[redacted]
National Institute for Health and Clinical Excellence
10 Spring Gardens
London
SW1A 2BU

BY EMAIL

28 January 2014

RE: Trastuzumab emtansine for treating HER2-positive, unresectable locally advanced or metastatic breast cancer after treatment with trastuzumab and a taxane [ID603]

Dear [redacted],

Please find attached our response to the clarification questions for the above mentioned appraisal.

We would be happy to provide further clarification or information if it would be of benefit to the Committee.

Yours Sincerely

[redacted]

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Section A: Clarification on search strategies

A1. **Priority question:** Please explain why the indirect and mixed treatment comparison search of The Cochrane library was limited to one year only (2011-2012)?

This is a typographical error; the search for all databases, including The Cochrane Library, was undertaken from Jan 1, 1998 to July 02, 2013.

A2. **The different search strategies vary in terms of the number of concepts, the number of key words and subject headings used to express those concepts, and the choice of terms such as those for the intervention. Given the limited search terms used, the clinical evidence and the cost-effectiveness searches may have missed relevant studies. Please comment on the extent to which your search results were inclusive of all relevant studies.**

Search terms all used the thesaurus function for Medline and Embase where this search term existed within them. In the case of the intervention, Kadcyla, this was not in the thesaurus function for Embase or Medline. Trastuzuamb emtanisne existed in the thesaurus for Embase only. Hence why Kadcyla and trastuzumab emtansine were entered as free text search terms as well as trastuzumab emtansine within the thesaurus function of Embase which included sub-terms of:

- pro 132365
- pro132365
- t dm 1
- t dm1
- tmab mcc dm1
- trastuzumab dm1

The search identified all studies we are aware of. As trastuzumab emtansine has only recently become commercially available it is highly unlikely there are any studies that we are not aware of.

A3. **There is variation in how an individual search was applied in different databases; for example, the clinical evidence search in Medline and The Cochrane Library. Please explain the reasons for this?**

The search function in the Cochrane library does not allow compound searching and does not have a thesaurus function. Free text search terms were used (Kadcyla and trastuzumab emtansine and these were searched for in the title and as key words).

Search of Medline was conducted through ProQuest Dialogue search engine which allowed compound searching of multiple databases at one time.

A4. In the quality-of-life and cost-effectiveness searches, please explain why subject headings were not used, and why was EconLit not searched?

Both these points are a fair critique of these searches. The absence of subject headings and a search of EcoLit were due to our oversight. If this were a first order issue to the appraisal we would be willing to repeat these searches with these amendments – however given the context we accept these criticisms as legitimate and have not repeated these searches.

A5. Please explain why you did not search trials registers, for example via the Current Controlled Trials website or a comprehensive database such as the Science Citation Index Expanded and Conference Proceedings Citation Index?

Biosis was used which searched for all conference abstracts as well as our own internal database PubCentre. Conference proceedings were also searched via relevant congress abstract books individually (e.g. ASCO, SABCS) so it was felt that any emerging trial data would have been captured.

Section B: Clarification on clinical effectiveness data

B1. The submission states in section 6.3.6, page 75, that '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.' Please present the number of events that were not counted in each treatment arm, and clarify why an interval censoring method of analysis was not considered?

Based on the censoring rules defined in the statistical analysis plan and planned study monitoring and follow-up, we anticipated predominantly right censored data and that there would be few patients that would be censored based on 2 consecutive missing scans prior to PD. This is supported by the data shown in Table 1. Therefore, interval censoring methods were not used.

Table 2 shows the number of events not counted in the main analysis by treatment arm. Two sensitivity analyses were performed with regards to missing tumor assessments. The results of these sensitivity analyses showed similar treatment effects to the results observed in the primary PFS analysis, demonstrating the robustness of the primary PFS analysis.

Table 1: Reasons for PFS Censoring (IRC assessment)

Table 1. Reasons for PFS Censoring (IRC assessment)

Time from Randomization to Censoring (month)	Censoring Reason	Lap+Cap (n=192)	T-DM1 (n=230)
0-3	Data cutoff	25 (13.0)	28 (12.2)
	Early Study Termination	7 (3.7)	2 (0.9)
	No post-baseline scan	27 (14.1)	14 (6.1)
	2 consecutive missing scans prior to PD	6 (3.1)	1 (0.4)
>3-6	Data cutoff	53 (27.6)	56 (24.4)
	Early Study Termination	2 (1.0)	3 (1.3)
	No post-baseline scan	0	0
	2 consecutive missing scans prior to PD	2 (1.0)	0
>6-9	Data cutoff	22 (11.5)	34 (14.8)
	Early Study Termination	2 (1.0)	3 (1.3)
	No post-baseline scan	0	0
	2 consecutive missing scans prior to PD	1 (0.5)	0
>9-12	Data cutoff	17 (8.9)	21 (9.1)
	Early Study Termination	1 (0.5)	0
	No post-baseline scan	0	0
	2 consecutive missing scans prior to PD	0	0
>12	Data cutoff	27 (14.1)	68 (29.6)
	Early Study Termination	0	0
	No post-baseline scan	0	0
	2 consecutive missing scans prior to PD	0	0

Data cutoff date: Jan 14, 2012.

Table 2: TDN4370g/BO21977, Population: Safety Nr of Progressed Patients after two or more missing scans

Study: TDM4370g/BO21977 , Population: Safety
Nr of Progressed Patients after two ormore missing scans

	Lapatinib+Capecitabine (N=496)	Trastuzumab emtansine (N=495)
_	n (%)	n (%)
Patients with Late PD	9 (44.64)	1 (4.95)

Source: SAS v9.2 damontee SPROD/cdt3502a.pbe/i21977c.pbe/i21977c_e_PDmiss.sas 22JAN2014 14:22

B2. Please clarify the reasons why 585 screened patients were considered ineligible for inclusion in the EMILIA trial prior to randomisation (Page 81, Figure 4).

Attached is the data from the clinical study report outlining reasons for screen failure. The top three reasons for screen failure were brain metastases, HER2 status, and organ function. With respect to organ function, in the general inclusion criteria it was stated:

9. Adequate organ function, evidenced by the following laboratory results within 30 days prior to randomization:

– Absolute neutrophil count > 1500 cells/mm3
– Platelet count > 100,000 cells/mm3
– Hemoglobin > 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 (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)

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Table scrnfl
Reasons for Screen Failures

	Screen failure subjects (n=585)
Reason for Screen failure	
n	585
>=18 years old	1 (0.2%)
Brain metastases	172 (29.4%)
Cardiac Ejection Fraction	20 (3.4%)
Current Severe Uncontrolled Systemic Disease	4 (0.7%)
Death	1 (0.2%)
Disease Progression	14 (2.4%)
ECOG Status	5 (0.9%)
Gastrointestinal Absorption	1 (0.2%)
HER2 Status	167 (28.5%)
HIV, HEPB, or HEPC	2 (0.3%)
History of CHF or Ventricular Arrhythmia	1 (0.2%)
History of chemo or other investigational product	2 (0.3%)
History of malignancy	2 (0.3%)
History of radiation	8 (1.4%)
Hypersensitivity to 5-fluorouracil/dihydropyrimidine dehydrogenase deficiency	1 (0.2%)
Invasive Breast Cancer	2 (0.3%)
Measurable/nonmeasurable disease	16 (2.7%)
Non-compliance of patient	47 (8.0%)
Organ function	60 (10.3%)
Pregnancy or Lactation	1 (0.2%)
Prior chemo treatments	12 (2.1%)
Severe Dyspnea	4 (0.7%)
Treatment with Lapatinib or capecitabine	4 (0.7%)
Withdrew Consent	38 (6.5%)

Page 142 of the submission states that the safety of trastuzumab emtansine was evaluated based on data from 884 patients. Table 23 on page 143 reports adverse reactions from 882 patients. Please clarify whether the pooled safety analysis contained data from 882 or 884 patients.

Both are correct; n = 884 is the updated number of patients available for analysis, however the detailed description of the data including 884 patients was not available to the UK affiliate at the time of submission. Since submission of the specification evidence to NICE an updated investigator's brochure has become available which outlines the summary information based on 884 patients (December 2013). The original submission contained the descriptions of the pooled analysis as available per the EPAR n=882 and the previous trastuzumab emtansine investigator's brochure. Where indicated in the submission, the description represents n=882, for example in Table 23, and also section 2.7 page 35.

The revised description based on n = 884 which supersedes the n=882 analysis is available now and is included as an appendix to this document.

B3. Please clarify why adverse event data from JO22997 were not included in the pooled safety analysis (section 6.9.3).

For reference, the abstract is as follows and is suitable for inclusion in the safety population, other than the fact that patients were 'heavily pretreated Japanese patients'.

However, the pooled safety analysis reported in section 6.9.3 did not include JO22997 as it was based upon only Roche sponsored studies. JO22997 was a study sponsored by Chugai in Japan and so was not included in this pooled safety analysis. In future analyses of this sort it may be reasonable to add JO22997 as an additional source of evidence on the safety of trastuzumab emtansine.

Poster Session 5 - Treatment: HER2-Targeted Therapy

A Multicenter Phase 2 Study (JO22997) Evaluating the Efficacy and Safety of Trastuzumab Emtansine in Japanese Patients With Heavily Pretreated HER2-Positive Metastatic Breast Cancer. N Masuda, Y Ito, S Takao, H Doihara, Y Rai, J Horiguchi, N Kohno, Y Fujiwara, Y Tokuda, J Watanabe, H Iwata, H Ishiguro, Y Miyoshi, M Matsubara, and M Kashiwaba

NHO Osaka National Hospital, Osaka, Japan; The Cancer Institute Hospital of JFCR, Tokyo, Japan; Hyogo Cancer Center, Akashi, Japan; Okayama University Hospital, Okayama, Japan; Sagara Hospital, Kagoshima, Japan; Gunma University, Maebashi, Japan; Tokyo Medical University, Tokyo, Japan; National Cancer Center Central Hospital, Tokyo, Japan; Tokai University, Isehara, Japan; Shizuoka Cancer Center, Sunto-gun, Japan; Aichi Cancer Center, Nagoya, Japan; Kyoto University, Kyoto, Japan; Hyogo College of Medicine, Nishinomiya, Japan; Chugai Pharmaceutical Co., Ltd., Tokyo, Japan; Iwate Medical University, Morioka, Japan

Background: Trastuzumab emtansine (T-DM1) is an anti-human epidermal growth factor receptor 2 (HER2) antibody-drug conjugate in development for the treatment of HER2-positive recurrent, locally advanced or metastatic breast cancer (MBC). T-DM1 comprises trastuzumab, DM1—a microtubule inhibitory cytotoxic agent derived from maytansine—and the stable linker ([N-maleimidomethyl] cyclohexane-1-carboxylate) that conjugates DM1 and trastuzumab. A phase 1 study in Japanese patients determined a maximum tolerated dose for T-DM1 of 3.6 mg/kg every 3 weeks (q3w), which was identical to that reported in Western populations (TDM3569g). Single-agent T-DM1 has demonstrated robust clinical efficacy in Western phase 2 and phase 3 clinical studies (TDM4258g, TDM4374g and EMILIA). Since the efficacy of T-DM1 in Japanese patients has not previously been

investigated, this study examined the efficacy and safety of T-DM1 in Japanese patients with pretreated HER2-positive MBC.

Methods: JO22997 is a phase 2, multicenter, single arm clinical study assessing the efficacy and safety of single-agent T-DM1 given at 3.6 mg/kg q3w to patients with HER2-positive MBC. Key eligibility criteria were prior treatment with trastuzumab and at least 1 chemotherapy, ECOG performance status (PS) of ≤2, and adequate organ function. Patients were required to have target lesions according to the guidelines of the Response Evaluation Criteria In Solid Tumors, v1.1. The primary objective of the study was to assess the objective response rate (ORR) by independent review committee (IRC); secondary objectives were progression-free survival (PFS), safety, and to obtain pharmacokinetic data in Japanese patients.

Results: 73 patients received T-DM1. Median age was 58 years (range, 36–82 years); 61 (83.6%), 10 (13.7%), and 2 (2.7%) patients had ECOG PS of 0, 1, and 2, respectively; 39 (53.4%) patients had tumors that were estrogen receptor– and/or progesterone receptor–positive. The median number of prior chemotherapy regimens for MBC was 3 (range, 1–8) including lapatinib in 43 (58.9%) patients. Median duration of treatment with T-DM1 was 23.1 weeks (range, 0.1–63.3 weeks). The ORR by IRC was 38.4% (90% confidence interval [CI], 28.8%–48.6%; partial response only), and clinical benefit rate (partial response + stable disease ≥24 weeks) was 45.2% (95% CI, 33.5%–57.3%). Median PFS by IRC was 5.6 months (95% CI, 4.6–8.2 months). The most frequently observed grade ≥3 adverse events were thrombocytopenia (21.9%), increased aspartate aminotransferase (13.7%), increased alanine aminotransferase (8.2%) and vomiting (5.5%). One patient (1.4%) discontinued treatment due to thrombocytopenia. No patient received platelet transfusion. Grade 3/4 hemorrhage was observed in one patient (1.4%). PK parameters for T-DM1 and its metabolites were consistent with previous phase I results.

Conclusion: Single-agent T-DM1 has promising activity in Japanese patients with previously treated HER2-positive MBC and was well tolerated. Although the incidence of grade 3/4 thrombocytopenia tends to be higher than in Western studies, this was not associated with clinically important manifestations. (JapicCTI-101277)

B4. Please provide a complete reference for Martin (2011) (Page 114 and Table 19).

The reference was omitted in error. The citation is: Clinical Advances in Hematology and Oncology 10.2: 12-13. Millennium Medical Publishing, Inc. (Feb 2012)

[S5-7] A Phase 2, Randomized, Open-Label, Study of Neratinib (HKI-272) vs Lapatinib Plus Capecitabine for 2nd/3rd-Line Treatment of HER2+ Locally Advanced or Metastatic Breast Cancer.

Martin M, Bonneterre J, Geyer, Jr CE, Ito Y, Ro J, Lang I, Kim S-B, Germa C, Vermette J, Vo Van ML, Wang K, Wang K, Awada A. Hospital Universitario Gregorio Marañón, Madrid, Spain; Centre Oscar Lambret, Lille, France; Allegheny Cancer Center, Pittsburgh, PA; The Cancer Institute Hospital of JFCR, Tokyo, Japan; National Cancer Center, Goyang, Korea; National Institute of Oncology, Budapest, Hungary; Asan Medical Center, Seoul, Korea; Pfizer Global Research and Development, Paris, France; Pfizer Inc, Collegeville, PA; Bristol Meyers Squibb, Princeton, NJ; Jules Bordet Institute, Brussels, Belgium

Background: Neratinib (N), an irreversible pan-tyrosine kinase inhibitor (TKI), with activity against HER1, -2 and -4, has shown antitumor activity in patients (pts) with HER2+ breast cancer (BC). Lapatinib (L), a reversible HER1 and -2 TKI is approved in combination with capecitabine (C) for treatment of pts with HER2+ advanced or metastatic BC who had prior therapy.

Materials and Methods: This phase 2, randomized, open-label study evaluated safety and efficacy of N 240 mg/day vs L 1,250 mg/day plus C 2,000 mg/m^2/day (14 days/21 day cycle) in pts with HER2+ locally advanced or metastatic BC. Eligible pts had: ≤2 prior trastuzumab regimens, prior taxane treatment, and no prior anthracycline treatment with cumulative dose >400 mg/m^{2}doxorubicin, >800 mg/m^2 epirubicin, or >equivalent dose of other anthracycline. Primary endpoint was progression-free survival (PFS; investigator-assessed); secondary endpoints included safety, overall survival (OS), objective response rate (ORR), and clinical benefit rate (CBR; % pts with complete response, partial response, or stable disease ≥24 wks). Tumor assessments were every 6 wks for the first 48 wks, then every 12 wks until progressive disease (PD; RECIST 1.0) or initiation of new anticancer therapy. **Results**: Overall, 117 pts were randomized to N and 116 to L plus C (LC). Mean age (SD; range) was 53.9 y (10.3; 28-79); 60% were White, 34% Asian, and 6% other. Prior treatments included: trastuzumab (229 pts: 168 metastatic or locally advanced, 51 adjuvant, 10 neoadjuvant), taxanes (230 pts), and anthracycline (156 pts). Median treatment duration (range) was 126.5 days (1-636) for N and 201 days (13-622) for LC. Median relative dose intensity (actual/expected exposure) for N was 100%. As of data cutoff, 84% had discontinued treatment; 65% from PD (N 63%, LC 67%), 9% for adverse events (AEs; N 7%, LC 11%). In the ITT cohort, for N and LC, respectively, median PFS (95% CI) was 4.5 mo (3.1-5.7) and 6.8 mo (5.9-8.2; *P* = 0.091; hazard ratio = 1.3 [95% CI, 1.0-1.8]); median

OS (95% CI) was 19.4 mo (19.4-22.2; 41 deaths) and 19.0 mo (16.9-NA; 35 deaths; *P* = 0.180); ORR (95% CI) was 29% (21-38) and 41% (32-50; *P* = 0.067); CBR (95% CI) was 44% (35-54) and 64% (54-73; *P* = 0.003). Most common drug-related treatment-emergent AEs (TEAEs; any grade) were diarrhea (N 84%, LC 67%), nausea (34%, 38%), palmar-plantar erythrodysesthesia (PPE; 5%, 63%), and rash (18%, 34%); for grade ≥3, diarrhea (28%, 10%) and PPE (0, 14%). Dose reductions/discontinuations from diarrhea occurred in 13/3 pts on N, and 15/7 pts on LC. Study deaths for N and LC, respectively, included: 36 pts (31%) and 32 pts (28%) from PD; 5 pts (4%) and 3 pts (3%) from AEs unrelated to study drug.

Discussion: In this setting of pts less heavily pre-treated than in the pivotal LC trial, single agent N demonstrated high anti-tumor activity (ORR 29%), confirming results from prior N phase 2 trials. N alone did not appear to be as effective as LC. No unexpected TEAEs were observed; N was well tolerated in pts with HER2+ locally advanced or metastatic BC; while diarrhea was more frequent on N than LC, it was manageable with antidiarrheals and did not lead to more treatment discontinuations.

B5. Please clarify which definition of visceral disease (Page 20) was used in the PFS subgroup analysis of the TH3RESA trial (Page 21, and Page 101, Figure 14).

The definition of visceral disease in TH3RESA is the same as the original definition in EMILIA; namely, it was based solely on the investigator's judgement. For the PFS subgroup analysis, the definition of "visceral disease" was based on data captured on the eCRF. Presence of visceral disease was set to 'Y' if the investigator answered 'yes' to the question 'Is the condition currently present?' (where the condition was referring to "visceral involvement by metastatic breast cancer") on the Targeted Medical History and Baseline Conditions Log eCRF.

The analysis results as presented are based on this definition as described by the investigator.

B6. Please clarify whether the first two paragraphs on Page 55 (section 6.3.2) refer only to EMILIA, or to both EMILIA and TH3RESA. If they refer only to EMILIA, please provide the frequency of tumour assessments for TH3RESA.

The description in the submission, as follows, refers to the EMILIA study:

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.

The detail as outlined in the TH3RESA protocol is as follows:

Eligible patients were randomized in a 2:1 ratio to either trastuzumab emtansine at a dose of 3.6 mg/kg given IV every 21 days or treatment of physician's choice (TPC). A permuted block randomization scheme was used to ensure an approximate 2:1 allocation of patients to receive trastuzumab emtansine or TPC, with respect to the following stratification factors: 1) world region (United States, Western Europe, or Other); 2) number of prior regimens (excluding single-agent hormones) for the treatment of metastatic or locally advanced/recurrent unresectable disease (2−3 or > 3); and 3) presence of visceral disease (any visceral disease vs. no visceral disease).

Tumor assessments were conducted every 6 weeks (± 7 days) from the date of randomization for the first 54 weeks and every 12 weeks (± 7 days) thereafter, regardless of dose delays or dose interruptions, until investigator-assessed PD, or death, whichever occured first. More frequent tumor assessments were performed as clinically indicated. PRO assessments were conducted before the administration of randomized study treatment on the first day of every cycle until PD. Patients who discontinued from their randomized study treatment for reasons other than PD continued to have any required tumor assessments and PRO assessments completed every 6 weeks (± 7 days) (or every 12 weeks [± 7 days] after 54 weeks as indicated above) until PD. Once patients had progressed, they were followed for survival approximately every 3 months. Subsequent anti-cancer therapies were documented until study completion. Frequency, method, and evaluation criteria of tumor assessments after crossover were done according to routine clinical practice per investigator.

Section C: Clarification on the indirect and mixed treatment comparisons

C1. Priority question: The submission states in section 6.7.5, page 122, that '… given where these treatments sit in relation to trastuzumab emtansine (T-DM1) they would not inform the comparisons of interest and hence would not change the results detailed However, trastuzumab plus vinorelbine is one of the comparators for trastuzumab emtansine, and a comparison with trastuzumab plus vinorelbine is possible only if the TH3RESA trial is included. Please clarify why the network described in Figure 18, which includes trastuzumab plus vinorelbine, was not used for this comparator or rerun the analysis including trastuzumab plus vinorelbine as a comparator.

The TH3RESA study randomized patients to either trastuzumab emtansine or to a treatment of "physicians choice". This selection of alternative therapy was made after randomization, there is no record of what therapy the patients randomized to trastuzumab emtanisne would have received had they been randomized to the comparator arm.

As the choice of therapy is highly influenced by a patient's characteristics (particularly characteristics indicative of their prognosis) it is not possible to make an unbiased, randomized comparison of trastuzumab emtansine and trastuzumab plus vinorelbine using this study. Comparing the two arms equates to a comparison of the ITT population of those randomized to trastuzumab emtansine to those selected to receive trastuzumab plus vinorelbine in the comparator arm. Whilst this issue could have been avoided by having the clinicians pre-specify the choice of alternative therapy (thereby allowing a comparison of those who would have received trastuzumab plus vinorelbine in both arms) this is unfortunately not the case.

As a result of the lack of randomized data capable of linking trastuzumab plus vinorelbine into the network the TH3RESA study was not utilized in this manner.

In the broader context of this appraisal and the cost-effectiveness figures presented, whilst it may be interesting to understand what impact this could have upon the network, this appears to be a second order issue for the appraisal that has minimal consequence upon the decision likely to be reached.

C2. Priority question: From a Bayesian perspective, using a fixed-effect analysis is not justifiable when there is insufficient sample data (i.e. studies) to estimate the parameters. Ideally, the analysis should incorporate genuine

prior beliefs about the parameters. In the absence of a formal elicitation method, a suitable prior distribution representing reasonable prior beliefs should be used. A prior distribution suggested in the Technical Supports Documents by NICE's Decision Support Unit is a HN(0, 0.322) distribution. Predictive distributions of a randomly chosen study would have wider confidence intervals reflecting heterogeneity between studies. Please rerun the mixed treatment comparison using a random-effect analysis and use the results of this analysis (joint posterior predictive distribution for a new study) within the economic model.

Table 3 and Table 4 below provide the results of the MTC if utilizing a random-effects analysis

Table 3: Relative effect of treatment Y compared to X for all possible treatment comparisons - base-case analysis (excluding CEREBEL and MARTIN), calculated using random-effects Bayesian analysis using stratified HRs

		Direct and indirect Treatment Comparisons (HR, 95%CI)	
X	**Y**	**Progression Free Survival (PFS)**	**Overall Survival (OS)**
Capecitabine + Lapatinib	T-DM1	0.69 (0.34-1.24)	0.72 (0.35-1.31)
Capecitabine+ Lapatinib	Capecitabine monotherapy	1.94 (0.90-3.65)	1.36 (0.66-2.50)
Capecitabine + Lapatinib	CapecitabineTrastuzumab	1.41 (0.45-3.37)	1.37 (0.46-3.21)
Capecitabine + Trastuzumab	Capecitabine Monotherapy	1.57 (0.72-3.01)	1.13 (0.52-2.17)
Capecitabine + Trastuzumab	T-DM1	0.63 (0.16-1.74)	0.67 (0.17-1.85)
CapecitabineTrastuzumab	Capecitabine + Lapatinib	0.71. (0.30-2.20)	0.73 (0.31-2.17)
Capecitabine monotherapy	T-DM1	0.32 (0.14-0.93)	0.47 (0.20-1.36)
Capecitabine monotherapy	Capecitabine+ Lapatinib	0.52 (0.27-1.11)	0.74 (0.40-1.52)
Capecitabine monotherapy	Capecitabine + Trastuzumab	0.63 (0.33-1.39)	0.88 (0.46-1.92)

Table 4: Relative effect of treatment Y compared to X for all possible treatment comparisons - sensitivity analysis, calculated using random-effects Bayesian analysis using stratified HRs

		Bayesian Results for Sensitivity analysis (HR, 95%CI)	
X	**Y**	**PFS**	**OS**
Capecitabine + Lapatinib	T-DM1	0.69 (0.34-1.25)	0.72 (0.35-1.32)
Capecitabine+ Lapatinib	Capecitabine monotherapy	1.70 (0.92-2.88)	1.21 (0.66-2.04)
Capecitabine + Lapatinib	Capecitabine + Trastuzumab	1.03 (0.56-1.74)	1.01 (0.53-1.77)
Capecitabine+ Lapatinib	Neratinib	1.38 (0.65-2.58)	Not reported
Capecitabine + Trastuzumab	Capecitabine Monotherapy	1.72 (0.93-2.96)	1.25 (0.67-2.16)
Capecitabine + Trastuzumab	Capecitabine + Lapatinib	0.97 (0.57-1.79)	0.99 (0.56-1.89)
Capecitabine + Trastuzumab	T-DM1	0.72 (0.28-1.54)	0.78 (0.29-1.73)
Capecitabine monotherapy	T-DM1	0.36 (0.17-0.94)	0.53 (0.24-1.41)
Capecitabine monotherapy	Capecitabine + Lapatinib	0.59 (0.35-1.09)	0.83 (0.49-1.52)
Capecitabine monotherapy	Capecitabine + Trastuzumab	0.58 (0.34-1.08)	0.80 (0.46-1.49)
Neratinib	T-DM1	0.44 (0.19-1.30)	NA

Table 5 and Table 6 below contain the updated economic analysis results utilizing the random effects mixed treatment comparison results.

Table 5: Increment analysis using the KM OS data and fitting a gamma tail from week 95 and 96 in the lapatinib and capecitabine and trastuzumab emtansine arms respectively

Technologies	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£/QALY gained)**
Capecitabine	£11,850	1.61	0.89				
Vinorelbine	£16,518	1.61	0.89	£4,668	0.00	0.00	Dominated
Lapatinib and capecitabine	£34,227	2.53	1.45	£17,709	0.92	0.57	£39,449
Trastuzumab and capecitabine	£35,784	2.24	1.28	£1,557	-0.29	-0.17	Dominated
Trastuzumab and vinorelbine	£36,662	2.24	1.28	£878	-0.29	-0.17	Dominated
Trastuzumab emtansine	£111,226	3.16	1.91	£74,565	0.92	0.63	£167,253

Table 6: Revised cost-effectiveness analysis vs capecitabine

Technologies	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£/QALY gained)**
Capecitabine	£11,850	1.61	0.89				

Trastuzumab emtansine	£111,226	3.16	1.91	£99,376	1.55	1.03	£96,707

C3. The assessment of proportional hazards in the submission is based on observed data only. Is there any reason *a priori* to believe that the treatment effect is constant over the lifetime of patients during both the observed and unobserved follow-up periods? Please present supporting evidence where possible.

This is an extremely challenging question and one that lies at the heart of all economic modelling of incomplete data and the application of all mixed treatment comparisons within economic models based upon incomplete data.

It can be hypothesized that the treatment effect observed continues after the observed period (it has been observed in the existing data so why wouldn't it continue in future?), it can be hypothesized that the treatment effect doesn't continue and the hazard ratio after the observed data becomes 1, it could be argued that the treatment effect may improve after the observed data (perhaps there is a patient subgroup with better prognosis who are more responsive to treatment?) or even that the hazard would become higher than 1 and that the survival curves would come together over time.

Each of these scenarios is a potential *a priori* hypothesis, each would have an impact upon the validity of assuming proportionality of hazards for the purposes of a mixed treatment comparison and each would have an impact upon the estimated cost-effectiveness of trastuzumab emtansine.

What is of prime importance is the impact variation in this assumption has upon the Committee's decision. On pages 214 to 216 of the submission the use of a worsening treatment effect over time was tested. In this scenario a hazard ratio of 1 was applied after 95 weeks. With this alternative extrapolation the final ICER compared to capecitabine increased to £153,319.

Given the magnitude of the ICERs presented it is our view that this is likely to be a second order issue – there is uncertainty present but this is not of consequence to the decision.

C4. Although inconsistency could not be assessed for all interventions (Section 6.7.7, page 125), in addition to the discussion on page 128 about the differences in baseline characteristics between studies, please discuss the imbalance in baseline characteristics between <u>treatment arms</u> and the impact that any imbalance is expected to have on treatment effects.

As each of the studies included in the network was a randomized study, or a stratified subgroup within a larger randomized study, it is expected that baseline characteristics would be balanced between arms.

C5. The submission states on page 114 that "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)" (also page 130). However, the intention-to-treat results are used from the other trials included in the analysis, although cross-over may have occurred in those trials. If it is not possible to adjust for cross-over consistently between trials, please present the analysis using the intention-to-treat results from the T-DM1 trial instead of the results adjusted for cross-over.

Neither the EMILIA trial nor other trials, with the exception of EGF100151 had cross-over. Therefore, for all trials except for EGF100151 trial ITT HRs were used. For EGF100151 we used only the HR imputed before cross-over (and not the ITT HR).

Section D: Clarification on cost-effectiveness data

D1. Priority question: Please provide the Excel spreadsheet referenced within the model for the PFS and OS parameters.

Please find attached the excel spreadsheets containing the estimated PFS and OS parameters.

D2. Priority question: Please clarify why the Kaplan–Meier data were used directly to model PFS but not OS within the base-case analysis, and comment on the likely impact on the ICER if the same approach was used for OS and PFS. Also, please clarify why only the gamma and Weibull distributions were compared with the Munich registry data in Figure 36 when the log-logistic and log-normal distributions gave lower AICs than the Weibull. Please include the log-logistic and log-normal distributions within the figure and confirm whether the gamma distribution remains preferable.

A range of parametric distributions (log normal, gamma, log-logistic, Weibull, exponential) were tested and applied to the KM PFS data within the model. However the resulting PFS curves all had a poor visual fit to the data (pages 167 to 169 of the submission depict the log normal which had the most favourable AIC and BIC results and the exponential which had the least favourable AIC and BIC results but may have been plausible based on inspection of the cumulative hazard plots).

In contrast when parametric functions were fitted to the KM OS data the log logistic and gamma distributions provided a strong visual fit to the data (pages 174 to 175). Using the

KM data up until 95 weeks in the lapatinib and capecitabine arm and 96 weeks in the tratuzumab emtansine arm (the respective points at which the slope of the hazards in each appear to increase again) and fitting a gamma function thereafter has little impact on the ICERs. The results of the incremental analysis are shown in Table 5.

Table 7: Incremental analysis using the KM OS data and fitting a gamma tail from week 95 and 96 in the lapatinib and capecitabine and trastuzumab emtansine arms respectively

Technologies	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£/QALY gained)**
Capecitabine	£13,163	1.87	1.03				
Vinorelbine	£18,864	1.87	1.03	£5,701	0.00	0.00	Dominated
Lapatinib and capecitabine	£34,261	2.56	1.47	£15,397	0.70	0.44	£48,145
Trastuzumab and capecitabine	£37,618	2.27	1.31	£3,357	-0.29	-0.16	Dominated
Trastuzumab and vinorelbine	£39,036	2.27	1.31	£1,418	-0.29	-0.16	Dominated
Trastuzumab emtansine	£111,256	3.20	1.93	£72,220	0.93	0.62	£167,040

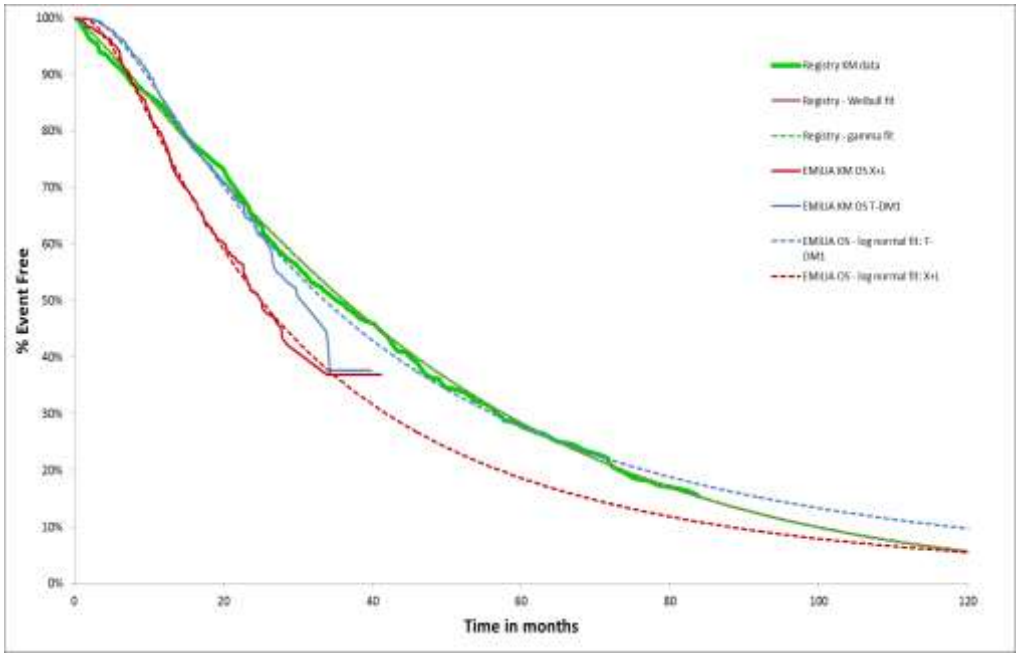
Although having a higher AIC than the log logistic and log normal functions, the Weibull was chosen on the basis of having a good visual fit to the data. At an independent advisory board one health economist who is a member of an ERG noted that the KM OS data appear to be increasing monotonically and a Weibull function may provide a good fit to the data.

The log logistic fit to the EMILIA data was validated against the Munich registry and included in the initial submission and subsequently rejected (see Figure 37 and explanation on page 178).

The log normal fit to the EMILIA data is provided in Figure 1. As with the log logistic distribution, it 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. Overall survival at ten years is predicted to be greater for trastuzumab emtansine (9.7%) as compared to the Munich registry (5.6%) and approximately the same (5.5%) for lapatinib and capecitabine; a highly implausible outcome given the majority of EMILIA patients have already had one or more lines of therapy as opposed to the Munich registry where overall survival is imputed with the inclusion of the patient's first line treatment and progression before moving onto subsequent treatments.

All things considered, the gamma distribution is therefore still regarded to be the most appropriate fit for the EMILIA OS data.

Figure 1: Log normal EMILIA OS extrapolation versus Munich registry



D3. Priority question: Please amend the cost of trastuzumab emtansine and trastuzumab both within the economic model and within the budget impact calculations to resolve the following issues:

a. The average weight of a person is used. When wastage is included this will lead to inaccuracies in the calculation of total cost since it does not consider the variation in weight between people and the impact of this upon vial usage. For example, for

individuals weighing 75kg rather than 70.1kg two 160mg vials would be required rather than one 160mg and one 100mg vial. The same limitation also applies to the calculation of the trastuzumab vials.

We accept this is a limitation of the analysis presented. Depending on the weight chosen and how close this lies to an 'efficient' administration (i.e. one requiring full vials and leaving none wasted) the model may give an overestimate or underestimate of the true ICER associated with introduction of trastuzumab emtansine. A more accurate estimate of the ICER could be derived via application of a weight distribution within the model, however give the magnitude of the base-case ICERs this appears to be a second order issue.

b. The formula used to calculate the number of 100mg and 160mg vials to be used per person according to their weight does not minimise the cost of the vials. For example, if a person's weight was 75kg rather than 70.1kg, the present formula would estimate that one 160mg vial and two 100mg vials should be used, whilst two 160mg vials would provide sufficient dosage at the lowest cost.

You are correct. If intending to change the weight in the model it would be necessary to change this formula in order to estimate the least costly combination of vials. In the case of a 75kg patient the least costly combination would be 3x100mg vials rather than 2x160mg vials.

c. In the base case, it would be preferable to use the actual dose (including wastage) rather than the planned dose.

Actual treatment dose including wastage was explored as a sensitivity analysis on page 228 of the submission and had minimal impact on the ICER.

D4. Priority question: Since lapatinib plus capecitabine is neither strongly or extendedly dominated by the other interventions, it should not be removed from the incremental analysis and the derivation of the efficiency frontier. Thus, trastuzumab emtansine should be compared with lapatinib plus capecitabine rather than capecitabine within the incremental analysis. Please recalculate the ICERs (with the identification of interventions that are dominated and the inclusion of lapatinib and capecitabine).

The revised results of the incremental analysis are shown in Table 6.

Table 8: Revised incremental cost-effectiveness analysis results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY gained)
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	£15,296	0.66	0.42	£49,798
Trastuzumab and	£37,629	2.27	1.31	£3,459	-0.26	-0.14	Dominated

capecitabine							
Trastuzumab and vinorelbine	£39,047	2.27	1.31	£1,418	-0.26	-0.14	Dominated
Trastuzumab emtansine	£111,162	3.16	1.91	£72,115	0.89	0.60	£167,236

The comparison of lapatinib in combination with capecitabine compared to capecitabine alone results in an ICER above the range typically considered acceptable by NICE (£49,798/QALY gained) Further trastuzumab in combination with either capecitabine or vinorelbine is dominated by lapatinib and capecitabine. The efficiency frontier therefore still consists of capecitabine alone and capecitabine should be the primary comprator for trastuzumab emtansine resulting in an ICER of £111,095 as shown below.

Table 9: Revised final cost-effectiveness analysis 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

D5. Please present the probabilistic results rather than the deterministic results for the base-case analysis, and provide 95% confidence intervals around the probabilistic ICERs.

Due to the volume of questions asked and extremely short time frame provided for response (35 questions to be answered in 10 working days) it was necessary to prioritize the questions asked. This question was assumed to be low priority given the magnitude of the deterministic base-case ICERs and so has not been answered. If the Committee would find this information valuable we would be happy to provide it in response to consultation.

D6. For the PFS hybrid Kaplan–Meier model, there is no justification for using a log-normal distribution to represent the tail of the survivor function other than it provides the best fit to the observed data. Please justify the use of the log-normal distribution to represent the tail of the survivor function.

This is the only justification. However given that the other extrapolations provided a statistically worse fit to the observed data and were not visually good fits either, it seemed unreasonable to use these versus the log normal distribution. Further, the extrapolation of PFS is not a major driver of the cost-effectiveness results (in contrast to OS) and hence varying the tail of the survivor function with alternative distributions has little impact. This was explored as a sensitivity analysis and results presented in Table 52 on page 223 of the submission.

D7. The submission states on page 182 that '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'. Please clarify whether this means that in their clinical opinion the progression-free survival and overall survival predicted by the log-normal extrapolation of the Kaplan-Meier and the Gamma fit, respectively, were reasonable.

Clinical experts in conjunction with two health economists (one a NICE committee member and the other a member of an ERG) were presented with the KM PFS and OS data and then a range of potential extrapolations, including piecewise analyses. Feedback was that whilst piecewise fits looked reasonable, simply fitting parametric distributions seemed equally plausible. In particular, regarding the OS data, it was noted that the hazard was increasing monotonically and therefore a Weibull or another suitable parametric distribution that accounts for this, might be reasonable. Further it was noted that given the indirect treatment comparison (ITC) was conducted using hazard ratios, piecewise analyses for both PFS and OS would violate the assumption of proportional hazards and hence might lead to inconsistencies within the ITC.

This advice was therefore considered alongside the analysis as presented in the submission (section 7.3 page 162 to page 182) when deciding on the extrapolations for PFS and OS.

D8. Please provide figures showing the PFS and OS curves predicted by the model for each comparator.

Figure 2: Trastzumab emtansine versus Tratuzumab & Capecitabine modelled PFS and OS curves

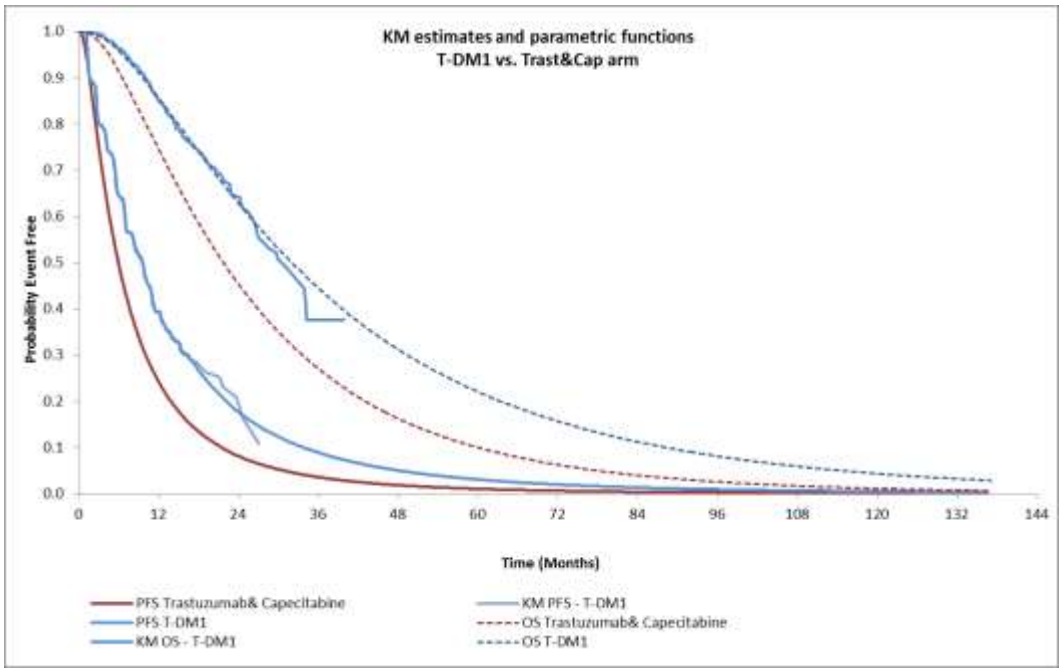


Figure 3: Trastzumab emtansine versus Tratuzumab & Vinorelbine modelled PFS and OS curves

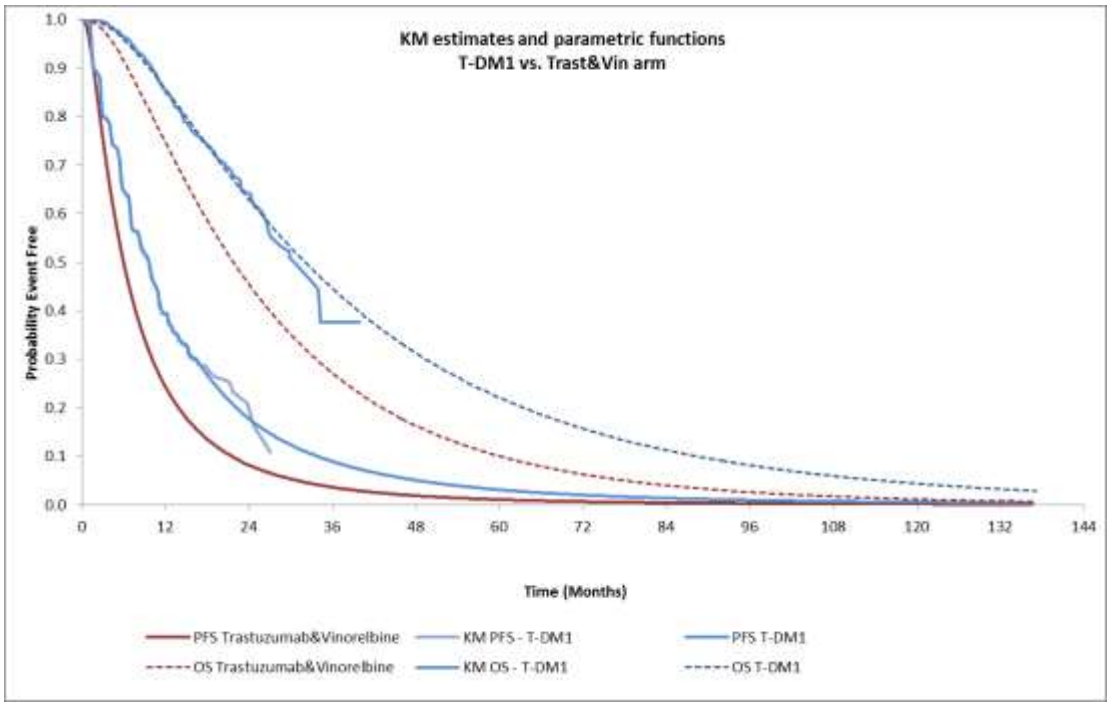


Figure 4: Trastzumab emtansine versus Capecitabine modelled PFS and OS curves

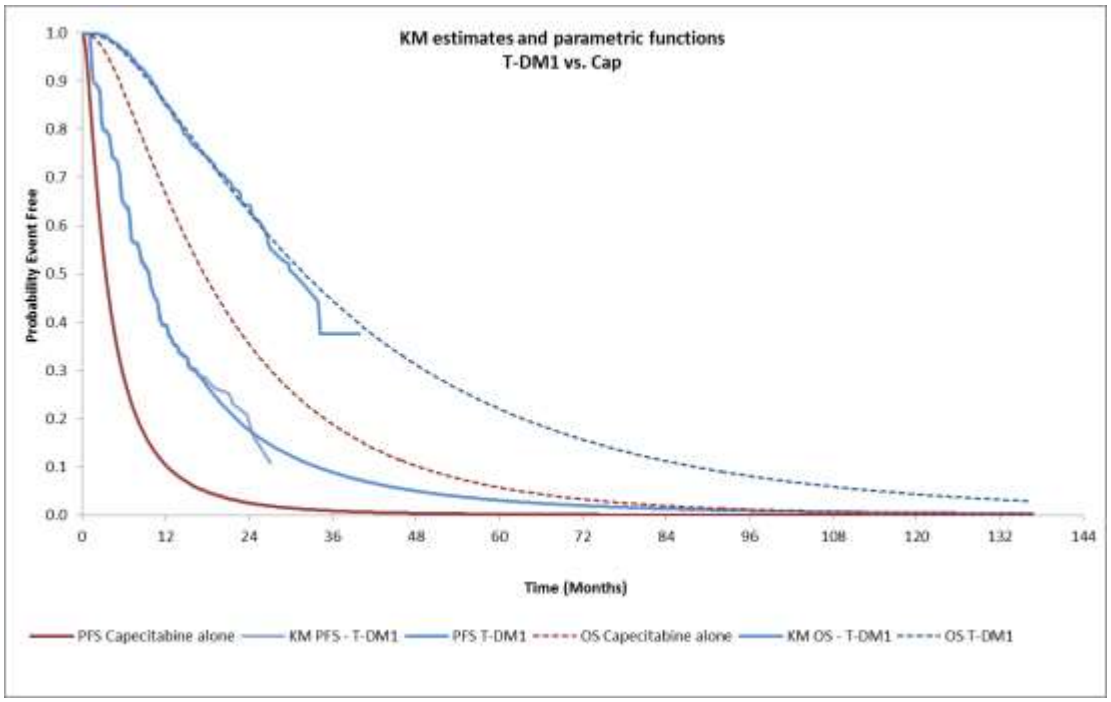
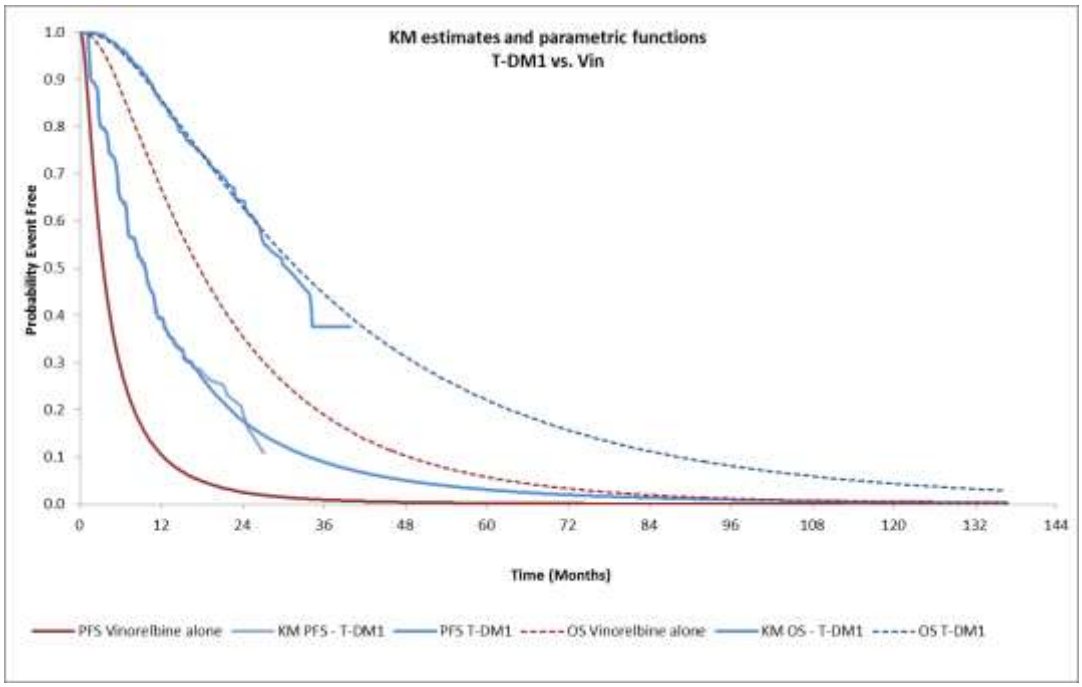


Figure 5: Trastzumab emtansine versus Vinorelbine modelled PFS and OS curves



D9. Please provide base-case results using a 15-year time horizon given that up to 3% of patients are alive at 10 years in the current analysis that uses a time horizon of 10 years.

The results using a 15 year time horizon are presented in Table 10 and Table 11 below.

Table 10: Cost-effectiveness results with 15 year time horizon

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY gained)
Capecitabine	£13,183	1.87	1.03				
Vinorelbine	£18,888	1.87	1.03	£5,705	0.00	0.00	Dominated
Lapatinib and capecitabine	£34,339	2.56	1.47	£15,451	0.68	0.43	£48,817
Trastuzumab and capecitabine	£37,757	2.28	1.32	£3,418	-0.27	-0.15	Dominated
Trastuzumab and vinorelbine	£36,188	2.28	1.32	-£1,569	-0.27	-0.15	Dominated
Trastuzumab emtansine	£112,216	3.24	1.95	£76,028	0.95	0.63	£160,070

Table 11: Final cost-effectiveness results with 15 year time horizon

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY gained)
Capecitabine	£13,183	1.87	1.03				
Trastuzumab emtansine	£112,216	3.24	1.95	£99,033	1.37	0.92	£107,657

D10. Please include other-cause mortality within the model or comment on why it was not included.

Overall survival within the model is taken from the EMILIA trial where the definition of event 'death' was all cause mortality. In essence, the overall survival curve should account for death for other causes.

D11. Within the submission and the Model Inputs sheet of the model, age is specified as 52.7, whilst in the operationalised model age 47 was used to calculate utilities. Please clarify whether an age of 52.7 (rather than 47) should have been used to calculate utilities, and if so please present results using this value.

The age used to calculate is intended to be 47. This is because the age variable in the utilities model refers to the average age of the one hundred members of the general public who were interviewed to elicit utilities for metastatic breast cancer (Lloyd, 2006 – clarified via personal commnuction with author). This was referred to on page 191 of the submission; *"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."

D12. Within the post-progression state, patients are allocated to no treatment (52%), 19 weeks of treatment (36%) or 38 weeks of treatment (12%) depending upon their line of therapy, and they stay in the state for approximately 1.5 - 2 years (depending upon treatment within the PFS state). This implies that patients remain alive but not on treatment for over a year. Please comment on the appropriateness of this assumption or increase the weekly cost to include longer term treatment within this state.

The assumption of 19 weeks of treatment was based on the best available evidence. Cameron et al (2008) showed that patients with metastatic breast cancer whose disease had progressed following treatment with trastuzumab were treated with capecitabine for an average 4.3 months (19 weeks). However 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. The length of time on post-progression treatment was therefore explored as a sensitivity analysis. When the length of time on post-progression treatment was doubled to 8.6 months, there was no substantial impact on the final ICER (£111,737 on page 228 of the submission).

D13. Within the Model Inputs spreadsheet, cells E131 and E132 are defined as the Duration of Treatment for AEs in weeks for T-DM1 and lapatinib plus capecitabine respectively. However, the values within these cells are 18,144 and 15,377 respectively. Please justify the use of these values which feed into the calculation of the cost of adverse events per patient week in the model.

These numbers reflect the exposure time. In other words, it is the total time at risk of an adverse event. So, rate of AE = no. of events / total time at risk.

D14. Page 185 of the submission states that 'Only adverse events with over 2% incidence in either treatment arm of EMILIA were assumed to have resource use and quality of life impact'; however within the model adverse events are included only if there is over 2% incidence overall within EMILIA (i.e. pooled over both arms). In addition, the model assumes a 2% incidence of grade 3 or 4 adverse events rather than a 2% incidence of grade 3 and 4 adverse events. Please amend so that the model and submission are consistent.

The model incorporates adverse events from each arm independently. All grade 3 and above adverse events that had at least a 2% incidence were accounted for.

D15. There are a number of assumptions around the costs and utilities associated with adverse events. Please provide a one-way sensitivity analysis around the costs and utilities associated with adverse events.

The costs of adverse events make up a very small fraction of the overall mean treatment cost for each intervention (~1%) and so one way sensitivity analyses of these costs would not have a substantial impact on the ICERs.

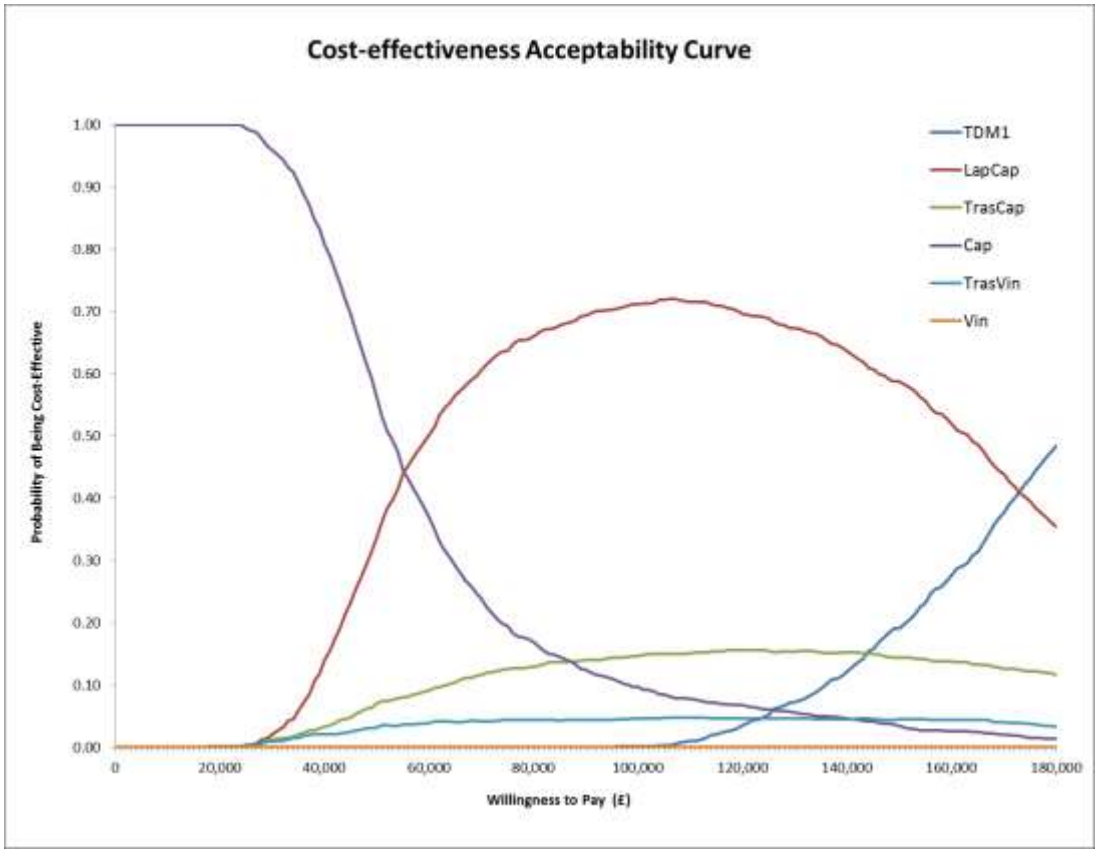
Regarding the (dis)utilities associated with adverse events, one way sensitivity analyses were conducted and presented around all utility values used in the model within a range of +/- 0.2 of the base case value. Varying the (dis)utilities associated with adverse events would not result in overall utility values outside of the ranges already presented in the sensitivity analyses.

D16. Please provide values and justification for the probabilistic sensitivity analysis parameters used in addition to the type of distribution. For the probabilistic costs of adverse events, some of the lower bounds used to calculate the standard error are the mean multiplied by 0.8 whilst others are the mean multiplied by 0.5; please clarify the reason for this?

Due to the volume of questions asked and extremely short time frame provided for response (35 questions to be answered in 10 working days) it was necessary to prioritize the questions asked. This question was assumed to be low priority given the magnitude of the deterministic base-case ICERs and so has not been answered. If the Committee would find this information valuable we would be happy to provide it in response to consultation.

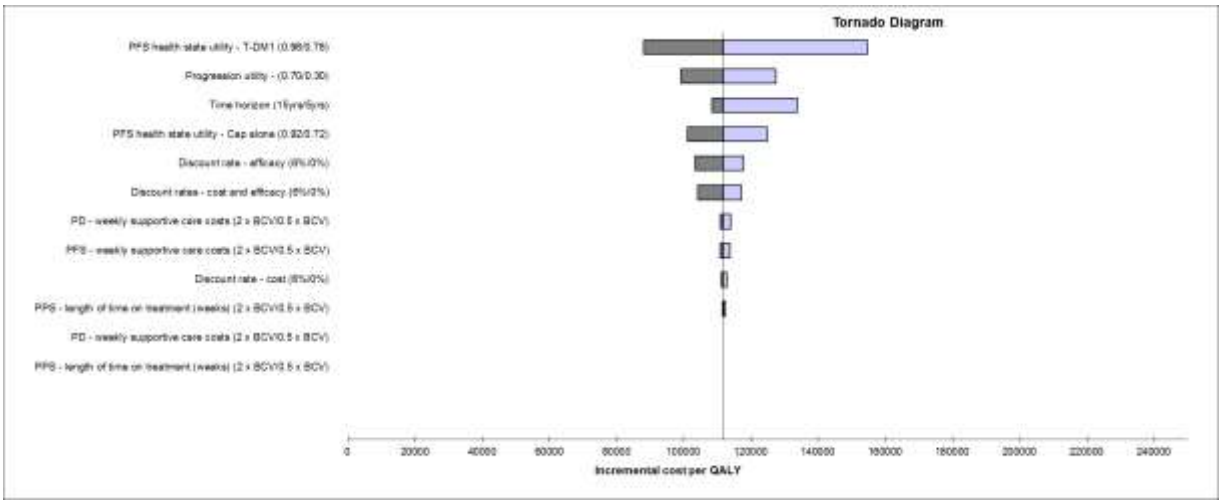
D17. The cost-effectiveness acceptability curve (CEAC) should detail the probability of each intervention being the most cost-effective, and therefore the individual probabilities should total 100%. Please correct the CEAC to consider all the interventions simultaneously.

Figure 6: Cost-effectiveness acceptability curve



D18. Please present a tornado diagram for the one-way sensitivity analyses, where the parameters are ordered (from highest to lowest) by their impact on the ICER.

Figure 7: Tornado diagram



D19. Please explain why vinorelbine was not included in Table 24 on page 156.

This is an error. No comparators were included in the search for cost-effectiveness studies since the intervention of interest was trastuzumab emtansine.

Appendix

Update to pooled safety analysis, trastuzumab emtansine investigator's brochure December 2013

Clinical Safety

Pooled analyses

• The pooled safety data from 884 patients with MBC receiving single-agent trastuzumab emtansine were updated based on a clinical cut-off date of 31 July 2012.
• The pooled safety data from 87 patients with MBC receiving trastuzumab emtansine plus pertuzumab were updated, based on a clinical cut-off date of 30 September 2013.

CLINICAL SAFETY

MBC

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 31 July 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.

In addition pooled safety data from patients receiving trastuzumab emtansine in combination with pertuzumab in two studies, for which the primary analysis has been performed, (TDM4688g and TDM4373g/BO22495) are presented. 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 (data cut-off date: 30 September 2013).

Trastuzumab Emtansine in Metastatic Breast Cancer:

Overview of Adverse Events

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).

The safety profile of trastuzumab emtansine in combination with pertuzumab is derived from a pooled analysis of data from the primary analyses of Study TDM4373g/BO22495 (N=67) and a subset of patients from Study TDM4688g (N=20), including follow-up data for any patients continuing to receive treatment in the extension study (TDM4529g/BO25430).

An overview of the safety of trastuzumab emtansine given alone, and in combination with pertuzumab for MBC is shown in Table 8.

Table 8 Overview of the Safety of Trastuzumab Emtansine Alone or in Combination with Pertuzumab in Patients with HER2-Positive MBC

Table 8 Overview of the Safety of Trastuzumab Emtansine Alone or in Combination with Pertuzumab in Patients with HER2-Positive MBC

Type of Event	T-DM1 N=884	T-DM1 + Pertuzumab N=87
AEs leading to death	12 (1.4%)	1 (1.1%)
SAE	175 (19.8%)	28 (32.2%)
Grade ≥3 AE	398 (45.0%)	52 (59.8%)
AEs leading to discontinuation of study drug	62 (7.0%)	18 (20.7%)

Cut-off dates for pooled analyses: T-DM1 = 31 July 2012; T-DM1 + pertuzumab = 30 September 2013.

A summary of common AEs (occurring with an incidence of ≥ 20% in either treatment group) is provided in Table 9.

Table 9 Common Adverse Events in Studies of Trastuzumab Emtansine Alone or in Combination with Pertuzumab in Patients with HER2-Positive MBC

Common Adverse Events[a]	T-DM1 N=884	T-DM1 + Pertuzumab N=87
BODY SYSTEM		
Preferred Term		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Fatigue	410 (46.4%)	46 (52.9%)
Pyrexia	209 (23.6%)	23 (26.4%)
Chills	95 (10.7%)	22 (25.3%)
GASTROINTESTINAL DISORDERS		
Nausea	380 (43.0%)	37 (42.5%)
Constipation	234 (26.5%)	23 (26.4%)
Vomiting	185 (20.9%)	24 (27.6%)
Diarrhea	188 (21.3%)	31 (35.6%)
NERVOUS SYSTEM DISORDERS		
Headache	260 (29.4%)	20 (23.0%)
Dysgeusia	70 (7.9%)	18 (20.7%)
RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS		
Epistaxis	223 (25.2%)	22 (25.3%)
Cough	181 (20.5%)	29 (33.3%)
Dyspnea	131 (14.8%)	20 (23.0%)
METABOLISM AND NUTRITION DISORDERS		
Decreased appetite	202 (22.9%)	27 (31.0%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Thrombocytopenia	262 (29.6%)	24 (27.6%)
INVESTIGATIONS		
Aspartate aminotransferase increased	208 (23.5%)	23 (26.4%)
Alanine aminotransferase increased	139 (15.7%)	20 (23.0%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Arthralgia	178 (20.1%)	15 (17.2%)
PSYCHIATRIC DISORDERS		
Insomnia	105 (11.9%)	18 (20.7%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Rash	115 (13.0%)	19 (21.8%)

[a] Individual AEs with an incidence of > 20% in at least one pooled group are shown.

Single-agent Trastuzumab Emtansine

The most common AEs associated with single-agent trastuzumab emtansine (in ≥ 25% of patients) were fatigue (46.4%), nausea (43.0%), thrombocytopenia (29.6%), headache (29.4%), constipation (26.5%) and epistaxis (25.2%). 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 (10.7%), increased AST (4.3%), fatigue (3.2%), increased ALT (3.1%), hypokalemia (2.9%) and anemia (2.9%). Sixty-two

patients (7.0%) 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%]).

Trastuzumab Emtansine plus Pertuzumab

The most common AEs were fatigue (52.9%), nausea (42.5%), diarrhea (35.6%), cough (33.3%) and decreased appetite (31.0%), with most of these events being Grade 1 or 2. The most common Grade ≥ 3 AEs (occurring in more than two patients [2.5%]) were fatigue (11.5%), thrombocytopenia (10.3%), increased AST (9.2%), dyspnea (9.2%), increased ALT (6.9%), anemia (5.7%), cellulitis (4.6%), peripheral sensory neuropathy (4.6%), hypokalemia (4.6%), pleural effusion (3.4%) and pneumonia (3.4%). Eighteen patients (20.7%) experienced AEs which resulted in their trastuzumab emtansine treatment being discontinued; apart from fatigue (in four patients [4.6%]) and increased AST (in two patients [2.3%]) all AEs leading to treatment discontinuation were singular occurrences.

Serious Adverse Events and Deaths

Single-agent Trastuzumab Emtansine

In the pooled analyses (cut-off date 31 July 2012) a total of 171 patients (19.3%) experienced a SAE during treatment with single-agent trastuzumab emtansine. Serious adverse events were reported across a number of body systems, with no single predominant event. SAEs recorded by more than 5 patients (ie, >0.5%) were pneumonia (1.7%), pyrexia (1.4%), cellulitis (1.1%), vomiting, thrombocytopenia (each in 0.9%); convulsion, dyspnea (each occurring in 0.8%); abdominal pain, sepsis, back pain (each occurring in 0.7%) and pleural effusion (0.6%).

Based on the pooled analyses, 12 patients receiving single-agent trastuzumab emtansine had AEs on study or within 30 days of their last trastuzumab emtansine treatment that led to death (see Table 8). The reported preferred terms were hepatic failure, hepatic function abnormal, bacterial sepsis, pneumonia [2 deaths], metabolic encephalopathy, respiratory failure [2 deaths], interstitial lung disease, neutropenic sepsis, and hepatic failure and encephalopathy (both in same patient), and sudden death. Of these, six patients had AEs (hepatic failure, hepatic function abnormal, bacterial sepsis, metabolic encephalopathy, neutropenic sepsis, hepatic failure and encephalopathy [same patient]) that were considered by the investigator to be related to

trastuzumab emtansine treatment.

Trastuzumab Emtansine plus Pertuzumab

Serious adverse events were recorded for 28 patients (32.2%) during treatment with trastuzumab emtansine plus pertuzumab. The majority of these events were singular occurrences. SAEs recorded by more than one patient (ie, > 1%) included: dyspnea (4.6%), pleural effusion, cellulitis, pneumonia (each occurring in 3.4% of patients), anemia, abdominal pain, nausea, vomiting and pyrexia (each occurring in 2.3% of patients). One patient in Study TDM4373g/BO22495 died as a result of an AE (pneumonia) following treatment with trastuzumab emtansine plus pertuzumab.

Additional AEs leading to Death in MBC

AEs leading to death which occurred either after the data cut off for analyses, or in studies not included in either pooled population, were not captured in the pooled analyses. The following additional AEs leading to death, assessed by the investigator to be related to trastuzumab emtansine treatment, have been reported into the safety database in studies in MBC, up to a clinical cut-off date of 30 September 2013: hepatic encephalopathy, neutropenic sepsis, subarachnoid hemorrhage, pneumonitis, death of unknown cause, pneumonitis, pneumonia, hepatotoxicity, multi-organ failure, acute renal failure, pneumonitis and respiratory failure.

In addition to the two fatal events of subarachnoid hemorrhage described, there have been seven further fatal hemorrhagic events reported in patients with MBC receiving trastuzumab emtansine in clinical trials (Studies TDM4997g/BO25734, TDM4788g/BO22589, MO28231, TDM4652g/GO01355, and TDM4884g/ML01356). None of the additional seven cases in the MBC trials were considered by the investigator to have a relationship to trastuzumab emtansine treatment, all had significant contributing medical conditions, such as underlying malignancy (eg, brain metastasis) and in some cases the patients were also receiving anticoagulation therapy. However a contributory role for trastuzumab emtansine cannot be excluded, as a decrease in platelet count was reported at the time of the event in five cases (in 2 cases, platelet counts were not reported). The majority (78%) of the fatalities were due to hemorrhagic events in the CNS.

Selected Adverse Events for Additional Analysis

The following types of events have been selected by the Sponsor for additional analysis, due to their observed frequency and/or clinical relevance: thrombocytopenia, hepatotoxicity (including increases in serum AST or ALT, and NRH of the liver),

peripheral neuropathy, infusion-related reactions/hypersensitivity, cardiac toxicity (left ventricular dysfunction), and pulmonary toxicity (cases of ILD, such as pneumonitis). An overview of these events (based on pooling of relevant preferred terms defined by the Sponsor) during treatment with trastuzumab emtansine as a single agent and in combination with pertuzumab is shown in Table 10.

Thrombocytopenia was the primary dose limiting toxicity in the dose-range finding studies. Approximately 30% of patients experienced thrombocytopenia (including decreased platelet count) during treatment with trastuzumab emtansine as a single agent or in combination with pertuzumab, with around 12% of cases being Grade ≥ 3. Declines in platelet counts were mostly transient; and levels generally recovered to baseline by Day 1 of the subsequent cycle. Less than 2% of patients had trastuzumab emtansine treatment withdrawn as a result of thrombocytopenia. A total of 36.5% of patients treated with single-agent trastuzumab emtansine had a hemorrhagic (ie, bleeding) event. The vast majority of these AEs were Grade 1-2 (principally epistaxis); a total of 2.0% of patients had a Grade ≥ 3 event. A total of 40.2% of patients treated with trastuzumab emtansine plus pertuzumab had a hemorrhagic AE, of whom 5.7% had a Grade ≥ 3 event.

Approximately one third of patients treated with trastuzumab emtansine had hepatotoxicity, most commonly asymptomatic increases in AST, ALT, alkaline phosphatase and bilirubin. Grade ≥ 3 events were recorded by 9.2% of patients following trastuzumab emtansine alone and 14.9% of patients following combined treatment with pertuzumab. Across both pooled analyses trastuzumab emtansine treatment was discontinued in 2.0%-3.4% of patients as a result of hepatotoxicity. Peripheral neuropathy has been observed in association with maytansine treatment. In the pooled analyses, approximately one third of patients treated with trastuzumab emtansine experienced peripheral neuropathy-related AEs. The majority of cases were Grade 1 or 2. Across both populations, two patients had SAEs, and five patients had AEs leading to treatment discontinuation.

Infusion-associated/hypersensitivity reactions were reported in less than 8% of patients, and most commonly occurred following the first trastuzumab emtansine infusion. These were mostly Grade 1 or 2 and occurred infrequently with subsequent infusions.
Given the known adverse effect of trastuzumab on cardiac function, manifesting as CHF and decreases in left ventricular ejection fraction (LVEF), the incidence of cardiac

dysfunction associated with the use of trastuzumab emtansine is being closely monitored. Two patients had trastuzumab emtansine treatment withdrawn due to decreased ejection fraction. A total of 16 patients (1.8%) treated with single-agent trastuzumab emtansine recorded an asymptomatic decrease from baseline LVEF of at least 15% concomitant with LVEF < 50%. The overall incidence of cardiac dysfunction observed was low (1.5% for single-agent treatment, 3.4% for combined treatment with pertuzumab).

Table 10 Overview of Selected Adverse Events for Trastuzumab Emtansine Alone or in Combination with Pertuzumab, in Patients with HER2-Positive MBC

	No (%) of Patients with Selected AE			
Type of Event	**Any**	**Grade ≥ 3**	**SAE**	**AE Leading to Withdrawal**
T-DM1 (N=884)				
Thrombocytopenia	285 (32.2%)	105 (11.9%)	8 (0.9%)	15 (1.7%)
Hemorrhage	323 (36.5%)	18 (2.0%)	14 (1.6%)	-
Hepatotoxicity	92 (33. 20%)	81 (9.2%)	10 (1.1%)	18 (2.0%)
Peripheral neuropathy	257 (29.1%)	22 (2.5%)	2 (0.2%)	4 (0.5%)
Infusion reactions/ hypersensitivity	61 (6.9%)	1 (0.1%)	2 (0.2%)	1 (0.1%)
Cardiac dysfunction	14 (1.6%)	2 (0.2%)	-	2 (0.2%)
Pneumonitis/ILD	10 (1.1%)	3 (0.3%)	3 (0.3%)	4 (0.5%)
T-DM1 + Pertuzumab (N=87)				
Thrombocytopenia	25 (28.7%)	9 (10.3%)	1 (1.1%)	-
Hemorrhage	35 (40.2%)	5 (5.7%)	5 (5.7%)	4 (4.6%)
Hepatotoxicity	28 (32.2%)	13 (14.9%)	2 (2.3%)	3 (3.4%)
Peripheral neuropathy	29 (33.3%)	5 (5.7%)	-	1 (1.1%)
Infusion reactions	3 (3.4%)	-	-	-
Cardiac dysfunction	3 (3.4%)	1 (1.1%)	-	1 (1.1%)
Pneumonitis/ILD	1 (1.1%)	1 (1.1%)	1 (1.1%)	-

Single-agent pooled analyses: cut-off date of 31 July 2012

Trastuzumab emtansine plus pertuzumab pooled analyses: cut-off date of 30 September 2013.