NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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

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Executive summary

HER2-positive metastatic breast cancer

Each year approximately 2,000 people in the United Kingdom die of HER2-positive (HER2+) metastatic breast cancer. The majority of the people diagnosed are women, with an average age at diagnosis of 55 years (Marty, 2005; Baselga, 2012).

With current treatments, 50% of women die within approximately three years of developing metastatic disease (Baselga, 2012). After progressing on treatment with trastuzumab and a taxane (the setting of this appraisal), median survival is only 15.4 months with capecitabine alone (Cameron, 2008).

The premature death of women with HER2+ metastatic breast cancer has a significant impact upon society. A family will lose a key contributor to household income, a key contributor to informal care of both children and elderly parents and a key influencer upon their child's future development.

The primary objective of the management of HER2+ metastatic breast cancer is to extend the person's length of life, whilst maintaining or improving quality of life. People with metastatic disease are unlikely to be cured.

There is a significant need for new treatments that extend the lives of women with HER2+ metastatic breast cancer (HER2+ mBC).

The current treatment algorithm

The majority of patients diagnosed with HER2+ breast cancer are diagnosed at an early stage of disease (HER2+ eBC) (Lyratzopoulos, 2012). For these patients the standard treatment is surgery followed by chemotherapy and trastuzumab (Herceptin) (NICE TA107). The primary aim of this treatment is curative.

For a proportion of patients this treatment will not be curative and their disease will recur as advanced/metastatic breast cancer. In addition to these patients with recurrent disease, a high proportion of patients diagnosed with

mBC will present with *'de novo'* disease (disease that hasn't been previously diagnosed in an earlier setting) (Lyratzopoulos, 2012).

The standard first-line treatment (first treatment for metastatic disease) for HER2+ mBC has historically been trastuzumab in combination with taxane (docetaxel or paclitaxel).

Following the recent EMA approval of, and introduction of Cancer Drugs Fund funding for, pertuzumab, the standard of care is evolving to a combination of pertuzumab, trastuzumab and docetaxel. A NICE Appraisal of pertuzumab is currently ongoing (NICE ID523).

After progressing on one of these 'first-line' therapies a patient will then typically receive a 'second-line' treatment. The treatments typically considered by a clinician in this setting include lapatinib in combination with capecitabine (approved by the Cancer Drugs Fund and AWMSG – NICE have not yet issued guidance on this regimen), monotherapy capecitabine or vinorelbine (NICE CG81) or continued use of trastuzumab with an alternative chemotherapy agent (NICE CG81) (not licensed, not CDF approved).

For those patients who progress rapidly (<6 months) following, or during, their adjuvant therapy with trastuzumab, a clinician will typically move directly to the second-line treatment options listed above. This is driven by a belief that rechallenging with trastuzumab in a patient who has progressed rapidly following previous treatment is likely to be ineffective.

Following progression on second line treatment a patient may be offered a third line treatment which typically consists of monotherapy capecitabine or vinorelbine (usually the alternative therapy to that given in second line).

Trastuzumab emtansine is a step-change in the treatment of HER2+ metastatic breast cancer

Trastuzumab emtansine (Kadcyla) is a new treatment for patients with HER2+ mBC who have previously received trastuzumab and a taxane, separately or in combination.

According to the license for trastuzumab emtansine, patients considered for treatment should have either:

- Received prior therapy for locally advanced or metastatic disease, or
- Developed disease recurrence during or within six months of completing adjuvant therapy

Our clinical advisors have indicated that, if funded, they would primarily utilise trastuzumab emtansine as a second line agent following progression on first line treatment. Under the license for trastuzumab emtansine it could also be utilised as a first line treatment in 'rapid relapsers' on adjuvant therapy (as defined above) or as a third or later line treatment.

What is trastuzumab emtansine?

Trastuzumab emtansine is part of a new class of drugs known as antibody-drug conjugates. It comprises three parts: trastuzumab, a HER2-directed antibody with proven anti-tumour effect in HER2+ breast cancer; a derivative of maytansine-1 (DM1), a potent cytotoxic from the maytansinoid family; and a 4-[N-maleimidomethyl]cyclohexane-1-carboxylate (MCC) thioether linker, shown to be stable in circulation and degraded in intracellular vesicles (Herceptin SPC, www.medicines.org; Lewis Phillips, 2008; Burris, 2011).

Trastuzumab emtansine has multiple modes of action. When it binds to the HER2 receptor on the tumour cell it reduces HER2-related signalling and targets the cell for antibody-dependent cellular cytotoxicity (ADCC). The trastuzumab emtansine-receptor complex is eventually internalised by endocytosis and undergoes lysosomal degradation, releasing the DM1 into the cell. DM1 is a microtubule inhibitor, and by binding to tubulin disrupts

intracellular tubulin networks inducing cell cycle arrest and apoptosis in dividing cells (Lewis Phillips, 2008; Juntilla, 2010).

As a result of this mechanism of action trastuzumab emtansine is able to specifically target HER2+ tumour cells, delivering targeted chemotherapy to these cells whilst limiting systemic exposure. This reduces the systemic toxicity compared with traditional systemic chemotherapy. This has resulted in increased efficacy and a reduction in symptomatic toxicity for patients as compared with a more conventional regimen of chemotherapy alone, or a targeted HER2-directed therapy in combination with chemotherapy, e.g. lapatinib plus capecitabine.

How efficacious is trastuzumab emtansine?

The pivotal study supporting use of trastuzumab emtainse is the 'EMILIA' study. This trial assessed the efficacy of trastuzumab emtansine compared to lapatinib plus capecitabine in patients who had progressed after having at least one previous line of therapy for HER2+ metastatic or locally advanced breast cancer, and patients who had relapsed on or within 6 months of completing adjuvant therapy for HER2+ breast cancer (Verma, 2012).

A primary analysis of the study for both progression-free survival (PFS) and overall survival (OS) was conducted in January 2012 with a further interim analysis for OS conducted in July 2012. The data presented are from the second interim analysis, which are the data as published in the New England Journal of Medicine, November 2012 (Verma, 2012).

EMILIA demonstrated a statistically significant increase in median survival of almost 6 months (from 25.1 months with lapatinib plus capecitabine to 30.9 months for trastuzumab emtansine [HR=0.682, p=0.0006]). It should be noted that this represents a survival advantage against an efficacious therapy that has not been NICE approved. Had this study been conducted against capecitabine alone this gain would likely have been even higher. This is a large and statistically significant survival gain and represents a significant step forward for women with HER2+ metastatic breast cancer, their families, and for all those affected by the premature death of these patients.

Trastuzumab emtansine also resulted in a median PFS gain of 3.2 months (9.6 months for trastuzumab emtansine compared to 6.4 months with lapatinib plus capecitabine [HR=0.650, p<0.0001]).

In addition to a significant gain in survival, patients treated with trastuzumab emtansine experienced numerically fewer severe (Grade ≥ 3) adverse events (40.8%) than patients who received lapatinib plus capecitabine (57.0%). This equates to a 28% reduction in severe adverse events. The most common severe AEs in the trastuzumab emtansine arm were predominately related to asymptomatic laboratory test abnormalities. In contrast, the most common severe AEs in patients who received lapatinib plus capecitabine tended to be symptom-driven (most commonly [in ≥ 10% of patients] diarrhoea [20.7%] and Palmar-Plantar Erythrodysesthesia (PPE) syndrome [16.4%].

This substantial reduction in the rate of severe, symptomatic adverse events is reflected in the patient quality of life data collected in EMILIA. Analysis of the FACT-B patient reported outcome questionnaire included in EMILIA demonstrates that patients in the trastuzumab emtansine arm had a statistically significant increase in the time to clinically significant patient reported symptom progression (median 7.1 months in the trastuzumab emtansine arm compared with 4.6 months in the lapatinib plus capecitabine arm) [HR=0.8, p=0.012] (as defined by the FACT-B TOI). Further, the number of patients reporting diarrhea symptoms increased 1.5- to 2-fold during treatment with capecitabine and lapatinib but remained near baseline levels in the trastuzumab emtansine arm (Welslau, 2013).

These data illustrate the opportunity for trastuzumab emtansine to significantly increase overall and progression free survival whilst both substantially reducing the number of severe, symptomatic adverse events experienced by patients and increasing their quality of life.

How is trastuzumab emtansine administered?

Trastuzumab emtansine is administered intravenously once every three weeks (21 day cycle). The starting dose of trastuzumab emtansine for all eligible patients is 3.6mg/kg. Treatment with trastuzumab emtansine is continued until disease progression or unmanageable toxicity.

The list price of one 100mg vial of trastuzumab emtansine is £1,641.01 and one 160mg vial is £2,625.62.

Cost-effectiveness

A cost utility analysis was conducted utilising data from the EMILIA study in order to evaluate the cost effectiveness of trastuzumab emtansine in people with HER2+, unresectable locally advanced or metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination (i.e. as per license).

Comparators considered included lapatinib in combination with capecitabine, capecitabine monotherapy, vinorelbine monotherapy, and either capecitabine or vinorelbine in combination with trastuzumab. As lapatinib in combination with capecitabine was the sole comparator in EMILIA, a mixed treatment comparison was conducted and incorporated into the model.

The model was a three state partitioned survival model (PFS, progressed disease, and death). This model structure has been utilised in numerous previous NICE technology appraisals in metastatic breast cancer. In accordance with the NICE reference case an NHS and personal social services perspective was used,and a 3.5% discount rate per annum for costs and QALYs was applied. A 10 year time horizon was utilised in order to capture all differences between the arms compared. A cycle length of one week was used in order to incorporate the 3-weekly dosing of trastuzumab emtansine and a half cycle correction where appropriate.

Resource use in each health state was based on NICE Clinical Guideline on Advanced Breast Cancer (NICE CG81, 2009). Costs were taken from BNF 65, PSSRU 2012 and NHS references costs 2012/13. The utilities were based on a study by Lloyd et al (2006). The Lloyd mixed model analysis has been applied in numerous NICE Technology Appraisals in this disease area (TA 257, TA 263, ID538, ID523).

The latest available data from EMILIA was utilised in order to develop the model (January 2012 data cut-off for PFS and July 2012 data cut-off for OS). As the survival data from EMILIA is not complete, it was necessary to apply parametric extrapolation in order to derive mean survival with and without the intervention.

In line with best practice in extrapolation, modelling was informed via interpretation of the EMILIA cumulative hazard plots, consultation with clinical and modelling experts (including a member of an ERG involved in the critique of manufacturer submissions) and validated through comparison with external data. The model has strong face validity when compared with the data available. Similarly the mixed treatment comparison was conducted in accordance with NICE recommended methods and consulted and validated with clinical and modelling experts (including a current NICE Committee member and expert in indirect and mixed treatment comparisons).

A simultaneous incremental analysis of all comparators was utilised in order to define the efficiency frontier and ensure that only cost-effective therapies were considered when evaluating the cost-effectiveness of trastuzumab emtansine.

The cost-effectiveness results are presented in Table 1, Table 2 and Table 3.

Table 1: Base-case results (costs, LYG and QALYs)

	Trastuzumab emtansine	Lapatinib and capecitabine	Trastuzumab and capecitabine	Capecitabine	Vinorelbine	Trastuzumab and vinorelbine
Technology acquisition cost	£90,831	£20,594	£21,811	£2,400	£559	£18,720
Other costs	£20,331	£13,576	£15,818	£10,773	£18,315	£20,326
Total costs	£111,162	£34,170	£37,629	£13,173	£18,874	£39,047
Difference in total costs (Trastuzumab emtansine – comparator)	-	£76,992	£73,533	£97,989	£92,288	£72,115
LYG	3.16	2.53	2.27	1.87	1.87	2.27
LYG difference (Trastuzumab emtansine – comparator)	-	0.63	0.89	1.29	1.29	0.89
QALYs	1.91	1.45	1.31	1.03	1.03	1.31
QALY difference (Trastuzumab emtansine – comparator)	-	0.46	0.60	0.88	0.88	0.60

LYG, life years gained; QALY(s), quality-adjusted life year(s); ICER, incremental cost-effectiveness ratio.

Table 2: Simultaneous incremental cost-effectiveness results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY gained) vs efficiency frontier regimen
Capecitabine	£13,173	1.87	1.03	-	-	-	-
Vinorelbine	£18,874	1.87	1.03	£5,701	0.00	0.00	Dominated (vs cap)
Lapatinib and capecitabine	£34,170	2.53	1.45	£20,997	0.66	0.42	£49,798 (vs cap)
Trastuzumab and capecitabine	£37,629	2.27	1.31	£24,456	0.40	0.28	£87,446 (vs cap)
Trastuzumab and vinorelbine	£39,047	2.27	1.31	£25,874	0.40	0.28	£92,516 (vs cap)
Trastuzumab emtansine	£111,162	3.16	1.91	£97,989	1.29	0.88	£111,095 (vs cap)

Table 1 shows the base case results for trastuzumab emtansine versus each comparator. It shows that trastuzumab emtansine is more effective but more costly than all other comparators.

The results in Table 2 demonstrate that when conducting a simultaneous cost-effectiveness analysis, no intervention is cost-effective.

Vinorelbine produced the same number of QALYs as capecitabine but was more expensive. As a result it was dominated and removed from the analysis.

The comparison of lapatinib in combination with capecitabine compared to capecitabine alone resulted in an ICER above the range typically considered acceptable by NICE (£49,798/QALY gained). Lapatinib in combination with capecitabine was therefore removed from the simultaneous incremental analysis.

Similarly, trastuzumab in combination with capecitabine and trastuzumab in combination with vinorelbine were found not be cost-effective against capecitabine monotherapy (with ICERs of £87,446 and £92,516 respectively) and were thus removed from the analysis.

The efficiency frontier therefore consists of only capecitabine monotherapy which represents which represents the primary comparator for trastuzumab emtansine.

The ICER of trastuzumab emtansine compared to capecitabine monotherapy was £111,095 per QALY gained (see Table 3).

Table 3: Final incremental cost-effectiveness results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY gained)
Capecitabine	£13,173	1.87	1.03	-	-	-	-
Trastuzumab emtansine	£111,162	3.16	1.91	£97,989	1.29	0.88	£111,095

Extensive deterministic sensitivity analyses were conducted – in each of these the ICER remained above £90,000 per QALY gained. These analyses indicate that the key drivers of the model are the cost of trastuzumab emtansine, the long term projection of progression-free survival and overall survival, the results of the mixed treatment comparison and the utility values used.

A 1,000 simulation probabilistic sensitivity analysis was conducted in order to evaluate the uncertainty associated with the base-case estimate. The probabilisitic sensitivity analysis (PSA) indicates that trastuzumab emtansine has a 0% chance of being cost-effective at a threshold of £30,000 per QALY gained at the list price.

The cost-effectiveness analysis highlights that even treatments such as trastuzmab emtansine - that demonstrate *both* a rarely seen substantial overall survival gain *and* reduced toxicity profile - are unable to meet NICE's current cost-effectiveness thresholds, unless major revisions to both the threshold and methodology employed for evaluating new treatments, are adopted.

Conclusion

Trastuzumab emtansine offers a substantial gain in survival compared with current standards of care to a group of women with life threatening disease and an extremely poor prognosis. It does so with reduced toxicity and improved quality of life. These improvements are of prime importance to women with HER2+ metastatic breast cancer, their families and society as a whole.

NICE's current methods and cost-effectiveness threshold do not allow for trastuzumab emtansine to be considered as being a 'cost-effective' use of NHS resources.

Section A – Decision problem

Manufacturers and sponsors will be requested to submit section A in advance of the full submission (for details on timelines, see the NICE document 'Guide to the single technology appraisal (STA) process' – www.nice.org.uk). A (draft) summary of product characteristics (SPC) for pharmaceuticals or information for use (IFU) for devices, a (draft) assessment report produced by the regulatory authorities (for example, the European Public Assessment Report [EPAR]), and a (draft) technical manual for devices should be provided (see section 10.1, appendix 1).

1 Description of technology under assessment

1.1 Give the brand name, approved name and, when appropriate, therapeutic class. For devices, provide details of any different versions of the same device.

Kadcyla®, trastuzumab emtansine, T-DM1, antineoplastic agent, Antibody-drug conjugate, ATC code: L01XC13.

1.2 What is the principal mechanism of action of the technology?

The human epidermal growth factor receptor (HER) family of cell surface receptors (HER1-4) mediate cell growth, differentiation and survival (Sundaresan, 1991; Yarden, 2001). Some breast cancers overexpress HER2 (HER2-positive breast cancer) leading to the activation of multiple signalling pathways within the cells resulting in an increase in their proliferation and a reduction in apoptosis (cell death). Overexpression of HER2 in breast cancer is present in approximately 23% of people with MBC (Roche data on file RXUKDONF00258, November 2012).

Trastuzumab emtansine is part of a new class of drugs known as antibody-drug conjugates. It comprises three parts: trastuzumab, a HER2-directed antibody with proved anti-tumour effect in HER2-positive breast cancer; derivative of maytansine-1 (DM1), a potent cytotoxic from the maytansinoid family; and a 4-[N-maleimidomethyl]cyclohexane-1-carboxylate (MCC)

thioether linker, shown to be stable in circulation and degraded in intracellular vesicles (Herceptin SPC, www.medicines.org; Lewis Phillips, 2008; Burris, 2011).

Trastuzumab emtansine therefore has multiple modes of action. When it binds to the HER2 receptor on the tumour cell it reduces HER2-related signalling and targets the cell for antibody-dependent cellular cytotoxicity (ADCC). The trastuzumab emtansine-receptor complex is eventually internalised by endocytosis and undergoes lysosomal degradation, releasing the DM1 into the cell. DM1 is a microtubule inhibitor, and by binding to tubulin disrupts intracellular tubulin networks inducing cell cycle arrest and apoptosis in dividing cells (Lewis Phillips, 2008; Juntilla, 2010).

As a result of this mechanism of action trastuzumab emtansine is able to specifically target HER2-positive tumour cells, delivering targeted chemotherapy to these cells and reducing systemic toxicity seen with systemic chemotherapy. This has resulted in increased efficacy and a reduction in toxicity for patients compared with a more conventional therapy of chemotherapy alone, or a targeted therapy in combination with chemotherapy, e.g. lapatinib plus capecitabine.

1.3 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

EU and UK marketing authorisation was received on 20th November 2013.

1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the marketing authorisation).

Risk of Medication errors

The manufacturer has been asked to update the product labels and packaging and to provide additional risk management procedures to prevent potential medication errors arriving from the potential confusion between the INNs trastuzumab (IV and SC) and trastuzumab emtansine. These, along with a comprehensive risk management plan and suite of HCP educational materials, have been submitted to the MHRA for review. These include clear written guidance for HCPs that will be provided proactively, a summary of similarities and differences including images of vials and packaging, and the EMA recommendation to use the brand name as well as the generic name to reduce the risk of medication errors amongst other risk mitigation measures. The products will also be distinguished by different colouring for packaging, vial labels and vial lids (trastuzumab IV colours are dark orange and red, trastuzumab SC colours are dark orange and light blue, trastuzumab emtansine colours are yellow and white (100 mg vial) or yellow and purple (160 mg vial)). Effectiveness of this programme will be monitored via an online survey as well as a paper based survey which can be returned by healthcare professionals via response-paid envelopes.

Lack of safety data after pertuzumab

The CHMP commented on the minimal safety data in patients who had previously received pertuzumab. It is anticipated that this will impact only early recipients of pertuzumab e.g. clinical trial patients. Given the high response rates (80.2% for pertuzumab, trastuzumab and docetaxel in the CLEOPATRA trial) and the long duration of progression free survival (PFS) (a median 18.7 months for pertuzumab, trastuzumab and docetaxel in the CLEOPATRA trial) few patients will have had an opportunity to receive pertuzumab (in a trial or in clinical practice), relapse, and start therapy with trastuzumab emtansine (Baselga, 2012, Swain, 2013) before further data become available.

An analysis of currently available safety data for patients who have received prior treatment with pertuzumab did not show any concerning safety signals, and the safety profile was consistent with the safety profile of the total patient

population in the trastuzumab emtansine arm (trastuzumab emtansine EPAR[1]). In addition, Roche will present data from the global safety data analysis every six months for four years post licence.

Prospective studies are planned to evaluate the safety of trastuzumab emtansine after pertuzumab. In addition, a registry of patients with HER2-positive MBC is planned. This registry will enroll HER2-positive patients within 6 months of their diagnosis of metastatic disease, regardless of treatment, and will follow them through multiple lines of treatment. This will provide valuable real world data on the efficacy and safety implications of sequencing anti-HER2 therapies, the quality of life in multiple lines (EQ-5D is included, as well as a breast cancer specific assessment), and health economic outcomes.

Subgroup analyses of PFS

The PFS efficacy benefit for trastuzumab emtansine in EMILIA was less pronounced for the subgroups of patients who were 65 - 74 years old, those with non-visceral disease and those with non-measurable disease, but there was no evidence of a detrimental effect in any of these subgroups. The data overall and by subgroup is shown in section 6.5.3. The reason for this is not clear; however, some imbalances in baseline factors that may have a prognostic impact (such as ECOG performance score, prior trastuzumab treatment, number of metastatic sites) favouring the lapatinib plus capecitabine arm were found and may have contributed to the observed results. There were also few patients in some of the respective subgroups, particularly patients ≥ 75 years (Total patient population: 991; patients 65-74 years of age: 113; patients ≥ 75 years: 25; patients with non-visceral disease: 322) (Verma, 2012).

The event rate in the non-visceral subgroup was lower (52%) than in the visceral disease subgroup (60%). This finding is consistent with the typical clinical scenario; patients with non-visceral metastases often have a less aggressive disease, further slowed by palliative radiotherapy and

[1] This will be provided once published on the EMA website.

bisphosphonates (permitted in the EMILIA study), resulting in slower tumour progression, and this may explain the lower effect. However, this was based solely on the study site classification at the time of randomisation for which explicit guidance had not been provided (the manufacturer had expectations that sites/investigators had adequate knowledge of visceral and non-visceral disease definitions). The sites of disease involvement have been subsequently reviewed according to the baseline assessments made during the independent review of tumour assessments, and further PFS (based on the independent assessments, data cut-off 14 January 2012) and OS (data cut-off 31 July 2012) subgroup analyses have been conducted applying the following two definitions of visceral disease (a) vs. non-visceral disease (b):

Definition 1: a) Presence of disease in the lungs or liver (either target or non-target lesions) vs. b) absence of disease in both the lungs and liver

Definition 2: a) Presence of disease in the lungs or liver or ascites or pleural effusion (either target or non-target lesions) vs. b) absence of disease in all these 4 sites

When the independently reviewed data are used and the revised classifications applied, a benefit of trastuzumab emtansine compared with lapatinib plus capecitabine was observed for patients with disease that did not involve visceral organs (RXUKDONF00337, December 2013).

Additional analyses were performed to evaluate the safety of patients with non-visceral disease according to Definition 2b. The incidence of deaths, SAEs, Grade ≥ 3 AEs and all AEs in the trastuzumab emtansine arm were consistently lower than in the control arm; there was no evidence of detriment associated with use of trastuzumab emtansine over lapatinib plus capecitabine (trastuzumab emtansine EPAR).

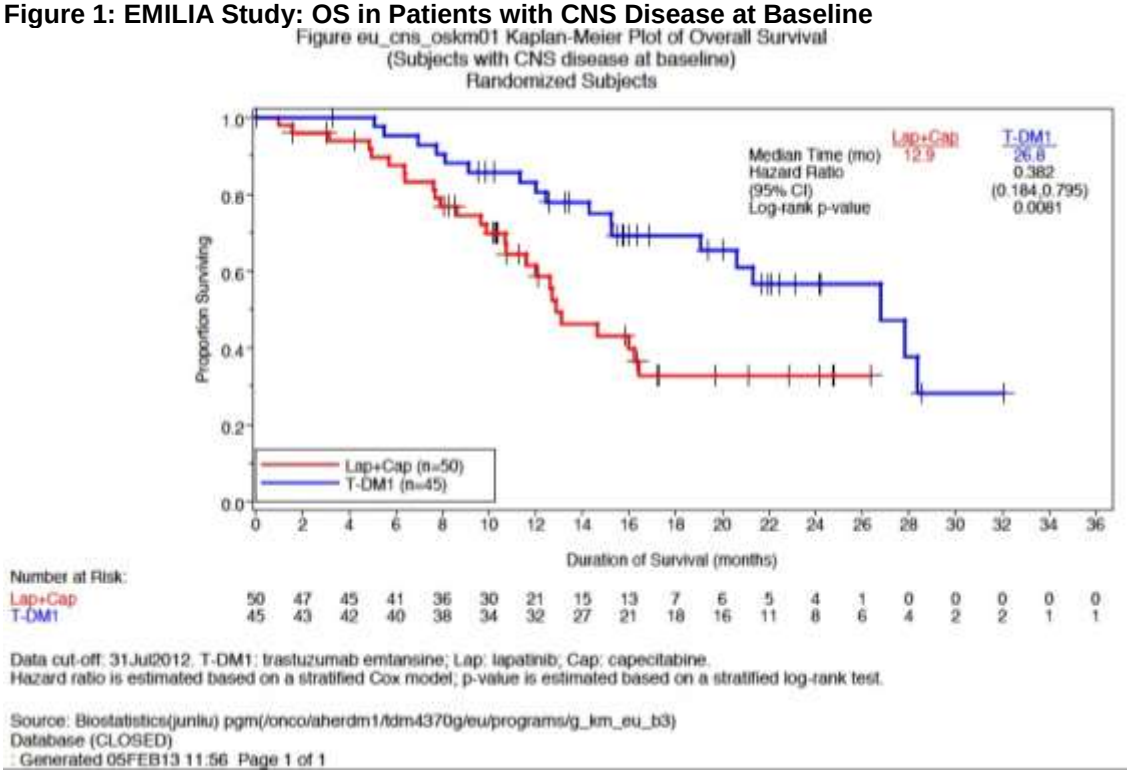
A similar analysis was performed for the PFS results from the TH3RESA study. TH3RESA was a Phase III, randomised, multicentre, two-arm, open-label clinical trial designed to compare the efficacy of trastuzumab emtansine with the physcian’s choice (TPC) for patients with HER2-positive MBC (see section 6.3). In this study all subgroups showed a clear benefit in favour of

trastuzumab emtansine including the subgroups mentioned above (Wildiers, 2013). The median PFS for patients with visceral disease was 3.4 months in the TPC arm compared to 6.2 months in the trastuzumab emtanisne arm (HR=0.56), and for patients with non-visceral disease was 3.1 months compared to 6.7 months, respectively (HR=0.41). The data overall and by subgroup is shown in section 6.5.

Patients with Brain Metastases

Patients with treated brain metastases not requiring therapy to control symptoms were included and treated in the EMILIA study. No difference in PFS was observed, but a clear benefit in favor of trastuzumab emtansine was seen with regard to OS (see Figure 1) (trastuzumab emtansine EPAR).

Figure 1: EMILIA Study: OS in Patients with CNS Disease at Baseline



1.5 What are the (anticipated) indication(s) in the UK? For devices, provide the (anticipated) CE marking, including the indication for use.

Kadcyla, as a single agent, is indicated 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 six months of completing adjuvant therapy

1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

Status	Details
Ongoing (Primary endpoints published (Verma 2012); final OS due 2014)	**EMILIA (TDM4370g, BO21977)** - Phase III, randomised, multicentre, international, two-arm, open-label clinical trial designed to compare the safety and efficacy of trastuzumab emtansine with that of capecitabine plus lapatinib in patients with metastatic or unresectable locally advanced/recurrent HER2-positive breast cancer who have previously received at least one line of therapy for MBC or who have relapsed on or within 6 months of receiving adjuvant therapy. (www.clinicaltrials.gov NCT00829166)
Ongoing (PFS primary endpoint presented ECC 2013; OS primary endpoint due 2014)	**TH3RESA (BO25734)** – Phase III, randomised (2:1), multicentre, international, two-arm, open-label clinical trial comparing the efficacy and safety of trastuzumab emtansine vs treatment of the physician's choice (TPC) in patients with metastatic or unresectable locally advanced/recurrent HER2-positive breast cancer who have previously received at least two lines of therapy for MBC. (www.clinicaltrials.gov NCT01419197)
Ongoing	**KAMILLA (MO28231)** – Phase IIIb, multicentre, international single-arm clinical trial assessing the efficacy and safety of trastuzumab emtansine in patients with metastatic or

	unresectable locally advanced/recurrent HER2-positive breast cancer who have previously received at least one line of therapy for MBC or who have relapsed on or within 6 months of receiving adjuvant therapy. (www.clinicaltrials.gov NCT01702571)
Ongoing	**TDM4529g/BO25430** - Multicentre, international single-arm clinical trial assessing the long term safety of trastuzumab emtansine in patients with metastatic or unresectable locally advanced/recurrent HER2-positive breast cancer who have previously received trastuzumab emtanine in a clinical trial and are still eligible to continue treatment (www.clinicaltrials.gov NCT00781612).
Ongoing	**NCT01513083** - Multicentre, international, open-label, parallel group clinical trial to evaluate the pharmacokinetics and safety of trastuzumab emtansine in patients with HER2-positive metastatic breast cancer and normal or reduced hepatic function (www.clinicaltrials.gov NCT00781612).
Ongoing	**TDM4688g** - Phase II, multicentre, US, single arm, open-label clinical trial evaluating the impact of trastuzumab emtansine on QTc interval in patients with metastatic or unresectable locally advanced/recurrent HER2-positive breast cancer. (www.clinicaltrials.gov NCT00943670)
Completed (Primary endpoints published – Hurwitz, 2012)	**TDM4450g/BO21976 –** Phase II, multicentre, international, two arm, open-label clinical trial comparing the efficacy and safety of trastuzumab emtansine with that of trastuzumab plus docetaxel in patients with metastatic or unresectable locally advanced/recurrent HER2-positive breast cancer who have not received chemotherapy for MBC. (www.clinicaltrials.gov NCT00679341)

Completed (Primary endpoint published – Yardley 2013)	**TDM4884g** - Phase II, multicentre, US, single arm, open-label expanded access study evaluating the efficacy and safety of trastuzumab emtansine in a real world population (www.clinicaltrials.gov NCT01120561)

Note: Summary of all ongoing and completed clinical studies with trastuzumab emtansine in LABC and MBC is included in section 10.13.8

1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

The anticipated date of availability in the UK is January 2014.

1.8 Does the technology have regulatory approval outside the UK? If so, please provide details.

Trastuzumab emtansine is approved in the following countries

- USA February 2013
- Kuwait May 2013
- Switzerland May 2013
- Australia August 2013
- New Zealand September 2013
- Ecuador August 2013
- Uruguay August 2013
- Japan September 2013
- Macao October 2013
- Mexico October 2013
- Canada September 2013
- Dominican Republic November 2013
- EU November 2013

The indications for the above countries are based on the EMILIA population and similar to the EU wording, with the exception of Switzerland which also has a broad indication in the first line setting.

1.9 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

An SMC appraisal of trastuzumab emtansine will begin in January 2014 with guidance expected May 2014.

For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Table 4: Unit costs of technology being appraised

Pharmaceutical formulation	Powder for concentrate for solution for infusion
Acquisition cost (excluding VAT)	£1641.01 per 100mg vial £2625.62 per 160mg vial
Method of administration	Intravenous Infusion
Doses	3.6 mg/kg
Dosing frequency	Every three weeks
Average length of a course of treatment	This will be evaluated formally in economic modelling. A summary of treatment duration seen in the EMILIA trial is included below. Median PFS for patients receiving trastuzumab emtansine in EMILIA was 9.6 months, treatment was until progression or unacceptable toxicity. Number of cycles: Number of patients (%) ≤ 6: 157 (32%) 6 - 12: 156 (31.8%) 12 -18: 84 (17.1%) 18 - 24: 43 (9.8%) >24: 50 (10.2%)
Average cost of a course of treatment	This will be evaluated formally in economic modelling.
Anticipated average interval between courses of treatments	A person with HER2-positive MBC will receive only one course of treatment with trastuzumab emtansine
Anticipated number of repeat courses of treatments	A person with HER2-positive MBC will receive only one course of treatment with trastuzumab emtansine
Dose adjustments	Dose adjustments are recommended for the following: **Thrombocytopenia**: Platelets 25,000 to <50,000/mm^3, delay trastuzumab emtansine until platelet count recovers to ≥75,000mm^3 then maintain previous dose. <25,000/mm^3, delay trastuzumab emtansine until platelet count recovers to ≥75,000mm^3 and then reduce the dose one level according to the dose reduction table. **Elevated liver transaminases**: >5 to ≤20 x ULN: delay trastuzumab emtansine until AST/ALT recover to >2.5 to ≤5 x ULN, then reduce dose one level. >20 x ULN: discontinue trastuzumab emtansine. >3 x ULN and concomitant bilirubin >2 x ULN: permanently discontinue trastuzumab emtansine. **Bilirubin**: >1.5 to ≤3 x ULN: delay trastuzumab emtansine until bilirubin recovers to >1 to 1.5 x ULN. Maintain dose. >3 to ≤10 x ULN: delay trastuzumab emtansine until total bilirubin recovers to >1 to 1.5 x ULN. Reduce dose by one level. >10 x ULN: discontinue trastuzumab emtansine. **Peripheral neuropathy**: delay trastuzumab emtansine for Grade 3 or 4 peripheral neuropathy until symptoms resolve or improve to Grade ≤ 2. At re-treatment a dose reduction may be considered. **Dose reduction schedule (Starting dose is 3.6 mg/kg)**: **Dose to be administered** First dose reduction: 3 mg/kg Second dose reduction: 2.4 mg/kg Requirement for further dose reduction: Discontinue treatment

1.10 For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide

details of the anticipated unit cost, including the range of possible unit costs.

N/a

1.11 Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

According to NICE Guideline CG81 and NICE Breast Cancer Quality Standard (QS) 12, people with breast cancer should have a HER2 test at initial diagnosis or at recurrence if not assessed at the time of initial diagnosis, or if it is felt the biology of the tumour may have changed. No additional tests are required to diagnose people for treatment with trastuzumab emtansine, or prior to the administration of trastuzumab emtansine.

1.12 Is there a need for monitoring of patients over and above usual clinical practice for this technology?

Minimal additional monitoring is required.

Patients receiving trastuzumab emtansine should be monitored for platelet counts and liver function prior to each dose, and the dose modified where appropriate. This is standard for people receiving chemotherapy which is usually part of a standard treatment regimen for advanced disease.

As with other infusional drugs including monoclonal antibodies, taxanes and platinum-bases therapies, patients should be monitored for infusion related reactions; as with other HER2-directed therapies, regular monitoring of left ventricular ejection fraction (LVEF) is recommended.

1.13 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

Trastuzumab emtansine is administered as a monotherapy.

2 Context

In this background section the manufacturer or sponsor should contextualise the evidence relating to the decision problem.

2.1 Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

Breast cancer is the most common malignancy affecting women in the UK. Approximately 50,000 people were diagnosed with breast cancer in the UK in 2010, of which 99.2% were women (CRUK 2012). Worldwide breast cancer is the leading cause of cancer death among women, accounting for 23% (1.38 million) of all new cancer cases and 14% of the cancer deaths in women in 2011 (Jemal, 2011). Although advancements in the detection and management of early stage disease have resulted in improvements in breast cancer mortality over recent years (Levi, 2005; Malvezzi, 2011), unresectable locally advanced breast cancer (LABC) and MBC remain largely incurable, with the majority of people dying due to their disease, with 5 year survival rates in Europe of only 55% for all (resectable/unresectable) LABC and 18% for MBC (Sant, 2003).

Overexpression of HER2 in breast cancer is present in approximately 23% of people with MBC (Roche data on file RXUKDONF00258, November 2012). Without targeted therapy, HER2-positive MBC is associated with aggressive disease, higher rates of recurrence, shorter disease-free survival and shorter overall survival as compared with tumours that do not overexpress HER2 (Borg, 1990; Ross, 1998; Menard, 2001; Brown, 2008; Crigliano, 2009; Ross, 2009; Pauletti, 2000). People with HER2-positive breast cancer are approximately five years younger than the general breast cancer population with an average age of around 53 (Neven, 2008; Kwan, 2009; Tripathy, 2013). Hence, this disease has significant societal impact.

Trastuzumab plus taxane (docetaxel or paclitaxel), and pertuzumab plus trastuzumab plus docetaxel, are approved for the treatment of first-line

metastatic HER2 positive tumours (Slamon, 2001; Marty, 2005; Baselga, 2012). The currently approved combination regimen for the treatment of second line HER2-positive MBC is lapatinib plus capecitabine (Cameron, 2008).

These targeted therapies brought significant advances in treatment for patients with HER2-positive MBC. A meta-analysis in 2009 of 39, 730 patients reported an OS rate of 25.1 months for HER2-positive MBC patients who received trastuzumab in combination with chemotherapy compared to 20.3 for those who received chemotherapy alone (p=0.01)(Ross, 2009). The recent CLEOPATRA study examining trastuzumab plus docetaxel against pertuzumab plus trastuzumab plus docetaxel improved on this with a HR for OS of 0.66. Median OS was 37.6 months in the trastuzumab plus docetaxel arm, however the data was not yet mature in the pertuzumab plus trastuzumab plus docetaxel arm (Swain, 2013). Landmark survival estimates at 1, 2 and 3 years were 94% vs 89%, 81% vs 69% and 66% vs 50% for the pertuzumab containing arm and the trastuzumab plus docetaxel arms, respectively (Swain, 2013). However, resistance and intolerability to HER2-targeted therapies is common and a majority of patients will relapse and eventually die from their HER2-positive MBC. This highlights an unmet need for an effective, novel, and HER2-targeted therapeutic agent offering improvement in efficacy and/or tolerability of therapy for patients whose advanced disease relapsed on trastuzumab.

2.2 Please provide the number of patients covered by this particular therapeutic indication in the marketing authorisation and also including all therapeutic indications for the technology, or for which the technology is otherwise indicated, in England and Wales and provide the source of the data.

Figure 2: Trastuzumab emtansine eligible population

Trastuzumab Emtansine Eligible Patient Population

(a)	England incident breast cancer population		41,236		
(b)	% Metastatic	26%	10,757		
(c)	% HER2 tested and +ve	21%	2,259		
(d)	% eligible for first line (1L) treatment	74%	1,667	% Early Relapsers 12%	200
(e)	% who progress and are eligible for second line (2L) treatment	65%	1,090		
(f)	**Total 1L Early Relapsers and 2L Eligible**		1,290		

(a) Incidence based on QOF, HES and NCIN data: Roche Data on File RXUKDONF00301, March 2013

(b) Data taken from a Roche-commissioned analysis of the IMS Oncology Analyzer, (UK MAT Quarter 2 2012): Roche Data on File RXUKDONF00258, November 2012

(c) Data taken from a Roche-commissioned analysis of the IMS Oncology Analyzer, (UK MAT Quarter 2 2012): Roche Data on File RXUKDONF00258, November 2012

(d) Internal Roche Assumption

(e) Internal Roche Assumption

(f) Calculation: Add 1L early relapsers to 2L eligible

Please provide information about the life expectancy of people with the disease in England and Wales and provide the source of the data.

People with HER2-positive MBC are generally around 5 years younger than patients with HER2-negative disease (Neven, 2008; Kwan, 2009) and have a poor prognosis after treatment with trastuzumab and a taxane. Median

survival in the control (standard of care; lapatinib plus capecitabine) arm in the EMILIA study was approximately two years (Verma, 2012).

The current standard of care in England for patients who have progressed on trastuzumab is lapatinib plus capecitabine, a licensed indication which was supported by data from the EGF100151 trial. In this study patients receiving capecitabine plus lapatinib therapy had a median overall survival (OS) of 15.6 months compared to 15.4 months with capecitabine alone (Cameron, 2008). In the CEREBEL study, within a subgroup of patients previously treated with trastuzumab for metastatic disease, patients receiving capecitabine plus trastuzumab versus capecitabine plus lapatinib demonstrated median OS of 27.3 months and 22.7 months, respectively (hazard ratio [HR] [95% CI]: 1.18 [0.76, 1.83]) (Pivot, 2012). This illustrates the unmet need in patients previously treated with trastuzumab, for an effective therapy which offers a potential gain in life expectency.

Other trials in this population show a similar life expectancy. In the GBG-26 study, patients receiving capecitabine plus trastuzumab or capecitabine monotherapy had a median OS of 24.9 months vs. 20.6 months, respectively (HR [95% CI]: 0.94 [0.65, 1.35], p=0.73) (Von Minckwitz, 2011).

In the NICE review of vinorelbine in this setting the median OS for intravenous vinorelbine monotherapy ranged from 9.9 to 16.8 months (Lewis, 2002).

It is important to note that the NICE approved therapies of capecitabine or vinorelbine monotherapy demonstrate a median OS of 15.4 months or 16.8 months, respectively.

2.3 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

- NICE Technology Appraisal No. 34, March 2002, ‘Trastuzumab for the treatment of advanced breast cancer’.

- NICE Technology Appraisal ID20. December 2006, 'Lapatinib in combination with capecitabine for women with previously treated advanced or metastatic breast cancer.'
- NICE Clinical Guideline No. 81, February 2009, 'Advanced breast cancer: diagnosis and treatment'
- NICE Advanced breast cancer: chemotherapy and biological therapy pathway
- NICE Breast Cancer QS12: Advanced breast cancer pathway, September 2011

Other Relevant Guidelines

- Breast cancer follow-up and management after primary treatment: American Society of Clinical Oncology Clinical Practice Guideline Update – Published in JCO, Vol 3, Issue 7 (March), 2013: 961-965
- Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Update – Posted ahead of print on www.jco.org on 7th October 2013
- Guidelines of the AGO Breast Committee: Targeted Agents. Update March 2012
- NCCN Clinical Practice Guidelines in Oncology – Breast Cancer V. 3.2012 dated 09/10/12
- Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up Published in Ann Oncol (2012) 23 (suppl 7): vii11-vii19

2.4 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

NICE Clinical Guideline 81 (CG81) includes recommendations on the diagnosis and treatment of people with HER2-positive MBC. The guideline recommends assessment of HER2 status at the time of disease recurrence if receptor status was not assessed at the time of initial diagnosis, unless the original diagnosis was made before testing for HER2 was routine or if it is felt the biology of the tumour may have changed.

Treatment of HER2-positive MBC is outlined in a treatment algorithm in CG81 (CG81, Page 24). The algorithm states that trastuzumab with paclitaxel in line with TA34, or docetaxel, is the standard first line treatment of HER2-positive MBC. The algorithm recommends treatment with vinorelbine or capecitabine in the second line setting with the option for retreatment with trastuzumab in addition to one of these chemotherapy agents if the patient has CNS only progression during first line trastuzumab treatment. Trastuzumab monotherapy can be used in patients who have received at least two lines of therapy for MBC.

It should be noted that CG81 has not been updated since 2009 and does not necessarily reflect the current standard of care for patients in England with HER2-positive MBC.

Due to the introduction of the Cancer Drugs Fund in October 2010 many patients will now receive pertuzumab in combination with trastuzumab and docetaxel as a first line treatment followed by lapatinib in combination with capecitabine in the second line setting (Roche data on file - IMS UK MBC Enhanced Tumour Study Q2 2012).

As a result there is significant divergence between the NICE approved pathway of care for a HER2-positive mBC patients and the clinical reality in England.

NICE approved clinical pathway:

- First line: trastuzumab plus paclitaxel

- Second line: capecitabine or vinorelbine (plus trastuzumab in CNS only progression) *Note: as this use is guideline recommended only and not associated with a funding mandate, trastuzumab retreatment use is variable throughout the country)*

- Third line: vinorelbine or capecitabine or trastuzumab

CDF approved clinical pathway would receive:

- First line: pertuzumab plus trastuzumab plus docetaxel; or trastuzumab plus taxane

- Second line: lapatinib plus capecitabine

- Third line: capecitabine or vinorelbine or trastuzumab

Following NICE approval of trastuzumab emtansine our clinical experts anticipate that it will be primarily given in as a single-agent to patients who have received one line of therapy for HER2-positive MBC, or whose cancer has relapsed on, or within six months of completing adjuvant treatment for HER2-positive MBC.

This will effectively displace lapatinib/capecitabine in the current clinical pathway in England or capecitabine or vinorelbine in Wales.

2.5 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

See response to 2.4 above.

2.6 Please identify the main comparator(s) and justify their selection.

- Lapatinib in combination with capecitabine (LAP-CAP)

- Trastuzumab in combination with capecitabine (TRA-CAP)

- Trastuzumab in combination with vinorelbine (TRA-VIN)

- Capecitabine (CAP)
- Vinorelbine (VIN)

These comparators are as per the final scope.

In the second line setting lapatinib in combination with capecitabine is the most dominant regimen in UK clinical practice, used in 41% of all patients. Trastuzumab in combination with capecitabine is the next most popular regimen, used in 13% of patients (RXUKDONF00338, December 2013)).

In the third line setting lapatinib in combination with capecitabine is also the most commonly used regimen (27% of all patients) followed by vinorelbine monotherapy (RXUKDONF00338, December 2013)). It should be noted that the data to support use of vinorelbine in third line HER2-positive MBC patients is sparce, consisting mainly of low patient number, non-comparative phase II trials or small RCTs.

2.7 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

In a pooled safety analysis review of 882 patients who received trastuzumab emtansine at 3.6 mg/kg in the most commonly reported adverse events of any grade were fatigue, nausea, headache, thrombocytopenia and constipation. Most adverse events were mild to moderate Grades 1/2. With the exception of fatigue, the most commonly reported Grade ≥ 3 adverse events were related to asymptomatic laboratory test abnormalities: thrombocytopenia, increased hepatic transaminases, hypokalaemia, and anaemia. The majority of adverse events were managed by delaying or reducing the dose of trastuzumab emtansine (Dieras, 2012).

The cost associated with treatment of adverse events will be considered in the economic analysis.

2.8 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

Trastuzumab emtanisine is being compared to both infusional and oral therapies.

Trastuzumab emtansine is administered on a three-weekly cycle, similar to trastuzumab. Both trastuzumab emtansine and trastuzumab are administered for 90 minutes for the first infusion, followed by 30 (±10) minute infusions if the first infusion was well tolerated. These infusions typically take place in a hospital within an established oncology unit, which has the staffing and infrastructure required for administration of cancer treatments.

The adverse events associated with trastuzumab emtansine which require monitoring are decreased platelets, increased liver enzymes, LVEF decline, infusion related reactions and hypersensitivity (Verma, 2012; Hurwitz, 2012). These are all routinely measured in patients receiving chemotherapy and anti-HER2 therapy.

Testing and monitoring of HER2-positive MBC is outlined in CG81.

No new resources are therefore required for trastuzumab emtansine.

2.9 Does the technology require additional infrastructure to be put in place?

No.

3 Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).

3.1 Identification of equality issues

3.1.1 Please let us know if you think that this appraisal:

- **could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;**
- **could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology**
- **could lead to recommendations that have any adverse impact on people with a particular disability or disabilities**

Please provide us with any evidence that would enable the Committee to identify and consider such impacts.

No equality issues have been identified.

3.1.2 How has the analysis addressed these issues?

No equality issues have been identified

4 Innovation

4.1.1 Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a 'step-change' in the management of the condition.

Treatment goals for unresectable LABC and MBC involve increasing the life expectancy, both overall and before progression, and improving patients' quality of life. Trastuzumab emtansine is the first treatment for HER2-positive unresectable LABC and MBC to address both of these, reducing the need for treatment compromise between efficacy and tolerability.

Trastuzumab emtansine is part of a new class of drugs known as antibody-drug conjugates (ADCs). The class has been the focus of research for several decades but, due to technological, targeting and potency issues, has only recently produced successful therapies (Zolot, 2013). ADCs link a highly potent drug to a targeting antibody thus delivering therapeutic benefit directly to the site of the disease. Thus, ADCs are able to harness the highly specific targeting ability of monoclonal antibodies, to distinguish between tumour and healthy cells (Chari, 2008).

Trastuzumab emtansine is the first HER2-targeted ADC to gain a licence for treatment of a solid tumour. It combines the currently most effective treatment for HER2-positive MBC, the monoclonal antibody trastuzumab, with a highly cytotoxic drug, DM1. These two are joined by a linker that is stable in circulation but is degraded in intracellular lysosomes after HER2 -receptor complex internalisation. This means that the cytotoxic agent is delivered to the interior of the tumour cell, resulting in a clinically significant reduction in systemic toxicity and an increase in tumour site toxicity, when compared with traditional systemic chemotherapy treatment combinations (Chari, 2008; Verma, 2012; Wildiers, 2013).

Compared with lapatinib and capecitabine, the innovative technology behind trastuzumab emtansine has resulted in a statistically and clinically significant

increase in efficacy, in terms of OS (30.9 months vs 25.1 months), and PFS (9.6 vs 6.4 months); at the same time as reducing the number of patients experiencing severe Grade ≥ 3 adverse events (40.8% vs 57%) or terminating treatment due to adverse events (5.9% vs 10.7%) (Verma, 2012).

This combination of increased efficacy and reduced toxicity resulted in increased patient quality of life as assessed by the patient reported outcomes survey FACT-B Trial Outcome Index (TOI; includes physical, functional and breast cancer specific subscales) compared to the standard of care alternative of lapatinib plus capecitabine (Verma, 2012).

Additionally, there was a consistent improvement in secondary efficacy endpoints, including independently-assessed objective response rate (ORR; 43.6% vs. 30.8%, difference 12.7% [6.0%, 19.4%]; $p = 0.0002$), and duration of response (DOR; median 12.6 as compared to 6.5 months) for trastuzumab emtansine as compared to lapatinib plus capecitabine, respectively (Verma, 2012).

4.1.2 Discuss whether and how you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation.

Wider Societal Benefits

The median age of women in both arms of the EMILIA study was only 53 years old (Verma, 2012).

The premature death of these women can have a significant impact upon families. A family may lose a key contributor to household income, a key contributor to informal care of both children and elderly parents and a key influencer upon their child's future development.

Trastuzumab emtansine can extend survival and grant women more time to contribute to their families (both financially and via informal care) as well as achieve personal milestones (for example build memories with their children). In addition, the reduction in toxicity over current care means that these women

are more fit and able to participate in family life, within their communities, and at work.

To date most studies in MBC have failed to demonstrate an appreciable difference in patient reported outcomes between standard of care therapy and experimental agents. In contrast, FACT-B TOI in the EMILIA study showed a statistically significant benefit in favour of trastuzumab emtansine over lapatinib plus capecitabine. Patient reported time to symptom progression was delayed from 4.6 months to 7.1 months with trastuzumab emtansine (HR=0.796, p=0.0121) (Verma, 2012).

In addition, patients were less bothered by the side effects of trastuzumab emtansine than lapatinib plus capecitabine, and on treatment incidence of patient reported diarrhoea symptoms was lower with trastuzumab emtansine than lapatinib plus capecitabine (Welslau, 2013).

These issues are not currently captured in the NICE process and should be considered be the Committee.

The Differential Value of QALYs Gained in Differential Circumstances

HER2-positive MBC is associated with a significant burden of illness. These women die approximately 30 years earlier than an equivalent healthy woman (ONS Interim Life Tables 2008-2010).

It is a widely held view that society places a preference upon QALYs gained by people in these circumstances (a view shared by the government in its consultations on “Value Based Pricing”). This preference is not captured in a simple QALY calculation and is not captured by the use of an arbitrarily defined ‘End of Life’ criteria.

We believe the Committee should carefully consider society’s potential preference of QALYs gained in areas of a higher burden of disease.

4.1.3 Please identify the data you have used to make these judgements, to enable the Appraisal Committee to take account of these benefits.

People's preference for QALYs gained in people with a high burden of illness is being investigated in an on-going Department of Health commissioned study. We envisage the results of this study to be published prior to the conclusion of this Appraisal.

5 Statement of the decision problem

In this section the manufacturer or sponsor should specify the decision problem that the submission addresses. The decision problem should be derived from the final scope issued by NICE and should state the key parameters that the information in the evidence submission will address.

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	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.	As per scope.	n/a
Intervention	Trastuzumab emtansine	As per scope.	n/a
Comparator(s)	-lapatinib in combination with capecitabine -capecitabine -trastuzumab in combination with capecitabine -vinorelbine -trastuzumab in combination with vinorelbine	As per scope.	n/a
Outcomes	-progression free survival -overall survival -adverse effects of treatment -health-related quality of life.	As per scope.	n/a
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.	As per scope.	n/a

	Costs will be considered from an NHS and Personal Social Services perspective.		
Subgroups to be considered	No subgroups identified.	As per scope.	n/a
Special considerations, including issues related to equity or equality	No potential equity or equality issues identified	As per scope.	n/a

Section B – Clinical and cost effectiveness

When estimating clinical and cost effectiveness, particular emphasis should be given to adhering to the 'reference case' (see the NICE document 'Guide to the methods of technology appraisal' – www.nice.org.uk). Reasons for deviating from the reference case should be clearly explained. Particularly important features of the reference case include those listed in the table below.

Element of health technology assessment	**Reference case**	**Section in 'Guide to the methods of technology appraisal'**
Defining the decision problem	The scope developed by NICE	5.2.5 and 5.2.6
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	5.2.5 and 5.2.6
Perspective costs	NHS and PSS	5.2.7 to 5.2.10
Perspective benefits	All health effects on individuals	5.2.7 to 5.2.10
Type of economic evaluation	Cost-effectiveness analysis	5.2.11 and 5.2.12
Synthesis of evidence on outcomes	Based on a systematic review	5.3
Measure of health effects	QALYs	5.4
Source of data for measurement of HRQL	Reported directly by patients and carers	5.4
Source of preference data for valuation of changes in HRQL	Representative sample of the public	5.4
Discount rate	An annual rate of 3.5% on both costs and health effects	5.6
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	5.12
HRQL, health-related quality of life; NHS, National Health Service; PSS, personal social services; QALY(s), quality-adjusted life year(s)		

6 Clinical evidence

Manufacturers and sponsors are requested to present clinical evidence for their technology in the following sections. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3 and 5.3.1 to 5.3.8.

6.1 Identification of studies

6.1.1 Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data that may be held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 10.2, appendix 2.

A systematic review was undertaken in order to identify all randomised evidence relevant to the decision problem.

Searches used index and text words which included trastuzumab emtansine and breast cancer as descriptors. The search was restricted to include only documents relating to humans and clinical trials where trastuzumab emtansine was the main focus or where trastuzumab emtansine was being investigated in combination with other agents. Only publications written in English were assessed. The search was restricted to metastatic or advanced breast cancer. The search was further restricted manually according to inclusion/exclusion criteria in section **Error! Reference source not found.**.

Full details of the searches conducted and terms used are provided in Appendix **Error! Reference source not found.**. Details of the search outputs/records obtained and reasons for exclusion/inclusion of records are also provided in Appendix **Error! Reference source not found.**.

6.2 Study selection

6.2.1 Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent. A suggested format is provided below.

Inclusion Criteria:

Published papers or abstracts which evaluated the following were included:

- Trastuzumab emtansine had to be the major focus of the study, in order to eliminate references which merely mentioned trastuzumab emtansine as part of a discussion of treatments for metastatic breast cancer or other cancers, for example review articles.
- Metastatic breast cancer was the major focus of the study, in order to eliminate papers addressing the use of trastuzumab emtansine in other breast cancers e.g. Inflammatory breast cancer, or in other settings eg. early breast cancer. MBC studies would normally have included patients with unresectable LABC.
- Data addressing the efficacy of trastuzumab emtansine in combination with other agents are not in line with this submission.
- Documents relating to humans – since work in animal models is not relevant to this submission.

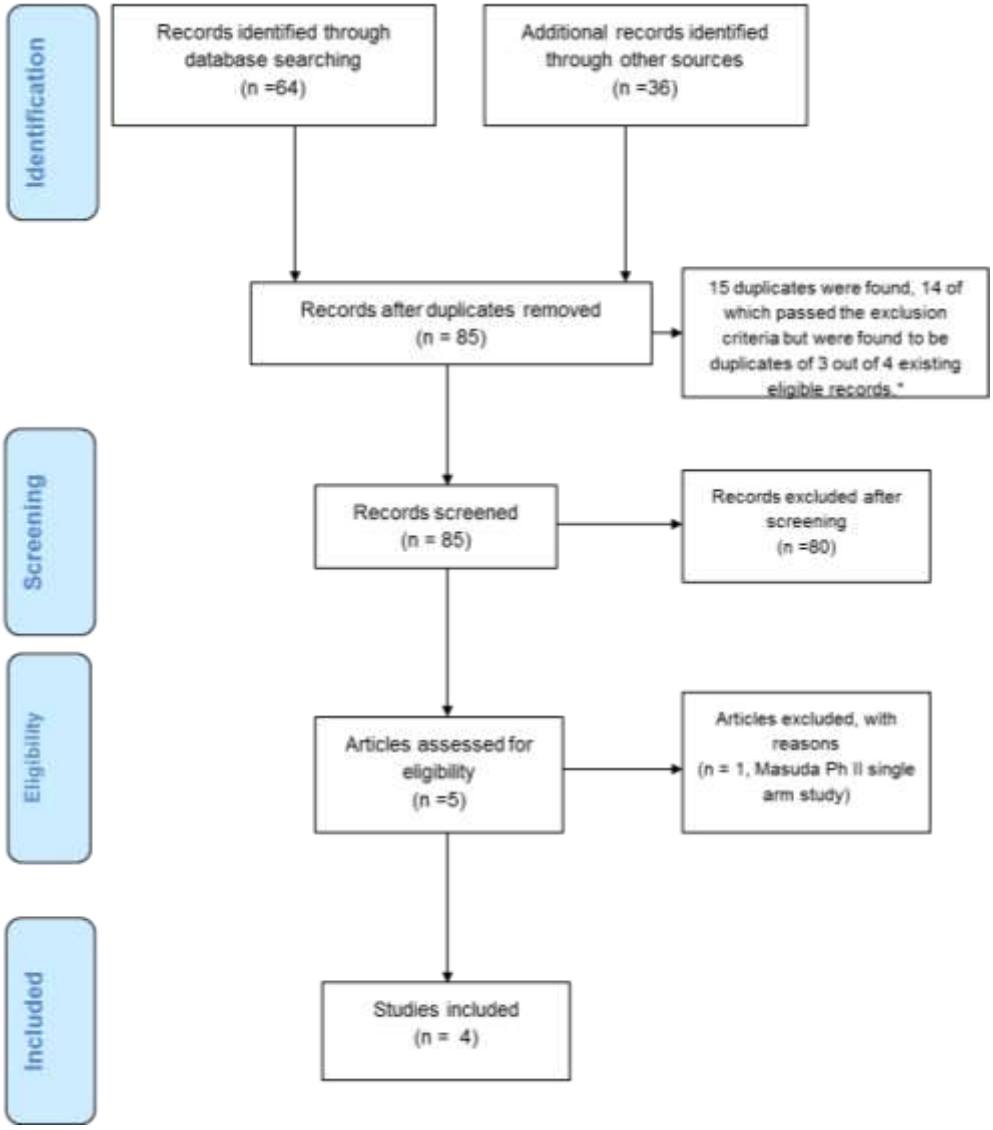
Exclusion criteria:

- References which were not randomised, controlled trials.
- Studies where trastuzumab emtansine was not included.
- Studies which were in non-relevant populations ie. Early breast cancer, other cancers.
- Studies which included other agents in combination with trastuzumab emtansine.

6.2.2 A flow diagram of the numbers of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses

such as the QUOROM statement flow diagram (www.consort-statement.org/?o=1065). The total number of studies in the statement should equal the total number of studies listed in section 6.2.4.

Figure 3: PRISMA flow diagram of literature search conducted



6.2.3 When data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or when trials are linked (for example, an open-label extension to an RCT), this should be made clear.

Three RCTs were identified – the EMILIA study, the TH3RESA study, and the TDM4450g study. Section 6.2.4 lists all publications founded upon these

studies. The fourth study sourced in Figure 3 is an additional analysis from the EMILIA data set, and for this reason it is not included for an independent analysis in section 6.2.4.

Complete list of relevant RCTs

6.2.4 Provide details of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the Evidence Review Group. This should be presented in tabular form. A suggested format is presented below.

Table 5: List of relevant RCTs

Trial no. (acronym)	Intervention	Comparator	Population	Primary study ref.
EMILIA (TDM4370g, BO21977)	Trastuzumab emtansine (3.6 mg/kg q3w)	Lapatinib (1250 mg/day od) in combination with capecitabine 1000 mg/m^2 bd, days 1–14, q3w)	People with HER2-positive advanced breast cancer who received at least one line of chemotherapy for their metastatic disease or who relapsed from adjuvant therapy within 6 months.	Verma NEJM 2012; 367(19): 1783-91 Welsau ESMO 2012, 329P poster presentation
TH3RESA (BO25734)	Trastuzumab emtansine (3.6 mg/kg q3w)	Treatment of physician's choice (TPC)	People with HER2-positive metastatic breast cancer who had received at least two lines of HER2-directed therapy for their metastatic disease.	Wildiers. ESMO 2013 38th Congress, oral presentation
TDM4450g (BO21976)	Trastuzumab emtansine (3.6 mg/kg q3w)	Trastuzumab (8 mg/kg loading dose; 6 mg/kg q3w) in combination with docetaxel (75 or 100 mg/m^2 q3w)	People with HER2-positive metastatic breast cancer who had not received chemotherapy or biologic therapy for their metastatic disease.	Hurvitz. JCO 2013; 31(9): 1157- 63

6.2.5 Please highlight which of the RCTs identified above compares the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, please state this.

EMILIA is a randomised open-label clinical trial comparing the intervention of interest, trastuzumab emtansine, against lapatinib in combination with capecitabine.

TH3RESA is a randomised open-label clinical trial comparing the intervention of interest with treatment of physician's choice (TPC). TPC could be

- Chemotherapy, any single agent
- Hormonal therapy for hormone receptor positive-disease, single-agent (eg, tamoxifen or aromatase inhibitor) or dual therapy (eg, aromatase inhibitor with luteinizing hormone releasing hormone [LHRH] agonist)
- HER2-directed therapy
    - Single agent (eg, trastuzumab or lapatinib)
    - Dual therapy (eg, trastuzumab with lapatinib)
    - Single agent in combination with single-agent chemotherapy (eg, lapatinib with capecitabine, trastuzumab with vinorelbine)
    - Single agent in combination with single-agent hormonal therapy (eg, lapatinib with letrozole, trastuzumab with anastrozole)

A combination of two agents maximum was allowed, such as: a HER2-directed therapy plus chemotherapy, a combination of two HER2-directed therapies, or HER2-directed therapy plus hormonal therapy. Dual hormonal therapies were also allowed but doublet chemotherapies were not permitted. 80% of patients in the TPC arm received a trastuzumab containing regimen.

Both of these studies are directly relevant to the decision problem.

6.2.6 When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of trial data required, this should be indicated.

TDM4450g has been excluded from further discussion. This is a phase II study which included previously untreated HER2-positive MBC patients and randomised them 1:1 to receive trastuzumab emtansine (67 patients) or trastuzumab in combination with docetaxel (70 patients). No disease free interval from adjuvant therapy restrictions were specified within the study protocol – this is counter to the inclusion population in the EMILIA study, and subequent license for trastuzumab emtansine, which features previously

untreated patients who had a disease free interval of less than 6 months. There is therefore some small overlap between TDM4450g and the trastuzumab emtansine label; however no separate analysis was performed of patients with a relapse interval ≤6 months. The majority of patients in the trial (65%) had at least 24 months since adjuvant therapy. Given the small number of possible within-licence patients involved, a subanalysis of this study was not considered useful. In addition, the comparator considered within this trial (trastuzumab and a taxane) is beyond the scope of this appraisal and cannot be linked to the comparators of interest via an indirect comparison.

This study has therefore not been included in further discussion.

List of relevant non-RCTs

6.2.7 Please provide details of any non-RCTs (for example experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion. Full details should be provided in section 6.8 and key details should be presented in a table; the following is a suggested format.

Due to the availability of randomised data on the relative efficacy directly relevant to the decision problem no non-RCT evidence has been presented in this submission.

6.3 Summary of methodology of relevant RCTs

6.3.1 As a minimum, the summary should include information on the RCT(s) under the subheadings listed in this section. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (www.consort-statement.org). It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be

requested from NICE. When there is more than one RCT, the information should be tabulated.

Methods

6.3.2 Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments. The following tables provide a suggested format for when there is more than one RCT.

Table 6: Comparative summary of methodology of the RCTs

Trial no. (acronym)	**EMILIA**	**TH3RESA**
Location	International	International
Design	Phase III, randomised, multicentre, international, two-arm, open-label clinical trial designed to compare the safety and efficacy of trastuzumab emtansine with that of capecitabine + lapatinib for HER2-positive MBC. 991 patients were enrolled at more than 200 sites worldwide.	Phase III, randomised, multicentre, two-arm, open-label clinical trial designed to compare the efficacy of trastuzumab emtansine with TPC for patients with HER2-positive MBC. 602 patients were enrolled at approximately 250 sites worldwide
Duration of study	The study will be terminated at time of final OS analysis, expected to be at 51 months.	The study will be terminated at time of final OS analysis, expected to be at 26 months.
Method of randomisation	1:1 randomisation (Independent IxRS)	2:1 randomisation (Independent IxRS)
Method of blinding (care provider, patient and outcome assessor)	Not blinded	Not blinded
Intervention(s) (n =) and comparator(s) (n =)	Trastuzumab emtansine (3.6 mg/kg q3w) (n=495) vs Lapatinib (1250 mg/day od) in combination with capecitabine 1000 mg/m^2 bd, days 1–14, q3w) (n=496)	Trastuzumab emtansine (3.6 mg/kg q3w) (n=404) vs Treatment of physician's choice (n=198)
Primary outcomes (including scoring methods and timings of assessments)	PFS by independent review, OS and safety	PFS by investigator and OS
Secondary outcomes (including scoring methods and timings of assessments)	PFS by investigator, ORR, duration of response, time to symptom progression and quality of life (FACT-B TOI)	ORR per investigator assessment, 1-year survival rate, and time to pain symptom progression (EORTC QLQ-C30), EQ-5D and safety
Duration of follow-up	At time of interim OS analysis median follow up: trastuzumab emtansine 19.1 months, capecitabine plus lapatinib 18.6 months. Study ongoing.	At time of PFS analysis median follow up: trastuzumab emtansine, 7.2 months TPC, 6.5 months. Study ongoing.

A hierarchical dynamic randomisation scheme was used to ensure an approximately equal sample size for the two treatment arms 1) overall, 2) by world region (United States, Western Europe, other), and 3) within each of the four categories defined by the following two prognostic factors, the number of prior chemotherapeutic regimens for unresectable, locally advanced or metastatic disease (0−1 vs. > 1), and visceral vs non-visceral disease. Patients with both visceral and non-visceral disease were considered as having visceral disease.

Tumour assessments were conducted approximately every 6 weeks from the date of randomisation or from Cycle 1 Day 1 (patients should have received their first dose of study treatment no later than 5 days after randomisation), regardless of dose delays or dose interruptions, until 6 weeks after investigator-assessed progression of disease (PD) or until death, whichever occurred first. Patient-reported outcomes (PROs) as assessed by the FACT-B (female patients only) and the DAS were completed every two-treatment cycles until 6 weeks after PD.

Participants

6.3.3 Provide details of the eligibility criteria (inclusion and exclusion) for the trial. The following table provides a suggested format for the eligibility criteria for when there is more than one RCT. Highlight any differences between the trials.

Key differences between the entry criteria for the RCTs:

Prior therapies

In the EMILIA trial patients could have either relapsed on or within 6 months of completing adjuvant therapy for HER2-positive breast cancer, or have progressed on at least one line of therapy for HER2-positive metastatic or locally advanced breast cancer. As a result 12% of patients were first line, 36% of patients were second line and 52% of patients were third or later lines. In the TH3RESA trial all patients had at least two prior therapies for metastatic

disease and so 35% of patients were third line, 36% of patients were fourth line and 29% of patients were fifth or later lines.

In the EMILIA trial, all patients were required to have previously received trastuzumab and a taxane. In the TH3RESA trial all patients had received trastuzumab, a taxane and lapatinib.

Performance status

In the EMILIA trial patients were required to have an ECOG performance status of 0 or 1 at baseline. In the TH3RESA trial patients could have a baseline ECOG performance status of 0, 1 or 2. A breakdown of performance status for each trial is shown below:

Table 7: ECOG PS in EMILIA and TH3RESA trials

ECOG PS	**EMILIA**		**TH3RESA**	
	Trastuzumab emtansine (n=495)	lapatinib plus capecitabine (n=496)	Trastuzumab emtansine (n=404)	TPC (n=198)
0	61%	64%	45%	41%
1	39%	36%	50%	51%
2	NA	NA	6%	8%

<u>EMILIA</u>

Inclusion Criteria

Disease-Specific Criteria

1. Prospective centrally confirmed HER2-positive (i.e., immunohistochemistry [IHC] 3 + and/or gene-amplified by FISH). Both IHC and FISH assays will be performed; however, only one positive result is required for eligibility. Additional tissue samples will be required to perform all mandatory testing (including qRT-PCR).
2. Histologically or cytologically confirmed invasive breast cancer: incurable, unresectable, locally advanced breast cancer previously treated with multimodality therapy or MBC

3. Prior treatment for breast cancer in the adjuvant, unresectable, locally advanced, or metastatic setting must include both:
   A taxane, alone or in combination with another agent, and trastuzumab, alone or in combination with another agent in the adjuvant, unresectable, locally advanced, or metastatic setting
4. Documented progression of incurable unresectable, locally advanced, or metastatic breast cancer, defined by the investigator:
   Progression must occur during or after most recent treatment for locally advanced/MBC or within 6 months after completing adjuvant therapy.
5. Measurable and/or non-measurable disease. Patients with CNS-only disease are excluded.

General Criteria

6. Age ≥ 18 years
7. Cardiac ejection fraction ≥ 50% by either ECHO or MUGA
8. ECOG performance status of 0 or 1
9. Adequate organ function, evidenced by the following laboratory results within 30 days prior to randomisation:
   - Absolute neutrophil count > 1500 cells/mm3
   - Platelet count > 100,000 cells/mm3
   - Haemoglobin > 9.0 g/dL (Patients were allowed to be transfused red blood cells to this level).
   - Albumin ≥ 2.5 g/dL
   - Total bilirubin ≤ 1.5 upper limit of normal (ULN)
   - SGOT (aspartate aminotransferase [AST]), SGPT (SGPT (alanine aminotransferase [ALT]), and alkaline phosphatase (ALP) ≤ 2.5 × ULN with the following exception: patients with bone metastases: ALP ≤ 5 × ULN
   - Creatinine clearance > 50 mL/min based on Cockroft-Gault glomerular filtration rate (GFR) estimation: (140 − Age) × (weight in kg) × (0.85 if female)/(72 × serum creatinine)

- International normalized ratio (INR) and activated partial thromboplastin time (aPTT) < 1.5 × ULN (unless on therapeutic coagulation)

10. For women of childbearing potential and men with partners of childbearing potential, agreement to use a highly effective, non-hormonal form of contraception. Acceptable forms of contraception should include two of the following:
    - Placement of non-hormonal intrauterine device (IUD)
    - Condom with spermicidal foam/gel/film/cream/suppository
    - Diaphragm or cervical/vault caps with spermicidal foam/gel/film/cream/suppository

    The above contraception is not a requirement in the case of any of the following:
    - Patient is surgically sterilized (i.e., who have undergone surgical sterilisation with a hysterectomy and/or bilateral oophorectomy)
    - Patient has had no menstrual period for 12 consecutive months, or
    - Patient truly abstains from sexual activity

    Contraception use should continue for the duration of the study treatment and for at least 6 months after the last dose of study treatment.

    Periodic abstinence (e.g., calendar ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Postmenopausal is defined as ≥ 12 months of amenorrhea.

    Specific country requirements will be followed (e.g., in the United Kingdom, women of childbearing potential and male subjects and their partners of childbearing potential must use two methods of contraception [one of which must be a barrier method] for the duration of the study).

Exclusion Criteria

Cancer-Related Criteria

1. History of treatment with trastuzumab emtansine
2. Prior treatment with lapatinib or capecitabine
3. Peripheral neuropathy of Grade ≥ 3 per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 3.0
4. History of other malignancy within the previous 5 years, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, Stage 1 uterine cancer, synchronous or previously diagnosed HER2-positive breast cancer, or cancers with a similar curative outcome as those mentioned above
5. History of receiving any anti-cancer drug/biologic or investigational treatment within 21 days prior to randomisation except hormone therapy, which can be given up to 7 days prior to randomisation; recovery of treatment-related toxicity consistent with other eligibility criteria
6. History of radiation therapy within 14 days of randomisation. The patient must have recovered from any resulting acute toxicity (to Grade ≤ 1) prior to randomisation
7. Brain metastases that are untreated, symptomatic, or require therapy to control symptoms, as well as a history of radiation, surgery, or other therapy, including corticosteroids, to control symptoms from brain metastases within 2 months (60 days) before randomisation

Cardiopulmonary Function

8. History of symptomatic CHF or serious cardiac arrhythmia requiring treatment
9. History of myocardial infarction or unstable angina within 6 months of randomisation
10. Current dyspnoea at rest due to complications of advanced malignancy or requirement for continuous oxygen therapy

General Criteria

11. Current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular, pulmonary, or metabolic disease)
12. Pregnancy or lactation
13. Currently known active infection with HIV, hepatitis B virus, or hepatitis C virus
14. Presence of conditions that could affect gastrointestinal absorption: malabsorption syndrome, resection of the small bowel or stomach, and ulcerative colitis
15. History of intolerance (such as Grade 3−4 infusion reaction) to trastuzumab
16. Known hypersensitivity to 5-fluorouracil or known dihydropyrimidine dehydrogenase deficiency
17. Current treatment with sorivudine or its chemically related analogs, such as brivudine
18. Assessed by the investigator to be unable or unwilling to comply with the requirements of the protocol (i.e., unable to swallow pills)

TH3RESA

Inclusion Criteria

1. Signed study-specific Informed Consent Form
2. Age ≥ 18 years
3. Histologically or cytologically documented breast cancer
4. Metastatic or unresectable locally advanced/recurrent breast cancer
5. HER2-positive disease documented as ISH-positive and/or 3+ by IHC on previously collected tumour tissue and prospectively confirmed by Sponsor-designated central laboratory prior to study enrollment

   Tumour material made available for confirmatory central laboratory HER2 testing and exploratory biomarker analyses. Both IHC and ISH assays will be performed; however, only one positive result is required for eligibility. For patients with a history of bilateral breast cancer, HER2-positive status must be demonstrated in primary tumours from both breasts or a biopsy from a single metastatic site

6. Disease progression on the last systemic anti-cancer regimen received as defined by the investigator unless they were intolerant

   Patients who were intolerant to their last systemic anti-cancer regimen may be considered eligible if they satisfy all other inclusion criteria. Intolerance is defined as any treatment-related Grade 4 AE, or any treatment-related Grade 2 or 3 AE that is unacceptable to the patient and persists despite standard countermeasures. The reason for intolerance will be fully documented
7. Prior treatment with trastuzumab, lapatinib, and a taxane in any setting (i.e., neoadjuvant, adjuvant, locally advanced, or recurrent/metastatic) and documented disease progression (by investigator assessment) after at least two regimens of HER2-directed therapy in the metastatic or unresectable locally advanced/recurrent setting. Disease progression must have occurred on both trastuzumab and lapatinib containing regimens except where there was intolerance of lapatinib as defined below
8. A minimum of 6 weeks of prior trastuzumab for the treatment of metastatic or unresectable locally advanced/recurrent disease is required
9. Trastuzumab must have been administered as six consecutive weekly doses or as two consecutive doses on a q3w schedule
10. Patients must have had at least 6 weeks of prior exposure in the metastatic (or unresectable locally advanced/recurrent) setting to lapatinib unless they were intolerant of lapatinib

    Intolerance is defined as any treatment-related Grade 4 AE, or any treatment-related Grade 2 or 3 AE that is unacceptable to the patient and persists despite standard countermeasures. The reason for intolerance will be fully documented

    Patients who were found to be intolerant to lapatinib can be considered eligible if they experienced disease progression during a single trastuzumab-based regimen in the metastatic (or unresectable locally advanced/recurrent) setting
11. Adequate organ function, as evidenced by the following laboratory results:

ANC > 1500 cells/mm^3

Platelet count > 100,000 cells/mm^3

Haemoglobin > 9.0 g/dL

Patients are allowed to receive transfused RBC to achieve this level.

Total bilirubin ≤ 1.5 × ULN, except in patients with previously documented Gilbert's syndrome, in which case the direct bilirubin should be less than or equal to the ULN

SGOT (AST) and SGPT (ALT) ≤ 2.5 × ULN

Alkaline phosphatase ≤ 2.5 × ULN

Patients with hepatic and/or bone metastases: alkaline phosphatase ≤ 5 × ULN

Serum creatinine < 1.5 × ULN

12. INR < 1.5 × ULN
13. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 (see Appendix B)
14. LVEF ≥ 50% by either ECHO or MUGA
15. Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures, including completion of PRO measures
16. Negative results of serum pregnancy test for premenopausal women of reproductive capacity and for women < 12 months after entering menopause
17. For women of childbearing potential and men with partners of childbearing potential, agreement by the patient and/or partner to use a highly effective, non-hormonal form of contraception or two effective forms of non-hormonal contraception:

    Acceptable forms of highly effective contraception include the following:

    True abstinence when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal post-ovulation methods) and withdrawal are not acceptable methods of contraception

    Male sterilization (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). For female patients, the

vasectomized male partner should be the sole partner. Tubal ligation is not considered a highly effective contraception

Acceptable forms of effective contraception include the following:

Placement of non-hormonal intrauterine device or intrauterine system

Condom with spermicidal foam/gel/film/cream/suppository

Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/film/cream/suppository

Contraception as described above is not a requirement in the case of any of the following:

The male patient or male partner of a female patient is surgically sterilized

The female patient is ≥ 45 years of age and is postmenopausal (has had no menstrual period for at least 12 consecutive months)

The female patient has undergone hysterectomy and/or bilateral oophorectomy

Contraception use should continue for the duration of the study treatment and for at least 6 months after the last dose of study treatment

Exclusion Criteria

Cancer-Related Criteria

1. Chemotherapy ≤ 21 days before first study treatment
2. Trastuzumab ≤ 21 days before first study treatment
3. Lapatinib ≤ 14 days before first study treatment
4. Hormone therapy ≤ 7 days before first study treatment
5. Investigational therapy or any other therapy ≤ 28 days before first study treatment
6. Prior enrollment in a trastuzumab emtansine−containing study, regardless of whether the patient received prior trastuzumab emtansine
7. Previous radiotherapy for the treatment of unresectable, locally advanced/recurrent or metastatic breast cancer is not allowed if:

   The last fraction of radiotherapy has been administered within 14 days prior to randomisation

The patient has not recovered from any resulting acute toxicity (to Grade ≤ 1) prior to randomisation

Brain metastases that are untreated or symptomatic, or require any radiation, surgery, or corticosteroid therapy to control symptoms from brain metastases within 1 month of randomisation

For patients with newly diagnosed brain metastases or unequivocal progression of brain metastases on screening scans, prior localized treatment (i.e., surgery, radiosurgery, and/or whole brain radiotherapy) is required

8. History of intolerance (including Grade 3 or 4 infusion reaction) or hypersensitivity to trastuzumab or murine proteins
9. History of exposure to the following cumulative doses of anthracyclines: Doxorubicin or liposomal doxorubicin > 500 mg/m^2 Epirubicin > 900 mg/m^2, Mitoxantrone > 120 mg/m^2

   If another anthracycline, or more than one anthracycline, has been used, the cumulative dose must not exceed the equivalent of 500 mg/m^2 doxorubicin
10. Current peripheral neuropathy of Grade ≥ 3 per the NCI CTCAE v4.0
11. History of other malignancy within the last 5 years, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, Stage I uterine cancer, or other cancers with a similar outcome as those mentioned above

Cardiopulmonary Function Criteria

12. Current unstable ventricular arrhythmia requiring treatment
13. History of symptomatic CHF (New York Heart Association [NYHA] Classes II−IV)
14. History of myocardial infarction or unstable angina within 6 months of enrolment
15. History of a decrease in LVEF to < 40% or symptomatic CHF with previous trastuzumab treatment
16. Severe dyspnoea at rest due to complications of advanced malignancy or requiring current continuous oxygen therapy

General Criteria

17. Current severe, uncontrolled system mic disease (e.g., clinically significant cardiovascular, pulmonary, or metabolic disease)
18. Major surgical procedure or significant traumatic injury within 28 days before enrollment or anticipation of the need for major surgery during the course of study treatment
19. Current pregnancy or lactation
20. Current known active infection with HIV, hepatitis B, and/or hepatitis C virus

    For patients who are known carriers of hepatitis B virus (HBV), active hepatitis B infection must be ruled out based on negative serologic testing and/or determination of HBV DNA viral load per local guidelines
21. Assessed by the investigator to be unable or unwilling to comply with the requirements of the protocol

6.3.4 Describe the patient characteristics at baseline. Highlight any differences between study groups. The following table provides a suggested format for the presentation of baseline patient characteristics for when there is more than one RCT.

Table 8: Characteristics of participants in the RCTs across randomised groups

Trial no. (acronym) **Baseline characteristic**	**Trastuzumab emtansine**	**Lapatinib plus capecitabine**
EMILIA (n = 991)	**(n = 495)**	**(n = 496)**
Race, n (%)		
White	358 (72)	374 (75)
Asian	94 (19)	86 (17)
Black/African American	29 (6)	21 (4)
Other	7 (1)	10 (2)
Not available	7 (1)	5 (1)
World region, n (%)		
United States	134 (27)	136 (27)
Western Europe	157 (32)	160 (32)
Asia	82 (17)	76 (15)
Other	122 (25)	124 (25)
Median age, y (range)	53 (25–84)	53 (24–83)
ECOG PS 0, n (%)	299 (61)	312 (64)
ECOG PS 1, n (%)	194 (39)	176 (36)
Measurable disease by	397 (80)	389 (78)

independent review, n (%)		
Metastatic involvement, n (%) Visceral Non-visceral	 334 (68) 161 (33)	 335 (68) 161 (33)
Metastatic sites, n (%) <3 ≥3 Unknown	 282 (57) 202 (41) 11 (2)	 307 (62) 175 (35) 14 (3)
ER/PR status, n (%) ER+ and/or PR+ ER- and PR- Unknown	 282 (57) 202 (41) 11 (2)	 263 (53) 224 (45) 9 (2)
	Trastuzumab emtansine	**TPC**
TH3RESA (n = 602)	**(n = 404)**	**(n = 198)**
Age, % <65 years 65–74 years ≥75 years	 85.4 11.4 3.2	 82.8 14.1 3.0
World region, % United States Western Europe Other	 24.5 42.3 33.2	 24.2 42.9 32.8
Race, % White Asian Other[a]	 80.4 14.1 5.4	 81.3 12.1 6.6
ECOG PS,[b] % 0 1 2	 44.8 49.8 5.5	 41.4 51.0 7.6
ER and/or PR-positive, %	51.5	52.0
Visceral involvement, %	74.8	75.8
Disease extent at study entry, % Metastatic Unresectable locally advanced/recurrent BC	 96.8 3.2	 94.4 5.6
Number of prior regimens for advanced BC, median (range) ≤3, % 4–5, %	4 (1–14) 32.6 37.1 30.3	4 (1–19) 39.4 32.8 27.8

>5, %		
Brain metastasis at baseline, %	9.9	13.6
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee		

In the EMILIA study the treatment groups were generally comparable with respect to demographic characteristics (see Table 8 for more details).

The vast majority of patients were female; five male patients enrolled (4 in the lapatinib plus capecitabine arm, 1 in the trastuzumab emtansine arm). As per protocol, all patients had a baseline ECOG performance status of 0 (61% vs 64%) or 1 (36% vs 39%) in the trastuzumab emtansine and lapatinib plus capecitabine arms, respectively.

The vast majority of patients were either white (72%vs 75%) or Asian (17% vs 19%) in the trastuzumab emtansine and lapatinib plus capecitabine arms, respectively. Patients were treated at study sites in the US, Europe, Latin America, and Asia and were stratified by world region (US, Western Europe, Other) ensuring similar percentages of patients in the two study arms for each region (see Table 8).

Baseline disease characteristics were also well−balanced between the two arms (Table 8). The majority of patients (80.2% for trastuzumab emtansine, 78.4% for lapatinib plus capecitabine) had measurable disease (as assessed by the IRC), and 68% of patients in each arm had visceral disease. Most patients in each arm (61.4% for trastuzumab emtansine, 61.5% for lapatinib plus capecitabine) had received 0 to 1 prior chemotherapy regimens for unresectable locally advanced/metastatic breast cancer. The number of metastatic sites reported in patients at baseline by IRC assessment was evenly distributed between the treatment arms, with 28.9% and 30.4% of all patients having one site, 31.3% and 31.5% having two sites, and 35.3% and 38.2% reported with three or more metastatic sites at baseline. The number

and location of baseline tumour lesions were well balanced between the two arms (Verma, 2012).

In the TH3RESA study the demographic characteristics were well balanced between the two treatment arms (Table 8). The arms were balanced in terms of age groups and ECOG performance status. Baseline ECOG performance status of 0 (44.8% vs 41.3%) or 1 (49.8% vs 51.0%) or 2 (5.5% vs 7.6%) in the trastuzumab emtansine and TPC arms, respectively.

The vast majority of patients were either white (80.4% vs 81.3%) in the trastuzumab emtansine and TPC arms, respectively. Baseline disease characteristics were also well−balanced between the two arms (Table 8). The majority of patients had visceral disease (74.8% for trastuzumab emtansine, 75.8% for TPC). The median number of prior therapies for MBC or LABC in each arm was 4.

The size and extent of baseline disease were well balanced between the two arms, with the exception of CNS metastases at baseline which were slightly higher in the TPC arm, 9.9%), vs 13.1% in the trastuzumab emtansine armtively (Wildiers, 2013).

Outcomes

6.3.5 Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life (HRQL), and any arrangements to measure compliance. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice). The following table provides a suggested format for

presenting primary and secondary outcomes when there is more than one RCT.

Table 9: Primary and secondary outcomes of the RCTs

Trial no. (acronym)	Primary outcome(s) and measures	Reliability/validity/ current use in clinical practice	Secondary outcome(s) and measures	Reliability/validity/ current use in clinical practice
EMILIA	PFS OS Safety	See below	CBR, DOR. FACT-B TOI	See below
TH3RESA	PFS OS	See below	Safety, CBR, EORTC QLQ-C30, EORTC QLQ-BM22 and EQ-5D	See below

PFS, ORR, clinical benefit rate (CBR) and DOR in both studies were based on the RECIST method of assessing tumour response. This is not used in daily practice but is a widely recognized standard for assessing solid tumours in clinical trials.

Safety in both studies was assessed using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE). Again, this is not used in daily practice but is a widely recognized standard for assessing the severity of adverse events commonly associated to cancer or cancer treatments in clinical trials.

FACT-B was used as a PRO in EMILIA, and EORTC QLQ-C30, EORTC QLQ-BM22 and EQ-5D were used in TH3RESA. FACT-B has been validated as a PRO in women with breast cancer. EORTC QLQ-C30 and QLQ-BM22 are validated tools for cancer patients. EQ-5D is a standardised tool for health outcomes. None of these are used in routine practice.

In EMILIA the primary outcomes were PFS by independent review, OS and safety. The secondary outcomes were PFS by investigator review, CBR, DOR and time to symptom progression as measured by FACT-B TOI (Verma, 2012; Welslau, 2013).

The analysis for PFS by independent review has been published and shows a median PFS for trastuzumab emtansine of 9.6 months as compared to 6.4 months with lapatinib plus capecitabine [HR=0.650, p<0.0001]. The analysis for PFS by investigator review showed very similar results [HR=0.658, p<0.001] (Verma, 2012).

Two interim analyses for OS have been performed, one at the time of PFS analysis and one, six months later, at the request of the health authorities. The second of these crossed the O'Brian-Fleming stopping boundary for an early analysis. These results show a statistically significant increase in OS from 25.1 months with lapatinib plus capecitabine to 30.9 months [HR=0.682, p=0.0006]. It should be noted that this median OS advantage is around double the median PFS advantage – a relationship seen in many studies of HER2 targeted monoclonal antibodies (see NICE ID523).

Landmark analyses at 1 and 2 years show 85.2% patients and 78.4% alive at 1 year and 64.7% patients and 51.8% patients alive at 2 years with trastuzumab emtansine and lapatinib plus capecitabine, respectively. A further OS analysis will occur in 2014 when the study reaches 632 events. However, any future analysis will be confounded by crossover as this was permitted following the results of the second interim analysis for OS (Verma, 2012).

Secondary endpoints all favoured trastuzumab emtansine over lapatinib plus capecitabine: ORR (43.6% vs. 30.8% $p = 0.0002$), DOR (median 12.6 as compared to 6.5 months), and time to symptom progression as measured by FACT-B TOI (7.1 vs 4.6 months, HR=0.796, p=0.0121) (Verma, 2012; Welslau, 2013). It should be remembered that this was an open-label study when considering the patient reported data.

In TH3RESA the primary outcomes were PFS by investigator review and OS. Secondary outcomes were safety, CBR, DOR and time to pain symptom progression as measured by EORTC-QLQ BM22. As this is an ongoing study, further PRO analyses will also be performed (Wildiers, 2013).

The analysis for PFS has been presented and shows a median PFS for trastuzumab emtansine of 6.2 months as compared to 3.3 months with TPC

(HR=0.528, p<0.0001) or 3.2 months for TPC-trastuzumab containing regimens only (HR=0.558, p<0.0001) (Wildiers, 2013).

An interim analysis for OS was performed at the time of PFS analysis. The median OS in the TPC arm was 14.9 months but had not yet been reached in the trastuzumab emtansine arm. The HR was 0.552 with a p value of 0.0034, however, these values did not cross the prespecified efficacy stopping boundry of HR <0.363 or P<0.0000013. A further interim analysis for OS will be performed at around 26 months with the final OS expected at around 45 months (Wildiers, 2013).

ORR was significantly higher in the trastuzumab emtansine arm 31.3% compared to TPC 8.6% (p < 0.0001); other secondary endpoints will only be available at the time of a positive interim OS result or the final OS analysis (Wildiers, 2013).

Statistical analysis and definition of study groups

6.3.6 State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken). The following table provides a suggested format for presenting the statistical analyses in the trials when there is more than one RCT.

EMILIA Study

Analysis Populations

The following analysis populations were defined for use in this study:

Intent-to-treat (ITT) population: The ITT population was the primary analysis population for the primary endpoint, and consisted of all patients who were randomised ≥ 3 months prior to the clinical data cut-off date for the final PFS

analysis (as determined by the study site being notified of the initial randomisation number assignation), regardless of whether they received any study drug or completed a full course of treatment. Because the actual data cut-off date for the final PFS analysis was 3 months after last patient in, by definition all patients were randomised ≥ 3 months prior to the clinical data cut-off date; thus, the ITT population consisted of all randomised patients on the basis of the treatment assigned at randomisation.

All efficacy endpoints were analyzed based on the ITT population.

Treated (Safety) population: Safety analyses were performed on the treated population, defined as patients who received at least one dose of study medication.

Safety analyses were based on the actual treatment received.

Primary Efficacy Endpoints

This study had co-primary endpoints of PFS by independent review and OS. To adjust for multiplicity due to having two primary endpoints, a fixed-sequence hypothesis testing procedure was implemented. The hypothesis test for PFS was conducted at a one-sided alpha of 2.5%. As the PFS was statistically different between the two arms, OS was tested at a one-sided alpha of 2.5% to determine if the two arms had significantly different OS.

The co-primary efficacy endpoint of PFS is based on independent review of tumour assessment, defined as the time from randomisation to documented IRC-assessed disease progression or death from any cause (whichever occurs earlier). For the analysis of PFS, data for patients without disease progression or death was censored at the time of the last tumour assessment (or, if no tumour assessment was performed after the baseline visit, at the time of randomisation plus 1 day). Data from patients who are lost to follow-up was included in the analysis as censored observations on the last date of tumour assessment that the patient was known to be progression free.

For patients who received non-protocol therapy (defined as any treatment the patient receives that is intended to treat his or her MBC) prior to documented disease progression, the primary PFS analysis will not censor patients at the initiation of non-protocol therapy. A sensitivity analysis of PFS censoring patients at the last tumour assessment before the initiation of non-protocol therapy will also be performed.

The two-sided log-rank test, stratified by world region (United States, Western Europe, Other), number of prior chemotherapeutic regimens for unresectable, locally advanced or metastatic disease (0−1 vs. > 1), and visceral versus non-visceral disease wwasused as the primary analysis to compare PFS between the two treatment arms. The results from the unstratified log-rank test and the stratified and unstratified Wilcoxon test are also be provided.

The Kaplan-Meier approach was used to estimate median PFS for each treatment arm. Cox proportional-hazards models, stratified by world region (United States, Western Europe, Other), number of prior chemotherapeutic regimens for unresectable, locally advanced or metastatic disease (0−1 vs. > 1), and visceral versus non-visceral disease was used to estimate the hazard ratio (HR) and its 95% CI.

OS, the co-primary endpoint, is defined as the time from the date of randomisation to the date of death from any cause. Patients who are alive at the time of the analysis data cut-off was censored at the last date they were known to be alive. Patients with no post-baseline information were censored at the date of randomisation plus 1 day.

Methods for OS analysis are similar to those described for the PFS endpoint, with the stratified log-rank test being the primary analysis and sensitivity analysis using the unstratified log-rank test and the stratified and unstratified Wilcoxon test. In addition, 1-year and 2-year survival rates and corresponding 95% CIs were estimated using the Kaplan−Meier approach, as appropriate.

The final analysis of OS will occur after 632 deaths have occurred. An interim analysis of OS was performed at the time of the primary efficacy analysis of PFS. A second interim analyses of OS was performed with the appropriate

control of the Type I error rate using the pre-specified Lan-DeMets function with O'Brien-Fleming boundary.

Determination of Sample Size and Power

The sample size of the study is determined by the analysis of OS. To detect an HR of 0.8 in OS (a 25% improvement in median OS; i.e., from 17.2 months in the control arm to 21.5 months in the treatment arm), approximately 632 deaths was required to achieve 80% power at a two-sided 5% alpha level. A total of 991 patients were enrolled into the study.

The primary efficacy analysis was event driven, and the primary analysis of PFS will take place when approximately 508 IRC-assessed PFS events have occurred. This provides 90% power to detect an HR of 0.75 in PFS (a 33% improvement in median PFS; i.e., from 6.2 months in the control arm to 8.3 months in the treatment arm), with a two-sided alpha of 5%.

Assumptions

Enrolment would take approximately 35 months. Therefore assuming a median PFS of 6.2 months in the control arm and an HR of 0.75, the date of data cut-off for the final analysis of PFS would be approximately 32 months from when the first patient is enrolled (FPI). However, the final analysis of PFS would not be conducted until the last patient was enrolled.

Assuming the median OS of 17.2 months in the control arm and an HR of 0.8, the data cut-off date for the final analysis of OS is projected to be approximately 51 months from FPI. It was estimated that approximately 290 deaths would occur at the time of the final analysis of the primary endpoint of PFS. It is estimated that 632 deaths would occur approximately 51 months from start of study.

The sample size was estimated using East® software.

Handling of Missing Data

For the primary analysis of PFS and duration of response, data from patients who were lost to follow-up was included in the analysis as censored observations on the last date that the patient is known to be progression free, defined as the date of the last tumour assessment. When disease progression occurred after two or more consecutive missed tumour assessments, these events were not counted; rather, the patient was censored at the patient's last tumour assessment prior to the missing assessments. If disease progression occurred after one missed tumour assessment, the event was counted at the respective event date. Overall survival could have been impacted by the loss-to-follow-up of too many patients, therefore sites were expected to make every effort to contact the patient for Survival Follow-up at the following time points: approximately every 3 months from study completion, and Immediately prior to the data cutoffs for the final PFS analysis and OS analyses (RXUKDONF00336, December 2013).

Patients who discontinued for reasons other than disease progression (i.e., because of the patient's or physician's choice or due to unacceptable toxicity) completed the Study Drug Completion Visit and continued to undergo tumour assessments, have concomitant medication data collected (anti-cancer therapies only), and completed the FACT-B approximately every 6 weeks until 6 weeks after PD. Once disease progression PD was reported, all patients were followed for survival every 3 months (or immediately before PFS or OS analyses) until death, loss to follow up, withdrawal of consent, or study termination. In addition, the FACT-B was completed and subsequent anti-cancer therapies were reported according to the same schedule as survival follow-up.

In order to assess the consistency of treatment benefit with respect to the primary efficacy endpoints of IRC-assessed PFS and OS across important subgroups, forest plots (including estimated hazard ratios) was planned for the following variables: race (White, Asian, other), age (<65 years, 65-74 years, ≥ 75 years), geographical region (USA, Western Europe, Asia, other), ECOG(0,1), sex, number of prior chemotherapeutic regimens for locally

advanced or metastatic disease (0-1, >1), prior trastuzumab regimens for locally advanced or metastatic disease (yes, no), presence of visceral disease (yes,no), prior anthracycline (yes, no), prior anti-cancer therapy for locally advanced or metastatic disease (yes, no), and key biomarkers.

The following analyses were not prespecified in the protocol but were considered clinically significant: Number of disease sites (<3, ≥3), presence of baseline liver metastases (yes, no), presence of baseline bone metastases (yes, no), baseline disease measurability (yes, no), ER and PR status (ER and/or PR positive, ER and PR negative), menopausal status (premenopausal, perimenopausal, postmenopausal), line of therapy by any systemic therapy (first, second, third or later).

The forest plots were created for IRC-assessed PFS and OS.

In addition, a multivariate Cox regression on IRC-assessed PFS and OS was run that includes all the aforementioned baseline characteristics. A stepwise backward regression or the fractional polynoms approach was applied to obtain a final multivariate model as appropriate.

TH3RESA Study

Analysis Populations

Two analysis populations were used for the analysis of data from this study: the randomised patient population (ITT) and the safety-evaluable population. In all efficacy analyses, patients will be included in the ITT treatment group. Patients in the TPC arm who received trastuzumab emtansine treatment after disease progression were included in the TPC arm as originally randomised. All patients who were randomised to the study were included in the randomised patient population, regardless of whether they received any study treatment; the safety-evaluable population included all randomised patients who received any amount of study treatment.

Analyses of demographics and other baseline information were based on the ITT treatment group.

The safety-evaluable population formed the basis for all safety analyses. Safety analyses will be performed separately for the two study periods: the planned treatment period and the post-crossover period. Currently only the former analysis is available. For patients who did not receive their planned treatment as assigned by the IVRS/IWRS, safety data was summarized accordingly in the two study periods.

Primary Efficacy Endpoints

PFS per investigator assessment and OS are co-primary efficacy endpoints for this study.

PFS was defined as the time from randomisation to first documented disease progression using RECIST (including progression of existing or new isolated brain metastasis) or death from any cause, whichever occurred first. Data for patients without disease progression or death was censored at the time of the last tumour assessment on or prior to the clinical data cutoff date, or if no tumour assessment was performed after the baseline visit, at the time of randomisation plus 1 day. Data from patients who were lost to follow-up was censored at the last tumour assessment date that the patient was known to be progression free on or prior to the clinical data cutoff date.

Data from patients who received non-protocol therapy (NPT), defined as any treatment the patient received intended to treat his or her MBC other than planned study treatment prior to documented disease progression, will not be censored at the initiation of NPT. A sensitivity analysis of PFS that censors patient data at the last tumour assessment prior to initiation of NPT was also performed. No interim analyses for PFS were performed.

OS was defined as the time from the date of randomisation to the date of death from any cause. Patients who were alive at data cutoff date were censored at the last date they were known to be alive. Patients with no post-baseline information will be censored at the date of randomisation plus 1 day. Two interim OS analyses and one final OS analysis are planned: the first

interim OS analysis was performed at the time of the primary PFS analysis (approximately 16 months from FPI); the second interim OS analysis will be performed when approximately 67% of the targeted deaths (492) have occurred (approximately 26 months from FPI). The final OS analysis will be performed when approximately 492 deaths have occurred. A survival data sweep, contacting all patients to confirm their survival status, will be conducted prior to each analysis.

The overall 5% type I error rate will be split asymmetrically between the two primary endpoints, with 0.5% allocated to PFS and 4.5% allocated to OS. The study will be declared positive if either PFS or OS (at any interim or final analysis) shows statistical significance. The study will be discontinued when approximately 492 targeted deaths have occurred (and the final OS analysis is completed) or when the OS crosses the efficacy stopping boundary at either of the interim OS analyses.

The two-sided log-rank test, stratified by the protocol-defined stratification factors, was used to compare PFS between the two treatment arms at the overall two-sided significance level of 0.5%. The unstratified log-rank test result was also provided as a sensitivity analysis. Cox proportional hazards models, stratified by the protocol-defined stratification factors, was used to estimate the HR and its 95% CI. The Kaplan-Meier approach was used to estimate median PFS and the corresponding 95% CIs for each treatment arm.

The two-sided log-rank test, stratified by the protocol-defined stratification factors, was used to compare OS between the two treatment arms at the overall two-sided significance level of 4.5%. The unstratified log-rank test result was also provided as a sensitivity analysis. Cox proportional-hazards models, stratified by the protocol-defined stratification factors was used to estimate the HR and its 95% CI. The Kaplan-Meier approach was used to estimate median OS and the corresponding 95% CIs for each treatment arm.

The overall type I error was controlled at 0.045 for the formal interim OS analyses and will be be controlled for the final OS analysis using the Lan-

DeMets α-spending function with an O'Brien-Fleming boundary. The boundaries used at each interim and final OS analysis will depend on the number of death events actually included in the analyses.

Determination of Sample Size and Power

The sample size of the study was driven by the analyses of PFS and OS. To detect an HR of 0.65 for PFS (a 54% improvement in median PFS from 4 months in the control arm to 6.15 months in the trastuzumab emtansine arm), approximately 324 PFS events were required to achieve 80% power at a two-sided significance level of 0.5%. To detect an HR of 0.76 for OS (a 32% improvement in median OS [i.e., from 12 months in the control arm to 15.8 months in the trastuzumab emtansine arm]), approximately 492 deaths will be required to achieve 80% power at a two-sided significance level of 4.5%. 602 patients were enrolled into the study.

The sample-size estimation was performed with the East® software v5.2.

Assumptions

The study was expected to be fully enrolled by 14 months from FPI.

The primary PFS analysis was estimated to occur approximately 16 months from FPI. The first OS interim analysis was performed at the time of the PFS analysis; the second interim OS analysis will be performed when approximately 67% of the targeted deaths have occurred (approximately 26 months from FPI). The final OS analysis will be performed when approximately 492 deaths have occurred.

Handling of Missing Data Points

For the analysis of PFS, data for patients who experienced no disease progression and no death were censored at the date of their last tumour assessment with an overall response other than "unknown" or "unevaluable" on or prior to the clinical data cut-off date. Data for patients who were lost to follow-up prior to documented disease progression were censored at the last tumour assessment date that the patient was known to be progression free on

or prior to the clinical data cut-off date. Data for patients were randomised but not treated was censored at the time of randomisation plus 1 day. Data for patients without any post-baseline tumour assessments was censored at the time of randomisation plus 1 day.

For the analysis of OS, data for patients who were alive at the time of the analysis data cut-off were censored at the last date they were known to be alive on or prior to the clinical data cut-off date. Data for patients with no post-baseline information will be censored at the date of randomisation plus 1 day.

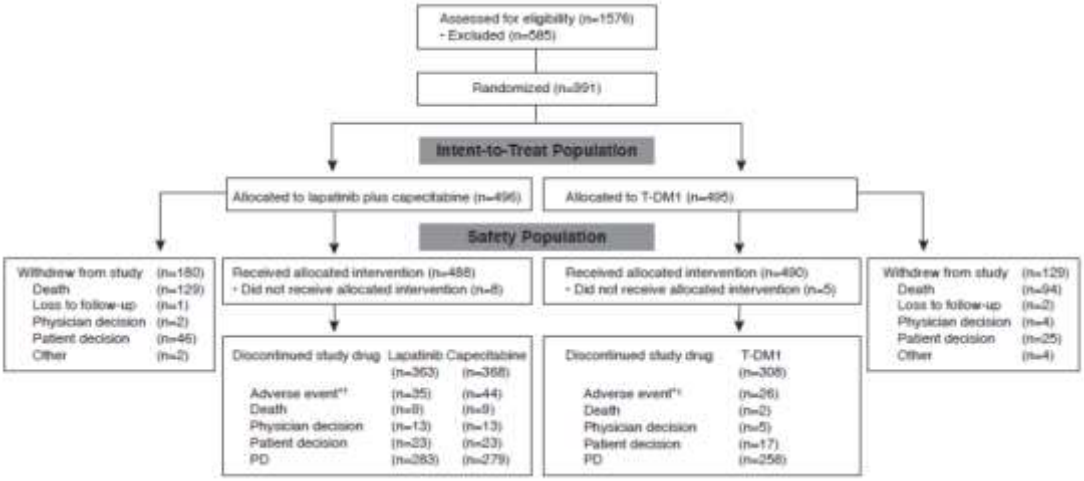
After the Study Treatment Discontinuation Visit, all patients (regardless of reason for discontinuation) will have anti-cancer therapies recorded and were followed for survival every 3 months until death, loss to follow-up, withdrawal of consent.

Patients who have discontinued their randomised study treatment for reasons other than disease progression continued to undergo tumour assessments and complete the PROs approximately every 6 weeks (± 7 days) from the date of randomisation for the first 54 weeks and every 12 weeks (± 7 days) thereafter until investigator-assessed disease progression. For patients who withdrew their consent from the study but accept to participate in the survival follow-up, only survival information was collected every 3 months, and just prior to PFS and OS analyses.

Participant flow

6.3.7 Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the RCT. This information should be presented as a CONSORT flow chart.

Figure 4 EMILIA Participant Flow (data as of 14 January 2012)



TH3RESA participant flow not available (narrative below)

A total of 972 patients with HER2-positive MBC were screened, of whom 370 patients failed screening. The most common reasons for screen failure were having brain metastases that were untreated or symptomatic, or required therapy to control symptoms (107 patients), or not having centrally-confirmed HER2-positive disease (100 patients). A total of 602 patients were therefore randomized (404 to receive trastuzumab emtansine and 198 to receive TPC). There were 15 patients (2 in the trastuzumab emtansine arm and 13 in the TPC arm) who did not receive any study treatment (see section 6.10.2 for details). As of the clinical cut-off date of 11 February 2013, 319 patients (79.0%) in the trastuzumab emtansine arm and 125 patients (63.1%) in the TPC arm were still on study. A total of 44 patients (22.2%) from the TPC arm had crossed over to receive trastuzumab emtansine. This was allowed on publication of the EMILIA OS results.

Table 10: TH3RESA study discontinuation

Study discontinuation	TPC (n=198)	T-DM1 (n=404)
Discontinued study, %	36.9	21.0
Reasons for study discontinuation, %		
Death	22.2	15.1
Withdrawal by patient	13.1	4.7
Physician's decision	1.0	0.5
Other	0.5	0.7

6.4 Critical appraisal of relevant RCTs

6.4.1 The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. The critical appraisal will be validated by the ERG. The following are the minimum criteria for assessment of risk of bias in RCTs, but the list is not exhaustive.

- **Was the method used to generate random allocations adequate?**
- **Was the allocation adequately concealed?**
- **Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?**
- **Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?**
- **Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?**
- **Is there any evidence to suggest that the authors measured more outcomes than they reported?**

- **Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?**

Data for both studies were recorded through an electronic data capture system using eCRFs. Exceptions to this procedure included films for radiographic tumour assessment, ECHO/MUGA cardiac assessments, and paper quality-of-life questionnaires completed by participants and data on HER2 status. Accurate and reliable data collection was assured by verification and cross-checking of the eCRFs against the investigator's records by the study monitor (source document verification), and by the maintenance of a drug-dispensing log by the investigator. A comprehensive validation check program utilising front-end checks in the eCRF and back-end checks in the Roche database was used to verify the data, and discrepancy reports were generated accordingly. These were transferred electronically to the eCRF at the site for resolution by the investigator.

Both the EMILIA and TH3RESA studies were open-label studies. Blinding was considered desirable but not feasible because of the number of placebo treatments that would be necessary for the control arm, and because blinding was known to be imperfect due to obvious drug effects in at least some patients. Both studies employed an interactive voice response service with a computer generated schedule to ensure high quality stratified randomization and adequate concealment of treatment allocation until randomisation for the study.

Some patients initially considered to have non-visceral disease in fact had visceral disease according to IRC assessments, and vice versa. Any discordant evaluation of visceral disease at randomization versus IRC assessment was driven by the lack of clear definitions of visceral disease for the user of the Interactive Voice Response System (IVRS) at the time of randomization. This lack of clarity was a specific issue applicable only to visceral disease, was independent of data entered into the CRF, and had no impact on data integrity. Additional analyses applying consistent definitions for visceral disease demonstrated a clear treatment benefit of trastuzumab

emtansine, regardless of visceral disease status (RXUKDONF00337, December 2013).

There could be a concern that trastuzumab emtansine is less active in patients with skeletal metastases, however there is no evidence of reduced activity in the bone for trastuzumab emtansine. No preferential progression in the bone was observed for patients treated with trastuzumab emtansine when compared with control therapy, and the efficacy of trastuzumab emtansine was consistently improved over lapatinib plus capecitabine in patients with bone metastasis at baseline (with or without known non-skeletal disease).

Potential limitations in the design of the PRO analyses should be considered when interpreting the results, such as the open-label nature of the study, which could have led to reporting bias. The assumption that the missing data were missing at random in the PRO analysis may be violated, and bias could occur as a result. The data analysis in this article was conducted under the assumption that the missing data were ignorable (ie, missing at random or completely random) and should be interpreted with caution when nonignorable missing data are present. In reality, it cannot be ruled out that nonignorable missing data may exist. However, relatively high compliance rates observed in the EMILIA study. PRO reporting occurred on day 1 of each cycle, and the results may have varied if a different reporting timeline was used. The dosing schedule and pharmacokinetics of the study drugs are not the same, and therefore symptoms may be experienced at different time points in the treatment cycle, which may have affected the results (Welslau, 2013).

In the EMILIA study, for the primary analysis of PFS and duration of response, the data from patients who were lost to follow-up were included in the analysis as censored observations on the date of the last tumor assessment when the patient was known to be progression-free. If PD occurred after two or more consecutive missed tumor assessments, the patient was censored at the patient's last tumor assessment prior to the missing assessments. If PD occurred after one missed tumor assessment, the event was counted at the respective event date. For the primary analysis of PFS and OS, a prospective

pooling algorithm was to be applied in the event that there were underrepresented strata, to ensure that all remaining strata had at least 10 PFS/OS events for the analysis. For the analyses of PRO data, if more than 50% of the constituent items for a FACT-B subscale (PWB, SWB, EWB, FWB and BCS) had been answered, then the subscale was calculated based on all the items that had been completed using the FACT-B scoring guideline; missing items were simply ignored when making the calculations. If the number of the items that had been completed was less than 50%, the subscale was considered missing. For a summary scale (FACT-B total, TOI-PFB), at least 80% of the items needed to be answered to be able to derive the scale score. If less than 80% of the items had been completed or if one of the component subscales was missing, the summary scale was considered missing (RXUKDONF00340, December 2013).

6.4.2 Please provide as an appendix a complete quality assessment for each RCT. See section 10.3, appendix 3 for a suggested format.

Table 11 Critical Appraisal of EMILIA

Study ID or acronym		
Study question	How is the question addressed in the study?	Grade (yes/no/not clear/N/A)
Was randomisation carried out appropriately?	After written consent was obtained and eligibility established, the study site obtained the patient's identification number and randomisation to treatment via an Interactive Voice Response System (IVRS). The hierarchical randomisation scheme is designed to ensure approximately equal number of patients in the two arms, within the following three categories: world region (United States, Western Europe, Other), the number of prior chemotherapeutic regimens for unresectable, locally advanced or metastatic disease, and visceral versus non-visceral disease.	Yes
Was the concealment of treatment allocation adequate?	Concealment of treatment allocation was achieved by IVRS.	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	The patient demographics and characteristics were generally well balanced in both arms of the study.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	This was an open-label study which does introduce the possibility of bias, particularly with reporting of adverse events. Blinding was considered desirable but was not possible due to the number of placebos required and the obviously different toxicity profiles of the drugs. Participants or reporters may tend to either over or under report adverse events from the active arm of a trial. The primary outcome of this study was PFS by independent review. These reviewers were blinded to the treatment allocation and so this analysis should not be biased by the open-label design. OS is unlikely to be affected by bias.	No, however there was an independent review of PFS by a blinded assessment group

Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	There were no unexpected imbalances in drop outs. At the clinical data cut-off there were 316 (63.7%) patients still on study in the lapatinib plus capecitabine arm and 366 (73.9%) patients still on treatment in the trastuzumab emtansine arm. The majority of patients discontinued study due to death: 129 (26.0%) in the lapatinib plus capecitabine arm and 94 (19.0%) in the trastuzumab emtansine arm. The rate of treatment discontinuation due to toxicity shows 37 of 488 patients (7.6%) discontinued treatment with lapatinib, 46 of 488 patients (9.4%) discontinued treatment with capecitabine, and 29 of 490 patients (5.9%) discontinued treatment with trastuzumab emtansine due to adverse events. These patients did not necessarily discontinue the study.	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	There is no evidence to suggest this	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Efficacy analyses were conducted on the intention to treat population. Safety analyses were conducted on people who received at least one dose of study medication	Yes
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Table 12 Critical Appraisal of TH3RESA

Study ID or acronym		
Study question	How is the question addressed in the study?	Grade (yes/no/not clear/N/A)
Was randomisation carried out appropriately?	After written consent was obtained and eligibility established, the study site obtained the patient's identification number and randomisation to treatment arm from the Interactive Voice/Web Response System (IVRS/IWRS). The permuted block randomisation scheme was designed to ensure an approximate 2:1 allocation of patients to receive trastuzumab emtansine or TPC, with the following stratification factors: world region (United States, Western Europe, or Other), number of prior regimens (excluding single-agent hormones) for the treatment of metastatic or locally advanced/recurrent unresectable disease (2−3 or > 3), and presence of visceral disease.	Yes
Was the concealment of treatment allocation adequate?	Treatment concealment was not possible. In TH3RESA the comparator was TPC which meant it was not possible to placebo-control this arm because of the variety of potential choices.	No
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	The patient demographics and characteristics were generally well balanced in both arms of the study.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	This was an open-label study which does introduce the possibility of bias, particularly with reporting of adverse events. Participants or reporters may either over or under report adverse events from the active arm of a trial. The primary outcome of this study was PFS by investigator review. There is a chance that these results may be biased by additional unscheduled tumour assessments and knowledge of treatment allocation, but the strict criteria for RECIST evaluation should reduce the risk for bias. OS is unlikely to be affected by bias.	No

Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	At time of data cut-off 125 (63.1%) were stil on treatment in the TPC arm compare with 319 (79.0%) patients in the trastuzumab emtansine arm. The most common reason for study discontinuation in either treatment arm was death, with 44 (22.2%) and 61 (15.1%) dying in the TPC and trastuzumab emtansine arms, respectively. There was an imbalance in the rate of drop outs in the TPC arm. More patients in the TPC arm (26 patients; 13.1%) than in the trastuzumab emtansine arm (19; 4.7%) decided to withdraw from the study. This was in part due to patients withdrawing after being informed they had been randomised to the study's control arm (13 patients withdrew from TPC prior to treatment, compared with 2 patients who withdrew prior to receiving trastuzumab emtansine).	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	There is no evidence to suggest this	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Efficacy analyses were conducted on the intention to treat population. Safety analyses were conducted on people who received at least one dose of study medication	Yes
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

6.4.3 If there is more than one RCT, tabulate a summary of the responses applied to each of the critical appraisal criteria. A suggested format for the quality assessment results is shown below.

Table 13: Quality assessment results for RCTs

Trial no. (acronym)	EMILIA	TH3RESA
Was randomisation carried out appropriately?	Yes	Yes
Was the concealment of treatment allocation adequate?	No	No
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	No, however there was an independent review of PFS by a blinded assessment group	No
Were there any unexpected imbalances in drop-outs between groups?	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

6.5 Results of the relevant RCTs

6.5.1 Provide the results for all relevant outcome measure(s) pertinent to the decision problem. Data from intention-to-treat analyses should be presented whenever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should

be given. If there is more than one RCT, tabulate the responses.

6.5.2 The information may be presented graphically to supplement text and tabulated data. If appropriate, please present graphs such as Kaplan–Meier plots.

6.5.3 For each outcome for each included RCT, the following information should be provided.

- **The unit of measurement.**
- **The size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio is an equivalent statistic. Both absolute and relative data should be presented.**
- **A 95% confidence interval.**
- **Number of participants in each group included in each analysis and whether the analysis was by 'intention to treat'. State the results in absolute numbers when feasible.**
- **When interim RCT data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of that RCT. Analytical adjustments should be described to cater for the interim nature of the data.**
- **Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication and/or study protocol.**
- **Discuss and justify definitions of any clinically important differences.**
- **Report any other analyses performed, including subgroup analysis and adjusted analyses, indicating those pre-specified and those exploratory.**

EMILIA

The primary analysis took place with a clinical data cut-off of 14 January 2012. Following the primary progression-free survival analysis, a formal request was received from regulatory authorities for an additional analysis of overall survival prior to the planned protocol-specified final analysis. This second interim analysis of overall survival was conducted with data cut-off date of 31 July 2012. Subsequent to the second interim analysis, as per protocol, patient crossover has been permitted; therefore any data obtained in future will be compounded by crossover. A final analysis of OS is expected in 2014 and will be triggered by reaching 632 events.

Primary Endpoints (Data cut-off 14 January 2012)

The study met both its co-primary endpoints. Treatment with trastuzumab emtansine resulted in a statistically significant improvement in independent review facility assessed progression-free survival (HR=0.65, 95% CI [0.55, 0.77], p <0.0001) with an increase in median progression-free survival of 50% (median progression-free survival of 9.6 months in the trastuzumab emtansine arm compared with 6.4. months in the lapatinib plus capecitabine arm).

A strong trend towards an overall survival benefit was observed in the trastuzumab emtansine arm (hazard ratio of 0.621 [0.48, 0.81, p=0.0005]). However the estimated hazard ratio did not meet the O'Brien-Fleming stopping boundary of the Lan-DeMets α-spending function for this interim analysis of survival (HR=0.617, p=0.0003) and was therefore not deemed statistically significant. The second interim analysis (data cut-off 31 July 2012) with an additional six months of data, however, was found to be statistically significant with a median OS in the trastuzumab emtansine arm of 30.6 months compared to 25.1 months in the lapatinib plus capecitabine (hazard ratio of 0.682 [0.55, 0.85, p=0.0006]).

Key Secondary Endpoints (Data cut-off 14 January 2012)

Median time to investigator-assessed progression-free survival was significantly improved in the trastuzumab emtansine arm compared with lapatinib plus capecitabine arm (18.5 months compared with 12.4 months), with a hazard ratio of 0.658 [0.56, 0.78], p<0.0001. The results were comparable with those observed for independent review facility assessed progression-free survival.

A higher percentage of people receiving trastuzumab emtansine achieved an objective response (complete response or partial response), as assessed by the independent review facility (173 of 397 patients [31.3%] in the trastuzumab emtansine arm compared with 120 of 389 patients [8.6%] in the lapatinib plus capecitabine arm (12.7% (95% CI, 6.0, 19.4) p=0.0002)

The duration of response was longer in people receiving trastuzumab emtansine compared with lapatinib plus capecitabine (12.6 week median overall response duration in the trastuzumab emtansine arm compared with 6.5 weeks in the lapatinib plus capecitabine).

Quality of life data from the EMILIA study has now been described in a further publication. Time to symptom worsening was delayed in the trastuzumab emtansine arm vs the lapatinib plus capecitabine arm (7.1 months versus 4.6 months, respectively; HR 0.796, p = 0.0121). In the trastuzumab emtansine arm, 55.3% of patients developed clinically significant improvement in symptoms from baseline versus 49.4% in the lapatinib plus capecitabine arm (p = 0.0842). Although similar at baseline, the number of patients reporting diarrhea symptoms increased 1.5- to 2-fold during treatment with lapatinib plus capecitabine but remained near baseline levels in the trastuzumab emtansine arm. Together with the EMILIA primary data, these results support the concept that trastuzumab emtansine has greater efficacy and tolerability than lapatinib plus capecitabine, which may translate into improvements in health-related quality of life (Welslau, 2013).

Figure 5: EMILIA trial - PFS curves

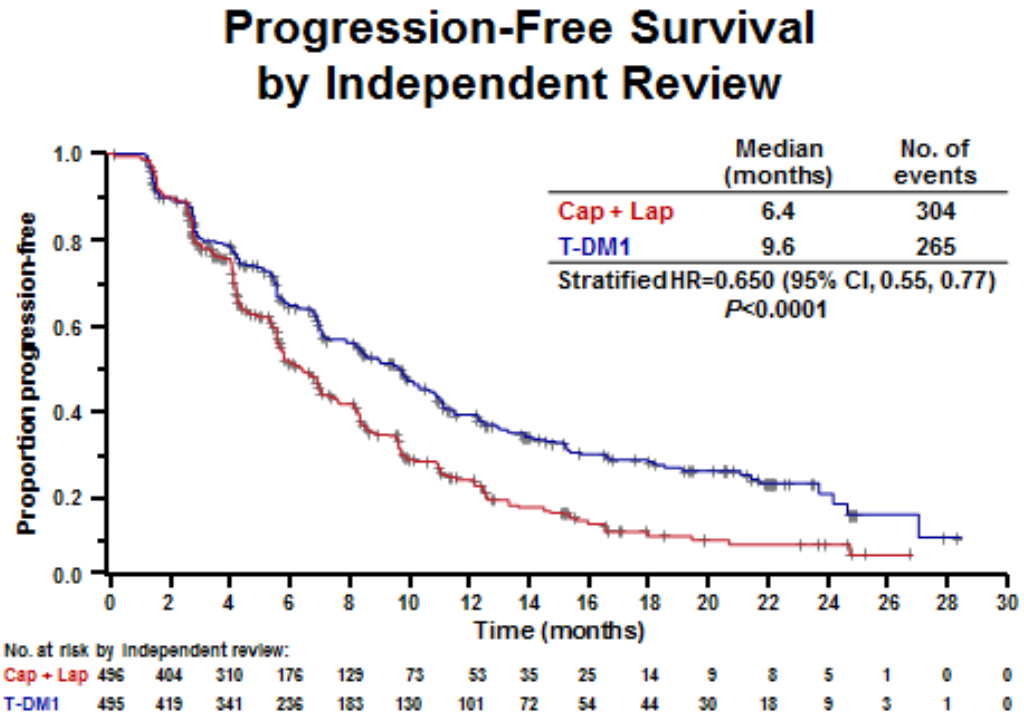


Figure 6: EMILIA trial - Forest plot of subgroup analyses

Subgroup	No. of Patients	Hazard Ratio (95% CI)
All patients	991	0.66 (0.56–0.78)
World region		
United States	270	0.70 (0.51–0.98)
Western Europe	317	0.56 (0.41–0.74)
Asia	158	0.74 (0.50–1.08)
Other	246	0.73 (0.51–1.03)
Number of prior chemotherapeutic regimens for LABC or MBC		
0–1	609	0.68 (0.55–0.85)
>1	382	0.63 (0.49–0.82)
Line of therapy by any systemic therapy		
First-line	118	0.51 (0.30–0.85)
Second-line	361	0.69 (0.53–0.91)
Third- and later-line	512	0.69 (0.55–0.86)
Disease involvement		
Visceral	669	0.55 (0.45–0.67)
Nonvisceral	322	0.96 (0.71–1.30)
Age group		
<65	853	0.62 (0.52–0.74)
65–74	113	0.88 (0.53–1.45)
≥75	25	3.51 (1.22–10.13)
Race		
White	732	0.63 (0.52–0.77)
Asian	180	0.82 (0.57–1.18)
Other	79	0.59 (0.31–1.11)
Gender		
Female	986	0.67 (0.57–0.79)
Male	5	0.00 (0.00–NE)
Baseline ECOG PS		
0	611	0.61 (0.49–0.77)
1	370	0.76 (0.59–0.98)
Number of disease sites		
<3	605	0.60 (0.48–0.75)
≥3	364	0.73 (0.57–0.94)
Prior anthracycline therapy		
Yes	605	0.70 (0.57–0.87)
No	386	0.61 (0.47–0.79)
Baseline liver metastases		
Yes	405	0.59 (0.45–0.76)
No	577	0.71 (0.57–0.89)
Unknown	9	1.73 (0.11–27.89)
Baseline bone metastases		
Yes	399	0.76 (0.58–0.99)
No	570	0.61 (0.49–0.76)
Unknown	22	1.30 (0.21–8.04)
ER and PR status		
ER-positive and/or PR-positive	545	0.72 (0.58–0.91)
ER-negative and PR-negative	426	0.56 (0.44–0.72)
Unknown	20	3.49 (0.75–16.30)
Baseline disease measurability		
Yes	786	0.62 (0.52–0.75)
No	205	0.91 (0.59–1.42)
Menopausal status		
Premenopausal	451	0.70 (0.54–0.90)
Perimenopausal	38	0.49 (0.20–1.22)
Postmenopausal	400	0.68 (0.53–0.87)
Unknown	79	0.55 (0.31–0.99)
Not applicable	23	0.74 (0.26–2.16)
Prior systemic therapy for MBC		
Yes	873	0.69 (0.58–0.82)
No	118	0.51 (0.30–0.85)
Prior trastuzumab treatment for MBC		
Yes	836	0.67 (0.56–0.81)
No	155	0.62 (0.40–0.95)

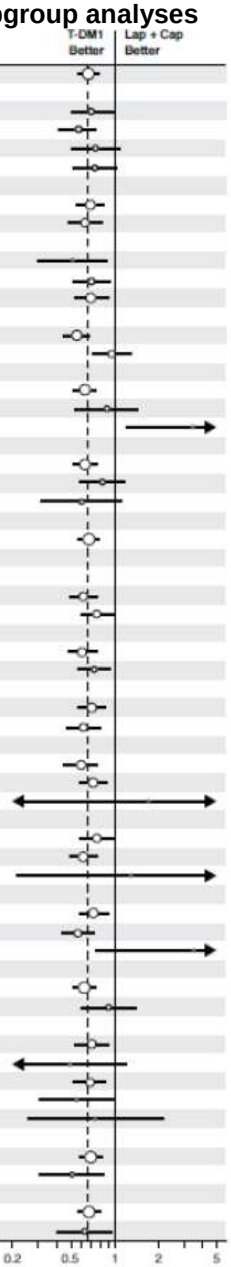


Table 14: EMILIA trial - OS results

	First interim OS analysis data cut-off Jan 14, 2012		Confirmatory OS analysis data cut-off July 31, 2012	
	Cap + Lap	Trastuzumab emtansine	Cap + Lap	Trastuzumab emtansine
Number of events	129	94	182	149
Percent of total targeted events	35%		52%	
Median follow-up time, months	12.4	12.9	18.6	19.1
Median survival, months	23.3	Not reached	25.1	30.9
Hazard ratio (95% CI)	HR=0.621 (0.475, 0.813)		HR=0.682 (0.548, 0.849)	
***P* value**	0.0005		0.0006	
Efficacy stopping boundary hazard ratio, *P* value	HR=0.617; *P*=0.0003		HR=0.727; *P*=0.0037	

Figure 7: EMILIA trial - OS curves: First interim analysis (Jan 2012)

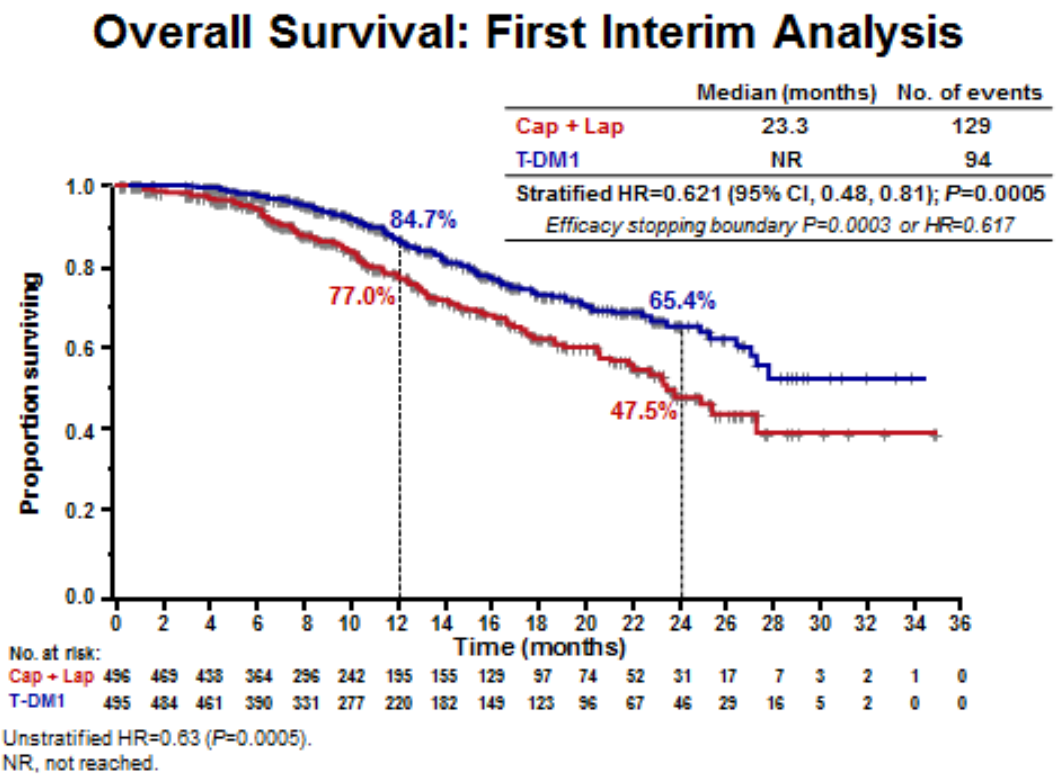
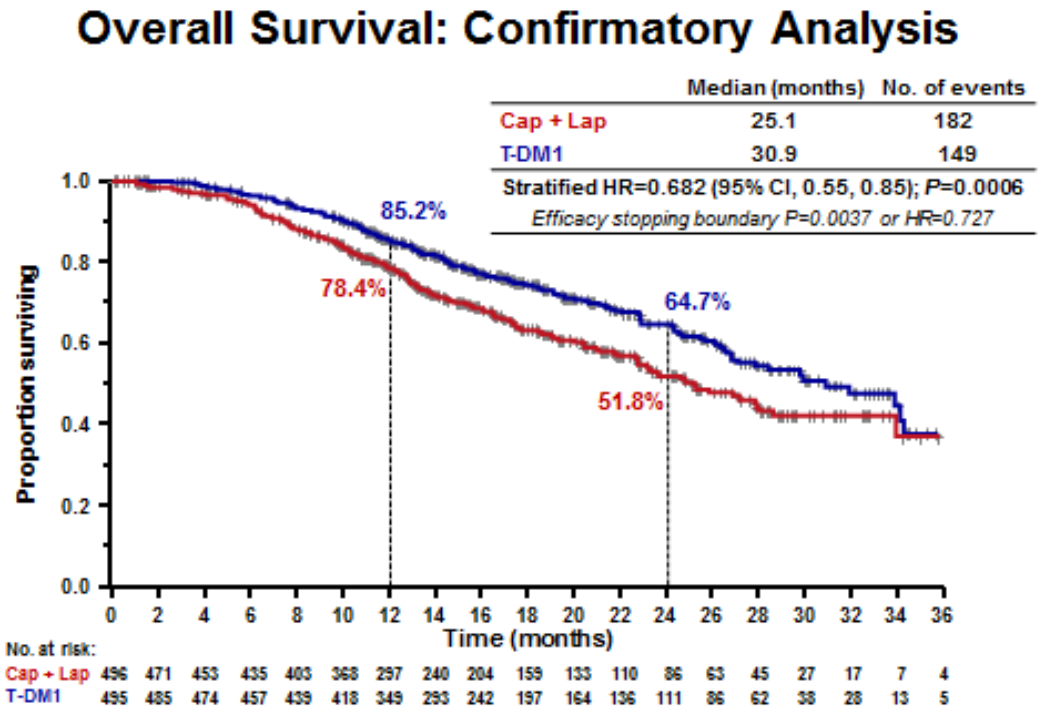
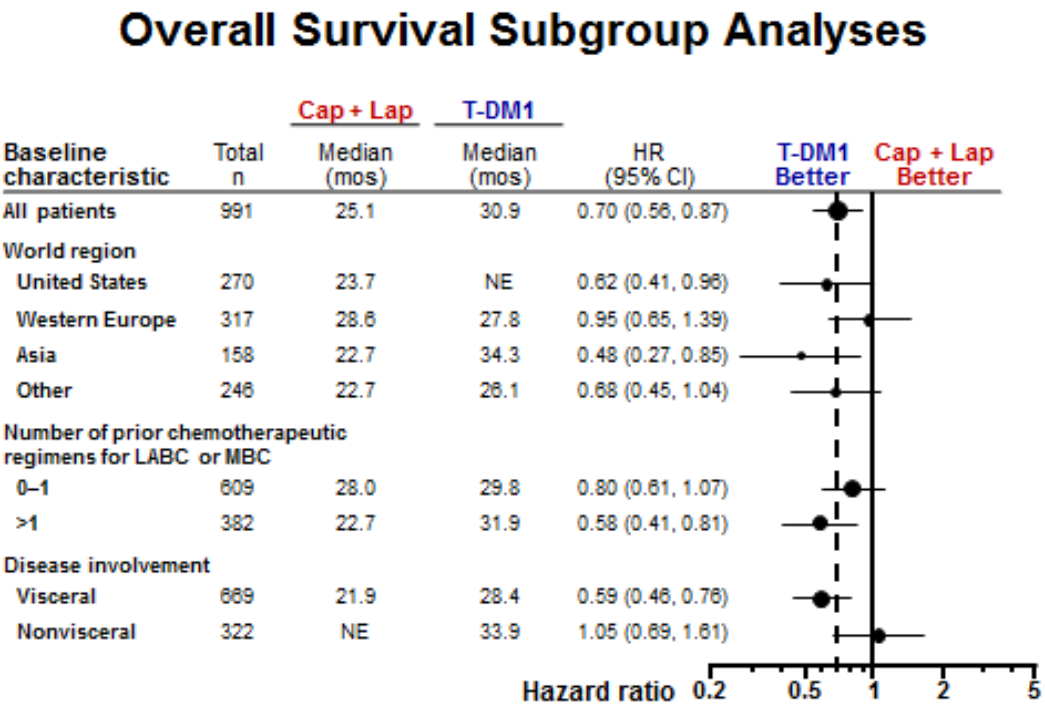


Figure 8: EMILIA trial - OS curves: Confirmatory analysis (July 2012)



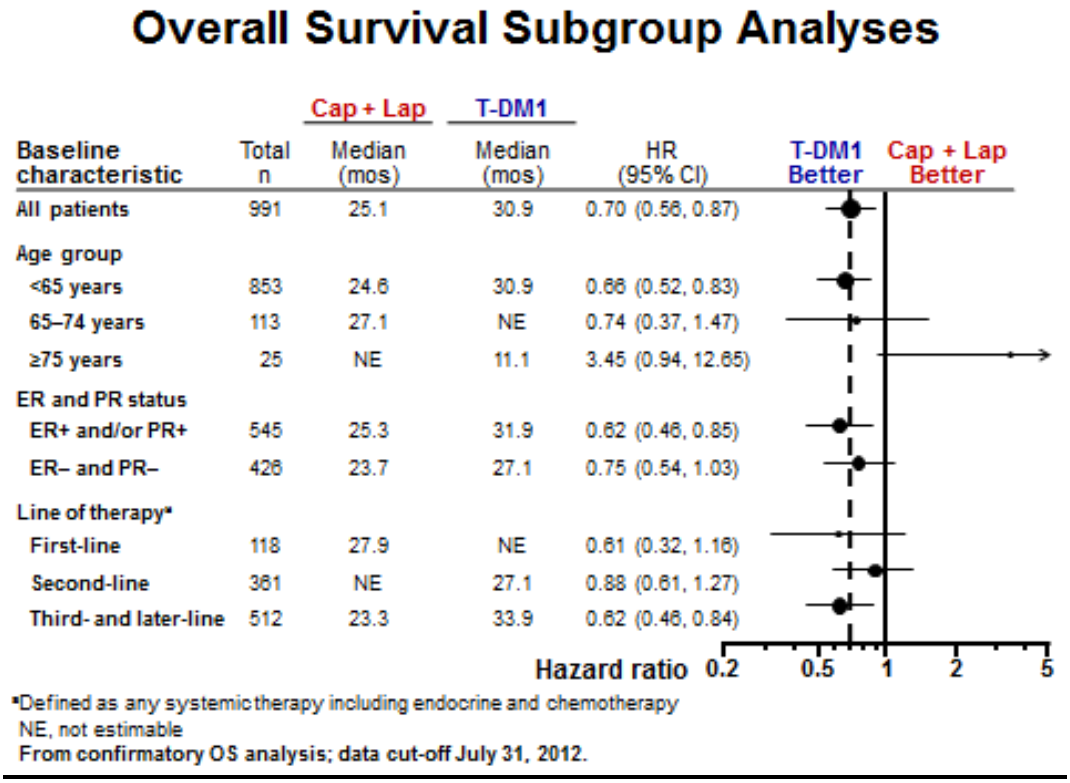
Data cut-off July 31, 2012; Unstratified HR=0.70 (P=0.0012).

Figure 9: EMILIA trial - OS subgroup analyses: world region, number of prior chemptherapy regimens and disease involvement



NE, not estimable
From confirmatory OS analysis; data cut-off July 31, 2012.

Figure 10: EMILIA trial - OS subgroup analyses: age, ER and PR status and line of therapy



TH3RESA

The primary analysis took place with a clinical data cut-off of 11 February 2012. All patients in the TPC arm were given the option of crossing over to the trastuzumab emtansine arm at progression. At the time of analysis 44 of the 198 patients in the TPC arm had crossed over to receive trastuzumab emtansine. A final analysis of OS is expected in 2014 and will be triggered by reaching 492 events.

Primary Endpoints (Data cut-off 11 February 2013)

The study met its first co-primary endpoint. Treatment with trastuzumab emtansine resulted in a statistically significant improvement in investigator assessed progression-free survival (HR=0.528, 95% CI [0.422, 0.661], p <0.0001) with an increase in median progression-free survival (median progression-free survival of 6.2 months in the trastuzumab emtansine arm compared with 3.3 months in the TPC arm).

A strong trend towards an overall survival benefit was observed in the trastuzumab emtansine arm (hazard ratio of 0.552 [0.369, 0.826, p=0.0034]). However the estimated hazard ratio did not meet the O'Brien-Fleming stopping boundary of the Lan-DeMets α-spending function for this interim analysis of survival (HR<0.363, p=0.0000013) and was therefore not deemed statistically significant. The final OS analysis will occur in 2014 when 492 events have occurred.

Secondary Endpoints (Data cut-off 11 February 2013)

A higher percentage of people receiving trastuzumab emtansine achieved an objective response (complete response or partial response), as assessed by the independent review facility (108 of 345 [31.3%] in the trastuzumab emtansine arm compared with 14 of 163 patients [8.6%] in the TPC arm (difference: 22.7% (95% CI, 16.2, 29.2) p<0.0001).

Figure 11: TH3RESA trial - PFS curves

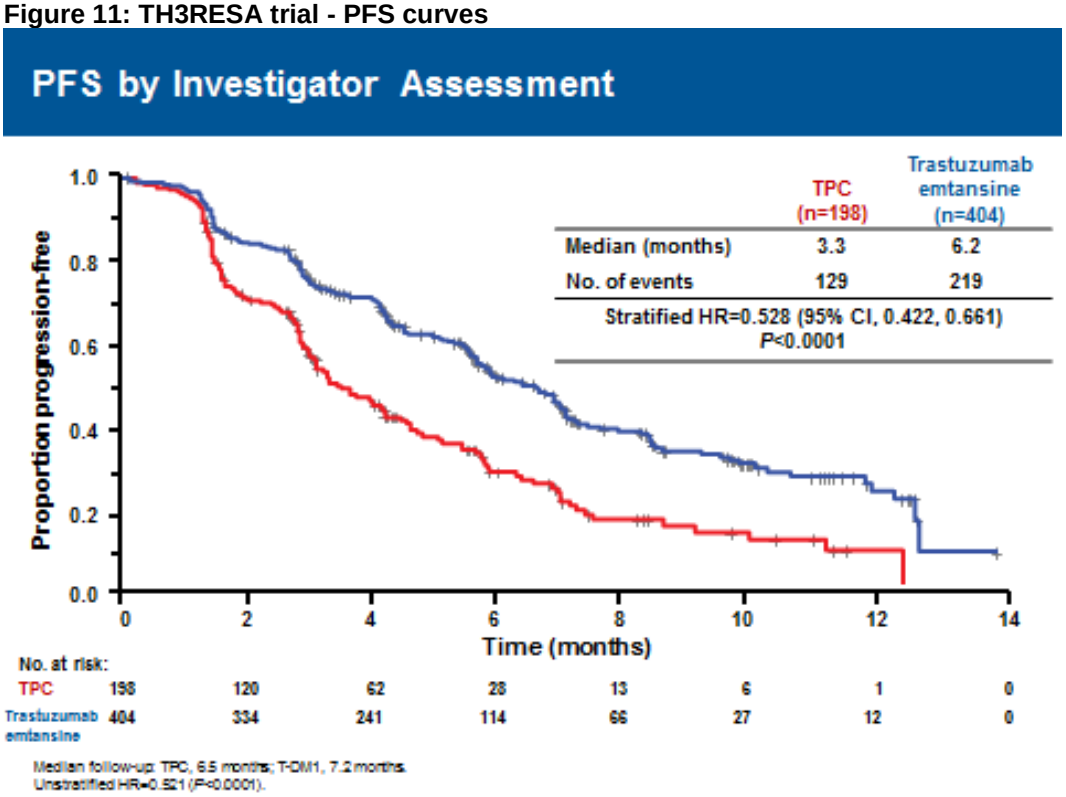


Figure 12: TH3RESA trial - PFS curves for patients treated with trastuzumab-containing regimens

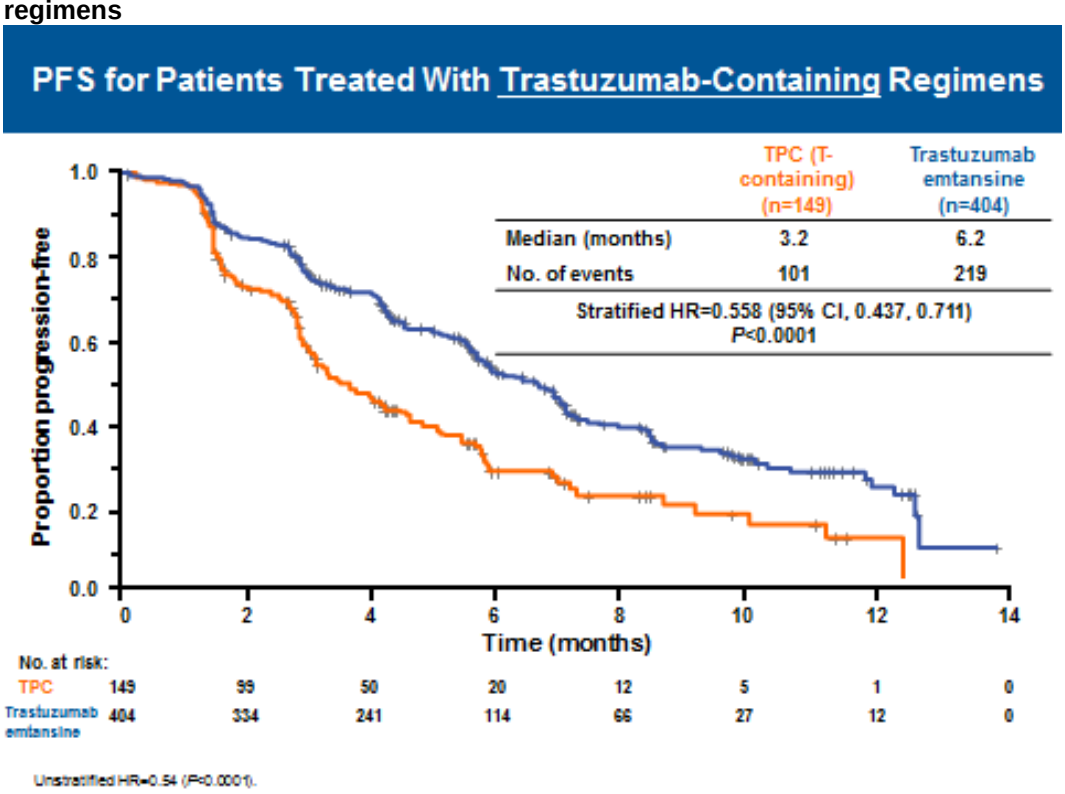


Figure 13: TH3RESA trial - PFS subgroup analysesage group, world region, race and baseline ECOG PS

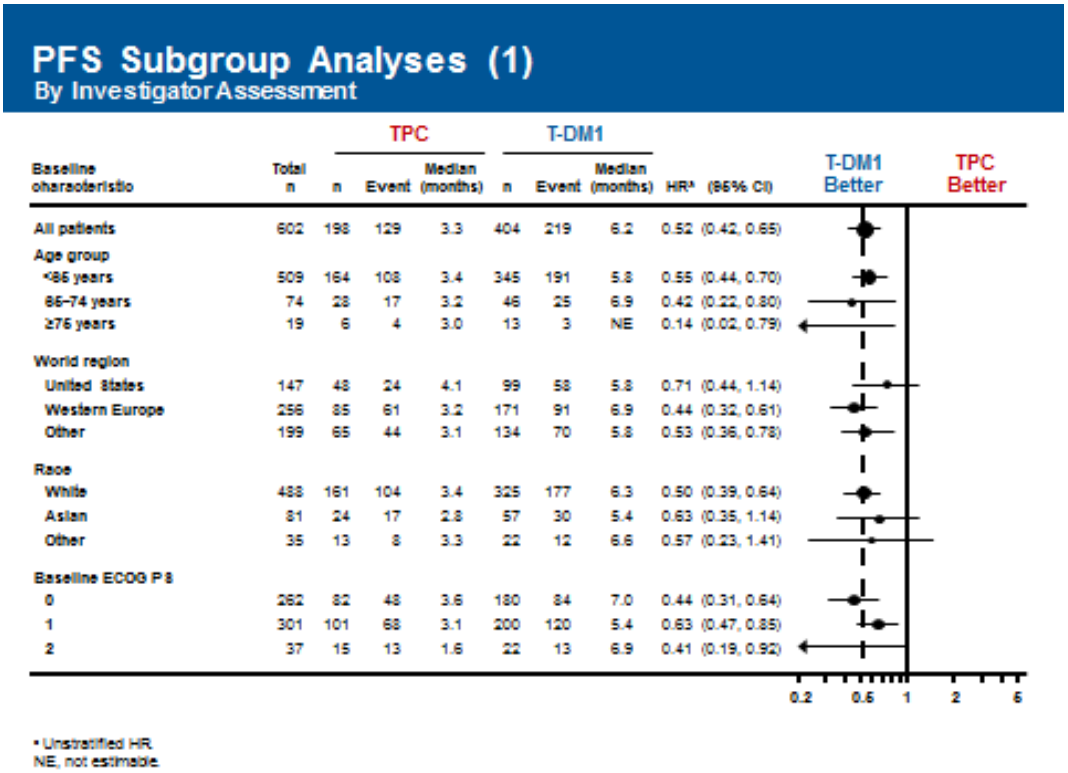
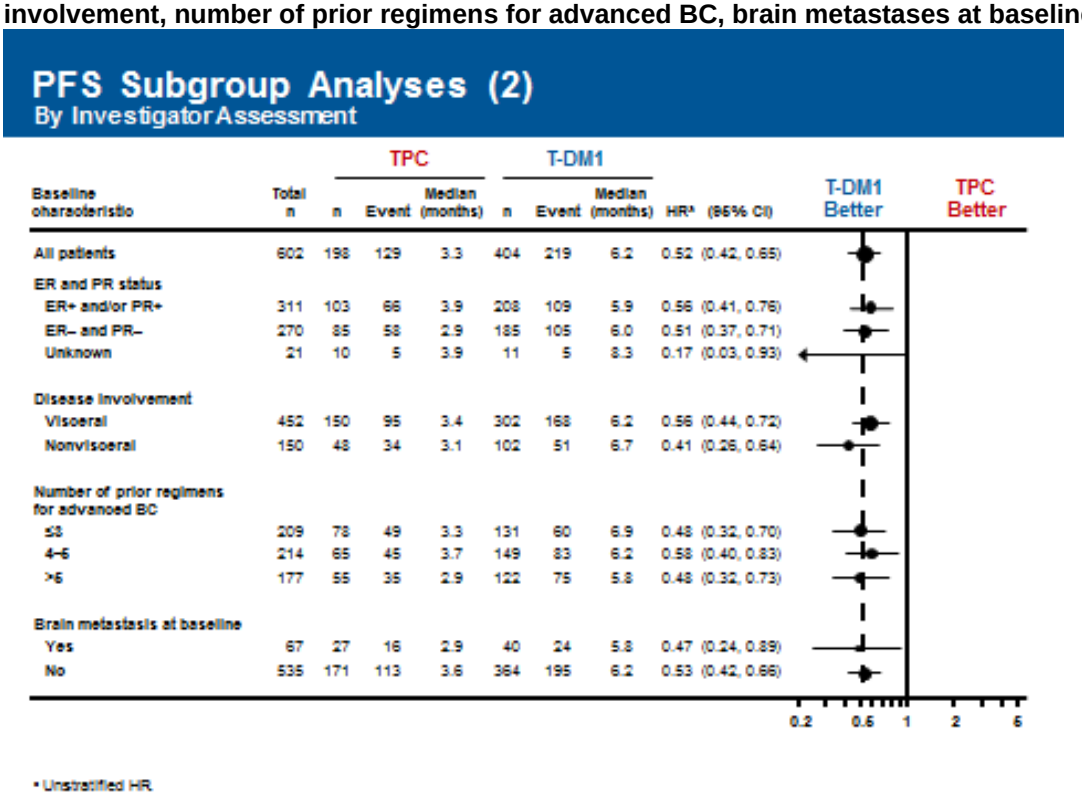
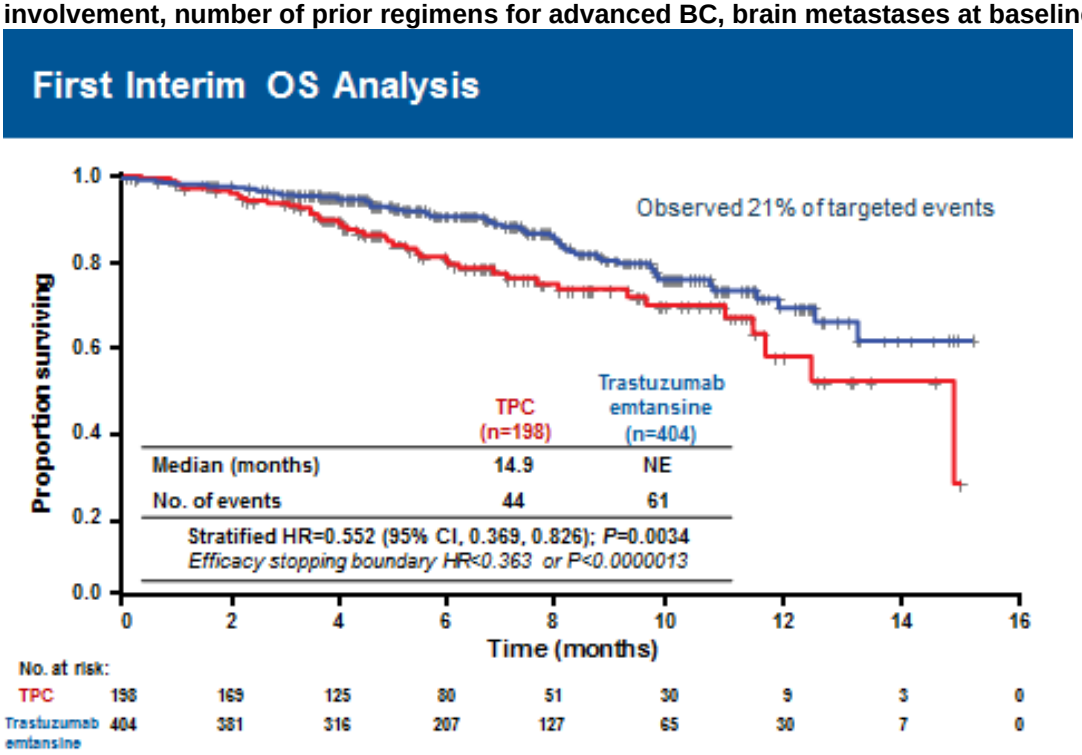


Figure 14: TH3RESA trial - PFS subgroup analyses: ER and PR status, disease involvement, number of prior regimens for advanced BC, brain metastases at baseline



Baseline characteristic	Total n	TPC n	TPC Event	TPC Median (months)	T-DM1 n	T-DM1 Event	T-DM1 Median (months)	HR* (95% CI)
All patients	602	198	129	3.3	404	219	6.2	0.52 (0.42, 0.65)
ER and PR status								
ER+ and/or PR+	311	103	66	3.9	208	109	5.9	0.56 (0.41, 0.76)
ER– and PR–	270	85	58	2.9	185	105	6.0	0.51 (0.37, 0.71)
Unknown	21	10	5	3.9	11	5	8.3	0.17 (0.03, 0.93)
Disease involvement								
Visceral	452	150	95	3.4	302	168	6.2	0.56 (0.44, 0.72)
Nonvisceral	150	48	34	3.1	102	51	6.7	0.41 (0.26, 0.64)
Number of prior regimens for advanced BC								
≤3	209	78	49	3.3	131	60	6.9	0.48 (0.32, 0.70)
4–6	214	65	45	3.7	149	83	6.2	0.58 (0.40, 0.83)
>6	177	55	35	2.9	122	75	5.8	0.48 (0.32, 0.73)
Brain metastasis at baseline								
Yes	67	27	16	2.9	40	24	5.8	0.47 (0.24, 0.89)
No	535	171	113	3.6	364	195	6.2	0.53 (0.42, 0.66)

Figure 15: TH3RESA trial - PFS subgroup analyses: ER and PR status, disease involvement, number of prior regimens for advanced BC, brain metastases at baseline



Summary of EMILIA and TH3RESA

Table 15: EMILIA and TH3RESA: summary of key results: PFS, OS and ORR

Results of phase III trials for Kadcyla (trastuzumab emtansine) in HER2+ MBC	EMILIA Relapse on or <6 months adjuvant treatment OR ≥ 1 line of treatment for MBC Prior treatments incl taxane, Herceptin (trastuzumab)		TH3RESA ≥ 2 line of treatment for MBC Prior treaments incl taxane, Herceptin, lapatinib	
	Kadcyla	Lapatinib + capecitabine	Kadcyla	TPC (TPC – H)
PFS (mo)	9.6	6.4	6.2	3.3 (3.2)
	HR=0.65, p<0.0001		HR=0.528 (0.558), p<0.0001 (p,0.0001)	
OS (mo)	30.9	25.1	14.9	NE
	HR=0.682, p=0.0006		HR=0.552, p=0.0034 (not sig)	
ORR (%)	43.6	30.8	31.3	8.6
	P=0.0006		p<0.0001	

TPC: Treatment of Physician's Choice, TPC could have been single-agent chemotherapy, hormonal therapy, or HER2-directed therapy, or a combination of a HER2-directed therapy with a chemotherapy, hormonal therapy, or other HER2-directed therapy. TPC-H: TPC with Herceptin containing therapy)

6.6 Meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be undertaken. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.9 to 5.3.12.

6.6.1 The following steps should be used as a minimum when presenting a meta-analysis.

- **Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to provide an explanation for the heterogeneity.**
- **Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).**
- **Provide an adequate description of the methods of statistical combination and justify their choice.**
- **Undertake sensitivity analysis when appropriate.**
- **Tabulate and/or graphically display the individual and combined results (such as through the use of forest plots).**

N/a

6.6.2 If a meta-analysis is not considered appropriate, a rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal.

Since the outcome of EMILIA is statistically significant and there are no specific subpopulations of interest there is no requirement for a meta-analysis.

6.6.3 If any of the relevant RCTs listed in response to section 6.2.4 (Complete list of relevant RCTs) are excluded from the meta-

analysis, the reasons for doing so should be explained. The impact that each exclusion has on the overall meta-analysis should be explored.

N/a

6.7 Indirect and mixed treatment comparisons

Data from head–to–head RCTs should be presented in the reference-case analysis, if available. If data from head–to–head RCTs are not available, indirect treatment comparison methods should be used. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.13 to 5.3.22.

6.7.1 Describe the strategies used to retrieve relevant clinical data on the comparators and common references both from the published literature and from unpublished data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 10.4, appendix 4.

Trastuzumab emtansine (T-DM1) is indicated for the treatment of unresectable HER2-positive (HER2+) locally advanced breast cancer (BC) or metastatic breast cancer (MBC) patients who progressed after treatment with trastuzumab and a taxane, progression being defined as having occurred during or after the most recent treatment for locally advanced BC or MBC or within six months after treatment for early-stage disease. Whilst trastuzumab as a single agent or in combination with chemotherapy for the first-line treatment of HER2+ MBC patients is the current recognised NICE approved standard of care (SoC), no one such clearly defined SoC exists for later lines of treatments.

The NICE approved clinical pathway in HER2+ MBC is as follows:

- First line: trastuzumab plus taxane
- Second line: capecitabine or vinorelbine (plus trastuzumab in CNS only progression) *Note: as this use is guideline recommended only and not associated with a funding mandate, trastuzumab retreatment use is variable throughout the country)*
- Third line: vinorelbine or capecitabine or trastuzumab

However due to the introduction of the Cancer Drugs Fund in October 2010 many HER2+ MBC patients receive as standard practice, treatments that have not been NICE approved.

CDF approved clinical pathway in HER2+ MBC:

- First line: pertuzumab plus trastuzumab plus taxane
- Second line: lapatinib plus capecitabine
- Third line: capecitabine or vinorelbine or trastuzumab

Further, trastuzumab in combination with either capecitabine or vinorelbine is frequently given second and third line.

Given the wide array of treatment options, trastuzumab emtansine ought to be compared against all of the following[2]:

- Lapatinib in combination with capecitabine (LAP-CAP)
- Trastuzumab in combination with capecitabine (TRA-CAP)
- Trastuzumab in combination with vinorelbine (TRA-VIN)
- Capecitabine (CAP)
- Vinorelbine (VIN)

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[2] Although funded as a monotherapy, trastuzumab is typically given in combination with another funded chemotherapy rather than alone.

However given that the EMILIA trial is the only RCT that looks at the efficacy of trastuzumab emtansine versus only one pre-specified comparator (LAP-CAP) in the second line setting or later, an indirect treatment comparison needs to be conducted to assess its efficacy against the other interventions. (TH3RESA assesses the efficacy of trastuzumab emtansine in the third line setting or later but this is against physician's choice which was not prespecified and therefore one cannot draw conclusions about the relative efficacy of trastuzumab emtansine versus these comparators.)

Further where both direct and indirect evidence is available, this indicates a potential for undertaking mixed treatment comparison (MTC). MTC, a special case of network meta-analysis, combines direct with indirect evidence for particular pair-wise comparisons thereby synthesising a greater share of the available evidence than traditional meta-analysis. MTC as compared with ITC has two important characteristics including strengthening the inference for relative efficacy determinations and facilitating the ranking or simultaneous comparisons of all the treatments. An MTC was therefore undertaken to determine the relative efficacy of trastuzumab emtansine and to simultaneously compare different interventions for the treatment of HER2+ MBC.

6.7.2 Please follow the instructions specified in sections 6.1 to 6.5 for the identification, selection and methodology of the trials, quality assessment and the presentation of results. Provide in section 10.5, appendix 5, a complete quality assessment for each comparator RCT identified.

6.7.3 Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent. A suggested format is provided below.

A systematic (literature) review (SR) was conducted (in order to ensure that the subsequent ITC would include all evidence) by following the most rigorous, up-to-date, and comprehensive methods for performing and reporting SRs and ITCs, including the Cochrane Handbook for SRs, the PRISMA statement, ISPOR guidelines and major HTA agency requirements including NICE.

The SR was conducted to identify randomised controlled trials (RCTs) and non-randomised clinical trials (n-RCTs) using MEDLINE, EMBASE, MEDLINE In-process, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Method Studies, Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE).

The databases searched studies published from 1998, the date of approval of trastuzumab, to December 20 2012.

To ensure that all comparable treatments for trastuzumab emtansine were captured, the eligibility criteria included rigorously defined EMILIA-matched population criteria: Patients were required to have unresectable HER2+ locally advanced BC or MBC that progressed after previous treatment with trastuzumab and a taxane in the adjuvant or metastatic setting; progression was defined according to the EMILIA definition, in that, it occurred during or after the most recent treatment for locally advanced BC or MBC or within six months after treatment for early-stage disease.

No pre-specified interventions or comparators were targeted and the study designs included not only RCTs, but also all controlled clinical trials, independent of randomisation, phase, or blinding status. All English and non-English publications were identified.

The inclusion and exclusion criteria are detailed below in Table 16. Further details on the search strategies can be found in **Error! Reference source not found.**.

Table 16: Eligibility criteria for trials to be included in the systematic review

Criteria	Inclusion criteria	Rationale
Inclusion criteria	**Population** Age: Adults (≥18 years) Gender: Any Race: Any Disease: HER2+ locally advanced BC or MBC Line of therapy: Progression during or after most recent treatment for locally advanced BC (with prior treatment with trastuzumab and a taxane) or MBC or within six months after treatment for early-stage disease.	The patient population was restricted to match that stated in the positioning of T-DM1 in the treatment of HER2+ unresectable locally advanced BC or MBC
	Intervention: Not prespecified or limited to, but could have included: Trastuzumab emtansine Bevacizumab Capecitabine Lapatinib Neratinib Pertuzumab Sunitinib Tamoxifen Toremifene Trastuzumab Vinorelbine Any other hormonal, biological, or chemotherapeutic agent	All pharmacological interventions for treatment of HER2+ unresectable locally advanced or MBC (not prespecified or limited a priori)
	Comparator: Not prespecified or limited to, but could have included: Any of the included interventions Placebo Best supportive care (BSC)* Any chemotherapy/immunotherapy	These comparators were selected to potentially enable both direct and indirect comparisons between the interventions of interest (not prespecified or limited a priori)
	Study design RCTs and n-RCTs with any blinding status	RCTs are the gold standard of clinical evidence, minimizing the risk of confounding and allowing the comparison of the relative efficacy of interventions To enhance completeness, n-RCTs and open-label studies were also searched for
	Phases of trial All phases	All phases of trials evaluating pharmacological interventions were included to avoid missing of any potential studies
	Language restrictions English included and non-English identified	The SR searched for English and non-English studies, being that the inclusion of English language only, would not limit results substantially due to data availability in English language
	Publication timeframe 1998 up to 20 December 2012 Last three years for conference searches	Publication searches were started from 1998 as trastuzumab was approved in this year Studies which are presented at conferences are usually published in journals within three years
Exclusion criteria	**No subgroup analysis** No subgroup analysis for disease of interest No subgroup analysis for disease stage of interest No subgroup analysis for prior treated patients	Studies with no subgroup data for the disease, disease stage and prior treatment were not included, since these studies would introduce heterogeneity into the review

BSC: Best Supportive Care *BSC definition: includes (though not restricted to) observation alone, non-chemotherapy drugs, palliative care, and even radiotherapy; HER2: Hormone Expression Receptor 2; MBC: Metastatic Breast Cancer; nRCT: non-Randomised Controlled Trials; RCT: Randomised Controlled Trials

Citations were screened by two independent reviewers first, based on the abstract supplied with each citation and subsequently based on the full-text citations. Any discrepancies between reviewers were reconciled by a third independent reviewer.

Critical appraisal for RCTs was undertaken based on NICE's recommended methods. The critical appraisal for RCTs assessed each trial for quality by considering the features summarised in Table 17. In addition, RCTs were graded by means of allocation concealment grade and Jadad score.

Table 17: Criteria for critical appraisal for RCTs

Criterion	Assessment
Randomisation	Was randomisation carried out appropriately?
Allocation concealment	According to the grading system
Baseline comparability	Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?
Blinding	Were the care providers, participants, and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?
Follow-up	Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?
Selective reporting	Is there any evidence to suggest that the authors measured more outcomes than they reported?
Analysis	Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
Other source of bias	State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry.

In addition to the descriptive critical appraisal, study quality was graded by assessing the adequacy of concealment of allocation.

Concealment of allocation was graded from A to D for each study, where the adequacy of allocation concealment was considered:

- Adequate, when studies reported allocation being centralised by central office unaware of subject characteristics, pharmacy-controlled randomisation, pre-numbered or coded identical containers which were administered serially to participants; on-site computer systems combined with allocations kept in a locked unreadable computer file that could be accessed only after the characteristics of an enrolled participant had been entered, sequentially numbered, and sealed in opaque envelopes

- Unclear, when studies did not report any concealment approach.
- Inadequate, when studies reported the use of case record numbers; dates of birth or day of the week; and any procedure that was entirely transparent before allocation, such as an open list of random numbers
- Not used, if studies reported that it was not undertaken.

A descriptive critical appraisal of each extracted study was made during the data extraction process. The details of factors used to assess the quality of a study are reported in Appendix **Error! Reference source not found.**.

In addition to the database searches, supplementary searches were also conducted to ensure all relevant literature was included in the review.

The following relevant conferences were hand searched for a review of the abstracts, covering, as a minimum, the past three years:

- American Society of Clinical Oncology (ASCO) Annual meeting (2010-2012)
- European Society for Medical Oncology (ESMO) (2009-2011)
- San Antonio Breast Cancer meeting (SABC) (2010-2012)
- International Society of Pharmacoeconomics and Outcomes Research (ISPOR) (2010-2012)

Critical appraisal for n-RCTs was undertaken using the quality scoring based on Downs and Black checklist in Appendix **Error! Reference source not found.**.

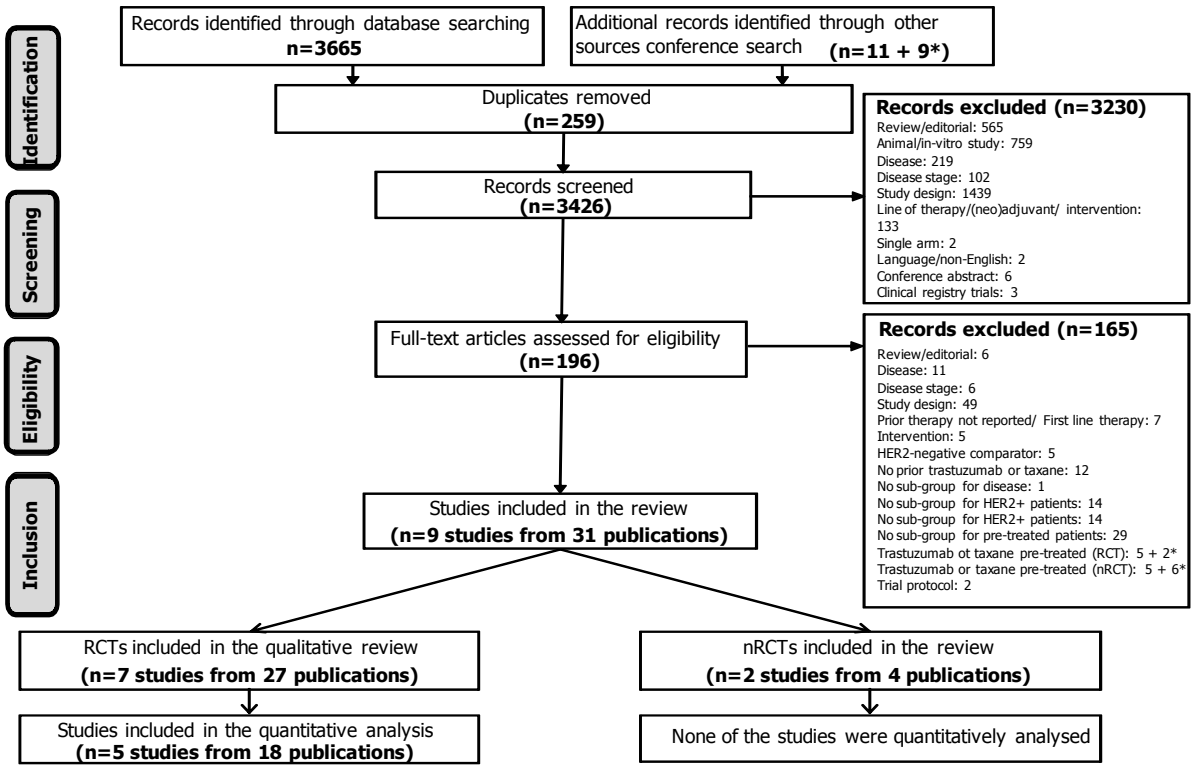
6.7.4 A flow diagram of the numbers of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses such as the QUOROM statement flow diagram (www.consort-statement.org/?o=1065). The total number of studies in the statement should equal the total number of studies listed in section 6.2.4.

Search of literature databases yielded 3665 potentially relevant references (Figure 16). Due to the overlap of coverage between the databases, 259 abstracts were found to be duplicates. Following the first-pass of these citations, 196 potentially relevant references were identified. Full-text reports of these citations were obtained for more detailed evaluation. During the first-pass, two studies published in non-English language were identified as potentially meeting the review inclusion criteria. The non-availability of the full-text in English language of both of these studies excluded the studies from the review. Following detailed examination of the 196 references, 165 references did not meet the eligibility criteria.

Nine further references were identified from conference proceedings. No relevant study was identified from the literature search of systematic reviews. Where more than one publication was identified as describing a single trial, references were linked together. Following linking of references, nine studies with data reported in 31 publications were identified as meeting the inclusion criteria (Figure 16). Of these, seven from 27 publications were RCTs, and two from four publications were n-RCTs.

Studies with potentially relevant treatments for the current patient population like the COMPLETE trial, TDM4450 trial, and Cobleigh 1999 were screened for inclusion for the SR. These studies, although clinically relevant, were not included, as the patients in these studies received prior therapy in neo-/adjuvant setting rather than in the metastatic setting. These trials did not meet the inclusion criteria for the review and were not included in the analysis.

Figure 16: Study selection flow



*Conference abstracts hand searched in patients treated with prior trastuzumab or taxane

List of relevant RCTs identified through literature review

EMILIA: Trastuzumab emtansine versus capecitabine plus lapatinib

EMILIA directly evaluated the clinical effectiveness of trastuzumab emtansine versus capecitabine plus lapatinib in patients with HER2+ unresectable, locally advanced or MBC who were previously treated with trastuzumab and a taxane. EMILIA was a Phase III, randomised, open-label, international trial. Patients were randomly assigned in a 1:1 ratio to trastuzumab emtansine or lapatinib plus capecitabine with the use of a hierarchical, dynamic randomisation scheme. Dosing of lapatininb and capecitabine in EMILIA was in line with the licence for this product (lapatinib (1,250 mg/day) plus capecitabine (1,000 mg/m2)). See section 6.3 for further details.

The primary endpoints were progression-free survival (PFS), assessed by independent review, overall survival (OS) and safety. The primary endpoints

were assessed in the ITT population, with stratification according to the factors used for randomisation.

The analysis for PFS by independent review shows a median PFS for trastuzumab emtansine of 9.6 months as compared to 6.4 months with lapatinib plus capecitabine [HR=0.650, p<0.0001]. The analysis for PFS by investigator review showed very similar results [HR=0.658, p<0.001] (Verma, 2012).

Two interim analyses for OS have been performed, one at the time of PFS analysis and one, six months later, at the request of the health authorities. The second of these crossed the O'Brian-Flemming stopping boundary for an early analysis. These results show a statistically significant increase in OS from 25.1 months with lapatinib plus capecitabine to 30.9 months [HR=0.682, p=0.0006].

CEREBEL: Capecitabine plus trastuzumab versus capecitabine plus lapatinib

Patients in CEREBEL were required to have received either a taxane or an anthracycline in the adjuvant setting. Patients with stable CNS metastases were not allowed into this study whilst 4%-7% of patients had never received treatment for metastic disease. Recruitment into CEREBEL was stopped early on the advice of the IDMC. Dosing of lapatininb and capecitabine was at 1,250 mg/day (lapatinib) plus 2,000 mg/m^2 (capecitabine).

In the ITT population, considering any line of therapy and prior-treatment status, OS was longer for those who received capecitabine plus trastuzumab compared with capecitabine plus lapatinib (OS: 27.3 months vs. 22.7 months, HR [95%CI]: 1.34 (0.95 - 1.90), but this was not statistically significant; PFS was statistically significantly longer for capecitabine plus trastuzumab vs. capecitabine plus lapatinib: (PFS: 8.0 months vs. 6.6 months, HR [95% CI]: 1.30 [1.04 - 1.64]).

Patients in CEREBEL were stratified based on their prior trastuzumab exposure:

- In the trastuzumab naïve group PFS was longer for those who received capecitabine plus trastuzumab compared with capecitabine plus lapatinib (10.9 months vs. 6.3 months HR [95% CI]: 1.70 [1.15 – 2.50]).

- In the group previously treated with trastuzumab (the subgroup that serves as an eligible population for comparison with trastuzumab emtansine), the direct head-to-head comparison for capecitabine plus trastuzumab vs. capecitabine plus lapatinib demonstrated no statistical difference in median PFS (6.1 months vs. 6.6 months; HR [95% CI]: 1.13 [0.85 - 1.50]) and median OS (27.3 months vs. 22.7 months; HR [95% CI]: 1.18 [0.76, 1.83]).

EGF100151 and Martin 2011: Capecitabine plus lapatinib versus capecitabine or neratinib monotherapy

In EGF1001551, capecitabine plus lapatinib therapy is associated with a significantly improved median OS and PFS (8.4 months vs. 4.1 months; HR [95% CI]: 0.55 [0.40, 0.74], p<0.001). OS data prior to cross-over was reported by several approaches. For the purpose of the current analyses we used, for the indirect comparison the one that excluded cross-over patients from the analysis (HR [95% CI]: 0.78 [0.62 – 0.97]; p=0.02).

EGF100151 enrolement was stopped early, based on an interim analysis of TTP showing a benefit for patients in the lapatinib plus capecitabine arm, and patients from the monotherapy arm were allowed to crossover, confounding further analyses. Prior exposure to anthracycline was an inclusion criterion for EGF100151.

The primary endpoint in Martin was PFS with OS as a secondary endpoint. Patients in Martin were required to have ≤2 prior trastuzumab regimens, prior taxane treatment. Regarding PFS, capecitabine plus lapatinib was associated with a higher median PFS (6.8 months) than neratinib (4.5 months), though the results were not statistically significant (HR [95% CI]: 1.30 [1.00, 1.80], p=0.09). Capecitabine plus lapatinib was associated with a median OS of 19.0 months as compared to a median OS of 19.4 months with neratinib.

Dosing of lapatininb and capecitabine was 1,250 mg/day (lapatinib) plus 2,000 mg/m^2 (capecitabine) in EGF100151 and Martin.

GBG-26: Capecitabine plus trastuzumab versus capecitabine

Patients with stable CNS metastases were not allowed into this study.
The primary endpoint in GBG-26 was PFS with OS as a secondary endpoint. Data was obtained from the clinical study report (CSR) of GBG26 study for PFS. PFS in GBG26 was imputed from time to progression (TTP). The CSR of the GBG26 study reported that the median PFS was the same as the median TTP in both treatment arms. Further, the number of events (n=62) and censored patients (n=15) in the capecitabine plus trastuzumab arm for PFS were the same as those for TTP.

Capecitabine plus trastuzumab resulted in a similar OS (24.9 months vs. 20.6 months; HR [95% CI]: 0.94 [0.65, 1.35], p=0.73), but longer median PFS (8.2 months vs. 5.6 months; HR [95% CI]: 0.68 [0.48, 0.96], p=0.03) when compared with capecitabine monotherapy.

EGF104900 trial: Lapatinib plus trastuzumab versus lapatinib monotherapy

EGF104900 showed a significantly longer median OS with the combination of lapatinib plus trastuzumab (14 months) as compared to lapatinib monotherapy (9.5 months) . Additionally, the study reported a 10% improvement in absolute OS rate at 6 months and a 15% improvement in OS rate at 12 months with the combination of lapatinib and trastuzumab as compared with lapatinib monotherapy. The benefit in terms of improved OS with the combination of lapatinib and trastuzumab when compared to lapatinib monotherapy was evident regardless of the fact that a high proportion of patients crossed-over the treatment.

Lapatinib plus trastuzumab demonstrated superiority to lapatinib monotherapy in terms of median OS (HR [95% CI]: 0.74 [0.57 - 0.97]; p=0.026). A benefit in terms of improved PFS at 6 months was also evident with the combination of lapatinib and trastuzumab as compared with lapatinib monotherapy (HR [95% CI]: 0.74 [0.58 - 0.93]; p=0.010).

EGF10004 trial: Dose-ranging phase I study for Lapatinib

This study was a dose-ranging study for lapatinib and will therefore was not assessed.

List of relevant non-RCTs identified through literature review

A total of two nRCTs with data reported in 4 publications were identified as meeting the inclusion criteria for the review. Both of these included studies were dose-escalation studies.

As per the review inclusion criteria, both studies enrolled adult patients (≥18 years of age) with locally advanced or MBC. Both studies recruited patients histologically confirmed mBC with demonstrated HER2 overexpression, defined as a score of 3 plus by IHC and/or amplification by FISH. Both studies enrolled patients pre-treated with anthracycline- and/or taxane based regimens.

Further details regarding the demographic and disease characteristics of study participants at baseline are presented. Both studies reported age of the included population; the median age of included patients ranged from 48 years to 58 years.

The details regarding the disease metastasis to visceral sites were reported in both studies. Across both studies, the disease had metastasised to visceral sites in approximately 70% of patients. Approximately 33% to 67% of patients had metastasis in liver and 23% to 50% had metastasis to lungs. The WHO performance status was reported in one study only . In this study, performance status 0 was reported in 29.4% to 66.7% of patients and performance status 1 was in 33% to 71% of patients.

In both the studies, patients included were those who had progressed with trastuzumab therapy. Over 80% of patients received prior anthracyclines and 90% to 100% of patients received taxanes. The mean number of prior chemotherapy regimens ranged from 2 regimens to 5 regimens across both the studies.

Across the two dose-ranging studies of everolimus, the results demonstrated that everolimus weekly was associated with a longer median progression-free survival as compared to the daily dose of everolimus.

Table 18: Summary of n-RCTs identified through systematic literature review

Study	Intervention	Comparator	Phase	N	Patient population	Primary study
Jerusalem 2011	Everolimus 5mg + Trastuzumab + Vinorelbine	Everolimus 20mg + Trastuzumab + Vinorelbine Everolimus 30mg + Trastuzumab + Vinorelbine	Ib	50	Patients with HER2-overexpressing metastatic breast cancer, verified by IHC (score of 3+) or FISH who progressed during or after treatment with trastuzumab alone or in combination with other anticancer agents	(Jerusalem 2011)
Andre 2010	Everolimus 5mg + Paclitaxel + Trastuzumab	Everolimus 10mg + Paclitaxel + Trastuzumab Everolimus 30mg + Paclitaxel + Trastuzumab	Ib	33	Patients with histologically confirmed metastatic breast cancer with demonstrated HER2 overexpression, defined as a score of 3 plus by IHC and/or amplification by FISH Patients were previously treated with trastuzumab	(Andre 2010)

6.7.5 Provide a summary of the trials used to conduct the indirect comparison. A suggested format is presented below. Network diagrams may be an additional valuable form of presentation.

Out of all studies identified through the systematic literature review, 5 RCTs were used to conduct the analysis and these are presented in Table 19 and Figure 17. The studies not included - EGF104900 trial and both non-RCTs - were not able to be linked into the network.

Table 19: Summary of the trials used to conduct the indirect comparison

Study	EMILIA trial	GBG26 Trial	EGF100151 trial	Martin 2011	CEREBEL trial subgroup (i.e. those pre-treated with trastuzumab)
Primary study reference	Verma, 2012	Von Minckwitz, 2011	Cameron, 2008	Martin, 2011	Pivot, 2012
Publication type	Journal article	Journal article	Journal article	Conference proceeding	Conference proceeding+ DHCP letter
Intervention	Capecitabine + Lapatinib (N=496)	Capecitabine + Trastuzumab (N= 78)	Capecitabine + Lapatinib (N=198)	Capecitabine + Lapatinib (N=116)	Capecitabine + Lapatinib (N=167)[3]
Comparator (all active controlled)	Trastuzumab emtansine (N=495)	Capecitabine (N= 78)	Capecitabine (N=201)	Neratinib (N=117)	Capecitabine + Trastuzumab (N= 159) [1]
Location	USA and non-USA sites[4]	Non-USA sites	USA and non-USA sites	NR	Non-USA sites
Design	RCT Phase III[2]	RCT Phase III[2]	RCT Phase III[2]	RCT, Phase II2	RCT Phase III[2]
Method of randomisation	Adequate	Unclear	Unclear	Unclear	Unclear
Method of blinding (care provider, patient, and outcome assessor)	Open-label but assessor-blind (IRC)[5]	Open-label	Open-label, but assessor-blind (IRC)	Open-label	Open-label

[3] The population presented here is the sub-group of patients who received prior trastuzumab in the adjuvant or metastatic setting (therefore, the numbers represent 100% of the subgroup), the ITT population for CEREBEL was N=269 for Capecitabine + Trastuzumab and N=271 for Capecitabine + Lapatinib

[4] ~ Approximately; AB: Assessor Blind; DOR: Duration of Response; DR: Dose Ranging; EQ-5D: EuroQol-5D; INV: Investigator; IRC: Independent Review Committee; MC: Multicentre; MCI: Multicentre International; OD: Once Daily; ORR: Overall Response Rate; OS: Overall Survival; PFS: Progression Free Survival; QoL: Quality of Life; R: Randomised; TTP: Time to Progression; UK: United Kingdom; USA: United States of America

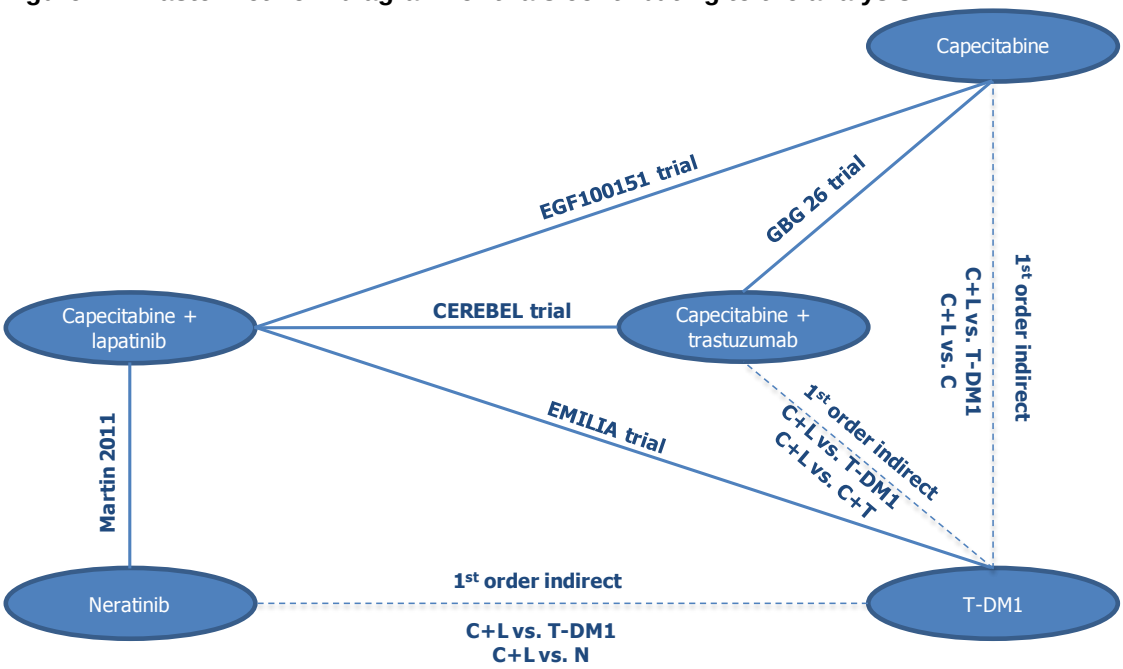
[5] A blinded IRC made evaluations for the primary study endpoint of Progression-free survival. Safety evaluations were made by an independent data monitoring committee (DMC);

Cross-over permitted	No		No		Yes		No		No	
Primary outcome	PFS by IRC, OS, safety		TTP		TTP		PFS		CNS metastases	
Secondary outcomes	PFS by INV, ORR, time to treatment failure, pharmacokinetics, DOR, patient-reported QoL, OS rate, TTP		OS, response rate, clinical benefit rate, DOR, safety, dose interruptions, withdrawal		PFS, OS, clinical benefit rate, withdrawal, safety, response rate, biomarker analysis		OS, safety, response rate, withdrawal, clinical benefit rate		PFS by INV, OS, ORR, CBR, time to first CNS progression, incidence of CNS progression at any time, safety	
Present line of therapy: First-line, n (%)	0 (0)		NR		88 (22)		All patients were previously treated in the first or second-line setting		NR	
Present line of therapy: first-line fast relapser, n (%)	118 (12)		NR		0 (0)					
Present line of therapy: Second-line, n (%)	361 (36)		156 (100)		NR					
Present line of therapy: third-line, n (%)	512 (52)		NR		NR		NR			
Advanced or metastatic sites in the brain, n (%)	50 (10)	45 (9)	3 (2)		NR		NR		0 (0)	
	Capecitabine + Lapatinib	**Trastuzumab emtansine**	**Capecitabine+ Trastuzumab**	**Capecitabine**	**Capecitabine + Lapatinib**	**Capecitabine**	**Capecitabine + Lapatinib**		**Capecitabine + Lapatinib**	**Capecitabine+ Trastuzumab**
Patients with ER+ and/or PR+, n (%)	155 (31)	176 (36)	41 (56) (N=73)	43 (62) (N=71)	96 (48)	93 (46)	NR		NR	NR
Patients with Performance Status=1, n (%)	176 (36)	194 (39)	NR	NR	76 (38)	83 (41)	NR	NR	NR	NR

Study duration	Capecitabine + Lapatinib: 53.73 weeks (range: 0 weeks -151.67 weeks); trastuzumab emtansine: 55.9 weeks (0 weeks - 147.33 weeks) – at first interim analysis Capecitabine + Lapatinib: 80.60 weeks (range: 0 weeks -177.67 weeks); trastuzumab emtansine: 82.76 weeks (0 weeks - 173.33 weeks) – at second interim analysis[2]	89.70 weeks (20.7 months)	Capecitabine + Lapatinib: ~20 weeks; Capecitabine: ~15 weeks[2]	NR	NR

[#]: The study was an open-label trial with efficacy measures including time to progression, progression-free survival, overall response rate, and clinical benefit rate assessed by an IRC under blinded conditions; [##]: A blinded IRC made evaluations for the primary study endpoint of Progression-free survival. Safety evaluations were made by an independent data monitoring committee (DMC); *: Mean duration of treatment reported; ~: Approximately; AB: Assessor Blind; AC: Active Controlled; DOR: Duration of Response; DR: Dose Ranging; EQ-5D: EuroQol-5D; INV: Investigator; IRC: Independent Review Committee; MC: Multicentre; MCI: Multicentre International; NR: Not reported; OD: Once Daily; OL: Open-label; ORR: Overall Response Rate; OS: Overall Survival; PFS: Progression Free Survival; QoL: Quality of Life; R: Randomised; TTP: Time to Progression; U: Unclear; UK: United Kingdom; USA: United States of Amer

Figure 17: Master network diagram for trials contributing to the analysis

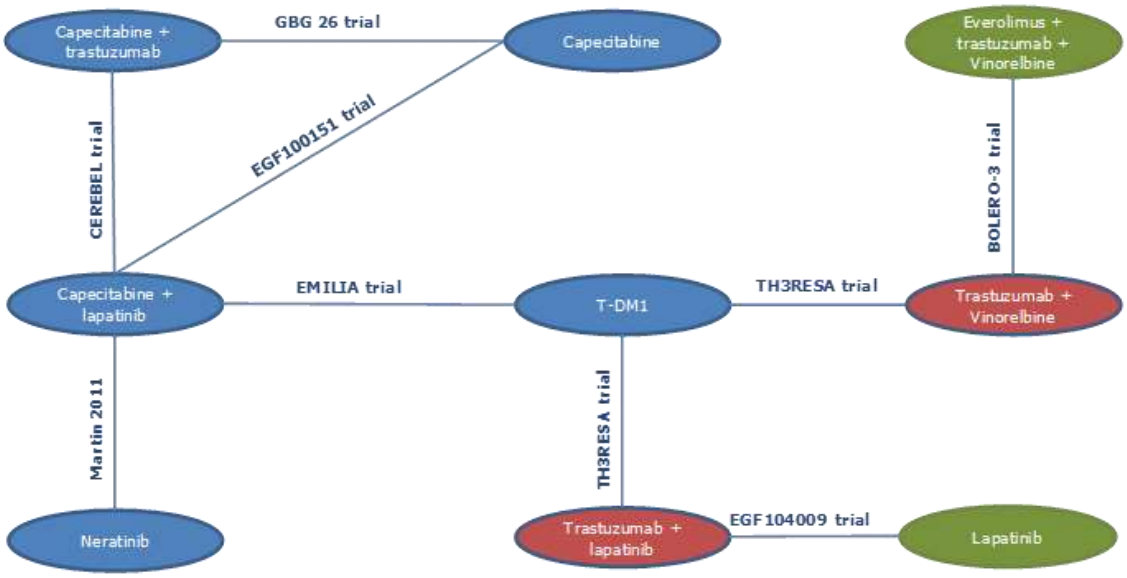


Absence of TH3RESA and BOLERO-3 studies in results of literature search

On the search date of the initial literature review (December 20th 2012), data for the TH3RESA and BOLERO-3 studies were not in the public domain and hence did not appear in the results of the literature search. However since then, data from these studies have been published. As a result of this TH3RESA would link into the network (see Figure 18) and specific subgroups from the comparator arm (i.e. those treated with trastuzumab and lapatanib and trastuzumab and vinorelbine) would also further inform the network by linking in the EGF104900 and BOLERO-3 trials. The resulting network is shown in Figure 18.

However given where these treatments sit in relation to trastuzumab emtansine (T-DM1) they would not inform the comparisons of interest (see section 5) and hence would not change the results detailed in section 6.7.8.

Figure 18: Network diagram including TH3RESA and BOLER0-3 studies for which data was not publically available at time of initial literature search (December 20 2012)



6.7.6 For the selected trials, provide a summary of the data used in the analysis.

PFS and OS stratified HRs (where available) from each trial for the whole ITT population were used in the analysis (see response to 0.) with the exception of the CEREBEL trial where the PFS and OS stratified HRs for the subgroup of patients previously treated with trastuzumab (the subgroup that serves as an eligible population for comparison with trastuzumab emtansine) were used.

Figure 19: Summary of key input data (PFS and OS HRs, Y versus X) used in MTC

Study name/Trial	Comparator X	Comparator Y	PFS HR [Y:X] (95% CI)	OS HR [Y:X] (95% CI)
EMILIA	Capecitabine + Lapatinib	Trastuzumab emtansine	0.65 (0.55-0.77)	0.68 (0.55-0.85)
EGF100151	Capecitabine+ Lapatinib	Capecitabine	1.82 (1.35-2.50)	1.28 (1.03-1.61)
GBG26	Capecitabine + Trastuzumab	Capecitabine	1.47 (1.04-2.08)	1.06 (0.74-1.54)
CEREBEL	Capecitabine + Trastuzumab	Capecitabine + Lapatinib	1.13 (0.85-1.50)	1.18 (0.76-1.83)
Martin 2011	Capecitabine+ Lapatinib	Neratinib	1.30 (1.00-1.80)	Not reported

6.7.7 Please provide a clear description of the indirect/mixed treatment comparison methodology. Supply any programming language in a separate appendix.

From the identified studies, network diagrams were drawn for each outcome of interest, to identify the possible indirect analyses. An adjusted MTC was performed according to the Bayesian methodology (in line with NICE guidance) with both the inclusion and exclusion of both the CEREBEL and Martin studies due to the uncertain heterogeneity of these two trials versus the rest (see section 6.7.11).

A fixed-effects model, within a Bayesian framework using Markov chain Monte Carlo (MCMC) methods in WinBUGS® was empoloyed. Random-effects models were not carried out due to the limited number of trials. WinBUGS® was used according to the routine which accommodates evidence structures which may consist of multi-arm trials.

We modelled the trial-based summary statistic, log-hazard ratios (LHR), and its sample variance, assuming a a normal distribution for the continuous measure of treatment effect of each active arm relative to the control/standard treatment arm of every trial making different comparisons.

Posterior densities for unknown parameters, such as the mean treatment effects, were estimated using MCMC methods. Point estimates and 95% credible intervals (conceptually similar to confidence intervals used in the frequentist approach) were used to summarise the findings and assess significance.

An identity link was used and since no trial-specific effects of the baseline or control treatment can be estimated the linear predictor was simply the treatment effect of the treatment arm versus the control treatment.

We also assessed the probability that each treatment was the most efficacious regimen, the second best, the third best, and so on, by calculating the HR for each drug compared with an arbitrary common control group, and counting the proportion of iterations of the Markov chain in which each drug

had the highest HR, the second highest, and so on. We ranked treatments in terms of acceptability with the same methods.

The comparative efficacy among the treatment options was evaluated across all treatments, using the current standards of care as the reference group.

Calculations for each analysis were based on employing 3 chains: ≥100,000 iterations, with a burn-in of ≥ 10,000 iterations (discarding the first 10,000 iterations).

Inconsistency factors can be interpreted as the difference between direct and indirect comparisons between the trials. Evidence network identified in this review did not assess the results of two biologics in a head to head trial. Therefore consistency between the direct and indirect results could not be evaluated.

The codes used for both PFS and OS and corresponding outputs can be found in Appendix **Error! Reference source not found.** and **Error! Reference source not found.**. A table that summarizes the results of the comparison of the treatment effects across trials, when compared to standards of care are presented in Figure 20.

An adjusted MTC was also performed according to the methodology of Bucher and colleagues (Bucher, 1997) for the scenario where CEREBEL and Martin were excluded. This method relies on the fact that the log of the effect size measure for drug A versus drug B is equal to the difference of the log effect size measures for drug A versus drug C and drug B versus drug C. However the results of the Bucher methodology are only shown for comparative purposes and were not used in the analysis.

6.7.8 Please present the results of the analysis.

The results from the MTC are presented in Figure 20 below. The results show that:

- For the ITC of trastuzumab emtansine versus trastuzumab and capecitabine the resulting PFS and OS HRs were 0.68 and 0.68

respectively when CEREBEL and Martin were included in the analysis (base case) versus 0.55 and 0.58 when they were excluded.

- For the ITC of trastuzumab emtansine versus capecitabine monotherapy the resulting PFS and OS HRs were 0.39 and 0.55 respectively when CEREBEL and Martin were included in the analysis (base case) versus 0.35 and 0.52 when they were excluded.

- For the comparison of capecitabine and trastuzumab versus capecitabine and lapatinib the results of the MTC excluding CEREBEL and Martin resulted in a reversal of the PFS and OS HRs as compared to those obtained from the CEREBEL trial (i.e. inconsistency). This is discussed in section 6.7.11.

Figure 20: Mixed treatment comparison results (Y compared to X)

Study name or MTC/ITC	Comparators		RCT results (HR, 95% CI)		Bayesian Results including CEREBEL & Martin (HR, 95% CI)		Bayesian Results excluding CEREBEL & Martin (HR, 95% CI)		Bucher method exclu CEREBEL & Marti (HR, 95% CI)	
	X (n)	Y (n)	PFS	OS	PFS	OS	PFS	OS	PFS	O
EMILIA	Capecitabine + Lapatinib (496)	Trastuzumab emtansine (T-DM1) (495)	0.65 (0.55-0.77)	0.68 (0.55-0.85)	0.65 (0.55-0.77)	0.68 (0.55-0.85)	0.65 (0.55-0.77)	0.68 (0.55-0.84)	0.65 (0.55-0.77)	0.6 (0.55-
EGF100151	Capecitabine+ Lapatinib (198)	Capecitabine monotherapy (201)	1.82 (1.35-2.50)	1.28 (1.03-1.61)	1.64 (1.26-2.10)	1.23 (1.00-1.50)	1.84 (1.33-2.49)	1.29 (1.03-1.59)	1.82 (1.35-2.50)	1.2 (1.03-
GBG26	Capecitabine + Trastuzumab (78)	Capecitabine Monotherapy (78)	1.47 (1.04-2.08)	1.06 (0.74-1.54)	1.70 (1.29-2.21)	1.22 (0.90-1.63)	1.50 (1.04-2.09)	1.08 (0.73-1.54)	1.47 (1.04-2.08)	1.0 (0.74-
CEREBEL	Capecitabine + Trastuzumab (159)	Capecitabine + Lapatinib (167)	1.13 (0.85-1.50)	1.18 (0.76-1.83)	1.03 (0.82-1.32)	0.98 (0.73-1.34)	0.79 (0.51-1.30)	0.81 (0.54-1.27)	0.81 (0.51-1.29)	0.8 (0.54-
Martin	Capecitabine+ Lapatinib (116)	Neratinib (117)	1.30 (1.00-1.80)	Not reported	1.31 (0.97-1.74)	Not Reported	n/a	n/a	n/a	n/
MTC/ITC	Capecitabine + Trastuzumab	Trastuzumab emtansine (T-DM1)	n/a	n/a	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)	0.5 (0.35-
MTC/ITC	Capecitabine monotherapy	Trastuzumab emtansine (T-DM1)	n/a	n/a	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)	0.5 (0.39-

6.7.9 Please provide the statistical assessment of heterogeneity undertaken. The degree of, and the reasons for, heterogeneity should be explored as fully as possible.

No statistical assessment of heterogeneity was undertaken.

6.7.10 If there is doubt about the relevance of a particular trial, please present separate sensitivity analyses in which these trials are excluded.

See section 6.7.8 where the analysis is repeated excluding the CEREBEL and Martin studies and section 6.7.11 which details their heterogeneity.

6.7.11 Please discuss any heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies.

All studies enrolled adult patients (≥18 years of age) with the same disease type (HER2+ locally advanced BC or MBC) and pre-treatment status (anthracycline and/or taxane-based regimens). The majority were female patients across all five trials. The median age of patients was comparable across studies included in the analysis. Mean age of patients when compared qualitatively in GBG26 and EGF100151, indicated that patients in the capecitabine arm of GBG26 were slightly older than the patients recruited in the capecitabine arm of EGF100151.

Across the studies included in the analysis comparability was evident among trials in terms of ECOG PS. Four of the five studies reported sites of disease metastases. EGF100151 and EMILIA reported metastases in terms of visceral and non-visceral sites. Visceral metastases occurred in approximately 70% in both trials. Liver metastases occurred in about 50% of patients in GBG26 and EGF100151 which was followed by lung, bone, and brain. In EGF100151, a similar proportion (about 50%) of patients had ≥3 metastatic sites and <3 metastatic sites, while for EMILIA the proportion of patients with <3 metastatic sites varied from 60% to 62% and the proportion of patients with ≥3 metastatic sites varied from 35% to 38%. Comparability across the studies included in the analysis in terms ≥3 metastatic sites was evaluated. This depicted that the studies were comparable in terms of number of metastatic sites. Sites of metastasis differed, however between CEREBEL and the remaining studies. In CEREBEL patients with brain metastases were excluded as the study aimed to evaluate the incidence of CNS metastasis.

The studies included in the analysis were comparable in terms of the prior therapy received. All studies included patients who had prior exposure to trastuzumab and taxane treatment regimens either in metastatic or adjuvant setting in 98% to 100%. In GBG26, approximately 70% of included patients were pre-treated with taxane plus trastuzumab. This study's population was, therefore not 100% comparable with the other studies. Nevertheless, considering that the majority of patients did have prior trastuzumab plus taxane, we considered the study to be appropriate to include in the indirect comparison. Most patients in these studies were previously treated with trastuzumab in the metastatic setting (71% to 95%). All studies enrolled patients pre-treated with anthracycline- and/or taxane-based regimens. The proportion of patients with prior anthracycline treatment generally varied from 61% to >99% in four studies reporting such data. In four studies, the proportion of patients with prior taxane regimens varied generally from 85% to 100%. The majority of patients were currently being treated for second-line and above treatments.

In CEREBEL, a pre-specified subgroup of patients (326 patients of 540

patients) were treated with prior trastuzumab therapy. For the remaining studies, the inclusion criteria stated that patients must have received trastuzumab in adjuvant or metastatic setting. Comparability assessment of studies for prior therapy with trastuzumab demonstrated that the studies included in the analysis were comparable in terms of proportion of patients receiving prior therapy with trastuzumab and the setting in which trastuzumab was. The inclusion criteria included prior treatment with trastuzumab. The studies reported the time interval between the end of last cycle of trastuzumab and the new randomised treatment. In EGF100151, nearly 38% of patients had a trastuzumab free interval of greater than 8 weeks, while in GBG26 all patients had to continue randomised treatment within 6 weeks of last infusion of trastuzumab. Trastuzumab has a long half-life therefore patients in the capecitabine arm of both studies might have an on-going exposure to trastuzumab thus having an impact on the results. Comparability of studies included in the analysis in terms of prior therapy with taxane demonstrated that the studies were comparable.

The EGF100151 study and GBG26 varied from the remaining studies included in the analysis in terms of patients receiving post-study therapy. Patients in GBG26 received post-study therapy with lapatinib and trastuzumab, while patients crossed-over the treatment in the EGF100151. Post-study therapy was unclear in Martin 2011 and CEREBEL. Post-study therapy upon discontinuation of study medication following disease progression, confound the results for OS. To overcome the effect of post-study therapy received by cross-over, data prior to any cross-over of treatment was used in the analysis from the EGF100151.

Martin and CEREBEL seemed more heterogeneous when compared to the other three trials. While the other studies were published as journal articles, Martin and CEREBEL were published as conference proceedings, having limited amount of detailed information regarding treatment regimens and patient baseline characteristics, such as visceral and non-visceral involvement, hormone receptor status, and exact prior treatment status. All studies except Martin reported details regarding sample size/power

calculation. The key eligibility criteria for CEREBEL required patients treated with prior anthracyclines or taxanes, which would not be an appropriate population for inclusion in our SR and indirect comparison. The availability of a sub-group of patients (326 patients of 540 patients) who were additionally treated with prior trastuzumab therapy provided a subgroup of patients of potential interest for inclusion in the indirect comparison. The limiting factor for the inclusion of such a subgroup in the indirect comparison is associated to the fact that an unknown proportion of these patients did not have prior treatment with trastuzumab plus taxane, since they could have been treated with prior trastuzumab plus anthracycline. Additionally, the primary objective of CEREBEL was the incidence of CNS metastases. Martin was also limited in information.

The heterogeneity assessment of these studies indicated that the patient population, prior treatment status and lack of detailed information on the study population's baseline characteristics in CEREBEL and Martin deemed these two studies not entirely comparable to the other trials. However at an independent advisory board with five expert UK clinicians, they advised that CEREBEL and Martin had sufficiently similar populations in terms of patient characteristics to the other trials and therefore should not be excluded from the analysis, in particular given that trials where not all patients had been pre-treated with trastuzumab and a taxane (i.e. GBG26) had been included. Therefore as the base case all trials were included in the analysis but a separate sensitivity analysis was conducted where CEREBEL and Martin were excluded.

The exclusion of CEREBEL and Martin results in inconsistency between the indirect and direct results for the comparison of capecitabine and trastuzumab versus capecitabine and lapatinib (see CEREBEL row of Figure 20). This is most likely explained by the lack of significance of the PFS and OS HRs from CEREBEL (the HRs cross 1); given the uncertainty in the analysis from the trial it is not possible to ascertain with any statistical significance the true efficacy of capecitabine and trastuzumab versus capecitabine and lapatinib. However, including CEREBEL (and Martin) allows us to synthesise a wider range of evidence (i.e. both direct and indirect results) and hence reduce the uncertainty associated with the efficacy of capecitabine and trastuzumab versus capecitabine and lapatinib.

6.8 Non-RCT evidence

Non-RCT, both experimental and observational, evidence will be required, not just for those situations in which RCTs are unavailable, but also to supplement information from RCTs when they are available. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3.2.8 to 3.2.10.

6.8.1 If non-RCT evidence is considered (see section 6.2.7), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection and methodology of the trials, and the presentation of results. For the quality assessments of non-RCTs, use an appropriate and validated quality assessment instrument. Key aspects of quality to be considered can be found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 10.6 and 10.7, appendices 6 and 7.

No further non-RCT is presented in this submission other than that identified for the systematic literature review for the MTC (section 6.7.4).

6.9 Adverse events

This section should provide information on the adverse events experienced with the technology in relation to the decision problem. Evidence from comparative RCTs and regulatory summaries is preferred; however, findings from non-comparative trials may sometimes be relevant. For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator, or the occurrence of adverse events is not significantly associated with other treatments.

6.9.1 If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection, methodology and quality of the trials, and the presentation of results. Examples for search strategies for specific adverse effects and/or generic adverse-effect terms and key aspects of quality criteria for adverse-effects data can found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 10.8 and 10.9, appendices 8 and 9.

Safety was an endpoint in both the EMILIA and TH3RESA studies. In light of this no additional searches have been undertaken.

6.9.2 Please provide details of all important adverse events for each intervention group. For each group, give the number with the adverse event, the number in the group and the percentage with the event. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse event. A suggested format is shown below.

AEs are summarized by intensity (NCI-CTCAE Grade 1−5). An overview of the cumulative safety data reported at the time of the primary data-cut (14 January 2012) for EMILIA, and at the time of the primary data-cut (14 February 2013) for TH3RESA.

Table 20: Adverse events across randomised groups: Adverse Events Occurring in ≥ 10% of Patients in Either Treatment Group (Safety Population)

System organ/ class/adverse events	EMILIA		TH3RESA	
	lapatinib plus capecitabine (n = 488)	trastuzumab emtansine (n = 490)	Treatment of physician's choice (n = 198)	trastuzumab emtansine (n = 403)
Any Adverse Events	477 (97.7%)	470 (95.9%)	141 (76.6%)	337 (83.6%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS				
Overall	87 (17.8%)	171 (34.9%)	54 (29.3%)	93 (23.1%)
THROMBOCYTOPENIA	12 (2.5%)	137 (28.0%)	6 (3.3%)	61 (15.1%)
NEUTROPENIA			40 (21.7%)	22 (5.5%)
ANAEMIA	39 (8.0%)	51 (10.4%)	19 (10.3%)	36 (8.9%)
GASTROINTESTINAL DISORDERS				
Overall	436 (89.3%)	352 (71.8%)	93 (50.5%)	224 (55.6%)
DIARRHOEA	389 (79.7%)	114 (23.3%)	40 (21.7%)	40 (9.9%)
NAUSEA	218 (44.7%)	192 (39.2%)	40 (21.7%)	133 (33.0%)
VOMITING	143 (29.3%)	93 (19.0%)	15 (8.2%)	71 (17.6%)
CONSTIPATION	47 (9.6%)	124 (25.3%)	29 (15.8%)	78 (19.4%)
DRY MOUTH	24 (4.9%)	77 (15.7%)	0 (0%)	49 (12.2%)
DYSPEPSIA	56 (11.5%)	43 (8.8%)		
ABDOMINAL PAIN UPPER	41 (8.4%)	57 (11.6%)	23 (12.5%)	26 (6.5%)
STOMATITIS	61 (12.5%)	16 (3.3%)	93 (50.5%)	224 (55.6%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
Overall	298 (61.1%)	331 (67.6%)	83 (45.1%)	198 (49.1%)
FATIGUE	136 (27.9%)	172 (35.1%)	46 (25.0%)	109 (27.0%)
ASTHENIA	81 (16.6%)	86 (17.6%)	29 (15.8%)	63 (15.6%)
MUCOSAL INFLAMMATION	93 (19.1%)	33 (6.7%)		
PYREXIA	37 (7.6%)	85 (17.3%)	22 (12.0%)	65 (16.1%)
INFECTIONS AND INFESTATIONS				
Overall	220 (45.1%)	213 (43.5%)		
PARONYCHIA	52 (10.7%)	1 (0.2%)		
INVESTIGATIONS				
Overall	139 (28.5%)	184 (37.6%)		
ASPARTATE AMINOTRANSFERASE INCREASED	46 (9.4%)	110 (22.4%)		
ALANINE AMINOTRANSFERASE INCREASED	43 (8.8%)	83 (16.9%)		
METABOLISM AND NUTRITION DISORDERS				
Overall	169 (34.6%)	144 (29.4%)	23 (12.5%)	58 (14.4%)
DECREASED APPETITE	113 (23.2%)	101 (20.6%)	23 (12.5%)	58 (14.4%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS				
Overall	180 (36.9%)	249 (50.8%)	20 (10.9%)	79 (19.6%)
ARTHRALGIA	38 (7.8%)	85 (17.3%)	7 (3.8%)	46 (11.4%)
BACK PAIN	50 (10.2%)	64 (13.1%)		
PAIN IN EXTREMITY	52 (10.7%)	52 (10.6%)		
MYALGIA	18 (3.7%)	69 (14.1%)	15 (8.2%)	42 (10.4%)
NERVOUS SYSTEM DISORDERS				
Overall	189 (38.7%)	245 (50.0%)	15 (8.2%)	89 (22.1%)
HEADACHE	68 (13.9%)	133 (27.1%)	15 (8.2%)	89 (22.1%)
DIZZINESS	51 (10.5%)	48 (9.8%)		
NEUROPATHY PERIPHERAL	28 (5.7%)	49 (10.0%)		

PSYCHIATRIC DISORDERS				
Overall	74 (15.2%)	101 (20.6%)		
INSOMNIA	41 (8.4%)	54 (11.0%)		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS				
Overall	156 (32.0%)	217 (44.3%)	23 (12.5%)	97 (24.1%)
COUGH	60 (12.3%)	83 (16.9%)	19 (10.3%)	63 (15.6%)
EPISTAXIS	39 (8.0%)	99 (20.2%)	5 (2.7%)	47 (11.7%)
DYSPNOEA	36 (7.4%)	56 (11.4%)		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
Overall	391 (80.1%)	159 (32.4%)	19 (10.3%)	19 (4.7%)
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME	283 (58.0%)	6 (1.2%)		
RASH	130 (26.6%)	52 (10.6%)	19 (10.3%)	19 (4.7%)
DRY SKIN	49 (10.0%)	17 (3.5%)		

Discussion of Adverse Events in EMILIA

In accordance with the differing mechanisms of action of the two treatments and known safety profiles, hepatotoxicity, thrombocytopenia/bleeding (epistaxis), and infusion reactions (including chills and pyrexia) were more common with trastuzumab emtansine; whereas, gastrointestinal (GI) toxicity, skin disorders (PPE, rash), and mucosal inflammation were more commonly associated with lapatinib plus capecitabine treatment.

Of the incidence of pyrexia and chills in the trastuzumab emtansine arm, 4.1% of pyrexia and 3.5% of chills AEs were associated with trastuzumab emtansine infusions, and tended to be transient in nature.

Patients who received trastuzumab emtansine reported fewer severe Grade ≥ 3 AEs (40.8%) than patients who received lapatinib plus capecitabine (57.0%). The most common Grade ≥ 3 AEs in the trastuzumab emtansine arm were predominately related to laboratory test abnormalities (most commonly [in ≥ 10% of patients] thrombocytopenia [12.9%]; other Grade ≥ 3 AEs that occurred in at least 2% of patients were increased AST and ALT, hypokalaemia, anaemia, neutropenia and fatigue). In contrast, the most common Grade ≥ 3 AEs in patients who received lapatinib plus capecitabine tended to be symptom-driven (most commonly [in ≥ 10% of patients] diarrhoea [20.7%] and PPE syndrome [16.4%]; other Grade ≥ 3 AEs occurring

in at least 2% of patients were nausea, fatigue, vomiting, mucosal inflammation, hypokalaemia and neutropenia).

The number of Grade 5 (fatal) AEs was low in both treatment arms (1 patient [0.2%] in the trastuzumab emtansine arm, vs. 4 patients [0.8%] in the lapatinib plus capecitabine arm.

The incidence of the following Grade ≥ 3 AEs was higher in the trastuzumab emtansine arm than in the lapatinib plus capecitabine arm (> 2% difference):

- Thrombocytopenia (12.9% of patients in the trastuzumab emtansine arm vs. 0.2% of patients in the lapatinib plus capecitabine arm)
- AST increased (4.3% of patients in the trastuzumab emtansine arm vs. 0.8% of patients in the lapatinib plus capecitabine arm).

The incidence of the following Grade ≥ 3 AEs was lower in the trastuzumab emtansine arm compared with the lapatinib plus capecitabine arm (> 2% difference):

- Diarrhoea (1.6% of patients in the trastuzumab emtansine arm vs. 20.7% of patients in the lapatinib plus capecitabine arm)
- PPE syndrome (0% of patients in the trastuzumab emtansine arm vs. 16.4% of patients in the lapatinib plus capecitabine arm)
- Vomiting (0.8% of patients in the trastuzumab emtansine arm vs. 4.5% of patients in the lapatinib plus capecitabine arm)
- Mucosal inflammation (0.2% of patients in the trastuzumab emtansine arm vs. 2.3% of patients in the lapatinib plus capecitabine arm)
- Neutropenia (2.0% of patients in the trastuzumab emtansine arm vs. 4.3% of patients in the lapatinib plus capecitabine arm).

<u>Serious Adverse Events</u>

A total of 76 patients (15.5%) who received trastuzumab emtansine developed SAEs, compared to 88 patients (18.0%) who received lapatinib plus capecitabine. Fewer Grade 3 SAEs were reported in the trastuzumab emtansine arm (34 patients [6.9%]) compared with the lapatinib plus

capecitabine arm (51 patients [10.5%]). A similar percentage of patients in both treatment arms developed Grade 4 SAEs (12 patients [2.4%] in the trastuzumab emtansine arm vs. 16 patients [3.3%] in the lapatinib plus capecitabine arm). Five patients died due to an AE whilst on study treatment, 1 patient in the trastuzumab emtansine arm (metabolic encephalopathy), and 5 patients in the lapatinib plus capecitabine arm (coronary artery disease, multi-organ failure, coma, hydrocephalus).

SAEs were reported across a number of body systems, with no single predominant event observed in either treatment arm. The most common body systems affected (≥ 1% of patients in either treatment arm) were:

- Gastrointestinal disorders: 14 patients (2.9%; most commonly vomiting) vs. 29 patients (5.9%; most commonly diarrhoea, vomiting)
- General disorders: 13 patients (2.7%; most commonly pyrexia) vs. 8 patients (1.6%) Infections and infestations: 20 patients (4.1%) vs. 12 patients (2.5%), variety of terms in both arms
- Injury, poisoning and procedural complications: 7 patients (1.4%) vs. 6 (1.2%), variety of terms in both arms
- Musculoskeletal and connective tissue disorders: 6 patients (1.2%) vs. 1 (0.2%), variety of terms in both arms
- Nervous system disorders: 6 patients (1.2%) vs. 8 (1.6%), variety of terms in both arms
- Respiratory, thoracic and mediastinal disorders: 4 patients (0.8%) vs. 14 patients (2.9%; most commonly pulmonary embolism)
- Vascular disorders: no patients vs. 5 (1.0%), variety of terms in both arms.

Table 21: Adverse events: Grade 3, 4, 5 AEs with ≥2% Incidence in Either Arm (Safety Population) in EMILIA

	Capecitabine plus lapatinib (n=488)		Trastuzumab emtansine (n=490)	
Adverse Event	**All Grades, %**	**Grade ≥3, %**	**All Grades, %**	**Grade ≥3, %**
Diarrhoea	79.7	20.7	23.3	1.6
Hand-foot syndrome	58	16.4	1.2	0
Vomiting	29.3	4.5	19	0.8
Neutropenia	8.6	4.3	5.9	2
Hypokalaemia	8.6	4.1	8.6	2.2
Fatigue	27.9	3.5	35.1	2.4
Nausea	44.7	2.5	39.2	0.8
Mucosal inflammation	19.1	2.3	6.7	0.2
Thrombocytopenia	2.5	0.2	28	12.9
Increased AST	9.4	0.8	22.4	4.3
Increased ALT	8.8	1.4	16.9	2.9
Anaemia	8	1.6	10.4	2.7

Discussion of Adverse Events in TH3RESA

Overall, AEs of any Grade were comparable between trastuzumab emtansine and TPC arms (93.5% vs. 88.6%, respectively). The majority of AEs in the trastuzumab emtansine were Grade 1-2 severity. The incidence of Grade ≥ 3 AEs in patients receiving trastuzumab emtansine was similar to, or lower, than patients receiving TPC. The most frequently reported AEs in the trastuzumab emtansine arm (in at least 20% of patients) were: nausea (33.0% of patients), fatigue (27.0%) and headache (22.1%). In the TPC arm the most frequently reported AEs were fatigue (25.0%), nausea (21.7%), neutropenia (21.7%) and diarrhoea (21.7%).

Events that were reported in more patients receiving trastuzumab emtansine (at least 5% more) were thrombocytopenia, nausea, vomiting, dry mouth, arthralgia, headache, cough and epistaxis. Events that were reported in more patients receiving TPC (at least 5% more) were neutropenia, leukopenia, diarrhoea, abdominal pain, rash and alopecia.

Fewer patients who received trastuzumab emtansine reported gade ≥ 3 AEs (32.3%) than patients who received TPC (43.5%). The most common Grade ≥ 3 AE (in at least 10% of patients) in the patients receiving TPC was neutropenia (15.8%). All other Grade ≥ 3 AEs in this treatment arm, and all Grade ≥ 3 AEs in patients receiving trastuzumab emtansine occurred in less than 5% of patients. Grade ≥ 3 events reported in at least 2% of patients were as follows:

- Trastuzumab emtansine: thrombocytopenia (4.7%), anaemia (2.7%), neutropenia (2.5%), AST increased (2.2%), fatigue (2.0%), dyspnoea (2.0%).
- TPC: diarrhoea (4.3%), febrile neutropenia (3.8%), abdominal pain (2.7%), anaemia (2.7%), leukopenia (2.7%), fatigue (2.2%), asthenia (2.2%), cellulitis (2.2%), AST increased (2.2%), pulmonary embolism (2.2%).

Serious Adverse Events

The incidence of SAEs was similar in both treatment arms. A total of 74 patients (18.4%) in the trastuzumab emtansine arm, and 38 patients (20.7%) in the TPC arm had at least one SAE. SAEs were reported across a number of body systems, with no single predominant event in either treatment arm. The most common SOCs affected (in at least 1% of patients in either treatment arm) were:

- Blood and lymphatic system disorders (1.0% for trastuzumab emtansine, vs. 4.9% for TPC)
- Gastrointestinal disorders (3.0%, vs. 4.3%)
- General disorders (3.0%, vs. 3.3%)
- Infections and infestations (4.2%, vs. 5.4%)
- Injury, poisoning and procedural complications (1.2%, vs. 1.1%)
- Metabolism and nutrition disorders (2.2%, vs. 0.5%)
- Musculoskeletal and connective tissue disorders (1.0%, vs. 1.1%)
- Nervous system disorders (3.2%, vs. 2.2%)
- Respiratory, thoracic and mediastinal disorders (3.0%, vs. 5.4%)

- Vascular disorders (1.2%, vs. 1.1%)

SAE preferred terms reported in at least 1% of patients receiving trastuzumab emtansine were dyspnoea, pneumonia and convulsion. SAEs occurring in at least 1% of patients receiving TPC were febrile neutropenia, cellulitis, dyspnoea, pleural effusion, pulmonary embolism, abdominal pain, neutropenia, diarrhoea, nausea, pyrexia and peripheral oedema.

Five patients (1.2%) in the trastuzumab emtansine arm and 3 patients (1.5%) in the TPC arm died as a result of an AE. In the trastuzumab emtansine arm reported reasons were: pneumonia, sepsis, hepatic encephalopathy, subarachnoid haemorrhage and pneumonitis. In the TPC arm the reasons for death cited were clostridium bacteremia, non-cardiogenic pulmonary oedema and pulmonary embolism.

Table 22: Adverse events: Any Grade and Grade >=3 in TH3RESA trial

	TPC (n=184)		**Trastuzumab emtansine (n=403)**	
	Any grade	**Grade ≥3**	**Any grade**	**Grade ≥3**
Diarrhoea	21.7	4.3	9.9	0.7
Abdominal pain	12.5	2.7	6.5	1.2
AST increased	5.4	2.2	8.4	2.2
Fatigue	25	2.2	27	2
Asthenia	15.8	2.2	15.6	1
Cellulitis	3.3	2.2	1.2	0.5
Pulmonary embolism	2.2	2.2	0.5	0.5
Dyspnoea	9.2	1.6	9.9	2
Neutropenia	21.7	15.8	5.5	2.5
Febrile neutropenia	3.8	3.8	0.2	0.2
Anaemia	10.3	2.7	8.9	2.7
Leukopenia	6	2.7	0.7	0.2
Thrombocytopenia	3.3	1.6	15.1	4.7[b]

6.9.3 Give a brief overview of the safety of the technology in relation to the decision problem.

The safety profile of trastuzumab emtansine as a single agent has been evaluated based on data from 884 patients with MBC receiving trastuzumab emtansine at the proposed dose of 3.6 mg/kg IV q3w, with a clinical cut-off date of 24 May 2012. Pooled data are included from patients receiving single-agent trastuzumab emtansine at a dose of 3.6 mg/kg in Studies TDM3569g, TDM4258g, TDM4374g, TDM4450g/BO21976, TDM4688g and TDM4370g/BO21977. (See section **Error! Reference source not found.** for a complete list of trastuzumab emtansine studies). Patients still benefiting from treatment at the completion of any of these studies were allowed to continue treatment in the open-label extension study TDM4529g/BO25430, and these data are also included in the pooled analyses. In addition, safety information is available for the following randomized studies, TDM4450g, EMILIA, THERESA.

The safety profile of single-agent trastuzumab emtansine is derived from a pooled analysis of 884 patients treated at a dose of 3.6 mg/kg q3w in six studies, as follows:

- TDM3569g: 15 patients
- TDM4258g: 112 patients
- TDM4374g: 110 patients
- TDM4688g: 51 patients from the single-agent phase of the study
- TDM4450g/BO21976: 69 patients who were randomized to receive trastuzumab emtansine in the first line setting, plus 37 patients who crossed over from the control arm to receive second line trastuzumab emtansine
- TDM4370g/BO21977: 490 patients

The analyses include the follow-up data for all patients from these studies who continued to receive treatment in the extension study (TDM4529g/BO25430).

Table 23 summarizes the adverse drug reactions (ADRs) that have been reported in association with the use of trastuzumab emtansine in clinical trials. In this section, the following categories of frequency have been used: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100).

Table 23: Adverse drug reactions (ADRs) from trastuzumab emtansine reported in clinical trials

ADR (MedDRA) Trastuzumab emtansine			
	System Organ Class All grades (%)	**Grade 3 - 5 (%)**	**Frequency Category**
	n = 882	**n = 882**	
Blood and Lymphatic System Disorders			
Thrombocytopenia	31.4	11.3	very common
Anaemia	15.4	2.8	very common
Neutropenia	6.5	1.9	common
Cardiac Disorders			
Left ventricular dysfunction	2	0.3	common
Eye Disorders			
Dry eye	5.4	0	common
Lacrimation increased	4.8	0	common
Vision blurred	4.8	0	common
Conjunctivitis	4	0	common
Gastrointestinal Disorders			
Nausea	42.3	1	very common
Constipation	25.5	0.6	very common
Vomiting	20.7	0.8	very common
Diarrhoea	20.3	0.9	very common
Dry Mouth	12.9	0	very common
Abdominal pain	12.9	0.9	very common
Stomatitis	14.5	0.1	very common
Dyspepsia	9	0.1	common
General Disorders and Administration			
Fatigue	45.4	3.2	very common
Pyrexia	22.9	0.2	very common
Asthenia	13.9	0.8	very common
Chills	11	0	very common
Oedema peripheral	8.4	0.1	common
Hepatobiliary Disorders			
Nodular regenerative hyperplasia	0.1	0	uncommon
Portal hypertension	0.1	0	uncommon
Immune System Disorders			
Drug hypersensitivity	2.6	0	common

Injury, Poisoning, and Procedural			
Infusion related reaction	4.5	0.1	common
Investigations			
Transaminases increased	28	7	very common
Blood alkaline phosphatase increased	5.9	0.3	common
Metabolism and Nutrition Disorders			
Hypokalaemia	15.4	3.3	very common
Musculoskeletal and Connective Tissue Disorders			
Musculoskeletal pain	39	3.1	very common
Arthralgia	18.8	0.9	very common
Myalgia	12.5	0.3	very common
Nervous System Disorders			
Headache	28.7	0.6	very common
Neuropathy peripheral	21.3	1.8	very common
Dizziness	9.4	0.2	common
Dysgeusia	7.4	0	common
Psychiatric Disorders			
Insomnia	10.9	0.2	very common
Respiratory, Thoracic, and Mediastinal Disorders			
Epistaxis	23.2	0.5	very common
Cough	19.5	0.1	very common
Dyspnoea	14.4	1.4	very common
Pneumonitis	0.9	0.1	uncommon
Skin and Subcutaneous Tissue Disorders			
Rash	12	0	very common
Pruritus	5.3	0.1	common
Vascular Disorders			
Haemorrhage	36.5	2	very common
Hypertension	6.1	0.9	common

The most common AEs associated with single-agent trastuzumab emtansine (in ≥ 25% of patients) were fatigue (45.4%), nausea (42.3%), musculoskeletal pain (39.0%), hemorrhage (36.5%), thrombocytopenia (31.4%), headache (28.7%), transaminases increased (28.0%) and constipation (25.5%). The vast majority of these events were Grade 1 or 2 in intensity. The most common Grade ≥ 3 AEs (occurring in more than 2% of patients) were thrombocytopenia (11.3%), transaminases increased (7.0%), fatigue (3.2%), hypokalemia (3.3%), musculoskeletal pain (3.1%), anaemia (2.8%) and hemorrhage (2.0%). Fifty-eight patients (6.6%) experienced AEs which

resulted in their trastuzumab emtansine treatment being discontinued: the most common AEs leading to discontinuation were blood and lymphatic system disorders (primarily thrombocytopenia [1.5%] and investigations (increased AST [0.8%] and increased ALT [0.5%]).

In summary, these data indicate that trastuzumab emtansine is well tolerated with manageable additional toxicity. The rates of Grade ≥3 AEs and SAEs are lower with trastuzumab emtansine than with current therapies for HER2-positive MBC as demonstrated by the EMILIA trial (lapatinib plus capecitabine) and the TH3RESA trial (TPC, ~80% trastuzumab containing therapy). The Grade ≥3 toxicities commonly associated with trastuzumab emtansine were generally laboratory abnormalities with limited impact on patient wellbeing, and were generally managed with dose reductions. Consequently the adverse event profile of trastuzumab emtansine is not expected to add any significant burden to people, their healthcare professionals or cost to the NHS.

Consistency of AEs with patients treated with trastuzumab and/or pertuzumab

Roche proposes to present data from the safety database for all cases in which patients have had previous exposure to trastuzumab and/or pertuzumab when such data are provided as follows:

- Data from the Roche's global safety database will be extracted for cases which reported previous exposure to trastuzumab and/or pertuzumab in the medical history field or where previous exposure was stated within the text narrative.

- The AEs reported in this dataset will be analyzed to determine whether the frequency and nature of the AEs reported are similar to the known safety profile for trastuzumab emtansine.

It is proposed that these data will be presented at 6-monthly intervals for the first two years following marketing approval in the EU and will be submitted as part of the PSUR/PBRER.

6.10 Interpretation of clinical evidence

6.10.1 Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

Patients with HER2-positive unresectable LABC or MBC represent an unmet medical need as the HER2-positive status of their breast cancer is associated with aggressive disease; those who progress rapidly during or soon after adjuvant therapy particularly so. Moreover, they are likely to present at a younger age than the general breast cancer population (Neven et al 2008; Kwan et al 2009) representing a potentially greater burden of illness with consequential wider societal impacts. These encompass effects on family life including changes in roles and responsibilities within families; relationships with partners, children and close family and friends; and concerns regarding becoming dependent and care requirements (Breast Cancer Care 2013). Financial and social impacts include the potential loss of income due to changes in working patterns, increased costs of living with an increased reliance on benefits.

It is common practice for patients with HER2-positive locally advanced and/or MBC in the UK to receive multiple lines of therapy, usually at least two containing an anti-HER2 component (trastuzumab or lapatinib). The addition of these anti-HER2 treatments has resulted in significant improvements in treatment and prognosis of people with HER2-positive MBC (Nahta and Esteva, 2007). Despite this, patients still suffer adverse drug reactions either from the anti-HER2 therapy or the companion chemotherapy, and the majority of patients will still progress and die of their metastatic disease. Treatment goals for HER2-positive MBC therefore involve increasing the life expectancy, both before progression and overall, and improving the quality of life.

Trastuzumab emtansine is the first in a new class of antibody drug conjugates targeted to solid tumours. Acting on HER2-positive cells, trastuzumab emtansine has two mechanisms of action:

1. on binding to the HER2 receptor it inhibits downstream signalling and targets the cell for ADCC
2. on receptor-antibody internalisation the cytotoxic DM1 is release into the cell resulting in apoptosis.

In the EMILIA study trastuzumab emtansine showed a clinically meaningful and statistically significant improvement in progression-free survival and overall survival with respect to lapatinib plus capecitabine. PFS was 9.6 months in the trastuzumab emtansine arm compared with 6.4 months in the lapatinib plus capecitabine arm (HR=0.65, 95% CI [0.55, 0.77], p <0.0001). This corresponds to a 50% increase in median PFSand a 35% reduction in risk of progression. Median OS was 30.6 months in the trastuzumab emtansine arm compared to 25.1 months in the lapatinib plus capecitabine (hazard ratio of 0.682 [0.55, 0.85, p=0.0006]).

In the TH3RESA study trastuzumab emtansine showed a statistically significant improvement in PFS and a trend towards improvement in OS (interim analysis). The analysis for PFS showed a median PFS for trastuzumab emtansine of 6.2 months as compared to 3.3 months with TPC (HR=0.528, p<0.0001) or 3.2 months for TPC-trastuzumab containing regimens only (HR=0.558, p<0.0001). The interim analysis showed a median OS in the TPC arm was 14.9 months but the data was not yet mature and had not been reached in the trastuzumab emtansine arm. The HR was 0.552 with a p value of 0.0034, however, these values did not cross the prespecified efficacy stopping boundry of HR <0.363 or P<0.0000013. A further interim analysis for OS will be performed at around 26 months with the final OS expected at around 45 months.

A statistically significant improvement in OS, particularly when seen in trials enrolling patients ≥2 line MBC, represents a clinically meaningful benefit for these patients.

In addition to the significant improvements in both progression-free and overall survival, the trastuzumab emtansine arm had a statistically significant

greater objective response rate with 43.6% of people in the trastuzumab emtansine arm experiencing a complete or partial response (as per RECIST criteria) to treatment compared to 30.8% in the lapatinib plus capecitabine arm, a difference of: 12.7% (95% CI, 6.0, 19.4) p=0.0002.

The safety profile of trastuzumab emtansine was generally favourable compared to that of lapatinib plus capecitabine (EMILIA) or trastuzumab based therapy (TH3RESA). Most AEs were mild to moderate in severity. Thrombocytopenia, transaminase increases, anaemia and fatigue occurred at a higher incidence in the trastuzumab emtansine arm than in the lapatinib and capecitabine arm of the EMILIA study, and thrombocytopenia and transaminase increases occurred at a higher incidence in the trastuzumab emtansine arm than in the TPC arm of the TH3RESA study. Importantly, based on the patient-completed FACT-B questionnaire, a significant improvement was seen in time to symptom progression with trastuzumab emtansine as compared to lapatinib plus capecitabine in the EMILIA study.

Conclusion

EMILIA and TH3RESA demonstrate that trastuzumab emtansine offers substantial and consistent clinically relevant benefits as a therapy for locally recurrent unresectable or metastatic HER2-positive breast cancer. These benefits included significant improvements in the proportions of people responding to treatment, progression-free survival and overall survival. Importantly these efficacy gains are delivered with a reduction in overall toxicity and an improvement in the patient-reported quality of life.

6.10.2 Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.

Strengths - The EMILIA study is a robust, high quality, adequately powered, centrally randomised trial that compared the intervention directly with the current gold standard. The TH3RESA study is a robust study that compared trastuzumab emtansine with TPC, reflecting the lack of a standard of care or clear treatment pathway for patients who have progressed on two or more lines of therapy for HER2-positive MBC.

Both studies were developed with the aid of EMA scientific advice, Investigator feedback, early phase studies and published data. The EMILIA study was conducted in 213 centres in 26 countries with a total of 991 patients randomised to trastuzumab emtansine arm (n=495) or lapatinib plus capecitabine arm (n=496). A total of 602 patients were randomised into the TH3RESA study (404 to receive trastuzumab emtansine and 198 to receive TPC).

The studies incorporated many of the standard features of clinical studies in people with advanced breast cancer, with additional features such as central confirmation of a positive HER2 status in EMILIA (the key biomarker, selective of patients most likely to receive benefit from treatment), and additional safety measures for monitoring hepatotoxicity, thrombocytopenia, IRR and hypersensitivity, pneumonitis, cardiac safety and hypokalaemia. The safety of participants in each study was overseen by an independent Data Monitoring Committee (DMC).

The international nature of the studies ensured that all major race groups and ages were enrolled. Benefit with the trastuzumab emtansine based treatment was seen across these groups and this would be expected in the clinical setting.

The comparator treatment in the EMILIA study is a licenced regimen and is considered to be standard of care and the most effective treatment for HER2 positive metastatic breast cancer. The comparator in TH3RESA reflects the lack of a standard of care once patients have progressed on both trastuzumab and lapatinib.

In EMILIA the primary efficacy parameter, progression-free survival, was determined by an Independent Review Facility with investigator assessed progression-free survival a secondary efficacy endpoint, which is considered to be of more relevance to routine clinical practice in the UK. The data from independent review and investigator assessment were very similar, indicative of the quality of data collection.

Limitations – Due to the routes of administration of treatment in each arm in both EMILIA – trastuzumab emtansine was delivered IV and lapatinib plus capecitabine is delivered orally - and the range of possible treatments available as TPC in TH3RESA, the number of placebos required to double blind these studies was considered prohibitive and unethical. This study was therefore open label. This was mitigated by independent review of the patient radiological scans for the co-primary PFS endpoint. The protocol selected people with good cardiac function and previous exposure to anti-HER2 treatment (trastuzumab in EMILIA and trastuzumab and lapatinib in TH3RESA) to limit the possible occurrence of any cardiac toxicity. Reassuringly, the rate of cardiac events was similar when compared to lapatinib plus capecitabine or TPC and this is expected in the clinic.

The TH3RESA study had a greater number of patients withdrew from treatment in the TPC arm (26 patients; 13.1%) than in the trastuzumab emtansine arm (19; 4.7%) decided to withdraw from the study. This was in part due to patients withdrawing after being informed they had been randomized to the study's control arm (13 patients withdrew from TPC prior to treatment, compared with 2 patients who withdrew prior to receiving trastuzumab emtansine).

6.10.3 Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

The primary and secondary outcomes adopted to assess efficacy and safety in the pivotal study have been well established in oncology, are familiar to oncologists, and are relevant to people with metastatic disease.

The main treatment challenge in clinical practice is how to increase the patient's life expectancy while still maintaining their quality of life. In particular patients who have either progressed on or within a short time after completing trastuzumab containing adjuavant therapy, or who have progressed on first line treatment for metastatic disease. Oncologists are anxious to observe

quickly if a new treatment is effective. Response rates are accepted as being an early indicator of efficacy of a treatment for metastatic breast cancer. The high objective response rate in EMILIA (43.6%) and TH3RESA (31.3%) will allow oncologists to adequately understand treatment decisions.

The efficacy endpoint of progression-free survival, using Response Evaluation Criteria in Solid Tumors (RECIST), has been accepted as an endpoint for registration of products for the treatment of metastatic breast cancer (Tuma, 2009**;** Burzykowski et al, 2008; Fleming et al, 2009). Prolongation of progression-free survival in itself provides a meaningful clinical benefit to people by extending the time without disease progression and its associated symptoms, and by delaying the need for further toxic chemotherapy.

Overall survival is arguably the outcome of greatest relevance to the treatment of all people with cancer. The EMILIA study shows a statistically significant and clinically meaningful increase in OS with trastuzumab emtansine, and the immature data from TH3RESA show a trend towards an OS benefit for patients receiving trastuzumab emtansine.

It is important to note these improvements have been seen with a reduction in Grade ≥3 toxicity and and statistically significant improvement in in patient quality of life. Other secondary endpoints such as objective response rate duration of response are highly pertinent to people and their clinicians when discussing treatment options at the onset of HER2-positive metastatic disease.

The outcomes assessed in EMILIA and TH3RESA, therefore, are expected to have a significant beneficial effect on people in clinical practice as trastuzumab emtansine has been shown to increase the proportion of breast cancers responding to treatment (the highest response seen in HER2-positive metastatic breast cancer studies) and that this response is durable as seen by the significant increases in progression-free survival with an associated significant increase in overall survival. For people with breast cancer being treated with trastuzumab emtansine, this would mean a higher likelihood of a

positive response to treatment, the disease being controlled for a longer period of time and a subsequently longer life expectancy.

6.10.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?

Overall the study populations of EMILIA and TH3RESA are representative of people with HER2-positive metastatic breast cancer who could be considered as candidates for further HER2-targeted treatment and, overall, the demographics of enrolled participants are considered to be reflective of the proposed population in the UK.

As these were was a global, multicentre study, the treatments that people received, either prior to enrolling or after disease progression, was not necessarily reflective of current UK practice. Importantly, however, the subsequent breast cancer therapies were generally balanced between both arms and treatment with trastuzumab emtansine was not permitted prior to positive OS results in EMILIA. Patients in either arm of the trial were not permitted to enrol in any further trastuzumab emtansine clinical trials.

The performance status of patients in the EMILIA trial (ECOG PS 0-1) may be a fitter population than the population as a whole. However, the TH3RESA study was permissive, allowing patients to enter the trial with ECOG PS 0-2.

The recent licence for pertuzumab and its availability via the NCDF means that HER2- positive MBC patients in England suitable for treatment with trastuzumab emtansine may have received a pertuzumab containing regimen previously. Currently there is a lack of data on the efficacy or safety of trastuzumab emtansine after this treatment. A review of available trial data

was performed by Roche for the CHMP. Patients who have received prior treatment with pertuzumab did not show any concerning safety signals, and the safety profile was consistent with the safety profile of the total patient population in the trastuzumab emtansine arm. In addition, Roche will present data from their global safety data every six months for four years post licence.

Prospective studies are planned to evaluate the safety and efficacy of trastuzumab emtansine after pertuzumab and a registry of patients with HER2-positive MBC will provide additional information.

It is anticipated that this will impact only early recipients of pertuzumab e.g. clinical trial patients. Given the median duration of treatment on pertuzumab (median approximately eighteen months) (Baselga, 2012) further data is expected before trastuzumab emtansine is regularly prescribed to patients with prior exposure to pertuzumab.

What proportion of the evidence base is for the dose(s) given in the SPC?

The starting dose 3.6mg/kg and recommended dose reductions were established in a dose escalation study (Krop, 2010). These doses have been used in all phase II or III trials with trastuzumab emtansine monotherapy and are reflected in the SPC.

7 Cost effectiveness

7.1 Published cost-effectiveness evaluations

Identification of studies

7.1.1 Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in section 10.10, appendix 10.

Embase (EMYY), Embase Alert (EMBA), Medline (MEYY) and NHS EED were searched for studies assessing the cost-effectiveness of trastuzumab emtansine. The search was designed to evaluate whether de novo modelling was necessary in order to answer the decision problem. The search included all papers in each database and the search strategy is provided in section **Error! Reference source not found.**. The methodology used was based upon on the methods outlined in the CRD's 'Guidance for undertaking reviews in health care' (2008).

7.1.2 Key word strategies were developed using key references retrieved initial scoping searches. ProQuest was used to search EMYY, MEYY whilst NHS EED was searched using The Centre for Dissemination's website (University of York) on 4th October 2013. search result's title and abstract were assessed for relevance pre-defined inclusion and exclusion criteria (

Table **24**).

Table 24: Inclusion and exclusion criteria for cost-effectiveness studies

Parameter	Inclusion Criteria	Exclusion Criteria
Population	Female, HER2 positive advanced or metastatic breast cancer patients	Non breast cancer patients, Non HER2 positive patients Non female (male)
Intervention	trastuzumab emtansine	-
Comparator	capecitabine + lapatinib, capecitabine + trastuzumab, capecitabine	-
Outcome	Cost per QALY gained, Cost per LY gained	-
Study Design	Economic Evaluations (cost effectiveness analyses, cost utility analyses, cost minimisation analyses)	RCTs, Observational Data, Budget Impact Assessments

The objectives of the search, and the inclusion criteria and exclusion criteria defined as a product of those objectives, were clearly aligned with the decision problem.

Seven studies were identified across the four databases. All of these were excluded by the independent reviewers after being assessed against the inclusion criteria. No cost-effectiveness studies of trastuzumab emtansine were thus identified.

Figure 21: PRISMA flow for economic evaluation studies identified through database searches

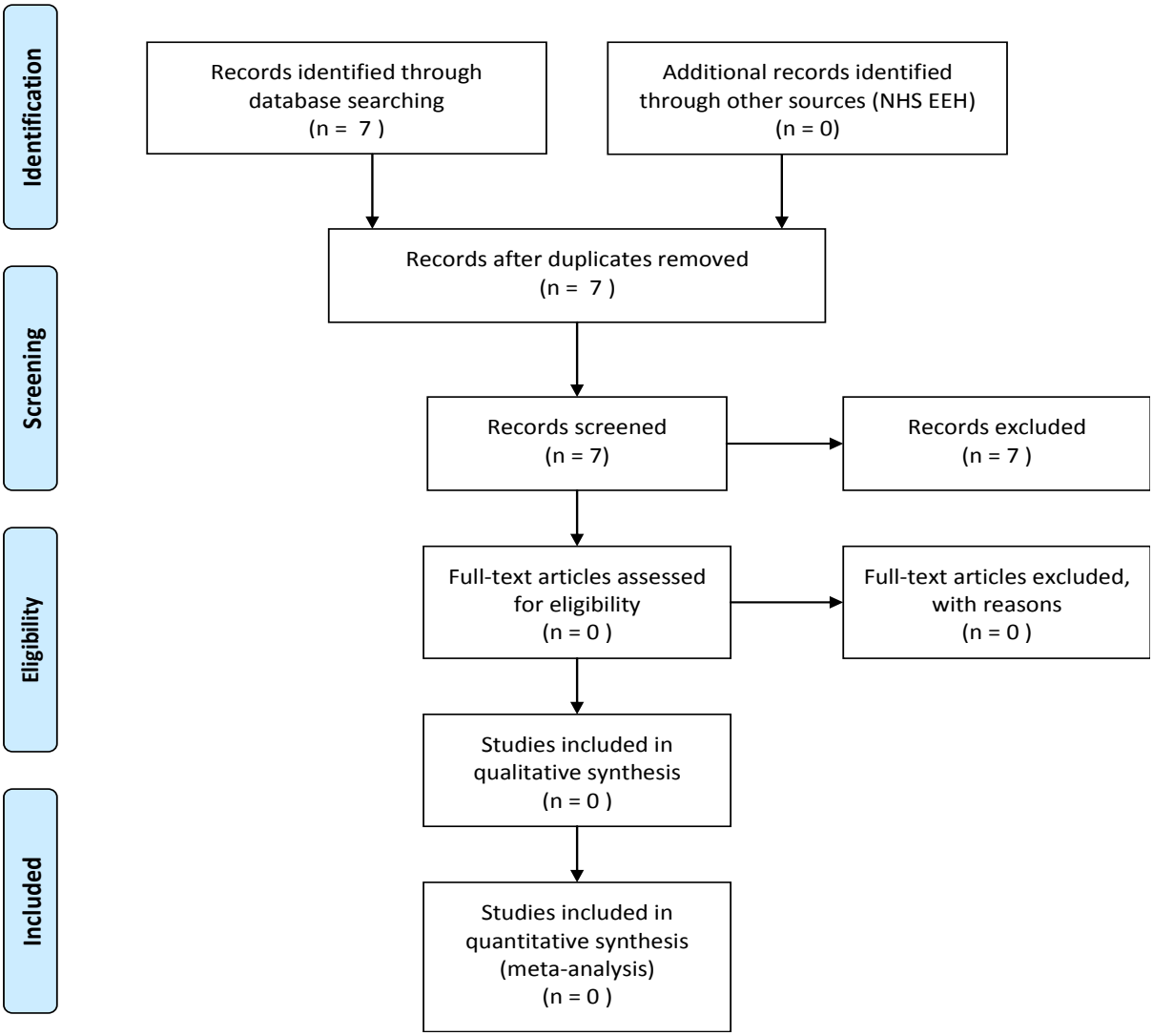


Figure 21 above illustrates the literature search in terms of identified and included/excluded cost-effectiveness studies.

Description of identified studies

7.1.3 Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided. If more than one study is identified, please present in a table as suggested below.

Not applicable. No studies were included in the appraisal.

7.1.4 Please provide a complete quality assessment for each cost-effectiveness study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996)[6] or Philips et al. (2004)[7]. For a suggested format based on Drummond and Jefferson (1996), please see section 10.11, appendix 11.

Not applicable. No studies were included in the appraisal.

7.2 De novo analysis

Patients

7.2.1 What patient group(s) is(are) included in the economic evaluation? Do they reflect the licensed indication/CE marking or the population from the trials in sections 1.3 and 6.3.3, respectively? If not, how and why are there differences? What are the implications of this for the relevance of the evidence

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[6] Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83.

[7] Philips Z, Ginnelly L, Sculpher M, et al. (2004) Quality assessment in decision-analytic models: a suggested checklist (Appendix 3). In: Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technology Assessment 8: 36.

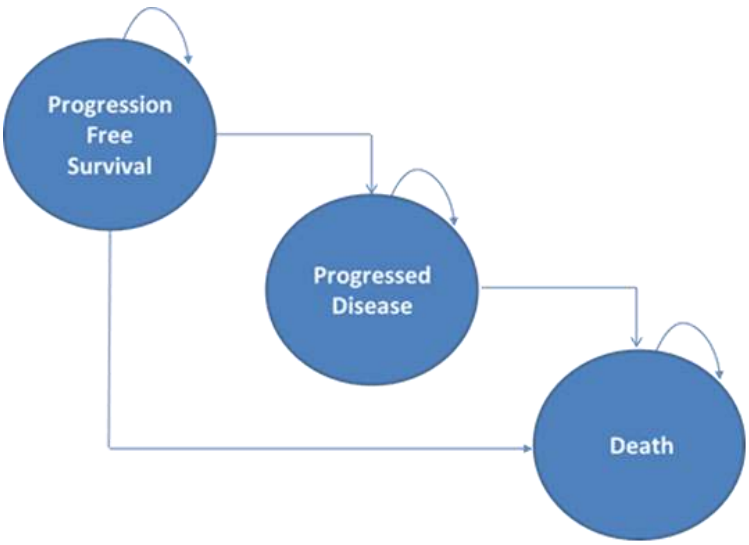
base to the specification of the decision problem? For example, the population in the economic model is more restrictive than that described in the (draft) SPC/IFU and included in the trials.

No cost-effectiveness models were identified in the search outlined in Section 7. Consequently a *de novo* economic model was constructed to assess the clinical and cost effectiveness of trastuzumab emtansine, as a single agent, 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. The model is thus aligned with the marketing authorization of trastuzumab emtansine and captures the key outcomes from the ITT population of the EMILIA trial.

Model structure

7.2.2 Please provide a diagrammatical representation of the model you have chosen.

Figure 22: Model Structure



7.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in section 2.5.

The model is constructed using Excel® featuring three health states; progression-free, progressed and death. The health states mirrored the main

endpoints measured in the EMILIA trial. The structure of stratifying the clinical outcomes of people with cancer into progression-free, progression, and death is common practice in the economic evaluation of oncology interventions. The health states align with the key objectives of treatment within this disease area: to extend duration of progression-free and overall survival for as long as possible. The progressed health state represents the duration from progression until death and therefore includes the possible sequence of remission and relapse following further lines of treatments common to metastatic breast cancer. Disease progression is represented in the model by people who are no longer classified as “progression free”, as defined by the EMILIA protocol.

7.2.4 Please define what the health states in the model are meant to capture.

All people in the model start in the progression-free health state. At the end of each discrete weekly cycle a person either remains in progression-free survival, moves to the progressed health state or dies. Once a person is within the progressed health state, they may remain in that health state or die at the end of each weekly cycle. People cannot move from the progressed health state back to progression-free survival health state in the model. Death is an absorbing health state in the model.

The model uses a partitioned survival approach, in which inputs are taken as estimated parametric survival functions for both overall survival and progression-free survival. The proportion of the initial cohort in the progressed state at each cycle is the difference between the proportion that is alive and the proportion that is progression-free. The area between these two curves is the mean life-years of people with progressed metastatic disease. This approach allows the model to be accurately calibrated with the trial results for progression-free survival and overall survival.

7.2.5 How does the model structure capture the main aspects of the condition for patients and clinicians as identified in section 2 (Context)? What was the underlying disease progression

implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to section 2.1.

The three health states within the model capture most conditions relevant to the decision problem. A limitation of this modelling approach is that it is not aligned with the available utilities data in the setting of metastatic breast cancer. Utility values in metastatic breast cancer are typically distinguished by the health states of response, stable disease, and progression, where response and stable disease are classified as progression-free survival. Due to the misalignment in model structure (which is driven by the endpoint of progression-free survival) and available utilities data in metastatic breast cancer (which is focused on understanding how different response states impact on quality of life), the model adjusts for the observed differences in utility values that occur within a single health state (see section 7.4 for more details on the utilities used in the model).

7.2.6 Please provide a table containing the following information and any additional features of the model not previously reported. A suggested format is presented below.

Table 25: Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	Lifetime (equating to a maximum of 10 years)	NICE reference case At 10 to 11 years there are approximately 1% of patients remaining alive in the comparator arm of the model	NICE methods guide
Cycle length	1 week	The three-weekly administration of drugs in the model supports the use of a weekly cycle length.	NICE methods guide
Half-cycle correction	Yes (half cycle correction is not applied to drug, administration and pharmacy costs)	NICE reference case	NICE methods guide
Were health effects measured in QALYs; if not, what was used?	QALY	NICE reference case	NICE methods guide
Discount of 3.5% for utilities and costs	3.5%	NICE reference case	NICE methods guide
Perspective (NHS/PSS)	NHS/PSS	NICE reference case	NICE methods guide
NHS, National Health Service; PSS, personal social services; QALYs, quality-adjusted life years			

Technology

7.2.7 Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?

The intervention and comparators are in line with the decision problem set out in the NICE scope. More details on the implementation of the technologies within the models can be found in Section 5.

7.2.8 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

- **The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).**
- **The robustness and plausibility of the endpoint on which the rule is based.**
- **Whether the 'response' criteria defined in the rule can be reasonably achieved.**
- **The appropriateness and robustness of the time at which response is measured.**
- **Whether the rule can be incorporated into routine clinical practice.**
- **Whether the rule is likely to predict those patients for whom the technology is particularly cost effective.**
- **Issues with respect to withdrawal of treatment from non-responders and other equity considerations.**

No treatment continuation rule has been applied in the economic model.

7.3 Clinical parameters and variables

When relevant, answers to the following questions should be derived from, and be consistent with, the clinical-evidence section of the submission (section 6). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided as well as a justification for the approach.

7.3.1 Please demonstrate how the clinical data were implemented into the model.

The model is a partitioned survival model which treats progression-free survival and overall survival as individual entities (i.e. no assumption is made about the relationship between the two). The proportion of people in the progression-free survival health state is derived using the hazard rates observed in the trastuzumab emtansine and lapatinib plus capecitabine arms of the EMILIA trial.

The model was developed using the January 2012 cut of PFS data and July 2012 cut of OS data from the EMILIA trial; the latest data cuts for each endpoint. The January 2012 cut of PFS data features investigator assessed progression-free survival. The progression-free and overall survival Kaplan-Meier curves are presented in Figure 24.

Figure 23 and Figure 24.

Figure 23: PFS KM Plots (January 2012 data cut)

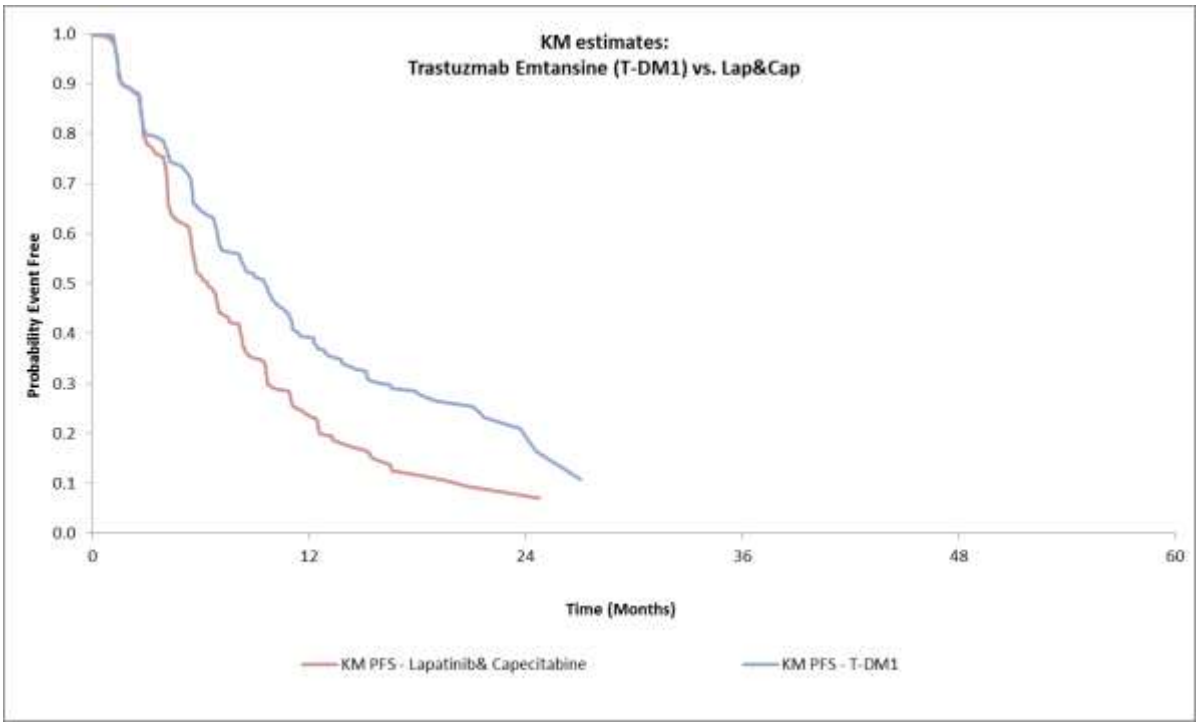
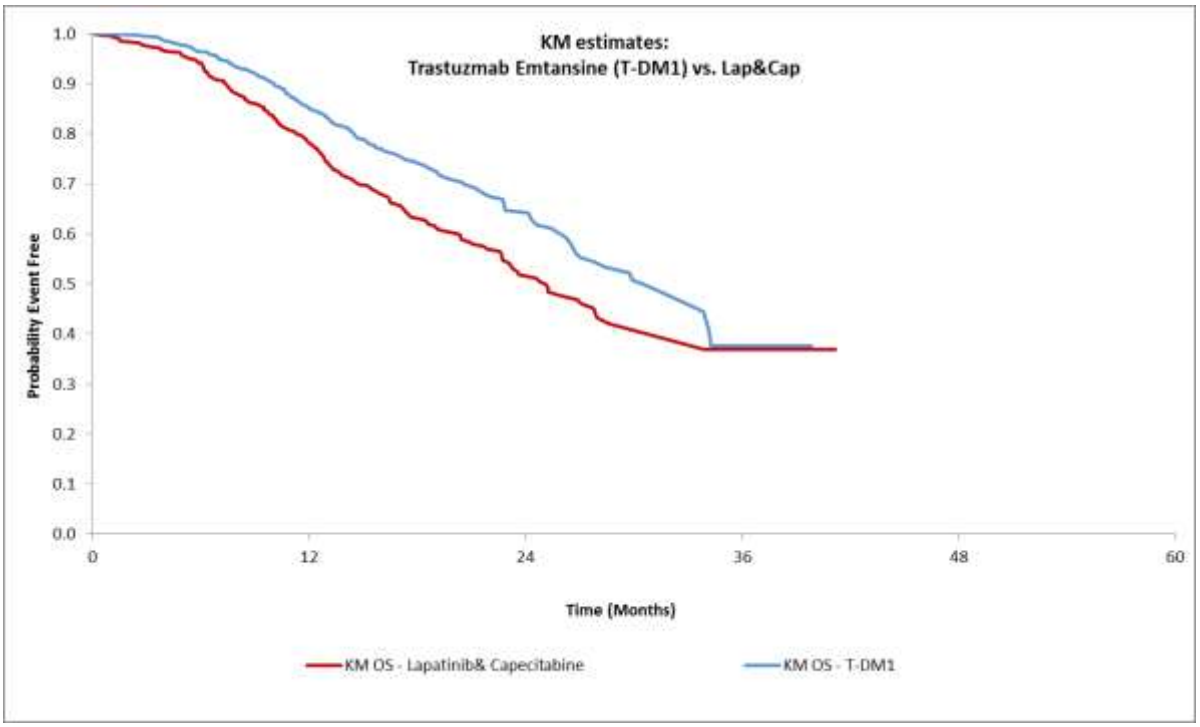


Figure 24: OS KM Plots (July 2012 data cut)



Cumulative hazard plots

Whilst survival data is typically presented in the form of Kaplan-Meier plots, the production of cumulative hazard plots allows simple examination of the trends in the data that can be difficult to interpret using Kaplan-Meier data alone. The slope of the cumulative hazard plot at any point in time can be interpreted as the hazard of the event of interest occurring at that point in time. The steeper a cumulative hazard plot is the higher the hazard of the event occurring and the flatter a cumulative hazard plot is the lower the hazard of the event occurring is. This property allows consideration of how the risk of an event occurring changes over time (i.e. *how does the slope change over time)* and the way in which the impact of some intervention changes over time (i.e. *how much does the ratio of the two slopes (the hazard ratio) change over time).* This method of analysing the data is important when considering extrapolation as it can inform both the extrapolation of the baseline risk without the intervention (i.e. *if the slope (hazard) of the cumulative hazard plot for the non-intervention curve has been straight for the period observed it may be reasonable to continue with a straight hazard beyond this point in time*) and how the intervention arm may differ from that baseline risk if further follow-up were available (i.e*. if the ratio of the two slopes (hazard ratio) has been constant throughout the data it may be reasonable to continue that ratio beyond the period of follow-up).*

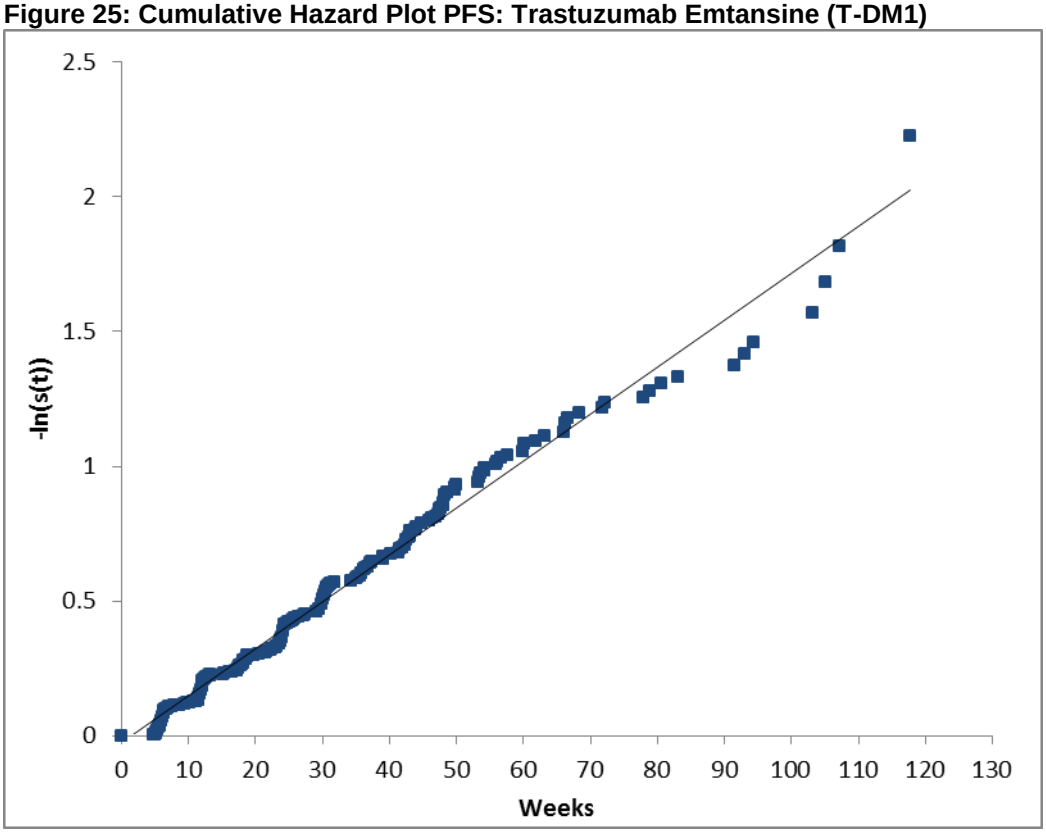
Progression Free Survival (PFS)

The cumulative hazard plot for the trastuzumab emtansine and lapatinib and capecitabine PFS arms are shown below in

Figure 25 and

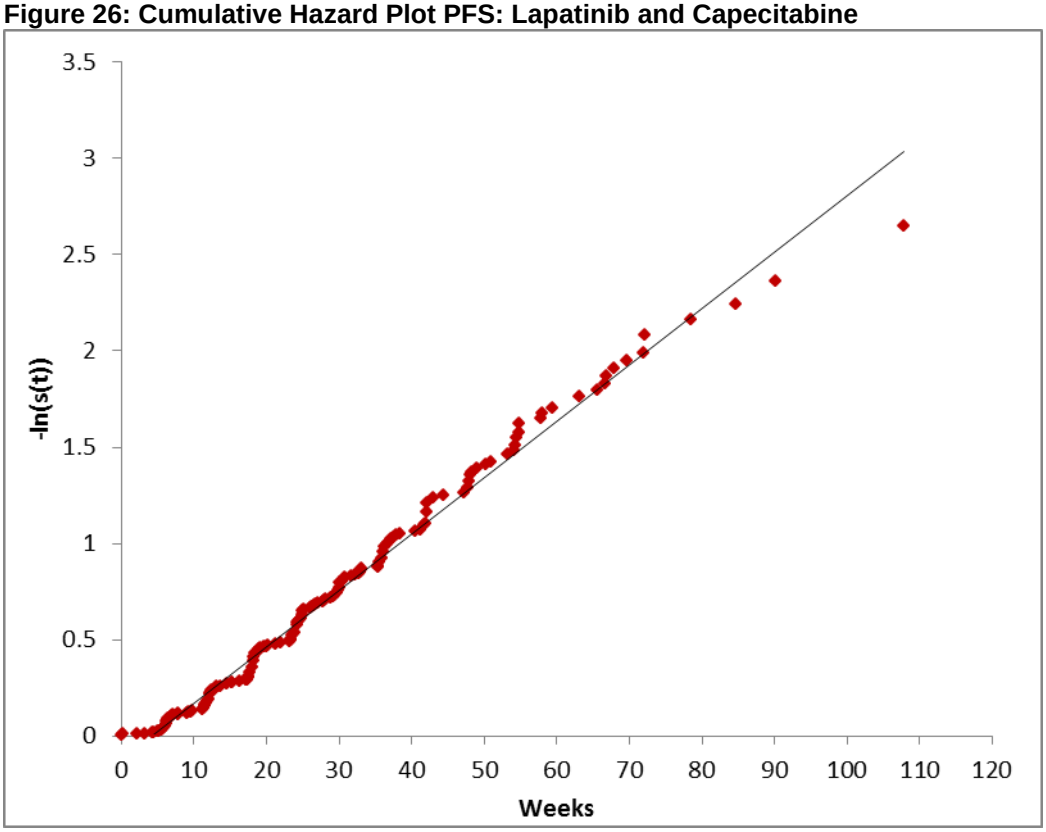
Figure 26 respectively.

Figure 25: Cumulative Hazard Plot PFS: Trastuzumab Emtansine (T-DM1)



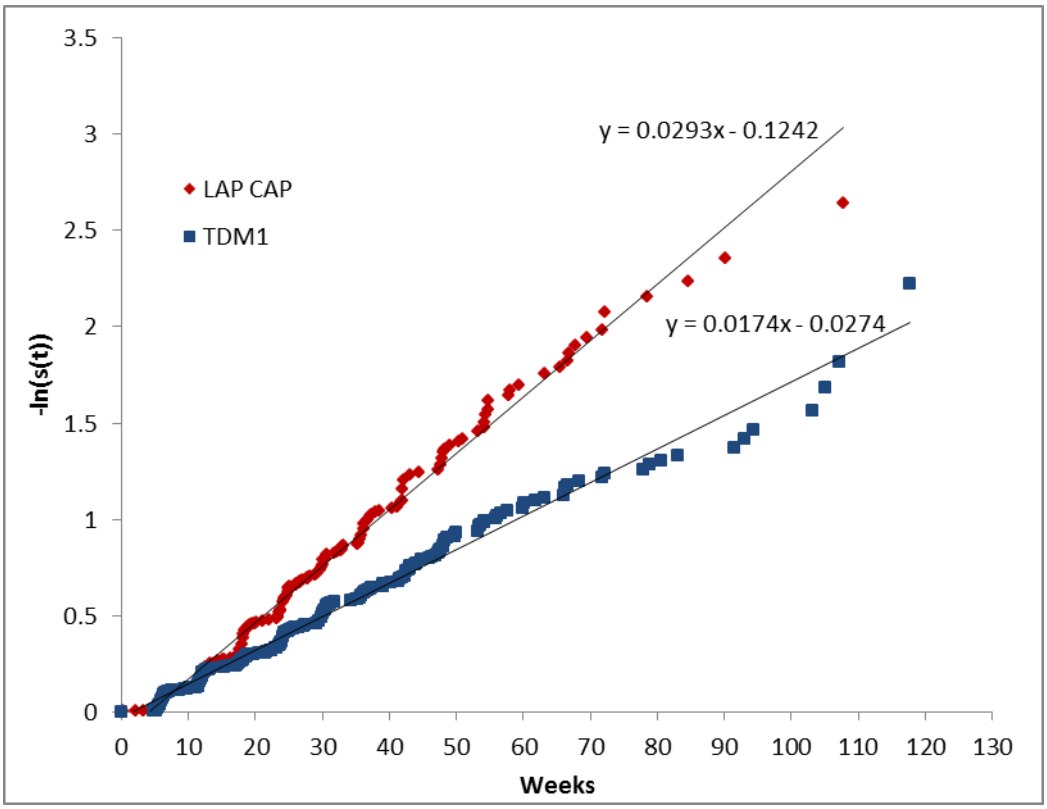
The trastuzumab emtansine plot appears to show a relatively constant hazard until approximately 72 weeks after which there appears to be a flattening of the curve followed by an increase again towards the end. Although it is possible that there could be a prognostic or responsive heterogeneity in the EMILIA trial population it is also plausible that the change in hazard is spurious and simply due to the low numbers at risk by this stage (51 people or ~10% of the starting population of the trastuzumab emtansine arm).

Figure 26: Cumulative Hazard Plot PFS: Lapatinib and Capecitabine



Likewise the lapatinib and capecitabine plot appears to show a relatively constant hazard until approximately 72 weeks after which the curve appears to flatten but at this point there are even fewer at risk than in the trastuzumab emtansine arm (20 people or ~4% of the starting population of the lapatinib and capecitabine arm).

Figure 27: Cumulative Hazard Plot PFS: Tratuzumab emtansine (T-DM1) and Lapatinib and Capecitabine (LAP CAP)

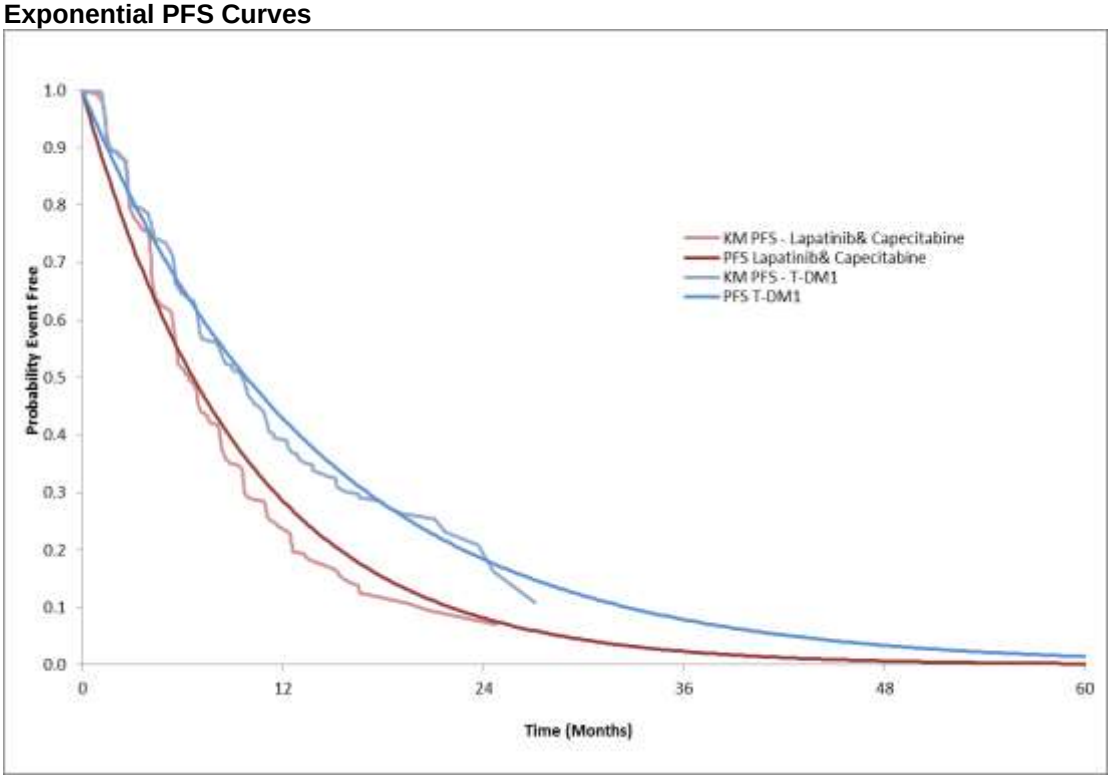


Comparing both plots with one another one can clearly see that although up until approximately 14 weeks the hazards are similar, at 14 weeks there is a divergence and over the time the lapatinib and capecitabine arm is associated with a higher constant hazard versus trastuzumab emtansine.

However when an exponential function is fitted to each arm this results in a very poor visual fit to the data. Figure 28 shows that the exponential function underestimates then overestimates the lapatanib and capecitabine arm and similarly for the trastuzumab emtansine arm but to a lesser extent. One explanation for this is that the fitting of the exponential must be done such that the curve starts from where the probability of being event free is 1 at time zero i.e. the cumulative hazard plot goes through the origin. However in

Figure 27 the exponential provides a good fit to the data but there is no requirement that the intercept is zero. This therefore results in a relatively poor translation of the exponential fit to the PFS curves.

Figure 28: Trastuzumab emtansine (T-DM1) and Lapatinib and Capecitabine KM and Exponential PFS Curves



Alternatively, given that the hazards seem fairly similar up until 14 weeks there may be some biological or clinical reason as so to why a divergence of hazards is only seen after this point and it is from this time point that the true hazard in each arm emerges. This then requires the fitting of each curve with two separate pieces; one which is the same for both arms until 14 weeks and a further piece which differs in each arm. This way of modelling PFS (and OS) is explored as a sensitivity analysis.

In terms of the best statistical fit, Table 26 shows that a log normal parametric fit produces the most favourable BIC and AIC results.

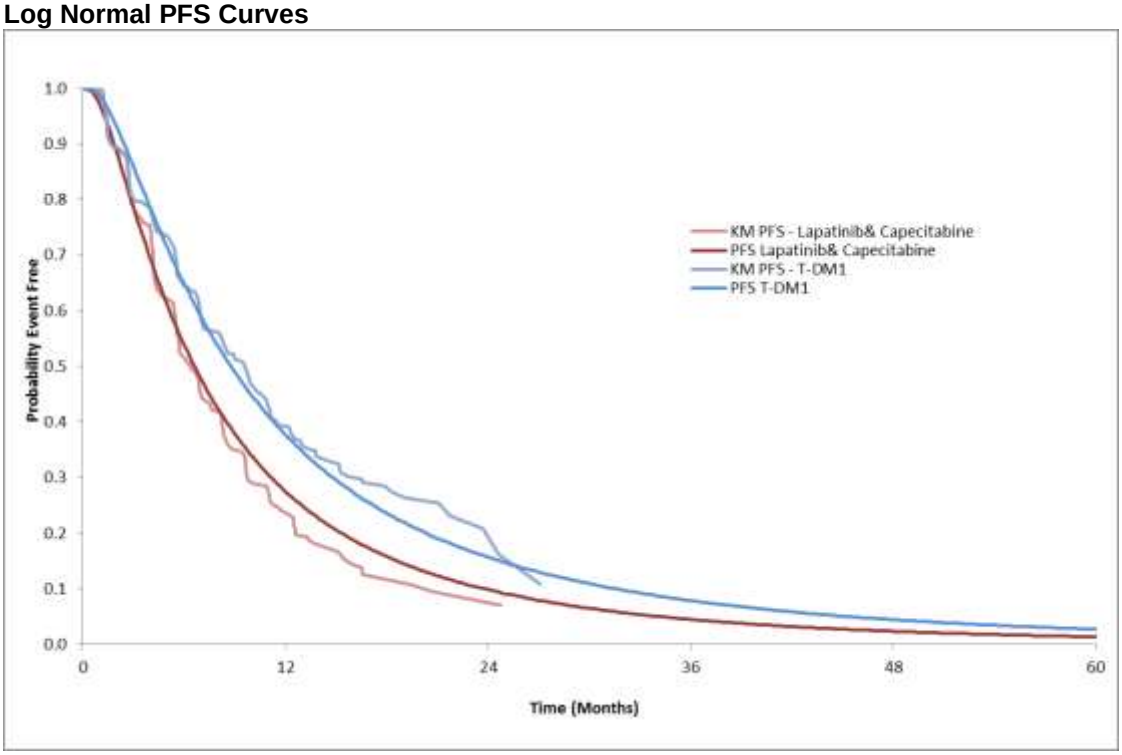
Table 26: BIC and AIC results for PFS

MODELTYPE	BIC	AIC	BESTFIT
LogNormal	2112.6	2097.9	LNORMAL

Gamma	2119.3	2099.7	
LogLogistic	2122.1	2107.4	
Weibull	2169.9	2150.3	
Exponential	2203.0	2193.2	

However as previously, fitting a log normal distribution does not provide a good visual result when compared against the KM data. Figure 29 shows that the log normal curve appears to fit the lapatinib and capecitabine arm reasonably well at the start, but overestimates it substantially after approximately 6 months. Conversely the log normal distribution overestimates the trastuzumab emtansine arm at the start and underestimates it after approximately 7 months.

Figure 29: Trastuzumab emtansine (T-DM1) and Lapatinib and Capecitabine KM and Log Normal PFS Curves

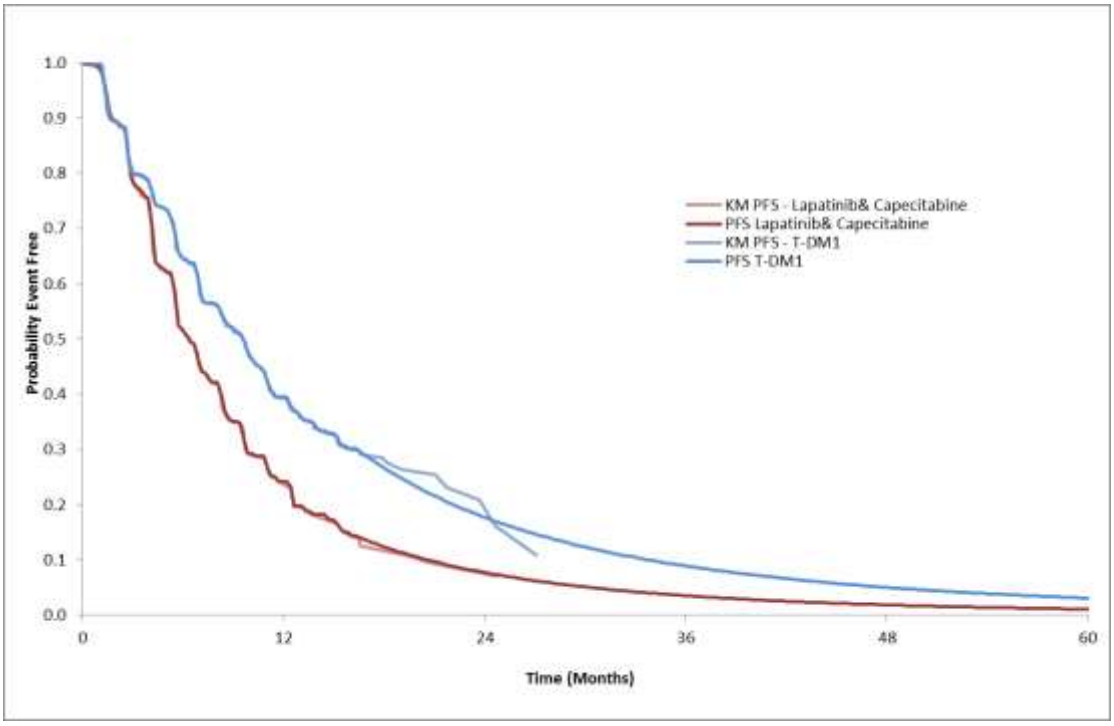


Similarly when other (poorer statistically fitting) distributions were considered they too they too provided a poor visual fit to the data. With this in mind, the most pragmatic pragmatic approach might be to use the KM data for as long as possible and simply fit simply fit a parametric distribution to the tails of the curves. Given that the log normal normal distribution provided the best statistical fit, this function was fitted to the tail of the tail of the curves from 72 weeks (17 months) as this was the point in both arms

arms where the hazard starts to become erratic by inspection of the cumulative hazard plots (see

Figure 27). Figure 30 shows the PFS curves with a log normal function fitted to the tail of each arm from 72 weeks (17 months).

Figure 30: Trastuzumab emtansine (T-DM1) and Lapatinib and Capecitabine KM PFS Curves with log normal distributions fitted to the tails from 72 weeks (17months) in each arm



The choice of a log normal function for projection on the basis of goodness of fit statistics derived from the data available could clearly be criticized. The log normal function has more flexibility to fit to data than other more restrictive functions and is therefore often found to be the 'best fit'. Fitting 'best' to existing data via increased flexibility does not necessarily indicate that this function will be preferable for projection. However due to the relatively poor for of all parametric distributions in Table 26, the decision to use the KM data up until the hazards start to become erratic and the relatively small impact of PFS (versus OS) in the model, it was decided to use the log-normal function for the trails of the curves only.

Further a range of alternative scenarios were tested in sensitivity analysis.

Overall Survival (OS)

7.3.2 The cumulative hazard plot for the trastuzumab emtansine and capecitabine OS arms are shown below in Figure 31 and

Figure 32 respectively.

Figure 31: Cumulative Hazard Plot OS: Trastuzumab Emtansine (T-DM1)

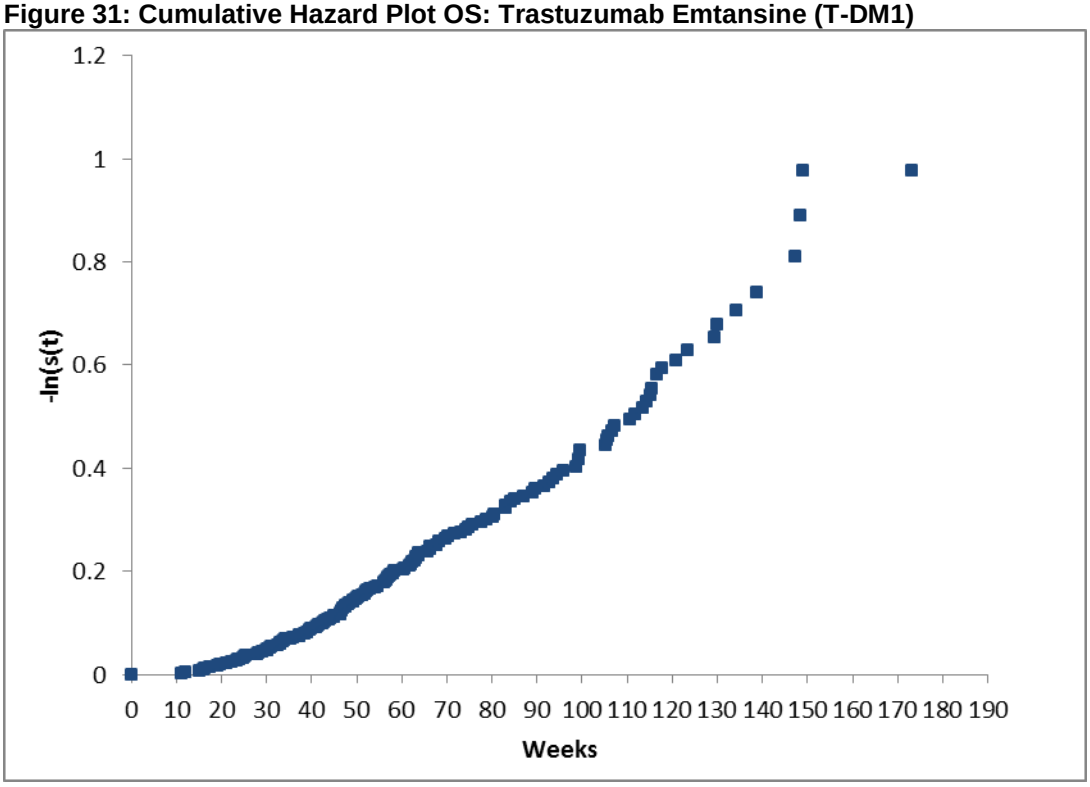
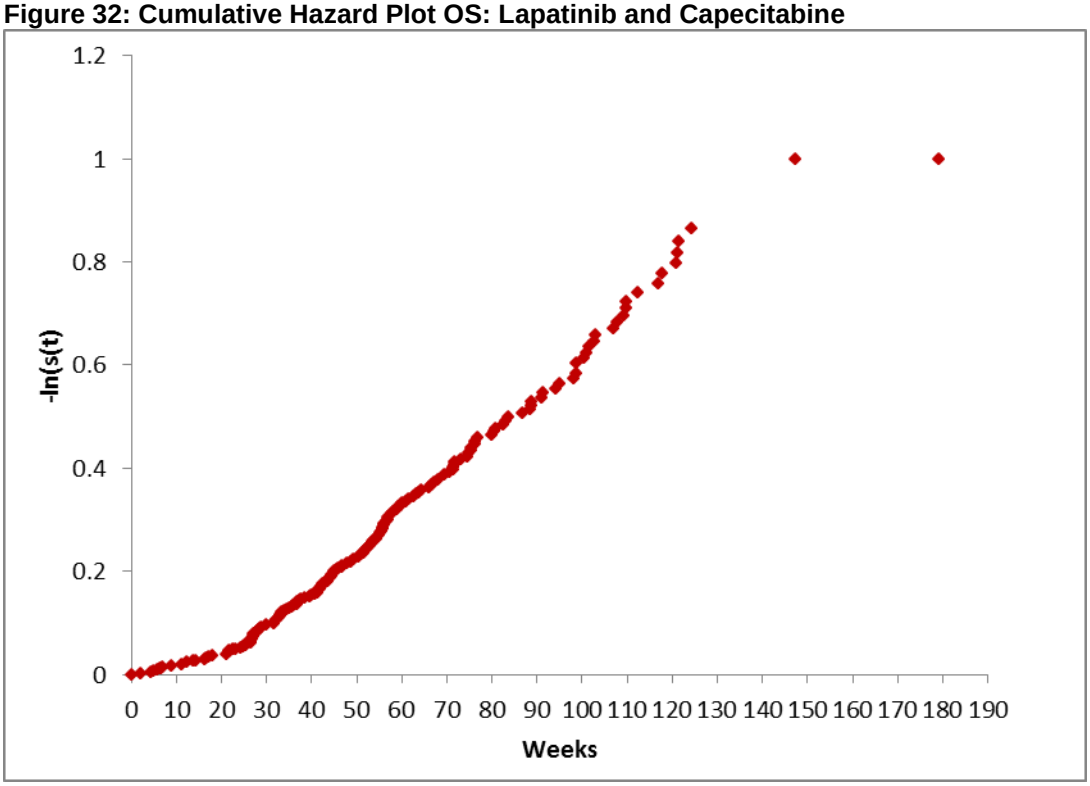


Figure 32: Cumulative Hazard Plot OS: Lapatinib and Capecitabine



Both plots appear to show that the hazard is increasing with time. Laying the plots next to each other enables us to see how the hazard changes in one arm versus the other.

Figure 33: Cumulative Hazard Plot OS: Trastuzumab emtansine (T-DM1) and Lapatinib and Capecitabine

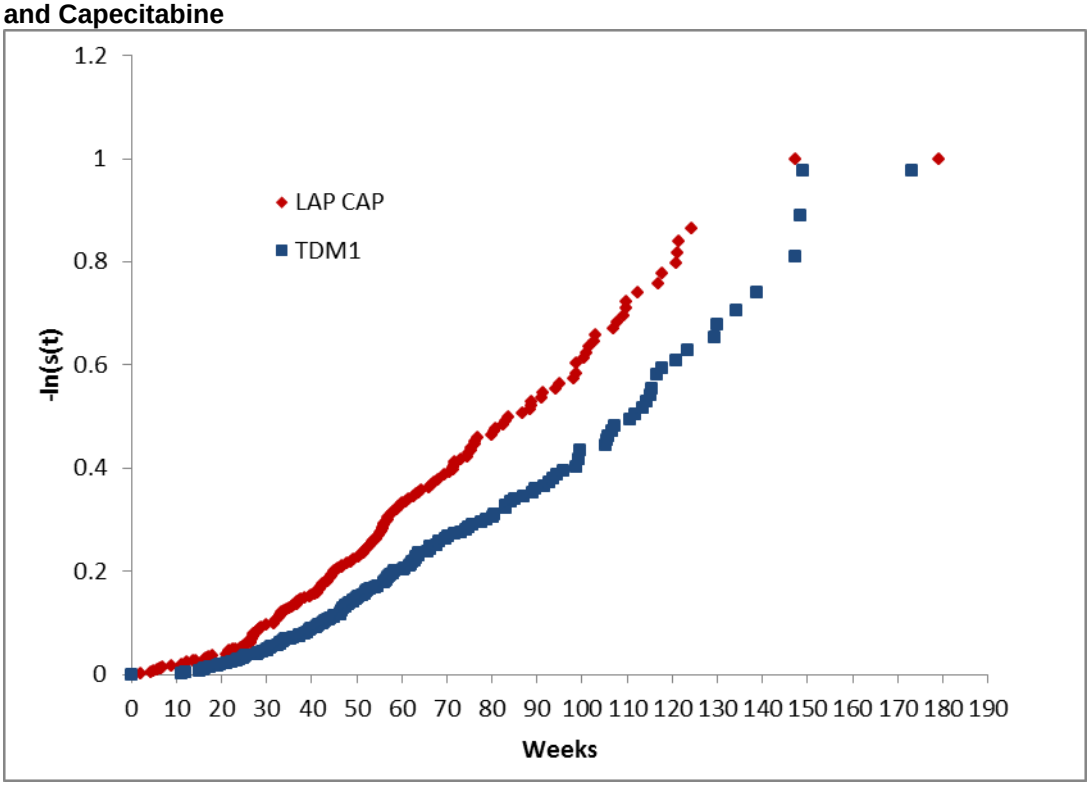


Figure 33: Cumulative Hazard Plot OS: Trastuzumab emtansine (T-DM1) and Lapatinib and Capecitabine appears to shows that up until approximately 29 weeks the hazards in both arms are fairly similar at which point there is a clear divergence with the lapatinib and capecitabine arm associated with a higher hazard than the trastuzumab emtansine arm. At approximately 95 weeks in the lapatinib and capecitabine arm and 96 weeks in the tratuzumab emtansine arm, the hazards in both arms increase again, thereafter visually increasing at approximately the same rate.

As with PFS, there may be some biological rationale as to why the true hazard in each arm might be seen only after 29 weeks. Similarly, it is possible that the treatment effect is no longer present after around 95 weeks but equally this could simply be a function of the low numbers at risk in each arm from this time point (135 or ~27% in the trastuzumab emtansine arm versus 112 or ~23% in the lapatinib and capecitabine arm). Therefore each curve could be segmented into two or three pieces and fitted accordingly. This approach is explored as a sensitivity analysis.

Table 27 below shows the BIC and AIC estimates for goodness of fit for OS. Both the log logistic and the gamma provide good statistical fits and are both considered below for visual inspection.

Table 27: BIC and AIC estimates for OS

MODELTYPE	BIC	AIC	BESTFIT
LogLogistic	1543.23	1528.54	LLOGISTIC
Gamma	1549.75	1530.15	
LogNormal	1546.89	1532.19	
Weibull	1552.70	1538.00	
Exponential	1634.68	1624.88	

Figure 34: Trastuzumab emtansine and lapatinib and capecitabine OS KM and log logistic distribution

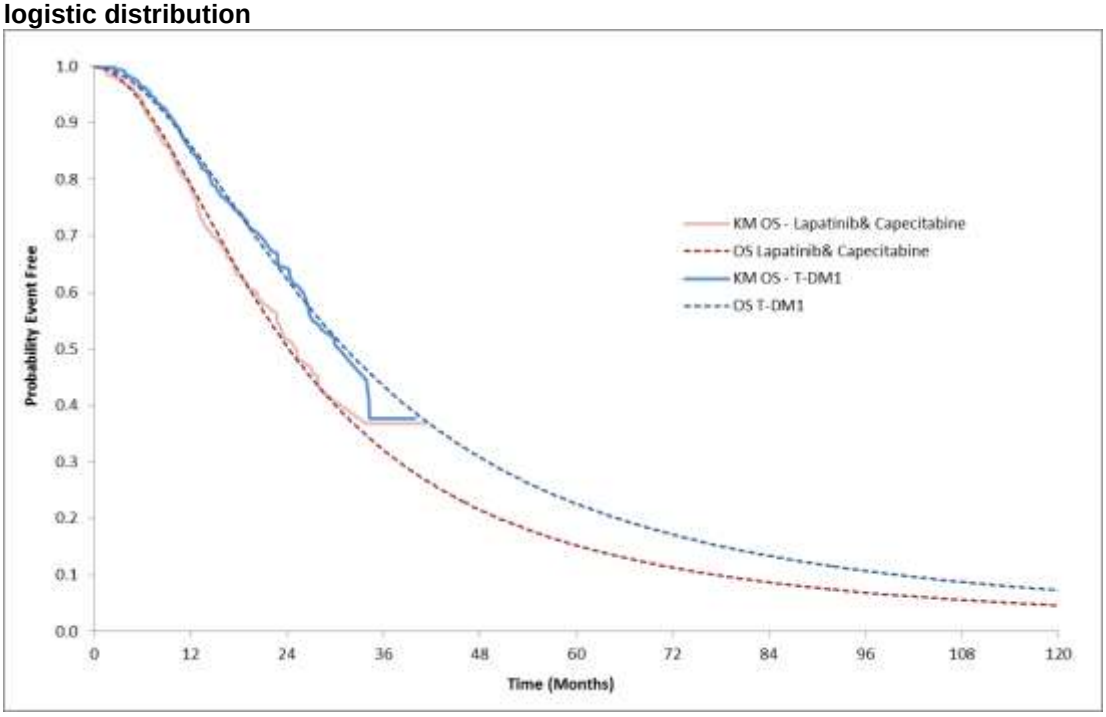
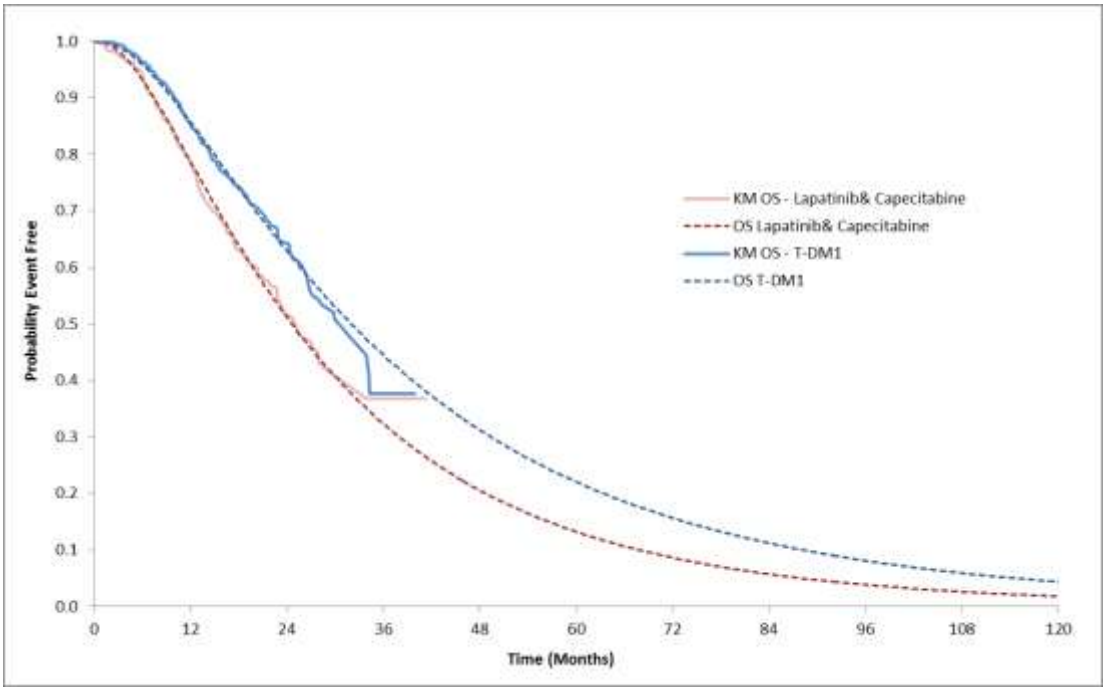


Figure 35: Trastuzumab emtansine and lapatinib and capecitabine OS KM and gamma distribution



Visually both distributions provide a good fit to each arm however the gamma distribution is preferred for a number of reasons.

First, the log logistic distribution results in a thicker tail for both arms versus the gamma distribution (approximately twice the overall survival rate at 10 years in each arm; 7.4% for trastuzumab emtansine and 4.7% for lapatinib and capecitabine with a log logistic distribution versus 4.4% for trastuzumab emtansine and 1.8% for lapatinib and capecitabine with a gamma distribution). Given that the EMILIA trial population are metastatic patients, 90% of whom are on second or third line treatments, overall survival at 10 years is likely to be extremely low (see third point below) and therefore a gamma distribution is considered more appropriate.

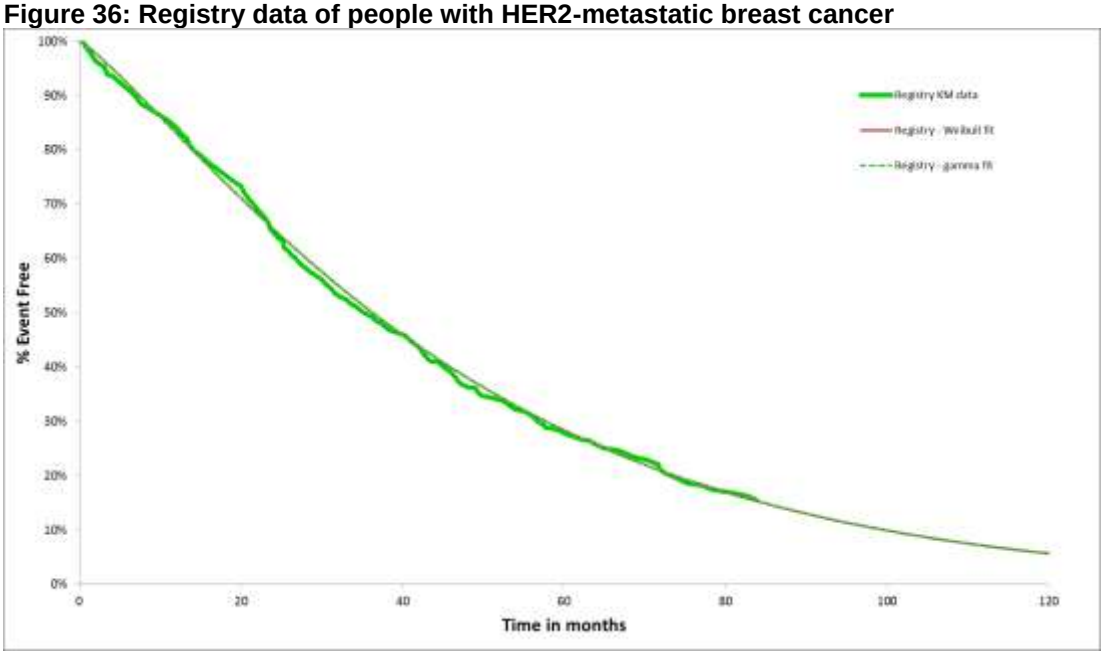
Second, the log logistic distribution underestimates the median OS versus the KM data in the lapatinib and capecitabine arm (24 months) whilst overestimates it in the trastuzumab emtansine arm (32 months). The gamma distribution however estimates the median OS for the lapatinib and capecitabine arm at 25 months (almost exactly equal to the KM data) and 32 months for the trastuzumab emtansine arm. Whilst still an overestimate for the

trastuzumab emtansine arm, not only is the overall gain more in line with KM estimates (7 months instead of 8 months versus 5.8 months), but it is also more plausible that the medians in each arm as calculated from the KM data would either remain the same or increase when imputed at a later date rather than decrease, due to the increased follow-up time of more patients and hence not having so few patients at risk at the end of each curve at the time the median is reached (censoring prior to the median being reached in each arm was approximately 50% in the lapatinib and capecitabine arm and 64% in the trastuzumab emtansine arm). This is especially the case for the trastuzumab emtansine arm which is less mature and so plausible that the median might increase at a later data cut.

Third, the gamma distribution appears to provide the most plausible external validity. The Munich registry is a database recording the survival 523 people diagnosed with HER2-positive metastatic breast cancer between 2002 and 2009 in Munich, Germany (Tumorregister-Muenchen, 2012). It is important to note that the registry records data from the first point of diagnosis for a metastatic patient and therefore overall survival is imputed with the inclusion of the patient's first line treatment and progression before moving onto subsequent treatments. The EMILIA trial however contains approximately 36% patients who are on second line treatment and 52% who are third line treatment. One would therefore expect the overall survival recorded and extrapolated from the Munich registry to be greater than that extrapolated from the EMILIA trial, although by what magnitude is hard to quantify. However given that the Munich registry contains similar types of patients to the EMILIA trial, only at an earlier stage of diagnosis, one might expect the shapes of the OS curves from EMILIA and the Munich registry to be fairly similar, especially after the period a first line patient is no longer in PFS and begins second line treatment. This would be from at least approximately 12 months as measured in the control arm of the CLEOPATRA trial (Herceptin plus docetaxel; this would have been the standard of care for the majority of patients in this registry since 2005), but may be even longer if a patient does not begin their second line treatment immediately after progressing.

The KM data from the Munich registry is presented in
Figure 36 below. Whilst this data is not a direct proxy for an EMILIA study with a longer follow-up period, as explained above the shape of this data may be useful to inform projection. In order to assess the shape of the registry data a range of functions were fitted and assessed. Both the Weibull and gamma distributions provide a strong fit to the data as shown in
Figure 36.

Figure 36: Registry data of people with HER2-metastatic breast cancer



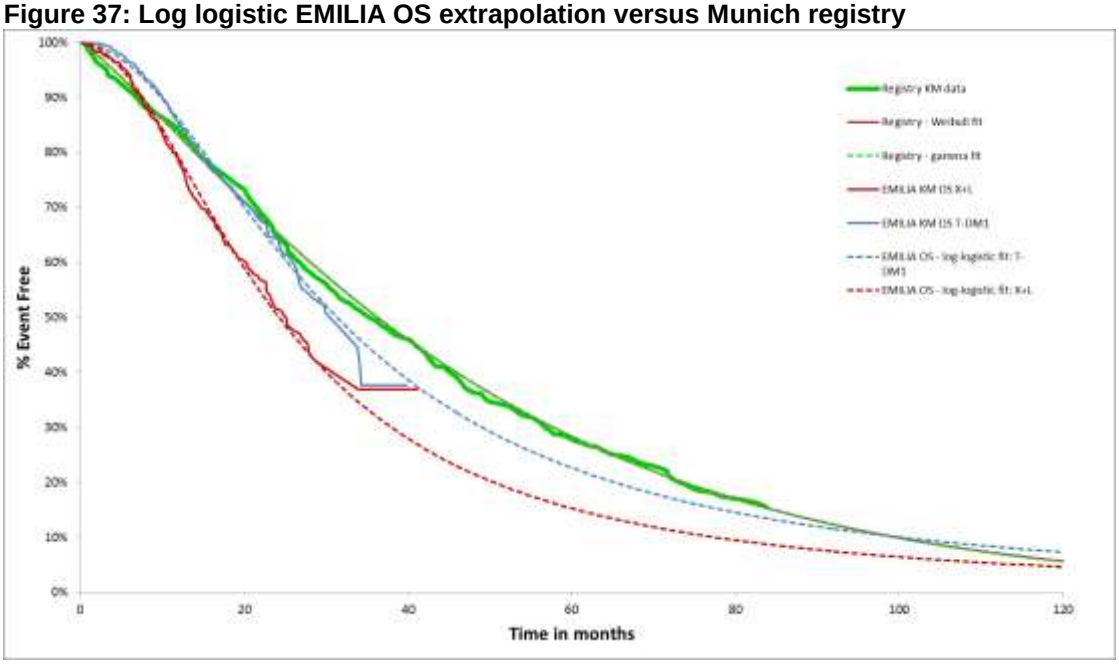
In

Figure 37,

Figure 38 and

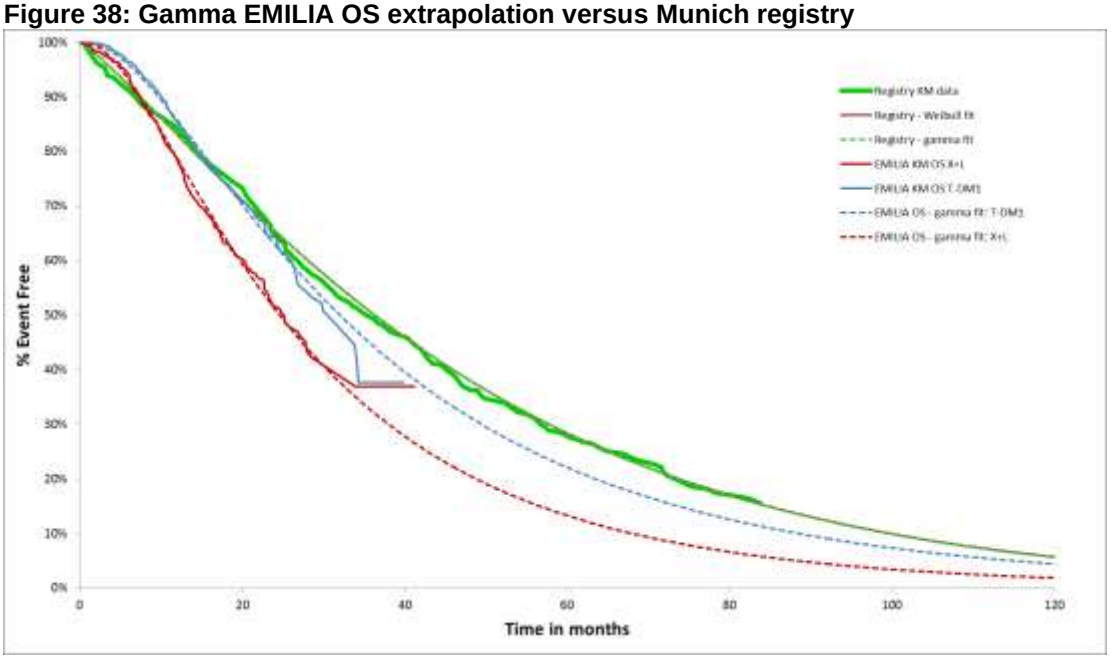
Figure 39 we overlay the log logistic, gamma and Weibull distributions respectively (as fitted to the EMILIA trial KM data for each arm) on top of the Munich data to test the external validity of each distribution, particularly after around 12 months.

Figure 37: Log logistic EMILIA OS extrapolation versus Munich registry



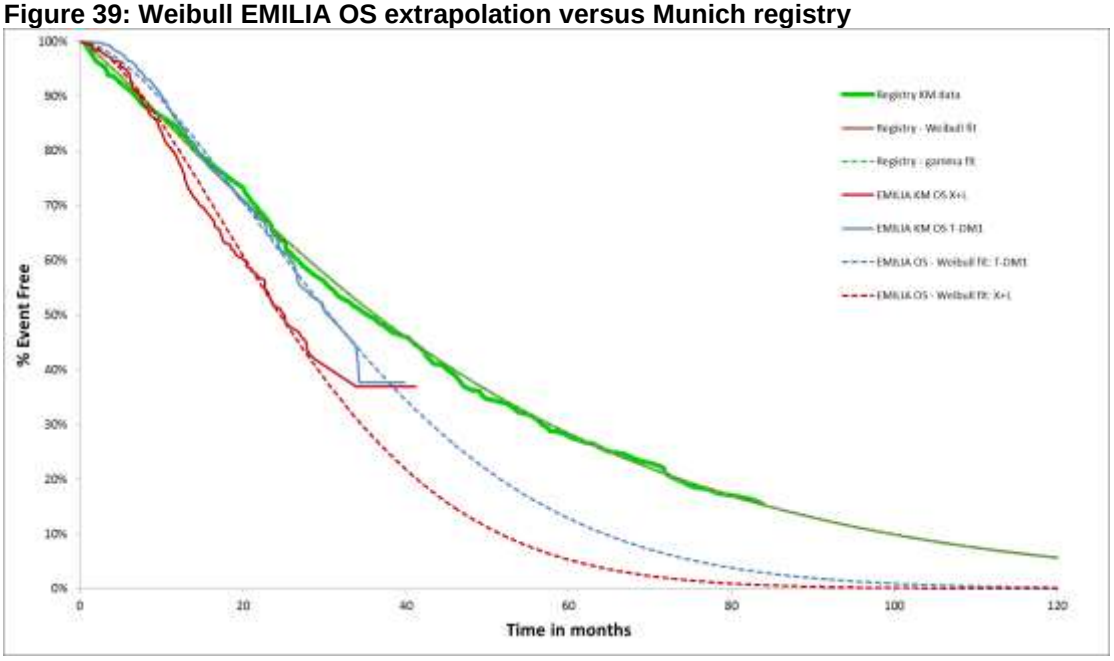
The log logistic distribution does not provide the most convincing fit to the data with respect to of the shapes of the curves, when compared to the Munich registry and further it leads to implausible results. The first part of both extrapolated curves from EMILIA predict OS greater than that from the Munich registry and whilst the middle parts result in overall survival less than from the Munich registry (as one would expect), the overall shape is not similar after around 12 months (which one might expect given that both sets of patients are HER2-positive patients with the same prognosis) and this leads to overall survival at ten years being greater for trastuzumab emtansine (7.4%) as compared to the Munich registry (5.6%) and only slightly less (4.7%) for lapatinib and capecitabine; a highly implausible outcome given the majority of EMILIA patients have already had one or more lines of therapy.

Figure 38: Gamma EMILIA OS extrapolation versus Munich registry



A gamma distribution for the EMILIA OS data provides a much stronger visual fit to the Munich data in terms of its shape after 12 months. Whilst the first parts of the EMILIA curves again predict greater OS than from the Munich registry, after this initial increment, both curves predict OS less than the Munich registry with a not dissimilar shape. At ten years overall survival in the trastuzumab emtansine arm is 4.4% and 1.8% in the lapatinib and capecitabine arm; far more plausible long term outcomes given the previous lines of treatment the majority of EMILIA patients have had.

Figure 39: Weibull EMILIA OS extrapolation versus Munich registry



Finally, we compare the Weibull distribution for the EMILIA curves against the Munich registry. Again, the shape of the curves is not convincing and further both curves drop off dramatically leaving nobody alive at ten years. Moreover the internal validity of the Weibull for the lapatinib and capecitabine arm seems questionable as it appears to overestimate a large portion of the curve (from 7 to 22 months). However a sensitivity analysis is conducted fitting a Weibull distribution to both arms.

Overall the gamma distribution appears to be the most plausible fit for OS data from the EMILIA trial fitting the lapatinib and capecitabine arm relatively well throughout and the trastuzumab emtansine arm well until approximately 26 months when it starts to overestimate versus the KM data. However this is likely due to the low numbers at risk at this point (85 or ~17% of the starting population).In order to explore alternative scenarios a sensitivity analysis was conducted using the KM data for as long as possible and a gamma distribution for the tail of the curves.

7.3.3 Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.

The hazards estimated using data from EMILIA were converted into weekly probabilities prior to inclusion in the model, as described in Section 7.3.1.

For comparisons of trastuzumab emtansine versus the four treatments that were not part of the EMILIA trial but in NICE's scope (trastuzumab and capecitabine, capecitabine, trastuzumab and vinorelbine, vinorelibine), the results of the base case MTC (Bayesian methodology with the network including the CEREBEL and Martin trials) in section 6.7 were used. Given that trastuzumab and vinorelbine and vinorelibine monotherapy were not part of the network, the same HRs versus trastuzumab emtansine, as trastuzumab and capecitabine and capecitabine monotherapy respectively, were assumed. An explanation of this assumption is provided in more detail in section 7.3.9.

The derived HRs from the MTC for both PFS and OS for each comparator (see Table 28) were then applied in the model using the trastuzumab emtansine curve as the baseline. Therefore in the base case, for PFS, the trastuzumab emtansine KM curve with log-normal extrapolation was used as the base curve, and for OS, the gamma function extrapolation for all of the trastuzumab emtansine KM OS data was used as the base curve. From these estimates of the PFS and OS relative efficacy for each of the four comparators were calculated.

7.3.4 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

Data from the EMILIA trial appears to show that the hazards for overall survival may increase with time (see section 7.3.1 above).

7.3.5 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

No, progression free survival and overall survival were modelled individually and no relationship between the two was specified.

7.3.6 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[8]:

- **the criteria for selecting the experts**
- **the number of experts approached**

[8] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

- **the number of experts who participated**
- **declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought**
- **the background information provided and its consistency with the totality of the evidence provided in the submission**
- **the method used to collect the opinions**
- **the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)**
- **the questions asked**
- **whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).**

Clinical specialists were consulted in an advisory board in the development of the submission and economic model. The clinical experts gave their opinion on the validity of the extrapolation conducted and the resource use and costing assumptions applied in the model based on their specialist knowledge of the subject.

Summary of selected values

7.3.7 Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table, as suggested below.

Table 28 Summary of variables applied in the economic model

Variable	Value	Reference to section in submission
Transition Probabilities		
Progression-free survival distribution in T-DM1 arm	KM data up to 72 weeks and log-normal distribution thereafter	7.3.1
Progression-free survival distribution in Lap+Cap arm	KM data up to 72 weeks and log-normal distribution thereafter	7.3.1
Progression-free survival distribution in Tra+Cap arm	HR = 1.47 (1/0.68) vs T-DM1 arm	6.7.8
Progression-free survival distribution in Cap arm	HR = 2.56 (1/0.39) vs T-DM1 arm	6.7.8
Progression-free survival distribution	HR = 1.47 (1/0.68) vs T-	6.7.8

in Tra+Vin arm	DM1 arm	
Progression-free survival distribution in Vin arm	HR = 2.56 (1/0.39) vs T-DM1 arm	6.7.8
Overall survival distribution in T-DM1 arm	Gamma distribution	7.3.1
Overall survival distribution in Lap+Cap arm	Gamma distribution	7.3.1
Overall survival distribution in Tra+Cap arm	HR = 1.47 (1/0.68) vs T-DM1 arm	6.7.8
Overall survival distribution in Cap arm	HR = 1.81 (1/0.55) vs T-DM1 arm	6.7.8
Overall survival distribution in Tra+Vin arm	HR = 1.47 (1/0.68) vs T-DM1 arm	6.7.8
Overall survival distribution in Vin arm	HR = 1.81 (1/0.55) vs T-DM1 arm	6.7.8
Utility Values		
Progression-free survival in T-DM1 arm	0.78	7.4.9
Progression-free survival in Lap+Cap arm	0.74	7.4.9
Progression-free survival in Tra+Cap arm	0.73	7.4.9
Progression-free survival in Cap arm	0.72	7.4.9
Progression-free survival in Tra+Vin arm	0.73	7.4.9
Progression-free survival in Vin arm	0.72	7.4.9
Progressed disease	0.50	7.4.9
Costs (£)		
Supportive care costs PFS (per week)	£43.45	7.4.21
Supportive care costs PD inc. post-progression treatments (per week)	£63.08	7.4.21
End of life costs (applied last week of life)	£3916.00	7.4.21
Administration costs (£)		
All cycles if at least one IV treatment present	£343	7.4.21
All cycles if no IV treatment present (i.e. only oral treatment)	£136	7.4.21
Pharmacy costs per dispensing for IV treatment (15 minutes)	£17.29	7.4.21
Pharmacy costs per dispensing for IV treatment (5 minutes)	£5.76	7.4.21
Adverse event costs (£)		
Diarrhoea	£797	7.4.22
Fatigue	£797	7.4.22
Thrombocytopenia	£0	7.4.22
Hand foot syndrome	£0	7.4.22
Aspertarte aminotransferase increased	£0	7.4.22
Drug costs(£)		
Trastuzumab Emtansine (T-DM1)	£1,641.01 (100 mg vial) £2.625.62 (160 mg vial)	7.4.20
Lapatinib	£965.16 (250mg * 84 tab packet)	7.4.20
Trastuzumab	£407.40 (150 mg vial)	7.4.20
Capecitabine	£40.02 (150mg * 60 tab packet) £265.55 (500mg * 120 tab packet)	7.4.20

Vinorelbine	£100.76 per 10mg/ml vial Pack size 10 £264.76 per 50mg/5ml Pack size 10	7.4.20
Discount rate (%)		
Costs	3.5	NICE Methods Guide
QALYs	3.5	NICE Methods Guide
Patient characteristics		
Age (years)	52.7	EMILIA
Weight (kg)	70.11	EMILIA
Body surface area (m^2)	1.74	EMILIA

7.3.8 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer term difference in effectiveness between the intervention and its comparator? For the extrapolation of clinical outcomes, please present graphs of any curve fittings to Kaplan–Meier plots.

See section 7.3.1.

7.3.9 Provide a list of all assumptions in the de novo economic model and a justification for each assumption.

Assumption 1: Capecitabine progression free survival curve and overall survival curves are assumed to be a reasonable proxy for the vinorelbine comparator. This is based on the fact NICE CG 81 recommends the alternate use of either vinorelbine or capecitabine second line and third line, implying they are largely interchangeable. This assumption was supported by clinicians at an independent advisory board.

Assumption 2: Trastuzumab and capecitabine progression free survival curve and overall survival curves are assumed to be a reasonable proxy for the trastuzumab and vinorelbine comparator. This is based on the fact that vinorelbine is a reasonable proxy for capecitabine as detailed above and further supported by All Wales Medicines Strategy Group Final Appraisal Recommendation Advice No: 1713 – July 2013, which recommends the use of lapatinib in combination with capecitabine for patients with advanced or

metastatic disease with progression following prior therapy, which must have included anthracyclines and taxanes and therapy with trastuzumab in the metastatic setting as an alternative to treatment with trastuzumab and capecitabine or trastuzumab and vinorelbine in patients in whom clinicians consider this clinically appropriate. This suggests that trastuzumab and capecitabine and trastuzumab and vinorelbine are largely interchangeable,

Assumption 3: Only adverse events with over 2% incidence in either treatment arm of EMILIA were assumed to have resource use and quality of life impact, due to the increased likelihood of the adverse event occurring via a true effect as opposed to random chance.

Assumption 4: Trastuzumab and capecitabine, and capecitabine monotherapy progression free quality of life (utility value) are assumed to be reasonable proxies for the trastuzumab and vinorelbine, and vinorelbine monotherapy progression free quality of life, respectively.

Assumption 5: Where two treatments are administered concomitantly and one is oral and one is IV, only the (more expensive) NHS reference cost code for the IV treatment is applied.

7.4 Measurement and valuation of health effects

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.4.

The HRQL impact of adverse events should still be explored regardless of whether they are included in cost-effectiveness analysis.

All parameters used to estimate cost effectiveness should be presented clearly in tabular form and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

Patient experience

7.4.1 Please outline the aspects of the condition that most affect patients' quality of life.

Studies have found that cancer survivors whose disease recurs have a worse quality of life in most indices than those who remain disease-free (Helgeson & Tomich, 2005) and the most important distress factor among people with cancer has been found to be the fear of disease progression (Herschbach, Keller, Knight, Huber, Enrich & Marten-Mittag, 2004).

7.4.2 Please describe how a patient's HRQL is likely to change over the course of the condition.

Health-related quality of life is expected to decrease with each line of treatment failure due to disease progression.

HRQL data derived from clinical trials

7.4.3 If HRQL data were collected in the clinical trials identified in section 6 (Clinical evidence), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.

- **Method of elicitation.**
- **Method of valuation.**
- **Point when measurements were made.**
- **Consistency with reference case.**
- **Appropriateness for cost-effectiveness analysis.**
- **Results with confidence intervals.**

A disease specific measurement (FACT-B) collected changes in quality of life in the EMILIA study. The NICE reference case specifies use of a generic quality of life measurement, preferably EQ-5D, to capture changes in quality of life.

Mapping

7.4.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

- **Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.**
- **Details of the methodology used.**
- **Details of validation of the mapping technique.**

As no mapping function exists for FACT-B to EQ-5D, quality of life data collected in the EMILIA trial could not be used in the economic model.

HRQL studies

7.4.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in section 10.12, appendix 12.

Embase (EMYY), Embase Alert (EMBA), Medline (MEYY)[9] and NHS EED were searched for studies assessing utility values for different health states in metastatic breast cancer. The searches were conducted on the 3rd and 4th October 2013 (date differing depending on the database) and was designed to evaluate all potentially relevant utility scores that have been used in metastatic breast cancer health technology evaluations. The complete search strategy is provided in section **Error! Reference source not found.**. The methodology used was based upon on the methods outlined in the CRD"s "Guidance for undertaking reviews in health care" (2008).

As a similar search was conducted for a recent NICE appraisal of pertuzumab in combination with trastuzumab and docetaxel for the treatment of HER2 positive metastatic or locally recurrent unresectable breast cancer (ID523) the search conducted was not completely de novo but an update of that search[10] designed to identify any newly published utility values (with the search

[9] Note Medline-In-Process is now nested within Medline in the new ProQuest.
[10] No relevant studies were identified in this previous search.

therefore limited from 31st October 2012 – the date the utility studies search was conducted for ID523).

If a record was deemed potentially relevant it was retrieved in full and re-assessed against the inclusion/exclusion criteria.

Table 29: Inclusion and exclusion criteria for utility studies

Inclusion Criteria	Exclusion Criteria
Metastatic or advanced breast cancer Health related quality of life QALY or quality adjusted life year SF-36 OR SF-12 OR EQ-5D OR EQ-5D-5L OR EUROQOL Utilities Time Trade Off or Standard Gamble	Review of studies already included Not quality of life studies Utility value not elicited by the general public Not in metastatic/advanced setting No useful health-related quality of life/Utility values for economic modelling

In total 38 records were identified across the 4 databases. Of these, 37 were excluded by the independent reviewers and one was deemed potentially relevant and read in full. This was excluded after being assessed against the exclusion criteria.

Figure 40: PRISMA flow for utility studies identified through database searches

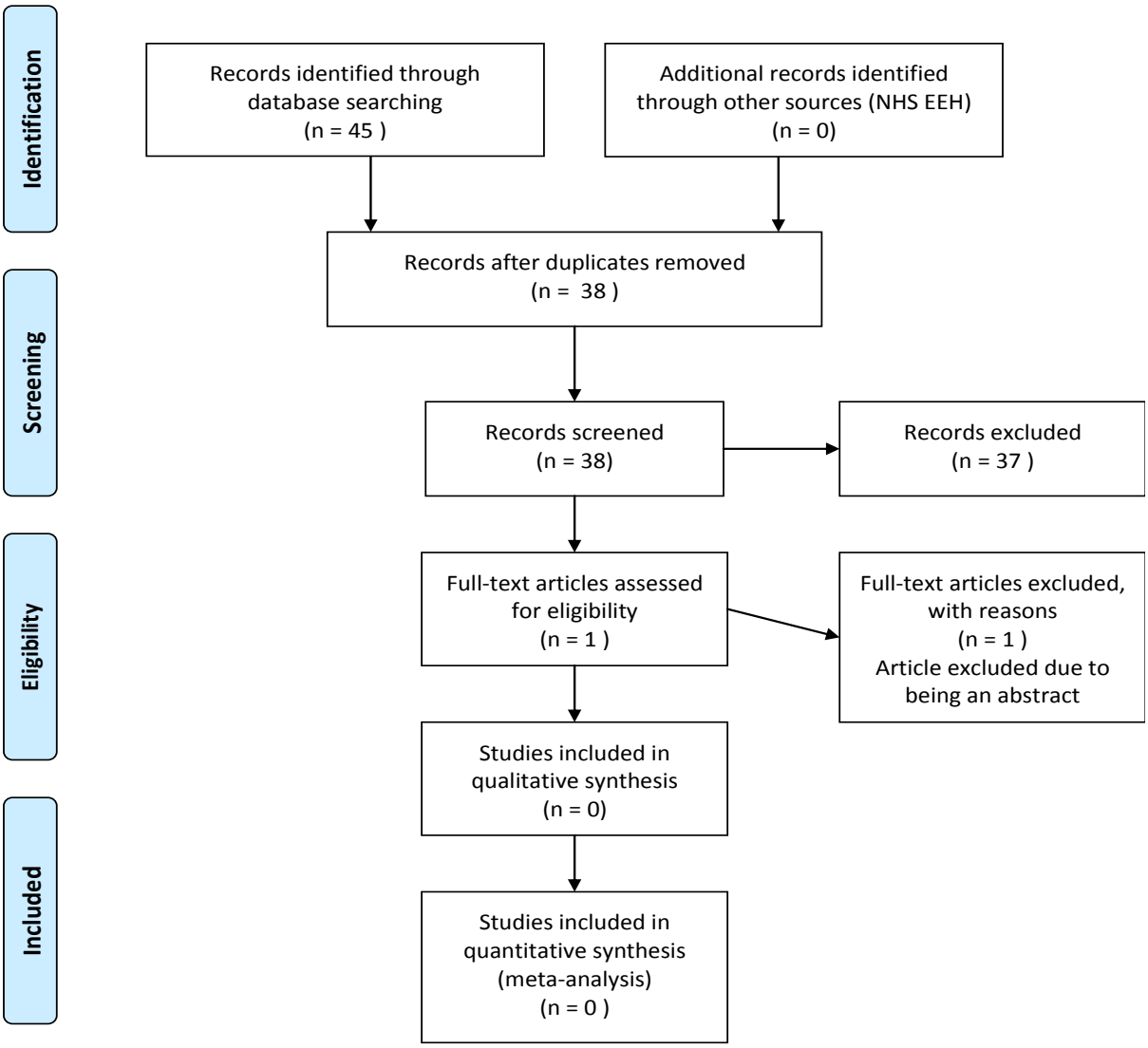


Figure 40 above illustrates the literature search in terms of identified and included/excluded utility studies.

7.4.6 Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

- Population in which health effects were measured.
- Information on recruitment.
- Interventions and comparators.
- Sample size.

- Response rates.
- Description of health states.
- Adverse events.
- Appropriateness of health states given condition and treatment pathway.
- Method of elicitation.
- Method of valuation.
- Mapping.
- Uncertainty around values.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.
- Appropriateness of the study for cost-effectiveness analysis.

Not applicable. No were studies included in appraisal.

7.4.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

No utility values were taken from EMILIA (directly via EQ-5D or via mapping of FACT-B).

Adverse events

7.4.8 Please describe how adverse events have an impact on HRQL.

Trastuzumab emtansine has an extremely manageable safety profile with very few life-threatening adverse events. Grade 1 and 2 adverse events were not included in the model as these were not associated with significant disutilities according to clinical specialists' opinion. The disutilities associated with treatment-related Grade 3, 4 and 5 adverse events were included in the model. Adverse events were included based on incidence in the EMILIA trial. The adverse events that have a significant quality of life impact are: diarrhoea and fatigue. It is assumed that the type and frequency of adverse events observed in lapatinib and capecitabine arm of the EMILIA trial can be applied

to treatment with capecitabine monotherapy, trastuzumab and vinorelbine therapy and vinorelbine monotherapy.

Quality-of-life data used in cost-effectiveness analysis

7.4.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 7.4.3 to 7.4.8. Justify the choice of utility values, giving consideration to the reference case.

There is a dearth of relevant utility studies appropriate to this appraisal and conforming to the NICE recommended approach (UK data capturing population preferences using EQ-5D or either time-trade off or standard gamble methodology).

The utility values used in the economic model have been estimated using the statistical model detailed in a study by Lloyd (Lloyd, 2006). The study considered health states and a limited set of treatment-related adverse events specific to metastatic breast cancer and developed a mixed model using data collected from a sample of 100 UK residents broadly similar in age and sex to the general population. The Lloyd model includes age and treatment response as model variables and features several factors including the rate of response to chemotherapy and the exposure to a set of important adverse events. It has been used in previous NICE Technology Appraisals and is the best source currently available (TA257, TA263).

It is important to note that the relevant age used in the mixed model is not that of the patient but of the study participant. An average age of respondents to the original multi-vessel disease study of 47 years is used in arriving at utility parameter values. This is to ensure consistency with the UK EQ-5D standard value scheme and is the mean age of population taking part in the original Kind et al study.

Utilities were calculated from the results of the mixed model analysis presented by Lloyd et al. The central estimates of the parameter coefficients (and their standard errors) are listed in Table 30.

Table 30: Results of the mixed model analysis

Parameter	Parameter estimate	Standard error
intercept	0.008871	0.3196
age	0.0239	0.006946
treatment response	0.4063	0.05521
disease progression	-1.1477	0.1031
febrile neutropenia	-0.6603	0.08501
diarrhoea and vomiting	-0.4629	0.09929
hand-foot syndrome	-0.5184	0.09929
stomatitis	-0.6634	0.09929
fatigue	-0.5142	0.09929
hair loss	-0.5086	0.09929

For people who are in the progression free survival state it is necessary to calculate a treatment-specific weighted average of the model values for stable disease and treatment response, based on the reported overall response rate (43.6% for trastuzumab emtansine, 30.8% for lapatinib and capecitabine) EMILIA trial. The response rates for trastuzumab and capecitabine and capecitabine monotherapy are estimated indirectly versus trastuzumab emtansine through using the response rates from the EGF100151 and GBG26 trials respectively. This results in an overall response rate of 32.1% for trastuzumab and capecitabine and 18.1% for capecitabine monotherapy. For people in the progressed health state, a common health state utility value of 0.53 from using parameters from the Lloyd study (age and disease progression) was estimated for use in all treatment arms.

All adverse events affecting more than 2% of participants in either treatment arm and which were deemed to affect quality of life according to clinical opinion, were used to calculate utility values. No disutility decrement was applied to increased level of aspartate amiontransferase as this is a lab abnormality and has no direct impact on quality of life. The utility decrements for diarrohea, fatigue and hand and foot syndrome (Palmar-Plantar Erythrodysaesthesia Syndrome) have been applied based on the outputs of the Lloyd study (Lloyd 2006). Thrombocytopenia can have varying effects on quality of life depending on its severity (mild to immune). The type of effects on quality of life from thrombocytopenia experienced by patients in the EMILIA trial were issues such as nose bleeds and bleeding gums. Although not

particularly pleasant, these issues were not associated with any meaningful deterioration in quality of life, especially given that they were managed by dose reduction and therefore endured only for a relatively short period of time. As such no utility decrement has been applied to thrombocytopenia in the model.

The utility values based on the Lloyd mixed model when adjusted for response rate and age are listed in Table 31.

Table 31 Summary of utility values for cost-effectiveness analysis

State	Utility value	Reference in submission	Justification
Progression-free survival Trastuzumab Emtansine	0.78	7.4.9	Utility values determined to be appropriate for use in metastatic breast cancer by Fleeman et al 2010 in NICE TA257.
Progression-free survival Lapatinib and Capecitabine	0.74		
Progression-free survival Trastuzumab and Capecitabine	0.73		
Progression-free survival Capecitabine	0.72		
Progression-free survival Trastuzumab and Vinorelbine	0.73		
Progression-free survival Vinorelbine	0.72		
Progressed	0.50		

It is important to note that the progressive state reflected patient's experience of disease and chemotherapy at that time in the UK when the study was conducted. This may not be representative of the patient population today who are able to receive more rounds of treatment which are proven to be more effective and can increase overall rate of survival considerably. Studies have now shown that many patients in progression state could have an overall survival rate of approximately two years based on the effectiveness of

chemotherapy regimens (Verma, 2012; Cameron, 2010). In 2005, studies demonstrated that although there were effective treatments available, median time to progression and overall survival rates were much lower (O'Shaughnessy, 2005). In light of new and improved treatments, it is important to note that the progressive state in the Lloyd study was intended to describe an average patient who was not receiving active treatment and was in palliative care. A progressive disease state which would capture a patient in the current treatment setting and perhaps on second-line treatment would show a patient with better functioning and better survival than the one in Lloyd study.

Further, although the HRQoL literature search in section 7.4.5 identified no studies, we are cognisant of the fact that the TH3RESA study contains EQ-5D data, but that this data is not yet in the public domain. PFS utility from TH3RESA was 0.71 for trastuzumab emtansine and 0.69 for the physician's choice (RXUKDONF00339, December 2013). The results support the argument of applying distinct utilities to the trastuzumab emtansine arm versus comparators due its unique adverse event and tolerability profile. However the utilities were not deemed appropriate to use in the economic model due to the population of TH3RESA being third line or later (67.1% of patients had received 4 or more prior lines of therapy for advanced breast cancer i.e. on fifth line treatment) and therefore being likely to have a worse quality of life than the EMILIA trial population, where the majority of patients were on second or third line treatments.

As a result of the above two points, the impact of varying utilities is explored as a sensitivity analysis.

7.4.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[11]:

[11] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Clinical specialists were consulted upon in the development of this submission and economic model. The specialists indicated the utility values are a conservative estimate of the quality of life with people with the disease, and that they would expect to see a higher quality of life in the progressed disease health state. The clinical specialists stated the calculation of utility values include all adverse events that have a significant impact on quality of life of people with the condition. The impact of varying utility values on the ICER has been explored in the sensitivity analysis.

7.4.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

Patient experience is described in section 7.4.1.

7.4.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

All relevant health effects identified in the literature have been taken into account.

7.4.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

The baseline quality of life has been assumed to be different in the two treatment arms of the economic evaluation (see 7.4.9 for justification). People in the progression-free survival health state are characterised as either responders, who have a slightly improved quality of life, or have stable disease. All people in the progressed health state are characterised as being progressed.

7.4.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

HRQL is assumed to be constant over time within each health state in the model.

7.4.15 Have the values in sections 7.4.3 to 7.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

The methodology used to analyse the published coefficients is described in section 7.4.8.

Resource identification, measurement and valuation

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.5.

All parameters used to estimate cost effectiveness should be presented clearly in a table and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

NHS costs

7.4.16 Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2.

The process for the clinical management of advanced breast cancer is recommended in NICE clinical guideline CG81 (2009). CG81 has formed the basis of the costing assumptions for disease management in the model.

7.4.17 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

NHS reference costs are the most appropriate source of cost data for this appraisal.

Resource identification, measurement and valuation studies

7.4.18 Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in section 10.13, appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:

- **country of study**
- **date of study**
- **applicability to UK clinical practice**
- **cost valuations used in study**
- **costs for use in economic analysis**
- **technology costs.**

Embase (EMYY), Embase Alert (EMBA), Medline (MEYY)[12] and NHS EED were searched for studies regarding resource use and costs related to metastatic breast cancer. The complete search strategy is provided in section **Error! Reference source not found.**. The methodology used was based upon on the methods outlined in the CRD‟s "Guidance for undertaking reviews in health care‟ (2008).

Similarly to the search of utility studies, a comparable search for resource utilisation studies was conducted for a recent NICE of pertuzumab in combination with trastuzumab and docetaxel for the treatment of HER2 positive metastatic or locally recurrent unresectable breast cancer (ID523). The search conducted in this submission was therefore not completely *de novo* but an update of the search in the STA designed to identify any newly published resource use data (with the search therefore limited from 15th March 2013 – the date the previous ID523 resource utilisation study search was conducted).

ProQuest was used to search EMYY, EMBA and MEYY and NHS EED was searched using The Centre for Reviews and Dissemination's website. All searches were undertaken on the 3rd October 2013. Titles and abstracts were assessed for relevance according to the pre-defined inclusion and exclusion criteria.

If a record was deemed potentially relevant it was retrieved in full and re-assessed against the inclusion/exclusion criteria are listed in Table 32.

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[12] Note Medline-In-Process is now nested within Medline in the new ProQuest.

Table 32: Inclusion and exclusion criteria for resource utilisation studies

Inclusion criteria	Exclusion criteria
Advanced or metastatic breast cancer Resource utilisation from a UK NHS Perspective	Early breast cancer Resource utilisation from a private/US setting and any other non-UK country. Costs derived from studies more than 5 years old.

In total 37 articles were identified across the four databases. Of these, all were excluded by the independent reviewers.

Figure 41: PRISMA flow for resource utilisation studies identified through database searches

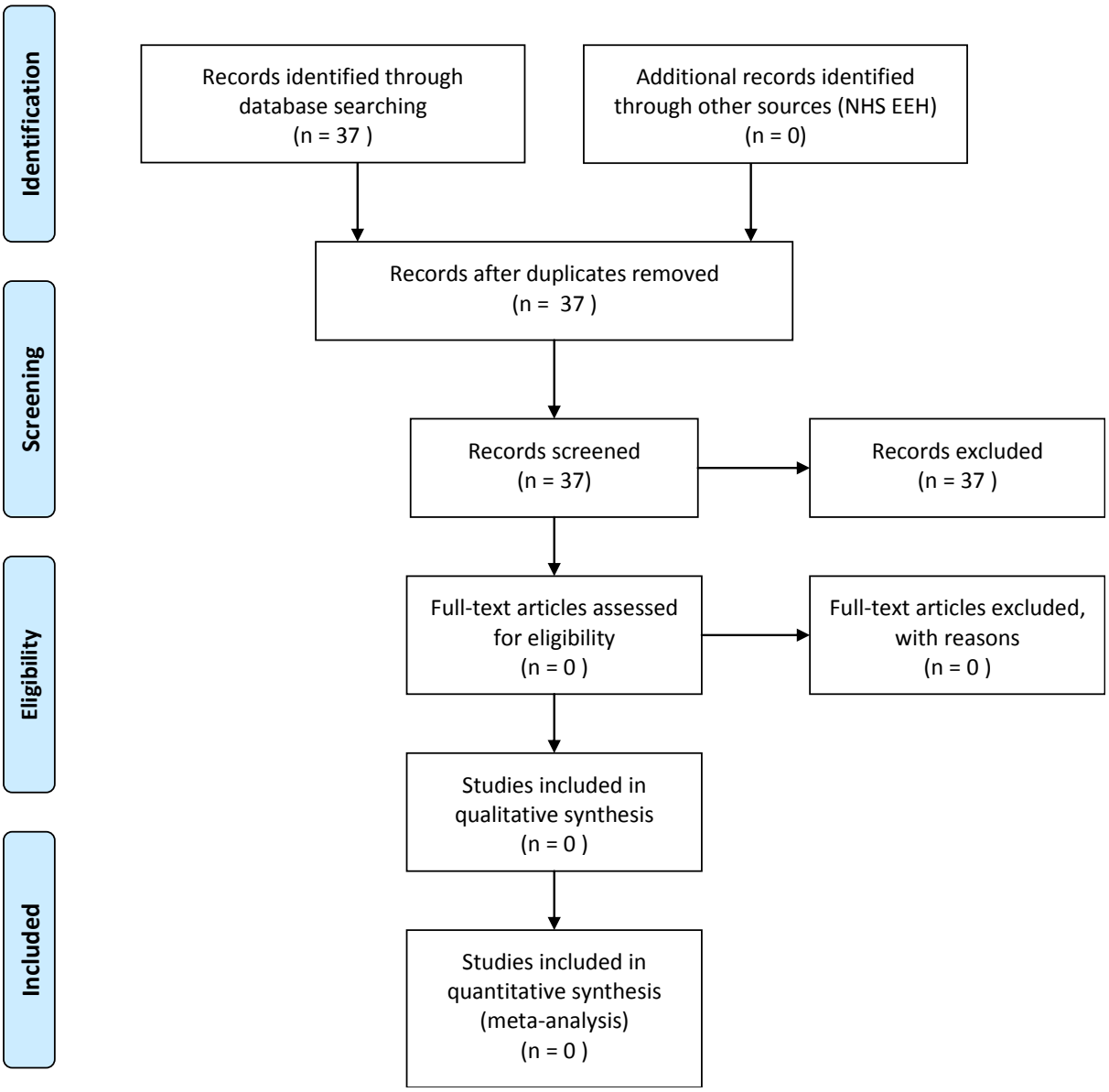


Figure 41 above illustrates the literature search in terms of identified and included/excluded studies.

7.4.19 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[13]:

- **the criteria for selecting the experts**
- **the number of experts approached**
- **the number of experts who participated**
- **declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought**
- **the background information provided and its consistency with the totality of the evidence provided in the submission**
- **the method used to collect the opinions**
- **the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)**
- **the questions asked**
- **whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).**

N/a.

Intervention and comparators' costs

7.4.20 Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, drugs costs should be cross-referenced to sections 1.10 and 1.11. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.

Table 33: Unit costs associated with the technology in the economic model

[13] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Items	Trastuzumab emtansine	Lapatinib	Capecitabine	Trastuzumab	Vinorelbine
Technology cost	£1641.01 per 100 mg vial £2625.62 per 160mg vial	£965.16 per 84 x 250mg tab packet	£40.02 per 60 x 150mg tab packet £266.55 per 120 x 500mg packet	£407.40 per 150mg vial	£100.76 per 10mg/ml vial Pack size 10 £264.76 per 50mg/5ml Pack size 10
Three week cost of drug (inc. wastage unless stated otherwise)	£4266.63	£1206.45	£223.24 (1000mg/kg) £285.20 (1250mg/kg)	£1629.60 (8mg/kg loading dose) £1222.20 (6mg/kg maintenance dose)	£69.17 (no wastage)
Administration cost	£343	£136	£136	£343	£343
Pharmacy cost	£17.29	£5.76	£5.76	£17.29	£17.29

All drugs in the model requiring dosing in relation to body weight or body surface area (BSA) are based on the distribution of body weight and body surface area of participants in the EMILIA trial. Based on the distribution of body weights in the EMILIA trial, the mean patient weight is 70.1kg, and mean BSA is 1.74m^2 (using the Dubois formula). For all drugs for which there are no generics or biosimilars available, an assumption of no vial sharing is made and therefore all calculations include drug wastage. The exception to this is vinorelbine which is available to the NHS in generic form and hence it is assumed vial sharing would be commonplace in its supply and usage, and the drug cost does not therefore account for any drug wastage.

Trastuzumab emtansine drug cost

Trastuzumab emtansine is administered by intravenous infusion once every 3 weeks at a dose of 3.6mg/kg. Trastuzumab emtansine can be purchased in a 100 mg vial for £1,641.01 and in a 160mg vial for £2,625.62. This equates to a cost of £4,266.63 per dose.

Lapatinib drug cost

Lapatinib is given orally, at a dose of 1250 mg (5 tablets) once daily on Days 1−21 of a 21 day cycle. Lapatinib can be purchased in an 84 tablet (250mg per tablet) for £965.16 (Joint Formulary Committee, 2012). This equates to a three weekly cost of £1206.45.

Capecitabine drug cost

Capecitabine can be purchased in tablet form in two pack sizes (Joint Formulary Committee 2012): 150 mg (60 tab pack) = £40.02 and 500 mg (120-tab pack) = £265.55. If used in combination with lapatinib, capecitabine is given orally at a dose of 1000mg/m^2 twice daily on days 1-14 of a 21 day cycle (as per the EMILIA trial). This equates to a three weekly cost of £223.24. If used in combination with trastuzumab or as a monotherapy 1250mg/m^2 twice daily on days 1-14 of a 21 day cycle. This equates to a three weekly cost of £285.20.

Trastuzumab drug cost

Trastuzumab is administered by intravenous infusion once every three weeks at a dose of 8 mg/kg for initial dose, followed by a 3 weekly maintenance dose of 6 mg/kg. Based on the mean weight of 70.1kg, the mean initial dose is 560.8 mg/kg, and maintenance dose is 420.6 mg/kg. Trastuzumab can be purchased in a powder for reconstruction of 150 mg vial for £407.40 (Joint Formulary Committee, 2012). The mean three weekly cost of treatment with trastuzumab including consideration of wastage and based on the distribution of patient weight is £1,629.60 for the initial dose and £1,222.20 for the maintenance dose.

Vinorelbine drug cost

Vinorelbine is a generic drug, and so acquisition costs of vinorelbine are obtained from the CMU eMIT (Commercial Medicines Unit: Electronic Market Information Tool, 2013). The lowest price per mg of vinorelbine obtained from CMU eMIT is £0.53 per mg (National Product Code – DHA221). Vinorelbine is administered intravenously as a weekly loading dose of 25 mg/m^2 body surface area for three weeks, followed by a weekly maintenance dose of 25 mg/m^2 body surface area. This equates to a three weekly cost of £69.17.

Administration and pharmacy cost

Trastuzumab emtansine and trastuzumab are administered by intravenous infusion in a hospital on the first day of each 21 day cycle and vinorelbine is administered by intravenous infusion on the first day of each weekly cycle. There is a cost associated with both the pharmacy preparation of the infusion and the administration of the technologies (typically within a hospital setting). The administration cost of the first cycle for each technology is based on NHS Reference costs 2012/13 (SB13Z): Deliver more Complex Parenteral Chemotherapy at First Attendance (£343). The administration cost of subsequent cycles is obtained from NHS Reference costs 2012/13 (SB15Z): Deliver subsequent elements of a chemotherapy cycle (£343).

The pharmacy time required for dispensing an intravenous drug is assumed to be 15 minutes (validated with clinicians at an advisory board). One hour of pharmacist time performing patient related activities (accounting for overheads, qualifications, and salary on costs) costs £69.18 (£67 inflated to 2013, PSSRU, 2012). The cost of dispensing of intravenous treatments in the economic model is estimated to be £17.29 (£69.18 x 15/60) per administration, based on 15 minutes of pharmacist preparation time.

Lapatinib and capecitabine are administered orally; lapatinib on every day of a 21 day cycle and capecitabine twice daily from day 1-14. There is a cost associated with both the pharmacy preparation of the oral drug and the administration of the technologies (typically within a hospital setting), on day 1 of each 21 day cycle. The administration cost of delivering an oral therapy is obtained from NHS Reference costs 2012/13 (SB11Z): Deliver exclusively oral chemotherapy (£136). The pharmacy time required for dispensing an oral drug is assumed to be 5 minutes (validated with clinicians at an advisory board). One hour of pharmacist time performing patient related activities (accounting for overheads, qualifications, and salary on costs) costs £69.18 (£67 inflated to 2013, PSSRU, 2012). The cost of dispensing of intravenous treatments in the economic model is estimated to be £5.76 (£69.18 x 5/60) per administration, based on 5 minutes of pharmacist preparation time.

Post-progression treatment costs

NICE CG 81 recommends the alternate use of either vinorelbine or capecitabine second line and third line, i.e. if vinorelbine was used second line then capecitabine should be used third line and vice-versa. Given that 52% are on third line treatment within EMILIA, these patients are assumed to have no further treatment once they progress. However for those patients who are on second line or first line treatment, their post-progression costs are captured within the model in line with CG81. For second line patients it is assumed that 50% would receive capecitabine third line and 50% would receive vinorelbine. For first line patients it is assumed that all would receive capecitabine and vinorelbine as second and third line treatments (in either order).

The model applies the cost of second and third line treatments to the progressed health state for 4.3 months (19 weeks). This is based on a study by Cameron et al (2008) in which people with metastatic breast cancer whose disease had progressed following treatment with trastuzumab were treated with capecitabine for an average 4.3 months. Given the paucity of evidence available to test the effectiveness of third-line therapy, both capecitabine and vinorelbine monotherapies were assumed to work as well as for second-line therapy, in the third line setting. The mean time spent in progressed disease across all six intervention arms was then imputed and applied to the total progressed disease cost in order to give a weekly supportive care cost in the progressed health state that included post-progression treatments.

It is recognised that, given that some patients have had more previous lines of treatment than others in the EMILIA study, an average length of time on post-progression treatment of 4.3 months is subject to an uncertainty. Varying the length of time on post-progression treatment is therefore explored as a sensitivity analysis.

Health-state costs

7.4.21 Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the

choice of values used in the cost-effectiveness model. The health states should refer to the states in section 7.2.4.

Table 34 List of health states and associated costs in the economic model

Health states	Items	Frequency	Unit cost (£)	Total Cost per month inflated to 2013 (£)	Reference in submission
Progression-free survival best supportive care	Community Nurse (home visit)	20 mins every 2 weeks	24	61.41	7.4.21
	GP Contact (surgery visit)	1 every month	34 (per patient contact lasting 11.7 mins)	40.15	
	Clinical Nurse Specialist	1hr every month	74 (per hour of client contact)	87.39	
	Total Monthly Cost	**-**	**-**	**188.94**	
Post progression survival best supportive care	Community Nurse (home visit)	20 mins every 2 weeks	24	61.41	
	GP Contact (surgery visit)	1 every month	34 (per patient contact lasting 11.7 mins)	40.15	
	Clinical Nurse Specialist	1hr every month	74 (per hour of client contact)	87.39	
	Total Monthly Cost	**-**	**-**	**188.94**	
End of life care cost	3,916.00				

Given uncertainty as to which package of care is appropriate for inclusion and the contents of packages, Roche approached the health economist who developed the economic model used in CG81. The health economist confirmed that ‘package 1’ is applied during chemotherapy treatment up until a patient receives only supportive and palliative care, irrespective of the line of treatment, and the cost of a social worker is applied only once per line of treatment.

The cost of palliative care is included within the model through application of costs from Guest et al (2006). Guest et al examined the treatment patterns and corresponding costs of healthcare resource use associated with palliative

care for people with different types of advanced cancer; from initiation of strong opioid treatment until death. Resource utilisation data associated with palliative care were obtained from the DIN-LINK database; DIN-LINK is an anonymised database of individual primary care records in the UK, from general practices that use a health information systems software program (iSOFT, formerly Torex; iSOFT Group, plc, Manchester, UK). Palliative care costs for breast cancer were estimated to be £2,482 per patient using costs from 2000–2001. This cost was inflated to 2013 prices (£3,916.00) using the PSSRU Hospital and Community Health Services index (PSSRU, 2012). The cost of palliative care is applied as one lump sum upon death in the model. This approach to modelling end of life costs is consistent with several recent oncology NICE Technology Appraisals (particularly those in metastatic non-small-cell lung cancer such as TA 258).

Adverse-event costs

7.4.22 Please summarise the costs for each adverse event listed in section 6.9 (Adverse events). These should include the costs of therapies identified in sections 2.7 and 2.8. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.

Only adverse events occurring in 2% or more people in either arm of the EMILIA trial at Grade 3, 4 or 5 severity are incorporated into the model. In all instances the most recent NHS reference costs are used in the model (NHS References costs 2012/13). The cost of adverse events were applied on a weekly basis and discounted through the lifetime of the model. Although there were five adverse events occurring in 2% or more people, only diarrhoea and fatigue have been costed. Increased aspartate aminotransferase is a lab abnormality and therefore has no cost associated with it. Hand and foot syndrome and thrombocytopenia, although associated with swollen hands and a bleeding nose and gums respectively, are typically managed by dose reductions of the respective treatments and therefore not associated with any notable costs.

Table 35 List of adverse events and summary of costs included in the economic model

Adverse events	% people in trastuzumab emtansine arm	% people in lapatinib and capecitabine	Cost per episode (£)	Source (NHS reference cost 2012/13)
Increased aspartate aminotransferase (Grade 3)	3.9	0.6	0	
Diarrhoea (Grade 3)	1.0	25.2	797	Malignant Breast Disorders with Major CC (reduced short stay emergency tariff) JA12A
Fatigue (Grade 3)	2.0	3.1	797	Malignant Breast Disorders with Major CC (reduced short stay emergency tariff) JA12A
Hand and foot syndrome (Palmar-Plantar Erythrodysaesthesia Syndrome) (Grade 3)	0.0	19.1	0	
Thrombocytopenia (Grade 3)	10.4	0.2	0	

Miscellaneous costs

7.4.23 Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.

None.

Sensitivity analysis

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.1.11, 5.8, and 5.9.4 to 5.9.12.

Sensitivity analysis should be used to explore uncertainty around the structural assumptions used in the analysis. Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

The uncertainty around the appropriate selection of data sources should be dealt with through sensitivity analysis. This will include uncertainty about the choice of sources for parameter values. Such sources of uncertainty should be explored through sensitivity analyses, preferably using probabilistic methods of analysis.

All inputs used in the analysis will be estimated with a degree of imprecision. Probabilistic sensitivity analysis (PSA) is preferred for translating the imprecision in all input variables into a measure of decision uncertainty in the cost effectiveness of the options being compared.

For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

7.4.24 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated, including a description of the alternative scenarios in the analysis.

The three state model structure used in this model has been used in previous NICE Technology Appraisals in metastatic oncology and is accepted as the appropriate method of modelling metastatic breast cancer, therefore no structural sensitivity analysis of the model has been undertaken.

7.4.25 Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in section 7.3.6

(Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

Deterministic sensitivity analysis was carried out on the parameters listed in Table 36 (note, all costs are monthly costs unless otherwise stated). Significant costs were varied and the impact of varying utility values individually as well as in combination with the others was explored. The impact of using different parametric functions, including piecewise extrapolations, to model progression-free survival and overall survival on the ICER were explored. The piecewise extrapolations are explained in more detail below. The discount rate for costs and outcomes was varied according to standard methods and the time horizon altered.

Table 36 Deterministic sensitivity analysis

	Base case value (BCV)	**High value**	**Low value**
Costs			
Progression-free survival supportive care cost (weekly)	£43.45	£86.91 (BCV x2)	£21.73 (BCV x 0.5)
Progressed disease supportive care cost (weekly)	£63.08	£126.17 (BCV x2)	£31.54 (BCV x 0.5)
Post-progression lines (2L/3L) of treatment duration	4.3 months (18.63 weeks)	8.6 months (37.27 weeks)	2.15 months (9.32 weeks)
Treatment dose	Planned treatment dose	Actual treatment dose observed in the trial for all whole duration of progression-free survival	
Drug costs	Including wastage	Excluding wastage (full vial sharing) for all drugs (except vinorelbine as generic and assumed to be made up through compounders)	
Outcomes			
PFS HR: Tra+Cap vs T-DM1	0.68	0.50 (95% CI)	0.91 (95% CI)
PFS HR: Cap vs T-DM1	0.39	0.29 (95% CI)	0.55 (95% CI)
OS HR: Tra+Cap vs T-DM1	0.68	0.46 (95% CI)	0.98 (95% CI)
OS HR: Cap vs T-DM1	0.55	0.41 (95% CI)	0.75 (95% CI)
PFS HR: Tra+Cap vs T-DM1	0.68	0.54 (excluding CEREBEL and Martin)	
PFS HR: Cap vs T-DM1	0.39	0.35 (excluding CEREBEL and Martin)	

OS HR: Tra+Cap vs T-DM1	0.68	0.58 (excluding CEREBEL and Martin)	
OS HR: Cap vs T-DM1	0.55	0.52 (excluding CEREBEL and Martin)	
Progression-free survival utility	Different values in arms	Same values as Lap+Cap arm in all arms (0.74)	
Progressed utility	0.50	0.70 (BCV +0.2)	0.30 (BCV -0.2)
Parametric functions			
Progression free survival	Kaplan-Meier data with log-normal tail	Kaplan-Meier data with other parametric tails (1) Weibull (2) Exponential (3) Log-logistic (4) Gamma (5) Piecewise exponential tail (one piece)	
Overall survival	Gamma distribution	Other parametric distributions (1) Weibull (2) Log-logistic (3) Log-normal (4) KM data with piecewise exponential tail (one piece) (5) KM data with piecewise exponential tail (two pieces)	
Other			
Cost discount rate	3.5%	6%	0%
Health outcomes discount rate	3.5%	6%	0%
Health and cost discount rates	3.5% both arms	6% both arms	0% both arms
Time horizon	10	15	5

Sensitivity analyses – piecewise extrapolations for PFS and OS

PFS – piecewise exponential tail from 15 weeks

In section 7.3.1 we observed the cumulative hazard plots for PFS and noted that the hazards in each arm seem fairly similar up until 14 weeks after which is there an apparent divergence. It may be that there is a biological reason as so to why a divergence of hazards is only seen after this point and it is from this time point that the true hazard in each arm emerges. If this is true, we can analyse the data after 14 weeks in each in order to observe any trends.

Figure 42: PFS cumulative hazard plot from 15 weeks: Tratuzumab emtansine and Lapatinib and Capecitabine

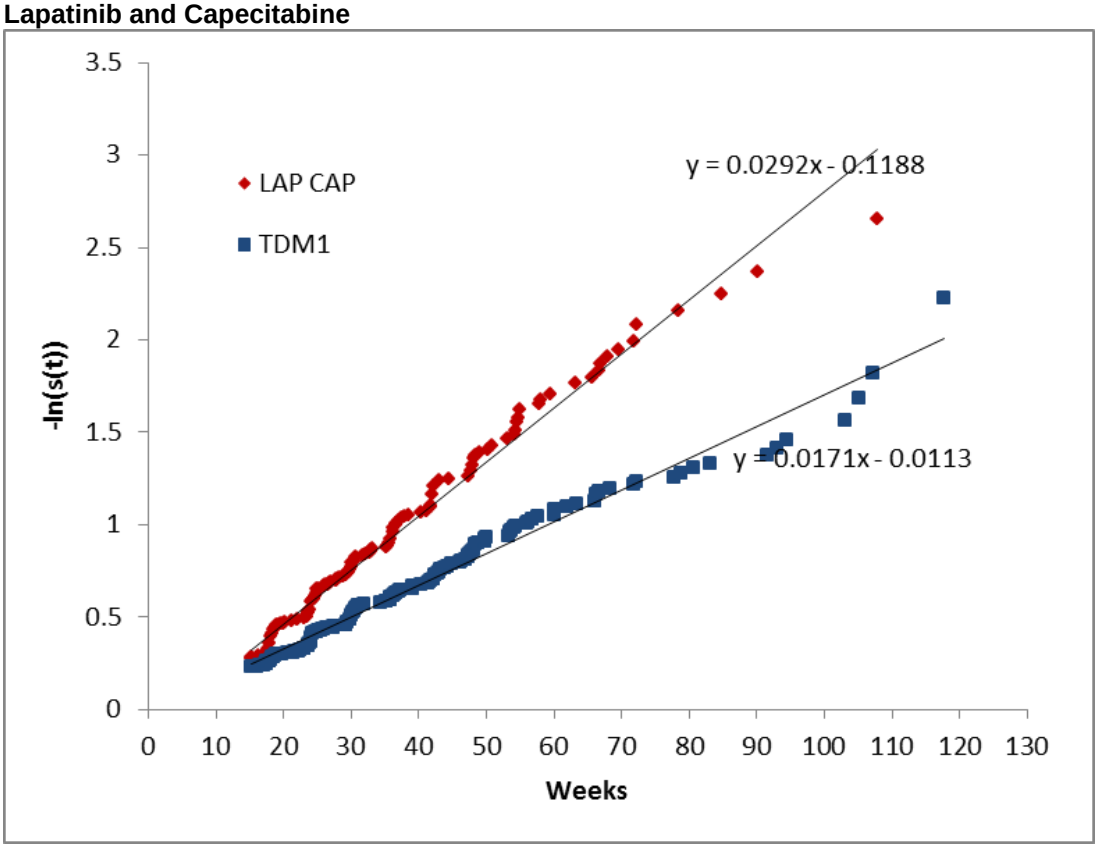
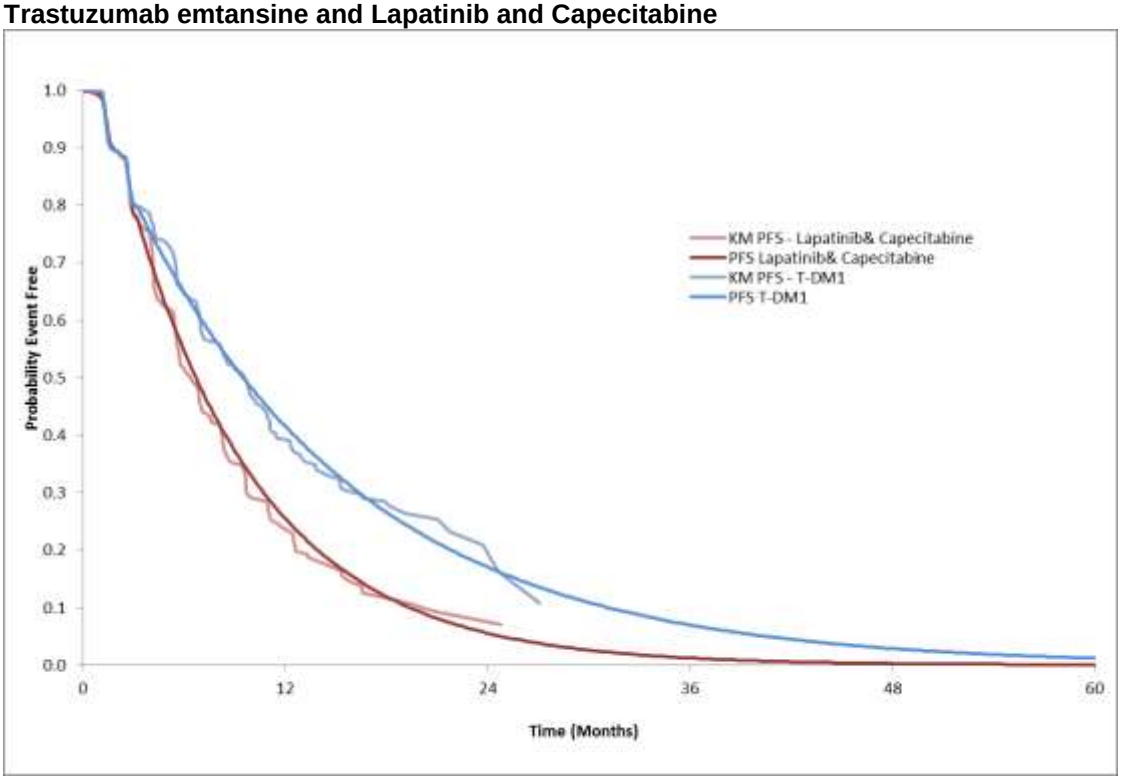


Figure 42 shows that for each arm an exponential extrapolation fits the data reasonably well up until approximately 80 weeks. Thereafter there are relatively low numbers at risk remaining; this arguably falsely causes the linear trend to be disturbed. One could therefore fit each curve with two separate pieces; one piece which is the same for both arms until 14 weeks (i.e. uses the KM data for each arm up until 14 weeks) and a further piece which is based on the slope of the cumulative hazard plots in each arm after 14 weeks; 0.0292 for lapatinib and capecitabine and 0.0171 for trastuzumab emtansine. This implies that after 14 weeks, although both slopes have a constant hazard, the hazard in the trastuzumab emtansine arm is less than that in the lapatinib and capecitabine arm, based on fitting the data in each arm separately. Modelling in this way produces extrapolated PFS curves as shown in

Figure 43.

Figure 43: PFS curve – piecewise exponential extrapolation from 15 weeks: Trastuzumab emtansine and Lapatinib and Capecitabine



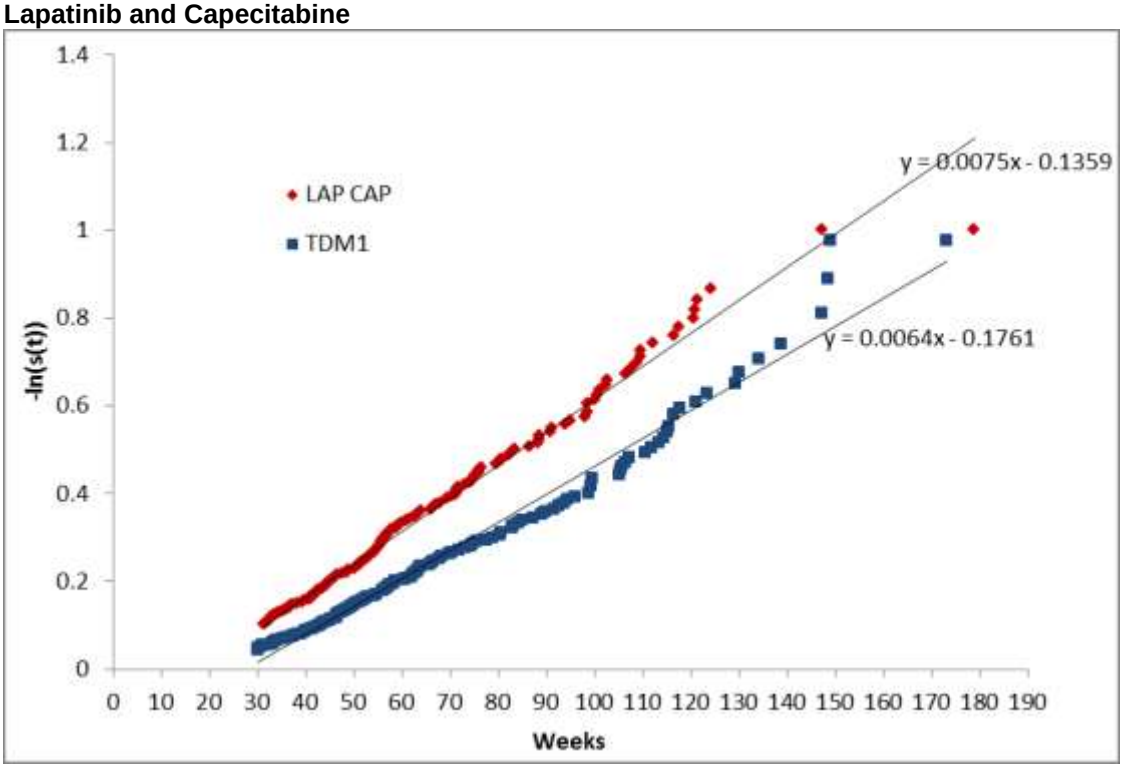
The extrapolation results in a reasonably good visual fit for the lapatinib and capecitabine arm although perhaps generally overestimating slightly the KM data, but the fit for the trastuzumab emtansine arm is less good, seemingly overestimating the middle part, whilst underestimating the tail. Moreover the assumption of proportional hazards is violated since a separate hazard ratio for each piece is implied; from 15 weeks this is approximately 0.59, less than the 0.65 imputed from the trial where all the data is used simultaneously.

Whilst this in itself is not problematic since it may be biologically plausible that two separate hazards are present, the results should be treated with caution, particularly given that we need to determine the efficacy of trastuzumab emtansine versus comparators for which there are no head-to-head data. The MTC (see section 6.7) is conducted using hazard ratios based on the assumption of proportional hazards and thus violating this assumption would add uncertainty to the results of the MTC.

OS – piecewise exponential tail from 29 weeks

Similarly with OS, in section 7.3.1 we observed the cumulative hazard plots for OS and noted that the hazards in each arm seem fairly similar up until 29 weeks after which is there an apparent divergence. Figure 44 shows that for each arm an exponential extrapolation fits the data reasonably well after 29 weeks, although it could be argued that there is another kink in each curve after approximately 95 to 100 weeks (see OS – 2 piece exponential tail at 30 weeks and 96 weeks). One could therefore fit each curve with two separate pieces; one piece which is the same for both arms until 29 weeks (i.e. uses the KM data for each arm up until 29 weeks) and a further piece which is based on the slop of the cumulative hazard plots in each arm; 0.0075 for lapatinib and capecitabine and 0.0064 for trastuzumab emtansine.

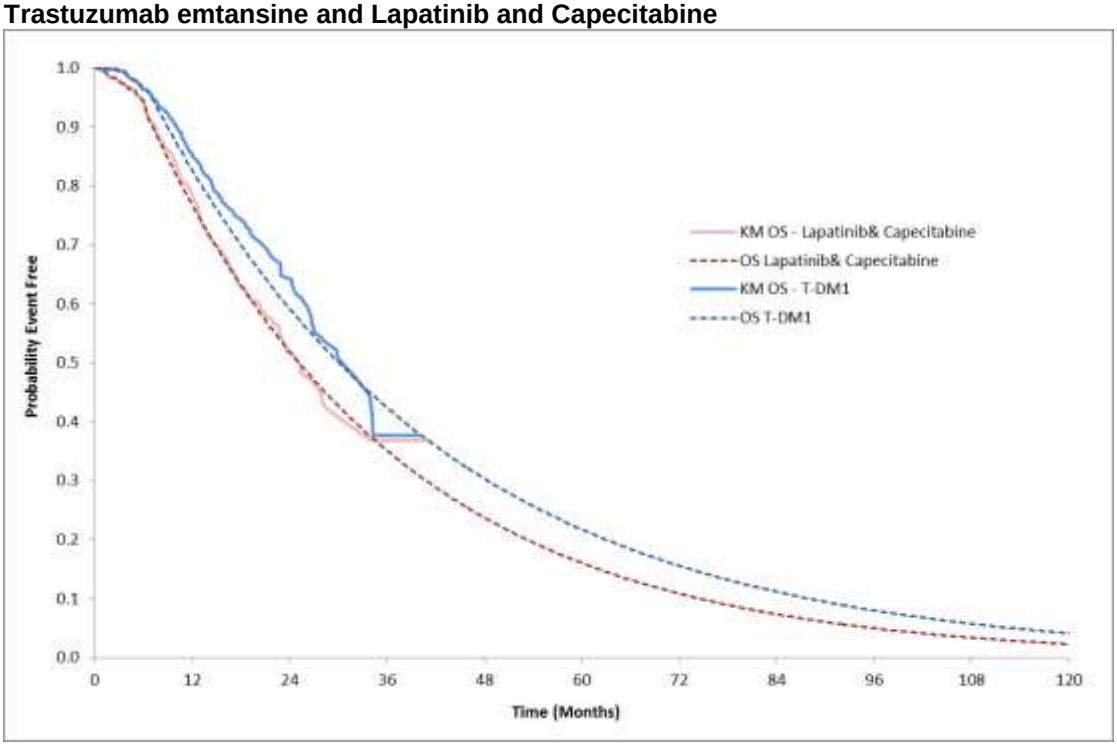
Figure 44: OS cumulative hazard plot from 30 weeks: Trastuzumab emtansine and Lapatinib and Capecitabine



Modelling in this way produces extrapolated OS curves as shown in Figure 45. The extrapolation results in a very good visual fit for the lapatinib and capecitabine arm, but the fit for the trastuzumab emtansine arm is poor, seemingly underestimating a large portion of the KM curve, whilst

overestimating the tail. However the tails of both curves are relatively thin which gives some external validation and plausibility when compared to the Munich registry since in both arms, the proportion of patients alive at 10 years is less than in the Munich registry (4.1% and 2.3% for trastuzumab emtansine and lapatinib and capecitabine respectively versus 5.7%).The resulting hazard ratio from 30 weeks is 0.85; an overestimate versus that as calculated from the trial, 0.68. As previously one must interpret the results of the piecewise approach with caution particularly when considering the use of the MTC where the overall survival efficacy of trastuzumab emtasinse versus other comparators is inferred, based on the assumption of proportional hazards.

Figure 45: OS curve – piecewise exponential extrapolation from 30 weeks: Trastuzumab emtansine and Lapatinib and Capecitabine

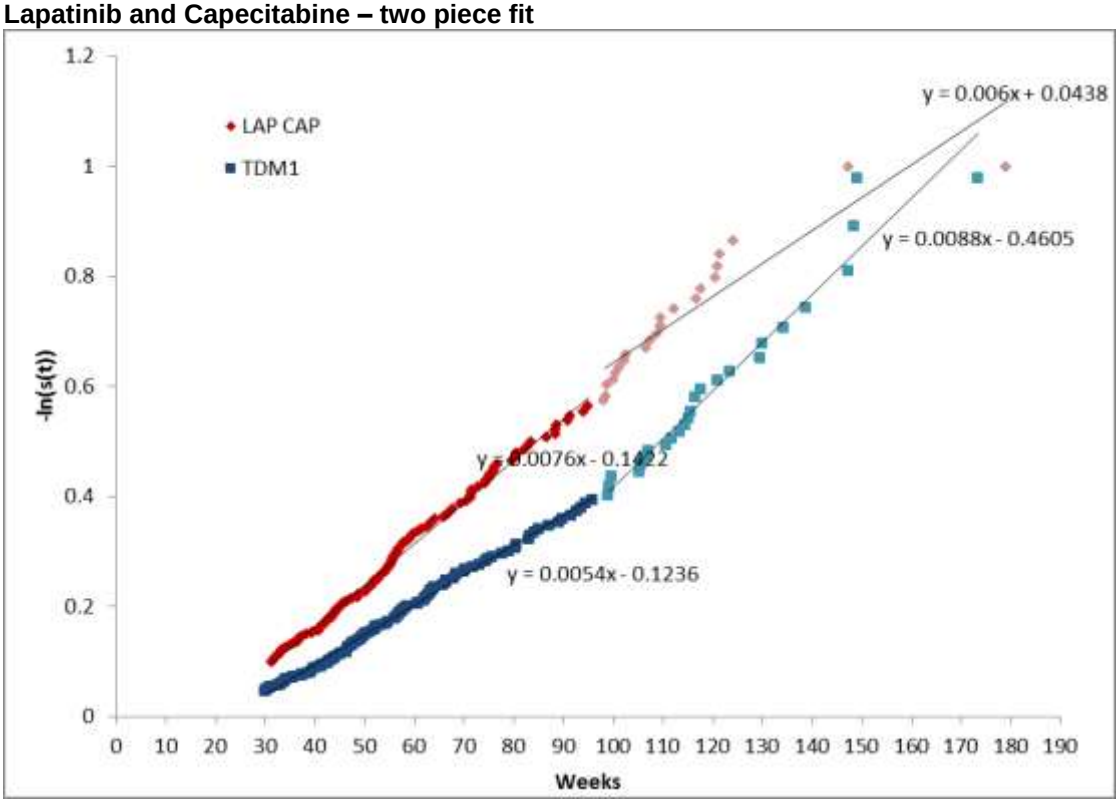


OS – 2 piece exponential tail at 30 weeks and 96 weeks

Lastly we consider an extrapolation where the cumulative hazard plots are fitted with three pieces - KM data for the first 29 weeks and then two further pieces; one piece from 30 to 95 weeks and another piece from 96 weeks as shown in Figure 46. This arguably provides a better fit to the data than simply fitting one piece after 30 weeks, particularly for the period 30 to 95 weeks in the trastuzumab emtamsine arm. However after 95 weeks, the hazard in the

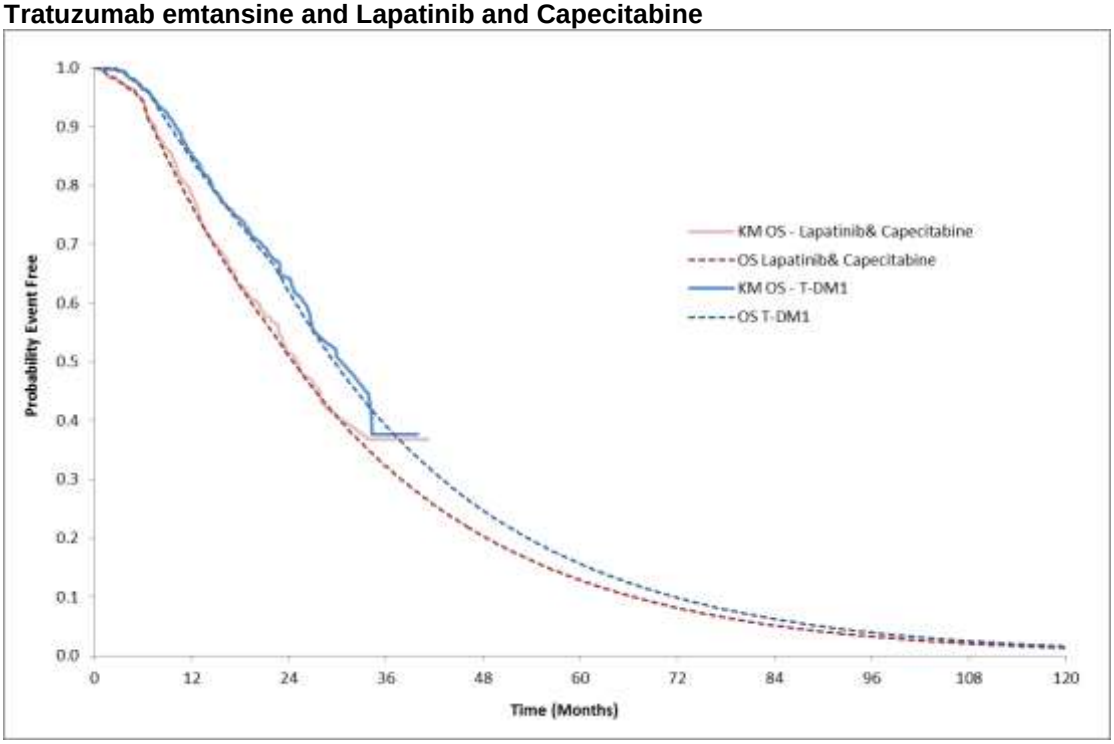
lapatinib and capecitabine arm is less than in the trastzumab emtamsine arm due to an outlier. Moreover due to the relatively small number of data after 95 weeks, it may be most reasonable to simply assume the same hazard in each arm; 0.0088. This implies a hazard ratio of 1 after 95 weeks which may be more plausible if we do not think that the treatment benefit of trastuzumab emtansine seen initially is maintained over a prolonged time period. Further it was noted at an independent advisory board (see section 7.6) that on visual inspection after 95 weeks the cumulative hazazrd plots are approximately parallel, thus corroborating the above approach.

Figure 46: OS cumulative hazard plot from 30 weeks: Trastuzumab emtansine and Lapatinib and Capecitabine – two piece fit



This produces OS curves as show in Figure 47 which provide good visual fits for both arms although both curves drop off rather steeply resulting in a very small proportion of patients being alive at 10 years. The inferred hazard ratios for each piecewise fit are 0.71 and 1 compared to 0.68 as calculated from the trial. However, whilst producing a better fit for the EMILIA data, dividing the OS curve into further pieces increases the uncertainty associated with the MTC and hence the efficacy of trastuzumab emtansine arm versus other comparators.

Figure 47: OS curve – 2 piece exponential extrapolation at 30 and 96 weeks: Tratuzumab emtansine and Lapatinib and Capecitabine



7.4.26 Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in section 7.3.6, including the derivation and value of 'priors'. If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).

A PSA was undertaken over 1000 iterations. The distributions used are listed in Table 37.

Table 37 PSA distributions

	Distribution
Utilities – the coefficients in the regression of the mixed model were varied	
Age	Normal
Treatment response	Normal
Diarrohea and vomiting	Normal
Progression-free survival Capecitabine	Normal
Fatigue	Normal
Costs	
Weekly supportive care PFS	Gamma
Weekly supportive care PFS	Gamma
Length of time on treatment in PPS	Gamma
Palliative care cost	Gamma
Cost of administering tratuzumab emtansine	Gamma
Cost of administering lapatinib and capecitabine	Gamma
Cost of administering trastuzumab and capecitabine	Gamma
Cost of administering capecitabine	Gamma
Cost of adminstering vinorelbine	Gamma
Cost of adminstering trastuzumab and vinorelbine	Gamma

7.5 Results

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following.

- Link between clinical- and cost-effectiveness results.
- Costs, QALYs and incremental cost per QALY.
- Disaggregated results such as LYG, costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment.
- A statement as to whether the results are based on a PSA.
- Cost-effectiveness acceptability curves, including a representation of the cost-effectiveness acceptability frontier.
- Scatter plots on cost-effectiveness quadrants.

- A tabulation of the mean results (costs, QALYs, ICERs), the probability that the treatment is cost effective at thresholds of £20,000–£30,000 per QALY gained and the error probability.

Clinical outcomes from the model

7.5.1 For the outcomes highlighted in the decision problem (see section 5), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

Table 38: Summary of model results compared with clinical data

Outcome	Clinical trial result	Model result
Trastuzumab emtansine		
Progression-free survival	Median = 9.6 months	Median = 9.6 months
Overall survival	Median = 30.9 months	Median = 32 months
Lapatinib and capecitabine		
Progression-free survival	Median = 6.4 months	Median = 6.4 months
Overall survival	Median = 25.1 months	Median = 25 months

Table 38 indicates that the model predicts exactly the median progression-free survival observed in the EMILIA trial. This is due to the use of KM progression-free survival curves from the study applied directly in the model until the start of extrapolation (which began after median progression-free survival). Table 38 indicates that the model predicts almost exactly the median overall survival observed in the EMILIA trial for the lapatinib and capecitabine arm and overestimates it slightly for the trastuzumab emtansine arm. A full explanation of this has been given in section 7.3.1.

The model predicts a median OS gain to PFS gain multiple of 2.2 which is slightly higher than that as predicted by the EMILIA trial; 1.8. As stated previously, the reason for this is primarily due to the model predicting a

median OS of 32 months in the trastuzumab emtansine arm as opposed to 30.9 months as seen in the trial, and a full justification for this and likely plausibility have been detailed in section 7.3.1. However, when considering the *mean* OS to PFS gain, the model predicts a lower multiple of 1.60, suggesting that the modelling method employed is conservative.

Further, the magnitude of the OS gain to PFS gain multiple is largely consistent with what one sees in other key trials HER2 targeted monoclonal antibodiesies, as shown in
Table 39, and hence it is not unreasonable to have a multiple of greater than 1.

Table 39: OS gain:PFS gain relationships for HER2 targeted monoclonal antibodies from key trials

Outcome	***GBG26 (2L trial)***	
	Intervention	**Comparator**
	Trastuzumab + Capecitabine	Capecitabine
Median progression-free survival	8.2 months	5.6 months
Median overall survival	24.9 months	20.6 months
OS gain:PFS gain multiple	1.65	
Outcome	***M77001 (1L trial)***[14]	
	Intervention	**Comparator**
	Trastuzumab + Docetaxel	Docetaxel
Median progression-free survival	11.7 months	6.1 months
Median overall survival	31.2 months	22.7 (16.6) months
OS gain:PFS gain multiple	1.51 (3.7)	
	Slamon (1L trial)[15]	

14 Slamon et al, 2001

15 Marty et al, 2005

Outcome		
	Intervention	**Comparator**
	Trastuzumab + chemotherapy	Chemotherapy
Median progression-free survival	7.4 months	4.6 months
Median overall survival	25.1 months	20.3 months
OS gain:PFS gain multiple	1.71	
Outcome	***TAnDEM (1L trial)*[16]**	
	Intervention	**Comparator**
	Trastuzumab + anastrazole	Trastuzumab
Median progression-free survival	5.6 months	3.8 months
Median overall survival	28.5 months	23.9 months (17.2 months)
OS gain:PFS gain multiple	2.55 (6.2)	
Outcome	***Blackwell (1L trial)*[17]**	
	Intervention	**Comparator**
	Trastuzumab + Lapatinib	Lapatinib
Median progression-free survival	2.56 months	1.87 months
Median overall survival	14 months	9.5 months
OS gain:PFS gain multiple	6.49	

7.5.2 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

The model runs for 10 years on a weekly cycle length for six interventions. Reproducing the Markov trace would substantially lengthen the submission

16 Kaufman et al, 2009

17 Blackwell et al, 2012

and thus has not been reproduced within the template. The trace is available within the model and can be provided as a separate appendix document if required.

7.5.3 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

See response to 7.5.2.

7.5.4 Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results. For example:

Table 40 Model outputs by clinical outcomes

Technologies	Outcome	LY	QALY
Trastuzumab emtansine	Progression-free survival	1.21	0.94
	Progressed disease	1.95	0.97
	Overall survival	3.16	1.91
Lapatinib and capecitabine	Progression-free survival	0.81	0.60
	Progressed disease	1.72	0.85
	Overall survival	2.53	1.45
Trastuzumab and capecitabine	Progression-free survival	0.80	0.58
	Progressed disease	1.47	0.73
	Overall survival	2.27	1.31
Trastuzumab and vinorelbine	Progression-free survival	0.80	0.58
	Progressed disease	1.47	0.73
	Overall survival	2.27	1.31
Capecitabine	Progression-free survival	0.46	0.34
	Progressed disease	1.40	0.70
	Overall survival	1.87	1.03
Vinorelbine	Progression-free survival	0.46	0.34
	Progressed disease	1.40	0.70
	Overall survival	1.87	1.03
LY, life years; QALY, quality-adjusted life year			

7.5.5 Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.

The interventions are presented as a simultaneous incremental analysis.

Table 41: Summary of QALY gain by health state: PFS

Technologies	Progression-free survival	Increment	(% absolute increment)
Capecitabine	0.34	-	-
Vinorelbine	0.34	-	-
Trastuzumab and capecitabine	0.58	0.25	73.24%
Trastuzumab and vinorelbine	0.58	0.25	73.24%
Lapatinib and capecitabine	0.60	0.02	3.33%
Trastuzumab emtansine	0.94	0.34	56.98%

Table 42: Summary of QALY gain by health state: Progressed

Technologies	Progression-free survival	Increment	(% absolute increment)
Capecitabine	0.70	-	-
Vinorelbine	0.70	-	-
Trastuzumab and capecitabine	0.73	0.03	3.37%
Trastuzumab and vinorelbine	0.73	0.03	3.37%
Lapatinib and capecitabine	0.85	0.12	17.63%
Trastuzumab emtansine	0.97	0.12	13.83%

Table 43 Summary of costs by health state: PFS

Technologies	Progression-free survival	Increment	(% absolute increment)
Capecitabine	£4,819.56	-	-
Vinorelbine	£10,520.77	£5,701.21	118.29%
Lapatinib and capecitabine	£24,886.41	£14,365.64	136.55%
Trastuzumab and capecitabine	£29,113.59	£4,227.18	16.99%
Trastuzumab and vinorelbine	£30,531.61	£1,418.02	4.87%
Trastuzumab emtansine	£101,289.07	£70,757.46	231.75%

Table 44: Summary of costs by health state: Progressed

Technologies	Progression-free survival	Increment	(% absolute increment)
Capecitabine	£4,615.82	-	-
Vinorelbine	£4,615.82	-	-
Trastuzumab and capecitabine	£4,839.41	£223.59	4.84%
Trastuzumab and vinorelbine	£4,839.41	£223.59	4.84%
Lapatinib and capecitabine	£5,653.02	£813.61	16.81%
Trastuzumab emtansine	£6,434.95	£781.93	13.83%

Table 45 Summary of predicted resource use by category of cost: mean treatment cost

Technologies	Progression-free survival	Increment	(% absolute increment)
Vinorelbine	£558.94	-	-
Capecitabine	£2,399.81	£1,840.87	329.35%
Trastuzumab and vinorelbine	£18,720.34	£16,320.53	680.08%
Lapatinib and capecitabine	£20,593.98	£1,873.64	10.01%
Trastuzumab and capecitabine	£21,810.81	£1,216.83	5.91%
Trastuzumab emtansine	£90,830.66	£69,019.86	316.45%

Table 46: Summary of predicted resource use by category of cost: administration cost

Technologies	Progression-free survival	Increment	(% absolute increment)
Capecitabine	£1,192.88	-	-
Lapatinib and capecitabine	£2,125.10	£932.21	78.15%
Trastuzumab and capecitabine	£5,197.67	£3,072.57	144.59%
Trastuzumab emtansine	£7,670.17	£2,472.50	47.57%
Vinorelbine	£8,734.96	£1,064.79	13.88%
Trastuzumab and vinorelbine	£9,706.15	£971.19	11.12%

Table 47: Summary of predicted resource use by category of cost: mean supportive care cost of PFS

Technologies	Progression-free survival	Increment	(% absolute increment)
Capecitabine	£1,053.47	-	-
Vinorelbine	£1,053.47	-	-
Trastuzumab and capecitabine	£1,807.59	£754.12	71.58%
Trastuzumab and vinorelbine	£1,807.59	£754.12	71.58%
Lapatinib and capecitabine	£1,840.07	£32.49	1.80%
Trastuzumab emtansine	£2,735.67	£895.60	48.67%

Base-case analysis

7.5.6 Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.

Table 48: Base case results (costs, LYG and QALYS)

	Trastuzumab emtansine	Lapatinib and capecitabine	Trastuzumab and capecitabine	Capecitabine	Vinorelbine	Trastuzumab and vinorelbine
Technology acquisition cost	£90,831	£20,594	£21,811	£2,400	£559	£18,720
Other costs	£20,331	£13,576	£15,818	£10,773	£18,315	£20,326
Total costs	£111,162	£34,170	£37,629	£13,173	£18,874	£39,047
Difference in total costs (Trastuzumab emtansine – comparator)	-	£76,992	£73,533	£97,989	£92,288	£72,115
LYG	3.16	2.53	2.27	1.87	1.87	2.27
LYG difference (Trastuzumab emtansine – comparator)	-	0.63	0.89	1.29	1.29	0.89
QALYs	1.91	1.45	1.31	1.03	1.03	1.31
QALY difference (Trastuzumab emtansine – comparator)	-	0.46	0.60	0.88	0.88	0.60

LYG, life years gained; QALY(s), quality-adjusted life year(s); ICER, incremental cost-effectiveness ratio.

Table 48 shows the base case results for trastuzumab emtansine versus each comparator. It shows that trastuzumab emtansine is more effective but more costly than all other comparators.

Table 49: Incremental cost-effectiveness results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY gained) vs efficiency frontier regimen
Capecitabine	£13,173	1.87	1.03	-	-	-	-
Vinorelbine	£18,874	1.87	1.03	£5,701	0.00	0.00	Dominated
Lapatinib and capecitabine	£34,170	2.53	1.45	£20,997	0.66	0.42	£49,798 (vs cap)
Trastuzumab and capecitabine	£37,629	2.27	1.31	£24,456	0.40	0.28	£87,446 (vs cap)
Trastuzumab and vinorelbine	£39,047	2.27	1.31	£25,874	0.40	0.28	£92,516 (vs cap)
Trastuzumab emtansine	£111,162	3.16	1.91	£97,989	1.29	0.88	£111,095 (vs cap)

Table 49 demonstrates that no intervention is cost-effective.

Vinorelbine produces the same number of QALYs as capecitabine but was more expensive. As a result it was dominated and removed from the analysis.

The comparison of lapatinib in combination with capecitabine compared to capecitabine alone resulted in an ICER above the range typically considered acceptable by NICE (£49,798/QALY gained). Lapatinib in combination with capecitabine was therefore removed from the simultaneous incremental analysis.

Trastuzumab in combination with capecitabine and trastuzumab in combination with vinorelbine were similarly found not be cost-effective against capecitabine monotherapy (with ICERs of £87,446 and £92,516 respectively).

The efficiency frontier therefore consists of capecitabine alone and capecitabine should be the primary comprator for trastuzumab emtansine.

The ICER of trastuzumab emtansine compared to capecitabine is £111,095 (see

Table 50).

Table 50: Incremental cost-effectiveness final result

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY gained)
Capecitabine	£13,173	1.87	1.03				
Trastuzumab emtansine	£111,162	3.16	1.91	£97,989	1.29	0.88	£111,095

Sensitivity analyses

7.5.7 Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

The results of the deterministic sensitivity analysis are presented in Table 51. All ICERs are for trastuzumab emtansine versus capecitabine unless otherwise stated. A tornado diagram of key inputs is presented in

Figure 48.

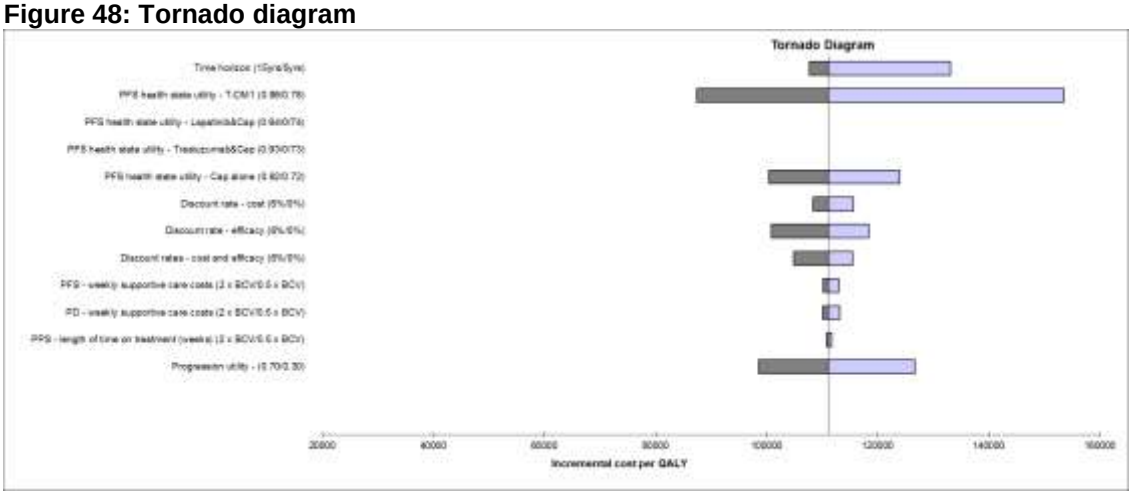
Table 51: Results of deterministic sensitivity analysis

	Base case value (BCV)	High value	Low value
Costs			
Progression-free survival supportive care cost (weekly)	£43.45	£86.91 (BCV x2)	£21.73 (BCV x 0.5)
	ICER	£113,003	£110,142
Progressed disease supportive care cost (weekly)	£63.08	£123.99 (BCV x2)	£31.54 (BCV x 0.5)
	ICER	£113,158	£110,064
Post-progression lines (2L/3L) of treatment duration	4.3 months (18.63 weeks)	8.6 months (37.27 weeks)	2.15 months (9.32 weeks)
	ICER	£111,737	£110,775
Treatment dose	Planned treatment dose	Actual treatment dose observed in the trial for all whole duration of progression-free survival	
	ICER	£111,871	
Drug costs	Including wastage	Excluding wastage (full vial sharing) for all drugs (except vinorelbine as generic and assumed to be made up through compounders)	
	ICER	£108,082	
Outcomes (Results from the MTC)			
PFS HR: Tra+Cap vs T-DM1	0.68	0.50 (95% CI)	0.91 (95% CI)
	ICER	£111,069	£111,132
PFS HR: Cap vs T-DM1	0.39	0.29 (95% CI)	0.55 (95% CI)
	ICER	£108,700	£115,191
OS HR: Tra+Cap vs T-DM1	0.68	0.46 (95% CI)	0.98 (95% CI)
	ICER	£111,205	£110,998
OS HR: Cap vs T-DM1	0.55	0.41 (95% CI)	0.75 (95% CI)
	ICER	£89,965	£165,517
PFS HR: Tra+Cap vs T-DM1	0.68	0.54 (excluding CEREBEL and Martin)	
	ICER	£111,075	
PFS HR: Cap vs T-DM1	0.39	0.35 (excluding CEREBEL and Martin)	

	ICER	£110,123	
OS HR: Tra+Cap vs T-DM1	0.68	0.58 (excluding CEREBEL and Martin)	
	ICER	£111,140	
OS HR: Cap vs T-DM1	0.55	0.52 (excluding CEREBEL and Martin)	
	ICER	£105,788	
Progression-free survival utility	Different values in arms	0.74 (same values as Lap and Cap arm in all arms)	
	ICER	£118,617	
Progression-free survival utility T-DM1	0.78	0.71 (T-DM1 PFS utilty from TH3RESA trial)	
		£123,257	
Progressed utility	0.50	0.70 (BCV +0.2)	0.30 (BCV -0.2)
	ICER	£98,511	£126,660
Progression free utility T-DM1	0.78	0.98 (BCV +0.2)	0.58 (BCV -0.2)
	ICER	£94,909	£179,337
Progression free utility Lap + cap	0.74	0.94 (BCV +0.2)	0.54 (BCV -0.2)
	ICER	£111,095	£111,095
Progression free utility Tra + cap/Tra + vin	0.73	0.93 (BCV +0.2)	0.53 (BCV -0.2)
	ICER	£111,095	£111,095
Progression free utility Cap/Vin	0.72	0.92 (BCV +0.2)	0.52 (BCV -0.2)
	ICER	£123,971	£100,371
Parametric functions			
Progression free survival	Kaplan-Meier data with log-normal tail	Kaplan-Meier data with other parametric tails (1) Weibull (2) Exponential (3) Log-logistic (4) Gamma (5) Piecewise exponential tail (one piece)	
	ICER	(1) £100,365 (2) £106,672 (3) £114,826 (4) £110,015 (5) £106,211	
Overall survival	Gamma distribution	Other parametric distributions (1) Weibull (2) Log-logistic (3) Log-normal (4) KM data with piecewise exponential tail (one piece) (5) KM data with piecewise exponential tail (two pieces)	

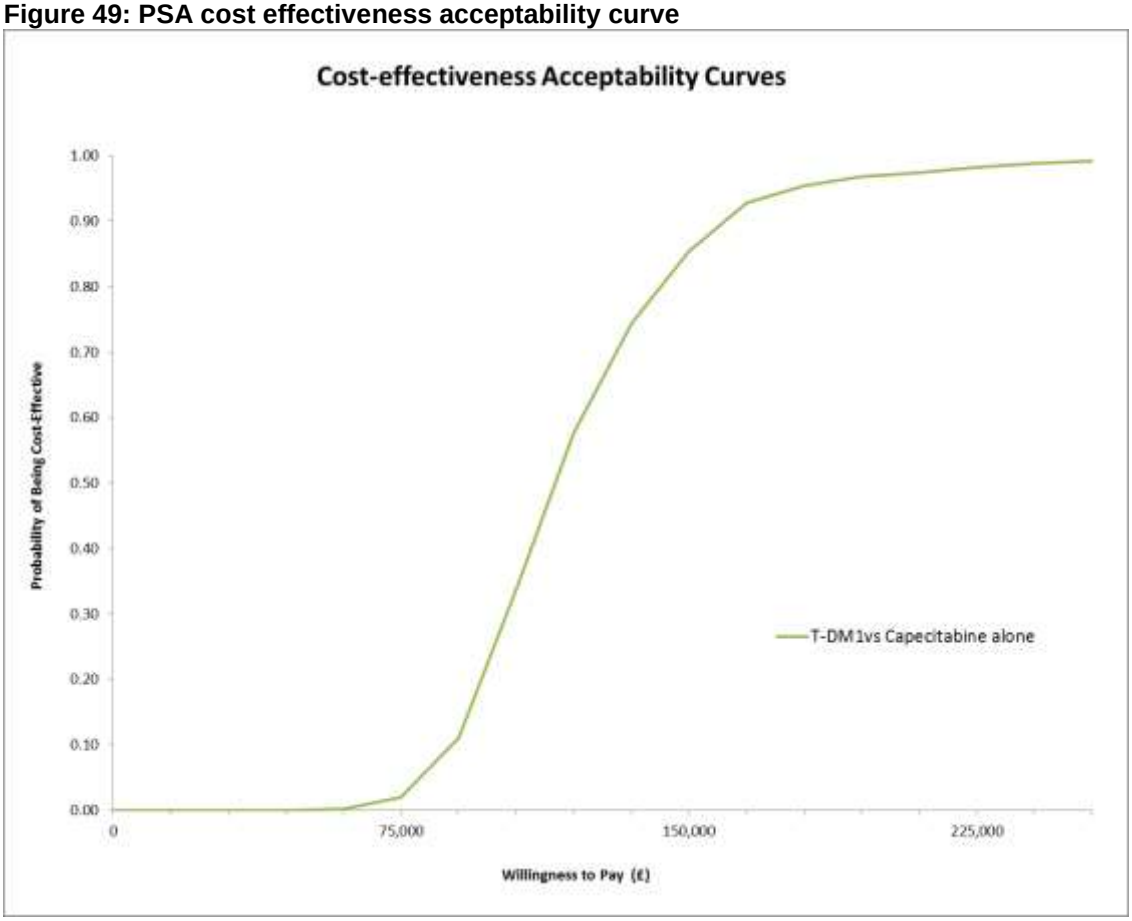
	ICER	(1) £151,208 (2) £115,020 (3) £111,004 (4) £138,286 (5) £153,319	
Other			
Cost discount rate	3.5%	6%	0%
	ICER	£108,305	£115,586
Health outcomes discount rate	3.5%	6%	0%
	ICER	£118,396	£100,816
Health and cost discount rates	3.5% both arms	6% both arms	0% both arms
	ICER	£115,413	£104,873
Time horizon	10	15	5
	ICER	£107,657	£133,103

Figure 48: Tornado diagram



7.5.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

Figure 49: PSA cost effectiveness acceptability curve



A 1,000 simulation probabilistic sensitivity analysis was conducted in order to evaluate the uncertainty associated with the base-case estimate. The results of the PSA indicate that trastuzumab emtansine has a 0% probability of being

cost-effective at a willingness-to-pay of £30,000 per QALY gained (see Figure 49).

7.5.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

See “Outcomes” and “Parametric functions” in Table 51.

7.5.10 What were the main findings of each of the sensitivity analyses?

In all the sensitivity analyses conducted the ICER associated with trastuzumab emtansine remained above the level considered acceptable.

The deterministic sensitivity analysis demonstrates the model is most sensitive to the long term extrapolation of progression-free survival and overall survival and the results of the MTC. The model is also sensitive to the utility values in progression-free survival for each intervention and progression health states, and the time horizon of the model.

7.5.11 What are the key drivers of the cost-effectiveness results?

The key drivers of the model are the cost of trastuzumab emtansine, the long term projection of progression-free survival and overall survival, the results of the MTC and the utility values used.

7.6 Validation

7.6.1 Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.

The model was validated at an advisory board meeting and by a health economics consultancy. The model functionality was checked and the clinical inputs and assumptions were validated. Further the model was externally validated as much as possible against the Munich registry; a database recording the survival 523 people diagnosed with HER2-positive metastatic

breast cancer between 2002 and 2009 in Munich, Germany (Tumorregister-Muenchen, 2012) (see section 7.3.1).

The extrapolations conducted were discussed with an academic health economist, a health economist who works for an Evidence Review Group and a panel of clinicians. All noted that whilst subject to uncertainty the extrapolation approach employed appeared reasonable given the evidence currently available.

The model also went an internal an external quality check and the model and submission was reviewed independently by an external agency.

7.7 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. This should be explored as part of the reference-case analysis by providing separate estimates of clinical and cost effectiveness for each relevant subgroup of patients.

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.10.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Individual utilities for health states and patient preference.
- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, when the costs of facilities available for providing the technology vary according to location).

7.7.1 Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost effectiveness because of known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 6.3.7.

No subgroup analysis was undertaken.

7.8 Interpretation of economic evidence

7.8.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

There are no economic evaluations in this indication and patient population with which these results may be compared (see Section 7 for more details of the search of cost-effectiveness studies undertaken).

7.8.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 5?

The evaluation is founded upon the EMILIA trial and so should be representative of all people who participated in the EMILIA trial.

7.8.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

Strengths

1. The model uses data from the pivotal clinical trial (EMILIA) wherever possible, and resource use and costs based on recent NICE clinical guidelines and NHS reference costs.

2. EMILIA is a robust and well conducted study in people broadly representative of the population expected to be treated in England and Wales.

3. The model uses costs and utilities that have been applied and accepted as appropriate in previous NICE Technology Appraisals in metastatic breast cancer where appropriate.

4. The extrapolated overall survival curves demonstrate external validity when compared against registry data of people with HER2-positive metastatic breast cancer.

Weaknesses

1. The model is heavily reliant upon long-term projection of overall survival.

2. For comparisons against interventions not included in the EMILIA trial the model is reliant on an indirect treatment comparison and thus all the caveats associated with making cross-trial comparisons. Whilst every effort has been made to only include trials that have a similar population to EMILIA (via the inclusion and exclusion criteria of the systematic literature review), it is inevitable that there are some underlying differences between the populations of each trial and this therefore might distort the efficacy data (PFS and OS hazard ratios) imputed versus had RCTs against each comparator being conducted.

3. There is a lack of data on both vinorelbine monotherapy and in combination with trastuzumab which means that the relative efficacy of trastuzumab emtansine versus these treatments is subject to considerable uncertainty.

7.8.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

Key drivers in the model are the extrapolation of overall survival and progression-free survival, and the utility values used to estimate the quality of life of people with the disease. Robustness of the model would be improved by the incorporation of more mature data on the baseline risk of death and the longer term treatment effect associated with trastuzumab emtansine.

Collection of EQ-5D values from participants in the trial would improve the estimates of the quality of life impact within the progression-free survival and progressed health states.

Section C – Implementation

8 Assessment of factors relevant to the NHS and other parties

The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical effectiveness and cost effectiveness. This will allow the subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

8.1 How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

It is estimated that approximately 1,290 people per annum will be eligible to receive trastuzumab emtansine. The derivation of this number is provided in

Figure 2. At a population growth rate of 0.5% per annum this results in the following yearly eligible populations

Table 52: Eligible population by year

Year	1	2	3	4	5
Eligible population	1290	1296	1303	1309	1316

8.2 What assumption(s) were made about current treatment options and uptake of technologies?

The analysis considers only the absolute budget impact of trastuzumab emtansine (i.e. the costs of any technologies displaced are not considered and hence the budget impact is conservative).

8.3 What assumption(s) were made about market share (when relevant)?

It is assumed that 30% of eligible people in the year following NICE approval would receive trastuzumab emtansine with that figure rising to 70% in the fifth year following approval. The market share figures used are presented in Table 53.

Table 53: Market share assumptions by year

Year	1	2	3	4	5
% people treated with trastuzumab emtansine	30%	40%	50%	60%	70%

8.4 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

The budget impact calculations include all the additional costs of treatment with trastuzumab emtansine as included in the de novo economic model and discussed in the cost-effectiveness section.

8.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

The budget impact calculations are based upon the output of the economic model.

8.6 Were there any estimates of resource savings? If so, what were they?

No.

8.7 What is the estimated annual budget impact for the NHS in England and Wales?

Table 54: Budget impact by year

Year	1	2	3	4	5
Budget impact - drug cost	£11,118,537	£26,017,377	£44,734,045	£57,983,664	£70,161,437
Budget impact - non-drug cost	£2,488,696	£5,823,548	£10,012,957	£12,978,659	£15,704,447
Total budget impact	**£13,607,233**	**£31,840,925**	**£54,747,002**	**£70,962,323**	**£85,865,884**

8.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

No.

9 References

Please use a recognised referencing style, such as Harvard or Vancouver.

All Wales Medicines Strategy Group Final Appraisal Recommendation Advice No: 1713 – July 2013. Lapatinib (Tyverb®) 250 mg film-coated tablets. Accessed online 10/09/2013 at: http://www.awmsg.org/awmsgonline/app/appraisalinfo/178

Baselga J et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med 2012;366:109-19

Blackwell KL, Burstein HJ, Storniolo AM, Rugo HS, Sledge G, Aktan G, Ellis C, Florance A, Vukelja S, Bischoff J et al: Overall survival benefit with lapatinib in combination with trastuzumab for patients with human epidermal growth factor receptor 2-positive metastatic breast cancer: final results from the EGF104900 Study. J Clin Oncol 2012, 30(21):2585-2592

Breast Cancer Care 2013 http://www.breastcancercare.org.uk/breast-cancer-information (Accessed: 04/12/13)

Borg A et al. HER-2/neu amplification predicts poor survival in node- positive breast cancer. Cancer Res. 1990; 50: 4322-4327

Brown M, Tsodikov A, Bauer KR, et al. The role of human epidermal growth factor receptor 2 in the survival of women with estrogen and progesterone receptor-negative, invasive breast cancer: the California Cancer Registry, 1999-2004. Cancer 2008; 112(4): 737-747

Bucher HC et al. The Results of Direct and Indirect Treatment Comparisons in Meta-Analysis of Randomized Controlled Trials. J Clin Epidemiol. 1997; 50(6):683-691

Burris HA et al. Trastuzumab emtansine: a novel antibody-drug conjugate for HER2-positive breast cancer. Expert Opin. Biol. Ther. 2011; 11(6): 807-819

Burzykowski et al. Burzykowski, T, Buyse M, Piccart-Gebhart M et al. Evaluation of tumour response, disease control, progression-free survival, and

time to progression as potential surrogate endpoints in metastatic breast cancer. J Clin Oncol 2008; 26(12): 1987-1992.

Cancer Research UK 2012 http://www.cancerresearchuk.org/cancer-info/cancerstats/types/breast/incidence/ (last accessed: 04/12/13)

Cameron D et al. A phase III randomized comparison of lapatinib plus capecitabine versus capecitabine alone in women with advanced breast cancer that has progressed on trastuzumab: updated efficacy and biomarker analyses. Breast Cancer Res. Treat. 2008; 112: 533-543

Cameron D et al. Lapatinib Plus Capecitabine in Women with HER-2-Positive Advanced Breast Cancer: Final Survival Analysis of a Phase III Randomized Trial. The Oncologist 2010; 15: 924-934

Chari RV et al. Targeted Cancer Therapy: Conferring Specificity to Cytotoxic Drugs. Acc Chem Res. 2008; 41:98-107

Commercial Medicines Unit. Electronic Market Information Tool. http://cmu.dh.gov.uk/electronic-market-information-tool-emit/.2012. Department of Health. Ref Type: Electronic Citation

Curigliano G, Viale G, Bagnardi V et al. Clinical relevance of HER2 overexpression/amplification in patients with small tumor size and node-negative breast cancer. J Clin Oncol 2009; 27(34): 5693-5699

Department of Health. NHS reference costs 2012/13. Accessed online 10/09/2013 at: https://www.gov.uk/government/uploads/system/.../dh_133578.xls

Dieras V et al. Trastuzumab Emtansine (T-DM1) in Human Epidermal Growth Factor Receptor 2–Positive Metastatic Breast Cancer: Pooled Safety Analysis. San Antonio Breast Cancer Symposium 2012; Abstract P5-18-06

Kadcyla (trastuzumab emtansine) European Public Assessment Report (EPAR) 2013. European Medicines Agency *pending publication - to be provided once published.

Fleeman, N., Bagust, A., Boland, A., Dickson, R., Dundar, Y., Moonan, M., Oyee, J., Blundell, M., Davis, H., Armstrong, A., & Thorp, N. Lapatinib and trastuzumab in combination with an aromatase inhibitor for the first-line treatment of metastatic hormone receptor positive breast cancer which over-expresses HER2 2010, NIHR HTA Programme (Project No. 09/101/01)

Fleming TR, Rothman MD, Hong LL. Issues in using progression-free survival when evaluating oncology products. J Clin Oncol 2009; 27(17): 2874-2880.

HM Treasury GDP deflator: September 2013. Accessed online 10/10/2013 at: https://www.gov.uk/government/publications/gdp-deflators-at-market-prices-and-money-gdp-march-2013

Helgeson, V. S. & Tomich, P. L. Surviving cancer: a comparison of 5-year disease-free breast cancer survivors with healthy women. Psychooncology 2005; 14(4): 307-317.

Herschbach, P., Keller, M., Knight, L., Brandl, T., Huber, B., Henrich, G., & Marten-Mittag, B. 2004, "Psychological problems of cancer patients: a cancer distress screening with a cancer-specific questionnaire", Br J Cancer., vol. 91, no. 3, pp. 504-511.

Herceptin Summary of Product Characteristics (SPC). http://www.medicines.org.uk/emc/medicine/3567/SPC/Herceptin+150mg+Powder+for+concentrate+for+solution+for+infusion/ (last accessed 10/12/13)

Hurvitz SA et al. Phase II Randomized Study of Trastuzumab Emtansine Versus Trastuzumab Plus Docetaxel in Patients With Human Epidermal Growth Factor Receptor 2–Positive Metastatic Breast Cancer. J Clin Oncol. 31(9):1157-1163

Guest JF, Ruiz FJ, Greener MJ, Trotman IF. Palliative care treatment patterns and associated costs of healthcare resource use for specific advanced cancer patients in the UK. Eur J Cancer Care (Engl.) 2006; 15(1):65-73

Jemal A et al. Global Cancer Statistics. CA Cancer J Clin 2011; 61(2): 69-90

Joint Formulary Committee. British National Formulary. 65. 2011. London, BMJ Goup and Pharmaceutical Press. Ref Type: Serial (Book,Monograph)

Juntilla TT et al. Trastuzumab-DM1 (T-DM1) retains all the mechanisms of action of trastuzumab and efficiently inhibits growth of lapatinib insensitive breast cancer. Breast Cancer Res. Treat. 2011; 128: 347-356

Kaufman B, Mackey JR, Clemens MR, et al. Trastuzumab plus anastrozole alone for the treatment of postmenopausal women with humen epidermal growth factor receptor 2-positive, hormone receptor- positive metastatic breast cancer: results from the randomised phase III TAnDEM study. J Clin Oncol 2009; 27(33): 5529-5537

Krop IE et al. Phase I study of trastuzumab-DM1, an HER2 antibody-drug conjugate, given every 3 weeks to patients with HER2-positive metastatic breast cancer. Journal Clin Oncol 2010; 28(16):2698-704

Kwan ML, Kushi LH, Weltzien E, et al. Epidemiology of breast cancer subtypes in two prospective cohort studies of breast cancer survivors. Breast Cancer Res 2009; 11(3): R31.

Levi F et al. Continuing declines in cancer mortality in the European Union 2005; Annals of Oncology; 18: 593-595.

Lewis R et al. The clinical effectiveness and cost effectiveness of vinorelbine for breast cancer: a systematic review and economic evaluation. Health Technology Assessment 2002; 6(14): 1-6

Lewis Phillips GD et al. Targeting HER2 Positive Breast Cancer with Trastuzumab-DM1 , an Antibody - Cytotoxic Drug Conjugate. Cancer Res 2008; 68:9280- 9290

Lloyd, A., Nafees, B., Narewska, J., Dewilde, S., & Watkins, J. Health state utilities for metastatic breast cancer. British Journal of Cancer 2006; 95(6): 683-690

Lyratzopoulos G et al. Variation in advanced stage at diagnosis of lung and female breast cancer in an English region 2006–2009. British Journal of Cancer 2012; 106:1068-1075 (PENDING INCLUSION/EXCLUSION?)

Malvezzi M. et al. European cancer mortality predictions for the year 2011. Ann Oncol. 2011; 22: 947-956.

Marty M, Cognetti F, Maraninchi D, et al. Randomised Phase II Trial of the Efficacy and Safety of Trastuzumab Combined with Docetaxel in Patients with Human Epidermal Growth Factor Receptor 2 Positive Metastatic Breast Cancer Administered at First Line Treatment (The M77001 Study group). J Clin Oncol 2005;23:4265−4274.

Menard S, Fortis S, Castiglioni F, et al. HER2 as a prognostic factor in breast cancer. Oncology 2001; 61(suppl 2): 67-72.

Munich Cancer Registry (MCR) of the Munich Cancer Center (MCC) at the Institute for med. Informatics, Biometry and Epidemiology (IBE) University Hospital Großhadern Ludwig-Maximilians-University (LMU) Munich, Marchioninistr. 15, D-81377 Munich (http://www.tumorregister-muenchen.de/facts/spec/spec_C50f__08_20130207_met_her2).

Nahta R & Esteva FJ. Trastuzumab: triumphs and tribulations. Oncogene 2007;26: 3637-43.

Neven P, Van Calster AE I, Van den Bempt AE et al. Age interacts with the expression of steroid and HER-2 receptors in operable invasive breast cancer. Breast Cancer Res Treat (2008) 110:153–159.

NCCN Guidelines Clinical Practice Guidelines in Oncology: Breast Cancer. Version 3. 2012

NICE clinical guideline 81: Advanced Breast Cancer, diagnosis and treatment. February 2009 Accessed online 10/01/2013 at: http://guidance.nice.org.uk/CG81

NICE technology appraisal 34. Guidance on the use of trastuzumab for the treatment of advanced breast cancer. March 2002

NICE technology appraisal 257. Lapatinib or trastuzumab in combination with an aromatase inhibitor for the first line treatment of metastatic hormone-receptor-positive breast cancer that overexpresses HER2. June 2012 Accessed online 10/09/2013 at: http://www.nice.org.uk/nicemedia/live/13777/59707/59707.pdf

NICE in development 523. Breast cancer (HER2 positive, metastatic) - pertuzumab (with trastuzumab and docetaxel) (July 2012)

O'Shaughnessy J et al. Extending Survival with Chemotherapy in Metastatic Breast Cancer. The Oncologist 2005; 10(S3): 20-29

Pauletti G, Dandekar S, Rong H, et al. Assessment of methods for tissue-based detection of the HER-2neu alteration in human breast cancer : a direct comparison of fluorescent in-situ hybridization and immunohistochemistry. J Clin Oncol 2000 ; 18 :3651−3664.

Pivot X et al. CEREBEL (EGF111438): An open label randomized Phase III study comparing the incidence of CNS metastases in patients with HER2+ metastatic breast cancer, treated with lapatinib plus capecitabine versus trastuzumab plus capecitabine. European Society of Medical Oncology 2012. Abstract.

Roche Assumption (April 2013)

Roche Assumption (Nov 2012)

Roche Data on File RXUKDONF00045 (May 2013)

Roche Data no File RXUKDONF00258 (November 2012)

Roche Data on File RXUKDONF00301 (March 2013)

Roche Data on File RXUKDONF00336 (December 2013)

Roche Data on File RXUKDONF00337 (December 2013)

Roche Data on File RXUKDONF00338 (December 2013)

Roche Data on File RXUKDONF00339 (December 2013)

Roche Data on File RXUKDONF00340 (December 2013)

Roche Data on File RXUKDONF00341 (December 2013)

Ross JS and Fletcher JA. The HER2/neu oncogene in breast cancer: Prognostic factor, predictive factor and target for therapy. Stem Cells 1998; 16: 413 - 428.

Ross JS et al. The HER-2 receptor and breast cancer: ten years of targeted anti-HER-2 therapy and personalized medicine. Oncologist. 2009; 14: 320-368.

Sant M, Allemani C, Capocaccia R, et al. Stage at diagnosis is a key explanation of differences in breast cancer survival across. Europe. Int J Cancer. 2003; 106(3): 416-422.

Scharl A et al. AGO Recommendations for Diagnosis and Treatment of Patients with Early and Metastatic Breast Cancer: Update 2012. Breast Care 2012; 7:322-335

Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med. 2001; 344: 783-92.

Sundaresan S, Penuel E, Sliwkowski MX. The biology of human epidermal growth factor receptor 2. Curr Oncol Rep 1999; 1:16-22.

Swain SM, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA study): overall survival results from a randomised, double-blind, placebo-controlled, phase 3 study. Lancet Oncol. 2013; 14:461-71

Tripathy D et al. First Line Treatment Patterns and Clinical Outcomes in Patients with Her2- positive and Hormone Receptor Positive Metastatic Breast Cancer From registHER. The Oncologist 2013; 18:501-510

Tuma R. Progression-free survival remains debatable endpoint in Cancer Trials. JNCI News 2009: 1439-1441.

Verma S et al. Trastuzumab Emtansine for HER2-Positive Advanced Breast Cancer. N Engl J Med 2012; 367:1783-91

Von Minckwitz G et al. Trastuzumab beyond progression: Overall survival analysis of the GBG 26/BIG 3-05 phase III study in HER2-positive breast cancer. Eur J Cancer 2011; 47: 2273-2281

Welslau M et al. Patient-Reported Outcomes From EMILIA, a Randomized Phase 3 Study of Trastuzumab Emtansine (T-DM1) Versus Capecitabine and Lapatinib in Human Epidermal Growth Factor Receptor 2–Positive Locally Advanced or Metastatic Breast Cancer. Canc er 2013; Published ahead of print DOI: 10.1002/cncr.28465

Welslau M et al. Patient-Reported Outcomes From EMILIA, a Phase 3 Study of Trastuzumab Emtansine (T-DM1) vs Capecitabine and Lapatinib in HER2-Positive Locally Advanced or Metastatic Breast Cancer. European Society for Medical Oncology 2012; poster presentation 329P

Wildiers H et al. T-DM1 for HER2-Positive MBC: Primary Results From TH3RESA, a Phase 3 Study of T-DM1 vs Treatment of Physician's Choice. European Society for Medical Oncology 2013 oral presentation

Wolff AC et al. Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Update. Journal of Clinical Oncology 2013; 31(31): 3997-4013

Yarden Y, Sliwkowski MX. Untangling the ErbB signalling network. Nature Rev Mol Cell Biol 2001;2:127–37.

Zolot RS et al. Antibody-drug conjugates. Nature Reviews: Drug Discovery 2013; 12: 259-260