 0.68 (0.55 to 0.85)		HR (95% CI) 0.55 (0.37 to 0.83)	
PFS, progression-free survival; OS, overall survival				

Source: Manufacturer's submission

4.11 For the secondary end points in EMILIA, trastuzumab emtansine increased objective response rate by 12.7% and prolonged the duration of response by 6.1 months compared with lapatinib plus capecitabine. Objective response rate also favoured trastuzumab emtansine in TH3RESA, with a difference of 22.7% compared with treatment of physician's choice. The manufacturer stated that the other secondary end points in TH3RESA were yet to be analysed.

4.12 Time to symptom progression was a proxy for health-related quality of life in EMILIA. It was defined as the time from randomisation to the first decrease of 5 points or more from baseline scores on the Trial Outcome Index of the patient-reported Functional Assessment of Cancer Therapy–Breast (FACT-B), which is scored from 0 to 92, with higher scores indicating a better quality of life. Trastuzumab emtansine delayed time to symptom progression by 2.5 months compared with the lapatinib plus capecitabine (trastuzumab emtansine: 7.1 months, lapatinib–capecitabine: 4.6 months; HR 0.796, p=0.0121). Of patients treated with trastuzumab emtansine and lapatinib plus capecitabine, 53.3% and 49.4% had a clinically significant improvement in symptoms from baseline, respectively (p=0.0842). TH3ERSA, which collected EQ-5D data, reported utility values of 0.71 and 0.69 for patients who received trastuzumab emtansine or treatment of physician's choice, respectively.

4.13 The manufacturer provided pre-specified subgroup analyses of EMILIA and TH3RESA for progression-free survival and overall survival. It stated that, in EMILIA, trastuzumab emtansine had a decreased effect on progression-free survival in patients aged between 65 and 74 years and in those with non-visceral or non-measurable disease. For patients who received study treatment as first, second, or third or subsequent line, the hazard ratios for overall survival were 0.61 (95% CI 0.32 to 1.16), 0.88 (95% CI 0.61 to 1.27) and 0.62 (95% CI 0.46 to 0.84), respectively. The manufacturer indicated that no subgroups are of particular clinical interest for this appraisal.

Manufacturer's mixed treatment comparison

4.14 The manufacturer performed a mixed treatment comparison between trastuzumab emtansine and the other comparators listed in the scope (capecitabine, vinorelbine, trastuzumab plus capecitabine, and trastuzumab plus vinorelbine) because no head-to-head data were available from RCTs. It used the following RCTs, which it identified from a review of the literature (figure 4):

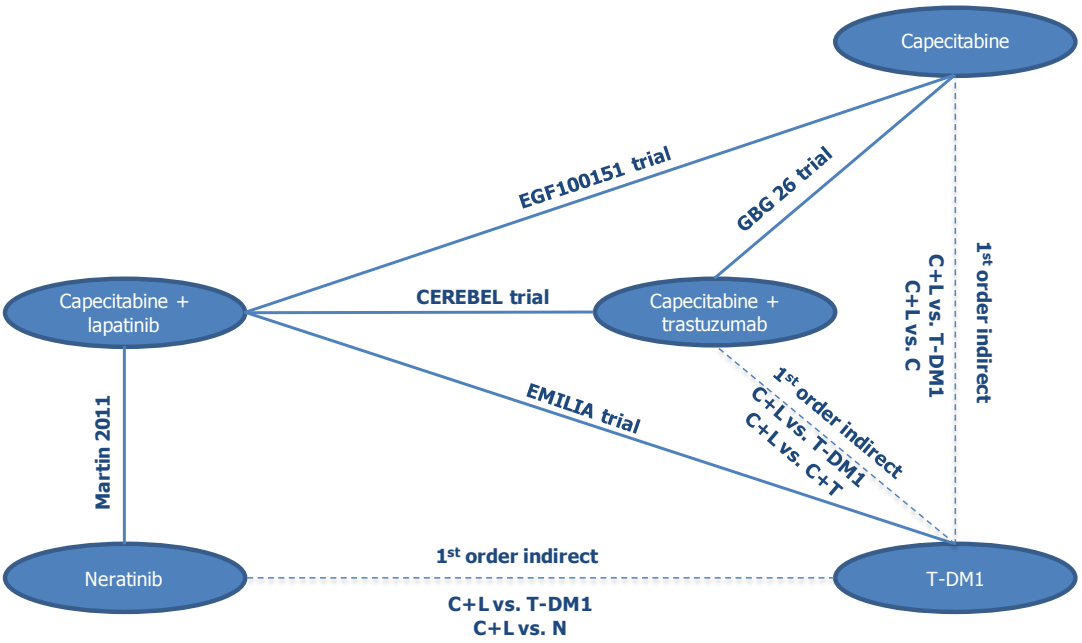
- EMILIA
- CEREBEL: A phase III, randomised, open-label trial comparing the incidence of central nervous system metastases in patients with HER2-positive metastatic breast cancer, treated with lapatinib plus capecitabine or trastuzumab plus capecitabine. Patients must have received either an anthracycline or a taxane in the adjuvant setting, and they may or may not have received trastuzumab. Randomisation in CEREBEL was stratified based on whether or not the patient had received prior trastuzumab. For the mixed treatment comparison, the manufacturer used the results of the subgroup that had received trastuzumab.
- EGF100151: A phase III randomised comparison of lapatinib plus capecitabine with capecitabine alone in patients with HER2-positive, locally advanced or metastatic breast cancer previously treated with

anthracycline-, taxane- and trastuzumab-containing regimens. Some patients initially randomised to capecitabine alone switched to lapatinib plus capecitabine. The manufacturer excluded those patients from the analysis.

- Martin et al. (2011): A phase II, randomised, open-label study of neratinib compared with lapatinib plus capecitabine for the second- or third-line treatment of HER2-positive locally advanced or metastatic breast cancer. Eligible patients had received up to 2 prior trastuzumab regimens and a taxane. Martin et al. did not report results for overall survival, so the manufacturer did not use this study for the analysis of overall survival.
- GBG26: A phase III study in patients with HER2-positive, advanced breast cancer whose disease progressed during treatment with trastuzumab in any breast cancer setting. In this study, the addition of capecitabine to continued trastuzumab therapy was compared with capecitabine alone.

Although TH3RESA provided a comparison of trastuzumab emtansine with trastuzumab plus vinorelbine (one of the comparators in the scope) received as a treatment of physician's choice, the manufacturer did not include TH3RESA in the analysis despite it being the only study that would allow a comparison of trastuzumab emtansine with trastuzumab plus vinorelbine. In response to clarification from the Evidence Review Group (ERG), the manufacturer indicated that the treatment of physician's choice was determined after patients had been randomised and considering each patient's characteristics. The manufacturer explained that, because of this, a comparison of trastuzumab emtansine with trastuzumab plus vinorelbine separately would break the randomisation in the trial and result in a biased comparison.

Figure 4 Network of trials included in the mixed treatment comparison



Source: Manufacturer's submission, figure 17, page 122

4.15 The manufacturer undertook a qualitative, but not a statistical, assessment of heterogeneity. It stated that the 5 included studies were comparable for age, ECOG performance status, disease stage and the number of sites with disease metastases. All studies included patients previously treated with an anthracycline or a taxane: in 4 studies, 61% to more than 99% of patients had received an anthracycline and 85% to 100% had received a taxane. Apart from CEREBEL, all other studies included patients who had received trastuzumab, of whom 71% to 95% received it in the metastatic setting. In GBG26, only 70% of patients had received a taxane, but the manufacturer considered this proportion large enough to include the study. The sites of disease metastases differed between CEREBEL and the remaining studies because CEREBEL excluded patients with brain metastases. The manufacturer stated that, overall, CEREBEL and Martin et al. (2011) seemed more heterogeneous than the other 3 trials. For CEREBEL, although the manufacturer used the subgroup of patients who had received trastuzumab, an unknown proportion of these patients could have received trastuzumab plus an

anthracycline, which mismatches the population specified in the decision problem. Furthermore, CEREBEL and Martin et al. were published as conference proceedings with limited information on patient characteristics at baseline. Because of this, the manufacturer presented the analysis with and without these 2 studies.

4.16 The manufacturer performed the mixed treatment comparison from a Bayesian perspective using a fixed-effect model (that is, a model that assumes that all trials estimate exactly the same treatment effect and that the variability between individual study results occurs by chance). It derived progression-free survival and overall survival hazard ratios and corresponding 95% credible intervals for each pairwise comparison that was possible from the network of trials. The manufacturer also presented results using the Bucher method for the analysis excluding CEREBEL and Martin et al. for comparative purposes.

4.17 The trials used by the manufacturer allowed the comparison of trastuzumab emtansine with capecitabine and with trastuzumab plus capecitabine, but not with vinorelbine or with trastuzumab plus vinorelbine. The results of the analysis are presented in table 3.

Table 3 Results of the manufacturer's mixed treatment comparison

Comparison	Bayesian analysis				Bucher method	
	Including CEREBEL & Martin et al. (HR, 95% CrI)		Excluding CEREBEL & Martin et al. (HR, 95% CrI)		Excluding CEREBEL & Martin et al. (HR, 95% CrI)	
	PFS	OS	PFS	OS	PFS	OS
Trastuzumab emtansine vs. capecitabine	0.39 (0.29-0.55)	0.55 (0.41-0.75)	0.35 (0.25-0.51)	0.52 (0.39-0.72)	0.36 (0.25-0.51)	0.53 (0.39-0.72)
Trastuzumab emtansine vs. trastuzumab + capecitabine	0.68 (0.50-0.91)	0.68 (0.46-0.98)	0.54 (0.32-0.87)	0.58 (0.35-0.91)	0.53 (0.32-0.86)	0.56 (0.35-0.91)
CrI, credible interval; PFS, progression-free survival; OS, overall survival						

Source: Manufacturer's submission, figure 20, page 127

4.18 The manufacturer estimated the probability of each treatment being the most effective with respect to progression-free survival and overall survival. Trastuzumab emtansine had a 99% probability of being the best treatment to reduce the risk of disease progression and a 98% probability of being the best treatment to reduce the risk of death.

Adverse events

4.19 In both EMILIA and TH3RESA, adverse events were analysed for a 'safety population' defined as patients who received at least 1 dose of study treatment. Additionally, the manufacturer presented a pooled safety analysis of 884 patients who had received trastuzumab emtansine in EMILIA and 5 other phase I or II studies (table 4). In this, the most common adverse events (occurring in 25% or more of patients) were fatigue (46.4%), nausea (43.0%), decreased platelet counts (29.6%), headache (29.4%), constipation (26.5%) and nosebleeds (25.2%). Serious adverse events reported by more than 5 patients were pneumonia (1.7%), fever (1.4%), cellulitis (1.1%), vomiting (0.9%), decreased platelet counts (0.9%), convulsion (0.8%), shortness of breath (0.8%), abdominal pain (0.7%), blood poisoning (0.7%), back pain (0.7%) and accumulation of fluid on the lungs (0.6%). The manufacturer considered that trastuzumab emtansine is well tolerated with additional toxicity that could be managed.

Table 4 Summary of adverse events with trastuzumab emtansine

	EMILIA		TH3RESA		Pooled analysis
	Trastuzumab emtansine (n=495)	Lapatinib + capecitabine (n=496)	Trastuzumab emtansine (n=404)	TPC (n=198)	Trastuzumab emtansine (n=884)
AEs (any grade)	95.9%	97.7%	93.5%	88.6%	NR
Grade 3 or above AEs	40.8%	57.0%	32.3%	43.5%	45.0%
SAEs	15.5%	18.0%	18.4%	20.7%	19.8%
AEs leading to treatment discontinuation	5.9%	17.0%	NR	NR	7.0%
AEs leading to death	0.2%	1.0%	1.2%	1.5%	1.4%
AEs, adverse events; SAEs, serious adverse events; TPC, treatment of physician's choice; NR, not reported					

Source: Manufacturer's submission and the European Public Assessment Report

Evidence Review Group critique and exploratory analyses

4.20 The ERG considered that the manufacturer's search of clinical evidence was well-developed and unlikely to have missed any relevant studies. It also considered that EMILIA, TH3RESA and the trials used in the mixed treatment comparison were described in sufficient detail by the manufacturer.

4.21 The ERG considered that EMILIA and THE3ERA were generally at low risk of bias. However, it stated that the lack of blinding in both trials is likely to have introduced bias, especially for the outcomes reported by patients. For progression-free survival, the ERG noted that the independent review committee in EMILIA was blinded to the intervention the patient had received, but study investigators in TH3RESA were not, which may have increased the risk of bias for progression-free survival in TH3RESA.

4.22 The ERG stated that the populations in EMILIA and TH3RESA were broadly similar to the population in UK clinical practice. However, it highlighted the following differences:

- Most patients in EMILIA and TH3RESA received study treatment as a third or subsequent line, but the manufacturer suggested that trastuzumanb emtansine would be used second line in clinical practice.
- The ERG noted that, because EMILIA and TH3RESA were international trials, not all patients would have received prior treatment according to UK practice.
- The ERG suggested that, in clinical practice, around one third of patients would have an ECOG performance status of 2, whereas in EMILIA and TH3RESA, 0% and 6.2% of patients had an ECOG performance status of 2, respectively.

4.23 The ERG noted that the treatment effect of trastuzumab emtansine in EMILIA was uncertain in 2 subgroups: patients aged 75 years or over and patients with non-visceral disease. For patients aged 75 years or over, progression-free survival and overall survival favoured lapatinib plus capecitabine over trastuzumab emtansine. However, this was based on 25 patients, a sample size the ERG considered too small to draw definitive conclusions. For patients with non-visceral disease, the ERG noted that the treatment effect of trastuzumab emtansine varied depending on the definition of 'visceral disease' used.

4.24 The ERG highlighted the following differences between the trials used in the manufacturer's mixed treatment comparison:

- Not all patients had received a taxane in GBG2615. The ERG's clinical experts believed that prior taxane therapy can modify the effect of subsequent therapy.
- The assessment of disease progression or time to progression was blinded to the intervention the patient had received in EMILIA and EGF100151 but not in the other trials included in the analysis.
- RECIST was used in EMILIA, EGF100151 and Martin et al. (2011) to assess disease progression, but it was unclear if it was used in CEREBEL and GBG26.

4.25 The ERG agreed that it was appropriate for the manufacturer to have excluded TH3RESA from the mixed treatment comparison. However, it did not agree that using a fixed-effect model was appropriate because heterogeneity between trials was likely to exist. Because of this, the ERG repeated the analysis that included CEREBEL and Martin et al. (2011) using a random-effect model (that is, a model that accounts for the variability between study results beyond that expected to occur by chance). It reported similar results to the manufacturer, but the ERG's results were more uncertain (wider confidence intervals) and did not dismiss the possibility that trastuzumab emtansine could have no treatment effect (table 5).

Table 5 Results of the ERG's mixed treatment comparison (presented alongside the manufacturer's results for the purpose of comparison)

Comparison	**ERG's analysis (random-effect model)** HR (95% CrI)		**Manufacturer's analysis (fixed-effect model)** HR (95% CrI)	
	PFS	OS	PFS	OS
Trastuzumab emtansine vs. capecitabine	0.40 (0.18-0.89)	0.57 (0.27-1.30)	0.39 (0.29-0.55)	0.55 (0.41-0.75)
Trastuzumab emtansine vs. trastuzumab + capecitabine	0.67 (0.29-1.48)	0.68 (0.31-1.60)	0.68 (0.50-0.91)	0.68 (0.46-0.98)
CrI, credible interval; PFS, progression-free survival; OS, overall survival				

Adapted from the ERG report, figures 7 and 8, pages 45 and 46

In the ERG's analysis, the probability of trastuzumab emtansine being the best treatment to reduce the risk of disease progression was 87%, and its probability being the best treatment to reduce the risk of death was 84%.

5 Comments from other consultees

5.1 Clinical specialists explained that, in the first-line setting, patients with metastatic HER2-positive breast cancer are currently treated with a combination of trastuzumab and chemotherapy (paclitaxel or docetaxel). On disease progression, patients may receive further chemotherapy, with or without continued trastuzumab therapy, or lapatinib plus capecitabine through the Cancer Drugs Fund. Clinical specialists stated that most

patients will remain fit enough to receive third- and subsequent line chemotherapy, but they noted that practice varies in those settings because of the lack of evidence to guide treatment decisions. They indicated that many patients will receive chemotherapy alone; some will receive lapatinib plus capecitabine through the Cancer Drugs Fund; and some will get local access to ongoing trastuzumab and third-line chemotherapy.

5.2 Clinical specialists considered that lapatinib plus capecitabine, the comparator intervention in EMILIA, was an accepted standard of care in the UK. They stated that, in EMILIA, trastuzumab emtansine was associated with a statistically significant and clinically relevant improvement in both progression-free survival and overall survival compared with lapatinib plus capecitabine, and was better tolerated. They stated that trastuzumab emtansine is likely to become the international standard of care in this setting.

5.3 Patient experts stated that patients with locally advanced or metastatic breast cancer highly value treatments that can control their cancer and prolong their lives. They considered that trastuzumab emtansine provides a clear survival benefit without comprising quality of life, which is of vital importance to patients. They noted that trastuzumab is the only HER2-targeted therapy currently approved in the NHS, and most cancers will develop resistance to it within approximately 12 months. They therefore regarded trastuzumab emtansine as a significant step forward for patients with this aggressive cancer. Although patient experts noted that having to administer trastuzumab emtansine intravenously could be a disadvantage for some patients, they believed that most patients would not feel that this outweighs the benefits of the drug.

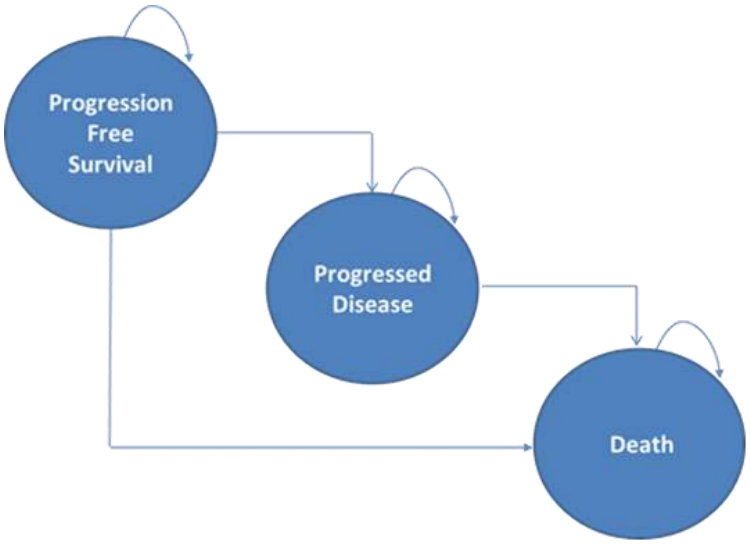
6 Cost-effectiveness evidence

6.1 The manufacturer submitted a de novo economic model to estimate the cost effectiveness of trastuzumab emtansine in adults with HER2-positive,

unresectable, locally advanced or metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. The manufacturer conducted the analysis from the perspective of the NHS and personal social services, and chose a time horizon of 10 years and a cycle length of 1 week. Costs and health effects were discounted at an annual rate of 3.5%.

6.2 The manufacturer's model was a state-transition Markov cohort model simulating 3 states: progression-free, progressed disease and death (figure 5). The manufacturer assumed a starting age in the model of 53 years (the average age of patients in EMILIA). All patients entered the model in the progression-free state and received trastuzumab emtansine or one of its comparators either as first, second or third line (based on the proportions in EMILIA, section 4.5). They could then remain in this state, move to the progressed-disease state or die. Once patients transitioned in the model, they could not return to their previous state. Patients whose disease progressed in the model stopped treatment and received capecitabine, vinorelbine or best supportive care, in line with Advanced breast cancer: Diagnosis and treatment (NICE clinical guideline 81).

Figure 5 The manufacturer's model



Source: Manufacturer's submission, figure 22, page 159

6.3 The manufacturer obtained the clinical effectiveness data for trastuzumab emtansine and the comparator lapatinib plus capecitabine from EMILIA. It used cut-off dates of 14 January 2012 and 31 July 2012 for progression-free survival and overall survival, respectively. Progression-free survival in the model was based on the assessment of study investigators (secondary end point) rather than the assessment by independent review (primary end point). To model the clinical effectiveness of the other comparators listed in the scope, the manufacturer used the results of its Bayesian mixed treatment comparison that included CEREBEL and Martin et al. (2011). It assumed that vinorelbine and trastuzumab plus vinorelbine, which could not be compared with trastuzumab emtansine indirectly, were clinically equivalent to capecitabine and trastuzumab plus capecitabine, respectively. This was because NICE clinical guideline 81 recommends capecitabine or vinorelbine as second- or third-line treatment for advanced breast cancer, and the All Wales Medicines Strategy Group recommends lapatinib plus capecitabine as an alternative to trastuzumab plus capecitabine or trastuzumab plus vinorelbine. The manufacturer suggested that this implies that capecitabine and vinorelbine, alone or in combination with trastuzumab, can be used interchangeably.

6.4 To estimate progression-free survival and overall survival for trastuzumab emtansine and lapatinib plus capecitabine, the manufacturer produced log-cumulative hazard plots to examine how the risk of disease progression and death change over time with each treatment. It then fitted alternative parametric functions to Kaplan–Meier data for each of EMILIA's treatment group, and extrapolated the curves beyond the end of the trial. The manufacturer chose the base-case survival functions for trastuzumab emtansine and lapatinib plus capecitabine based on statistical tests, visually inspecting the curves' fit to the data, and the clinical plausibility of the extrapolation. The survival functions for the other comparators were estimated by applying the respective hazard ratio from the mixed treatment comparison to the survival function of trastuzumab

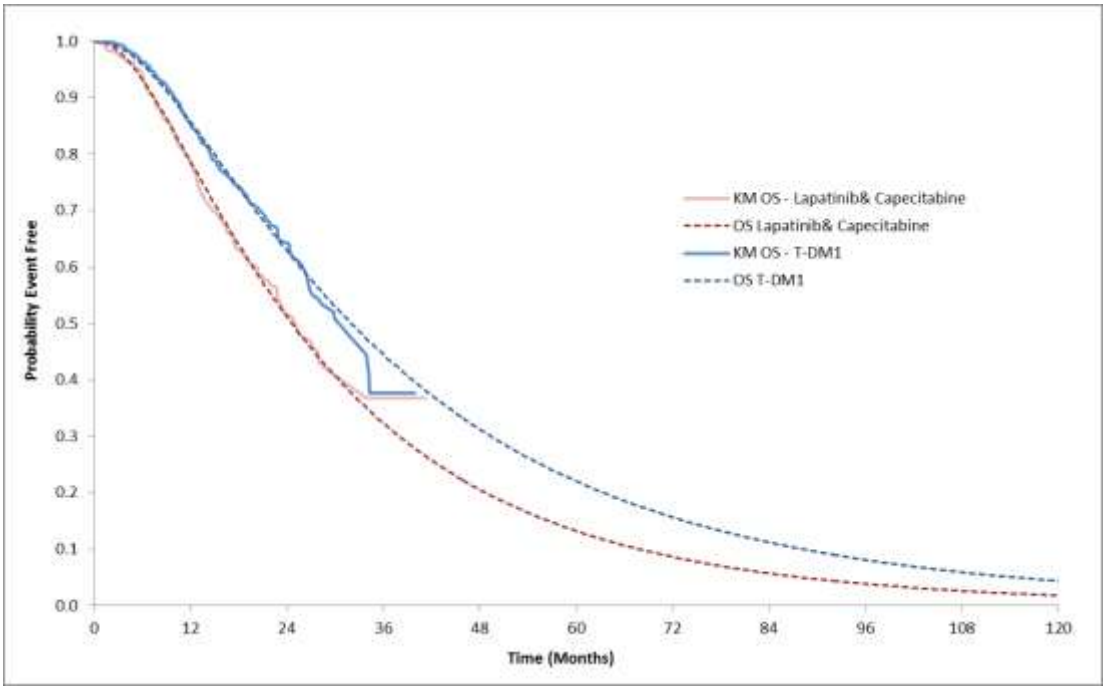
emtansine. In extrapolating the curves for progression-free survival and overall survival, the manufacturer assumed that the treatment effect of trastuzumab emtansine was maintained during the entire time horizon (that is, the hazard ratio for trastuzumab emtansine remained below 1), and that there was no relationship between progression-free survival and overall survival.

6.5 On examining the log-cumulative hazard plots for progression-free survival, the manufacturer noted that the risk of disease progression with trastuzumab emtansine and with lapatinib plus capecitabine was relatively constant during the first 17 months (72 weeks) after starting treatment then started changing irregularly. It stated that, while this might have a clinical explanation, it could be spurious because there were few patients at risk of developing disease progression after 17 months. According to statistical tests, the log-normal function provided the best fit to the Kaplan–Meier data for trastuzumab emtansine and lapatinib plus capecitabine. However, on visual inspection, the manufacturer noted a poor fit (see figure 29 on page 174 of the manufacturer's submission). Furthermore, it stated that no other parametric function provided a good fit. Because of this and the small impact progression-free survival had in the model compared with overall survival (sections 6.14 and 6.15), the manufacturer chose to use in its base case the Kaplan–Meier data for each treatment group up to 17 months after starting treatment, the point at which the risk of disease progression starts changing irregularly, and fit the log-normal function beyond 17 months.

6.6 For overall survival, the log-logistic and gamma functions provided the best fit to the Kaplan–Meier data according to statistical tests. However, the manufacturer chose the gamma function for 3 reasons. Firstly, the proportion of patients alive at 10 years was more plausible with the gamma function (4.4% with trastuzumab emtansine and 1.8% with lapatinib plus capecitabine compared with 7.4% and 4.7% with the log-logistic function, respectively). Secondly, for both trastuzumab emtansine

and lapatinib plus capecitabine, the estimated median overall survival with the gamma function was closer to the median from the Kaplan–Meier data than it was with the log-logistic function. Thirdly, when the manufacturer tested the log-logistic and gamma functions against external data (the Munich registry), the latter provided more plausible results in relation to the external data and had a shape that was more comparable to the external data (see figure 38 on page 188 of the manufacturer's submission). Because of this, the manufacturer fitted the gamma function to the entire curves to model overall survival (figure 6). This produced a difference in mean overall survival between trastuzumab emtansine and lapatinib plus capecitabine of 7.6 months.

Figure 6 Survival function for overall survival used in the manufacturer's base case



Source: Manufacturer's submission, figure 35, page 182

6.7 The manufacturer noted that the model predicted a gain in median overall survival with trastuzumab emtansine that was 2.2 times the gain in median progression-free survival, compared with 1.8 times in EMILIA. However, it considered that the model's prediction was reasonable in view

of the relationships between overall survival and progression-free survival reported in other trials of HER2-targeted therapies.

6.8 The manufacturer could not map the FACT-B Trial Outcome Index data collected from EMILIA onto EQ-5D, and it did not use the utility values from TH3RESA because patients in TH3RESA received only third- or subsequent-line treatment. The manufacturer stated that the best available source of health-related quality of life data was Lloyd et al. (2006), which was used in previous NICE technology appraisals for metastatic breast cancer. Lloyd et al. obtained UK-based societal preferences for 3 stages of metastatic breast cancer, namely, progressive, responding and stable disease on treatment, and 6 common adverse events. Health states were developed as combinations of disease states and adverse events, and rated by members of the public (n=100) using the standard gamble technique. Data were analysed using a statistical model that included variables for age, response to treatment, disease progression, and each of the 6 adverse events. The study reported a utility value of 0.72 for stable disease on treatment, with a gain of 0.07 if the disease responds to treatment and a decline by 0.27 if it progresses.

6.9 To derive the utility values for the model, the manufacturer set the age variable to 47 years, which it stated was the average age of the UK population. It estimated treatment-specific utility values in the progression-free state by weighting the response to treatment variable according to the objective response rate reported for the treatment in the trials (table 6).

Table 6 Utility values used in the manufacturer's base case

Health state – treatment	Source of response rate	Utility value
Progression-free – trastuzumab emtansine	EMILIA	0.78
Progression-free – lapatinib plus capecitabine	EMILIA	0.74
Progression-free – capecitabine	GBG26	0.72
Progression-free – trastuzumab plus capecitabine	EGF10015	0.73
Progression-free – vinorelbine	GBG26*	0.72
Progression-free – trastuzumab plus vinorelbine	EGF10015†	0.73
* Assumed equal to capecitabine; † Assumed equal to trastuzumab plus capecitabine		

Source: Manufacturer's submission, table 31, page 202

For the progressed-disease health state, the manufacturer used the model in Lloyd et al. (2006) to estimate a utility value of 0.50 that it applied to all patients in that state. The manufacturer stated, however, that this value was likely to be an underestimate because Lloyd et al. was designed to estimate a progressed-disease utility value for patients receiving palliative care. The manufacturer indicated that patients whose disease progressed would normally receive active treatment, which would increase their survival and improve their quality of life. To capture the decrease in utility associated with adverse events, the manufacturer included utility decrements for diarrhoea and vomiting, fatigue, and hand-foot syndrome. It applied for capecitabine, trastuzumab plus capecitabine, vinorelbine and trastuzumab plus vinorelbine the same adverse events it applied for lapatinib plus capecitabine based on EMILIA, with the same frequency.

6.10 The manufacturer included the following costs in the model: drug costs, the costs of preparing and administering drugs, the costs of 2 adverse events (diarrhoea and fatigue), and supportive care costs. It calculated the doses of drugs that are dosed by body weight or body surface area based on the average body weight and body surface area of patients in EMILIA. The manufacturer assumed that any unused drug in a vial was discarded (wasted) for trastuzumab emtansine and trastuzumab, but not for vinorelbine because vinorelbine was available in generic form (lapatinib and capecitabine are oral drugs, and so are not associated with wastage).

To model the cost of capecitabine and vinorelbine in the progressed-disease state, the manufacturer assumed that each treatment the patient received was received for 4.3 months based on Cameron et al. (2008). For a summary of the costs associated with each treatment, see table 33 on page 210 of the manufacturer's submission. To capture the costs likely to be incurred at the end of life, the manufacturer incorporated a palliative care cost of £3916 per patient as a transition cost to the death state.

6.11 The manufacturer's deterministic base-case results suggested that trastuzumab emtansine was more costly and more effective than all of its comparators. Trastuzumab plus capecitabine, vinorelbine and trastuzumab plus vinorelbine were more costly than trastuzumab emtansine, lapatinib plus capecitabine or capecitabine, and less or equally effective (dominated), so they were excluded from the analysis (table 7). The manufacturer stated that lapatinib plus capecitabine should also be excluded from the analysis because when lapatinib plus capecitabine is compared with capecitabine, the resulting ICER (£49,798 per QALY gained) is above the normally acceptable maximum ICER. For the cost-effectiveness results including all the comparators, see table 8 on page 19 of the manufacturer's response to the clarification letter.

Table 7 Manufacturer's base-case results

Technologies	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER incremental (£/QALY)	ICER vs. capecitabine (£/QALY)
Capecitabine	13,173	1.03	-	-	-	-
Lapatinib plus capecitabine	34,170	1.45	20,997	0.42	49,798	49,798
Trastuzumab emtansine	111,162	1.91	76,992	0.46	167,236	111,095
QALYs, quality-adjusted life years; Inc., incremental; ICER, incremental cost-effectiveness ratio						

Adapted from the manufacturer's response to the clarification letter, table 8, page 19

6.12 In the manufacturer's base case which used a 10-year time horizon, 3% of patients were alive at 10 years. In response to clarification from the ERG, the manufacturer presented cost-effectiveness results using a 15-year

time horizon (table 8). At the end of the 15 years, 1% of patients were alive.

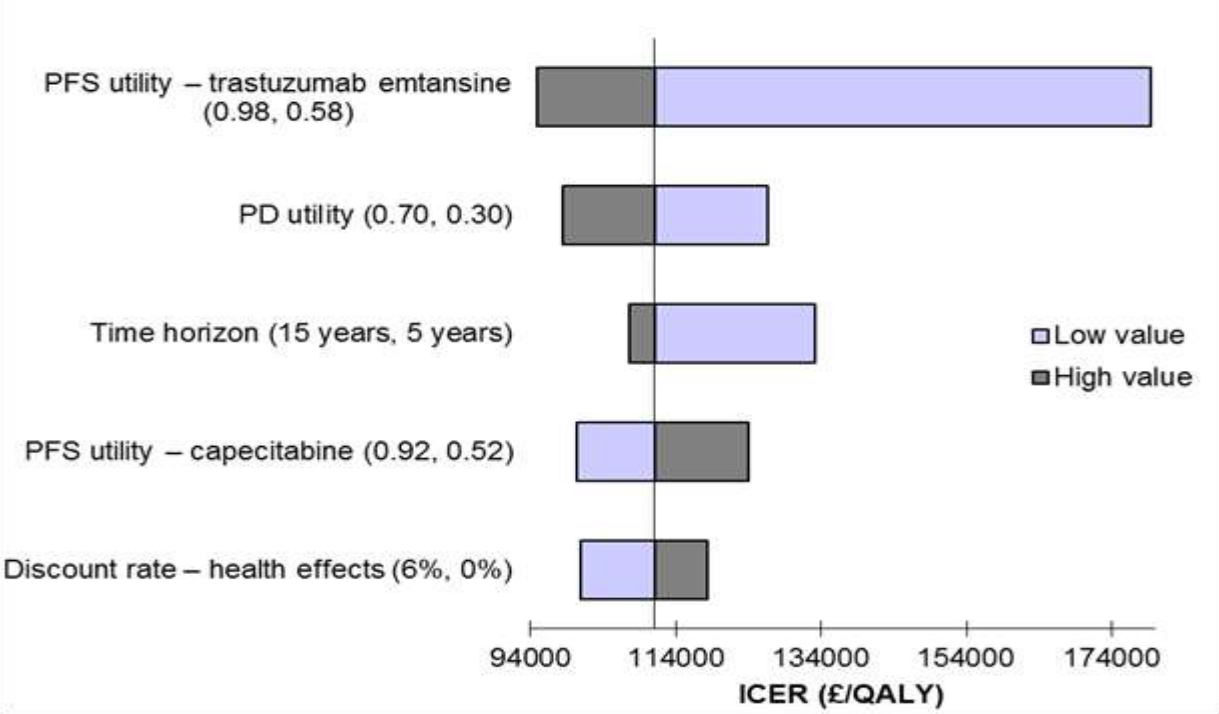
Table 8 Manufacturer's cost-effectiveness results using a 15-year time horizon

Technologies	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER incremental (£/QALY)	ICER vs. capecitabine (£/QALY)
Capecitabine	13,183	1.03	-	-	-	-
Lapatinib plus capecitabine	34,339	1.47	15,451	0.43	48,817	48,817
Trastuzumab emtansine	112,216	1.95	77,877	0.48	162,244	107,657
QALYs, quality-adjusted life years; Inc., incremental; ICER, incremental cost-effectiveness ratio						

Adapted from the manufacturer's response to the clarification letter, table 10, page 24

6.13 The manufacturer presented one-way sensitivity analyses in which it varied most parameters to the lower and upper limit of their 95% confidence interval. Additionally, it explored alternative approaches to extrapolate progression-free survival and overall survival in the model (sections 6.14 and 6.15). In all these analyses, the manufacturer investigated the impact of varying the parameters only on the ICER for trastuzumab emtansine compared with capecitabine (£111,095 per QALY gained). It found that, for this comparison, the ICER was most sensitive to the utility value applied for patients receiving trastuzumab emtansine in the progression-free state (figure 7). When varied, this resulted in ICERs ranging from £94,909 to £179,337 per QALY gained. The manufacturer stated that, compared with capecitabine, the cost effectiveness of trastuzumab emtansine was most sensitive to how progression-free survival and overall survival were extrapolated in the model, the hazard ratios estimated from the mixed treatment comparison, and the utility values used.

Figure 7 The 5 parameters with the largest impact on the ICER for trastuzumab emtansine compared with capecitabine (£111,095 per QALY gained); parameter (high value, low value)



PFS, progression-free survival; PD, progressed disease; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year
Adapted from the manufacturer's submission, table 51, page 241

6.14 In its base case, the manufacturer modelled progression-free survival by using the Kaplan–Meier data for each treatment group up to 17 months (72 weeks) after starting treatment and fitting the log-normal function beyond 17 months. The manufacturer explored the uncertainty around this method by:

- Using the Kaplan–Meier data up to 17 months after starting treatment and fitting alternative parametric functions (Weibull, exponential, log-logistic and gamma) beyond 17 months instead of the log-normal function.
- Using the Kaplan–Meier data for each treatment group up to 3.5 months (14 weeks) after starting treatment, and fitting the exponential function to each group separately beyond 3.5 months. The manufacturer explored this method because from the log-cumulative

hazard plots, the risk of disease progression with trastuzumab emtansine and lapatinib plus capecitabine was similar during the first 3.5 months. The manufacturer stated that this might have biological plausibility, by which the true risk of disease progression with each treatment only becomes observed after 3.5 months.

In the first analysis (fitting alternative parametric functions beyond 17 months), the ICERs ranged from £100,365 per QALY gained (Weibull) to £114,826 per QALY gained (log-logistic). In the second analysis, the ICER was £106,211 per QALY gained.

6.15 The manufacturer also investigated the uncertainty around how it modelled overall survival in its base case (gamma function fitted to the entire survival curves) by exploring the following methods:

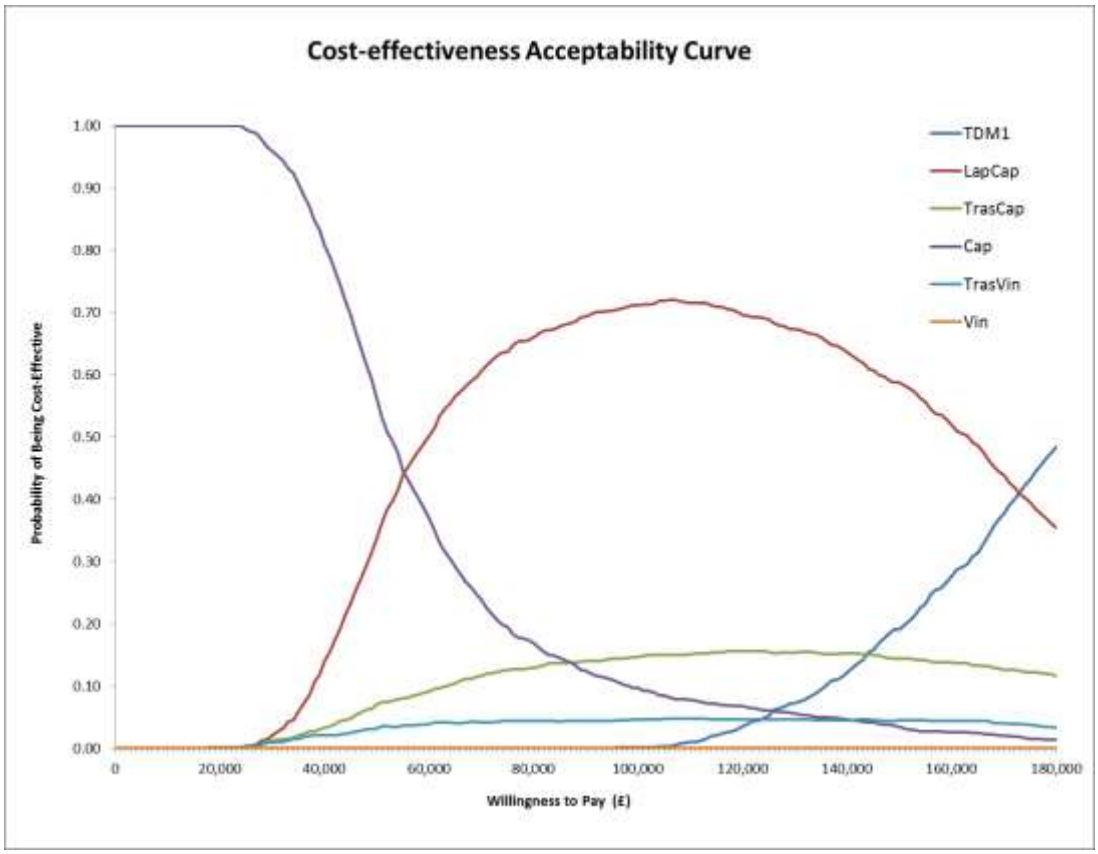
- Fitting alternative parametric functions (Weibull, log-logistic and log-normal) instead of the gamma function to the entire survival curves.
- Using the Kaplan–Meier data for each treatment group up to 7.3 months (29 weeks) after starting treatment, and fitting the exponential function to each treatment group separately beyond 7.3 months. The manufacturer explored this method because from the log-cumulative hazard plots, the risk of death with trastuzumab emtansine and lapatinib plus capecitabine was similar during the first 7.3 months.
- Using the Kaplan–Meier data for each treatment group up to 7.3 months (29 weeks) after starting treatment, and fitting the exponential function to each treatment group separately beyond 7.3 months, but assuming no treatment effect (hazard ratio of 1) beyond 23.8 months (95 weeks) after starting treatment. The manufacturer explored this method because there were few patients at risk of dying after 23.8 months and the treatment effect of trastuzumab emtansine beyond that time was uncertain.

The first analysis (alternative parametric functions fitted to entire curves) resulted in ICERs ranging from £111,004 per QALY gained (log-normal) to

£151,208 per QALY gained (Weibull). The second and third analyses resulted in ICERs of £138,286 and £153,319 per QALY gained, respectively.

6.16 To characterise the uncertainty in the base-case ICER, the manufacturer performed a probabilistic sensitivity analysis, varying parameters simultaneously with values from a probability distribution (figure 8). The probability of trastuzumab emtansine being the most cost-effective intervention at a maximum acceptable ICER of £50,000 per QALY gained was 0%.

Figure 8 Cost-effectiveness acceptability curve



TDM1, trastuzumab emtansine
Source: Manufacturer's response to the clarification letter, figure 6, page 27

Evidence Review Group critique

6.17 The ERG stated that the manufacturer's model was clinically appropriate for the decision problem defined in the scope, and generally well described and justified in the manufacturer's submission.

6.18 The ERG indicated that, compared with other parametric functions, the log-normal and gamma functions used by the manufacturer to model progression-free survival and overall survival provided the most clinically plausible extrapolation. However, it noted that in the model the treatment benefit of trastuzumab emtansine on progression-free survival and overall survival was maintained during the entire time horizon (that is, the hazard ratio remained below 1). The ERG considered this subject to uncertainty and explored in a one-way sensitivity analysis the conservative assumption of no treatment benefit with trastuzumab emtansine (hazard ratio of 1) beyond the time points at which the treatment effect was uncertain (section 6.28).

6.19 The ERG stated that the utility values used in model were consistent with values reported from a literature review of health-state utility values in breast cancer (0.72 to 0.81, Peasgood et al. [2010]). Additionally, the ERG's clinical advisers considered that it was reasonable to assume higher utility with trastuzumab emtansine than with its comparators because trastuzumab emtansine has a better safety profile. However, the ERG indicated that the manufacturer estimated utility values assuming an average patient age of 47 years, while the starting age of patients in the model was 53 years.

6.20 The ERG noted that the model incorporated utility decrements for 3 adverse events only and costs for 2 adverse events only. It stated that this did not capture the decrease in utility and costs associated with many grade 3 or above adverse events that occurred frequently in EMILIA. The ERG included the costs of those adverse events in exploratory analyses (section 6.26) and doubled the weekly costs of adverse events in a one-way sensitivity analysis (section 6.28).

6.21 The manufacturer calculated the doses of trastuzumab emtansine, trastuzumab, capecitabine and vinorelbine based on the average body weight and body surface area of patients in EMILIA (this assumed that all

patients receive the same dose of the treatment). The ERG indicated that the manufacturer, having assumed that any unused drug in a vial was discarded for trastuzumab emtansine and trastuzumanb, calculated costs inaccurately. This was because patients' weight varies, so the combination of vial sizes patients would receive to administer the drug efficiently would also vary. In its exploratory analyses, the ERG applied alternative costs for trastuzumab emtansine, trastuzumab and capecitabine based on an approximated weight distribution of patients with HER2-positive metastatic breast cancer to account of the variation in patients' body weight (section 6.26).

6.22 The ERG identified an error in the model relating to how the cost of administering trastuzumab plus vinorelbine was implemented, which resulted in incorrect costs. The ERG corrected this error in its exploratory analyses (section 6.26).

6.23 In the model, some patients remained in the progressed-disease state longer than others depending on the treatment they had received in the progression-free state, but most patients who received treatment in the progressed-disease state (capecitabine or vinorelbine) received it for 4.3 months. The ERG noted that, in the model, patients who spent more time in the progressed-disease state incurred more treatment costs than patients who spent less time despite receiving the same treatments for the same duration. The ERG corrected this in its exploratory analyses by calculating the average cost of each treatment received in the progressed disease-state (section 6.26).

6.24 The ERG did not consider the manufacturer's one-way sensitivity analyses to have established the robustness of the model or to have determined the key drivers of the cost-effectiveness of trastuzumab emtansine. This was because the manufacturer investigated the impact of varying the parameters only on the ICER for trastuzumab emtansine compared with capecitabine. The ERG indicated that it was important to

include all the comparisons because the appropriate incremental comparison may change for each analysis.

6.25 The ERG stated that the manufacturer did not present or justify the parameters it varied in the probabilistic sensitivity analysis and appeared to have selected the parameters arbitrarily. Furthermore, it noted that the analysis did not appropriately reflect the uncertainty around certain parameters. However, the ERG stated that it was unlikely that the probabilistic ICER for trastuzumanb emtansine would fall below £30,000 per QALY gained if the probabilistic sensitivity analysis was performed correctly.

Evidence Review Group exploratory analyses

6.26 To address its concerns about the manufacturer's model, the ERG made the following changes:

a. Including the costs of all adverse events that occurred in more than 2% of patients in either treatment group of EMILIA.
b. Correcting the error relating to how the cost of administering trastuzumab plus vinorelbine was implemented, and calculating average costs for each treatment received in the progressed-disease state, together with analysis 'a'.
c. Applying the hazard ratios for progression-free survival and overall survival from the ERG's mixed treatment comparison that used a random-effect model, together with analysis 'b'.
d. Using a 15-year time horizon, together with analysis 'c'.
e. Calculating the cost of trastuzumab emtansine, trastuzumab and capecitabine based on an approximated weight distribution of patients with HER2-positive metastatic breast cancer, together with analysis 'd' (that is, applying all individual changes simultaneously).

6.27 In the above-listed analysis 'e' (hereafter 'the ERG's base case'), trastuzumab plus capecitabine, vinorelbine and trastuzumab plus vinorelbine were dominated and excluded from the analysis. The

incremental ICER for trastuzumanb emtansine compared with lapatinib plus capecitabine was £166,429 per QALY gained (table 9), which was similar to the manufacturer's ICER of £167,236 per QALY gained. The ERG explained that this was because the changes it made did not act on the ICER in the same direction (all changes, except applying revised drug costs, decreased the ICER).

Table 9 ERG's base-case results (analysis 'e')

Technologies	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER incremental (£/QALY)	ICER vs. capecitabine (£/QALY)
Capecitabine	13,628	1.07	-	-	-	-
Lapatinib plus capecitabine	33,821	1.47	20,193	0.40	50,620	50,620
Trastuzumab emtansine	114,792	1.95	80,971	0.49	166,429	114,959
QALYs, quality-adjusted life years; Inc., incremental; ICER, incremental cost-effectiveness ratio						

Adapted from the ERG report, table 26, page 74

Trastuzumab plus capecitabine, vinorelbine and trastuzumab plus vinorelbine were also dominated in the above-listed analyses 'a', 'b', 'c' and 'd'. The incremental ICERs for trastuzumanb emtansine compared with lapatinib plus capecitabine from these analyses were £167,246, £166,701, £166,701 and £159,486 per QALY gained, respectively.

6.28 Based on key areas of uncertainty it identified, the ERG repeated within its base case selected sensitivity analyses performed by the manufacturer. Additionally, it explored the following:

- Assuming that, compared with lapatinib plus capecitabine, trastuzumanb emtansine had no effect on progression-free survival beyond 17.0 months after starting treatment and no effect on overall survival beyond 23.8 months after starting treatment (that is, beyond the points at which the treatment effect of trastuzumab emtansine was uncertain).
- Doubling the weekly costs associated with adverse events.

- Decreasing the drug and administration cost of trastuzumanb to investigate the impact of administering trastuzumab in its alternative form as a fixed subcutaneous dose.

In all the ERG's one-way sensitivity analyses, the incremental ICER for trastuzumanb emtansine compared with lapatinib plus capecitabine remained above £147,000 per QALY gained. The key drivers in the model were the relative treatment effect of trastuzumab emtansine on overall survival, the utility values, and the assumptions about drug wastage. The ERG noted that, given the uncertainty in the results of its mixed treatment comparison, if any of the comparators were equally effective as trastuzumab emtansine, the comparator would dominate trastuzumab emtansine because it is less expensive. For the full results of the ERG's one-way sensitivity analyses, see table 27 on page 75 of the ERG's report.

7 End-of-life considerations

The manufacturer did not request that trastuzumab emtansine be considered in the context of life-extending treatments at the end of life.

<table>
<tr><th>Criterion</th><th>Data available</th></tr>
<tr><td>The treatment is indicated for patients with a short life expectancy, normally less than 24 months</td><td>The median life expectancy of patients in the control group of EMILIA (lapatinib plus capecitabine) was 25.1 months.</td></tr>
<tr><td>There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment</td><td>Trastuzumab extended median overall survival in EMILIA by 5.8 months.

<u>Base-case model estimates of mean overall survival</u>

<table>
<tr><th></th><th>Life years gained</th><th>Difference</th></tr>
<tr><td>Trastuzumab emtansine</td><td>3.16</td><td>-</td></tr>
<tr><td>Lapatinib + capecitabine</td><td>2.53</td><td>0.63
(7.6 months)</td></tr>
<tr><td>Capecitabine</td><td>1.87</td><td>1.29
(15.5 months)</td></tr>
</table>
</td></tr>
<tr><td>The treatment is licensed or otherwise indicated for small patient populations</td><td>The manufacturer estimated the potential patient population for trastuzumab emtansine at 1290 patients.</td></tr>
</table>

8 Equality issues

8.1 No potential equality issues have been identified during the scoping process or in the evidence submitted.

9 Innovation

9.1 The manufacturer stated that trastuzumab emtansine combines the most effective treatment for HER2-positive metastatic breast cancer currently available (trastuzumab) with a highly cytotoxic drug (maytansine), and is

the first treatment in a new class of antibody-drug conjugates targeted to solid tumours. It indicated that trastuzumab emtansine has a high ability to target cancer cells specifically, which reduces systemic toxicity while increasing tumour site toxicity.

9.2 The manufacturer indicated that trastuzumab emtansine has benefits on the wider society because it can extend survival and improve quality of life, thereby offering women more time to contribute to their families and at work. Additionally, it noted that HER2-positive metastatic breast cancer is associated with a significant burden of illness because women with the disease die approximately 30 years younger than women of the same age without the disease. The manufacturer suggested that the health-related benefits of trastuzumab emtansine in relation to wider societal benefits and burden of illness are unlikely to be included in the QALY calculation.

10 Authors

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Appendix A: Supporting evidence

Related NICE guidance

Published

- Advanced breast cancer: diagnosis and treatment. NICE clinical guideline 81(2009).
- Eribulin for the treatment of locally advanced or metastatic breast cancer. NICE technology appraisal guidance 250 (2012).
- Fulvestrant for the treatment of locally advanced or metastatic breast cancer. NICE technology appraisal guidance 239 (2011).
- Guidance on the use of trastuzumab for the treatment of advanced breast cancer. NICE technology appraisal guidance 34 (2002).

Under development

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

- Pertuzumab in combination with trastuzumab and docetaxel for treating HER2-positive metastatic or locally recurrent unresectable breast cancer. NICE technology appraisal. Publication date to be confirmed

NICE pathways

- There is a NICE pathway on Advanced breast cancer, which is available from http://pathways.nice.org.uk/pathways/advanced-breast-cancer.

Hyperlink to the European Public Assessment Report