NICE National Institute for Health and Care Excellence

CDF Rapid Reconsideration

Trastuzumab emtansine for the treatment of locally advanced or metastatic HER2-positive breast cancer after treatment with trastuzumab and a taxane (review of TA371)

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF Rapid Reconsideration

Trastuzumab emtansine for the treatment of locally advanced or metastatic HER2-positive breast cancer after treatment with trastuzumab and a taxane (review of TA371) [ID1013]

Contents:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NICE National Institute for Health and Care Excellence

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

Rapid reconsideration of TA371

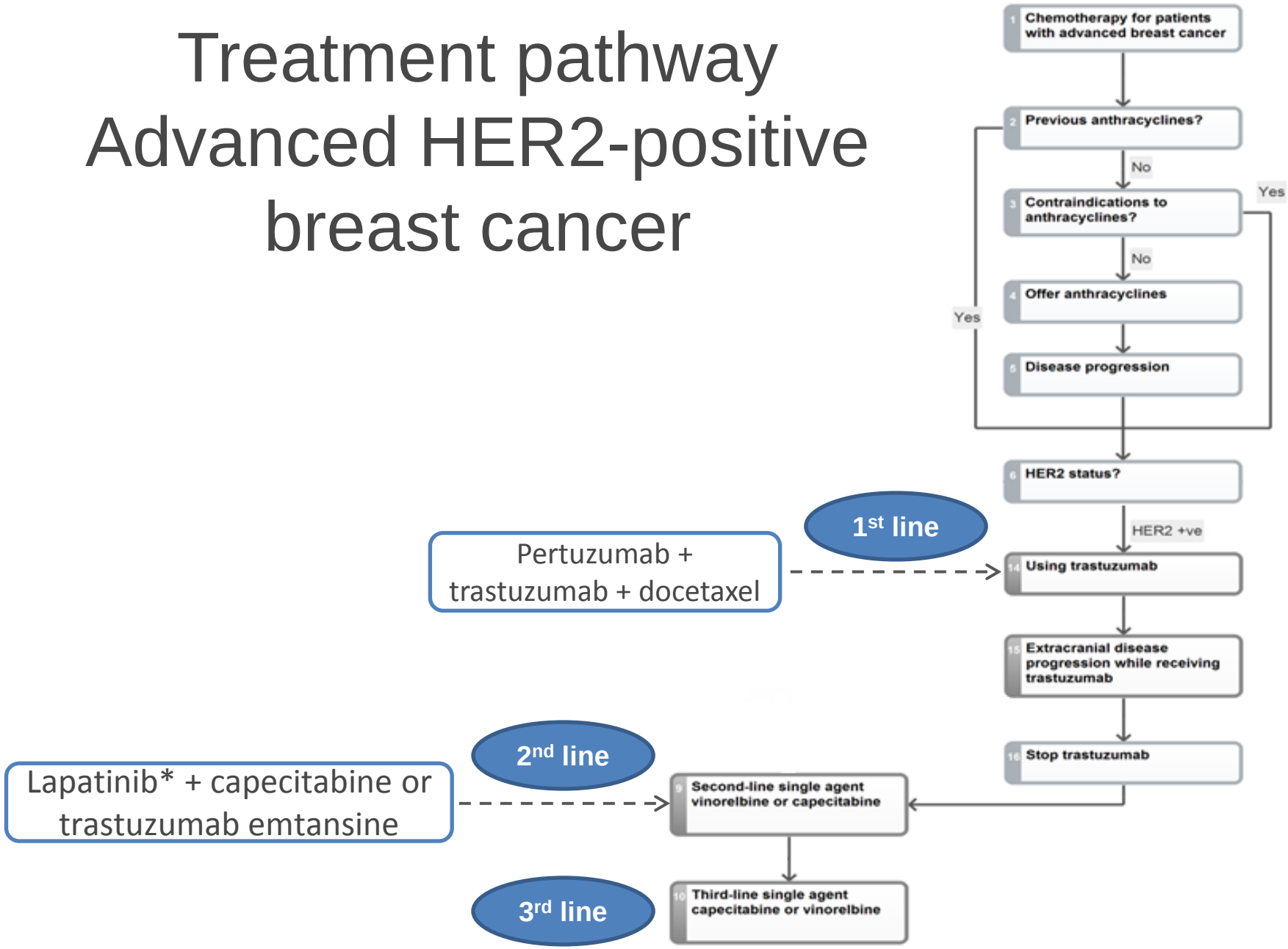
Public observer slides

29 November 2016

Trastuzumab emtansine

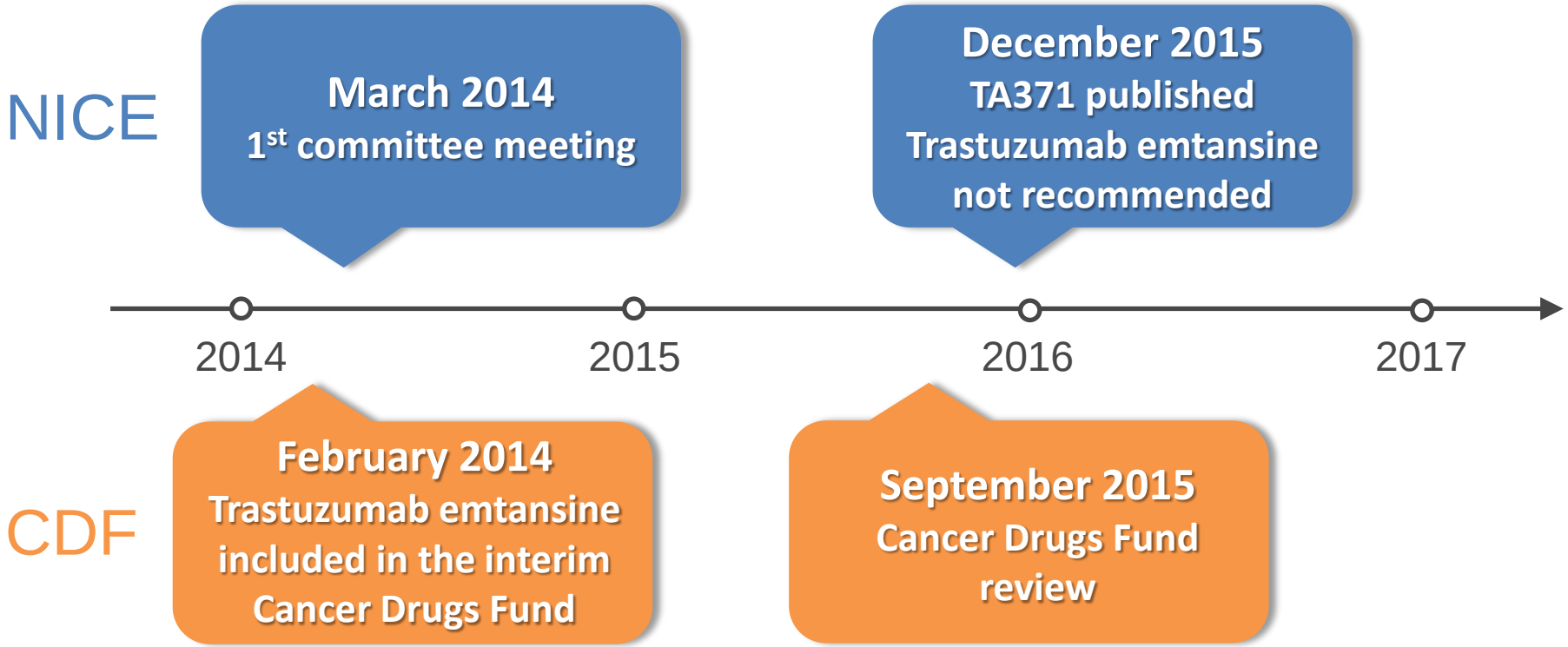
Mechanism of action	Antibody-drug conjugate combining: • Trastuzumab, a recombinant humanised IgG1 antibody to human epidermal growth factor receptor 2 (HER2) - Inhibits cell proliferation and angiogenesis • Emtansine (DM1), a cytotoxic maytansine derivative - Inhibits cell division
Marketing authorisation	'Treatment of adult patients with HER2-positive, unresectable locally advanced or metastatic breast cancer who have previously received trastuzumab and a taxane, separately or in combination. Patients should have either: • received prior therapy for locally advanced or metastatic disease, or • developed disease recurrence during or within 6 months of completing adjuvant therapy'
Dose	3.6 mg/kg body weight every 3 weeks (21-day cycle) i.v. administration

Treatment pathway Advanced HER2-positive breast cancer



Treatments available through the Cancer Drugs Fund
*Lapatinib no longer available

Trastuzumab emtansine for HER2-positive, unresectable locally advanced or metastatic breast cancer – history



Trastuzumab emtansine considered insufficient value for retention within the Cancer Drugs Fund but retained after discount agreed with Roche

Company's original decision problem (TA371)

Population	People with HER2-positive, unresectable advanced or metastatic breast cancer whose disease has progressed after treatment with trastuzumab and a taxane
Intervention	Trastuzumab emtansine
Comparators	Capecitabine Lapatinib in combination with capecitabine Trastuzumab in combination with capecitabine Vinorelbine Trastuzumab in combination with vinorelbine
Outcomes	Overall survival Progression-free survival Adverse events Health-related quality of life

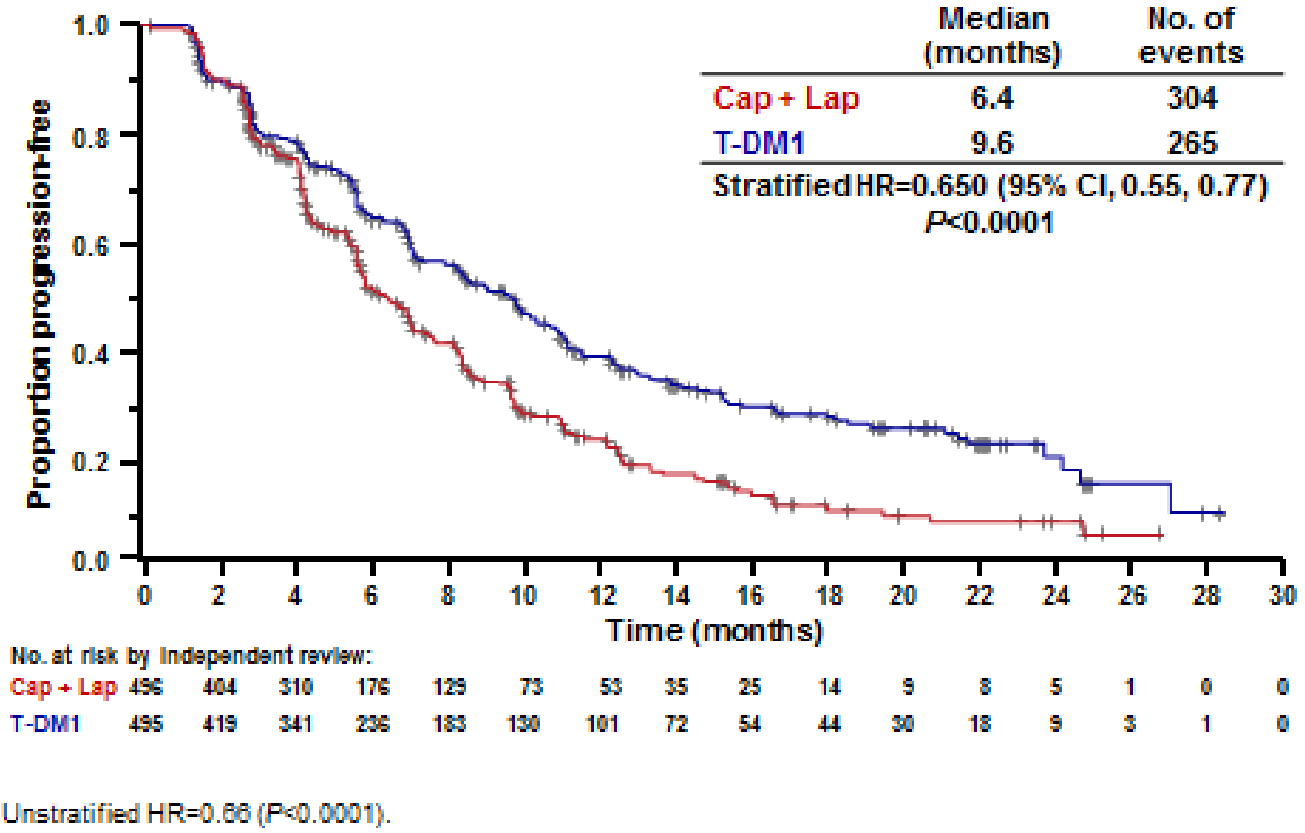
Overview of clinical evidence: EMILIA and TH3RESA trials

Trial	Population	Intervention	Outcomes
EMILIA • Randomised open-label phase III • Study treatment given as 1st (12%), 2nd (36%), or 3rd or subsequent (52%) line	Adults with HER2-positive locally advanced or metastatic breast cancer who have received prior trastuzumab and a taxane	Trastuzumab emtansine (n=495) **Comparator** Lapatinib plus capecitabine (n=496)	**Primary** • Progression-free survival (independent) • Overall survival • Adverse events **Secondary** • Progression-free survival (investigator) • Objective response rate (independent) • Duration of objective response • Time to treatment failure • Time to symptom progression • Quality of life (FACT-B TOI)
TH3RESA • Randomised open-label phase III • Patients had previously received, on average, 4 lines of therapy for locally advanced or metastatic disease	Adults with metastatic or unresectable locally advanced/ recurrent HER2-positive breast cancer who have received prior trastuzumab, a taxane and lapatinib	Trastuzumab emtansine (n=404) **Comparator** Treatment of physician's choice (n=198) • Chemotherapy • Hormonal therapy • Biologic drug • HER2-directed therapy	**Primary** • Progression-free survival (investigator) • Overall survival **Secondary** • Objective response rate (investigator) • Duration of objective response • 6-month and 1-year survival rate • Time to pain symptom progression (EORTC QLQ-BM22)

EMILIA and TH3RESA trials

- 70% of patients in both trials had visceral disease
- EMILIA (comparator lapatinib plus capecitabine)
  - Treatment given as 1st (12%), 2nd (36%), or 3rd or subsequent (52%) line
  - Patients in the lapatinib plus capecitabine arm were allowed to switch treatment after the January 2012 data cut
    - 136 ([redacted]%) patients switched to trastuzumab emtansine
- TH3RESA (comparator treatment of physician's choice)
  - Patients previously received, on average, 4 lines of therapy for locally advanced or metastatic disease
  - Patients could switch from treatment of physician's choice to trastuzumab emtansine at progression. Of the patients who switched:
    - 68.5% received chemotherapy plus trastuzumab
    - 16.8% received single-agent chemotherapy
    - 10.3% received lapatinib plus trastuzumab
    - 2.7% received chemotherapy plus lapatinib
    - 1.6% received hormonal therapy plus trastuzumab

TA371 EMILIA trial
Median progression-free survival

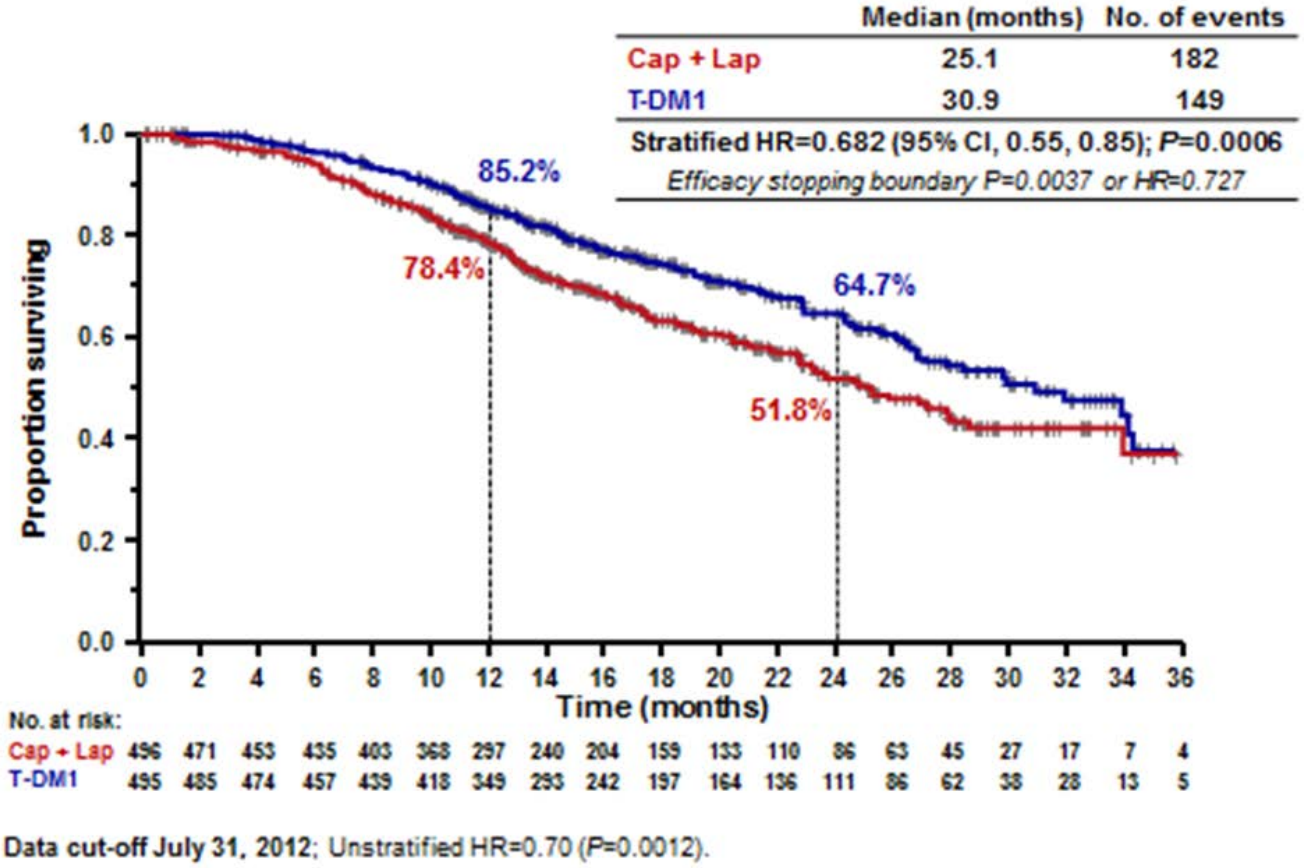


Unstratified HR=0.66 (*P*<0.0001).

- Median progression-free survival benefit 3.2 months compared with lapatinib and capecitabine (Jan 2012 cut-off)

Cap=capecitabine; Lap=lapatinib; T-DM1=trastuzumab emtansine
Source: Figure 5, page 94 of the original company submission for TA371

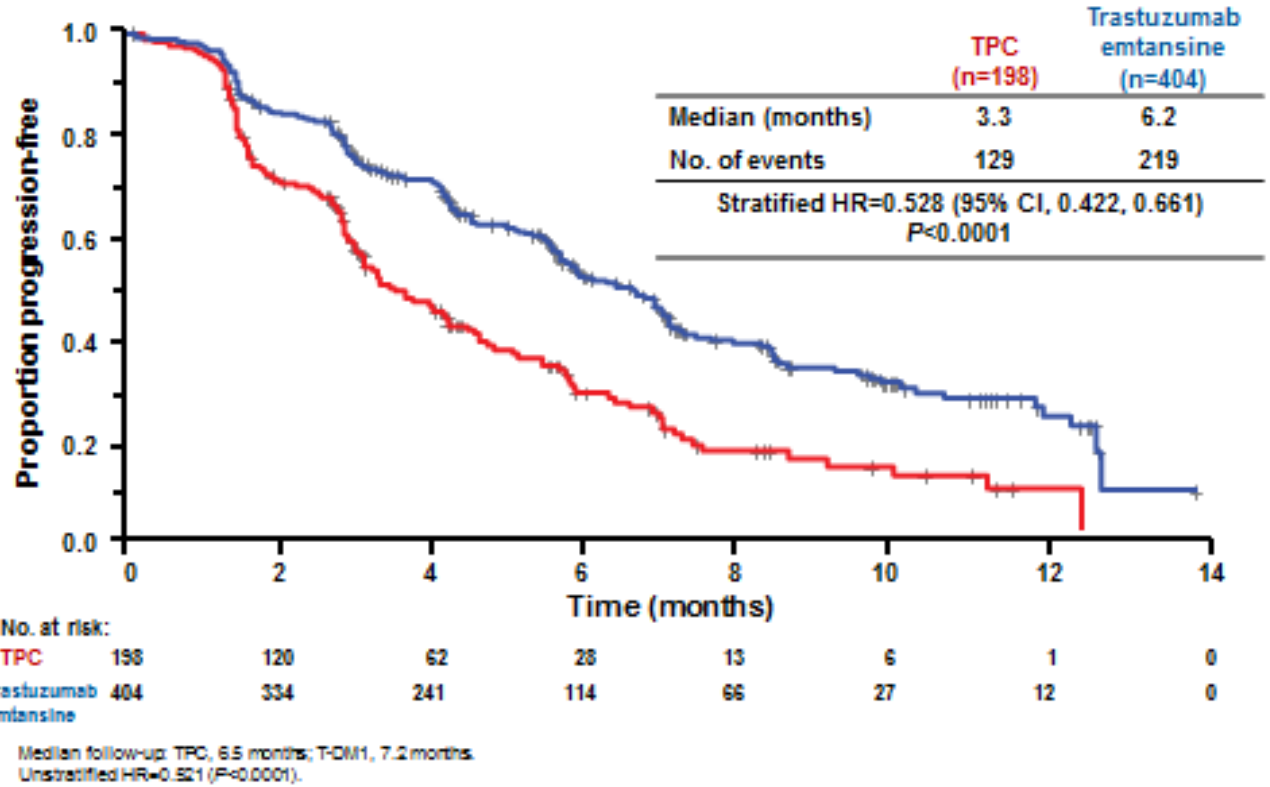
TA371 EMILIA trial
2nd interim analysis – Median overall survival



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

- Median overall survival benefit 5.8 months compared with capecitabine and lapatinib (Jan 2012 cut-off)

TA371 TH3RESA trial
Median progression-free survival



Median follow-up: TPC, 6.5 months; T-DM1, 7.2 months.
Unstratified HR=0.521 (P<0.0001).

- Median progression-free survival benefit 2.9 months compared with treatment of physician's choice
- Median overall survival in the trastuzumab emtansine group had not been reached by the time of the interim analysis

TPC=Treatment of physician's choice

Source: Figure 11, page 99 of the original company submission for TA371

TA371 summary of key results EMILIA and TH3RESA

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

TA371 summary of adverse effects EMILIA and TH3RESA

	EMILIA		TH3RESA		Pooled analysis
	Trastuzumab emtansine (n=495)	Lapatinib + capecitabine (n=496)	Trastuzumab emtansine (n=404)	TPC (n=198)	Trastuzumab emtansine (n=884)
AEs (any grade)	95.9%	97.7%	93.5%	88.6%	NR
Grade 3 or above AEs	40.8%	57.0%	32.3%	43.5%	45.0%
SAEs	15.5%	18.0%	18.4%	20.7%	19.8%
AEs leading to treatment discontinuation	5.9%	17.0%	NR	NR	7.0%
AEs leading to death	0.2%	1.0%	1.2%	1.5%	1.4%

TPC=Treatment of physician's choice; AEs=adverse events; SAEs=serious adverse events; NR=not reported

CDF reconsideration
Company submission - What's new (1)?

- Changes in response to the critique of the original submission:
  - Extending the model time horizon from 10 to 15 years
  - Including the costs of left ventricular ejection fraction monitoring follow-up
  - Correction of the utility values for AEs (although the ERG thinks these are still incorrect)
  - Using the actual dosing of trastuzumab emtansine and lapatinib in combination with capecitabine rather than the planned dose
  - Revising the parameters for the probabilistic sensitivity analysis
  - Estimating the post-progression treatment costs

[1]*Roche market research (2015)*

CDF reconsideration
Company submission - What's new (2)?

- More than 2 additional years of follow-up data from the EMILIA trial (December 2014 cut-off) have been used to model overall survival, time on treatment and adverse events
  - Original data cut-off (January 2012) used to model progression-free survival but parametric distribution used to extrapolate PFS has changed
- Network meta-analysis has been updated
  - Includes additional follow-up data and adjustment for treatment switching
- The way in which adverse events and treatment duration are incorporated into the model has been changed

CDF reconsideration
Company submission - What's new (3)?

- Patient access scheme agreed
- New economic model
- The comparators in the NICE scope have been excluded from the incremental analysis
  - lapatinib in combination with capecitabine
  - vinorelbine
  - trastuzumab in combination with vinorelbine
    - Removal of lapatinib from the Cancer Drugs Fund in January 2015 has resulted in a change in the standard of care in the UK
    - Trastuzumab emtansine was the most commonly used second-line therapy for HER2-positive breast cancer in 2015[1]
    - Vinorelbine is expected to be dominated by capecitabine

[1]*Company data on file (2015)*

Trastuzumab emtansine costs

	Without PAS	With PAS
Intervention cost (£)	[redacted]	[redacted]

Costs are based a 3-weekly dose of 3.6 mg/kg, a patient weight of 70.1 kg and an average length of treatment of 14.5 months

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Sources: Tables 12 and 13, page 39 of the company submission

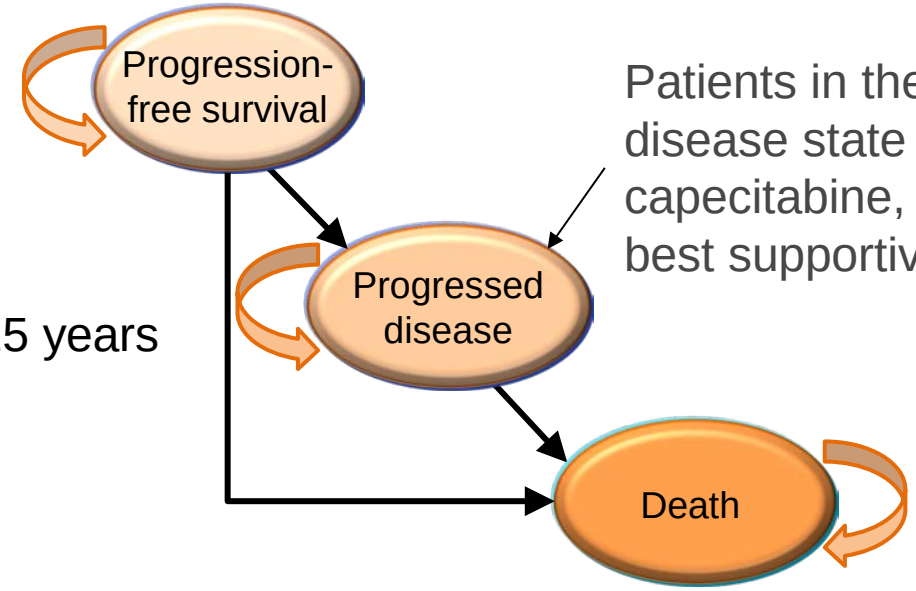
New submission
Summary of key results – EMILIA

	EMILIA ITT population	
	Trastuzumab emtansine	**Lapatinib plus capecitabine**
Median progression-free survival (months)	9.6	6.4
	Difference: **3.2**	
	Hazard ratio (95% CI) 0.65 (0.55 to 0.77)	
Median overall survival (months)	29.9	25.9
	Difference: **4.0**	
	Hazard ratio (95% CI) 0.75 (0.64 to 0.88)	

Sources: Tables 1, page 12 of the company submission and page 92 of the original company submission for TA371

Company's economic model

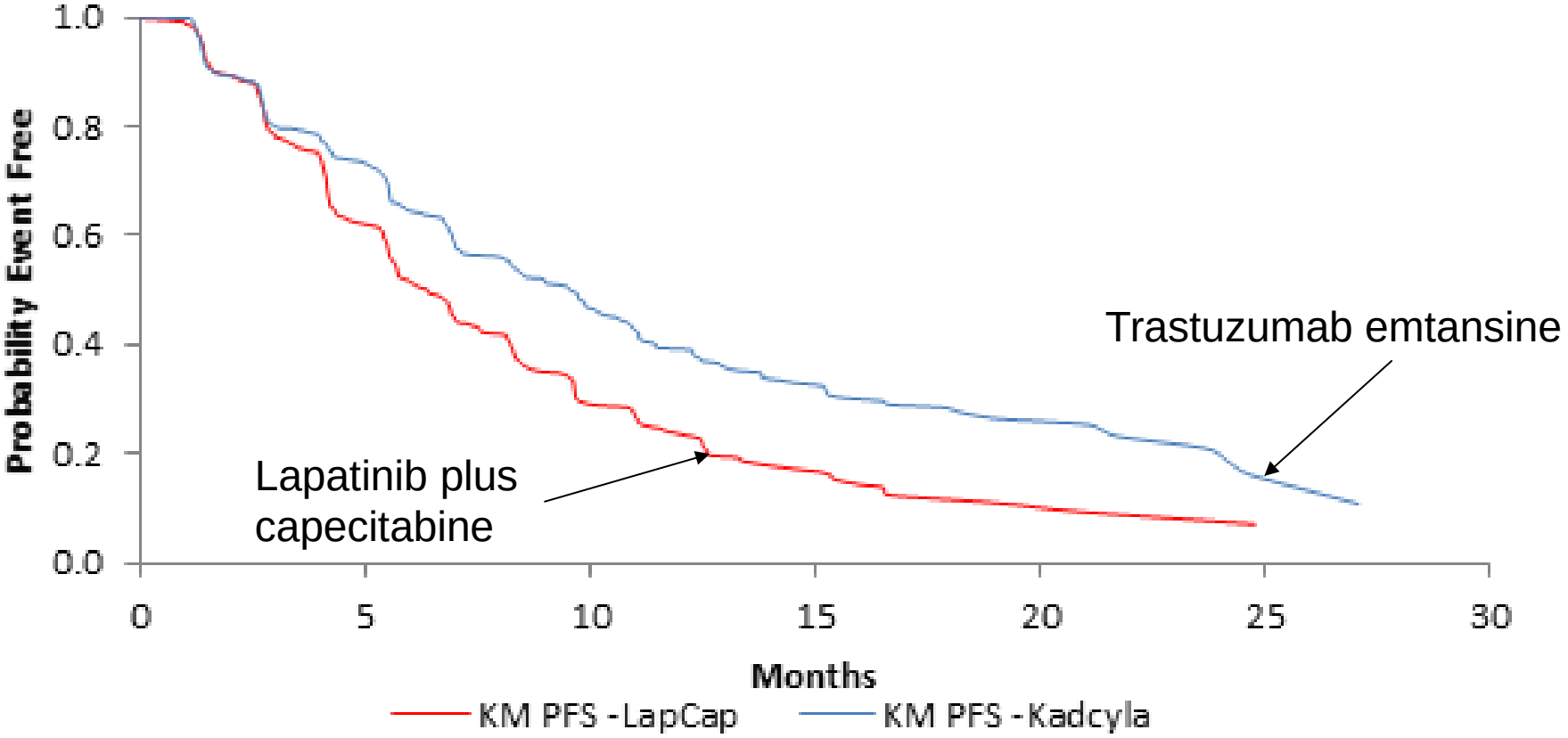
- Partitioned survival model
  - Treats progression-free survival and overall survival as separate entities
  - Uses hazard rates derived from the trastusumab emtansine and lapatinib/capecitabine arms of the EMILIA trial



Patients in the progressed disease state receive capecitabine, vinorelbine or best supportive care

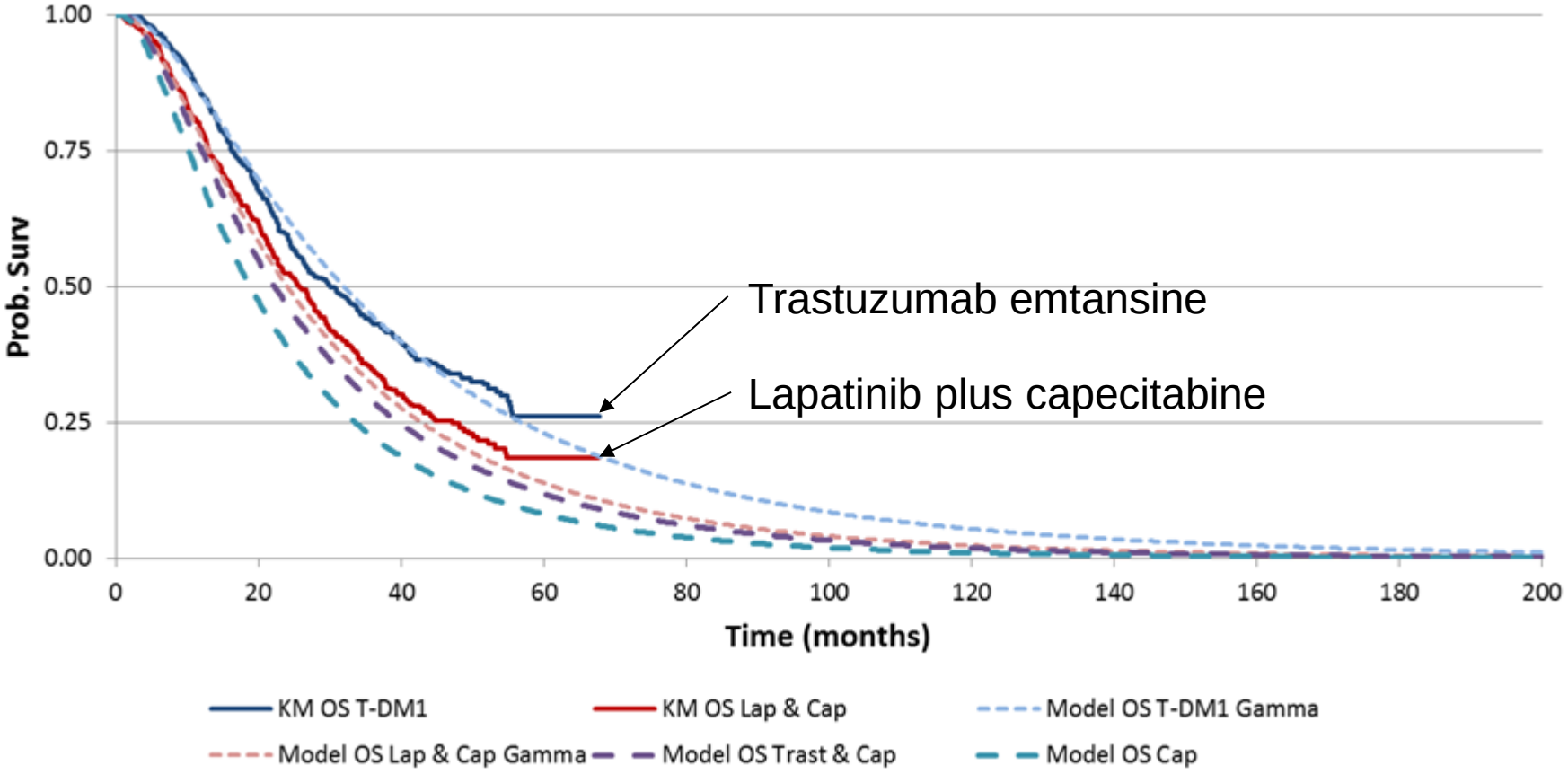
Time horizon: 15 years

Company modelling of progression-free survival



Lap=lapatinib; Cap=capecitabine; Kadcyla=trastuzumab emtansine
Source: Figure 6, page 33 of the company submission

Company modelling of overall survival



T-DM1=trastuzumab emtansine; Lap=lapatinib; Cap=capecitabine; Trast=trastuzumab
Source: Results charts tab of the company's model

Company's new deterministic base case with the PAS

Technology	Total		Incremental		ICER (£/QALY)
	Costs (£)	QALY	Costs (£)	QALY	
Capecitabine	£13,424	1.20	-	-	-
Trastuzumab plus capecitabine	£36,833	1.45	£23,409	0.25	£93,636
Trastuzumab emtansine	[redacted]	2.09	[redacted]	0.64	[redacted]*

*The ICER for trastuzumab emtansine ignores that trastuzumab in combination with capecitabine is extendedly dominated. The ICER compared with the next best non-dominated option (capecitabine) is estimated to be [redacted] per QALY gained

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Source: Table 15, page 42 of the company submission and page 20 of the ERG report

Company's corrected incremental analysis of the base case with the PAS

Technology	Total		Incremental		ICER (£/QALY)
	Costs (£)	QALY	Costs (£)	QALY	
Capecitabine	£13,425	1.20	-	-	-
Vinorelbine	£23,649	1.20	£8201	0	Dominated by capecitabine
Trastuzumab plus capecitabine	£36,834	1.45	-	-	Dominated by lapatinib plus capecitabine
Lapatinib and capecitabine	£30,785	1.56	£17,360	0.35	£49,061
Trastuzumab emtansine	[redacted]	2.09	[redacted]	0.53	[redacted]

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Source: Table 7, page 22 of the ERG report

Company's new probabilistic base case with the PAS

Technology	Total		Incremental		ICER (£/QALY)
	Costs (£)	QALY	Costs (£)	QALY	
Capecitabine	£14,667	1.27	-	-	-
Trastuzumab and capecitabine	£39,208	1.52	-	-	Dominated by lapatinib plus capecitabine
Lapatinib and capecitabine	£31,484	1.55	£16,817	0.28	£60,065
Trastuzumab emtansine	[redacted]	2.07	[redacted]	0.52	[redacted]

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Source: Table 8, page 23 of the ERG report

Company's probabilistic sensitivity analysis

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Source: Figure 8, page 44 of the company submission

End of life criteria

	TA371 (compared with lap/cap)	EMILIA trial (compared with lap/cap)	New submission (compared with trastuzumab/cap)
Life expectancy (months)	25.1 (median)	25.9 (median)	Likely to be around 24
Extension to life (months)	5.8 (median)	4.0 (median)	7.56

- The committee agreed that trastuzumab emtansine met the end of life criteria during the original appraisal based on lapatinib plus capecitabine being the standard of care
- The company states that trastuzumab with capecitabine is now the standard of care
- The company recognises that there are limited data on the life expectancy of a patient with metastatic breast cancer receiving trastuzumab with capecitabine as a second line treatment, however data from the CEREBEL study[1] suggest that it is likely to be around 24 months
- Together with the expected overall survival gain of 7.56 months, the company claim that trastuzumab emtansine should be considered under the end of life criteria

[1]*Pivot et al. (2015) J. Clin. Oncol. 33: 1564-73*

ERG critique

- Choice of comparators
- Progression-free survival and overall survival
- Treatment costs
- Extended dominance
- End of Life

ERG critique
Choice of comparators

- The ERG suggests that that lapatinib in combination with capecitabine should be included as a comparator because it is a licensed treatment option for this indication and was included in the original scope
- The company states that lapatinib-capecitabine should be excluded from the incremental analysis because it is no longer current practice in the UK as Lapatinib was delisted from the Cancer Drugs Fund in January 2015, and the company claims that trastuzumab emtansine has become the standard of care
- Vinorelbine was also excluded with no justification. The ERG assumes this is because vinorelbine is expected to be dominated by capecitabine
- Using the company model, when all treatment options are included, the ICER for trastuzumab emtansine is estimated to be [redacted]/QALY gained compared with lapatinib in combination with capecitabine

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ERG critique
Progression-free survival

- The company used different time points for the switch from Kaplan-Meier survivor function to gamma distribution in different arms, judged by when the K-M curves became erratic
- The company justify the use of Kaplan-Meier survivor function because parametric functions appear to overestimate and underestimate PFS in the comparator arm and the intervention arm respectively
- The company did not incorporate uncertainty associated with using Kaplan-Meier survivor function
- The ERG favour parametric models rather than Kaplan-Meier curves

ERG critique
Overall survival

- The ERG suggest that the hazard ratio may not be sufficient to estimate mean overall survival because proportional hazards assumption over the lifetime of the patients may not be assumed
- The company used a gamma distribution to model overall survival, although the loglogistic and log normal distributions both provided a better fit to the observed data
  - However the ERG consider the gamma distribution to be clinically plausible over the long term
- Crossover was adjusted for, but only 1 type of analysis was used out of a number of different possible analyses
- The ERG carried out a conservative sensitivity analysis which does not adjust for treatment switching to assess the impact of the company's switching assumptions upon the model results
  - This results in an ICER of [redacted]

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ERG critique
Treatment costs

- The company calculated the actual dose by using the average dose from the EMILIA trial to estimate average vial usage within their base case.
  - This results in the same cost as the planned dose estimate for trastuzumab emtansine which was used in the original company submission, since in both cases it results in the assumption that one 160g vial and one 100mg vial is used per person per administration, and does not account for the distribution of patient weight
- The company also obtained patient-level data for patient weight from the EMILIA trial to estimate planned vial usage more accurately to account for the variability in patient weight
  - This does not account for dose reductions and treatment breaks
- The ERG has tested the impact of using the patient-level data to account for variability around vial usage within a sensitivity analysis

ERG critique
Extended dominance

- The ERG believe that the ICER for trastuzumab emtansine with the PAS ([redacted]/QALY gained) is inapplicable as it reflects a comparison with trastuzumab in combination with capecitabine which is ruled out due to extended dominance, resulting in an ICER for trastuzumab emtansine versus capecitabine of [redacted]/QALY gained

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ERG critique
End of life criteria

- Trastuzumab emtansine is likely to generate at least 3 additional months of life compared with existing treatments, but within the economic model patients in all treatment groups were predicted to have a life expectancy of more than 24 months on average

ERG revised base case

- Corrected a model error in the calculation of post-progression treatment costs (minor effect)
- Included all comparators
- Conducted univariate analysis to explore key uncertainties
  - Treatment doses, utilities, hazard ratios for overall survival, extrapolation of overall survival and progression-free survival
- Key drivers
  - Inclusion or exclusion of lapatinib in combination with capecitabine
  - Treatment effect beyond trial follow-up
  - Inclusion of vial wastage if patient-level data is used to estimate treatment costs

ERG's deterministic base case with the PAS

Technology	Total		Incremental		ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Capecitabine	£14,610	1.20			
Trastuzumab and capecitabine	£38,009	1.45			Dominated by lapatinib/capecitabine
Lapatinib and capecitabine	£31,958	1.56	£17,348	0.35	£49,025
Trastuzumab emtansine	[redacted]	2.09	[redacted]	0.53	[redacted]

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Source: Table 9, page 24 of the ERG report

ERG's one-way sensitivity analyses with the PAS: Key drivers

Analysis	Capecitabine	Trastuzumab and capecitabine	Lapatinib and capecitabine	Trastuzumab emtansine
Base case	-	Dominated	£49, 025	[redacted]
Treatment dose (BC: Incl. wastage – actual estimate)				
Excl. wastage – actual estimate	-	Dominated	£47,292	[redacted]
Incl. wastage - planned	-	Dominated	£49,679	[redacted]
Excl. wastage – planned	-	Dominated	£49,796	[redacted]
Incl. wastage – patient level weight data*	-	Dominated	£49,883	[redacted]
Excl. wastage – patient level weight data	-	Dominated	£49,772	[redacted]
Overall survival extrapolation* (*BC: Adjusting for treatment switching*) Not adjusting for treatment switching	-	Extendedly dominated by trastuzumab emtansine	£68,213	[redacted]
Progression-free survival & overall survival of trastuzumab emtansine equivalent to lapatinib and capecitabine after week 72 and 4 years respectively*	-	Dominated	£49,025	[redacted]

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*Key drivers. Source: Table 10, page 25 of the ERG report

ERG's one-way sensitivity analyses with the PAS: Hazard ratios

Analysis	Capecitabine	Trastuzumab and capecitabine	Lapatinib and capecitabine	Trastuzumab emtansine
Base case	-	Dominated	£49, 025	[redacted]
Lapatinib and capecitabine vs T-DM1 HR (BC: No HR, use KM survivor function) PFS 0.65, OS 0.69 (Means)	-	Extendedly dominated by lap/cap	Extendedly dominated by T-DM1	[redacted]
PFS 0.65 (Mean), OS 1.32 (Upper CrI)	-	Dominated by lap/cap	£17,206	Dominated by lap/cap
Trastatuzumab and capecitabine vs T-DM1 HR OS (BC: 0.70) 1.72 (Upper CrI)	-	£17,116	Extendedly dominated by trast/cap	Dominated by trast/cap
Capecitabine vs T-DM1 HR OS (BC: 0.59) 1.43 (Upper CrI)	Dominates comparators	Dominated by capecitabine	Dominated by capecitabine	Dominated by capecitabine

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Source: Table 10, page 25 of the ERG report

ERG's one-way sensitivity analyses with the PAS: Utilities and extrapolation

Analysis	Capecitabine	Trastuzumab and capecitabine	Lapatinib and capecitabine	Trastuzumab emtansine
Base case	-	Dominated	£49, 025	[redacted]
PFS utility: (*BC: See Table 4 of ERG report*)				
Same values as lap and cap in all arms	-	Dominated	£49,547	[redacted]
TH3RESA trial (0.71 trastuzumab emtansine, 0.69 comparators)	-	Dominated	£55,622	[redacted]
Progressed utility (*BC: 0.530*) 0.73	-	Dominated	£44,772	[redacted]
PFS extrapolation (*BC: KM until 72 weeks + gamma tail*)				
As original submission (KM until 72 weeks + lognormal tail)	-	Dominated	£49,496	[redacted]
KM + Weibull tail	-	Dominated	£48,900	[redacted]
Weibull	-	Dominated	£48,647	[redacted]

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Source: Table 10, page 25 of the ERG report

Key issues for consideration

- Is lapatinib in combination with capecitabine an appropriate comparator?
- Does trastuzumab emtansine meet the criteria for a life-extending treatment at the end of life?
- Are the ERG adjustments preferable?
- Which ICER estimates are the most plausible?

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Technology appraisals

Submission template for the re-consideration of current CDF technologies under the new proposed CDF criteria

Trastuzumab Emtansine (Kadcyla® ▼)

HER2-positive, unresectable locally advanced or metastatic breast cancer after treatment with trastuzumab and a taxane [TA371]

Roche Products Limited

June 2016

1 Introduction

1 All cancer drugs that were previously appraised by NICE and are currently funded through the current Cancer Drugs Fund (CDF) will be re-considered by NICE in line with Guide to the methods of technology appraisal (2013) and modifications to incorporate the proposed new CDF criteria outlined in the CDF consultation paper.

2 In order to allow for the transition of drugs currently in the CDF to take place before 31 March 2017, NICE needs to prepare for re-considering those drugs. This preparation is taking place in parallel with the consultation on the new CDF arrangements, without prejudging the outcome of that consultation. This content of this submission template is therefore provisional and may change if the proposed CDF arrangements are amended after the consultation. Companies will have the opportunity to change their evidence submissions to NICE if substantial changes are made to the proposals after the CDF consultation.

3 The scope for re-consideration remains the same as the final scope used for the published technology appraisal guidance.

4 The company evidence submission should focus on cost effectiveness analyses using a new patient access scheme, an amendment to the existing patient access scheme agreed with the Department of Health (see Appendix 5.1) or as a commercial access arrangement with NHS England (for a definition of commercial access arrangement please see the CDF consultation paper).

5 A new patient access scheme, an amendment to an existing patient access scheme, or a commercial access arrangement, must have been formally agreed with the relevant organisation (that is, the Department of Health for a patient access scheme or NHS England for a commercial access arrangement by the time the Appraisal Committee meets for the first Committee meeting.

6 Some details of patient access schemes or commercial access arrangements, submitted through the rapid re-consideration process, can be treated by NICE as commercial in confidence if the company requests this.

7 The cost-effectiveness analyses included in the company evidence submission must use the assumptions that determined the most plausible incremental cost-effectiveness ratio(s) as identified in the published guidance. If the published guidance refers to more than one plausible ICER, analyses relating to all plausible ICERs should be included in the submission.

8 Only in exceptional circumstances and with prior written agreement from NICE should new clinical evidence be included. New clinical evidence is acceptable only when it addresses uncertainties identified previously by the Appraisal Committee. Submission of new clinical evidence must not lead to structural changes in the company's cost-effectiveness model.

9 The submission should take account of the proposed changes to NICE's methods of technology appraisal set out in the CDF consultation paper, in particular those concerning the appraisal of life-extending products at the end of life.

2 Instructions for companies

If companies want the National Institute for Health and Care Excellence (NICE) to re-consider a NICE recommendation for a drug currently funded through the CDF, they should use this template.

The template contains the information NICE requires to assess the impact of a patient access scheme or commercial access agreement on the clinical and cost effectiveness of a technology, in the context of this re-consideration, and explains the way in the evidence should be presented. If you are unable to follow this format, you must state your reasons clearly. You should insert 'N/A' against sections that you do not consider relevant, and give a reason for this response.

In addition to the CDF consultation paper, please refer to the following documents when completing the template:

- 'Guide to the methods of technology appraisal'
- 'Specification for company submission of evidence' and
- Pharmaceutical Price Regulation Scheme 2014.

For further details on the technology appraisal process, please see NICE's 'Guide to the processes of technology appraisal'. The 'Specification for company submission of evidence' provides details on disclosure of information and equality issues.

Make the submission as brief and informative as possible. Only mark information as confidential when absolutely necessary. Sufficient information must be publicly available for stakeholders to comment on the full content of the technology appraisal, including details of the proposed patient access scheme or commercial access agreement. Send submissions electronically via NICE docs: https://appraisals.nice.org.uk.

Appendices may be used to include additional information that is considered relevant to the submission. Do not include information in the appendices that has been requested in the template. Appendices should be clearly referenced in the main submission.

When making a submission, include:

- an updated version of the checklist of confidential information, if necessary
- an economic model with the patient access scheme or commercial access agreement incorporated, in accordance with the 'Guide to the methods of technology appraisal'.

3 Details of the patient access scheme/ commercial access agreement

3.1 Please give the name of the technology and the disease area to which the patient access scheme/ commercial access agreement applies.

Trastuzumab emtansine (brand name Kadcyla) is licensed "for the treatment of adult patients with HER2-positive, unresectable locally advanced or metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either:

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

3.2 Please outline the rationale for developing the patient access scheme/ commercial access agreement.

The patient access scheme was developed to reduce the ICER to a level that the NICE committee may consider cost effective for an end of life medicine during this reconsideration of Cancer Drug Fund (CDF) treatments; in order that eligible patients can continue to benefit from this transformational medicine as they have done since February 2014 when Kadcyla first became available on the CDF.

3.3 Please describe the type of patient access scheme (as defined by the PPRS)/ commercial access agreement.

This patient access scheme is such that the NHS pays for patients who are being treated with Kadcyla for HER2-positive, unresectable locally advanced or metastatic breast cancer who previously received trastuzumab (brand name Herceptin) and a taxane, for the first fourteen (14) months, with Roche

providing Kadcyla free of charge thereafter for as long as each individual patient continues to receive Kadcyla.

3.4 Please provide specific details of the patient population to which the patient access scheme/ commercial access agreement applies. Does the scheme apply to the whole licensed population or only to a specific subgroup (for example, type of tumour, location of tumour)? In case of the latter, please state:

- How is the subgroup defined?
- If certain criteria have been used to select patients, why have these have been chosen?
- How are the criteria measured and why have the measures been chosen?

The proposed patient access scheme will apply to any patients from the whole licensed population, as defined in section 3.1, who are still on treatment after the time cap of 14 months has been reached.

3.5 Please provide details of when the scheme/ commercial access agreement will apply to the population specified in 3.4. Is the scheme dependent on certain criteria, for example, degree of response, response by a certain time point, number of injections? If so:

- Why have the criteria been chosen?
- How are the criteria measured and why have the measures been chosen.

A patient level episode of care cap payable via a simple rebate mechanism has been selected for the patient access scheme which allows it be to applied

to all patients treated for the indication detailed in section 3.1 whom are still on treatment past 14 months. The NHS will pay for a patient's treatment with Kadcyla for the first 14 months with Roche rebating the cost of all Kadcyla for that patient thereafter and for as long as that patient continues to be treated with Kadcyla.

3.6 What proportion of the patient population (specified in 3.4) is expected to meet the patient access scheme/ commercial access agreement criteria (specified in 3.5)?

All patients within the licensed population who are still on treatment after 14 months are expected to meet the requirements for this patient access scheme.

3.7 Please explain in detail the financial aspects of the patient access scheme/ commercial access agreement. How will any rebates be calculated and paid?

The proposed scheme will be administered using the Blueteq Patient Access Scheme Administration System (PASAS). Each trust will enter the data into the PASAS and then at an agreed frequency the Trust will check and submit their claim data. Roche will then receive an aggregated data report from Blueteq on which the rebate will be calculated and paid back to the Trust either in the form of a BACs payment or credit note.

If the Trust has purchased the product via a 3rd party such as a compounding company Roche can only provide a BACs payment.

3.8 Please provide details of how the patient access scheme/ commercial access agreement will be administered. Please specify whether any additional

information will need to be collected, explaining when this will be done and by whom.

The proposed scheme will be administered using the Blueteq Patient Access Scheme Administration System (PASAS). Each trust will manually enter or upload the data into the PASAS and then at an agreed frequency the Trust will then check and submit their claim data. Roche will then receive an aggregated data report from Blueteq on which the rebate will be calculated

The following steps are required:

Patient Registration: Oncology pharmacist (Band 8a) or treating oncologist (consultant grade). Patient registration can be carried out either when the patient first starts treatment, or at the point of making the claim. This is beneficial for two reasons. Firstly the flexibility ensures that problems are not created should patient registration not have been completed, for whatever reason, when the patient first started treatment. Secondly hospitals and trusts have different preferences for who performs the patient registration; some prefer this to be the treating clinician, and others the oncology pharmacist. Where registration will be performed by the treating clinician, Roche would expect that the procedure be for patients to be registered when starting treatment, but when the oncology pharmacist is registering patients they may prefer to do this at the point of making the claim as they will also be making the claim.

Making a Claim: Oncology pharmacist (Band 8a). Two options exist for making a claim, manual data entry or automated data entry. Automated data entry has the advantage that usage data can be exported directly from the pharmacy system and uploaded into PASAS. Once all data has been entered into PASAS the claimant may want to check that they are happy and either make adjustments if they are not, or notify Roche of the claim through PASAS.

Issuing a VAT Invoice: Trust Finance (Grade 6). If the claimant would like the claim to be paid via a BACS payment (necessary if a credit note can't be issued due to the hospital if they are not purchasing Kadcyla directly from Roche), then Roche will require a VAT invoice. Once Roche has accepted the claim via PASAS, Roche will notify the claimant through PASAS that the claim has been approved and the trust would then need to issue a VAT invoice to Roche for the value of the claim.

Processing the Payment: Trust Finance (Grade 6). As Kadcyla is a high cost oncology drug paid for centrally within England, Roche anticipates that English trusts will pass the claim value directly back to NHS England. Within Wales the rebate payment would need to be credited back to the relevant Health Board. Patient Registration: Oncology pharmacist (Band 8a) or treating Oncologist (consultant grade) registers the patient in to the PASAS. Patient registration can be carried out either when the patient first starts treatment, or at the point of making the claim. This is beneficial for two reasons. Firstly the flexibility ensures that problems are not created should patient registration not have been completed, for whatever reason, when the patient first started treatment. Secondly hospitals and trusts have different preferences for who performs the patient registration; some prefer this to be the treating clinician, and others the oncology pharmacist. Where registration will be performed by the treating clinician, Roche would expect that the procedure be for patients to be registered when starting treatment, but when the oncology pharmacist is registering patients they may prefer to do this at the point of making the claim.

3.9 Please provide a flow diagram that clearly shows how the patient access scheme/ commercial access agreement will operate. Any funding flows must be clearly demonstrated.

A flow chart is included in the embedded file


Kadcyla treatment cap scheme operatior


Blueteq Patient Access Scheme (PAS)

3.10 Please provide details of the duration of the patient access scheme/ commercial access agreement.

Following positive guidance this patient access scheme will continue until such time as NICE undertakes a further review of the Product and withdraws its positive final NICE TA Guidance in respect of Kadcyla®. In the event of positive guidance being withdrawn then any patients already registered on the scheme will continue to benefit until or unless an alternative scheme is agreed with NICE and DH. If at any time outside of a NICE re-review Roche wishes to

withdraw the scheme this would only be done in full discussions with DH and NICE and 6 months' notice would be provided to Hospitals.

3.11 Are there any equity or equalities issues relating to the patient access scheme/ commercial access agreement, taking into account current legislation and, if applicable, any concerns identified during the course of the appraisal? If so, how have these been addressed?

An equalities assessment has been undertaken and no issues have been identified.

3.12 If available, please list any patient access scheme/ commercial access agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians and patient information documents. Please include copies in the appendices.

Section 5.2.1 contains the terms and conditions that will cover the scheme.

3.13 In the exceptional case that you are submitting an outcome-based scheme, as defined by the PPRS, please also refer to appendix 5.2.

Roche are not submitting an outcome based scheme and therefore this is not applicable.

4 Cost effectiveness

4.1 Please show the changes made to the original company base case to align with the assumptions that determined the most plausible incremental cost effectiveness ratio(s) as determined by the Appraisal Committee and presented in the published guidance. A suggested format is presented in table 1. **Error! Hyperlink reference not valid.**Provide sufficient detail about how the Appraisal Committee's preferred assumptions have been implemented in the economic model. Provide sufficient detail to allow the replication of the changes made to the original base case. For example, include sheet and cell references and state the old and new cell values. No other changes should be made to the model.

Please see below an explanation of the changes that have been made to the economic model since the original NICE submission in December 2013.

Original cost effectiveness results

The FAD reported on the Roche ICER and the ERG ICER, both were noted as being above the level normally considered to be cost effective. The Roche ICER was £167.2k and the ERG ICER £166.4k.

The FAD did not specify which ICER the Committee considered to be the most plausible. The committee noted that the ERG's base case was similar to the Roche base case. The committee agreed that the most plausible ICER was above the ICER range that would normally be considered a cost-effective use of NHS resources. As such our original base case has been used as the basis for this submission however the economic model has been adjusted to address the ERG's comments and criticisms of our original submission.

New base case cost-effectiveness

The changes made to the submission are summarised below. The changes are split into three broad categories: incorporation of new data into the model, corrections that are made following ERG's recommendations and other.

1) Incorporation of updated data based on cut-off of EMILIA study at 31th December 2014

As highlighted in the clinical appendix there has been a later data cut from the EMILIA trial in December 2014 post the original NICE submission. This data has been incorporated into the economic model. As a result the following adjustments have been made:

- *Cross over*

According to the EMILIA clinical trial protocol, patients in the Lapatinib/Capecitabine (lap/cap) arm were allowed to switch treatment after the July 2012 data cut. In the final data cut of December 2014, 136 (27%) patients in the lap/Cap arm switched to Kadcyla. Out of these, 55 patients had an event (death) and 81 were censored (Table 1).

Table 1: Number of censored and dead patients by treatment switching

Lap/Cap			
	xo NO	***xo YES***	***Total***
Censor	*82*	*81*	*163*
Death	*278*	*55*	*333*
Total	*360*	*136*	*496*

In order to adjust for the overall survival estimate that is confounded due to treatment switching, we applied Rank Preserving Structural Failure Time Model (RPSFTM) (1)(2). In the section below we describe the method applied (RPSFTM), its assumption, and its plausibility to adjust for treatment switching. In addition, we discuss the suitability of other treatment switching adjustment methods and their comparison with RPSFTM.

The RPSFTM method (3) is based on an Accelerated Failure Time (AFT) model that allows the estimation of the expected survival time had patients not switched and remained on their randomized treatment. This is achieved by shrinking the additional survival benefit applied to patients in the lap/cap arm who switched to receive Kadcyla.

This is achieved by considering three different survival times for a patient 'i':

T_i – the observed survival time with the observed treatment history (observed)

U_i– the latent survival time with no treatment (baseline characteristic unobserved)

An AFT Ψ model that depends on a patient's treatment history is then developed that relates T_i with U_i through some unknown parameters Ψ. The key assumption is that this model fully captures the relationship between the observed treatment history, the observed survival time and the unobserved latent survival time. A known limitation of the RPSFTM approach is that this assumption is untestable.

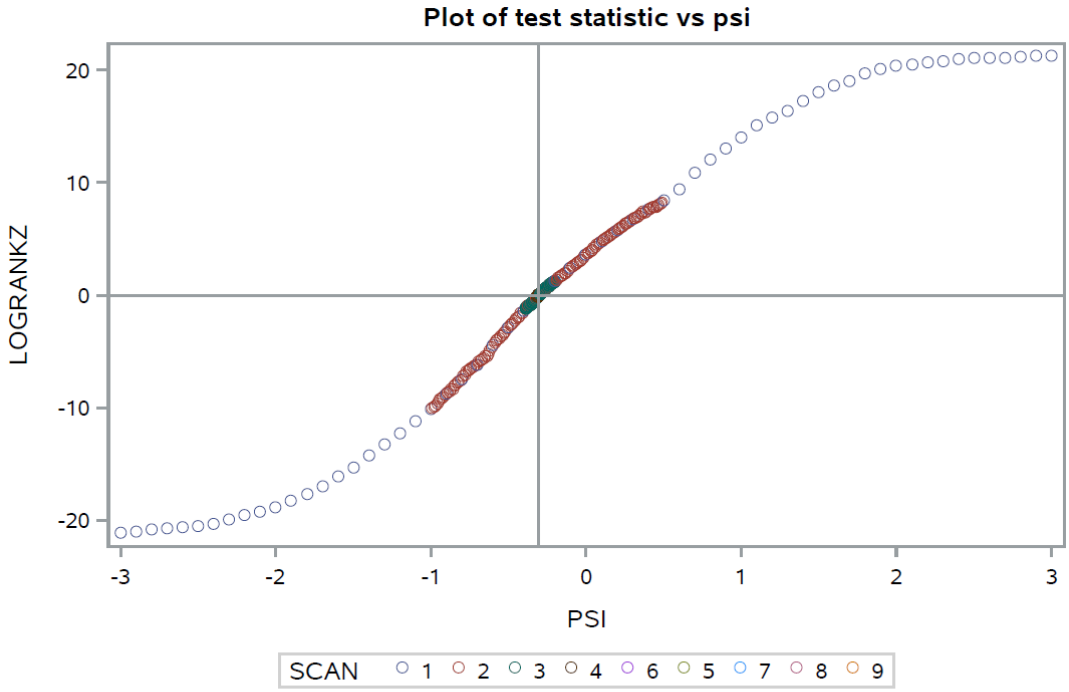
For this study the model was designed under the assumptions that a single treatment effect applied regardless of when Kadcyla was administered and that this effect applied pre and post treatment switching. That is the AFT model relating $U_i = T_i$ was defined to be $U_i = X_i + (Ti-X_i)exp(\Psi)$ where X_i is the time from randomization to treatment switching to Kadcyla and the treatment effect is assumed to apply over the whole lifetime of a patient post treatment. A patient randomised to Kadcyla X_i is defined as 0 while a patient randomized to lap/cap who does not cross over has X_i is defined as Ti.

The unknown parameter Ψ was estimated using a grid based estimation approach with a stratified log rank test using SAS code previously validated by an independent vendor against the Stata's STRBEE package. This SAS code is available upon request.

The derived U_i for the lap/cap arm and the observed T_i for the Kadcyla arm were then used to derive Kaplan Meier survival estimates.

We present the applicability of RPSFTM to the EMILIA data. The grid search plot (Figure 1) shows that only a single value of psi gives the equal counterfactual survival on both arms. Therefore in terms of the single solution, RPSFTM fits well to the data.

Figure 1: Diagnostic plot for unique solution for psi



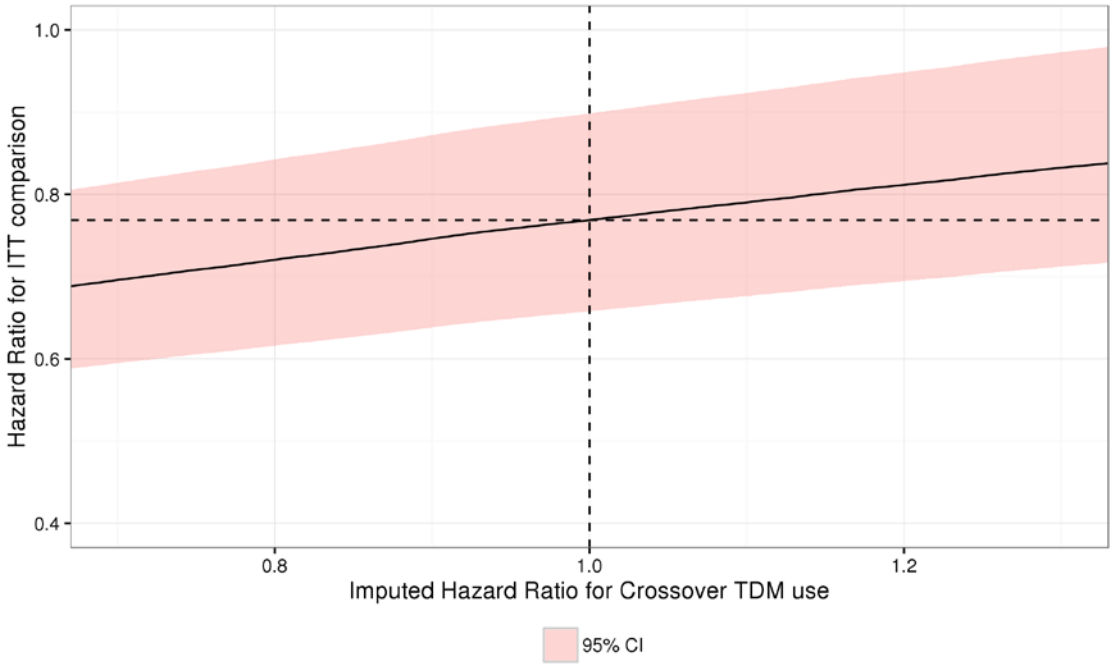
Clinical cut-off: 31 December 2014
Source: SAS v9.4 damontee $HOME/cdt3502a.pbe/i21977e.
pbe/i21977e_rpsft_strat_new_cens.sas 15MAR2016 16:45

RPSFTM assumes that the benefit of the experimental treatment is the same regardless of the time since randomization that the switching occurred (referred to as the constant treatment effect i.e. treatment effect at randomization and post treatment switching is the same).

Figure 2 multiplies (discounts) the observed time after treatment switching until death or censor by 0.7 to 1.3 on lap/cap arm and calculates the HR with the total duration (for lap/cap arm, time to treatment switching + multiplied

observed time and for Kadcyla arm, time to event without any adjustment) between arms. As a result, the treatment switching could affect the ITT result even when assuming a small treatment effect of Kadcyla when used after lap/cap. As such it is necessary to perform an adjustment for treatment switching.

Figure 2: Overall HR and its 95% CI over HR discount rate after treatment crossover



Out of the four methods (i.e. Rank Preserving Structural Failure Time Model (RPSFTM), Iterative Parameter Estimation (IPE), Inverse Probability of Censoring Weight (IPCW) and the two-stage method), we conducted IPE to compare with our base case analysis using RPSFTM. We concluded that IPCW and the two-stage method could not be applied due to lack of appropriate data needed to apply the adjustment.

Stratified HR on each datacuts with all methods that were implemented is summarized in Table 2. At the datacut of January 2012 and July 2012, there was no treatment crossover. On the datacut of December 2014, following analysis were conducted: ITT analysis without crossover adjustment,

crossover adjusted without recensoring and crossover adjusted with recensoring. The HR of Kadcyla compared to lap/cap is 0.693 and 0.706 using RPSFTM and IPE, respectively. The difference observed between the methods is small and negligible.

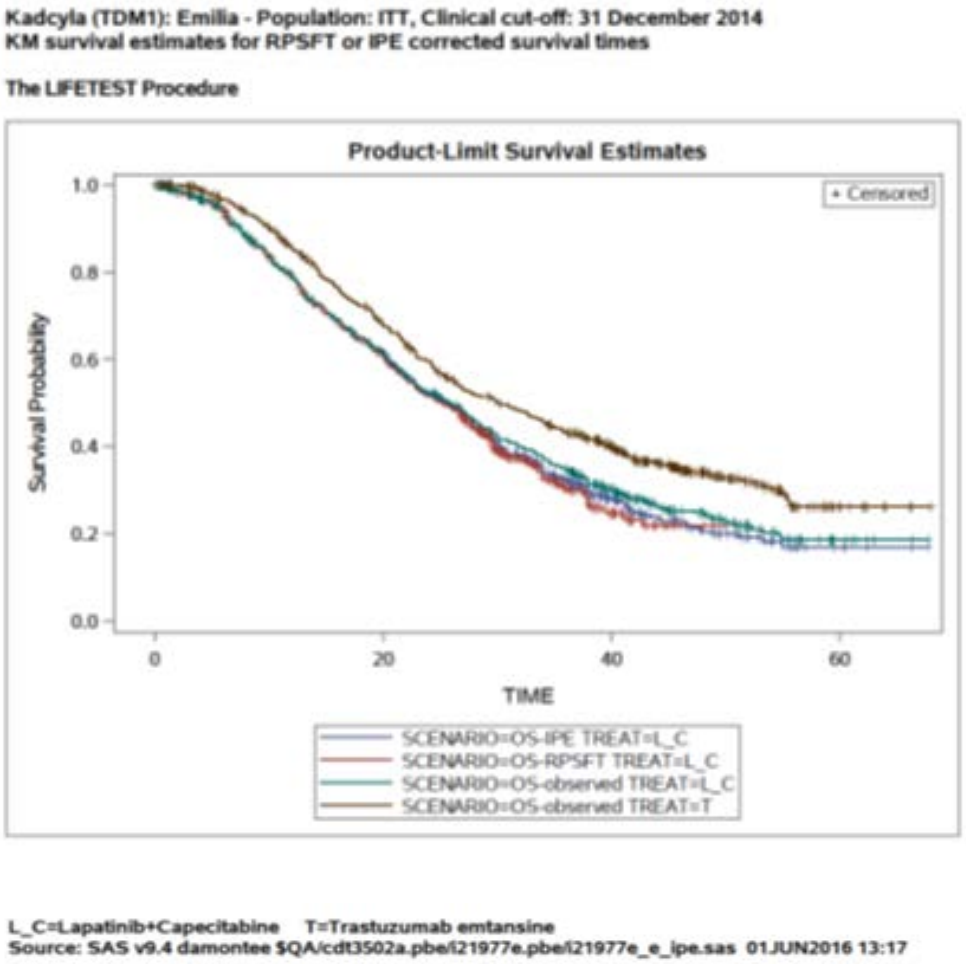
Note that on IPE the 95% CI were not taken from the Weibull model used to estimate the acceleration factor but were estimated using the test based adjustment proposed by White for RPSFTM (4) for this analysis.

Table 2 Stratified HR with each crossover and recensoring adjustment

Data cut	**Stratified HR**		**LCI**	**UCI**
Jan 2012	*ITT w/o xo*	*0.677*	*0.566*	*0.810*
July 2012	*ITT w/o xo*	*0.682*	*0.548*	*0.849*
Dec 2014	*ITT w/ xo (no adjustment applied)*	*0.749*	*0.639*	*0.877*
Dec 2014	*RPSFTM Adjusted‡*	*0.704*	*0.582*	*0.852*
Dec 2014	*RPSFTM Adjusted***	*0.693*	*0.577*	*0.848*
Dec 2014	*RPSFTM IPE*	*0.706*	*0.575*	*0.867*
‡ *no recensoring (psi is estimated without recensoring)*				
*** recensoring: distinguish patients who were censored due to reasons other than data cutoff (e.g. loss to follow up). Replace datacut time with actual censoring time for patients who were censored (4)*				

Figure 3 shows the Kaplan-Meier plots with Kadcyla, lap/cap without any treatment switching adjustment, lap/cap with RPSFTM and lap/cap with IPE.

Figure 3: Kaplan-Meier plots with IPE, with RPSFTM and without any treatment switching



The IPCW approach is a method (5) to correct for the selection bias involved in censoring at crossover by reweighting the remaining observations based on covariates that predict the probability of crossover. The idea is to replace the artificially censored observations with information from equivalent patients who did not crossover. A key requirement for the method to work is the assumption that there are no unmeasured confounders. Due to the design of EMILIA study this assumption was unlikely to be true. As the crossover to Kadcyla could occur after the start of survival follow-up for many patients, no covariates were captured in the time between end of study treatment and the

start of cross over treatment. As such for this study IPCW was considered inappropriate and not applied.

A key assumption of the two-stage method (6) is that an appropriate "second baseline" can be defined in the context of the trial and that treatment switching only occurs at this time point. Also assumed is that the covariates captured at this "second baseline" are enough to adjust for all other differences between the lap/cap group patients who switch and those who do not. However, in EMILIA trial study protocol there is no time point defined which restricts treatment switching only at the point. Patients who were randomized to lap/cap arm are allowed to switch treatment anytime. In addition, covariates which adjust the difference between the patients with and without switch were not collected in EMILIA trial. With this reason two-stage method would not be justified in this case.

- *Treatment Duration*

Treatment duration and adverse events rates were updated using the latest cut of data. In addition, in the original model, treatment duration curve was used until median survival; thereafter, progression free duration curve was used to estimate mean treatment duration/cost. In the updated model, a separate time to event analysis was conducted on the treatment duration data, and mean trement duration and cost was calculated based on this approach.

- *Network Meta-Analysis (NMA)*

The network meta-analysis (using random effects model) has been updated. Additionally, analysis which included the corrected OS treatment switching hazard ratio was used to conduct intent to treat analysis.

2) <u>Corrections based on ERG's recommendation</u>

Based on the recommendations made by the ERG the following changes have been made:

- *Time horizon*

The time horizon in the previous model was 10 years. It was changed to 15 years (when more than 99% of patients have died).

- *Inclusion of left ventricular ejection fraction (LVEF) monitoring follow up cost*

A follow up cost of 130 GBP every three months was included in the model based on clinical guideline 81 and the ERG's suggested cost.

- *Utility values*

An error was made in the original submission, which was highlighted by the ERG, in the way the coefficients from Lloyd et al were used to derive health state utility values. The way in which they were incorporated into the model was also changed so that the frequency of each AE is now multiplied by the binary variable (i.e. experience AE or not), and then the total is weighted according to the frequency of that AE.

Table 3: Summary of utility values used in original and updated analysis

Health State	***Original Utility Values***	***Updated Utility Values***
Progression-free survival Kadcyla	*0.78*	*0.807*
Progression-free survival lap/cap	*0.74*	*0.8*
Progression-free survival Her/cap (Herceptin & Capcitabine)	*0.73*	*0.8*
Progression-free survival Capecitabine	*0.72*	*0.792*
Progressed	*0.50*	*0.53*

- *Treatment cost*

The updated model is based on actual dose from EMILIA rather than planned dose to calculate treatment cost.

- *PSA*

Probabilistic sensitivity analysis was criticised by ERG. The current model makes the recommended corrections including:

- *the use of Convergence Diagnostic and Output Analysis (CODA) to include uncertainty around the log hazard ratios from WinBUGS*
- *accounting for uncertainty around the treatment response and AE rates for utility analysis*

- *Post progression treatment cost implementation*

In the original submission, the weekly cost of progressed disease state is independent of treatment. However the ERG stated that 'this results in these treatments, such as TDM-1 (Kadcyla), where patients spend a longer duration in progressed disease state, being associated with greater costs than those with shorter durations, despite having similar post-progression treatments.'

The ERG preferred method was to calculate the average costs per week for each individual treatment rather than assuming the weekly cost in the progressed disease state is independent of treatment as in the Roche base case.

3) Other

- *The patient access scheme (which is currently waiting to be referred by the Department of Health to PASLU) has been factored into the cost effectiveness model.*

- *The model originally had five comparators (lap/cap, Herceptin & Capecitabine (Her/cap), vinorelbine , Herceptin/vinorelbine and capecitabine) since the original appraisal lapatinib was delisted from the Cancer Drugs Fund and as such we now consider Her/cap to be the main comparator. The model now includes 3 comparators Her/cap and in addition includes capecitabine monotherapy and lap/cap.*

- *Adverse Events (AEs)*

  AE rates for indirect comparators Her/cap plus Capecitabine and Capecitabine alone were calculated using the weighted average approach (i.e. weighted by the numbers of patients in each trial) using the trials included in the network meta analysis (NMA).

  A weighted average of the adverse events seen on the CEREBAL and GBG was used to estimate the adverse events for Her/cap. For the capecitabine monotherapy arm a weighted average of Cameron and GBG trials was used. Table 4 below shows the values used in the economic model, the weight average values shown in bold are inputted into the economic model.

Table 4: Weighted average of adverse events rates from trials

Adverse Event		*HerCap*		*Cap*	
		n	*%*	*n*	*%*
Febrile Neutropenia	*GBG*	*2*	*3%*	*0*	*0*
	CEREBBAL	*0*	*0*	*-*	*-*
	Cameron	*-*	*-*	*0*	*0*
	Weighted Average	***2***	***3%***	*0*	*0*
Diarrhoea and vomiting	*GBG*	*13*	*17%*	*17*	*23%*
	CEREBBAL	*24*	*9%*	*-*	*-*
	Cameron	*-*	*-*	*23*	*12%*
	Weighted Average	***22***	***11%***	***21***	***15%***

Hand and foot syndrome	*GBG*	*25*	*32%*	*18*	*24%*
	CEREBBAL	*40*	*15%*	*-*	*-*
	Cameron	*-*		*27*	*14%*
	Weighted Average	***37***	***19%***	***24***	***17%***
Stomatitis	*GBG*	*-*	*-*	*0*	*0%*
	CEREBBAL	*4*	*1%*	*-*	*-*
	Cameron	*-*	*-*	*0*	*0%*
	Weighted Average	***4***	***1%***	*-*	*-*
Fatigue	*GBG*	*3*	*4%*	*4*	*5%*
	CEREBBAL	*0*	*0%*	*-*	*-*
	Cameron	*-*	*-*	*6*	*3%*
	Weighted Average	***3***	***4%***	***5***	***4%***
Hair loss/Alopcia	*GBG*	*6*	*8%*	*2*	*3%*
	CEREBBAL	*0*	*0%*	*-*	*-*
	Cameron	*-*	*-*	*-*	*0*
	Weighted Average	*6*	*8%*	*0*	*3%*
Trial numbers: GBG cap=74 HerCap n= 77; CEREBAL HerCap n=267; Cameron Cap n=191					

Only adverse events occurring in 2% or more people of the Kadcyla arm of EMILIA trial or of the weight average of the HerCap AE rates at Grade 3, 4 or 5 severity are incorporated into the model.

Although there were seven adverse events occurring in 2% or more people, only febrile neutropenia, fatigue diarrhoea and vomiting 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. The cost of managing alopecia and acute respiratory distress syndrome has not been included in the base case

Table 5: Costs of adverse events

Adverse events	***Cost per episode (£)***	***Source (NHS reference cost)***
Febrile Neutropenia (Grade 3 and 4)	*8,662*	*NHS ref costs 2012/13 Febrile Neutropenia with Malignancy - Non-Elective Inpatient long stay HRG Data: PA45Z*
Diarrhoea and vomiting (Grade 3)	*789*	*Malignant Breast Disorders without intervention with CC (non-elective short stay) JA12G*
Hand and foot syndrome (Grade 3)	*0*	*-*
Acute respiratory distress syndrome	*0*	*-*
Hair loss/Alopecia	*0*	*-*
Aspartate aminotransferase increased	*0*	*-*
Thromocytopenia	*643*	*Thrombocytopenia with CC (weighted average of SA12G, SA12H, SA12J and SA12K)*

- *The same sources of data and methodology have been used to calculate cost of administration, pharmacy and supportive care costs as in the original model. However, the costs have been updated to reflect current 2014/15 NHS prices. The updated costs are summarised in the table 6 below.*

Table 6: Summary of administration, pharmacy, monitoring and adverse event costs

Administration Costs	**Items**	**Frequency per cycle**	**Unit cost (£)**	**Source**	
capecitabine	*Admin cost per cycle*	*1*	*£192*	*NHS Reference costs 2014/15 (SB11Z)*	
	Pharmacy cost	*1*	*£6 per cycle for oral*	*PSSRU 2015*	
Her/cap	*Admin cost per cycle*	*1*	*£329 first cycle* *£362 Subsequent cycles*	*NHS Reference costs 2014/15 (SB13Z)* *NHS Reference costs 2014/15 (SB15Z)*	
	Pharmacy cost	*1*	*£18 per cycle for IV* *£6 per cycle for oral*	*PSSRU 2015*	
Kadcyla	*Admin cost per cycle*	*1*	*£329 first cycle* *£362 Subsequent cycles*	*NHS Reference costs 2014/15 (SB13Z)* *NHS Reference costs 2014/15 (SB15Z)*	
	Pharmacy cost	*1*	*£18 per cycle for IV*	*PSSRU 2015*	
Health states	**Items**	**Frequency**	**Unit cost (£)**	**Total Cost per month (£)**	**Source**
Progression-free survival best supportive care	*Community Nurse (home visit)*	*20 mins every 2 weeks*	*22*	*47.67*	*PSSRU 2015*
	GP Contact (surgery visit)	*1 every month*	*44 (per patient contact lasting 11.7 mins)*	*44*	*PSSRU 2015*
	Clinical Nurse Specialist	*1hr every month*	*81 (per hour of client contact)*	*81*	*PSSRU 2015*
	Total Monthly Cost	***-***	***-***	***172.67***	
Post progression survival best supportive care	*Community Nurse (home visit)*	*20 mins every 2 weeks*	*24*	*47.67*	*PSSRU 2015*
	GP Contact (surgery visit)	*1 every month*	*44 (per patient contact lasting 11.7 mins)*	*44*	*PSSRU 2015*

	Clinical Nurse Specialist	*1hr every month*	*81 (per hour of client contact)*	*81*	*PSSRU 2015*
	Total Monthly Cost	***-***	***-***	***172.67***	
End of life care cost				*4,032.94*	*PSSRU, 2015*

- *Choice of parametric function for PFS extrapolation*

  Given that a later data cut from EMILIA was used, it was necessary to reassess which parametric function should be used to extrapolate the PFS.

  Parametric functions were assessed based on model goodness of fit using Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) as well as a visual assessment of each parametric function. Table 7 provides the goodness of fit statistics for the functions used to model PFS.

  Based on the AIC statistics (lowest being the best fit), the lognormal function was determined to be the best fit to the data but there is little difference between the gamma and log-logistic functions.

Table 7: Parametric functions' goodness of fit for EMILIA PFS (both arms)

Parametric Model (PFS)	***AIC***	***BIC***
LogNormal	*2097.9*	*2112.6*
Gamma	*2099.7*	*2119.3*
LogLogistic	*2107.4*	*2122.1*
Weibull	*2150.3*	*2169.9*
Exponential	*2193.2*	*2203.0*

Parametric functions with more parameters (e.g. the gamma) are penalized even if they display a better visual goodness of fit. In addition, lognormal and logistic have long tails and generally provide implausible extrapolations.

Figure 4 displays the graphical assessment of each parametric distribution for the Kadcyla treatment arm and little difference can be seen between the fit of the log-normal, log-logistic and gamma functions. Similarly in the lap/cap treatment arms (Figure 5).

Figure 4: Progression-free survival KM data modelled with all parametric functions -Kadcyla EMILIA

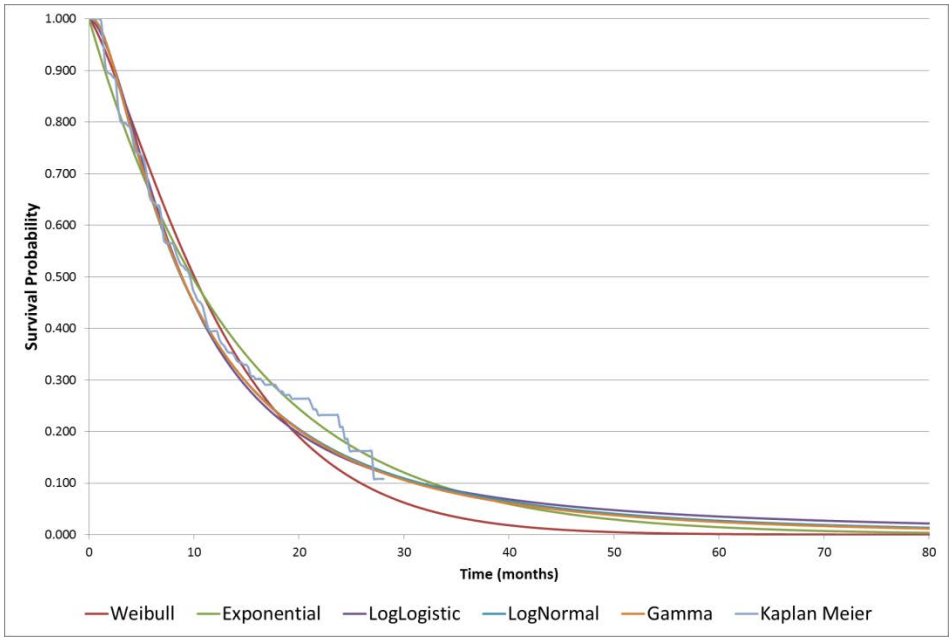
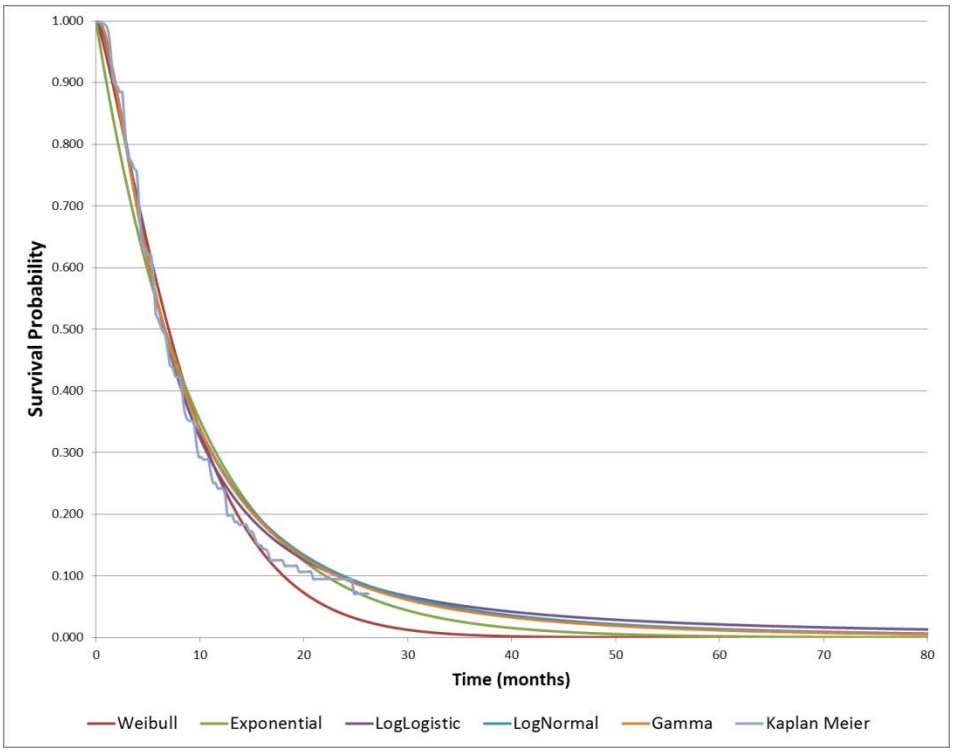


Figure 5: Progression-free survival KM data modelled with all parametric functions - Lap/cap EMILIA



The Gamma function was the second best fit for PFS estimates and had more plausible future model predictions than the log normal function.

Sensitivity analysis

Table 8 below shows the sensitivity of the model to different parametric function for the PFS extrapolation.

Table 8: Deterministic sensitivity analysis for choice of parametric function

Parametric function for PFS	***ICER without PAS***	***ICER with PAS***
KM with Gamma tail (Base case)	*£100,579*	[redacted]
KM with log normal tail	*£100,594*	[redacted]

KM with log logistic tail	*£98,145*	[redacted]
KM with exponential tail	*£96,283*	[redacted]
KM with weibull tail	*£88,731*	[redacted]
KM with gompertz tail	*£89,657*	[redacted]
Gamma	*£100,310*	[redacted]
Log normal	*£100,672*	[redacted]
Log logistic	*£98,354*	[redacted]
Exponential	*£95,582*	[redacted]
Weibull	*£86,144*	[redacted]
Gompertz	*£88,405*	[redacted]

Summary

A summary of all the changes carried out in the updated economic model is presented in Table 9.

Table 9: Summary of changes to input values in updated economic model

Model Variable	Company base case	ERG base case	New base case
Time horizon	*10*	*15*	*15*
Utility values	*Source: Lloyd*	*Source: Lloyd, with correction made*	*Source: Lloyd, with correction made*
Dosing	*Planned dose*	*Actual dose*	*Actual dose*
Supportive care costs	*Based on CG81 and inflated to 2013 prices using PSSRU*	*Based on CG81 and inflated to 2013 prices using PSSRU*	*Based on CG81 and inflated to 2015 prices using PSSRU*
Palliative care	*Based on PSSRU 2012*	*Based on PSSRU 2012*	*Same source inflated to 2015 prices*
LVEF monitoring	*Not included*	*Included based on CG81*	*Included based on CG81*
Costs of treatment within progressed disease state	*Same weekly cost independent of treatment*	*Average per week cost for individual treatment*	*Average per week cost for individual treatment*
AE costs	*Weekly cost of AEs multiplied by proportion of patients on treatment*	*Weekly cost of AEs multiplied by proportion of patients in PFS*	*Weekly cost of AEs multiplied by proportion of patients in PFS*
Parametric functions	*PFS: KM until week 72 then the lognormal OS: Gamma*	*Accepted company base case*	*PFS:KM with Gamma tail OS: Gamma*
PSA	*PSA and univariate sensitivity analysis*	*ERG focused on deterministic SA rather than correcting PSA*	*PSA with ERG criticisms addressed*
Pharmacy/administration costs	*Based on PSSRU 2012 inflated to 2013 NHS reference costs 2012/13*	*Based on PSSRU 2012 inflated to 2013 NHS reference costs 2012/13*	*Based on PSSRU 2015 NHS reference costs 2014/15*

4.2 If the population to whom the patient access scheme/ commercial access agreement applies (as described in sections 3.4 and 3.5) is not the same as that in the published technology appraisal (for example, the population is different as there has been a change in clinical outcomes or a new continuation rule), please (re-)submit the relevant sections from the 'Specification for company submission of evidence' (particularly sections 5.5, 6.7 and 6.9). You should complete those sections both with and without the patient access scheme/ commercial access agreement. You must also complete the rest of this template.

The population to whom the patient access scheme applies is equal to that detailed in section 3.1 and considered in the scope of the published technology appraisal TA371.

4.3 Please provide a summary of the clinical effectiveness parameters (resulting from the Committee's preferred evidence synthesis) which are used in the economic model which includes the patient access scheme/ commercial access agreement.

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 Kadcyla and lap/cap arms of the EMILIA trial.

The model was developed using the January 2012 cut of PFS data and December 2014 cut of OS data from the EMILIA trial. The January 2012 cut of PFS data features investigator assessed progression-free survival. The

progression-free and overall survival Kaplan-Meier curves are presented below.

Figure 6: PFS KM Plots (January 2012 data cut)

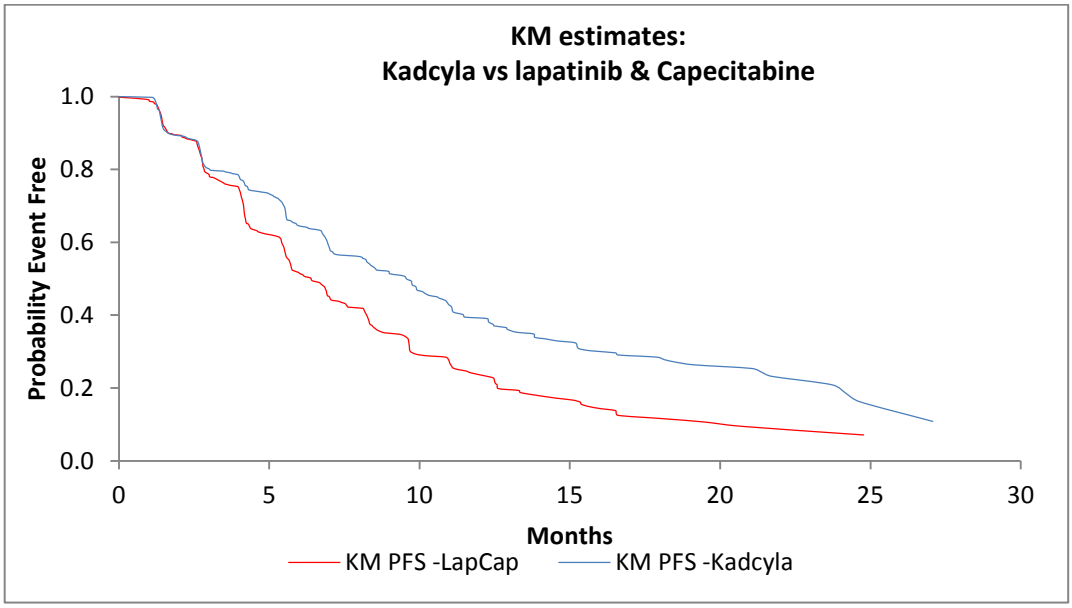


Figure 7: OS KM Plots (December 2014 data cut)

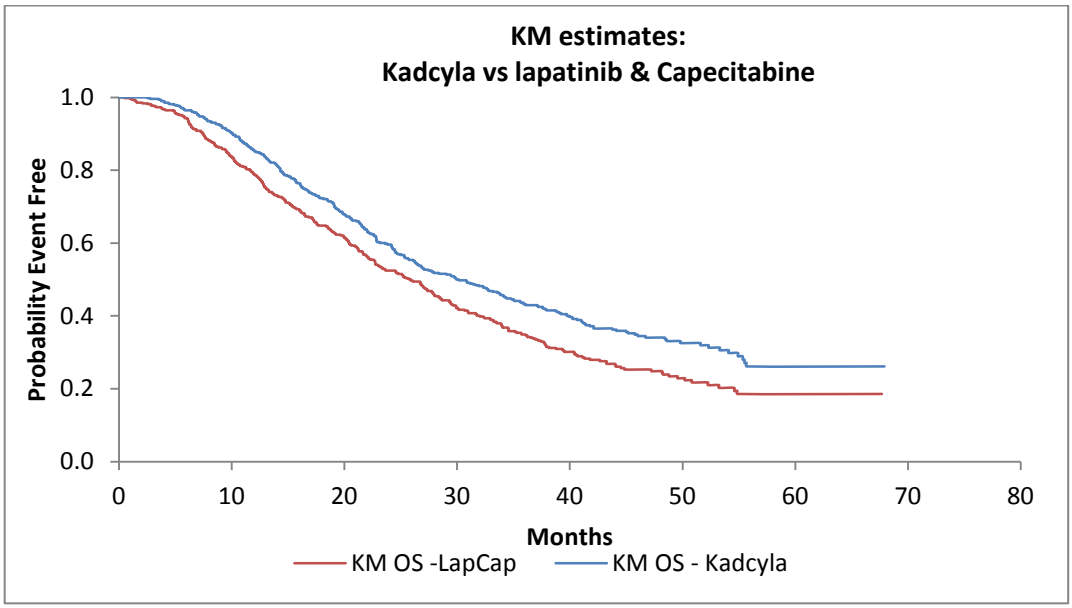


Table 9: Clinical effectiveness parameters within the base case

Variable (tranisiton Probabilities)	*Value*	*Reference to TA371 section in submission*
Progression-free survival distribution in Kadcyla arm	*KM data up to 74 weeks and gamma distribution thereafter*	*Explained above in section 4.1*
Progression-free survival distribution in lap/cap arm	*KM data up to 52 weeks and log-normal distribution thereafter*	*Explained above in section 4.1*
Progression-free survival distribution in Her/cap arm	*HR = 1.49 (1/0.67) vs T-DM1 arm*	*Updated*
Progression-free survival distribution in Cap arm	*HR = 2.50 (1/0.40) vs T-DM1 arm*	*Updated*
Overall survival distribution in Kadcyla arm	*Gamma distribution*	*7.3.1*
Overall survival distribution in lap/cap arm	*Gamma distribution*	*7.3.1*
Overall survival distribution in Her/cap arm	*HR = 1.28 (1/0.78) vs T-DM1 arm*	*Updated based on new data*
Overall survival distribution in Cap arm	*HR = 1.49 (1/0.67) vs T-DM1 arm*	*Updated based on new data*

Lap – lapatinib, Cap – capecitabine

4.4 Please list any costs associated with the implementation and operation of the patient access scheme/ commercial access agreement (for example, additional pharmacy time for stock management or rebate calculations). A suggested format is presented in table 2. Please give the reference source of these costs. Please provide sufficient detail to allow the replication of changes made to the original base case. For example, include sheet and cell references and state the old and new cell values. Please refer to section 6.5 of the 'Specification for company submission of evidence'.

There are a small amount of costs associated with operationalising this patient access scheme. All costs are detailed in Table 10 together with reference sources. Roche agrees to reimburse the NHS for any reasonable costs directly incurred as a result of administering this agreement.

Table 10 Costs for administering Kadcyla® ▼ Patient Access Scheme

	Calculation of cost	**Reference source**
Stock management	N/A	
Administration of claim forms	£10,581	1292 patients taking 5 minutes per patient 4 times per year processed by a Band 8a pharmacist at £24.57 per hour
Staff training	N/A	
Tracking of supplies	N/A	
Other costs	One-off Implementation Costs = £14,924	One-off Implementation Costs = 1 hour meeting consisting of Band 8d pharmacist at £31.92 per hour, Band 8a pharmacist at £24.57 per hour, 3 Band 6 staff (finance, business manager, procurement) at £18.02 per hour for 135 Trusts.

	Registration = £2645 - £5020 Issue VAT Invoice = £4865 Process payment = £4865	Registration = 90 patients taking 5 minutes per patient processed by a Band 8a pharmacist at £24.57 per hour, or a consultant at £46.63 per hour Issue VAT Invoice = grade 6 finance at £18.02 per hour, 30 minutes per invoice with 135 trusts each issuing invoices 4 times per year Process payment = grade 6 finance at £18.02 per hour, 30 minutes per invoice with 135 trusts each issuing invoices 4 times per year
Other [add more rows as necessary]		
Total implementation and operation costs	One-off implementation costs = £14,924 Operation costs = £25,332year Cost per Trust: One-off implementation costs = £111 Operation costs = £188/year	[Pay rates taken from the pay bands and pay points on the second pay spine in England from 1 April 2016 Currently approximately 135 Trusts are purchasing Kadcyla, so for the purposes of costing we have assumed that this will remain the same Roche will reimburse the Customer for any reasonable costs incurred directly by the Customer in complying with its obligation to submit its Data Report through the Blueteq Patient Access Scheme module.

4.5 Please provide details of any additional treatment-related costs incurred by implementing the patient

access scheme/ commercial access agreement. A suggested format is presented in table 3. The costs should be provided for the intervention both with and without the patient access scheme. Please give the reference source of these costs.

There are no additional treatment related costs associated with implementing the patient access scheme agreement. Table 11 is therefore not completed.

Table 11: Additional treatment-related costs for the intervention both with and without the patient access scheme (PAS)/ commercial access agreement (CAA)

	Intervention without PAS/ CAA		*Intervention with PAS/ CAA*		*Reference source*
	Unit cost (£)	*Total cost e.g. per cycle, per patient (£)*	*Unit cost (£)*	*Total cost e.g. per cycle, per patient (£)*	
Interventions	-	-	-	-	-
Monitoring tests	-	-	-	-	-
Diagnostic tests	-	-	-	-	-
Appointments	-	-	-	-	-
Other costs…	-	-	-	-	-
Total treatment-related costs	-	-	-	-	-

Summary results

New base-case analysis

4.6 Please present in separate tables the cost-effectiveness results as follows.[1]

- the results for the intervention without any (new) patient access scheme/ commercial access agreement; that is with the price for the technology considered in the published guidance.
- the results for the intervention with the patient access scheme/ commercial access agreement.

A suggested format is shown below (table 4).

Since TA371, there has been a change in the treatment regimens that should be considered as appropriate comparators. Lap/cap was delisted from the cancer drugs fund in January 2015 and therefore should no longer be considered an appropriate comparator for this appraisal.

Since Kadcyla was funded via the CDF from February 2014, it has become standard of care in England for second line treatment of patients with HER2-positive metastatic breast cancer and is recommended by international consensus treatment guidelines (7)(8)(9). Clinical expert opinion indicates that if Kadcyla were no longer funded that patients would be likely to receive Her/cap. Therefore Her/cap should now be considered as the appropriate comparator.

[1] For outcome-based schemes, please see section 5.2.8 in appendix B.

Table 12: New base-case cost-effectiveness results using the price as in the published technology appraisal

	Kadcyla	Lap/Cap	Her/cap	Capecitabine
Intervention cost (£)	£91,614	£22,499	£28,808	£5,473
Other costs (£)	£9,014	£8,287	£8,026	£7,952
Total costs (£)	£100,628	£30,785	£36,834	£13,425
Difference in total costs (£)	N/A	£69,843	£63,794	£87,203
LYG	3.32	2.58	2.41	2.06
LYG difference	N/A	0.74	0.91	1.25
QALYs	2.09	1.56	1.45	1.20
QALY difference	N/A	0.53	0.63	0.89
ICER (£)	N/A	£131,473	£100,579	£98,525

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Table 13: New base-case cost-effectiveness results using the patient access scheme commercial agreement

	Kadcyla	Lap/Cap	Her/cap	Capecitabine
Intervention cost (£)	[redacted]	£22,499	£28,808	£5,473
Other costs (£)	£9,014	£8,287	£8,026	£7,952
Total costs (£)	[redacted]	£30,785	£36,834	£13,425
Difference in total costs (£)	N/A	[redacted]	[redacted]	[redacted]
LYG	3.32	2.58	2.41	2.06
LYG difference	N/A	0.74	0.91	1.25
QALYs	2.09	1.56	1.45	1.20
QALY difference	N/A	0.53	0.63	0.89
ICER (£)	N/A	[redacted]	[redacted]	[redacted]

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

End of Life Criteria

In the final appraisal document the committee concluded that Kadcyla meets the end of life criteria as the committee was prepared to accept that Kadcyla fulfilled the criterion for short life expectancy based on a standard of care of

lap/cap. The standard of care in England is now considered to be Her/cap; despite this we still feel that Kadcyla meets this criteria.

There is limited data on the life expectancy of a patient with metastatic breast cancer receiving Her/cap as a second line treatment, however on the basis of the evidence below that it is likely to be around 24 months.

The key data for this combination comes from the CEREBEL study, that compared the incidence of CNS metastases in patients with HER2+ mBC receiving lap/cap or Her/cap (Pivot et al 2015). The median overall survival in the Her/cap arm was 27.3 months, however 45% of the patients in the Her/cap arm were being treated first line. Thus the survival seen is likely to be considerably higher than would be achieved in a solely 2nd line population.

In the absence of robust supporting data for the Her/cap combination, it is reasonable to consider the outcomes of patients treated with lap/cap to build the body of evidence to describe the life expectancy of this population. Patients treated in the lap/cap arm of the CEREBEL study had a median overall survival of 22.7 months, with 43% of patients being treated in the first line setting. In the licensing study for the lap/cap combination (EGF100151) the median overall survival for the lap/cap arm was 75 weeks, albeit in a more heavily pre-treated patient population (Cameron et al 2010). While in the EMILIA control arm (lap/cap) the median OS was 25.1 months (Verma et al 2012), this outcome is notably incongruent with the above.

While we have sought to reflect the standard of care in England (Her/cap), it is worth noting that the only treatments that are reimbursed according to product licences in this setting are chemotherapies. In the capecitabine only control arm of EGF100151 the median overall survival was 64.7 weeks (although in a more heavily pre-treated patient population (Cameron et al 2010)). Additionally, in a predominantly first and second line population, the combination of capecitabine and docetaxel resulted in a median overall survival of 14.5 months (O'Shaugnessy et al 2002).

The trial evidence suggests that treatment with Her/cap results in survival outcomes that lie close to the upper bound of the short life expectancy criteria. When considered with the evidence that the addition of Kadcyla improves life expectancy significantly more than the minimum survival gain criteria (with an expected OS gain of 7.56 months) we feel that this therapy should be considered under the end of life criteria.

4.7 Please present in separate tables the incremental results as follows. [2]

- the results for the intervention without the (new) patient access scheme/ commercial access agreement, that is with the price for the technology considered in the published appraisal.
- the results for the intervention with the patient access scheme/ commercial access agreement.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 5.

Incremental results are shown below in Table 14 as per the pricing included in the original published appraisal and Table 15 with the new patient access scheme commercial agreement.

Since lap/cap is no longer funded in England, it has been removed from the incremental analysis.

[2] For outcome-based schemes, please see section 5.3.9 in appendix 5.3.

Table 14: New base-case incremental results using the price as in the published technology appraisal

Technologies	*Total costs (£)*	*Total LYG*	*Total QALYs*	*Incremental costs (£)*	*Incremental LYG*	*Incremental QALYs*	*ICER (£) incremental (QALYs)*
Capecitabine	*£13,424*	*2.06*	*1.20*				
Her/cap	*£36,834*	*2.41*	*1.45*	*£23,410*	*0.35*	*0.25*	*£93,640*
Kadcyla	*£100,628*	*3.32*	*2.09*	*£63,794*	*0.91*	*0.64*	*£99,678*

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Table 15: New base-case incremental results using the patient access scheme/ commercial access agreement

Technologies	*Total costs (£)*	*Total LYG*	*Total QALYs*	*Incremental costs (£)*	*Incremental LYG*	*Incremental QALYs*	*ICER (£) incremental (QALYs)*
Capecitabine	*£13,424*	*2.06*	*1.20*				
Her/cap	*£36,833*	*2.41*	*1.45*	*£23,409*	*0.35*	*0.25*	*£93,636*
Kadcyla	[redacted]	*3.32*	*2.09*	[redacted]	*0.91*	*0.64*	[redacted]

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Sensitivity analyses with the relevant PAS/CAA

4.8 Please refer to the published guidance to identify the key sensitivity and scenario analyses (that is, analyses that were discussed in the 'considerations' section and which alter the ICER). Present the results of these sensitivity and scenario analyses with the patient access scheme/ commercial access agreement.

There were no major areas of uncertainty noted within the considerations section of the FAD.

It is noted that the Committee preferred a 15 year time horizon, in place of the 10 year horizon in the original base case. A 15 year time horizon is used in the new base case. A 10 year time horizon increases the ICER by £3,190 for

the Her/cap comparator and by £3,345 in the capecitabine monotherapy comparison.

It is also noted that the Committee preferred to incorporate increased costs and decrease in utility associated with treating adverse events. However in exploratory analysis the ERG noted that inclusion of adverse event costs had little impact on the ICER.

As a new model has been created and new clinical data has been inputted into the model it is not possible to see how each change to the model or model inputs affects the original ICER. However from the new base case we have done analysis using the original assumptions/values from the original model to highlight how sensitive the model is to each of these changes.

Table 16: Sensitivity of results to new model input values with PAS

Value	***Value in updated base case*** [redacted]	***Value used in original submission***	***ICER result for updated model with original value***
Time horizon	*15*	*10*	[redacted]
LVEF	*£150*	*£0*	[redacted]
Utility values *PFS –TDM-1* *PFS – Her/Cap* *PFS – Cap* *PD*	 *0.807* *0.8* *0.792* *0.53*	 *0.7* *0.7* *0.72* *0.5*	[redacted]
Treatment dose	*Actual dose without vial sharing*	*Planned dose without vial sharing*	[redacted]

4.9 Please present any probabilistic sensitivity analysis results, and include scatter plots and cost-effectiveness acceptability curves.

A 1,000 simulation probabilistic sensitivity analysis was conducted in order to evaluate the uncertainty associated with the base-case estimate.

Table 17: PSA results using the patient access scheme

	Kadcyla	***Her/cap***	***Capecitabine***
Total costs (£)	[redacted]	*£39,571*	*£14,730*
Difference in total costs (£)	*N/A*	[redacted]	[redacted]
LYG	*3.33*	*2.54*	*2.21*
LYG difference	*N/A*	*0.75*	*1.08*
QALYs	*2.09*	*1.54*	*1.29*
QALY difference	*N/A*	*0.55*	*0.80*
ICER (£)	*N/A*	[redacted]	[redacted]

Figure 8: Cost -effectiveness acceptability curve

Redacted

Figure 9: Cost-effectiveness plane

Redacted

4.10 If any of the criteria on which the patient access scheme/ commercial access agreement depends is a clinical variable (for example, choice of response measure, level of response, duration of treatment), sensitivity analyses around the individual criteria should be provided, so that the Appraisal Committee can determine which criteria are the most appropriate to use.

The patient access scheme is not dependant on any clinical variable.

5 Appendices

5.1 Information about patient access schemes

5.1.1 The 2014 Pharmaceutical Price Regulation Scheme (PPRS) is a non-contractual scheme between the Department of Health and the Association of the British Pharmaceutical Industry. The purpose of the 2014 PPRS is to ensure that safe and cost-effective medicines are available on reasonable terms to the NHS in England and Wales. One of the features of the 2014 PPRS is to improve patients' access to medicines at prices that better reflect their value through patient access schemes.

5.1.2 Patient access schemes are arrangements which may be used on an exceptional basis for the acquisition of medicines for the NHS in England and Wales. Patient access schemes propose either a discount or rebate that may be linked to the number, type or response of patients, or a change in the list price of a medicine linked to the collection of new evidence (outcomes). These schemes help to improve the cost effectiveness of a medicine and therefore allow the National Institute for Health and Care Excellence (NICE) to recommend treatments which it would otherwise not have found to be cost effective. More information on the framework for patient access schemes is provided in the 2014 PPRS.

5.1.3 Patient access schemes are proposed by a pharmaceutical company and agreed with the Department of Health, with input from the Patient Access Schemes Liaison Unit (PASLU) within the Centre for Health Technology Evaluation at NICE.

5.2 Additional documents

5.2.1 If available, please include copies of patient access scheme agreement forms/ commercial access agreement, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians, patient information documents.

These are the terms and conditions that will cover the scheme, this does not need to be signed but NHS Hospitals will agree to these at the point at which they register their patients.

Kadcyla Patient Access Agreement 07

5.3 Details of outcome-based schemes

5.3.1 If you are submitting a proven value: price increase scheme, as defined in the PPRS, please provide the following information:

- the current price of the intervention
- the proposed higher price of the intervention, which will be supported by the collection of new evidence
- a suggested date for when NICE should consider the additional evidence.

Not applicable

5.3.2 If you are submitting an expected value: rebate scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the planned lower price of the intervention in the event that the additional evidence does not support the current price
- a suggested date for when NICE should consider the additional evidence.

Not applicable

5.3.3 If you are submitting a risk-sharing scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the proposed relationship between future price changes and the evidence to be collected.

Not applicable

5.3.4 For outcome-based schemes, as defined in the PPRS, please provide the full details of the new information (evidence) planned to be collected, who will collect it and who will carry the cost associated with this planned data collection. Details of the new information (evidence) may include:

- design of the new study
- patient population of the new study
- outcomes of the new study
- expected duration of data collection
- planned statistical analysis, definition of study groups and reporting (including uncertainty)
- expected results of the new study
- planned evidence synthesis/pooling of data (if applicable)
- expected results of the evidence synthesis/pooling of data (if applicable).

Not applicable

5.3.5 If you are submitting a risk-sharing scheme, please specify the period between the time points when the additional evidence will be considered.

Not applicable

5.3.6 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered.

Not applicable

5.3.7 Please provide the other data used in the economic modelling of the patient access scheme at the different

time points when the additional evidence is to be considered. These data could include cost/resource use, health-related quality of life and utilities.

Not applicable

5.3.8 Please present the cost-effectiveness results as follows.

- For proven value: price increase schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the anticipated results based on the expected new evidence and the proposed higher price.
- For expected value: rebate schemes, please summarise in separate tables:
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming).
- For risk-sharing schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming)
  - the anticipated results based on the expected new evidence and the proposed higher price.

A suggested format is shown in table 3, section 4.7.

5.3.9 Please present in separate tables the incremental results for the different scenarios as described above in section 5.2.8 for the type of outcome-based scheme being submitted.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4, section 4.8.

Not applicable

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(1) Morden JP, Lambert PC, Latimer N, Abrams KR, Wailoo AJ. Assessing methods for dealing with treatment switching in randomised controlled trials: a simulation study. BMC medical research methodology. 2011 Jan 11;11(1):1.

(2) Watkins C, Huang X, Latimer N, Tang Y, Wright EJ. Adjusting overall survival for treatment switches: commonly used methods and practical application. Pharmaceutical statistics. 2013 Nov 1;12(6):348-57.

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Economic Evaluation Context Methods, Limitations, and Recommendations. Med Decis Making. 2014, 34: 387-402.

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(9) Hurvitz SA. Regimens in HER2-positive metastatic breast cancer. San Antonio Breast Caacer Symposium, presentation 2015)

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CANCER DRUGS FUND

Appendix

CDF Rapid reconsideration process: Breast cancer (refractory, HER2 positive) - trastuzumab-emtansine (T-DM1; Kadcyla®▼) [TA371]

26th February 2016

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1 Executive Summary

Human epidermal growth factor receptor 2 (HER2) positive disease accounts for 15-20% of all breast cancers and has a poorer prognosis compared to other breast cancers when diagnosed (Dawood et al. 2010, Wolff et al. 2013). HER2-targeted treatments have revolutionised outcomes for these patients, with prognosis now similar between patients with HER2-positive and HER2-negative disease (Dawood et al. 2010, Clarke et al. 2014). Since the NICE single technology appraisal (STA) submission for trastuzumab emtansine (T-DM1; Kadcyla®) in December 2013 (TA371), the creation of the Cancer Drugs Fund (CDF) has improved the availability of HER2-directed therapies and therefore clinical practice in England, affecting the standard-of-care (SOC).

Lapatinib, a small molecule targeting the HER2 pathway, was funded on the CDF from 2010 until being de-listed in January 2015, and Kadcyla became available on the CDF in February 2014 (Cancer Drugs Fund 2014, Cancer Drugs Fund 2015). Kadcyla has since become the SOC for the second-line treatment of patients with HER2-positive metastatic breast cancer (mBC) based on the demonstration of superior efficacy and tolerability compared to lapatinib and capecitabine (Verma et al. 2012). Kadcyla has become the treatment of choice within its indication, demonstrated by market share data, and is recommended by international consensus treatment guidelines for treatment in the second-line and beyond (Cardoso et al. 2014, Hurvitz 2015, Roche data on file 2015).

In a situation where access to Kadcyla was not available, clinical expert opinion indicates that patients would likely receive capecitabine plus Herceptin. Capecitabine plus Herceptin is therefore the relevant comparator for the appraisal of Kadcyla, rather than capecitabine and lapatinib, which was used in the NICE STA submission as lapatinib is no longer funded or available as a treatment option in this setting.

Longer follow-up data for the use of Kadcyla in its licenced indication is available from the final overall survival (OS) analysis of the EMILIA study and the second interim OS analysis from the TH3RESA study. Both studies were multi-national, multi-centre, open-label, phase 3, randomised controlled studies. The descriptive final OS analysis from the EMILIA study investigating Kadcyla in the second-line setting used a data cut-off of 31st December 2014. Results reported that the median OS was significantly longer in the Kadcyla arm (29.9 months) versus capecitabine plus lapatinib (25.9 months); stratified hazard ratio (HR)=0.75 (95% confidence interval [CI] 0.64-0.88, P=0.0003). A significant survival benefit was reported despite 27% of patients crossing over from capecitabine plus lapatinib to Kadcyla. These data are consistent with results from the second interim, confirmatory OS analysis which demonstrated a 5.8 month OS benefit for Kadcyla compared to lapatinib and capecitabine (Verma et al. 2012).

Longer follow-up supportive evidence from the TH3RESA study in patients who had received >2 previous HER2 targeted agents for mBC is now also available, demonstrating that Kadcyla is efficacious versus treatment of physician's choice (TPC); the majority of patients assigned to TPC were on a Herceptin-based regimen). At the data cut-off of 13th February 2015 for the second interim OS analysis, median OS improved by 6.9 months from 15.8 months with TPC, which

was Herceptin-based most frequently, to 22.7 months with Kadcyla (stratified HR=0.68 [95% CI 0.54-0.85, P=0.0007]), again despite substantial crossover (Wildiers et al. 2015).

In addition to the significant survival gains reported for Kadcyla, both the EMILIA and TH3RESA studies continue to demonstrate that Kadcyla is well-tolerated with a safety profile that is consistent with earlier analyses; no new safety signals have been observed. These studies indicate that Kadcyla treatment and the patient benefits achieved can be sustained for longer; drug exposure was numerically longer in the Kadcyla study arms in both EMILIA (median drug exposure: Kadcyla: 7.6 months; capecitabine: 5.3 months; lapatinib: 5.5 months) and TH3RESA (mean treatment duration: Kadcyla: 7.9 months; TPC: 4.1 months). Furthermore, dose reduction due to adverse events (AEs) was reported in a lower proportion of patients treated with Kadcyla in both EMILIA (Kadcyla: 18.6%; capecitabine: 42.0%; lapatinib: 20.1%) and TH3RESA (Kadcyla, 13.4%; TPC, 20.7%) (Diéras et al. 2015, Wildiers et al. 2015). This is consistent with the clinical rationale underlying the design of antibody-drug conjugates – that targeting delivery of chemotherapy to tumour cells would reduce systemic toxicity, thereby allowing higher doses and a longer treatment duration (Lianos et al. 2014). It is anticipated that these factors support improved efficacy outcomes. Furthermore, the favourable safety profile of Kadcyla may translate into an improvement in patient quality of life, as suggested by the health-related quality of life data for EMILIA that was presented in the NICE STA submission in December 2013 (Welslau et al. 2014).

The longer follow-up analyses from EMILIA and TH3RESA confirm that Kadcyla continues to fulfil the end-of-life criteria, which the NICE Committee previously accepted (NICE 2015). The EMILIA study reported that Kadcyla extends life by more than 3 months versus capecitabine plus lapatinib (median OS 29.9 months vs 25.9 months). Longer follow-up data from the TH3RESA study also show that Kadcyla extends life by more than 3 months versus TPC where over 80% of patients were on a Herceptin-based regimen (median OS 22.7 months vs 15.8 months) (Diéras et al. 2015, Wildiers et al. 2015).

Kadcyla has offered patients with HER2-positive mBC life-extending treatment compared to currently funded alternatives, and is now SOC for patient who have received at least one prior HER2-targeted agent for mBC. The removal of access to Kadcyla would significantly and unnecessarily reduce the life expectancy and quality of life of many women who, despite treatment advances, still face a life-limiting disease.

2 Context

- Since the NICE STA submission for Kadcyla in December 2013 (TA371), there have been changes to clinical practice in England, affecting the standard-of-care.
    - Lapatinib, used in combination with capecitabine, was used as the comparator in the NICE STA submission for Kadcyla in December 2013 (TA371); however lapatinib is no longer funded or available as a treatment option.
    - Kadcyla now represents standard-of-care for second-line treatment of HER2-postitive mBC based on the demonstration of superior efficacy and tolerability compared to lapatinib and capecitabine (Verma et al. 2012).
- If Kadcyla were removed from the CDF, clinical expert opinion indicates that patients would likely receive capecitabine plus Herceptin. Capecitabine plus Herceptin is therefore the relevant comparator for Kadcyla in this appraisal.

2.1 Burden of HER2-positive Breast Cancer

Breast cancer is the second most common cause of cancer-related death in women, with 11,716 deaths from breast cancer in the UK in 2012 (Cancer Research UK 2016). Between 15-20% of all breast cancers have gene amplification and/or overexpression of HER2, which is associated with a more aggressive phenotype and a poorer prognosis (Dawood et al. 2010, Wolff et al. 2013). The introduction of HER2-targeted therapies has dramatically improved clinical outcomes for patients with HER2-positive disease, with survival outcomes now similar to those with HER2-negative disease (Dawood et al. 2010, Clarke et al. 2014). However, despite these improvements, ~50% of patients will have died at 3 years following diagnosis with metastatic disease (Clarke et al. 2014).

2.2 Standard-of-care

Kadcyla is an antibody-drug conjugate. It consists of trastuzumab, a HER2-directed antibody with proven anti-tumour effects in HER2-positive breast cancer, linked to the cytotoxic microtubule inhibitor DM1. It therefore targets HER2-positive cells, delivering the chemotherapy to these cells, and also inhibits HER2-related signalling.

Kadcyla was submitted to NICE for a STA in December 2013 (ID603) and the technology appraisal guidance was published in December 2015 (TA371) (NICE 2015). In the guidance, Kadcyla was not recommended, within its marketing authorisation, for treating adults with HER2-positive, unresectable locally advanced breast cancer (laBC) or mBC previously treated with Herceptin and a taxane.

However, Kadcyla has been an available treatment option for patients via the CDF since February 2014 (Cancer Drugs Fund 2014). The CDF made Kadcyla available to patients with HER2-positive locally advanced/unresectable or metastatic (Stage

IV) breast cancer who had previously received Herceptin and a taxane, separately or in combination as a result of the significant survival benefit offered to patients compared to the previous SOC.

The changes to SOC in England over the past 2 years have been largely driven by the CDF. As well as listing Kadcyla since February 2014, the small molecule protein kinase inhibitor lapatinib, which blocks HER2 signalling, was de-listed in January 2015 (Cancer Drugs Fund 2015). Lapatinib is therefore no longer funded or available as a treatment option in combination with capecitabine chemotherapy for HER2-positive laBC or mBC for patients whose disease has progressed on HER2-targeted treatment. In addition, lapatinib is not recommended for use by NICE in this setting (NICE 2012).

Since Kadcyla was submitted to NICE for consideration in December 2013 the SOC for patients in the second-line mBC setting in the UK has changed drastically, as a result of Kadcyla being funded by the CDF and lapatinib being de-listed. UK market research data from 2015 show that Kadcyla has become SOC in second-line treatment of HER2-positive breast cancer; [redacted] of patients in the UK received Kadcyla in the latest data set from Q3 2015 (Roche data on file 2015). This pattern is similar to other European countries where Kadcyla is also the SOC for patients in the second-line setting (Roche data on file 2015).

2.3 Treatment Guidelines

At the present time there is no NICE-approved algorithm for the treatment of HER2-positive mBC. The availability of treatments via the CDF described above has affected the treatment algorithm that is used in clinical practice, with Kadcyla now representing the preferred choice for patients in the second-line setting in the UK.

The use of Kadcyla as SOC in this setting is in line with international treatment guidelines. Kadcyla is the preferred choice for patients with disease progression after treatment with at least one line of Herceptin-based therapy in the ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2) (Cardoso et al. 2014). Furthermore, the updated ABC3 guidelines presented the San Antonio Breast Cancer Symposium suggest the following (Hurvitz 2015):

- Patients progressing on an anti-HER2 therapy combined with a cytotoxic or endocrine agent should be offered additional anti-HER2 therapy with subsequent treatment since it is beneficial to continue suppression of the HER2 pathway.
- After first-line Herceptin-based therapy, Kadcyla provides superior efficacy relative to other HER2-based therapies in the second-line (vs capecitabine plus lapatinib) and beyond (vs treatment of physician's choice). Kadcyla should be preferred in patients who have progressed through at least one line of Herceptin-based therapy, since it provides an OS benefit. However, there are no data on the use of Kadcyla after dual blockade with Herceptin plus pertuzumab.

The availability of Kadcyla via the CDF allows patients in England to access treatment that is in line with international consensus guidelines on the treatment of advanced breast cancer.

2.4 Comparator

The treatment regimen of capecitabine plus lapatinib was used as the comparator in the December 2013 STA submission. However, the introduction of Kadcyla on the CDF, together with the loss of lapatinib as a second-line treatment option from the CDF, has resulted in a dramatic change in second-line treatment regimens since the initial NICE STA for Kadcyla.

Kadcyla is now SOC, based on the demonstration of superior efficacy and tolerability compared to lapatinib and capecitabine, with lapatinib-based regimens representing [redacted] of the market share; [redacted] of patients were prescribed a lapatinib-based regimen in the latest market research data from 2015 (Verma et al. 2012, Roche data on file 2015). Given the lack of funding for lapatinib and the resulting drop in usage of lapatinib, capecitabine plus lapatinib is no longer a relevant comparator for Kadcyla in this indication.

The change to SOC necessitates a change in the relevant comparator for Kadcyla in this submission. However, UK market share data alone is not useful in defining a relevant comparator. Market share data indicates that patients not treated with Kadcyla, who may, for example, not meet the eligibility criteria for Kadcyla funding from the CDF or have contraindications to Kadcyla, will receive one of a number of different treatment options, such as Herceptin plus taxane, Herceptin plus hormones, or hormones without chemotherapy (Roche data on file 2015). Defining the most relevant comparator for this submission has therefore been performed using expert clinical opinion.

Clinical opinion on which regimen would replace Kadcyla, should access to Kadcyla be withdrawn, suggested that capecitabine plus Herceptin would most likely become the acceptable and accessible treatment option for patients currently offered Kadcyla in England. It should be noted that use in patients who have progressed on one previous HER2-targeted treatment for mBC is not a licenced indication of Herceptin. However, in the absence of a more viable alternative capecitabine plus Herceptin is therefore considered the main relevant comparator to Kadcyla throughout this submission.

3 Clinical Evidence

- Longer follow-up data for the use of Kadcyla as a second-line treatment is available from the final OS analysis of the EMILIA study.
    - This descriptive analysis reported that the median OS was 29.9 months with Kadcyla versus 25.9 months with capecitabine plus lapatinib; stratified HR=0.75 (95% CI 0.64-0.88, P=0.0003).
    - A survival benefit was reported despite 27% of patients crossing over from capecitabine plus lapatinib to Kadcyla.
    - These data are consistent with results from the second interim, confirmatory OS analysis.
- Longer follow-up supportive evidence from the TH3RESA study in the third-line and beyond is now also available, demonstrating that Kadcyla is efficacious versus TPC (the majority of patients assigned to TPC were on a Herceptin-based regimen).
- Both the EMILIA and TH3RESA studies continue to show that Kadcyla is well-tolerated with a safety profile that is consistent with earlier analyses; no new safety signals have been observed.
- Real-world studies are in progress; the ESTHER study of HER2-positive metastatic disease in the UK is enrolling. However, data are not yet mature.

Kadcyla has been studied in two pivotal phase 3 studies and these have reported survival and tolerability outcomes at later data cut-offs compared to those in the STA submission to NICE made in December 2013 for the appraisal of Kadcyla:

- The EMILIA study in patients who had progressed after having at least one previous line of therapy for HER2-positive mBC or laBC, and patients who had relapsed on or within 6 months of completing adjuvant therapy for HER2-positive breast cancer (Diéras et al. 2015).
- The TH3RESA study in patients who had received at least two prior therapies for HER2-positive mBC (Wildiers et al. 2015).

The latest analyses of these two studies are presented here.

3.1 EMILIA Study

The EMILIA study is a phase 3, randomised, multi-centre, international, two-arm, open-label clinical trial designed to compare the safety and efficacy of Kadcyla with that of capecitabine plus lapatinib in patients who had progressed after having at least one previous line of therapy for HER2-positive mBC or laBC, and patients who had relapsed on or within 6 months of completing adjuvant therapy for HER2-positive breast cancer (Verma et al. 2012). The full methodology of the EMILIA study is described in Section 6.3 of the NICE STA submission for Kadcyla (December 2013 [TA371]). The results from the first and second interim analyses were presented in the NICE STA submission.

Patients in the EMILIA study were randomised 1:1 to Kadcyla (n=495) or capecitabine in combination with lapatinib (n=496). Kadcyla was administered intravenously at 3.6 mg/kg every 3 weeks, capecitabine was given orally at 1000 mg/m^2 twice daily on days 1–14 of a 21-day cycle, and lapatinib was given orally at 1250 mg/day. Patients were stratified by world region (United States, Western Europe, or other), number of prior chemotherapy regimens for laBC or mBC (0 or 1 vs >1) and disease involvement (visceral vs non visceral) (Verma et al. 2012).

The baseline characteristics of the included patient population are described in full in Section 6.3.4 of the NICE STA submission for Kadcyla (December 2013 [TA371]). Most patients in each arm (61.4% for Kadcyla, 61.5% for capecitabine plus lapatinib) had received 0 to 1 prior chemotherapy regimens for unresectable laBC, or mBC (Verma et al. 2012), and [redacted]

The co-primary outcomes of the EMILIA study were progression-free survival (PFS) by independent review and OS. A primary analysis of the study for both PFS and OS was conducted in January 2012 with a second interim analysis for OS conducted in July 2012. This second analysis crossed the O'Brien-Fleming stopping boundary for an early analysis (HR<0.73 or P<0.0037) (Verma et al. 2012). The data from the second interim, confirmatory OS analysis, as published in the New England Journal of Medicine in November 2012 (Verma et al. 2012), were presented in the NICE STA submission for Kadcyla (December 2013 [TA371]).

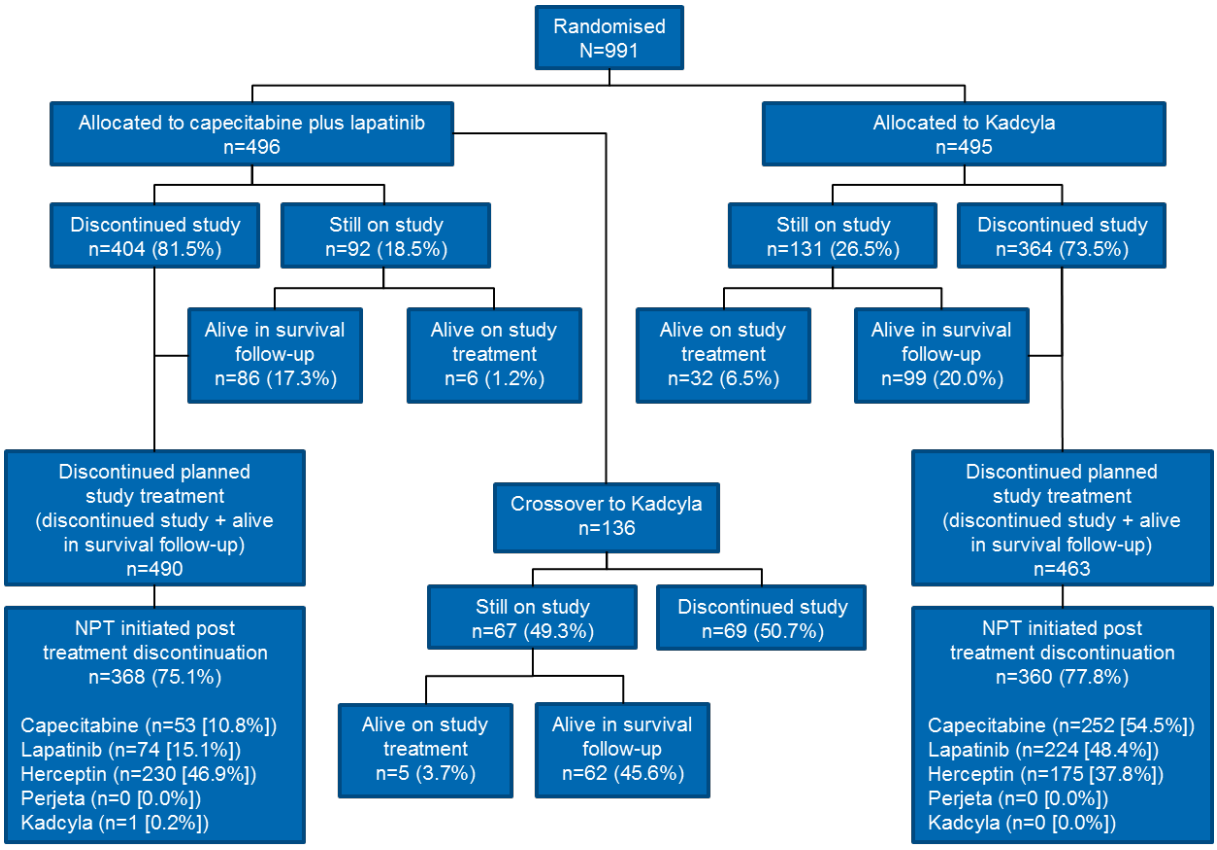
Following the second interim, confirmatory OS analysis, crossover from capecitabine plus lapatinib to Kadcyla was permitted, and all patients continuing in the study were followed until the final OS analysis. The clinical cut-off date for the final analysis was 31st December 2014. This final analysis, which is descriptive, is presented here and was presented at conference for the first time in December 2015 at the San Antonio Breast Cancer Symposium (Diéras et al. 2015).

3.1.1 Patient Disposition

At the time of the final OS analysis the median follow-up duration was 47.8 months in the Kadcyla group and 41.9 months in the capecitabine plus lapatinib group. Median treatment duration was 7.6 months with Kadcyla, 5.3 months with capecitabine and 5.5 months with lapatinib. Participant flow at the time of the final OS analysis can be found in Figure 1 (Diéras et al. 2015).

A total of 136 (27.4%) patients crossed over from capecitabine plus lapatinib to Kadcyla following the second interim, confirmatory OS analysis and subsequent protocol amendment (Figure 1). Median follow-up duration in these crossover patients was 24.1 months (Diéras et al. 2015).

Figure 1: EMILIA participant flow (data as of 31st December 2014)



NPT, non-protocol treatment; Kadcyla, trastuzumab emtansine

Source: Diéras et al. 2015

3.1.2 Efficacy

3.1.2.1 Overall Survival

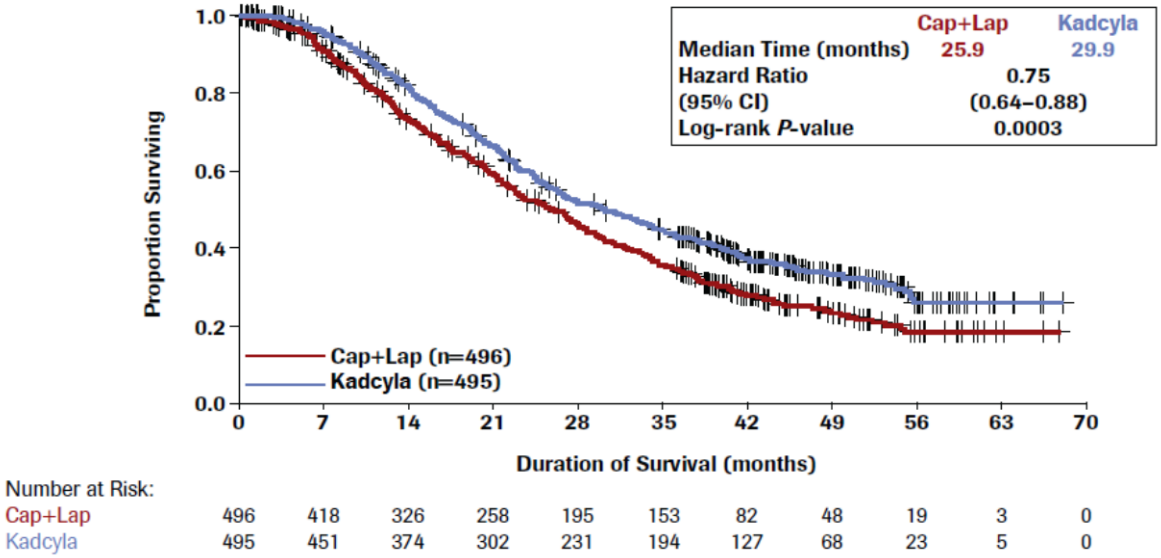
At the time of the final analysis in the intention-to-treat (ITT) population, the median OS was 29.9 months with Kadcyla versus 25.9 months with capecitabine plus lapatinib; stratified HR=0.75 (95% CI 0.64-0.88, P=0.0003) (Figure 2). The analysis is consistent with results from the second interim, confirmatory OS analysis (described in full in Section 6.5.3 of the NICE STA submission for Kadcyla (December 2013 [TA371]). A survival benefit for Kadcyla compared with capecitabine plus lapatinib was reported despite 27% of patients crossing over from the control arm to Kadcyla at the time of final analysis. Across all interim and final analyses median OS was numerically longer with Kadcyla than capecitabine plus lapatinib (Table 1) (Diéras et al. 2015).

[redacted]

A sensitivity analysis on OS was conducted in which crossover patients were censored at the time of switching from capecitabine plus lapatinib to Kadcyla. These results were consistent with the primary results. The stratified HR was 0.69 (95% CI 0.59-0.82, P<0.0001), with a median OS of 24.6 months in the capecitabine plus lapatinib group censored at crossover (Figure 3; Table 1) (Diéras et al. 2015).

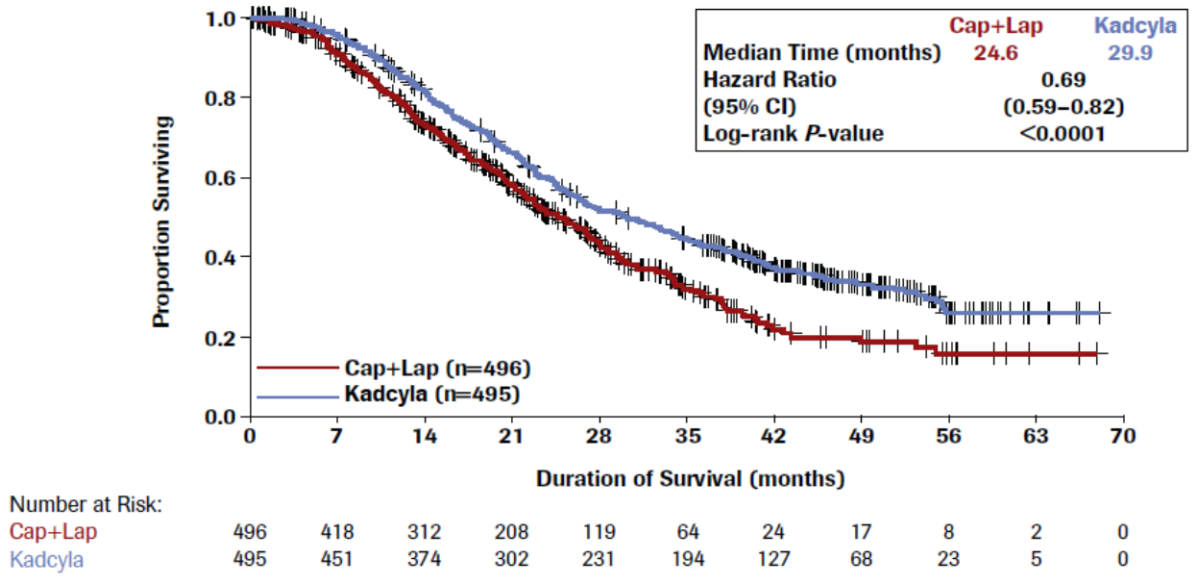
In both the confirmatory second interim and descriptive final OS analyses, consistent survival benefits with Kadcyla treatment were generally observed across clinically relevant subgroups: presence of visceral disease, age, world region, and race (Figure 4) (Diéras et al. 2015). [redacted]

Figure 2: Final OS analysis of the EMILIA study – ITT population



Cap+lap, capecitabine plus lapatinib; CI, confidence interval; Kadcyla, trastuzumab emtansine (Diéras et al. 2015)

Figure 3: Sensitivity analysis of the final OS analysis of the EMILIA study – crossover patients censored



Cap+lap, capecitabine plus lapatinib; CI, confidence interval; T-DM1, Kadcyla (trastuzumab emtansine)

(Diéras et al. 2015)

Table 1. Summary of overall survival analyses

	Cap + lap	Kadcyla	HR [95% CI]	P-value	Stopping boundary
First interim analysis[a]					
n (% OS events)	129 (26.0)	94 (19.0)	0.62 [0.48-0.81]	P=0.0005	P<0.0003 or HR<0.617
Median (months)	23.3	NE			
Second interim analysis[b]					
n (% OS events)	182 (36.7)	149 (30.1)	0.68 [0.55-0.85]	P=0.0006	P<0.0037 or HR<0.727
Median (months)	25.1	30.9			
Final analysis[c]					
n (% OS events)	333 (67.1)	303 (61.2)	0.75 [0.64-0.88]	P=0.0003	Boundary met at second interim analysis – descriptive only
Median (months)	25.9	29.9			
Sensitivity analysis with crossover patients censored[c]					
n (% OS events)	278 (56.0)	303 (61.2)	0.69 [0.59-0.82]	P<0.0001	Descriptive only
Median	24.6	29.9			

(months)					

[a]Data cut-off January 2012; [b]Data cut-off July 2012; [c]Data cut-off December 2014

Cap + lap, capecitabine plus lapatinib; CI, confidence interval; HR, hazard ratio; NE, not estimatable; OS, overall survival; Kadcyla, trastuzumab emtansine

(Diéras et al. 2015)

Table 2. Summary of overall survival rates at one and two years (ITT population), estimated using Kaplan-Meier method

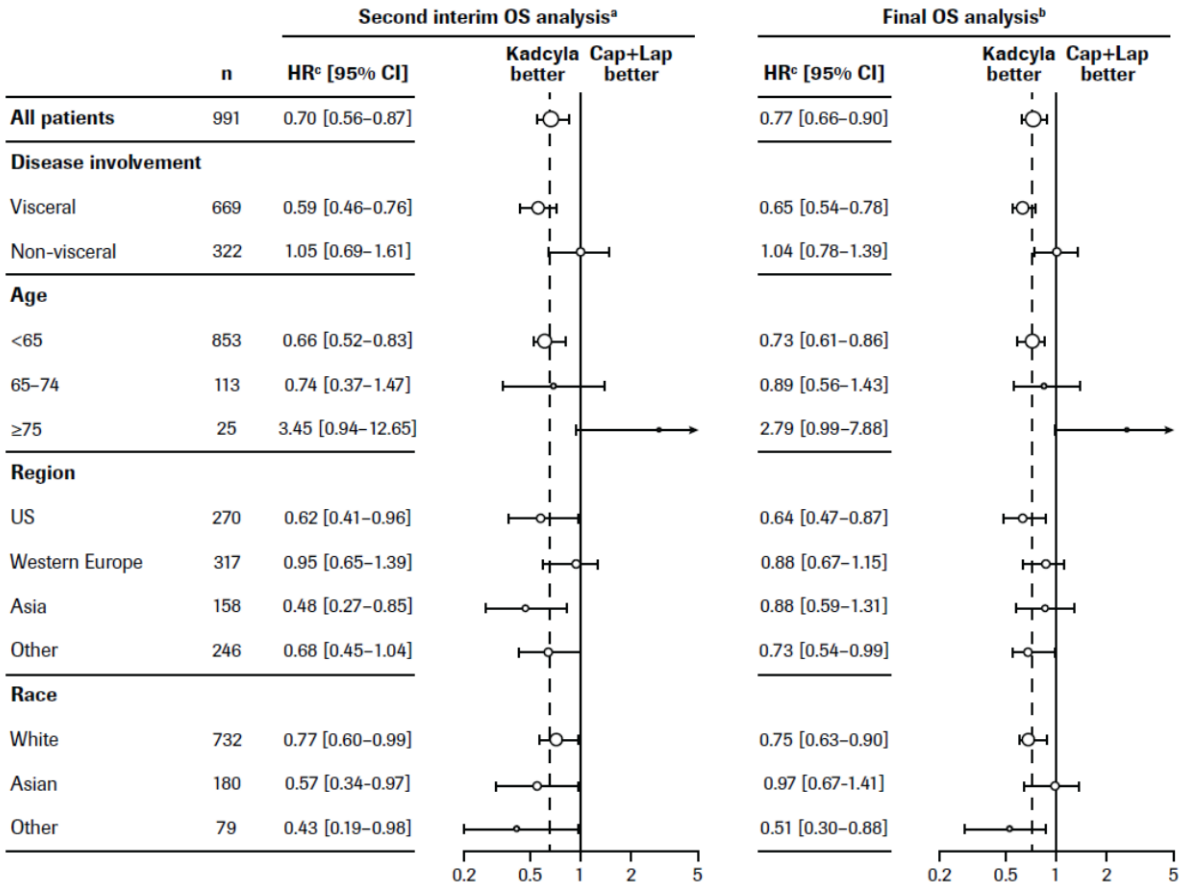
		Cap + lap	Kadcyla	Difference in rates[c] (95% CI)	P-value[d] (log-rank test)
Second interim analysis[a]					
One-year survival	Number of patients who died at 12 months (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Survival rate	[redacted]	[redacted]		
Two-year survival	Number of patients who died at 24 months (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Survival rate	[redacted]	[redacted]		
Final analysis[b]					
One-year survival	Number of patients who died at 12 months (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Survival rate	[redacted]	[redacted]		
Two-year survival	Number of patients who died at 24 months (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Survival rate	[redacted]	[redacted]		

[a]Data cut-off July 2012; [b]Data cut-off December 2014; [c]Relative to capecitabine plus lapatinib; [d]p-vlue and 95% CI for difference in rates were derived from the z-test using the standard errors computed using Greenwood's method

Cap + lap, capecitabine plus lapatinib; CI, confidence interval; OS, overall survival; Kadcyla, trastuzumab emtansine

(Roche Clinical Study Report 2015)

Figure 4: Second interim and final OS subgroup analyses of the EMILIA study



[a]Data cut-off July 2012; [b]Data cut-off December 2014; [c]Hazard ratios are from unstratified analyses

Cap+lap, capecitabine plus lapatinib; CI, confidence interval; T-DM1, Kadcyla (trastuzumab emtansine)

(Diéras et al. 2015)

[redacted]

REDACTED

[redacted]

3.1.2.2 Other Efficacy Outcomes

Other efficacy outcomes from this data cut-off, including quality-of-life data, will be available in the next update to the EMILIA study clinical study report (CSR), due May 2016.

3.1.3 Tolerability

3.1.3.1 Overview of Safety

The safety profile of Kadcyla remained consistent between the second interim and final OS analyses. There were no marked increased in high-grade AEs despite longer follow-up (median follow-up of 47.8 months in the final analysis). Kadcyla treatment appeared to have a favourable safety profile with numerically fewer grade ≥3 AEs than capecitabine plus lapatinib (47.6% vs 59.6%) and AEs leading to dose reduction (18.6% vs 42.0% for capecitabine and 20.1% for lapatinib) (Table 3), despite Kadcyla-treated patients having had a longer median drug exposure (7.6 months) than patients treated with capecitabine plus lapatinib (capecitabine: 5.3 months, lapatinib: 5.5 months) (Diéras et al. 2015).

Table 3. Overview of safety at the final OS analysis of the EMILIA study

	Second interim, confirmatory OS analysis[a]		Final OS analysis[b]		
	Cap + lap (n=488)	Kadcyla (n=490)	Cap + lap (n=488)	Kadcyla (n=490)	Crossover (n=136)
Median follow-up, months	~19		41.9	47.8	24.1
Median drug exposure, months	-	-	Cap: 5.3 Lap: 5.5	7.6	■
Grade ≥3 AEs, n (%)	291 (59.6)	218 (44.5)	291 (59.6)	233 (47.6)	41 (30.1)
AEs leading to treatment discontinuation, n (%)	Cap: 54 (11.1) Lap: 43 (8.8)	35 (7.1)	Cap: 53 (10.9) Lap: 42 (8.6)	49 (10.0)	14 (10.3)
AEs leading to a dose reduction , n (%)	Cap: 201 (41.2) Lap: 96 (19.7)	81 (16.5)	Cap: 205 (42.0) Lap: 98 (20.1)	91 (18.6)	18 (13.2)
AEs with fatal outcome, n (%)	5 (1.0)[c]	3 (0.6)[d]	5 (1.0)[c]	4 (0.8)[d]	0 (0.0)

[a]Data cut-off July 2012; [b]Data cut-off December 2014; [c]Coronary artery disease, multi-organ failure, coma, hydrocephalus, and acute respiratory distress syndrome; [d]Metabolic encephalopathy, neutropenic spesis, and pneumonia by the second interim analysis, with an additional death via acute myeloid leukemia by the final analysis

AE, adverse event; cap + lap, capecitabine plus lapatinib; OS, overall survival; Kadcyla, trastuzumab emtansine

(Diéras et al. 2015, Roche Clinical Study Report 2015)

3.1.3.2 Grade 3 or Above Adverse Events

The incidence of grade 3 or above cardiac dysfunction was similar between the Kadcyla (0.2%) and capecitabine plus lapatinib (0.6%) arms. Thrombocytopenia (14.3%) was the most frequently reported grade ≥3 AE in patients treated with Kadcyla, followed by increased aspartate transaminase (AST) (4.5%) and anaemia (3.9%) (Table 4). Diarrhoea (21.1%) was the most frequently reported grade ≥3 AE with capecitabine plus lapatinib, followed by palmar-plantar erythrodysesthesia syndrome (17.8%) and vomiting (4.9%) (Table 4) (Diéras et al. 2015).

Table 4. Summary of grade ≥3 AEs with at least 2% incidence in either arm at the final OS analysis of the EMILIA study

Grade ≥3 AEs, n (%)	Second interim, confirmatory OS analysis[a]		Final OS analysis[b]		
	Cap + lap (n=488)	Kadcyla (n=490)	Cap + lap (n=488)	Kadcyla (n=490)	Crossover (n=136)
Diarrhoea	102 (20.9)	9 (1.8)	103 (21.1)	9 (1.8)	1 (0.7)
PPE syndrome	86 (17.6)	0 (0.0)	87 (17.8)	0 (0.0)	0 (0.0)
Vomiting	22 (4.5)	4 (0.8)	24 (4.9)	5 (1.0)	1 (0.7)
Hypokalemia	21 (4.3)	11 (2.2)	22 (4.5)	11 (2.2)	0 (0.0)
Neutropenia	21 (4.3)	11 (2.2)	21 (4.3)	11 (2.2)	2 (1.5)
Fatigue	17 (3.5)	12 (2.4)	17 (3.5)	12 (2.4)	2 (1.5)
Nausea	12 (2.5)	4 (0.8)	13 (2.7)	4 (0.8)	0 (0.0)
Anaemia	11 (2.3)	17 (3.5)	11 (2.3)	19 (3.9)	4 (2.9)
Mucosal inflammation	11 (2.3)	1 (0.2)	11 (2.3)	1 (0.2)	0 (0.0)
ALT increased	8 (1.6)	15 (3.1)	9 (1.8)	15 (3.1)	0 (0.0)
Asthenia	8 (1.6)	2 (0.4)	9 (1.8)	4 (0.8)	4 (2.9)
Rash	10 (2.0)	0 (0.0)	8 (1.6)	0 (0.0)	1 (0.7)
AST increased	6 (1.2)	22 (4.5)	7 (1.4)	22 (4.5)	2 (1.5)
Thrombocytopenia	2 (0.4)	68 (13.9)	2 (0.4)	70 (14.3)	6 (4.4)
GGT increased	0 (0.0)	4 (0.8)	0 (0.0)	6 (1.2)	3 (2.2)

[a]Data cut-off July 2012; [b]Data cut-off December 2014

AE, adverse event; ALT, alanine trasaminase; AST, aspartate transaminase; Cap + lap, capecitabine plus lapatinib; GGT, gamma-glutanyl-transpeptidase; OS, overall survival; PPE, palmar-plantar erthythrodysesthesia; Kadcyla, trastuzumab emtansine

(Diéras et al. 2015)

3.1.3.3 Herceptin-associated Adverse Events

The incidence of AEs that have been associated with Kadcyla or Herceptin in previous studies in this analysis is shown in Table 5, and was consistent between the second interim and final OS analyses (Diéras et al. 2015).

The incidence of cardiac dysfunction was similar between the Kadcyla and capecitabine plus lapatinib arms. However, comparison of safety data between the second interim and final OS analyses are limited by differences in basket term

definitions used in each analysis; the versions of MedDRA used at the second and final data cut-offs were different (second interim, confirmatory OS analysis: MedDRA version 15.0; final OS analysis: MedDRA version 17.1) (Diéras et al. 2015).

Table 5. Incidence of grade ≥3 AEs associated with Kadcyla or Herceptin in previous analysis at the final OS analysis of the EMILIA study

Grade ≥3 AEs, n (%)	Second interim, confirmatory OS analysis[a]		Final OS analysis[b]		
	Cap + lap (n=488)	Kadcyla (n=490)	Cap + lap (n=488)	Kadcyla (n=490)	Crossover (n=136)
Cardiac dysfunction	3 (0.6)	0 (0.0)	3 (0.6)	1 (0.2)	0 (0.0)
Haemorrhage	4 (0.8)	10 (2.0)	4 (0.8)	12 (2.4)	1 (0.7)
Hepatotoxicity	25 (5.1)	45 (9.2)	27 (5.5)	48 (9.8)	7 (5.1)
IRR/Hypersensitivity[c]	0 (0.0)	0 (0.0)	N/A	N/A	N/A
IRR/Hypersensitivity (Type I)[d]	N/A	N/A	0 (0.0)	1 (0.2)	1 (0.7)
IRR/Hypersensitivity (symptoms)	N/A	N/A	0 (0.0)	1 (0.2)	0 (0.0)
Peripheral neutopathy	2 (0.4)	14 (2.9)	4 (0.8)	18 (3.7)	0 (0.0)
Pneumonitis	2 (0.4)	1 (0.2)	2 (0.4)	1 (0.2)	0 (0.0)
Thrombocytopenia	2 (0.4)	73 (14.9)	2 (0.4)	75 (15.3)	6 (4.4)

[a]Data cut-off July 2012, MedDRA v15.0; [b]Data cut-off December 2014, MedDRA v17.1; [c]Based on MedDRA v15.0: AEs; includes anaphylactic reaction and angioedema (SMQ, narrow) occurring on the day of or the day after treatment infusion. Note that IRR/hypersensitivity, as defined by Roche, was expanded after the second interim, confirmatory OS analysis to include events potentially indicative of symptoms of IRR (termed IRR/Hypersensitivity [Type1][d] in subsequent analyses); [d]Based on MedDRA v17.1: Type 1; includes hypersensitivity (SMQ term) and potentially related symptoms occurring within 24 hours of infusion

AE, adverse event; Cap+Lap, capecitabine plus lapatinib; IRR, infusion-related reaction; MedDRA, Medical Dictionary for Regulatory Activities; N/A, not applicable; OS, overall survival; SMQ, Standardized MedDRA Queries; Kadcyla, trastuzumab emtansine

(Diéras et al. 2015)

3.2 TH3RESA Study

The TH3RESA study is a phase 3, randomised, multi-centre, two-arm, open-label clinical trial designed to compare the efficacy of Kadcyla with treatment of physician's choice (TPC) for patients with HER2-positive mBC who had received prior treatment with Herceptin, lapatinib and a taxane during the course of their disease. In the TH3RESA study all patients had received at least two prior therapies for mBC; 35% of included patients had received ≤3 regimens for advanced breast cancer, 36% had received 4-5 regimens, and 28% had received more than 5 regimens (Krop et al. 2014). The full methodology of the TH3RESA study is described in Section 6.3 of the NICE STA submission for Kadcyla (December 2013 [TA371]). The results from the first interim analysis were presented in the NICE STA submission.

Although the TH3RESA study investigated the efficacy and tolerability of Kadcyla in third-line and beyond, it allows comparison of Kadcyla with regimens other than capecitabine plus lapatinib, and particularly with Herceptin-based regimens (80.4% of patients were on a Herceptin-based regimen; Table 6) (Wildiers et al. 2015). The TH3RESA study is therefore considered relevant to this submission and has been included in this appendix.

Patients in the TH3RESA study were randomised 2:1 to Kadcyla given intravenously at 3.6 mg/kg every 3 weeks (n=404) or TPC (n=198) (Krop et al. 2014). 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 luteinising hormone releasing hormone agonist)
- HER2-directed therapy
    - Single agent (eg. Herceptin or lapatinib)
    - Dual therapy (eg. Herceptin with lapatinib)
    - Single agent in combination with single-agent chemotherapy (eg. Herceptin with capecitabine)
    - Single agent in combination with single-agent hormonal therapy (eg. lapatinib with letrozole, Herceptin 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.

Patients in the TPC arm with documented progressive disease were permitted to crossover to Kadcyla, following an amendment to the study protocol.

Patients were stratified by world region (United States, Western Europe, or other), number of prior regimens for advanced breast cancer, and disease involvement (visceral vs non visceral) (Krop et al. 2014). The baseline characteristics of the included patient population are described in full in Section 6.3.4 of the NICE STA submission for Kadcyla (December 2013 [TA371]).

The co-primary outcomes of the TH3RESA study were PFS by independent review and OS. A primary analysis of the study for PFS was conducted in February 2013. This showed a median PFS for Kadcyla of 6.2 months as compared to 3.3 months with TPC (HR=0.528, p<0.0001) or 3.2 months for TPC-Herceptin containing regimens only (HR=0.558, p<0.0001) (Krop et al. 2014). These data were presented in the NICE STA submission for Kadcyla (December 2013 [TA371]), Section 6.5.3.

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 Kadcyla arm. The HR was 0.552 with a p-value of 0.0034, however, these values did not cross the pre-specified efficacy stopping boundary (HR<0.370 or P<0.0000016) (Krop et al. 2014).

A second interim analysis for OS was performed with a data cut-off of 13th February 2015. This analysis is presented here and was presented at conference for the first time in December 2015 at the San Antonio Breast Cancer Symposium (Wildiers et al. 2015).

3.2.1 Patient Disposition

The TH3RESA study enrolled 602 patients at approximately 250 sites worldwide. The majority of patients randomised to TPC received a Herceptin-based regimen (80.4%; Table 6). 93 patients in the TPC group had crossed over to Kadcyla (Wildiers et al. 2015).

Table 6. TPC regimen – TH3RESA study

TPC treatment regimen	TPC (n=184[a])
Combination with HER2-directed agent, %	**83.2**
Combination with Herceptin	*80.4*
Chemotherapy[b] + Herceptin	68.5
Lapatinib + Herceptin	10.3
Hormonal therapy + Herceptin	1.6
Chemotherapy[b] + lapatinib	*2.7*
Single-agent chemotherapy[b], %	**16.8**

[a]Includes patients who received study treatment. Excludes one patient who was randomized to the TPC arm but received two cycles of Kadcyla by mistake; [b]The most common chemotherapy agents used were vinorelbine, gemcitabine, eribulin, paclitaxel, and docetaxel.
(Wildiers et al. 2015)

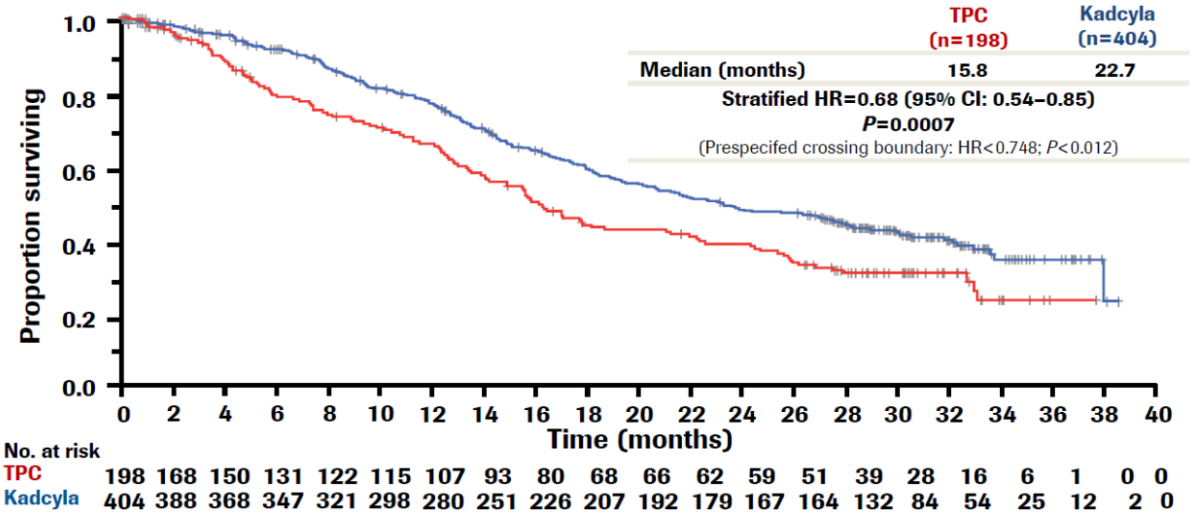
3.2.2 Efficacy

3.2.2.1 Overall Survival

At the most recent data cut (13th February 2015) Kadcyla demonstrated a clinically meaningful and statistically significant improvement in OS compared to TPC in patients with HER2-positive mBC previously treated with taxane, Herceptin and lapatinib in any setting. Median OS improved by 6.9 months from 15.8 months with TPC to 22.7 months with Kadcyla, stratified HR=0.68 (95% CI 0.54-0.85, P=0.0007) (Figure 6). The survival benefit was reported despite substantial crossover (Wildiers et al. 2015).

A sensitivity analysis on OS was conducted in which crossover patients were censored at the time of switching from TPC to Kadcyla. These results were consistent with the primary results. The stratified HR was 0.58 (95% CI 0.43-0.77, P=0.0002) with a median OS of 15.6 months in the TPC group censored at crossover (Figure 7) (Wildiers et al. 2015).

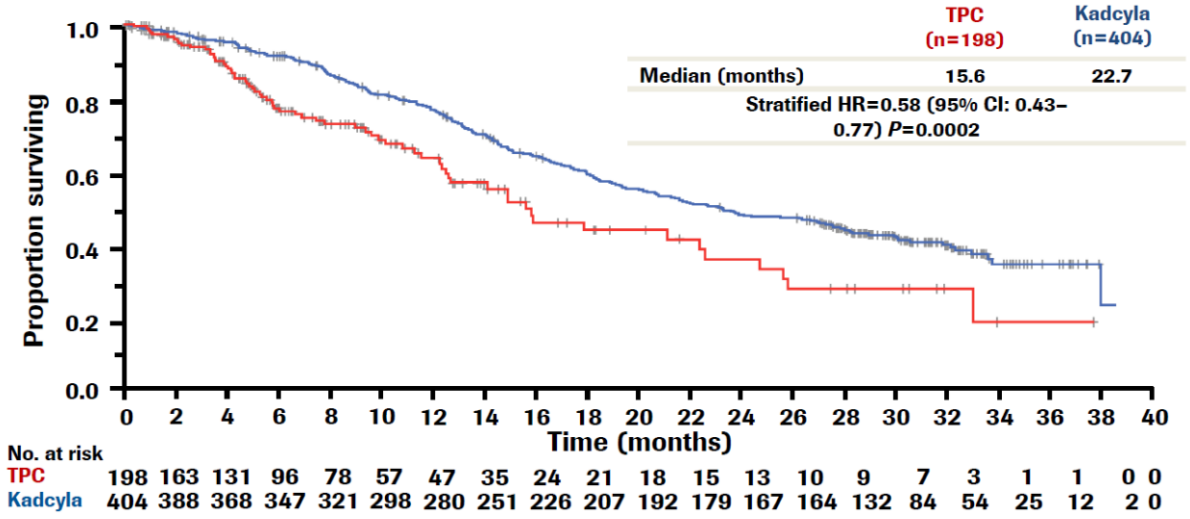
Figure 5: Final OS analysis of the TH3RESA study – ITT population



CI, confidence interval; HR, hazard ratio; Kadcyla, trastuzumab emtansine; TPC, treatment of physician's choice

(Wildiers et al. 2015)

Figure 6: Sensitivity analysis of the final OS analysis of the TH3RESA study – crossover patients (n=93) censored



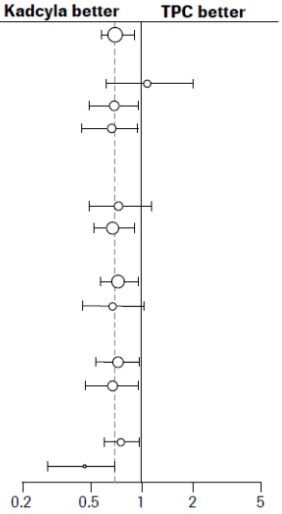
CI, confidence interval; HR, hazard ratio; Kadcyla, trastuzumab emtansine; TPC, treatment of physician's choice

(Wildiers et al. 2015)

Subgroup analyses show that Kadcyla has a clinically meaningful survival benefit across world region, number of prior regimens, visceral vs non-visceral disease and hormonal status (Figure 8). The subgroup analyses also show that Kadcyla has a clinically meaningful survival benefit versus different TPC categories (Figure 8); Kadcyla versus combination with HER2-directed therapy, HR 0.75 (0.59-0.95); Kadcyla versus single-agent chemotherapy, HR 0.44 (0.28-0.68). This subgroup analysis by TPC category suggests that Kadcyla has an important survival benefit when compared with various alternative treatment regimens (Wildiers et al. 2015).

Figure 7. Subgroup analysis of OS in the TH3RESA study

Baseline Characteristic	Total n	TPC (n=198) Median, mo.	Kadcyla (n=404) Median, mo.	Unstratified HR (95% CI)
All Patients	602	15.8	22.7	0.69 (0.55–0.86)
World Region[a]				
United States	147	NE	30.1	1.04 (0.59–1.84)
Western Europe	256	14.9	21.8	0.66 (0.48–0.91)
Other	199	16.1	20.6	0.62 (0.42–0.90)
Number of Prior Regimens in Advanced Setting (excluding hormonal therapy)[a]				
≤3	200	17.0	24.0	0.73 (0.49–1.09)
>3	402	15.5	21.6	0.65 (0.50–0.86)
Disease Involvement[a]				
Visceral	451	15.6	21.8	0.71 (0.55–0.92)
Non-visceral	151	17.0	27.2	0.65 (0.42–1.02)
Hormonal Status[b]				
ER+ and/or PR+	313	16.4	26.3	0.71 (0.52–0.97)
ER- and PR-	270	15.5	21.2	0.65 (0.46–0.90)
TPC Category				
Combination with HER2-directed therapy	154	17.1	n/a	0.75 (0.59–0.95)
Single-agent chemotherapy	31	11.5	n/a	0.44 (0.28–0.68)



[a]Stratification factor; [b]19 patients had unknown HR status
n/a, not available; NE, not estimable
(Wildiers et al. 2015)

3.2.2.2 Other Efficacy Outcomes

Other efficacy outcomes from this data cut-off, including quality-of-life data, will be available in the next update to the TH3RESA study CSR, due April 2016.

3.2.3 Tolerability

3.2.3.1 Overview of Safety

Kadcyla had a favourable safety profile which was consistent with prior studies and the previous analysis. At the time of the second OS analysis the mean treatment duration was 7.9 months (range: 0.03-38.0 months) in the Kadcyla group and 4.1 months (range: 0.03-31.2 months) in the TPC group. A numerically higher proportion of patients experienced any grade AEs in the Kadcyla group (95.8%) than in the TPC group (89.1%). However, the proportion was numerically lower when considering AEs of grade 3 or above (Kadcyla: 40.0%; TPC: 47.3%) (Table 7) (Wildiers et al. 2015).

Table 7. Overview of safety at the final analysis of the TH3RESA study

	TPC (n=184[a])	Kadcyla (n=403[a])
Mean treatment duration (range), months	4.1 (0.03-31.2)	7.9 (0.03-38.0)
All grade AEs, %	89.1	95.8
Grade ≥3 AEs[b], %	47.3	40.0
AEs leading to treatment discontinuation[c], %	10.9	14.6
AEs leading to dose reduction[c], %	20.7	13.4

[a]Safety population. The Kadcyla group includes one patient randomised to TPC who received 2 cycles of Kadcyla by mistake; [b]The Grade 5 AEs: TPC, 1.6% (n=3); Kadcyla, 2.2% (n=9); [c]For any study drug
AEs, adverse events; Kadcyla, trastuzumab emtansine; TPC, treatment of physician's choice
(Wildiers et al. 2015)

3.2.3.2 Grade 3 or Above Adverse Events

The most common grade 3 or above AEs in the Kadcyla arm were thrombocytopenia (6.0%), anaemia (3.5%), increased AST (2.5%) and dyspnea (2.5%) (Table 8). In the TPC arm, the most common grade 3 or above AEs were neutropenia (15.8%), diarrhoea (4.3%), febrile neutropenia (3.8%) and dyspnea (3.8%) (Table 8) (Wildiers et al. 2015).

Table 8. Summary of grade ≥3 AEs with at least 2% incidence in either arm at the final analysis of the TH3RESA study

	TPC (n=184[a])		Kadcyla (n=403[a])	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Non-haematologic AEs, %				
Diarrhoea	22.3	4.3	12.7	0.7
Dyspnea	13.0	3.8	11.7	2.5
Asthenia	17.9	3.3	19.1	1.0
Abdominal pain	12.5	2.7	7.4	1.2
AST increased	7.1	2.7	12.4	2.5
Fatigue	26.1	2.7	30.8	2.2
ALT increased	5.4	2.2	9.2	1.5
Cellulitis	3.8	2.2	1.7	0.5
Pulmonary embelism	2.2	2.2	0.5	0.5
Haematologic AEs, %				
Neutropenia	21.7	15.8	7.7	2.5
Febrile neutropenia	3.8	3.8	0.2	0.2
Anemia	11.4	3.3	11.4	3.5
Leukopenia	6.0	2.7	2.2	0.5
Thrombocytopenia[a]	3.8	2.7	20.6	6.0

[a]Incidence of grade ≥3 haemorrhage of any type (basket term) was 4.2% (Kadcyla) and 0.5% (TPC)

AEs, adverse events; ALT, alanine trasaminase; AST, aspartate transaminase; Kadcyla, trastuzumab emtansine; TPC, treatment of physician's choice

(Wildiers et al. 2015)

3.3 Real-world Evidence

Since the NICE STA submission for Kadcyla in December 2013 (TA371), Roche has initiated recruitment into the ESTHER study (NCT02393924), which is a UK-based observational cohort study of patients with HER2-positive unresectable laBC, or mBC who have been diagnosed with advanced disease within the previous 6 months (ClinicalTrials.gov). The ESTHER study will ultimately form part of a larger international study.

The aim of the ESTHER study is to observe the different anti-cancer treatment regimens, including Kadcyla, and their sequencing throughout the course of the disease and as such will provide further data on the use of Kadcyla in the UK. The primary analysis will be PFS for each treatment regimen, but a range of other endpoints will be assessed as secondary outcomes, to include OS, objective response rate, serious AEs, and patient-reported outcomes to assess quality of life.

The ESTHER study started enrolling in 2015 and it is estimated that recruitment of the target enrolment of 390 patients will be complete in 2018. Reporting of PFS is estimated for 2019 and beyond, with study completion estimated for 2023.

In addition to the ESTHER study, Roche is also undertaking the SystHERs (NCT01615068) observational study of patients with HER2-positive mBC in the US (Tripathy et al. 2014). Enrolment is ongoing and study completion is estimated for 2020.

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The table below describes the costs included in the economic model. All costs have been entered into the model on the 'PAS' sheet and then included trace in column 'BB' in the T-DM1 Markov trace sheet.

Including the costs listed below increase the ICER from [redacted].

	Calculation of cost	**Reference source**	**Per patient value entered into economic model**
Stock management	N/A		N/A
Administration of claim forms	£10,581	1292 patients taking 5 minutes per patient 4 times per year processed by a Band 8a pharmacist at £24.57 per hour	£2.05 every 3 months
Staff training	N/A		N/A
Tracking of supplies	N/A		N/A
Other costs	One-off Implementation Costs = £14,924 Registration = £2645 - £5020	One-off Implementation Costs = 1 hour meeting consisting of Band 8d pharmacist at £31.92 per hour, Band 8a pharmacist at £24.57 per hour, 3 Band 6 staff (finance, business manager, procurement) at £18.02 per hour for 135 Trusts. Registration = 90 patients taking 5 minutes per	£11.55 one off cost applied in week 1 (=£14,924/1292) £3.89 (=£46.63/12)

	Issue VAT Invoice = £4865 Process payment = £4865	patient processed by a Band 8a pharmacist at £24.57 per hour, or a consultant at £46.63 per hour Issue VAT Invoice = grade 6 finance at £18.02 per hour, 30 minutes per invoice with 135 trusts each issuing invoices 4 times per year Process payment = grade 6 finance at £18.02 per hour, 30 minutes per invoice with 135 trusts each issuing invoices 4 times per year	Cost per patient Applied as one off cost in week 1 £3.77 applied at start of each year (=4865/1292) £3.77 applied at start of each year (=4865/1292)
Other [add more rows as necessary]			N/A

Total implementation and operation costs	One-off implementation costs = £14,924 Operation costs = £25,332year Cost per Trust: One-off implementation costs = £111 Operation costs = £188/year	[Pay rates taken from the pay bands and pay points on the second pay spine in England from 1 April 2016 Currently approximately 135 Trusts are purchasing Kadcyla, so for the purposes of costing we have assumed that this will remain the same Roche will reimburse the Customer for any reasonable costs incurred directly by the Customer in complying with its obligation to submit its Data Report through the Blueteq Patient Access Scheme module.	(see above)

T-DM1 for treating HER2-positive, unresectable locally advanced or metastatic breast cancer after treatment with trastuzumab and a taxane: A Cancer Drugs Fund review

Key questions for the company

Please note that all the analyses presented below are based on the updated base case model which includes the costs of implementing and operationalising the patient access scheme. The new base case ICER is [redacted]

1) Please confirm which data cut has been used to inform the modelled PFS. If it is based on the Jan 2012 data cut, please explain why later data has not been used and why the parametric distributions used for extrapolation have changed from the original submission. It would be preferable to use the Dec 2014 data cut for PFS if available. Also the two Table 9s on p31 and p34 of the submission seem inconsistent in terms of PFS extrapolation; please clarify which is correct.

The data cut used to model PFS is the January 2012 data cut. The required number of events had been reached by the Jan 2012 data cut. Therefore PFS data was not collected after the January 2012 data cut off.

Apologies for the inconsistency in the document - the table on page 31 is incorrect. In the base case the PFS is estimated using the KM data until week 74 followed by the gamma function. The Gamma function was fitted to the tail of the Kadcyla curve from 72 weeks (17 months) and in the lap/cap arm from 52 weeks (12 months) as this was the point at which the hazard starts to become erratic by inspection of the cumulative hazard plots.

The log normal distribution provided the best statistical fit followed by the gamma function. The log normal had a slightly longer tail than the gamma function and as such the gamma was chosen for the base case. However as shown below the difference between the curves is minor and as such we feel the use of either the gamma or the log normal function is appropriate to use to extrapolate the PFS KM data. Figure 1 below shows the KM data with both gamma and log normal parametric functions applied to the tails of the curves. Figure 2 is the same graph but focused on the tails.

Figure 1: KM data with gamma and log-normal distributions fitted to the tails

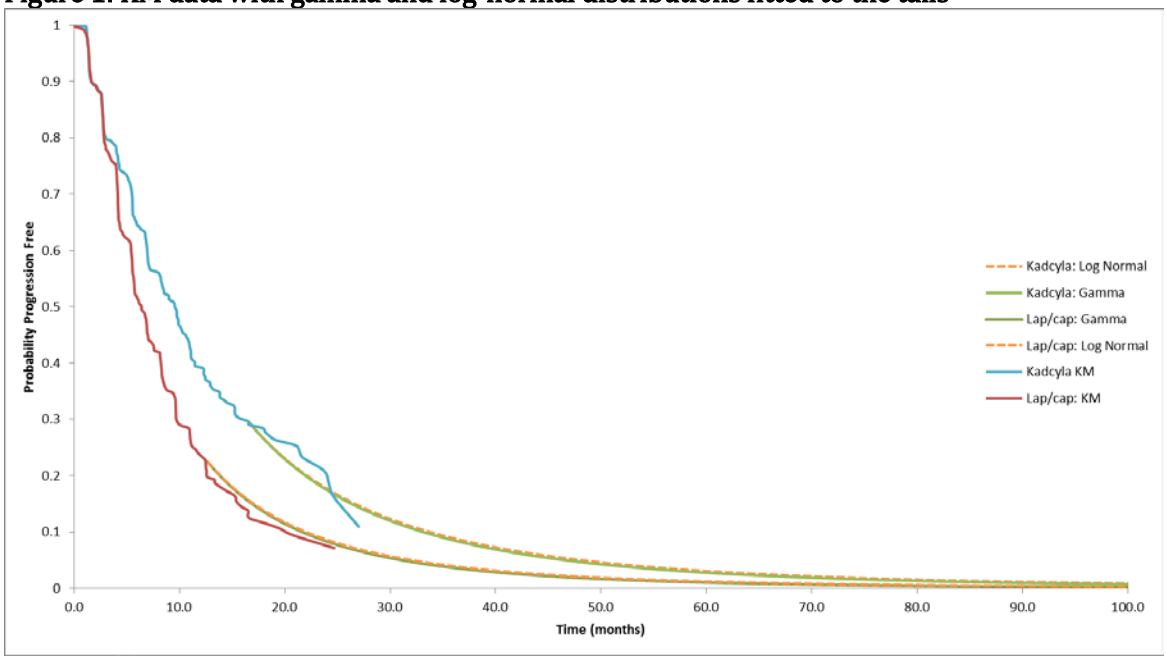
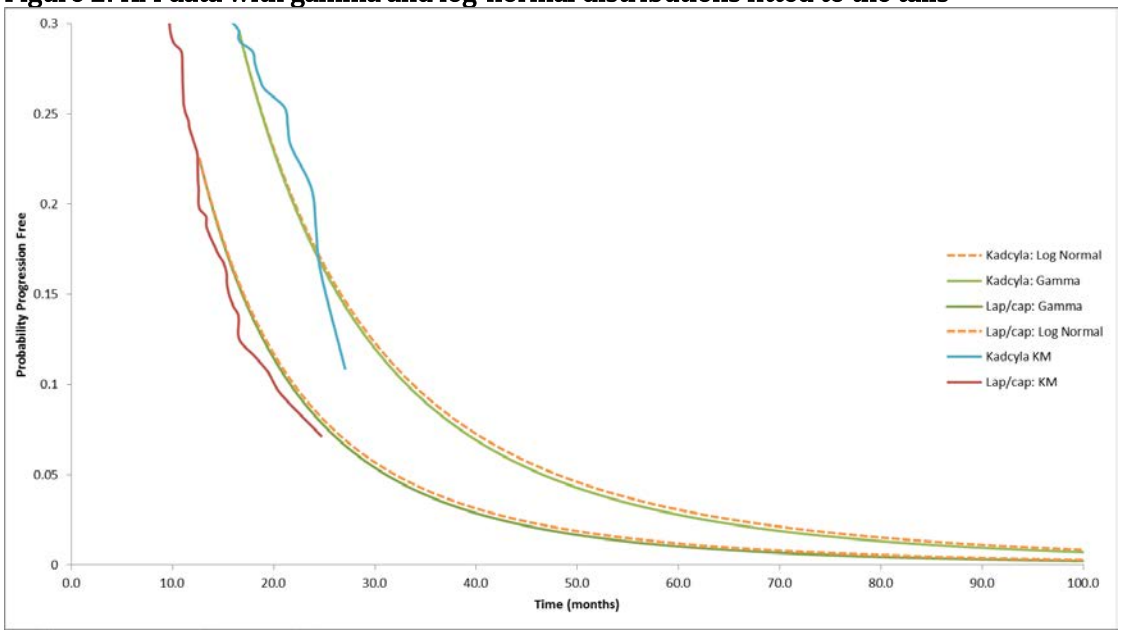


Figure 2: KM data with gamma and log-normal distributions fitted to the tails



As the figures above suggest, sensitivity analysis shows that the model is not particularly sensitive to the choice between log normal and gamma parametric functions. The ICER decreases from [redacted] to [redacted] when the log normal parametric function is used instead of the gamma function.

Visual inspection of the tails of the KM curves shows that the parametric functions appear to overestimate PFS in the comparator arm but underestimate the PFS in the intervention arm. This may be as a result of the small number of patients at risk but could lead to a conservative estimate of the cost-effectiveness.

2) Please provide more detail around the methods used to estimate the treatment duration. Within the model this seems to be calculated independently of PFS, and then limited to be no greater than PFS; please justify this approach and explain why it is preferable to using the PFS curve directly. Please consider in your description (i) the statistical analysis undertaken (see point 3 below), (ii) the approach used for the other comparators, (iii) the different data cuts used for PFS and treatment duration, and (iv) the implications for the PSA. Please also consider undertaking an analysis assuming treatment duration is equivalent to PFS.

It is correct that the model limits treatment duration to be no longer than PFS. This is in line with the summary of product characteristics for Kadcyla which states that 'patients should be treated until disease progression or unacceptable toxicity' and the trial protocol. The following statement is taken verbatim from EMILIA clinical trial protocol:

"Patients received study treatment until disease progression (as assessed by the investigator), unmanageable toxicity, or study termination by Genentech and Roche (the Sponsors)".

Treatment duration data is analysed as time to event where an event is defined as treatment discontinuation (due to any reason) and patients still on treatment are considered censored. 32 (6.5%) patients on Kadcyla were still on treatment at the end of the December 2014 data cut (Table 1) which suggests only minimal extrapolation is needed to estimate the mean treatment duration.

Table 1: Reasons for treatment discontinuation

Reasons for Drug Discontinuation	Freq.^	%
Adverse Event	87	9
Death	11	1
Disease Progression	721	74
Lost to follow-up	1	0
Physician decision to discontinue treatment	31	3
Sponsor decision to terminate study	29	3
Subject decision to discontinue treatment	60	6
Patients still on treatment*	38	4
Total	**978**	**100**

^ Safety population

* 32 on Kadcyla and 6 on LapCap

Time to event data analysis is conducted using treatment as a covariate meaning proportional hazards (PH) or accelerated failure time (AFT) assumption is applied to the parametric survival

models. The log-log and Q-Q plots showed some evidence of violation of PH (non parallel lines) and AFT assumption (plotted points do not fall on an approximately straight line passing through the origin), respectively (Figure 3, Figure 4).

Figure 3: Plot to test PH assumption for treatment duration

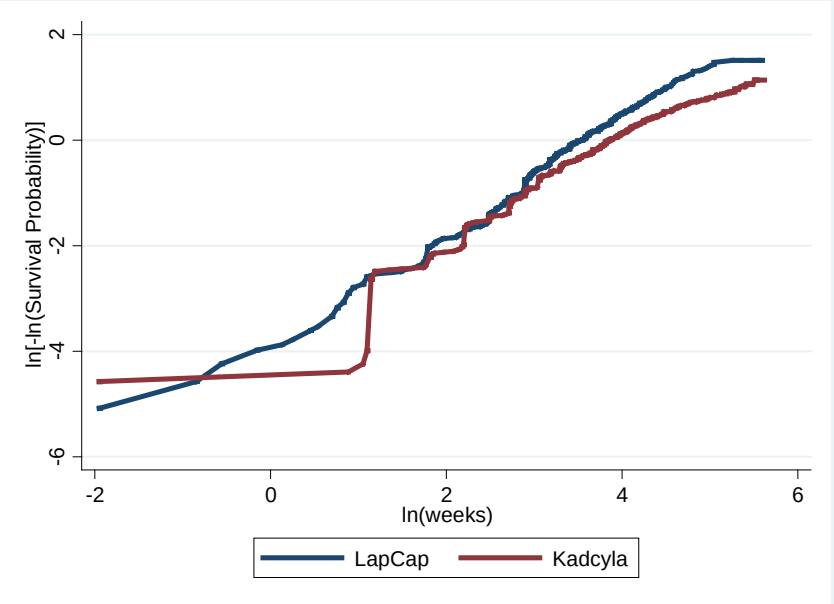
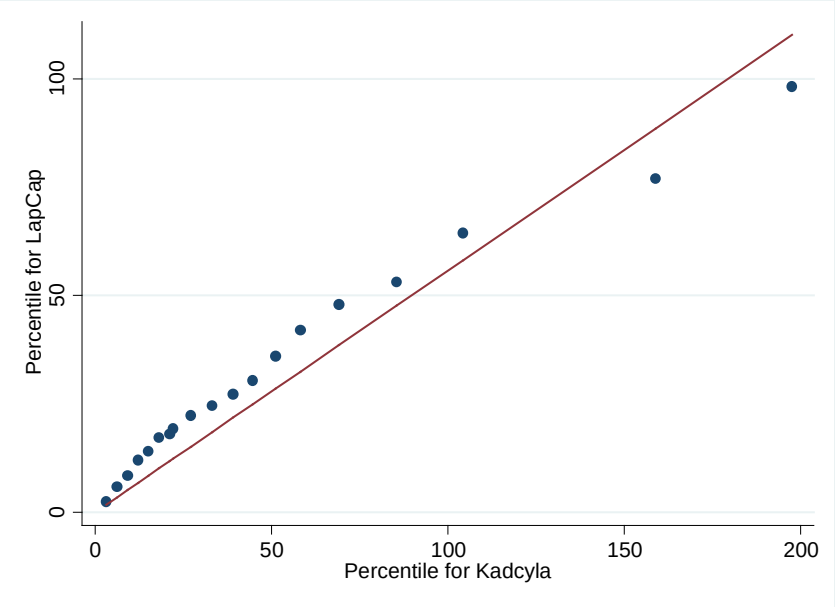


Figure 4: Q-Q plot to assess the adequacy of AFT assumption for treatment duration



In order to address the violation of the PH and AFT assumptions, KM data plus parametric extrapolation is used. The model goodness of fit statistics using the akaike information criterion (AIC) for five (with the exception of Gompertz) parametric models showing log logistic fitted the data the best followed by generalised gamma (Table 2).

Table 2: Goodness of fit statistics for treatment duration

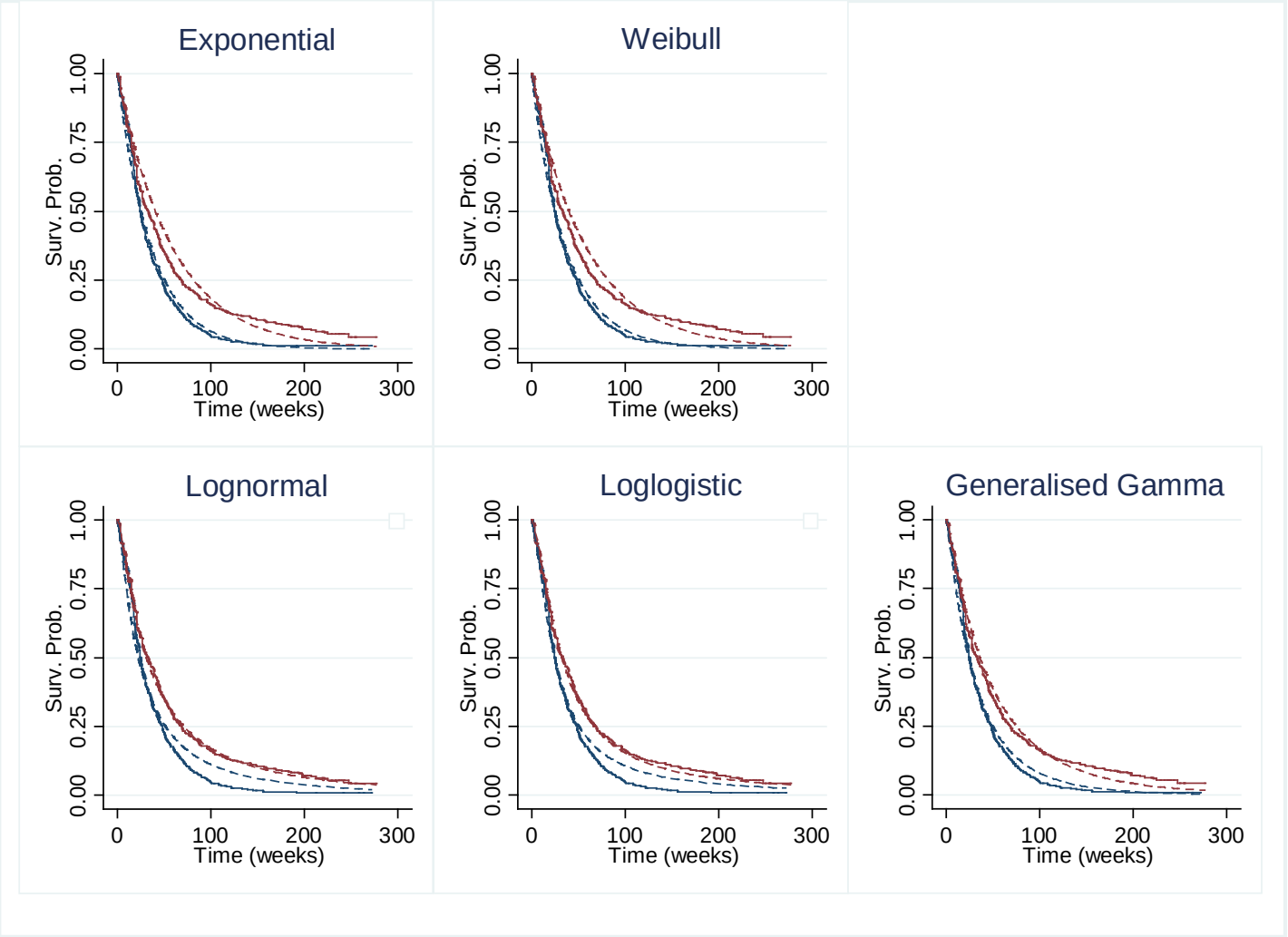
Model	Obs*	AIC	BIC

Exponential	978	3129	3139
Weibull	978	3129	3144
Lognormal	978	3163	3178
Loglogistic	978	3093	3108
Gen Gamma	978	3099	3119

* Safety population

However, parametric models with KM data overlaid shows poor prediction accuracy of log logistic distribution especially for LapCap arm (Figure 5). Although, it is acknowledged that none of the parametric distributions fitted the data accurately, generalised gamma was preferred over other distributions in order to be consistent with PFS extrapolation (detail below).

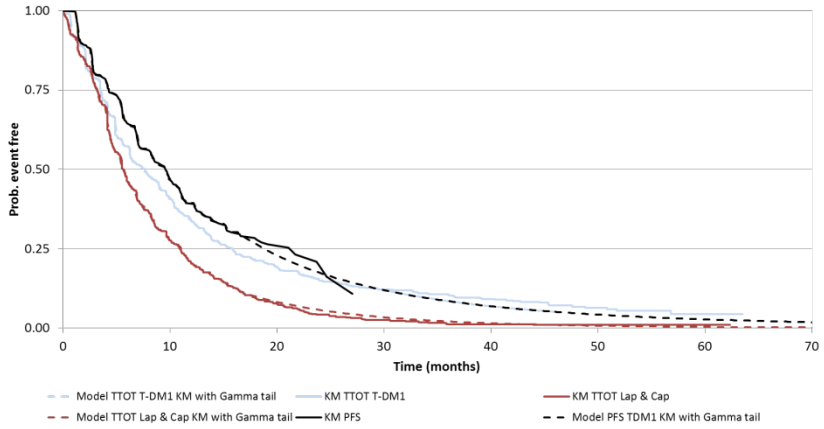
Figure 5: Parametric models with KM data overlaid for treatment duration endpoint



Parametric extrapolation was applied when approximately 10% patients were at risk of treatment discontinuation (36 months for KADCYLA and 17 months for LapCap). This is in line with previously accepted extrapolation for PFS in the original NICE submission (TA371) where parametric extrapolation was applied after 72 weeks (approximately 17 months) which translated into 10% patients being at risk of disease progression.

In addition, a criterion was set in the model (including PSA) so that treatment duration is never longer than PFS which is in line with the EMILIA study protocol. However, as shown in figure 6 this is only applied after approximately 30 months as the rest of the treatment duration KM curve is consistently below PFS. This may be due to the two different data cuts being used to extrapolate PFS and treatment duration which makes it important that extrapolation methods for PFS and treatment duration are consistent.

Figure 6: KM plus gamma extrapolation with KM overlay for treatment duration



* TDM-1=Kadcyla

Treatment until progression was assumed for trastuzumab plus capecitabine and capecitabine alone. A scenario where treatment duration is set to PFS for Kadcyla and LapCap was run and the results and presented in Table 3.

Table 3: Results of scenarios assuming alternative treatment duration assumptions

Description	Kadcyla cost*	ICER
Treatment as per protocol	[redacted]	[redacted]
Treatment as per PFS	[redacted]	[redacted]
* [redacted]		

The analysis shows that when treatment is assumed until progression the ICER increases from [redacted] to [redacted]. However as shown in Table 1 there a numerous reasons why a

patient may discontinue treatment apart from just disease progression therefore assuming treatment until progression overestimates the total cost of Kadcyla.

3) Within the document setting out what we would require from the company, we stated: *'The ERG requires sufficient detail within the report to understand exactly what has been changed within the model, why it has been changed and what sources of evidence have been used. In order to incorporate the new effectiveness data, the ERG would require the company to:*

- *accurately describe and justify the methods, including providing statistical output, validating any long term survivor functions and graphically displaying model fit to the data;*
- *clearly describe all assumptions made;*
- *test alternative plausible assumptions within sensitivity analyses.'*

This has not been provided by the company. In particular, the company have not provided sufficient information about the survival analysis (i.e. how the evidence has been extrapolated and justification for model choice) and the MTC (i.e. what evidence has been included from which trials, model fit and assessment of consistency of evidence, and how the output is used subsequently in the economic model). Please could the company provide more detail?

In the original submission (TA371), generalised gamma was deemed an appropriate parametric distribution to model overall survival. Generalised gamma model prediction showed that approximately 99% patients died by 15 years which was also the reason provided for the choice of 15 year time horizon. In addition, AIC statistics showed it to be second best fit after log logistic which had a long survival tail (96% patients died by 15 years).

Similar conclusions were reached with the use of December 2014 data cut with generalised gamma being the best parametric distribution to model overall survival (Figure 7). Time horizon of 15 years also seemed adequate (99% patients died by that time). Goodness of fit statistics showed log logistic as the best fit followed by generalised gamma (with two point difference between the two distributions) (Table 4). The AFT assumption was tested using a review of Quantile-Quantile (Q-Q) plot (i.e. if plotted points fall on an approximately straight line passing through the origin then the AFT assumption is supported). Figure 8 shows that the AFT assumption was adequate for the overall survival endpoint.

Figure 7: Kaplan-Meier plot of overall survival

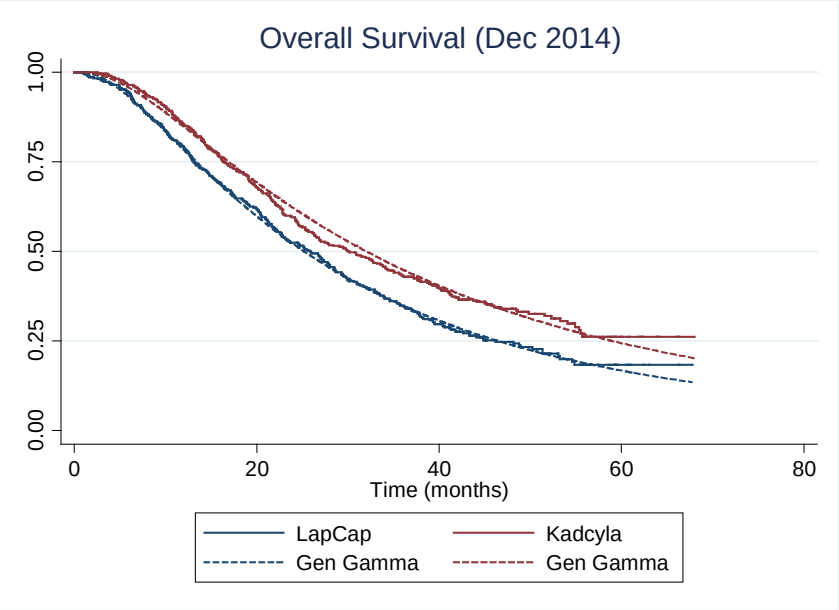
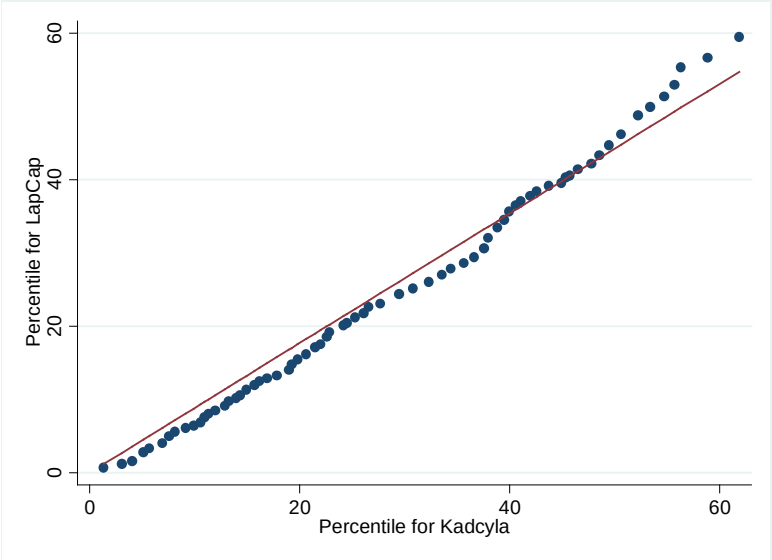


Figure 8: Q-Q plot to assess the adequacy of AFT model for overall survival endpoint



For the Mixed Treatment Comparison (MTC), the original submission TA371 suggested the use of a five study network using log hazard ratios, and a preference was made for the random effects model by the ERG. The resulting (log) hazard ratios were then applied to the Kadcyla survival curve to calculate mean costs and QALYs for the comparators of interest (trastuzumab plus capecitabine and capecitabine alone).

With the inclusion of the 2014 overall survival data, the MTC is re-run using the same network and analytical technique (i.e. using log hazard ratios and random effects model) as in the previous submission (see section 6.7 of TA371). The trials contained in the network remain as per the original submission.

In total, two analyses are conducted: one using ITT (log) hazard ratios (Table 4 and Table 6), second using RPSFTM (log) hazard ratios (Table 5 and Table 6). Please note for the second scenario, with the exception of EMILIA, crossover adjusted (log) hazard ratio was only provided by Cameron et al., 2008[2] (lapcap vs. cap) study. The resulting hazard ratios from the MTC were then applied to the Kadcyla survival curve to estimate mean costs and QALYs for the comparators of interest (as previously conducted in the original submission). Table 6 and Table 8 provide the results of the random effects MTC for the overall survival endpoint using ITT and crossover adjusted, respectively. Table 10 shows the result of the random effects MTC for the progression free survival endpoint.

Table 4: Goodness of fit statistics for overall survival (ITT)

Model	Obs	AIC	BIC
Exponential	991	2368	2377
Weibull	991	2290	2304
Gompertz	991	2343	2357
Lognormal	991	2252	2267
Loglogistic	991	2250	2265
Gen Gamma	991	2252	2272

Table 5: Input data for MTC overall survival (ITT)

study	t1	t2	HR	Study	UCI	LCI
1	Kadcyla	LapCap	0.750	EMILIA Dec 2014[1]	0.880	0.640
2	LapCap	Cap	0.870	Cameron et al., 2008[2]	1.080	0.700
3	TrasCap	Cap	0.940	GBG-26[3]	1.350	0.650
4	Niratinib	LapCap	1.250	Martin et al., 2013[4]	1.860	0.830
5	LapCap	TrasCap	1.180	CEREBAL slide 20[5]	1.830	0.760

Table 6: Results from random effects MTC ITT model for overall survival

TDM1 vs.	HR	LCrI	UCrI
LapCap	0.75	0.44	1.30
Cap	0.69	0.34	1.40
TrasCap	0.80	0.39	1.67
Niratinib	0.59	0.25	1.37

Table 7: Input data for MTC overall survival (crossover adjusted analysis)

study	t1	t2	HR	Study	UCI	LCI
1	Kadcyla	LapCap	0.693	EMILIA* Dec 2014	0.848	0.577
2	LapCap	Cap	0.800	Cameron et al^., 2008	0.990	0.640
3	TrasCap	Cap	0.940	GBG-26	1.350	0.650
4	Niratinib	LapCap	1.250	Martin et al., 2013	1.860	0.830
5	LapCap	TrasCap	1.180	CEREBAL slide 20	1.830	0.760

* RPSFTM; ^ adjusted: crossover as a time varying covariate

Table 8: Results from a random effects MTC crossover model for overall survival

TDM1 vs.	HR	LCrI	UCrI
LapCap	0.69	0.36	1.32
Cap	0.59	0.25	1.43
TrasCap	0.70	0.29	1.72
Niratinib	0.55	0.21	1.46

Table 9: Input data for progression free survival

study	t1	t2	HR	Study	UCI	LCI
1	Kadcyla	LapCap	0.650	EMILIA Jan 2012	0.771	0.549
2	LapCap	Cap	0.550	Cameron et al., 2008	0.740	0.400
3	TrasCap	Cap	0.675	GBG-26	0.958	0.476
4	Niratinib	LapCap	1.190	Martin et al., 2013	1.600	0.890
5	LapCap	TrasCap	1.130	CEREBAL slide 20	1.500	0.850

Table 10: Results from a random effects MTC for progression free survival

TDM1 vs.	HR	LCrI	UCrI
LapCap	0.65	0.32	1.17
Cap	0.40	0.16	0.89
TrasCap	0.67	0.27	1.45
Niratinib	0.55	0.21	1.28

4) For the crossover analysis, please:

- Specify in the EMILIA trial in which situations treatment switching was allowed? Eg. Did patients have to have progressed? Was switching only permitted after an interim analysis?

Following statement is taken verbatim from the clinical trial protocol amendment:

> "The additional interim analysis of OS demonstrated a statistically significant benefit in favour of trastuzumab emtansine; therefore, the co-primary endpoint of OS was considered as met and at that time patients randomized to the control arm was allowed to cross over to receive trastuzumab emtansine. Patients randomized to the control arm who have discontinued from the study were not eligible for cross-over"

- Provide an explanation for the upwards sloping logrank test plot;

Following Collett[6] formulation which compares a Group-I and a Group-II, the log-rank test statistic measures the number of additional deaths at the time of each death in Group-I

compared to those expected under the null hypothesis if there is no difference between Group-I and Group-II. That is, if there are more deaths in Group-I than expected then the log-rank test statistic (and associated Z value) will be positive.

For the purposes of g-estimation the choice of which treatment is Group-I and which is Group-II is entirely arbitrary as the interest is in finding the value of psi that satisfies the null hypothesis on the counterfactual time scale. In this application, Group-I was selected to be LapCap meaning Z (psi) in this application is a measure of additional deaths in the LapCap arm compared to those expected under the null hypothesis of no difference with the Kadcyla arm for latent survival time. This leads to the increasing trend seen in the plot. If Kadcyla was chosen as Group-I then the plot would be flipped on the horizontal access (and show a decreasing trend); however, the g-estimated value of psi would be identical as this is an arbitrary choice.

- Provide an explanation of how the confidence intervals were calculated;

Confidence intervals are calculated using the bootstrap method. Samples from the dataset are taken with replacement stratified within study arms and the entire RPSFT procedure is repeated including grid search. Confidence intervals are computed using the percentile method.

- Apply recensoring to all patients that were randomised to the lap/cap group following White (1999) [White IR, Babiker AG, Walker S, Darbyshire JH: Randomization-based methods for correcting for treatment changes: Examples from the Concorde trial. Statistics in Medicine 1999, 18(19):2617–2634];

Both results including re-censoring using White et al., 1999[7] and without re-censoring are presented in the Table 12.

Table 11: Stratified RPSFTM hazard ratio with/without re-censoring

Data cut		Stratified HR	LCI	UCI
Dec 2014	RPSFTM no re-censoring	0.704	0.582	0.852
Dec 2014	RPSFTM with re-censoring	0.693	0.577	0.848

- Assess the impact of recensoring on survival times and deaths;

Table 12 below shows the impact of re-censoring using RPSFTM procedure on patients who were deemed censored and those who had an event. In addition, it shows the impact on median and restricted mean survival.

Table 12: Impact of re-censoring (using RPSFTM) on survival and event numbers

	LapCap	
	ITT	**Adjusted***
Censor	163	193
Death	333	303
Median survival (weeks)	112.4	109.1
Restricted mean survival (weeks)	136.1	117.1
* RPSFTM		

- Perform some analyses to assess the plausibility of the common treatment effect;

The following analysis has been conducted to address the common treatment effect assumption:

Normal model:

$$U = T_{off} + T_{on} e^{\varphi}$$

Toff is time without Kadcyla

Ton is time from start of Kadcyla to Death/censoring

$e^{-\varphi_1}$ is Acceleration factor for use of Kadcyla

Sensitivity model:

$$U = T_{off} + T_{on_1} e^{\varphi_1} + T_{on_2} e^{\varphi_2}$$

Toff is time without Kadcyla

Ton1 is time from start of Kadcyla to Death/censoring in first line use

Ton2 is time from start of Kadcyla to Death/censoring in second line use

$e^{-\varphi_1}$ is Acceleration factor for use of Kadcyla in first line

$e^{-\varphi_2}$ is Acceleration factor for use of Kadcyla in second line

Normal model is that $\varphi_1 = \varphi_2$

For purposes of sensitivity we assume all patients randomized to Kadcyla get first line use only and all patients not randomized to Kadcyla get second line use only. Please note that here first and second line means pre and post treatment switching, respectively.

Furthermore we have made an assumption that 2nd line effect as AFT is a function of first line effect discounted by d where if first line use doubled life $e^{-\varphi_1} = 2$ then second line use got d% of this increase e.g. $d = 0.5$ then $e^{-\varphi_2} = 1 + (2 - 1) * 0.5 = 1.5$ so a 1.5 increase in life.

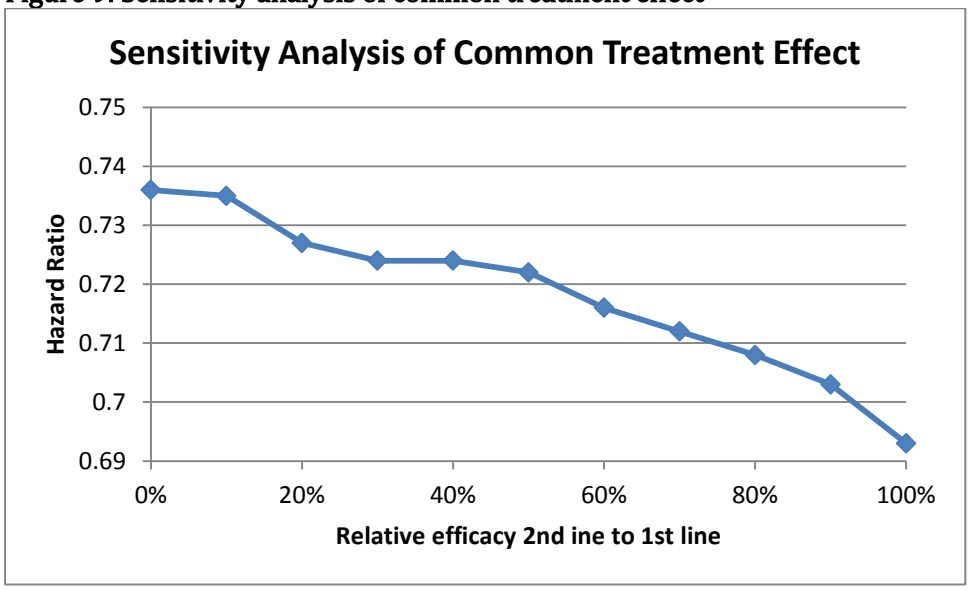
$$e^{-\varphi_2} = 1 + (e^{-\varphi_1} - 1)d$$

$$\varphi_2 = -\log[1 + (e^{-\varphi_1} - 1)d\,]$$

The estimation of psi is then performed in the normal way for a d in a range from 0 to 1. With 0 signifying no second line effect and 1 meaning second line effect equal to first line effect. Figure 9 shows that even by considering reduced effect at second line, the hazard ratio is similar to the estimated one with the common treatment effect assumption.

From these models a HR was estimated in the usual way by comparing the observed survival in the Kadcyla arm to the counterfactual survival U in the control arm (using a cox model stratified by region, prior chemo and visceral disease) where 0% is comparable to ITT analysis. Please note that due to re-censoring with RPSFT model this does not exactly match ITT analysis.

Figure 9: Sensitivity analysis of common treatment effect



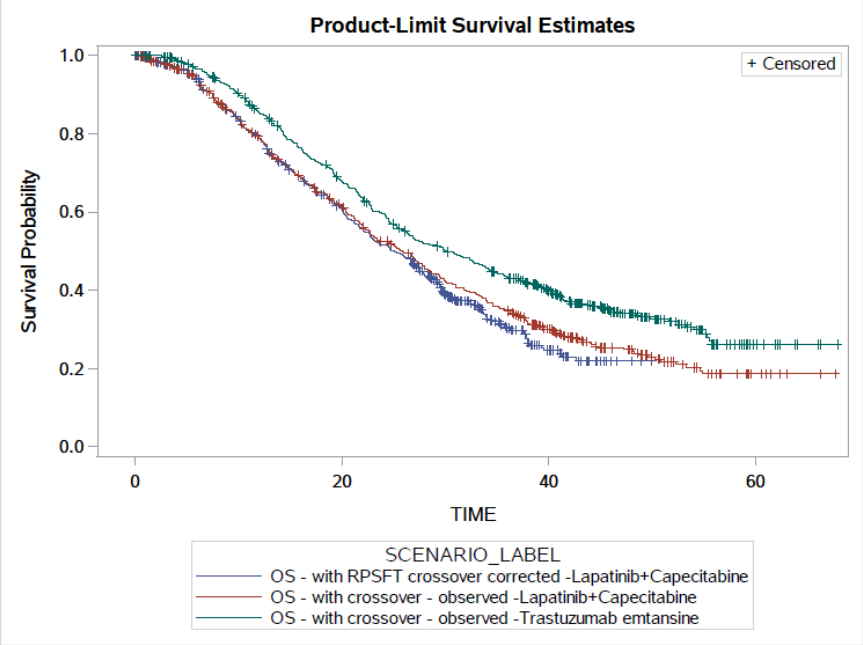
- Clarify which crossover analysis has been used to model OS within the model in the base case, with reference to Table 2;

The RPSFTM hazard ratio of 0.693 (95% CI: 0.848, 0.577) was used as the base case.

- Clarify whether Figure 7 is based on the observed or adjusted OS. It would be useful for the company to provide both within one figure for comparison.

As requested, please see Figure 10 which shows both adjusted and unadjusted KM plot for overall survival.

Figure 10: Kaplan-Meier plot of overall survival including ITT and RPSFTM adjusted curves



5) Please explain why the adverse events febrile neutropenia and thrombocytopenia have been included in the model since they were not included within the original submission. If it is because of the adjustment to the approach to estimate the AE costs associated with trastuzumab and capecitabine and capecitabine monotherapy, then please explain why costs of other AEs were not included in the model. Please also comment on why febrile neutropenia is not included in Table 4 of the Appendix and provide this information if possible. In addition, please clarify whether the time at risk relates to PFS or time on treatment and consider whether it is possible to provide a time at risk for the

comparators rather than assuming it is the same as lapatinib in combination with capecitabine.

To estimate the rates of adverse event in the Her/cap and cap arms of the model, rates were taken from the CEREBEL, GBG and Cameron. The significant severe adverse events found to occur in more than 2% of patients were febrile neutropenia, diarrhoea and vomiting, hand foot syndrome, fatigue and alopecia.

In the Her/Cap arm it was estimated that the rate of febrile neutropenia in the GBG was 3% meaning the cost of managing this adverse event is now included in the model. Similarly the cost of managing fatigue, diarrhoea and vomiting have also been costed in the model. The cost of managing hand and foot syndrome and alopecia has not been included in the model. Hand and foot syndrome although associated with swollen hands is typically managed by dose reductions of the respective treatments and therefore not associated with any notable costs. There is not considered to be a treatment for alopecia and therefore a cost has not been included in the model.

In addition to the adverse events highlighted above the following adverse events were experienced in more than 2% of the patients in the Kadcyla arm of EMILIA; aspartate aminotransferase increased and thrombocytopenia. Increased aspartate aminotransferase is a lab abnormality and therefore has no cost associated with it. Given that the rate of thrombocytopenia is significantly higher in the Kadcyla arm (14%) than estimated in the comparator arm we felt it was appropriate to include a cost for this adverse event.

If the cost of thrombocytopenia is not included the ICER decreases from [redacted] to [redacted]. If the cost of febrile neutropenia is not included the ICER increases from [redacted] to [redacted].

There are no rates for febrile neutropenia reported in table 4 apart from in the GBG trial. This is because in the Capecitabine arm of the GBG trial and in both arms in the CEREBEL trial there were no reports of febrile neutropenia reported in CEREBEL. Cameron reported the most frequent adverse events of all grades and febrile neutropenia was not included in this list.

It is possible that the rate of febrile neutropenia in the comparator arms is higher than currently estimated in the model. If so this means the cost of the comparator arms have been underestimated meaning the current ICER is a conservative estimate of the true cost-effectiveness. However the ICER is not sensitive to the costs of adverse events so any underestimation is likely to have a small impact.

If the total weekly adverse event cost per patient is increased by 50% in the Her/cap arm the ICER falls from [redacted] to [redacted]. Similarly if the cost is increased in the Capecitabine arm the ICER falls from [redacted] to [redacted].

The time at risk relates to the time on treatment.

6) Please provide all health economic model results including lapatinib in combination with capecitabine as a comparator so that the appraisal committee has both sets of results available to them depending on which they think is the most appropriate comparator. This includes a full incremental analysis, PSA results and a CEAC. Please clarify why the vinorelbine treatment pathways are excluded.

Whilst completing this question we noticed an error in the model. The duration of capcitabine and vinorelbine post progression treatment was calculated in the model incorrectly. This however has minimal impact on the ICER. The ICER decreases from [redacted] to [redacted].

Unfortunately this rest of the analysis had already been undertaken when this error was found and due to time constraints the base case has only been corrected for the response to this question. However given the difference in the ICER is small we hope you will accept the result of the analysis in the rest of this document.

Vinorelbine was not included in the submission as it was no longer considered to be a relevant comparator. Market research carried out in Q4 2015 – Q1 2016 did not detect any use of vinorelbine monotherapy in this population during this time.

Despite this we have added vinorelbine monotherapy as a comparator into the model. To include vinorelbine monotherapy into the model it is assumed, as in the original submission, that the efficacy is comparable to Capecitabine monotherapy.

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. Vinorelbine can be purchased in 50mg vial for £139 or a 10mg vial for £29. This equates to a cycle cost of £435. The cost of administering vinorelbine is assumed to be £329 (NHS reference costs 2014/2015) and £18 for the pharmacy cost (PSSRU 2015). This equates to a monthly administration cost of £1,388.

The updated base case results are presented in Table 11.

Table 11: New base-case cost-effectiveness results using the patient access scheme

	Kadcyla	Lap/Cap	Her/cap	Capecitabine	Vinorelbine
Intervention cost (£)	[redacted]	£22,499	£28,808	£5,473	£13,674
Other costs (£)	£10,992	£10,289	£10,033	£9,975	£5,917
Total costs (£)	[redacted]	£32,787	£38,840	£15,488	£23,649
Difference in total costs (£)	N/A	[redacted]	[redacted]	[redacted]	[redacted]
LYG	3.32	2.58	2.41	2.06	2.06
LYG difference	N/A	0.74	0.91	1.25	1.25
QALYs	2.09	1.56	1.45	1.20	1.20
QALY difference	N/A	0.53	0.63	0.89	0.89
ICER (£)	N/A	[redacted]	[redacted]	[redacted]	[redacted]

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Vinorelbine is given weekly and as such the cost of administering the drug is higher than capecitabine. Given that vinorelbine is assumed to have the same efficacy as Capecitabine but is more expensive, vinorelbine is dominated (as shown in Table 12 below).

Herceptin + vinorelbine is another comparator identified in the original scope. Due to short timelines this has not been included in the model. However given the efficacy of Her/vin is assumed to be the same as Her/cap but the cost will again be higher in the Her/vin arm it will again be dominated.

Please see the results for Lapatinib in combination with Capecitabine as a comparator below:

Table 12: Incremental cost effectiveness results including the patient access scheme

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£) incr. (QALYs)
Capecitabine	£15,448	2.06	1.20	N/A			
Vinorelbine	£23,649	2.06	1.20	£8201	0	0	Dominated
Lap/cap	£32,787	2.58	1.56	£17,339	0.49	0.36	£48,163 (vs cap)
Her/cap	£38,840	2.41	1.45	£23,392	0.35	0.25	£93,568 (vs cap)
Kadcyla	[redacted]	3.32	2.09	[redacted]	1.26	0.89	[redacted]

Table 12 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 ([redacted]/QALY gained). Lapatinib in combination with capecitabine was therefore removed from the simultaneous incremental analysis.

Trastuzumab in combination with was similarly found not be cost-effective against capecitabine monotherapy (ICER of [redacted]).

The efficiency frontier therefore consists of capecitabine alone and lapatinib and capecitabine which should be the primary comparators for trastuzumab emtansine.

The ICER of trastuzumab emtansine compared to capecitabine is [redacted] (see Table 13).

Table 13: Incremental cost-effectiveness final result including patient access scheme

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY gained)
Capecitabine	£15,448	2.06	1.20				

Trastuzumab emtansine	[redacted]	3.32	2.09	[redacted]	1.26	0.89	[redacted]

The PSA was re-run and the results are presented in table 14.

Table 14: PSA results using the patient access scheme

	Kadcyla	Her/cap	Lap/cap	Vinorelbine	Capecitabine
Total costs (£)	[redacted]	£41,651	£33,427	£25,803	£16,894
Difference in total costs (£)	N/A	[redacted]	[redacted]	[redacted]	[redacted]
LYG	3.324	2.648	2.86	2.262	2.266
LYG difference	N/A	0.68	0.74	1.06	1.06
QALYs	2.080	1.584	1.550	1.317	1.316
QALY difference	N/A	0.495	0.530	0.763	0.764
ICER (£)	N/A	[redacted]	[redacted]	[redacted]	[redacted]

The cost-effectiveness acceptability curve is presented below in Figure 11 below.

Figure 11: PSA cost effectiveness acceptability curve

REDACTED

7) It would be useful if the company could provide a fuller explanation about the changes they have made to the PSA.

In the original submission, the ERG criticised PSA implementation and described it to be "substantially limited". Following the advice, following changes are made to the PSA:

- Use of joint posterior distribution of (log) hazard ratios from the random effects NMA using Convergence Diagnostic and Output Analysis (CODA) samples directly from WinBUGS. This is done both for ITT and crossover adjusted analyses. The CODA samples are randomly sampled in the PSA.
- For treatment duration endpoint uncertainty around parameter estimates are taken from the Cholesky decomposition matrix. It acknowledged, where KM plus parametric extrapolation is used (i.e. for treatment duration and PFS curves), no uncertainty is assumed until beyond where parametric extrapolation is applied.

- Survival analysis using RPSFTM, standard errors/variance covariance were inflated using bootstrapping and the resulting Cholesky decomposition matrix was used in the PSA
- AE proportion and cost both are varied in PSA as opposed to only cost as previously conducted in the submission

8) Please clarify where the 7.56 months expected OS gain is from on page 41.

The expected OS gain of 7.56 months comes from the economic model. The economic model estimates that Kadcyla offers an incremental QALY gain of 0.64 years versus Herceptin and capcitabine. This equates to a 7.56 month OS gain. In addition, the model predicts an increase in life years of 0.91 equating to a 10.92 month extension in life when not adjusting for quality of life.

9) Can the company share the quality of life data from the EMILIA and TH3RESA studies that became available in May 2016 and April 2016 respectively (see p15 and p22 of the Appendix)?

TH3RESA

Patient reported outcomes (PROs) from the TH3RESA study were analysed in the primary endpoint analysis (data cut off Dec 2013) and reported by Bartley et al, ASCO-BCS 2014[8] (data not previously submitted to NICE for consideration). Data are briefly summarised below and the poster is enclosed.

Patients enrolled in the TH3RESA study completed the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30; a 30-item questionnaire assessing patient functioning [physical, emotional, role, cognitive, and social] symptom bother, and global health/quality of life) and the EORTC QLQ-Bone Metastasis (BM) 22 (EORTC QLQ-BM22; a 22-item survey evaluating pain from BM). Time to pain symptom progression (TPP; a secondary endpoint in the study) was defined as the time from randomisation to the first documented increase in narcotic use and/or a 10-point increase in pain characteristics score index from baseline, as measured by the EORTC QLQ-BM22.

Completion rates for the EORTC QLQ-C30 and EORTC QLQ-BM22 questionnaires were higher in the Kadcyla than the Treatment of Physician's Choice (TPC) arm potentially resulting in selection bias. The median TPP was similar between arms, and there were no clinically meaningful changes in pain levels from baseline over time in either arm, as measure by EORTC

QLQ-BM22. A greater proportion of patients treated with Kadcyla experienced a clinically meaningful improvement in global health status compared to those who received TPC. The proportion of patients who experienced a clinically meaningful improvement in functioning and symptoms was similar between both arms. The most impactful symptoms for patients receiving Kadcyla were fatigue and pain and the least concerning were diarrhoea and nausea/vomiting.

In a change to the original protocol, PROs were only collected in the TH3RESA study until study treatment discontinuation or investigator-assessed disease progression. As such, there have been no further analyses of PROs.

EMILIA

PROs from the EMILIA were analysed in the primary endpoint analysis (data cut off Jan 2012), published by Welslau et al, Cancer 2013[9], and discussed in the NICE STA submission for Kadcyla (December 2013 [TA371][10]).

No further data have been reported in the subsequent analyses including in the final Clinical Study Report, from May 2016.

Added 29th July - TH3RESA data – further analysis of the EQ-5D-3L data is currently being worked on. This can be provided when it becomes available, date not yet confirmed.

References

[1] Verma S et al. Trastuzumab Emtansine for HER2-Positive Advanced Breast Cancer. N Engl J Med 2012; 367:1783-91

[2] 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 Research and Treatment 2008; 112(3) 533–543

[3] Von Minckwitz et al. Trastuzumab Beyond Progression in Human Epidermal Growth Factor Receptor 2–Positive Advanced Breast Cancer: A German Breast Group 26/Breast International Group 03-05 Study. Journal of Clinical Oncology 2009; 27(12) 1999-2006

[4] 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. Cancer Research; 2011.

[5] Pivot X et al. CEREBEL (EGF111438): A Phase III, Randomized, Open-Label Study of Lapatinib Plus Capecitabine Versus Trastuzumab Plus Capecitabine in Patients With Human Epidermal Growth Factor Receptor 2–Positive Metastatic Breast Cancer. Journal of Clinical Oncology 2015; 33(14) 1564-1573

[6] David Collett, Modelling Survival Data in Medical Research, Second Edition 2003, Chapman & Hall/CRC

[7] White IR, Babiker AG, Walker S, Darbyshire JH: Randomization-based methods for correcting for treatment changes: Examples from the Concorde trial. Statistics in Medicine 1999, 18(19):2617–2634

[8] Bartley K et al. Patient-reported outcomes from TH3RESA, a phase 3 study of trastuzumab emtansine (T-DM1) versus treatment of physician's choice in patients with pretreated HER2–positive advanced breast cancer. ASCO-BCS 2014

[9] 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. *Cancer 2013; Published ahead of print DOI: 10.1002/cncr.28465* 2013.

[10] NICE Technology Appraisal 371: ERG report. T-DM1 for treating HER2-positive, unresectable locally advanced or metastatic breast cancer after treatment with trastuzumab and a taxane 2014

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission

Trastuzumab emtansine for the treatment of locally advanced or metastatic HER2-positive breast cancer after treatment with trastuzumab and a taxane (review of TA371)

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

1. About you and your organisation

Your name: [redacted]

Name of your organisation: Breast Cancer Now

Your position in the organisation: [redacted]

Brief description of the organisation: Breast Cancer Now is the UK's largest breast cancer charity, dedicated to funding ground-breaking research into the disease. Our ambition is that by 2050, everyone who develops breast cancer will live. We're bringing together all those affected by the disease to improve the way we prevent, detect, treat and stop breast cancer. We're committed to working with the NHS and governments across the UK to ensure that breast cancer services are as good as they can be, and that breast cancer patients benefit from advances in research as quickly as possible.

This submission reflects the views of Breast Cancer Now, based on our experience of working with people who are affected by breast cancer. In late 2015, Breast Cancer Now ran a campaign aimed at Roche, asking the company to lower their prices so that trastuzumab emtansine could remain on the old Cancer Drugs Fund. 42,000 people signed the online petition and many patients and their families also provided us with their experience of taking the drug. We have included quotes from patients throughout this submission.

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

Metastatic breast cancer is when cancer originating in the breast has spread to distant parts of the body, most commonly the lungs, brain, bones and liver. There is no cure for metastatic breast cancer, so most medicines aim to extend the length of life or to improve quality of life for patients. A patient can be diagnosed with metastatic (stage 4) cancer to begin with or they can develop the condition many years after treatment for their primary breast

cancer has ended. Living with metastatic breast cancer is difficult to come to terms with for both the patient and their family. Patients' time is limited and the treatments usually have some side effects. A patient living with metastatic cancer will usually have continuous treatment with the aim of controlling the spread or progression of their cancer. Patients therefore tell us that they value being able to spend quality time with their loved ones, with quality of life being just as important to take into account as length of life.

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

As mentioned above, both quality of life and extension of life are important to patients with metastatic breast cancer. Patients also value knowing that additional treatment options are available, as it gives them some comfort to know that there are more options available once their cancer progresses on current treatment. More targeted treatments rather than traditional chemotherapies may also enable patients to avoid some of the more unpleasant side effects associated with standard chemotherapy.

One patient told us: "I was on Kadcyla through CDF for 12 months, it completely cleared my liver of multiple lesions, I was able to continue with my life with very little side effects, I kept my hair and that was a massive bonus."

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

Treatment options for patients with HER2+ metastatic breast cancer patients are limited. Currently, patients in this group can be offered either general chemotherapies or trastuzumab, which is a targeted therapy. Trastuzumab is usually only offered to women if their cancer has sufficiently high levels of HER2+ expression. Furthermore, once trastuzumab stops being effective for women in controlling the growth of their cancer, patients will need to revert back to non-targeted chemotherapies.

We would like to point out that one of the comparators in the scope provided for this Technology Appraisal is lapatinib. This drug used to be available via the Cancer Drugs Fund, but had been delisted last year. It is therefore no longer available as a treatment option in England.

4. What do patients or carers consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

Trastuzumab emtansine is a first in class cancer drug and is extremely innovative. We have been in contact with many women, for whom this drug has kept their metastatic cancer under control for many years, allowing them to continue living a more or less normal life and spend quality time with their loved ones. From our experience of working with women taking this drug, we understand that the quality of life is generally good for patients taking this drug, allowing many patients to return to work and resume normal life.

One relative told us: “My 47 year-old wife has had 21 doses of Kadcyla so far, and we can pretty much attribute her still being alive two years after HER2 grade 3 stage 4, to the fact that our consultant managed to get funding.”

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

Some younger women we have been in touch with tell us how access to this drug has enabled them to see their children grow up. The patients themselves have often been able to return to work and lead a more or less normal life. The introduction of trastuzumab emtansine into the treatment pathway for patients with HER2+ metastatic breast cancer would be a significant step forward for patients with this aggressive form of the disease. The improvements in progression free survival and overall survival are significant and are associated with a reduction in the types of side effects likely to impact substantially on quality of life, when compared to existing treatments. The introduction of targeted therapies for HER2+ breast cancer is particularly important as the only HER2-targeted drug approved for routine use on the NHS is trastuzumab, to which most patients will develop resistance to within approximately 12 months.

One patient told us: “I was diagnosed with secondary breast cancer at the age of 41 in 2010. My disease has been kept in check so far with a couple of courses of docetaxel and Herceptin and most recently Kadcyla. I have been receiving 3 weekly Kadcyla since April 2014 and have been able to maintain a normal life as wife and mother of 3 children in full time education. I have also been able to continue to work as a teacher for two days a week. It would be devastating if Kadcyla and other brilliant life extending drugs were not available. They work so well for some people and I strongly feel that we deserve the right to live for as long as possible. My youngest daughter is now 13 and she and my other two teenagers have experienced this disease at first hand for most of their lives since I was first diagnosed 9 years ago. I need to be here for them and for my husband for as long as possible.”

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

This drug does not work well for every patient with HER2+ breast cancer. However, if there is progression of disease on this drug, the clinician will usually recommend another course of treatment to a particular patient. All

patients we have spoken to still very much value having the option of several different medicines to try. This gives patients reassurance that there may be another option once their treatment progresses, as well as increasing the chances of finding a medicine that an individual patient can tolerate and in whom the medicine works effectively to prolong life and halt progression.

5. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

There is currently only one targeted treatment routinely available to patients with HER2+ metastatic breast cancer on the NHS: trastuzumab. This is an effective treatment but all patients on this drug eventually progress. On average, it takes around 12 months for patients' cancer to progress on this drug, after which time they will need to revert back to general chemotherapies. General chemotherapies are known for their severe side effects and often a worsening effect on quality of life.

Please list any concerns patients or carers have about the treatment being appraised.

Trastuzumab emtansine is administered intravenously whereas lapatinib and capecitabine are taken orally and therefore do not require a hospital visit for

administration. Some patients may prefer to take their medication orally, at home, rather than being required to travel to hospital for intravenous treatment. However, regular hospital visits are still required when being treated with lapatinib and capecitabine in order to monitor treatment-related side effects. We know from speaking to patients with metastatic breast cancer that treatments which extend their lives and allow them to continue to live as well as possible for as long as possible are hugely important to them, so it is likely that the majority of patients would not feel that the requirement for intravenous administration would outweigh the benefits of the drug.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

Not that we are aware of.

6. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

Trastuzumab emtansine is only suitable for patients with HER2+ disease as it is a targeted therapy directed at the HER2 receptor. HER2+ breast cancer is often described as being particularly aggressive and the only targeted therapy which has been approved by NICE for use in these patients is trastuzumab. Trastuzumab emtansine is therefore likely to result in substantial benefits in treatment outcomes for this group of patients, for whom options for treatment are limited to standard, untargeted chemotherapy, once the cancer progresses on trastuzumab.

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

Not that we are aware of.

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

☐ Yes

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.

From our experience of working with patients, we would support the findings of the clinical trials, where patients tolerated trastuzumab emtansine better than generic chemotherapies and the side effects in the trastuzumab emtansine arm were generally lower and manageable.
(http://www.ncbi.nlm.nih.gov/pubmed/24222194)

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

We have not managed to locate detailed data on quality of life, but have seen studies on side effects and patient reported outcomes. These suggest that quality of life for patients taking trastuzumab emtansine is improved, compared to capecitabine plus lapatinib. Anecdotally, our contact with patients taking the drug via the old Cancer Drugs Fund also confirms that patients have a generally good quality of life, whilst taking trastuzumab emtansine.

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Not that we are aware of.

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

Yes

If yes, please provide references to the relevant studies.

Breast Cancer Now ran a campaign in late 2015, targeted at Roche, asking the company to lower the price of trastuzumab emtansine to enable it to stay on the old Cancer Drugs Fund. 42,000 people signed our online petition, many of these patients and their families. This shows the level of support this drug has with the patient population and the importance of agreeing some

way of making this treatment available to patients. We also received many written comments from patients, some of which we have included throughout this submission.

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having 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 treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

Not that we are aware of.

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

Not that we are aware of.

9. Other issues

Do you consider the treatment to be innovative?

☐ Yes

If yes, please explain what makes it significantly different from other treatments for the condition.

This is a very effective drug that has the potential to change the lives of women with metastatic breast cancer. The drug is a first in class and works

exceptionally well for some women, often keeping their cancer controlled for many years.

Are there any other issues that you would like the Appraisal Committee to consider?

This treatment has been available as a standard treatment in the United States for a number of years. Trastuzumab emtansine is also available to women with HER2+ metastatic breast cancer in Australia, Canada, France and Germany. The health systems of these four countries are relatively similar to that of the NHS. Whilst we understand that NICE will be making an independent decision on the cost and clinical effectiveness of this medicine, we would like these points to be taken into account as testament to the importance of this particular medicine, which is recognised in clinical practice abroad as being worthy of receiving funding from the health system. If NICE is unable to approve this drug it would represent a significant step back for breast cancer treatment in the UK. We urge the Committee and the manufacturer to work together, and with other stakeholders, to ensure UK breast cancer patients are able to access the most effective treatment for their condition.

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- This is an innovative targeted treatment for women with HER2+ metastatic breast cancer which presents a step forward in breast cancer treatment.
- Some patients we are in touch with have been on this drug for many years, allowing them to spend precious quality time with their loved ones.
- The effectiveness of this treatment will vary from patient to patient, but the option of taking trastuzumab emtansine is hugely important to patients.
- Once patients have taken trastuzumab – the only other targeted treatment available for this group of patients – options for further treatment are limited.
- This drug is already considered standard treatment in other countries with similar health systems.

Appendix F - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF Rapid reconsideration process

Trastuzumab emtansine for the treatment of locally advanced or metastatic HER2-positive breast cancer after treatment with trastuzumab and a taxane (review of TA371)

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted], submitting on behalf of:

Name of your organisation: NCRI-ACP-RCP-RCR

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry No

Appendix F - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF Rapid reconsideration process

Trastuzumab emtansine for the treatment of locally advanced or metastatic HER2-positive breast cancer after treatment with trastuzumab and a taxane (review of TA371)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Trastusumab emtasine is an antibody cytotoxic conjugate comprising the HER-2 targetting antibody trastusumab and the microtubule targeting cytotoxic emtansine. This conjugate has demonstrated activity against HER-2 positive breast cancer in a variety of situations here we are focussing on the current licenced indication as summarised above.
The primary registration study for trastusumab emtasine (EMELIA) [1] has demonstrated a significant prolongation of median progression free survival advantage and a significant and somewhat larger overall survival advantage of approximately 6 months compared to the use of capecitabine and lapatinib in patients with HER-2 positive locally advanced or metastatic breast cancer . In addition the toxicity profile is markedly in favour of trastusumab emtansine.

Trastusumab emtansine has been in widespread use within England to treat advanced breast cancer following disease progression after taxane and trastusumab treatment. Many UK clinicians have been involved in the early and late phase studies of this agent and there is now extensive experience in the UK using this agent in multiple clinical situations but predominantly within the current licenced indication. The treatment off study within licence has been funded through the Cancer drugs fund has become incorporated (subject to successful funding application) into many local guidelines for the management of advanced HER-2 positive breast cancer. The overall experience has been very positive and the provision of access to an effective

therapy with a very favourable and manageable toxicity profile has been very welcome. We are of course aware that this is a very costly medicine and that previous cost utility assessment has been unfavourable.

In England some eligible patients are now treated with docetaxel pertuzumab and trastusumab. The addition of pertuzumab (a second monoclonal antibody targeting a second epitope on the HER-2 oncoprotien) to the taxane trastusumab combination is associated with a dramatic median survival advantage of almost 16 months. The registration study population for the EMELIA study was predominantly not exposed to pertuzumab. There is no rationale however for suspecting that pertuzumab pre-treated patients will not experience similar benefits from second line treatment with trastusumab emtansine. .

Most NHS patients currently do not have access to lapatinib for use in combination with capecitabine (not recommended by NICE and no longer funded by the cancer drugs fund). The consequences of an ongoing negative NICE recommendation for trastusumab emtansine would be very concerning as this would leave no access to any second line HER-2 directed treatment options for patients with advanced breast cancer.
While not directly relevant to the current appraisal we note there is considerable concern over the ongoing availability of pertuzumab in the balance and subject to reapraisal (pertuzumab is currently only funded through the cancer drugs fund). In the event that pertuzumab is not recommended the only remaining targeted anti HER-2 therapy available to NHS patients would be trastusumab. This would represent a serious impact to our ability to manage patients with advanced HER-2 positive breast cancer and put treatment for this disease back 15 years. A perverse situation would arise where medicines with the largest impact on advanced breast cancer survival would be unavailable leaving clinician's access only to non-targeted approaches with associated limited activity, often worse toxicity and in some instances still very costly. Should this situation arise we would anticipate a strong reaction from the medical and patient advocacy communities and without doubt from the lay press.

We would very much prefer to see a successful interaction between NICE and Industry to ensure that access to all clinically appropriate anti HER-2 based therapies can be accessed by NHS patients and would strongly encourage where necessary a dialogue towards this aim.

1 Verma *et al* NEJM 201,367 (19) 1783-91
2 Swain *et al* N Engl J Med. 2015 Feb 19;372(8):724-34

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF Rapid reconsideration process

Trastuzumab emtansine for the treatment of locally advanced or metastatic HER2-positive breast cancer after treatment with trastuzumab and a taxane (review of TA371)

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF Rapid reconsideration process

Trastuzumab emtansine for the treatment of locally advanced or metastatic HER2-positive breast cancer after treatment with trastuzumab and a taxane (review of TA371)

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. 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.

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Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

NHS England submission into the NICE re-appraisal of trastuzumab emtansine November 2016

This submission contains information that is commercial in confidence (paragraph 18)

1. Single-agent trastuzumab emtansine has a licensed indication for the treatment of HER-2 positive patients with unresectable locally advanced or metastatic breast cancer who had previously received trastuzumab and a taxane, separately or in combination. Patients should have either received previous treatment for their locally advanced or metastatic disease (ie already have received chemotherapy given with palliative intent) or suffered a disease recurrence during or within 6 months of completing adjuvant therapy. Patients should be treated until disease progression or unacceptable toxicity.

2. There are 2 main trials which show the benefit of trastuzumab emtansine in advanced breast cancer.

   Trastuzumab emtansine vs the combination of lapatinib plus capecitabine

3. The first trial is the EMILIA study which randomised 991 patients with previously treated HER-2 positive metastatic breast cancer with previous treatment with trastuzumab and a taxane to receive either trastuzumab emtansine chemotherapy or the combination of lapatinib and capecitabine. The primary efficacy endpoints of the study were progression free survival (as assessed by independent review) and overall survival. Only patents of ECOG performance score of 0-1 were enrolled. Crossover was allowed in this study.

4. The median progression free survival (PFS) was significantly greater with trastuzumab emtansine than with the combination of lapatinib and capecitabine (9.6 vs 6.4 mo, Δ 3.2 mo, hazard ratio 0.65, 95% confidence interval 0.55-0.77, p<0.001). Overall survival (OS) was significantly greater at the time of the 2nd interim analysis (30.9 vs 25.1 mo, Δ 5.8 mo, HR 0.68, 95% CI 0.55-0.85, p<0.001), respectively. At the time of the final analysis when 27% of lapatinib/capecitabine patients had crossed over, the median OS durations were 29.9 vs 25.9 mo, Δ 4.0 mo, HR 0.75, 95% CI 0.64-0.88, p=0.0003.

5. Toxicity was decreased in the trastuzumab emtansine arm. Grade 3 or 4 adverse events occurred in 41% vs 57%, grade 3 or 4 diarrhoea in 2% vs 21%, and grade 3 or 4 palmar-plantar erythrodysaesthesia in 1% vs 16% although thrombocytopenia occurred in 13% vs 0%, respectively.

6. Quality of life (QOL) was assessed in this trial using the FACT-B questionnaire and patient-reported outcomes have been published. The time to symptom worsening as determined by the FACT-B trial outcome index was delayed in the trastuzumab emtansine arm versus the lapatinib-capecitabine arm (7.1 vs 4.6 mo, HR 0.80, 95% CI 0.67=0.95, p=0.012).

   Comment on the EMILIA trial

7. The survival difference is impressive for a taxane pre-treated population of patients with advanced breast cancer: the demonstration of an OS benefit of 6 months (at a time of minor crossover) is unusual in advanced breast cancer. To still gain an OS advantage of 4 months in the final analysis despite significant crossover is noteworthy. Although the combination of lapatinib and capecitabine was then the internationally recognised comparator at the time for trastuzumab emtansine, this comparator is no longer relevant to NHS practice in England as lapatinib was removed from the CDF in 2015 on account of its low efficacy.

   <u>The TH3RESA trial</u>

8. The second study was called the TH3RESA trial which compared trastuzumab emtansine in 602 patients who had previously received 2 previous treatments for advanced breast cancer including trastuzumab a taxane and the combination of lapatinib and capecitabine. Randomisation was to trastuzumab emtansine vs treatment of physician's choice. Physician's choice of treatment was one of the following: the combination of trastuzumab and chemotherapy (69%, although not recommended by a NICE breast cancer guideline, this is commissioned on a widespread basis in England), trastuzumab plus lapatinib (10%, not recommended in England), trastuzumab plus hormonal therapy (1.6%, not recommended in England), lapatinib plus chemotherapy (3%, not recommended in England) and single agent chemotherapy (17%). At least 15% of the treatments delivered in this trial as treatments of physician's choice were therefore not ones routinely commissioned in England but 85% of the patients were treated with options in routine use. Crossover was allowed in this trial. The primary endpoints of the study were investigator-assessed PFS and OS. More than 50% of patients had been treated with 4 lines of treatment for advanced breast cancer.

9. The median progression free survival (PFS) was significantly greater with trastuzumab emtansine than the physician's choice arm (6.2 vs 3.3 mo, Δ 2.9 mo, HR 0.53 95% CI 0.42-0.66, p<0.0001). Overall survival (OS) was not significantly different when first reported and with a median duration of follow-up of only 7.2 months. Mature results were reported in December 2015 with a median duration of follow-up of 30.5 months. The OS for the trastuzumab emtansine arm was 22.7 mo vs 15.8 mo for the treatment of physician's choice (Δ 6.9 mo, HR 0.68, 95% CI 0.54-0.85, p=0.0007). Cross over was allowed in the trial once the results of the EMILIA study were known and this occurred in about 50% of patients.

10. Toxicity was decreased in the trastuzumab emtansine arm, there being grade 3 or 4 adverse events in 32% vs 43%, respectively. Diarrhoea (<1% vs 4%) and febrile neutropenia (<1% vs 4%) were grade 3 or 4 adverse events which were more common in the arm of treatment of physician's choice. Thrombocytopenia (5% vs 2%) was the grade 3 and 4 adverse event which was more common in the trastuzumab emtansine arm.

    <u>Comment on the TH3RESA trial</u>

11. Trastuzumab emtansine thus produced a 7 month survival benefit in the TH3RESA study in a more heavily pre-treated population than in the EMILIA trial and also despite a very significant degree of crossover. In terms of the trial design and the treatment against which trastuzumab emtansine should be compared, the TH3RESA trial much more broadly reflects the right comparator in use in the NHS in England as the combination of lapatinib and capecitabine has not been available since 2015.

Comment on the EMILIA and TH3RESA trials

12. Of note too are the clinically relevant increases in unadjusted OS in both the EMILIA and TH3RESA trials despite the crossover allowed in both studies. The lower median OS in the control arm of TH3RESA vs that seen in the control arm of EMILIA reflects the more heavily pre-treated patients entered into the TH3RESA trial. Of note too is the reduced toxicity seen in the trastuzumab emtansine arms in both trials. Clinical feedback to NHS England has been very consistent in describing how generally well tolerated is trastuzumab emtansine and the very rare need for intervention by GP, A&E and oncology services to treat drug toxicity (unlike some other chemotherapies). Clinically meaningful increases in OS in the systemic therapy of cancer usually come at the expense of increased toxicity: this is not the case for trastuzumab emtansine.

The advanced breast cancer treatment pathway and where trastuzumab emtansine would be placed

13. NHS England is developing chemotherapy algorithms for breast cancer including HER-2 positive breast cancer and expects to publish and commission with these in 2017. As one might expect, oncologists and patients generally choose the most efficacious treatment first. Advanced breast cancer can take an unpredictable course which can result in unexpected deterioration and so one would not want patients to miss out on the best options of therapy. Thus in these algorithms (which reflect current practice), a taxane in combination with trastuzumab would usually be used first and this would be followed by trastuzumab emtansine if it were available.

14. The EMILIA study thus better places trastuzumab emtansine in the treatment pathway (ie earlier), rather than TH3RESA (ie later). The difficulty in this appraisal is that the comparator used in EMILIA although in the right position in the treatment pathway is the wrong treatment to assess the clinical and cost effectiveness of trastuzumab emtansine as it is not commissioned in England. The fact that lapatinib plus capecitabine is licensed is irrelevant: it is not standard treatment in England, is not commissioned and thus not used in the NHS. NHS England thus urges NICE to maintain its direct relevance to clinical practice in England which of course in turn is largely shaped by NICE TA recommendations.

Lapatinib plus capecitabine versus trastuzumab plus capecitabine

15. The CEREBEL study compared the combination of lapatinib plus capecitabine with the combination of trastuzumab plus capecitabine although the primary endpoint was relapse rate in the central nervous system. The study was terminated after 540 patients (out of a planned 650 patient accrual) had been randomised as it was clear that the primary endpoint would not be reached as the study was underpowered (the CNS relapse rate was under-estimated in the power calculations). Median PFS was a 2° endpoint and was significantly shorter in the lapatinib/capecitabine arm, 6.6 vs 8.1 mo, HR 1.30 (95% CI 1.04-1.64, p=0.021), respectively. Median OS was another 2° endpoint and was not significantly different, 22.7 vs 27.3 mo respectively, HR 1.34 (95% CI 0.95-1.90, p=0.095) but only 24% of patients had died at the time of this analysis. The problem with assessing the CEREBEL data in relation to the question of the comparison of trastuzumab/capectitabine with trastuzumab emtansine is that 39% of patients in the CEREBEL study had not received trastuzumab and in addition 44% had not received a taxane.

16. Thus, NHS England regards the correct comparator for this NICE appraisal of trastuzumab emtansine to be trastuzumab/capecitabine as lapatinib/capectaibine is not used in the NHS in England.

<u>The proposed Patient Access Scheme</u>

17. The PAS describes a treatment duration cap at 14 months after which Roche will rebate the cost of trastuzumab emtansine back to the treating hospital Trust. The PAS requires Trusts to regularly submit details of individual patient's treatments with trastuzumab emtansine so that the rebates can commence and then continue as appropriate after the initial 14 month has elapsed.

18. Roche estimates that [redacted] of patients are still on treatment at 14 months: the numbers of patients that require tracking let alone the regular submission of information are therefore very significant. The administrative burden for Trusts is thus likely to be considerable.

19. A further concern is that the PAS as stated relates to trastuzumab emtansine given to patients previously treated with trastuzumab, the latter specifically called Herceptin, the Roche brand name. Trastuzumab biosimilars are due in 2017 and any PAS should not have any mention of which trastuzumab may have been used previously.

<u>Treatment beyond disease progression</u>

20. The SPC is very clear that patients treated with trastuzumab emtansine should continue on treatment until disease progression or unacceptable toxicity. Of course patients can decide to discontinue treatment at any stage before either of the above two events. There is no evidence of the clinical effectivenss of trastuzumab emtansine when given beyond disease progression. Should NICE recommend the use of this drug to the NHS, then it would be important for NICE to specifically state that it received no evidence

of the effectiveness of trastuzumab emtansine beyond disease progression and thus cannot recommend this use of the drug beyond progression.

Summary

21. NHS England regards trastuzumab emtansine to be a highly clinically effective drug in the treatment of advanced and pre-treated HER-2 positive breast cancer. The comparator should be the combination of trastuzumab and capecitabine although NHS England recognises the difficulties of translating all the trial evidence into this comparison. Cost effectiveness remains the key consideration. NHS England has concerns as to the PAS that has been proposed in view of the administrative burden to Trusts.

[redacted]

November 2016

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF Rapid Reconsideration

Trastuzumab emtansine for the treatment of locally advanced or metastatic HER2-positive breast cancer after treatment with trastuzumab and a taxane (review of TA371)

Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the statement submitted by NCRI-RCP-ACP-RCR and consequently I will not be submitting a personal statement.

Name: [redacted]

Signed: [redacted]

Date: 16/11/16

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF Rapid Reconsideration

Patient/carer expert statement

[Trastuzumab emtansine for the treatment of locally advanced or metastatic HER2-positive breast cancer after treatment with trastuzumab and a taxane (review of TA371)

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, including health-related quality of life)
- preferences for different treatments and how they are given
- expectations about the risks and benefits of the treatment.

We have already asked your nominating organisation to provide an organisation's view. We are asking you to give your views as an individual whether you are:

- a patient
- a carer (who may be voicing views for a patient who is unable to) or
- somebody who works or volunteers for a patient organisation.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The response area will expand as you type. The length of your response should not normally exceed 10 pages.

1. About you

Your name: [redacted]
Name of your nominating organisation: Breast Cancer Now
Do you know if your nominating organisation has submitted a statement?

x Yes ☐ No

Do you wish to agree with your nominating organisation's statement?

x Yes ☐ No

(We would encourage you to complete this form even if you agree with your nominating organisation's statement.)

Are you:

- a patient with the condition?

x Yes ☐ No

- a carer of a patient with the condition?

☐ Yes x No

- a patient organisation employee or volunteer?

☐ Yes x No

Do you have experience of the treatment being appraised?

x Yes ☐ No

If you wrote the organisation submission and do not have anything to add, tick here ☐ (If you tick this box, the rest of this form will be deleted after submission.)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: N/A

2. Living with the condition

What is your experience of living with the condition as a patient or carer?

I was diagnosed with inflammatory breast cancer (right breast) in July 2012, and re-diagnosed with secondary skin metastases and associated lymphodaema in November 2014. Physically, this condition caused pain, fatigue and difficulties using my right arm. I have experienced the effects of surgery (double mastectomy), chemotherapy (FEC/Docataxel), herceptin (12 months) and radiotherapy (21 treatments) following my first diagnosis, and following my second diagnosis, further chemotherapy (6x docetaxel) and treatment with monoclonal antibodies (pertuzumab). I started Kadcyla in April 2015 and have just had my 27th cycle of treatment.

Since my original diagnosis I have only enjoyed around 12 months free of treatment. Treatment has extended my life, but has had a profound impact on it. I have had to come to terms with changes in my body (loss of both breasts, loss of hair, weight gain, reduced strength and mobility and reduced use of my right arm), learn to cope with pain (including treatment-related peripheral neuropathy) and impaired concentration and memory. Previously active and relatively fit, I am no longer able to enjoy some activities (at least to their fullest degree) that were central to my wellbeing, such as long-distance walking, squash and gardening. At the time of my original diagnosis I was researching my PhD, and looking forward to a future in academia. Whilst I was able to complete and successfully defend my thesis prior to re-diagnosis, reduced energy levels and impaired cognitive performance (largely due to the effect of chemotherapy) left me unable to contemplate pursuing a career in this competitive field as planned. Whilst on a toxic chemotherapy regime (FEC and docetaxel) – which rendered me neutropenic and septic almost every cycle - I was unable to plan ahead and had to limit trips away from

home to locations close to NHS A&E facilities. I also had to limit my contact with other people, and avoid crowds, for fear of exposing myself to infection.

In terms of the psychological impact of coping with a life-limiting disease, I am lucky insofar as I enjoy a happy, optimistic and humorous disposition. I enjoy life, which has treated me well, and am supported and heartened by caring and nurturing partner, friends and family. Nevertheless, the impact of toxic chemotherapy regimens tested me and my partner and our support network – often unwell (frequently seriously as a result of neutropenia and requiring hospitalisation) it was easy to lose my sense of self and perspective and to feel like a patient waiting to die, rather than an individual living her life. Kadcyla has not only extended my life for 18 months, but has done so in a way that has allowed me to *live* my life, albeit within certain inescapable constraints; I am living well, and I no longer feel as though I am simply waiting to die.

3. Current practice in treating the condition

Which treatment outcomes are important to you? (That is, what would you like treatment to achieve?) Which of these are most important? If possible, please explain why.

I want to live longer, but only if I can enjoy that life. I don't want to feel so unwell that I can only lie around and sleep, and need lots of care from others. I don't want to spend regular periods of time in hospital as a result of treatment side-effects. I don't want my partner to feel constantly anxious that I may need medical intervention. I don't want treatment to kill my spirit and rob me of the pleasure I take in life. Kadcyla has achieved all these outcomes for me, where standard chemotherapy failed.

What is your experience of currently available NHS care and of specific treatments? How acceptable are these treatments – which did you prefer and why?

As explained above, toxic chemotherapy regimens are difficult to bear, even when they are effective. FEC/docetaxel/Herceptin shrunk my original lesions prior to surgery, but docetaxel was ineffective in relation to my skin metastases, as was pertuzamab. Kadcyla has successfully reduced my skin

lesions and prevented a further spread. And it has done so without impairing my quality of life

4. What do you consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that you expect to gain from using the treatment being appraised.

- Effect on skin mets. Immediately before starting Kadcyla my metastatic skin cancer was visibly progressing in the form of red lesions spreading across my chest wall. After the second treatment the lesions had faded and remain well controlled, pale and almost invisible for most of each cycle.

- Extended life – I have enjoyed 18 months of living without disease progression; time I did not anticipate having.

- Good quality life – given that I experience relatively few side effects from Kadcyla, I have been able to enjoy the extra time it has given me; I have been able to pursue academic projects (some of my work is soon to be published and I am on an advisory board for an academic research project looking at the concept of powerlessness through the prism of end of life care), I have embarked on new hobbies and pastimes to replace those I am no longer able to pursue, I have had the

opportunity to spend time with my partner, friends and family enjoying their company, creating memories, allowing us all to come to terms with my illness and the likelihood of it ending my life prematurely. I enjoy greater autonomy and freedom on this drug than I did when on standard chemotherapy, which had considerable side effects.

- Kadcyla is administered through a port in my chest every three weeks at a chemotherapy suite at my local hospital – it is convenient and takes only a few hours, taking into account pre-med and flushes and average wait for pharmacy to dispense it.

- Generally, the after effects of treatment are minimal – tiredness for a day or so, probable peripheral neuropathy which causes numbness in fingers and feet and pain in legs (adding to exisiting neuropathy caused by previous treatment), and possible reaction causing fever and problems with vision for a few days after treatment. This possible reaction has been resolved with a course of post-treatment steroids. Whilst the steroids present their own problems – particularly sleep disturbance – they are short lived and are outweighed by the benefits of treatment.

- It can be difficult to distinguish between pain associated with my disease and the treatment used to halt its progression. However, fatigue, pain, loss of stamina and reduced mental acuity to an extent must be attributable to years of chemotherapy and other therapies. However, the only alternative to palliative treatment is to accept the likelihood of an earlier death. A key benefit of Kadcyla is that, in my case, it has proved effective at minimal cost to my quality of life. Kadcyla is not without side effects, but these – in my case – have been managed with steroids, painkillers and strategies for maximising energy and improving stamina and mobility.

- Kadcyla has controlled the spread of my cancer and allowed me to live longer, in relative comfort and with autonomy and wellbeing.

Emotionally and physically, Kadcyla has proved to be best therapy I have received.

Please explain any advantages that you think this treatment has over other NHS treatments in England.

As above, it allows a patient to enjoy a better quality of life because (for me at least) it has fewer side effects, certainly none has harsh as conventional chemotherapy.

If you know of any differences in opinion between you and other patients or carers about the benefits of the treatment being appraised, please tell us about them.

N/A

5. What do you consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns you have about current NHS treatments in England.

My worry is that traditional, more toxic forms of chemotherapy will be administered to patients because other available, less toxic and perhaps more effective, forms of treatment are not affordable. For those patients with a terminal diagnosis, this could blight the remaining months of life which should be spent coming to terms with the future, enjoying time with family and friends

and preparing themselves and their family (in particular children) for their likely death.

Please list any concerns you have about the treatment being appraised.

My only concern regarding Kadcyla is its availability. Should its access be denied to those currently not receiving it, it will beg the following question: Why should my life be extended, when other patients denied access will die sooner than they might otherwise? I want other people to have access to this treatment, and will feel morally compromised if I can continue to enjoy its life extending/enhancing benefits, whilst others (including those patients I currently sit alongside in the chemotherapy suite) are denied this opportunity.

If you know of any differences in opinion between you and other patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

n/a

6. Patient population

Do you think some patients might benefit more from the treatment than others? If so, please describe them and explain why.

see below

Do you think some patients might benefit less from the treatment than others? If so, please describe them and explain why.

I see no reason to discriminate against any group of patients. Provided it is effective and side effects do not outweigh the benefits, all patient should have access.

7. Research evidence on patient or carer views of the treatment

Are you familiar with the published research literature for the treatment?

x Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether your experience of using the treatment as part of routine NHS care reflects the experience of patients in the clinical trials.

I have some awareness of the summary of trials. My understanding is that one key trial compared Kadcyla with Lapatinib, and Kadcyla was found to be more effective with respect to length of progression-free survival. Lapatinib was an alternative to Kadcyla which my consultant discussed with me when (after the first treatment) I expressed concern about whether my skin mets were showing signs of improving. As I understand it Lapatinib is no longer available, so current treatment options for someone facing a similar situation to me would be Kadcyla or standard chemo. And in my case standard chemo for the skin mets had not worked and the disease had continued to progress. Hence my conclusion it is essential to make Kadcyla available to new patients, especially as there are now no real alternatives.

Finally it seems that I have had a longer than average period of progression-free survival than those on the trial. I have no way to know if this is typical or unusual among non-trial patients.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

n/k

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

I have experienced some apparent reactions as mentioned above, which are mitigated by using steroids after treatment.

Are you aware of any relevant research on patient or carer views of the condition or existing treatments?

☐ Yes x No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity and eliminating discrimination. Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, who they are and why.

no

9. Other issues

Do you consider the treatment to be innovative?

x Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

It has less side effects that traditional toxic chemotherapy drugs and thus promises a better quality of life for patients.

Is there anything else that you would like the Appraisal Committee to consider?

It is difficult to put a price on the extra, good-quality time Kadcyla has afforded me – to me, and my family and friends, it is priceless, for policymakers it is incalculable (in moral terms, at least) – and as a patient it is difficult to look coldly upon my life in economic terms and weigh it up in cost/benefit terms. To me, it is ironic that the value of a terminally ill patient's life should be subject to an economic reckoning, whilst that same patient would be denied euthanasia on the incontrovertible ground that life is sacred, and thus presumably beyond value. However, we live in times when such excruciating judgements are required, and I would like to thank the review panel for their careful consideration of the evidence and for allowing me the opportunity to share my perspective,

.

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Kadcyla has given me 18 months of good quality life that I did not expect to have.

- In my experience, the effects of traditional chemotherapy drugs are brutal and can blight one's life, whilst innovative treatments like kadcyla can extend life, do so without serious side- effects and, ultimately, provide for a good death.
- On Kadcyla, I have been able to live a productive life, where I have been able to contribute and participate, and an enjoyable life in which every day counts. I am living, not simply waiting to die.
- .
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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF Rapid Reconsideration

Trastuzumab emtansine for the treatment of locally advanced or metastatic HER2-positive breast cancer after treatment with trastuzumab and a taxane (review of TA371)

Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the statement submitted by Breast Cancer Now and consequently I will not be submitting a personal statement.

Name: [redacted]

Signed: [redacted]

Date: 26/10/16

T-DM1 for treating HER2-positive, unresectable locally advanced or metastatic breast cancer after treatment with trastuzumab and a taxane: A Cancer Drugs Fund review

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
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Declared competing interests of the authors

None.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Hazel Squires acted as project lead and health economic modeller on this review and critiqued the company's economic evaluation. Helen Bell critiqued the treatment switching analysis within the submission and John Stevens critiqued all other statistical analyses included in the company's submission. All authors contributed to writing of the report.

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LIST OF ABBREVIATIONS

AE	Adverse event
AIC	Akaike Information Criterion
BC	Base case
BIC	Bayesian Information Criterion
CDF	Cancer Drugs Fund
CEREBEL	Trial name
CI	Confidence interval
CODA	Convergence diagnostic and output analysis
CS	Company submission
EMILIA	Trial name
ERG	Evidence Review Group
HER2	Human epidermal growth factor receptor 2
HER2-positive	Overexpression of HER2
HR	Hazard ratio
ICER	Incremental cost-effectiveness ratio
IPCW	Inverse Probability of Censoring Weight
KM	Kaplan-Meier
LVEF	Left ventricular ejection fraction
LY	Life year
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
OS	Overall survival
PFS	Progression-free survival
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RPSFTM	Rank Preserving Structural Failure Time Model
T-DM1	T-DM1
TH3RESA	Trial name
TPC	Treatment of physician’s choice

1. SUMMARY

1.1 Background

The original evidence of the effectiveness and cost-effectiveness of trastuzumab emtansine (T-DM1) in patients with overexpression of the human epidermal growth factor receptor 2 (HER2-positive), unresectable locally advanced or metastatic breast cancer whose disease has progressed after treatment with trastuzumab and a taxane was submitted to the National Institute for Health and Care Excellence (NICE) and reviewed by the Evidence Review Group (ERG) in 2013 (TA371). The company have submitted new evidence for consideration as part of the Cancer Drugs Fund (CDF) transition. The remit of this report is to review the new cost-effectiveness evidence submitted by the company.

1.2 Summary of cost effectiveness evidence submitted by the company

In keeping with the original submission, within the new company submission (CS), a partitioned survival model was provided including three health states: (i) progression-free; (ii) post-progression; and (iii) dead. A completely new economic model was employed. The key differences between the company's original model and the new model are:

1) The comparators in the NICE scope (i) lapatinib in combination with capecitabine, (ii) vinorelbine, and (iii) trastuzumab in combination with vinorelbine, were excluded from the incremental analysis (although (i) and (ii) have been included within a response to informal clarifications);
2) More than two additional years of follow-up (December 2014 data cut-off) from the EMILIA trial of TDM-1 and lapatinib in combination with capecitabine have been used to model overall survival (OS), time on treatment and adverse events (AEs). The original January 2012 data cut-off was used to model progression-free survival, although the parametric distribution used to extrapolate progression-free survival has been altered;
3) The network meta-analysis (NMA) has been updated to include the additional follow-up and has been adjusted for treatment switching;
4) The way in which AEs have been incorporated has been revised;
5) The way in which treatment duration is incorporated into the model has been revised;
6) A patient access scheme (PAS) has been incorporated;
7) Several changes in response to the ERG's critique of the original submission have been made:
    a. Extending the model time horizon from 10 to 15 years
    b. Including the cost of left ventricular ejection fraction monitoring follow up
    c. Intended correction of the utility values (although the ERG believe this is incorrect)
    d. Using the actual dosing of trastuzumab emtansine and lapatinib in combination with capecitabine rather than the planned dose

e. Revising the parameters for the probabilistic sensitivity analysis (PSA)
f. Estimation of the post-progression treatment costs

Within the CS, the company estimated that the incremental cost-effectiveness ratio (ICER) associated with T-DM1, with and without the patient access scheme, would be £99,678 and [redacted] per quality-adjusted life year (QALY) gained respectively, compared with trastuzumab in combination with capecitabine; however the latter value is incorrect because when the pricing scheme for T-DM1 is incorporated, trastuzumab in combination with capecitabine is ruled out due to extended dominance, resulting in an ICER for T-DM1 versus capecitabine of [redacted] per QALY gained.

1.3 Summary of the ERG's critique of cost effectiveness evidence submitted by the company

Generally, the analysis undertaken by the company was reasonable, although it was not well described. The model submitted by the company had several minor errors which did not substantially impact upon the results. However, a key issue which affects the ICER for T-DM1 is the choice of comparators. The company argues that lapatinib in combination with capecitabine should be excluded from the analysis because it is no longer current practice in the UK. Conversely, the ERG suggests that lapatinib in combination with capecitabine should be included as a comparator as it is a licensed treatment option for this indication and was included in the original NICE scope. Using the company's model, when all options are included within a full incremental analysis including the PAS, the ICER for T-DM1 is estimated to be [redacted] per QALY gained compared with lapatinib in combination with capecitabine, which has an ICER of £49,061 per QALY gained compared with capecitabine monotherapy.

The ERG produced a revised base case which corrected a model error around the calculation of post-progression treatment costs, although this did not substantially alter the ICERs. The ERG also undertook univariate sensitivity analyses to explore key uncertainties, including the treatment doses, utilities, hazard ratios for OS, and the extrapolation of PFS and OS. These analyses suggested that the key drivers of the model results are the treatment effect beyond trial follow-up, the adjustment for treatment switching and the inclusion of vial wastage if patient-level data is used to estimate treatment costs. The ICER for T-DM1, including the PAS, was greater than [redacted] per QALY gained for all analyses.

1.4 Conclusions

A key driver of the ICER for T-DM1 is the inclusion or exclusion of lapatinib in combination with capecitabine as a comparator; this increases the ICER, including the PAS, from around [redacted] to [redacted] per QALY gained. The ICER for lapatinib in combination with capecitabine is around £49,000 per QALY gained compared with capecitabine monotherapy. There is substantial uncertainty

around the results: within the ERG's univariate sensitivity analyses, the ICER for T-DM1 compared with lapatinib in combination with capecitabine ranged from [redacted] to [redacted] per QALY gained. Key drivers of the model results are the treatment effect beyond trial follow-up, the adjustment for treatment switching and the inclusion of vial wastage if patient-level data is used to estimate treatment costs. The company suggests that T-DM1 should be considered as an end-of-life treatment. The evidence suggests that TDM-1 is likely to generate at least an additional three months of life compared to existing treatments; however, within the economic model, patients in all treatment groups were predicted to have more than 24 months life expectancy on average.

2. BACKGROUND

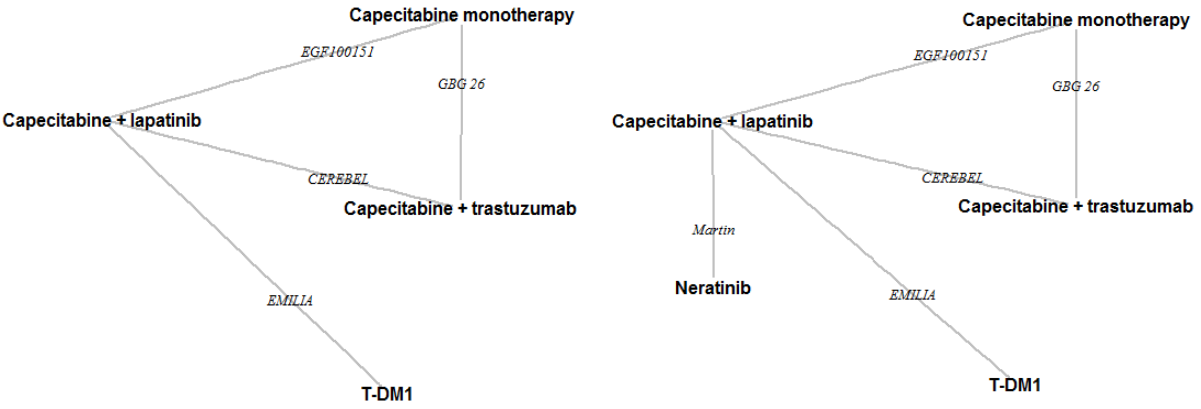
2.1 Original submission

Evidence relating to the clinical effectiveness and cost-effectiveness of T-DM1 in patients with HER2-positive, unresectable locally advanced or metastatic breast cancer whose disease has progressed after treatment with trastuzumab and a taxane was submitted to NICE and reviewed by the ERG in 2013 (https://www.nice.org.uk/guidance/ta371). There were two key randomised controlled trials (RCTs) of T-DM1: the EMILIA trial,[1] which compared T-DM1 versus capecitabine in combination with lapatinib, and; the TH3RESA trial,[2] which compared T-DM1 with treatment of physician's choice (TPC, consisting of chemotherapy, hormonal therapy, biologic drug and/or HER2-directed therapy). Both studies reported PFS, OS and AEs. The EMILIA trial had an interim data cut-off of January 2012 and July 2012 for PFS and OS, respectively. Up until this interim analysis, no switching between treatments was allowed.

Within the original submission, the results of these two RCTs suggested a significant advantage in PFS for T-DM1 over lapatinib in combination with capecitabine (P<0.0001) and TPC (P<0.0001). Data also reported a statistically significant advantage in OS (p=0.0006) and time to symptom worsening for T-DM1 compared with lapatinib in combination with capecitabine. The most common grade 3 or greater AEs for T-DM1 were thrombocytopenia and hepatotoxicity. The majority of patients in the trials had received two or more prior lines of therapy, whereas the company and clinical experts suggested T-DM1 as second-line treatment.

A network meta-analysis (NMA) was undertaken by the company to compare treatment effectiveness, for OS and PFS, as shown in
Figure 1 below. An additional treatment option, neratinib, was included within the network for PFS; however this was not included as a comparator within the analysis.

Figure 1: **Network of evidence for OS and PFS**



The TH3RESA trial was not included within this network meta-analysis (NMA) because patients were randomised to either T-DM1 or TPC and the selection of therapy within the TPC arm was made after randomisation. This means that there is no record of what therapy the patients randomised to T-DM1 would have received had they been randomised to the comparator arm. The company argued that 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, randomised comparison of T-DM1 and trastuzumab in combination with vinorelbine using this study. The ERG agreed that it was reasonable to exclude the TH3RESA trial from the NMA.

Within the original submission, the company employed a partitioned survival model including three health states: (i) progression-free; (ii) post-progression; and (iii) dead. T-DM1 was compared with: capecitabine; vinorelbine; trastuzumab in combination with capecitabine; trastuzumab in combination with vinorelbine, and; lapatinib in combination with capecitabine. The incremental cost-effectiveness results from the company's original base case analysis are presented in Table 1.

Table 1: Company's base case

Technologies	**Total**			**Incremental**			
	Costs (£)	**LYs**	**QALYs**	**Costs (£)**	**LYG**	**QALYs**	**ICER (Cost per QALY gained)**
Capecitabine	£11,850	1.61	0.89				
Vinorelbine	£16,518	1.61	0.89	£4,668	0.00	0.00	Dominated
Trastuzumab and capecitabine	£35,784	2.24	1.28	£19,266	0.63	0.40	Dominated
Trastuzumab and vinorelbine	£36,662	2.24	1.28	£878	1.61	0.89	Dominated
Lapatinib and capecitabine	£34,227	2.53	1.45	-£2,435	0.29	0.17	£39,449
T-DM1	£111,226	3.16	1.91	£76,999	0.63	0.46	£167,253

Whilst the ERG identified two key errors in model implementation and four key assumptions which were considered to be methodologically weak, the predicted ICERs remained similar.

3. ERG SUMMARY AND CRITIQUE OF NEW EVIDENCE SUBMITTED BY THE COMPANY

3.1 Methods used to critically appraise the company's model

The company submitted a document describing the key changes to the health economic model, an entirely new health economic model in Excel, an appendix describing a PAS and an appendix describing the new clinical data used in the model. The accompanying report did not provide sufficient information explaining what had been done in the economic model and why. An informal clarification process was undertaken which partially addressed this. However, for some model assumptions, the ERG needed to examine the model in an attempt to identify what the company had done; this does not provide justification for the company's approach, nor was it always clear whether a change in the model was intentional or not. The ERG employed a number of methods to explore and critically appraise the model. These included:

- Comparing the model parameters and assumptions in the new model with those in the original submission;
- Examination of the consistency between the description of the model reported within the company submission (where reported) and the executable model;
- Assessing the statistical validity and clinical plausibility of the trial data extrapolation and other model assumptions;
- Checking all formulae within the Excel model;
- The use of extreme values (e.g. zero for utilities/costs) to check for errors in the programming and logic of the model.

3.2 Summary of key differences between the original model and the new model

The key differences between the company's original model and the new model are:

1) The comparators in the NICE scope (i) lapatinib in combination with capecitabine, (ii) vinorelbine, and (iii) trastuzumab in combination with vinorelbine, were excluded from the incremental analysis (although (i) and (ii) have been included within a response to informal clarifications);
2) More than two additional years of follow-up (December 2014 data cut-off) from the EMILIA trial of TDM-1 and lapatinib in combination with capecitabine have been used to model overall survival (OS), time on treatment and adverse events (AEs). The original January 2012 data cut-off was used to model progression-free survival, although the parametric distribution used to extrapolate progression-free survival has been altered;
3) The network meta-analysis (NMA) has been updated to include the additional follow-up and has been adjusted for treatment switching;
4) The way in which AEs have been incorporated has been revised;

5) The way in which treatment duration is incorporated into the model has been revised;
6) A patient access scheme (PAS) has been incorporated;
7) Several changes in response to the ERG's critique of the original submission have been made:
    a. Extending the model time horizon from 10 to 15 years
    b. Including the cost of left ventricular ejection fraction monitoring follow up
    c. Intended correction of the utility values (although the ERG believe this is incorrect)
    d. Using the actual dosing of trastuzumab emtansine and lapatinib in combination with capecitabine rather than the planned dose
    e. Revising the parameters for the probabilistic sensitivity analysis (PSA)
    f. Estimation of the post-progression treatment costs

Each of the above are described and critiqued in section 3.3.

3.3 Comparison of the submitted model scope with the original NICE scope

The population, intervention and outcomes of the model are in line with the original NICE scope. However, the company has excluded some of the comparators which were listed in the original NICE scope, as shown in Table 2.

Table 2: Comparators in the NICE scope and the company submission

NICE scope	Company CDF review submission	Reason provided
Lapatinib in combination with capecitabine	Lapatinib in combination with capecitabine was excluded from the full incremental analysis, although estimated costs, LYs and QALYs are provided within the submission.	Lapatinib was delisted from the CDF in January 2015 and no longer represents current practice in England, with lapatinib-containing regimens taking only around 8% of the market share in 2015.
Capecitabine	Capecitabine	N/A
Vinorelbine	Not included within the model	No justification for the exclusion of vinorelbine was provided by the company. However, within the original company submission it was assumed that the effectiveness and AE profile of vinorelbine was equivalent to that of capecitabine. Given that vinorelbine costs more than capecitabine, it is expected to be dominated by treatment with capecitabine.
Trastuzumab in combination with capecitabine	Trastuzumab in combination with capecitabine	N/A
Trastuzumab in combination with vinorelbine	Not included within the model	See reason provided for vinorelbine.

The ERG considers that all relevant options should be included within a full incremental analysis. Lapatinib is a licensed treatment option for this indication and was included (in combination with capecitabine) in the original NICE scope. This is discussed further in Section 3.11.

3.4 Treatment effectiveness and extrapolation

3.4.1 Progression-free survival

3.4.1.1 Progression-free survival network meta-analysis

The CS includes results of an NMA of PFS hazard ratios, which have altered marginally compared to the original submission, although the PFS data have not been updated and there is no description of any change to the analysis. No details were provided regarding the goodness-of-fit, inconsistency between direct and indirect evidence in the feedback loop, the magnitude of the between-study standard deviation, or whether the mean of the random effects distribution or the predictive distribution of a new study is used to characterise uncertainty in the economic model.

3.4.1.2 Progression-free survival estimates for T-DM1 and lapatinib in combination with capecitabine

The PFS data used within the model did not change from the original submission because no additional PFS data was collected within the EMILIA trial (informal clarification with the company, question 1). However, the company has revised their assumptions around the extrapolation of the survivor function.

The company fitted five standard parametric distributions to the PFS data which were all members of the Generalised F distribution family (i.e. gamma, Weibull, log normal exponential and log-logistic distributions).[*] Independent parametric survival models were fitted to each arm of the EMILIA trial. An assessment of the relative goodness-of-fit of each distribution was made using the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC). No assessment was made of the absolute goodness-of-fit of each distribution, for example by using Cox Snell residuals. The log normal distribution provided the best fit to the observed data (BIC 2112.6) and there was strong evidence based on the differences in BIC to suggest that this is the preferred model of those considered compared with the gamma distribution (BIC 2119.3) and log-logistic distribution (BIC 2122.1). The choice of distribution was also made based on a visual inspection of the fitted survivor functions.

[*] Throughout both the original submission and the current submission where a generalised gamma distribution is used, the company have described it as a gamma distribution. For consistency, the term 'gamma' has therefore been used throughout to mean 'generalised gamma'. A two parameter gamma distribution has not been used within the submission.

Within the original submission, the base case PFS for both T-DM1 and lapatinib in combination with capecitabine was based on a Kaplan-Meier survivor function estimated from the observed data with a log normal distribution used to represent the tail of the survivor function. Within the current submission, the company's base case analysis of PFS is based on Kaplan-Meier survivor functions estimated from the observed data (up to week 74), and a gamma distribution fitted to the observed data but applied to the tail of the T-DM1 survivor function (from 72 weeks), and a gamma distribution fitted to the observed data but applied to the tail of the lapatinib in combination with capecitabine survivor function (from 52 weeks) to characterise the unobserved periods. This was described incorrectly within the company submission, but was corrected in the informal clarification response to question 1. Within this response the company stated that the time points for the two groups were chosen because these were the points at which the hazards start to become erratic by inspection of the cumulative hazard plots. The ERG were unable to verify this as no information was presented on the empirical hazard functions. A gamma distribution was used in preference to a log normal distribution because the log normal distribution had a slightly longer tail. In response to a request for clarification by the ERG (see clarification response, question 1), the company justified the use of the Kaplan-Meier survivor function by stating that "*the parametric functions appear to overestimate PFS in the comparator arm but underestimate the PFS in the intervention arm.*"

The ERG has a preference for using parametric models rather than a combination of Kaplan-Meier survivor functions and parametric distributions fitted to the tails of the survivor functions to represent uncertainty in the PSA; the former captures parameter uncertainty while the latter would be based on a mixture of sampling variation and parameter uncertainty. In the CS, the company did not incorporate uncertainty associated with the Kaplan-Meier survivor function, which means that the estimate of the ICER would be biased in the case of any non-linearity in the model and not adequately capture uncertainty.

3.4.2 Overall survival

OS within the original submission was based upon the July 2012 data cut from the EMILIA trial. The company submitted new data from the EMILIA trial based on a data cut of December 2014.

3.4.2.1 Overall survival network meta-analysis

The company's submission states that the OS NMA was updated; however, no further detail was provided. In response to clarification question 3, the company confirmed that the original NMA was re-run using a random effects model of log hazard ratios from the same five studies used in the original submission but using data from the December 2014 data-cut. Two analyses of OS were performed: one using ITT log hazard ratios and one using log hazard ratios adjusted for treatment

switching in EMILIA and Cameron et al., 2008[3]. While a hazard ratio may be sufficient for making inferences about relative effectiveness based on the observed data, it is not necessarily sufficient as a basis for estimating mean OS. For a hazard ratio to be relevant for estimating OS a justification must be made for the proportional hazards assumption over the lifetime of the patients, which was not provided witin the CS.

Hazard ratios estimated from the NMA are not used to estimate the survivor functions for both lapatinib in combination with capecitabine and TDM-1; this is discussed further in Section 3.4.2.3. Within sensitivity analysis, the ERG assesses the impact of using the hazard ratios directly.

3.4.2.2 Adjusting for treatment switching

Within the base case analysis, the company adjusted the treatment effect within the lapatinib in combination with capecitabine arm to account for patient switching to T-DM1. Given that 27% of patients switched from lapatinib in combination with capecitabine to T-DM1 within EMILIA (December 2014 data cut), a treatment effect estimated using an ITT analysis is likely to underestimate the treatment effect of T-DM1 relative to lapatinib in combination with capecitabine, if patients who switched received a greater survival benefit from T-DM1 than they would have received if they had not switched. Hence, it is appropriate to apply treatment switching adjustment methods to obtain an estimate of what the treatment effect would have been in the absence of switching.

The company chose a Rank Preserving Structural Failure Time model (RPSFTM) approach with recensoring within the base case analysis. The text states that there was a single solution for psi (ψ) which suggests that the model has performed well (where ψ equals the –ln(acceleration factor)). The company presented a log-rank Z statistic plot depicting the log-rank Z statistic as a monotonically increasing function of psi. When the RPSFTM is performed using the Strbee package in Stata and there is a single solution of psi, the line on the log-rank Z statistic plot produced in the output would be expected to slope downwards. The ERG requested a justification for the upward sloping line. The company explained that it is due to the calculation of the log-rank test, in which the sign of the log-rank statistic depends upon which way around the lapatinib in combination with capecitabine arm to the TDM-1 arm comparison was made. The ERG accepts this as a plausible explanation for the upward sloping plot, particularly as the analysis was not performed in Stata, so that the automated Strbee output would not have been used.

Within the lapatinib in combination with capecitabine group, switching to T-DM1 was likely to depend on prognostic factors, and if T-DM1 extends survival for those patients, they were also more likely to have their survival time censored; hence, censoring may be informative. Recensoring aims to break the dependency between the treatment received and the time of censoring at the earliest possible

time given the treatment effect. It should be applied to all patients who were randomised to the lapatinib in combination with capecitabine group. In the CS it is stated that recensoring was applied to the RPSFTM in the following way: *"distinguish patients who were censored due to reasons other than data cutoff (e.g. loss to follow up). Replace datacut time with actual censoring time for patients who were censored (4)."* This appears to be a misinterpretation of the recensoring defined in the White (2002) reference cited in the CS; hence, the ERG could not be certain that recensoring was applied correctly.

During the clarification process, the ERG requested that the company provide an assessment of the impact of recensoring on survival times and deaths. In response, the company provided a comparison of the number of censored patients and deaths for the ITT analysis and recensored RPSFTM. As would be expected, the number of deaths in the recensored RPSFTM analysis is fewer and the number of patients censored is higher than in the ITT analysis. However, the company dis not assess whether any changes in the treatment effect over time could affect the hazard ratio when recensoring is applied. Hence, the reduction in the hazard ratio of the RPSFTM with recensoring compared with the RPSFTM without recensoring could be a direct result of the earlier censoring times. Therefore, the ERG cannot assess whether the application of recensoring in this case is likely to reduce bias or exacerbate bias in the RPSFTM hazard ratio estimates.

The pivotal assumption underpinning RPSFTM is the common treatment effect assumption (otherwise termed constant treatment effect assumption). Although there are no definitive tests of whether or not the common treatment effect assumption holds, its plausibility can usually be assessed in some way. During the informal clarification process, question 4, the ERG asked the company to provide additional analyses to assess the plausibility of the common treatment effect. The company provided an assessment of the sensitivity of the hazard ratio to the common treatment effect assumption. The analysis shows that when the relative efficacy of post-switching to pre-switching treatment with T-DM1 is reduced to 75%, the adjusted hazard ratio is around 0.71, compared with 0.69 in the base case. The ERG consulted a clinician regarding the plausibility of the common treatment effect assumption. The clinician expected the duration of response to decline with each line of treatment. On this basis, the ERG suggests that a slightly higher hazard ratio than that used in the base case would be more plausible, as this would reflect the likely reduced relative efficacy of the treatment post-switch.

Within the CS, it is stated that the Inverse Probability of Censoring Weight (IPCW) and the two-stage method could not be applied due to lack of appropriate data, however the ERG does not consider this justification convincing. The company should have assessed the length of time (in days/months) between the end of the study treatment and start of treatment switching. A large gap, where time dependent confounding is likely to occur, could have acted as justification. In most cases, it may be

reasonable to assume that the last recorded observation can be carried forward over subsequent time periods. There was no discussion of the availability of data beyond the end of study treatment for patients that did not switch treatments.

In the response to clarification question 4, the company stated that treatment switching could occur at anytime during the trial; however, treatment switching did not occur prior to the July 2012 data-cut. Therefore, the company could have assessed the possibility of applying the 2-stage method with July 2012 as the secondary baseline. Within the CS, it is stated that: *"A key assumption of the two-stage method (6) is that an appropriate "second baseline" can be defined in the context of the trial and that treatment switching only occurs at this time point."* However, it is possible to apply the method under the assumption that no additional confounding occurs between the secondary baseline and time of switch. If switches occur close to the secondary baseline, the assumption may be plausible. The justification for not applying the IPCW and 2 stage methods provided by the company were inadequate.

Overall, based on the description of the application of the RPSFTM analysis (which excludes recensoring) in the CS and the company's responses to the ERG's clarification questions, the ERG is reasonably confident that RPSFTM has been applied correctly. However, the ERG is concerned that there may have been a misinterpretation regarding the application of recensoring and is also unclear about the impact of recensoring on the estimated hazard ratio. Furthermore, clinical advice received by the ERG suggests that it was likely that the treatment effect in patients who switched treatments would be lower than for those originally randomised to T-DM1; hence the RPSFTM approach, which relies upon the common treatment effect, would be likely to overestimate the treatment benefit of T-DM1 compared to lapatinib in combination with capecitabine. Given these issues, the ERG has performed a conservative sensitivity analysis which does not adjust for treatment switching to assess the impact of these assumptions upon the model results.

3.4.2.3 Extrapolation of OS

The derivation of the OS survivor functions is done differently for lapatinib in combination with capecitabine and TDM-1 compared to trastuzumab plus capecitabine and capecitabine alone.

Firstly, a model for the OS data is generated for the baseline treatment. Within the original submission, the company used a gamma distribution to model the OS data. In the new submission, the company used a gamma distribution (BIC 2272), although the loglogistic (BIC 2265) and log normal (BIC 2267) distributions both provided a better fit to the observed data. Within their response to clarification question 3, the company suggested that the gamma distribution was chosen because its shorter tail was considered to be more clinically reasonable. After 10 years, within the T-DM1 group, the gamma distribution estimates that 5.4% of patients will remain alive compared with 7.5% and 7.8% for the loglogistic and log normal distributions respectively.

Table 9 [sic] on page 34 of the CS suggests that the T-DM1 survivor function does not make use of the additional evidence available in the later data cut of EMILIA. However, based upon the ERG's review of the economic model and confirmation within a clarification response (question 4), this is incorrect and the base case analysis includes the additional evidence and an adjustment for treatment switching.

Within the model, the OS survivor functions for lapatinib in combination with capecitabine and T-DM1 are based upon hard-coded results of a time-to-event analysis performed in SAS, presented with and without adjustment for crossover, with lapatinib in combination with capecitabine defined as the baseline treatment and a treatment effect estimated for T-DM1; thus, it is not possible for the ERG to comment on the validity of the analysis or the origin of the parameter estimates but these are most likely based on the EMILIA data. The survivor function for T-DM1 was derived by projecting the T-DM1 treatment effect on to the survivor function for lapatinib in combination with capecitabine from this analysis. The survivor functions for trastuzumab plus capecitabine and capecitabine alone are derived by projecting the hazard ratios from the NMA for the effect of treatment relative to TDM-1 on to the derived TDM-1 survivor function.

There are several issues associated with the approach used to estimate the survivor functions for each treatment. Firstly, it is not necessarily appropriate to use data from an arm of a treatment to represent the survivor function of the target patient population, although such data might be relevant, particularly in the absence of any external evidence. Secondly, the approach has effectively made use of two baseline treatments corresponding to the treatments in the EMILIA study. If the survivor function based on treatment with lapatinib in combination with capecitabine had been used as the baseline treatment then the survivor functions for all other treatments could have been derived using

the hazard ratios from the NMA. Thirdly, by using the hazard ratios from the NMA for trastuzumab plus capecitabine and capecitabine alone but not for T-DM1, the joint distribution for the effect of each treatment relative to lapatinib in combination with capecitabine is not preserved; in addition to the impact of ignoring correlation, the uncertainty associated with T-DM1 is likely to be under-estimated. A further issue concerns the use of the samples from the Markov chain Monte Carlo (MCMC) simulation used in the estimates of parameters in the NMA. Rather than taking sufficient samples and using these as a look-up table, the company has randomly sampled the draws from the MCMC simulation.

3.4.3 Key differences around the effectiveness data and assumptions

The changes to the effectiveness data used and assumptions compared with the original company's submission are shown within Table 3.

Table 3: Effectiveness data and assumptions

	Original submission	Current submission
PFS – data cut used	January 2012	January 2012
PFS extrapolation – lapatinib in combination with capecitabine	KM survivor function until week 72, log normal for tail of the curve	KM survivor function until week 74, gamma for tail of the curve
PFS extrapolation – T-DM1	KM survivor function until week 72, log normal for tail of the curve	KM survivor function until week 52, gamma for tail of the curve
OS – data cut used	July 2012	December 2014
OS extrapolation – lapatinib in combination with capecitabine	Gamma distribution	Data adjusted for treatment switching, Gamma distribution
OS extrapolation – T-DM1	Gamma distribution	Gamma distribution
NMA for PFS	Fixed effects model. Cerebral, GBG 26, EGF199151, Neratinib, EMILIA data cut January 2012.	Random effects model. Cerebral, GBG 26, EGF199151, Neratinib, EMILIA data cut January 2012.
NMA for OS	Fixed effects model. Cerebral, GBG 26, EGF199151, EMILIA data cut July 2012.	Random effects model. Cerebral, GBG 26, EGF199151, EMILIA data cut Dec 2014.

3.5 Adverse events

The appendix to the current company's submission provides information about AE rates from EMILIA and TH3RESA. There was no substantial increase in grade 3 or higher AEs within the December 2014 data cut compared with the interim analyses. Grade 1 and 2 AEs are not mentioned within the current submission.

The way in which AEs associated with trastuzumab in combination with capecitabine and capecitabine monotherapy are incorporated into the model has been altered from the original submission. Within the original submission, costs and utilities associated with AEs were assumed to

be the same as those for lapatinib in combination with capecitabine. Within the current CS, AE rates from the five trials included in the evidence base have been used to estimate the probability of each AE for each treatment, although they are estimated using an arm based approach rather than a study based approach, which is not recommended. Within the original model, only costs associated with diarrhoea and fatigue were included. Within the new model, costs associated with febrile neutropenia, vomiting and thrombocytopenia have now also been included because they were found to occur in more than 2% of the patients within the arms of the trials (the criteria by which AEs were included in the original submission).

As in the original submission, the cost of AEs is assumed to be spread equally over the remaining time by dividing the total probabilities by the time at risk. However, the time at risk of AEs for trastuzumab in combination with capecitabine and capecitabine monotherapy is assumed to be the same as that of lapatinib in combination with capecitabine. This means that the data for the numerator and denominator for this calculation are now inconsistent where they were previously consistent (though both based on another treatment pathway). In addition, there is no information within the CS to determine whether the time at risk in all arms is defined by PFS or time on treatment. However, as shown within the original submission, the costs and utilities associated with AEs do not have a substantial impact upon the model results.

3.6 Health-related quality of life

The company have not used any additional data to estimate quality of life compared with their original submission. The company state that they have corrected an error from the original submission highlighted by the ERG when using the study by Lloyd et al.[4] to predict utilities. Using this study, the utility associated with PFS in the absence of AEs is calculated, weighted according to response, and then the weighted disutility associated with AEs is subtracted. However, the ERG believes that this is still implemented incorrectly, because the mixed model by Lloyd et al.[4] should have been used to calculate the utilities associated with all possible states and then to weight them, which would lead to slightly different utilities. In addition, the concern raised by the ERG within the original report that the AEs included within the study by Lloyd et al. are not directly comparable with the serious adverse events experienced by patients on T-DM1 or its comparators remains. However, given that the impact of AEs on utilities is minimal, the impact of these issues upon the model results is expected to be negligible.

Table 4 shows the revised utilities for each health state compared with those from the original submission. The impact of alternative utility values is tested within the ERG's sensitivity analysis.

Table 4: Utilities from the original submission and the current submission

	Original submission	Current submission	Difference (increase)
PFS: T-DM1	0.78	0.807	0.027
PFS: lapatinib + capecitabine	0.74	0.8	0.06
PFS: trastuzumab + capecitabine	0.73	0.8	0.07
PFS: capecitabine	0.72	0.792	0.072
Progressed	0.5	0.53	0.03

3.7 Treatment costs and Patient Access Scheme

3.7.1 Time on treatment

In the CS, time on treatment for patients on T-DM1 and lapatinib in combination with capecitabine has now been estimated based upon the extrapolation of treatment duration within the EMILIA trial. This new analysis is not well described within the company submission; however, based on examination of the model and informal clarification responses provided by the company, it has been estimated using the same approach as for PFS and OS (see Section 3.4) and is based on the December 2014 data cut of the EMILIA trial. It is estimated independently of PFS and then limited to be no greater than PFS. This approach means that patients can remain in PFS whilst bearing no treatment costs. As for PFS, the Kaplan-Meier survivor function for time on treatment is used directly for the first few months and then a gamma distribution is applied beyond that time period. It is unclear why for PFS the Kaplan-Meier survivor function is used until months 17 and 12 for T-DM1 and lapatinib in combination with capecitabine, respectively, whilst for time on treatment, the Kaplan-Meier survivor function is applied until months 36 and 17, respectively. Time on treatment for patients on trastuzumab in combination with capecitabine and capecitabine monotherapy is assumed to be equivalent to PFS, which is inconsistent with the other treatment options. This will impact only on the ICER comparing lapatinib in combination with capectiabine with capecitabine monotherapy. Since capecitabine is relatively inexpensive, this assumption is unlikely to impact substantially upon the ICER.

Within the model, patients spend an average of about 7 weeks in PFS and not on treatment. Within an informal clarification the company suggested that there are other reasons why patients discontinue treatment other than progression. These include AEs, death, loss to follow up, physician or patient decision to discontinue treatment, and termination of clinical study. Clinical advisors to the ERG suggest that it is clinically plausible that some patients would remain progression-free whilst not on treatment for this time period.

3.7.2 Treatment costs

Within the original ERG report, the ERG suggested using the actual dose rather than the planned dose of treatment within the base case where possible. The company has attempted to calculate the actual dose by using the average dose from the EMILIA trial to estimate average vial usage within their base case. However, this results in the same cost as the planned dose estimate for T-DM1 (£4,267) which was used in the original company submission, since in both cases it results in the assumption that one 160g vial and one 100mg vial is used per peson per administration, and does not account for the distribution of patient weight. The company has also obtained the patient-level data for patient weight from the EMILIA trial to estimate planned vial usage more accurately to account for the variability in patient weight, although this does not account for dose reductions and treatment breaks. This approach results in a cost per cycle for T-DM1 of £4,963 with no vial sharing. The ERG has tested the impact of using the patient-level data to account for variability around vial usage within a sensitivity analysis (see Section 4.2).

3.7.3 Patient Access Scheme (PAS)

The company has proposed a PAS in which the NHS will pay for T-DM1 up to the first 14 months of treatment for each patient, and the company will pay for T-DM1 for any patients remaining on treatment beyond 14 months. The company predicts that 28% of patients will still be on treatment at 14 months. This has been appropriately implemented within the company's model.

The submission highlights that the PAS will be associated with administration costs. These costs are calculated based on the assumption that 135 trusts will purchase T-DM1 for this indication. The estimated total administration costs for England include a one-off implementation cost of £14,924 and operation costs of £25,332 per year. These costs were not included initially, but they have subsequently been incorporated into the model by the company during the informal clarification process. The inclusion of these costs has a minimal impact upon the model results.

3.8 Other amendments to costs

3.8.1 Inclusion of left ventricular ejection fraction monitoring follow up cost

As suggested by the ERG within the original appraisal, a cost of £130 every three months was added to the model, based on an economic analysis undertaken to support NICE Clinical Guidelines 81. This was incorporated within the model appropriately, and does not substantially affect the model results.

3.8.2 Post-progression treatment cost implementation

Within the original model critique, the ERG stated that: *"the method used by the company assumes the weekly cost in the progressed disease state is independent of treatment. This results in those treatments, such as T-DM1, where patients spend a longer duration in the progressed disease state,*

being associated with greater costs than those with shorter durations, despite having similar post-progression treatments." The CS suggests that the company has amended this; however, based upon a review of the model, the ERG believes that rather than applying a weekly cost, the new analysis applies an average cost at the point of progression to account for the individual's entire post-progression treatment. This is therefore not discounted correctly and does not account for patients dying prior to completing the post-progression treatment. Moreover, there is an error in the calculation of the average cost of post-progression treatment. The original model assumed that after progression, based on the EMILIA trial, first-line patients (12%) are assumed to receive 38 weeks of treatment (19 weeks on vinorelbine and 19 weeks on capecitabine); second-line patients (36%) are assumed to receive 19 weeks of treatment (half on capecitabine and half on vinorelbine), and; those failing on third-line (52%) are assumed to receive no further active treatment following progression. The current model estimates only the cost of 50% of patients who are assumed to be on second-line treatment and does not include the cost of post-progression treatment following first-line treatment. This cost is therefore underestimated. The ERG has corrected the formula to reflect the above assumptions within their revised base case, although the other issues associated with the calculation of post-progression treatment costs have not been resolved.

3.8.3 Uplifting of cost

The company state that all costs within the model have been uplifted to 2014/15 prices. This has generally been done throughout appropriately, although some costs have not been uplifted. This is unlikely to substantially affect the model results.

3.9 Time horizon

As suggested by the ERG within the original appraisal, the company has extended the model time horizon from 10 years to 15 years to account for a substantial proportion of patients who are estimated to remain alive at 10 years. This has been implemented in the model appropriately.

3.10 Sensitivity analysis

The CS suggests that the probabilistic sensitivity analysis (PSA) has been improved within the model. In response to informal clarification question 7, the company stated that the PSA made *"use of joint posterior distribution of (log) hazard ratios from the random effects NMA using Convergence Diagnostic and Output Analysis (CODA) samples directly from WinBUGS… …The CODA samples are randomly sampled in the PSA."* As discussed in Section 3.4.2, this was only done for the comparators trastuzumab in combination with capecitabine and capecitabine monotherapy. Using the CODA samples preserves the underlying joint distribution between treatment effects, which is not dealt with in the case of the other comparators. In addition, the samples should be used row by row (corresponding to the Markov chain Monte Carlo (MCMC) iteration) rather than sampling the draws

from the Markov chain. The company state that they have incorporated uncertainty around the treatment duration extrapolation using the Cholesky decomposition matrix, although it was acknowledged during informal clarification that for both treatment duration and PFS no uncertainty is assumed for the first few months where the Kaplan-Meier survivor functions are applied. Finally, AE proportions were associated with some uncertainty, although based upon review of the model this appears to be arbitrary.

The ERG identified two cell referencing errors within the 'simulation' model worksheet, whereby the incorrect input values for the PSA were being used for the costs and utilities associated with capecitabine. This has only a minor impact upon the probabilistic model results. However, the ERG also notes that within a small number of the Monte Carlo simulation runs, the estimated life years and QALYs associated with capecitabine are vastly overestimated, which leads to the expected values being overestimated. Given the time and resource constraints for this work, and given the other issues with the PSA discussed above, the ERG has chosen not to amend this within the model and instead focus upon the deterministic analyses.

The company also submitted sensitivity analyses around the time horizon, left ventricular ejection fraction (LVEF) cost, utility values and treatment dose, which assess the impact of including the individual values from the original model upon the model results. However, within this analysis T-DM1 was compared with trastuzumab in combination with capecitabine, this is inappropriate as this comparator is ruled out due to extended dominance (see Section 3.11 below).

3.11 Cost-effectiveness results

The company's model results presented in the new submission do not include lapatinib in combination with capecitabine, trastuzumab in combination with vinorelbine or vinorelbine monotherapy; these options were all listed as comparators within the NICE scope. Within the CS, the company argue that they have excluded the former because lapatinib was delisted from the CDF in January 2015 and no longer represents current practice in England, with lapatinib-containing regimens taking only around 8% of the market share in 2015. In response to a request for clarification (question number 6), the company explained that vinorelbine was also excluded because it no longer represents current practice.

The deterministic incremental cost-effectiveness results with and without the PAS submitted within the report by the company are shown in Table 5 and Table 6. These tables show that the costs associated with T-DM1 per patient on average are £100,628, reducing to [redacted] when the PAS is included. They also show that T-DM1 is predicted by the model to be associated with 3.32 life years and 2.09 QALYs. The ICER for T-DM1 in Table 6 is incorrect, because when the PAS for T-DM1 is

incorporated, trastuzumab in combination with capecitabine becomes extendedly dominated, and therefore the ICER for T-DM1 versus the next best non-dominated option (capecitabine) is estimated to be [redacted] per QALY gained.

Table 5: Company's deterministic new base case without patient access scheme

Technologies	Totals			Incrementals			
	Costs (£)	**LYs**	**QALYs**	**Costs (£)**	**LYG**	**QALYs**	**ICER (Cost per QALY gained)**
Capecitabine	£13,424	2.06	1.20				
Trastuzumab and capecitabine	£36,834	2.41	1.45	£23,410	0.35	0.25	£93,640
T-DM1	£100,628	3.32	2.09	£63,794	0.91	0.64	£99,678

Table 6: Company's deterministic new base case with patient access scheme

Technologies	Totals			Incrementals			
	Costs (£)	**LYs**	**QALYs**	**Costs (£)**	**LYG**	**QALYs**	**ICER (Cost per QALY gained)**
Capecitabine	£13,424	2.06	1.20				
Trastuzumab and capecitabine	£36,833	2.41	1.45	£23,409	0.35	0.25	£93,636
T-DM1	[redacted]	3.32	2.09	[redacted]	0.91	0.64	[redacted]

The ERG considers that all relevant options should be included within a full incremental analysis. Given that lapatinib and vinorelbine are licensed for this indication and were included in the original NICE scope, the ERG considers that they should be considered within a full incremental analysis. Within the informal clarification process, the company provided another analysis which included the comparators laptinib in combination with capecitabine and vinorelbine. Within this analysis, the company also included the initial and operational costs associated with the PAS and the correction of an error that they identified around the duration of capecitabine and vinorelbine post-progression treatment, both of which affected the ICERs by less than £100. The results presented in the clarification response do not exactly match those within the accompanying model. In addition, the incremental results within the clarification responses have been calculated incorrectly. The ERG has therefore reported the results from the model and recalculated the ICERs, as shown in Table 7 and

The probabilistic results, shown in Table 8, are similar to the determininstic results, except for the life years and QALYs associated with capecitabine, which result in a higher ICER for lapatinib in combination with capecitabine of £60,065 per QALY gained compared with capecitabine monotherapy. This is due to the error discussed in Section 3.10 that within a small number of the Monte Carlo simulation runs, the estimated life years and QALYs associated with capecitabine are vastly overestimated, which leads to the expected values being overestimated.

Table 8 for the deterministic and probabilistic analyses, respectively. Vinorelbine is not incorporated within the submitted economic model. Table 7 therefore includes the costs, LYGs and QALYs associated with vinorelbine from the company responses to the clarification questions. This comparator is not expected to impact upon the results associated with T-DM1 because it is assumed to be equally effective to capecitabine whilst also being more expensive (hence, it is dominated by capecitabine) and is included here for completeness. Vinorelbine has therefore been excluded from all subsequent analysis.

As shown in Table 7, the company's model suggests that both vinorelbine and trastuzumab in combination with capecitabine are expected to be ruled out due to dominance. T-DM1 is associated with a deterministic ICER of [redacted] per QALY gained compared with lapatinib in combination with capecitabine, the latter of which has an ICER of £49,061 per QALY gained compared with capecitabine monotherapy.

Table 7: Incremental deterministic cost effectiveness results including the PAS

Technologies	**Totals**			**Incrementals**			
	Costs (£)	**LYs**	**QALYs**	**Costs (£)**	**LYG**	**QALYs**	**ICER (Cost per QALY gained)**
Capecitabine	£13,425	2.06	1.20	-	-	-	-
Vinorelbine	£23,649	2.06	1.20	£8201	0	0	Dominated by cap
Trastuzumab and capecitabine	£36,834	2.41	1.45	-	-	-	Dominated by lap/cap
Lapatinib and capecitabine	£30,785	2.58	1.56	£17,360	0.52	0.35	£49,061
T-DM1	[redacted]	3.32	2.09	[redacted]	0.74	0.53	[redacted]

The probabilistic results, shown in Table 8, are similar to the determininstic results, except for the life years and QALYs associated with capecitabine, which result in a higher ICER for lapatinib in combination with capecitabine of £60,065 per QALY gained compared with capecitabine monotherapy. This is due to the error discussed in Section 3.10 that within a small number of the Monte Carlo simulation runs, the estimated life years and QALYs associated with capecitabine are vastly overestimated, which leads to the expected values being overestimated.

Table 8: Company's probabilistic new base case with patient access scheme

Technologies	**Totals**			**Incrementals**			
	Costs (£)	**LYs**	**QALYs**	**Costs (£)**	**LYG**	**QALYs**	**ICER (Cost per QALY gained)**
Capecitabine	£14,667	2.19	1.27	-	-	-	-
Trastuzumab and capecitabine	£39,208	2.55	1.52	-	-	-	Dominated by lap/cap
Lapatinib and capecitabine	£31,484	2.59	1.55	£16,817	0.40	0.28	£60,065
T-DM1	[redacted]	3.32	2.07	[redacted]	0.73	0.52	[redacted]

4. EXPLORATORY AND SENSITIVITY ANALYSIS UNDERTAKEN BY THE ERG

4.1 The ERG's suggested base case

The ERG has corrected the error around the calculation of the cost of post-progression treatment to produce a revised base case analysis, shown within Table 9. The ERG's base case results are very similar to the company's results, with the ERG's corrected calculation of the ICERs. All other alternative model assumptions are tested within a univariate sensitivity analysis in Section 4.2.

Table 9: ERG's deterministic new base case with patient access scheme

Technologies	Totals			Incrementals			
	Costs (£)	LYs	QALYs	Costs (£)	LYG	QALYs	ICER (Cost per QALY gained)
Capecitabine	£14,610	2.06	1.20				
Trastuzumab and capecitabine	£38,009	2.41	1.45				Dominated by lap/cap
Lapatinib and capecitabine	£31,958	2.58	1.56	£17,348	0.52	0.35	£49,025
T-DM1	[redacted]	3.32	2.09	[redacted]	0.74	0.53	[redacted]

4.2 Sensitivity analysis undertaken by the ERG

The ERG has limited the sensitivity analysis to explore those assumptions which were considered to impact substantially upon the model results by the ERG within their original report. These are:

- Whether wastage is included within the drug costs. The ERG have also tested the impact of incorporating treatment costs of T-DM1 and lapatinib in combination with capecitabine using the individual patient-level data on patient weight to estimate vial usage (see Section 3.7.2);
- The relative OS associated with the interventions. The ERG have also tested the impact of incorporating lapatinib in combination with capecitabine using a hazard ratio relative to T-DM1 rather than the SAS regression output hard coded within the model (see Section 3.4.2);
- The utility values associated with PFS and post-progression;
- The distribution employed for extrapolation of PFS and OS. The ERG have also tested the impact of not adjusting for treatment switching within the estimates of OS (see Section 3.4.2);
- Whether the treatment effect is assumed to continue beyond the trial data.

Results of these analyses are shown in Table 10 below.

Table 10: Results of ERG's univariate sensitivity analysis

Analysis (BC = Base case)	**Capecitabine**	**Trastuzumab and capecitabine**	**Lapatinib and capecitabine**	**T-DM1**
Base case	-	Dominated	£49,025	[redacted]
Treatment dose (*BC: Incl. wastage – actual estimate*)				
Excl. wastage – actual estimate	-	Dominated	£47,292	[redacted]
Incl. wastage - planned	-	Dominated	£49,679	[redacted]
Excl. wastage – planned	-	Dominated	£49,796	[redacted]
Incl. wastage – patient level weight data	-	Dominated	£49,883	[redacted]
Excl. wastage – patient level weight data	-	Dominated	£49,772	[redacted]
Lapatinib and capecitabine vs T-DM1 HR (*BC: No HR, use KM survivor function*)				
PFS 0.65, OS 0.69 (Means)	-	Extendedly dominated by lap/cap	Extendedly dominated by T-DM1	[redacted]
PFS 0.65 (Mean), OS 1.32 (Upper CrI)	-	Dominated by lap/cap	£17,206	Dominated by lap/cap
Trastatuzumab and capecitabine vs T-DM1 HR OS (*BC: 0.70)* 1.72 (Upper CrI)	-	£17,116	Extendedly dominated by trast/cap	Dominated by trast/cap
Capecitabine vs T-DM1 HR OS (*BC: 0.59*) 1.43 (Upper CrI)	Dominates comparators	Dominated by capecitabine	Dominated by capecitabine	Dominated by capecitabine
PFS utility: (*BC: See Table 4*)				
Same values as lapatinib and capecitabine in all arms	-	Dominated	£49,547	[redacted]
TH3RESA trial (0.71 T-DM1, 0.69 comparators)	-	Dominated	£55,622	[redacted]
Progressed utility (*BC: 0.530*) 0.730	-	Dominated	£44,772	[redacted]
PFS extrapolation (*BC: KM until 72 weeks+gamma tail*)				
As original submission (KM until 72 weeks+lognormal tail)	-	Dominated	£49,496	[redacted]
KM+Weibull tail	-	Dominated	£48,900	[redacted]
Weibull	-	Dominated	£48,647	[redacted]
OS extrapolation (*BC: Adjusting for treatment switching*)				
Not adjusting for treatment switching	-	Extendedly dominated by T-DM1	£68,213	[redacted]
PFS & OS of T-DM1 equivalent to lapatinib and capecitabine after week 72 and 4 years respectively	-	Dominated	£49,025	[redacted]

This analysis suggests that the key drivers of the model results are the treatment effect beyond trial follow up, the adjustment for treatment switching and the inclusion of vial wastage if patient-level data are used to estimate treatment costs. The ICER for T-DM1 does not fall below £64,000 per QALY gained for any of the analyses tested.

5. END OF LIFE

To meet NICE end of life criteria both of the below must be satisfied:

1) The treatment is indicated for patients with a short life expectancy, normally less than 24 months;
2) There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment.

Within the CS, the company makes the case that T-DM1 meets the end of life criteria. The company highlight that within the final appraisal document of this appraisal, the committee concluded that T-DM1 fulfilled the criterion for short life expectancy based on a standard of care of lapatinib in combination with capecitabine. However, the company suggest that the standard of care in England is now trastuzumab in combination with capecitabine, but argue that T-DM1 continues to meet the short life expectancy criterion.

Based upon the EMILIA trial[1], for the lapatinib in combination with capecitabine arm, 51.8% of patients remained alive at 24 months and patients had a median overall survival of 25.1 months from treatment initiation. Based upon the CEREBEL trial[5] of lapatinib in combination with capecitabine versus trastuzumab in combination with capecitabine, median survival was 22.7 months and 27.3 months respectively. However, not all patients within these trials were treated in the second-line setting as would be expected in practice, and hence the company argue that these may be overestimates. Within the economic model, patients in all arms were predicted to have more than 24 months life expectancy on average (see Table 7).

Within EMILIA, life expectancy was extended with T-DM1 by 5.8 months to a median overall survival of 30.9 months, with 64.7% of patients remaining alive at 24 months.

Thus the ERG believes that end of life criterion 2 would be met by T-DM1, whilst it is debatable whether criterion 1 is fulfilled.

6. CONCLUSIONS

A key driver of the ICER for T-DM1 is the inclusion or exclusion of lapatinib in combination with capecitabine as a comparator; this increases the ICER, including the PAS, from around [redacted] to [redacted] per QALY gained. The ICER for lapatinib in combination with capecitabine is around £49,000 per QALY gained compared with capecitabine monotherapy. There is substantial uncertainty around the results: within the ERG's univariate sensitivity analyses, the ICER for T-DM1 compared with lapatinib in combination with capecitabine ranged from [redacted] to [redacted] per QALY gained. Key drivers of the model results are the treatment effect beyond trial follow-up, the adjustment for treatment switching and the inclusion of vial wastage if patient-level data is used to estimate treatment costs. The company suggests that T-DM1 should be considered as an end-of-life treatment. The evidence suggests that TDM-1 is likely to generate at least an additional three months of life compared to existing treatments; however, within the economic model, patients in all treatment groups were predicted to have more than 24 months life expectancy on average.

7. REFERENCES

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Addendum to: T-DM1 for treating HER2-positive, unresectable locally advanced or metastatic breast cancer after treatment with trastuzumab and a taxane: A Cancer Drugs Fund review

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The ERG considers that all relevant options should be included within a full incremental analysis. Lapatinib is a licensed treatment option for this indication and was included (in combination with capecitabine) in the original NICE scope. This is discussed further in Section 3.11.

3.4 Treatment effectiveness and extrapolation

3.4.1 Progression-free survival

3.4.1.1 Progression-free survival network meta-analysis

The CS includes results of an NMA of PFS hazard ratios, which have altered marginally compared to the original submission, although the PFS data have not been updated and there is no description of any change to the analysis. No details were provided regarding the goodness-of-fit, inconsistency between direct and indirect evidence in the feedback loop, the magnitude of the between-study standard deviation, or whether the mean of the random effects distribution or the predictive distribution of a new study is used to characterise uncertainty in the economic model.

3.4.1.2 Progression-free survival estimates for T-DM1 and lapatinib in combination with capecitabine

The PFS data used within the model did not change from the original submission because no additional PFS data was collected within the EMILIA trial (informal clarification with the company, question 1). However, the company has revised their assumptions around the extrapolation of the survivor function.

The company fitted five standard parametric distributions to the PFS data which were all members of the Generalised F distribution family (i.e. gamma, Weibull, log normal exponential and log-logistic distributions).[*] Parametric survival curves were fitted as a covariate for each endpoint. An assessment of the relative goodness-of-fit of each distribution was made using the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC). No assessment was made of the absolute goodness-of-fit of each distribution, for example by using Cox Snell residuals. The log normal distribution provided the best fit to the observed data (BIC 2112.6) and there was strong evidence based on the differences in BIC to suggest that this is the preferred model of those considered compared with the gamma distribution (BIC 2119.3) and log-logistic distribution (BIC 2122.1). The choice of distribution was also made based on a visual inspection of the fitted survivor functions.

[*] Throughout both the original submission and the current submission where a generalised gamma distribution is used, the company have described it as a gamma distribution. For consistency, the term 'gamma' has therefore been used throughout to mean 'generalised gamma'. A two parameter gamma distribution has not been used within the submission.

the hazard ratios from the NMA. Thirdly, by using the hazard ratios from the NMA for trastuzumab plus capecitabine and capecitabine alone but not for T-DM1, the joint distribution for the effect of each treatment relative to lapatinib in combination with capecitabine is not preserved; in addition to the impact of ignoring correlation, the uncertainty associated with T-DM1 is likely to be under-estimated. A further issue concerns the use of the samples from the Markov chain Monte Carlo (MCMC) simulation used in the estimates of parameters in the NMA. Rather than taking sufficient samples and using these as a look-up table, the company has randomly sampled the draws from the MCMC simulation.

3.4.3 Key differences around the effectiveness data and assumptions

The changes to the effectiveness data used and assumptions compared with the original company's submission are shown within Table 3.

Table 1: Effectiveness data and assumptions

	Original submission	Current submission
PFS – data cut used	January 2012	January 2012
PFS extrapolation – lapatinib in combination with capecitabine	KM survivor function until week 72, log normal for tail of the curve	KM survivor function until week 52, gamma for tail of the curve
PFS extrapolation – T-DM1	KM survivor function until week 72, log normal for tail of the curve	KM survivor function until week 74, gamma for tail of the curve
OS – data cut used	July 2012	December 2014
OS extrapolation – lapatinib in combination with capecitabine	Gamma distribution	Data adjusted for treatment switching, Gamma distribution
OS extrapolation – T-DM1	Gamma distribution	Gamma distribution
NMA for PFS	Fixed effects model. Cerebral, GBG 26, EGF199151, Neratinib, EMILIA data cut January 2012.	Random effects model. Cerebral, GBG 26, EGF199151, Neratinib, EMILIA data cut January 2012.
NMA for OS	Fixed effects model. Cerebral, GBG 26, EGF199151, EMILIA data cut July 2012.	Random effects model. Cerebral, GBG 26, EGF199151, EMILIA data cut Dec 2014.

3.5 Adverse events

The appendix to the current company's submission provides information about AE rates from EMILIA and TH3RESA. There was no substantial increase in grade 3 or higher AEs within the December 2014 data cut compared with the interim analyses. Grade 1 and 2 AEs are not mentioned within the current submission.

The way in which AEs associated with trastuzumab in combination with capecitabine and capecitabine monotherapy are incorporated into the model has been altered from the original submission. Within the original submission, costs and utilities associated with AEs were assumed to

Table 2: Utilities from the original submission and the current submission

	Original submission	Current submission	Difference (increase)
PFS: T-DM1	0.78	0.807	0.027
PFS: lapatinib + capecitabine	0.74	0.8	0.06
PFS: trastuzumab + capecitabine	0.73	0.8	0.07
PFS: capecitabine	0.72	0.792	0.072
Progressed	0.5	0.53	0.03

3.7 Treatment costs and Patient Access Scheme

3.7.1 Time on treatment

In the CS, time on treatment for patients on T-DM1 and lapatinib in combination with capecitabine has now been estimated based upon the extrapolation of treatment duration within the EMILIA trial. This new analysis is not well described within the company submission; however, based on examination of the model and informal clarification responses provided by the company, it has been estimated using the same approach as for PFS and OS (see Section 3.4) and is based on the December 2014 data cut of the EMILIA trial. It is estimated independently of PFS and then limited to be no greater than PFS. This approach means that patients can remain in PFS whilst bearing no treatment costs. As for PFS, the Kaplan-Meier survivor function for time on treatment is used directly for the first few months and then a gamma distribution is applied beyond that time period. For PFS the Kaplan-Meier survivor function is used until months 17 and 12 for trastuzumab emtansine and lapatinib in combination with capecitabine, respectively. This is in line with previously accepted extrapolation for PFS in the original NICE appraisal where parametric extrapolation was applied after 72 weeks (approximately 17 months) which translated into 10% patients being at risk of disease progression. For time on treatment, the Kaplan-Meier survivor function is applied until months 36 and 17, for trastuzumab emtansine and Lapatinib in combination with Capecitabine respectively. Parametric extrapolation was applied when approximately 10% patients were at risk of treatment discontinuation. Time on treatment for patients on trastuzumab in combination with capecitabine and capecitabine monotherapy is assumed to be equivalent to PFS, which is inconsistent with the other treatment options. This will impact only on the ICER comparing lapatinib in combination with capectiabine with capecitabine monotherapy. Since capecitabine is relatively inexpensive, this assumption is unlikely to impact substantially upon the ICER.

Within the model, patients spend an average of about 7 weeks in PFS and not on treatment. Within an informal clarification the company suggested that there are other reasons why patients discontinue treatment other than progression. These include AEs, death, loss to follow up, physician or patient decision to discontinue treatment, and termination of clinical study. Clinical advisors to the ERG suggest that it is clinically plausible that some patients would remain progression-free whilst not on treatment for this time period.

(corresponding to the Markov chain Monte Carlo (MCMC) iteration) rather than sampling the draws from the Markov chain. The company state that they have incorporated uncertainty around the treatment duration extrapolation using the Cholesky decomposition matrix, although it was acknowledged during informal clarification that for both treatment duration and PFS no uncertainty is assumed for the first few months where the Kaplan-Meier survivor functions are applied. Finally, AE proportions were associated with some uncertainty, although based upon review of the model this appears to be arbitrary.

The ERG identified two cell referencing errors within the 'simulation' model worksheet, whereby the incorrect input values for the PSA were being used for the costs and utilities associated with capecitabine. This has only a minor impact upon the probabilistic model results. However, the ERG also notes that within a small number of the Monte Carlo simulation runs, the estimated life years and QALYs associated with capecitabine are vastly overestimated, which leads to the expected values being overestimated. Given the time and resource constraints for this work, and given the other issues with the PSA discussed above, the ERG has chosen not to amend this within the model and instead focus upon the deterministic analyses.

The company also submitted sensitivity analyses around the time horizon, left ventricular ejection fraction (LVEF) cost, utility values and treatment dose, which assess the impact of including the individual values from the original model upon the model results. However, within this analysis T-DM1 was compared with trastuzumab in combination with capecitabine, this is inappropriate as this comparator is ruled out due to extended dominance (see Section 3.11 below).

3.11 Cost-effectiveness results

The company's model results presented in the new submission do not include lapatinib in combination with capecitabine, trastuzumab in combination with vinorelbine or vinorelbine monotherapy; these options were all listed as comparators within the NICE scope. Within the CS, the company argue that they have excluded the former because lapatinib was delisted from the CDF in January 2015 and no longer represents current practice in England, with lapatinib-containing regimens taking only around 8% of the market share in 2015. In response to a request for clarification (question number 6), the company explained that vinorelbine was also excluded because it no longer represents current practice.

The deterministic incremental cost-effectiveness results with and without the PAS submitted within the report by the company are shown in Table 5 and Table 6. These tables show that the total costs associated with T-DM1 per patient on average are £100,628, reducing to [redacted] when the PAS is

5. END OF LIFE

To meet NICE end of life criteria both of the below must be satisfied:

1) The treatment is indicated for patients with a short life expectancy, normally less than 24 months;
2) There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment.

Within the CS, the company makes the case that T-DM1 meets the end of life criteria. The company highlight that within the final appraisal document of this appraisal, the committee concluded that T-DM1 fulfilled the criterion for short life expectancy based on a standard of care of lapatinib in combination with capecitabine. However, the company suggests that if T-DM1 were no longer to be funded then the standard of care would revert back to trastuzumab in combination with capecitabine, but argue that T-DM1 continues to meet the short life expectancy criterion.

Based upon the EMILIA trial[1], for the lapatinib in combination with capecitabine arm, 51.8% of patients remained alive at 24 months and patients had a median overall survival of 25.1 months from treatment initiation. Based upon the CEREBEL trial[5] of lapatinib in combination with capecitabine versus trastuzumab in combination with capecitabine, median survival was 22.7 months and 27.3 months respectively. However, not all patients within these trials were treated in the second-line setting as would be expected in practice, and hence the company argue that these may be overestimates. Within the economic model, patients in all arms were predicted to have more than 24 months life expectancy on average (see Table 7).

Within EMILIA, life expectancy was extended with T-DM1 by 5.8 months to a median overall survival of 30.9 months, with 64.7% of patients remaining alive at 24 months.

Thus the ERG believes that end of life criterion 2 would be met by T-DM1, whilst it is debatable whether criterion 1 is fulfilled.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Trastuzumab emtansine for the treatment of locally advanced or metastatic HER2-positive breast cancer after treatment with trastuzumab and a taxane (review of TA371) [ID1013]

You are asked to check the ERG report from ScHARR to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm, Monday 31 October 2016** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 – Exclusion of Herceptin in combination with Capecitabine as an appropriate comparator

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
It is felt to be incorrect that Herceptin in combination with capectiabine is excluded from the ERG's analysis while lapatinib in combination with capecitabine is included. Despite being unlicensed Herceptin is used post progression in clinical practice in combination with capecitabine. Lapatinib in combination with capectiabine is no longer funded in England and Wales, having lost CDF funding from March 2015, and therefore represents a small percentage ([redacted]) of the medicines patients treated at second line for mBC receive (Roche data on file December 2015).	Herceptin in combination with Capecitabine should be included as a comparator	In the Guide to methods of technology appraisal 2013 it states the following: *6.2.3 When the assessment suggests that an established practice may not be considered a good use of NHS resources relative to another available treatment, the Committee will decide whether to include it as an appropriate comparator in the appraisal, after reviewing an incremental cost–utility analysis. The Committee's overall decision on whether it is a valid comparator will be guided by whether it is recommended in other extant NICE guidance, and/or whether its use is so embedded in clinical practice that its use will continue unless and until it is replaced by a new technology. The Committee will also take into account the uncertainty associated with the estimates of clinical and cost effectiveness, and whether the new technology under appraisal could provide a cost-saving alternative* *6.2.4 The Appraisal Committee can consider as comparators technologies that do not have a marketing authorisation (or CE mark for medical devices) for the indication defined in the scope when they are considered to be part of established clinical practice for the indication in the NHS. Long-standing treatments often lack a sponsor to support the licensing process. Specifically when considering an 'unlicensed' medicine, the Appraisal Committee will have due regard for the extent and quality of evidence, particularly for safety and efficacy, for the unlicensed use.*	This is not a factual inaccuracy. The ERG has not excluded trastuzumab (Herceptin) in combination with capecitabine from the analysis. The estimates from the model, however, suggest that this comparator is more costly and less effective than lapatinib in combination with capecitabine i.e. it is dominated. Even if lapatinib in combination with capecitabine was excluded from the analysis as the company propose, trastuzumab in combination with capecitabine would be extendedly dominated by trastuzumab emtansine (with the patient access scheme). Please see the ERG report, Section 3.11 p19 – 22 for a discussion of this.

		Given that Kadcyla is currently funded through the CDF it currently represents standard of care. However, if Kadcyla was no longer available to patients, it is argued that Herceptin in combination with capecitabine would be the standard of care in England and Wales In the NICE appraisal of Lapatinib for the treatment of women with previously treated advanced or metastatic breast cancer [ID20] the committee considered Herceptin containing regimens as a relevant comparator. We feel it would therefore be inconsistent if it was not considered again in this appraisal.	

Issue 2 - 3.11

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Given that lapatinib and vinorelbine are licensed for this indication and were included in the original NICE scope, the ERG considers that they should be considered within a full incremental analysis	We do not feel Lapatinib should be included in the full incremental analysis.	The medicine is not available through a routine funding mechanism in England and Wales. Therefore there is no mechanism for Lapatinib to reach patients. Whereas off-label treatment has been part of an oncologist's treatment decision and as such both Herceptin and Capecitabine can be made available to a patient. We therefore this is the appropriate comparator.	This is not a factual inaccuracy. We have included within the report both the company's results (with ICERs recalculated correctly by the ERG) excluding lapatinib in combination with capecitabine and the ERGs preferred base case including lapatinib in combination with capecitabine.

Issue 3 - 3.4.1.2 Progression-free survival for T-DM1 and lapatinib in combination with capecitabine

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 8 it states that: "Independent parametric survival curves were fitted to each arm of the EMILIA trial"	"separate parametric survival models were fitted using treatment as a covariate for each endpoint" (this information was provided in our clarification response)	Clarification to provide correct data -there is no impact on the analysis	The ERG has amended this to 'parametric survival curves were fitted as a covariate for each endpoint'.

Issue 4 – 3.4.2.2 Adjusting for treatment switching

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 10 it states that ".. [recensoring] should be applied to all patients who were randomised to the lapatinib in combiniation with Capecitabine group" implying that Roche has not carried this out	"Recensoring was applied to all patients who were randomised to Lap/cap. The end of the study data cut off was specified for both censored and uncensored subjects. However, as suggested by White (2002), censoring due to random effects (e.g. loss to follow up) was treated differently from censoring at the end of the study. Actual time of random censoring was replaced only for patients who were censored due to reasons other than data cut off"	To clarify that recensoring was applied correctly	This is not a factual inaccuracy. Based on the description of recensoring provided, the ERG is not convinced that recensoring has been applied correctly.

On page 12 it states “In the response to clarification question 4, the company stated that treatment switching could occur at any time during the trial; however, treatment switching did not occur prior to the July 2012 data-cut. Therefore, the company could have assessed the possibility of applying the 2-stage method with July 2012 as the secondary baseline”		As stated in the Guidance Document by Green Park Collaborative “It should be noted that if the trial is stopped because of interim analysis results and control group patients are offered the opportunity to switch to the experimental treatment before reaching a patient level trigger event, the two-stage method might not usefully be employed” http://www.cmtpnet.org/docs/resources/Treatment_Switching_Guidance_Document_OCT_2016.pdf In the literature the secondary baseline is always defined as a clinically relevant patient endpoint e.g. progression where the patients are in some sense familiar. A fixed date like July 2012 does not make sense as the secondary baseline as it has no clinical reason.	
On page 12 is states “Overall, based on the description of the application of the RPSFTM analysis (which excludes recensoring) in the CS and the company’s responses to the ERG’s clarification questions, the ERG is reasonably confident that RPSFTM has been applied correctly”	“Overall, based on the description of the application of the RPSFTM analysis in the CS and the company’s responses to the ERG’s clarification questions, the ERG is reasonably confident that RPSFTM has been applied correctly”	Recensoring was not excluded. Recensoring was applied for administrative censoring (i.e. censoring at the data cut off point). For non-administrative censoring (i.e. drop out prior to the data cut off point) it was assumed that this was random and defined to the date of administrative censoring giving a random censoring date for this patients. This follows White (2002).	This is not a factual inaccuracy. Based on the description of recensoring provided, the ERG is not convinced that recensoring has been applied correctly.

Issue 5 - 3.4.3 Key differences around the effectiveness data and assumptions

Description of problem	Description of proposed amendment	Justification for amendment	
Error in table 3	In the current submission column it should state that for PFS extrapolation KM survival is used until week 52 in Lap/cap arm and 74 in trastuzumab emtansine arm (currently it is the other way around)		The ERG has corrected the two numbers in this table.

Issue 6 - 3.7.1 Time on treatment

Description of problem	Description of proposed amendment	Justification for amendment	
In the ERG report it states "It is unclear why for PFS the Kaplan-Meier survivor function is used until months 17 and 12 for T-DM1 and lapatinib in combination with capecitabine, respectively, whilst for time on treatment, the Kaplan-Meier survivor function is applied until months 36 and 17, respectively" however further clarification was offered in response to the clarification questions	"As for PFS, the Kaplan-Meier survivor function for time on treatment is used directly for the first few months and then a gamma distribution is applied beyond that time period. For PFS the Kaplan-Meier survivor function is used until months 17 and 12 for trastuzumab emtansine and lapatinib in combination with capecitabine, respectively. This is in line with previously accepted extrapolation for PFS in the original NICE appraisal where parametric extrapolation was applied after 72 weeks (approximately 17 months) which translated into 10% patients being at risk of disease progression For time on treatment, the Kaplan-Meier survivor function is applied until months 36 and 17, for trastuzumab emtansine and Lapatinib in combination with Capecitabine respectively. Parametric extrapolation was applied when approximately 10% patients were at risk of treatment discontinuation."	To incorporate clarification question response. Justification of the 10% assumption comes from the Pocock et al 2002	This is not a factual inaccuracy; however the ERG has amended the text as suggested by the company.

Issue 7 - 3.11 Cost-effectiveness results

Description of problem	Description of proposed amendment	Justification for amendment	
On page 20 it states that “These tables show that the cost associated with T-DM1 per patient are on average...”	“These tables show that the total cost associated with trastuzumab emtansine per patient are on average…”	It could be interpreted that the costs reported are associated with the cost of Kadclya alone	The ERG has added ‘total’ to this sentence as suggested.

Issue 8 – 5 End Of Life

Description of problem	Description of proposed amendment	Justification for amendment	
On page 26 it states that “the company suggests that the standard of care in England is now trastuzumab in combination with capectiabine…”	“the company suggests that if trastuzumab emtansine were no longer to be funded then the standard of care would revert back to trastuzumab in combination with Capecitabine…”	Kadcyla is the current standard of care in England	The ERG has amended this as suggested within the report.

Issue 9 - Terminology

Description of problem	Description of proposed amendment	Justification for amendment	
Throughout the document Kadcyla is referred to as T-DM1	The correct generic name for Kadcyla is trastuzumab emtansine		This is not a factual error. Throughout the report the ERG have used abbreviations which are clearly defined on first use and within an abbreviations list

			at the beginning of the report. This is one such abbreviation.

References

Pocock S. J., Clayton T. C., Altman. Survival plots of time-to-event outcomes in clinical trials *The lancet 2002*; 359 1686-1689

White I. R., Walker S. Babiker A. strbee: Randomization-based efficacy estimator *The stata Journal 2002;* 2; 2 140-150

NICE National Institute for Health and Care Excellence

NICE guidance

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

Technology appraisal guidance
Published: 16 December 2015
nice.org.uk/guidance/ta371

Contents

1 Guidance

1.1 Trastuzumab emtansine is not recommended, within its marketing authorisation, for treating adults with human epidermal growth factor 2 (HER2) positive, unresectable locally advanced or metastatic breast cancer previously treated with trastuzumab and a taxane.

1.2 People currently receiving treatment initiated within the NHS with trastuzumab emtansine that is not recommended for them by NICE in this guidance should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

2 The technology

2.1 Trastuzumab emtansine (Kadcyla, Roche) is an antibody–drug conjugate consisting of trastuzumab linked to maytansine, which is a cytotoxic agent. Because the antibody targets human epidermal growth factor receptor 2 (HER2), and HER2 is overexpressed in breast cancer cells, the conjugate delivers the toxin directly to the cancer cells. Trastuzumab emtansine, as a single agent, has a UK marketing authorisation 'for the treatment of adult patients with HER2-positive, unresectable locally advanced or metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either:

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

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

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

2.3 Trastuzumab emtansine costs £1641.01 per 100 mg vial and £2625.62 per 160 mg vial (excluding VAT; MIMS, March–May 2014). The company estimated that the average cost of a course of treatment with trastuzumab emtansine is £90,831 (excluding administration costs), assuming a 3-weekly dose of 3.6 mg/kg, a patient weight of 70.1 kg and an average length of treatment of 14.5 months. Roche has agreed a patient access scheme with the Department of Health. If trastuzumab emtansine had been recommended, this scheme would provide a simple discount to the list price of trastuzumab emtansine, with the discount applied at the point of purchase or invoice. The level of the discount is

commercial in confidence. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

3 The company's submission

The Appraisal Committee (section 6) considered evidence submitted by Roche and a review of this submission by the Evidence Review Group (ERG; section 7).

Clinical-effectiveness evidence

3.1 The company's systematic review of clinical evidence identified 2 relevant randomised controlled trials for inclusion in its submission: EMILIA and TH3RESA. Both trials were international, open-label trials evaluating the safety and efficacy of trastuzumab emtansine (3.6 mg/kg every 3 weeks) for human epidermal growth factor receptor 2 (HER2) positive, unresectable, locally advanced or metastatic breast cancer. EMILIA compared trastuzumab emtansine with lapatinib plus capecitabine, and TH3RESA compared it with treatment of physician's choice (defined in section 3.3). Both trials were ongoing at the time of the company's submission to NICE. The company used 4 additional randomised controlled trials, together with EMILIA, to perform a mixed treatment comparison between trastuzumab emtansine and the other comparators listed in the scope (that is, an analysis combining direct and indirect evidence for particular pairwise comparisons).

3.2 Patients in EMILIA had documented progression of unresectable, locally advanced or metastatic HER2-positive breast cancer previously treated with trastuzumab, alone or in combination with another agent, and a taxane, alone or in combination with another agent. The trial's inclusion criteria stipulated that disease progression must have occurred:

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

Patients were randomised in a 1:1 ratio to trastuzumab emtansine (n=495) or lapatinib plus capecitabine (n=496). More than 50 patients were randomised from the UK. Stratification factors were geographical region (USA, Western Europe, or other), the number of previous chemotherapy regimens for unresectable, locally advanced or metastatic disease (0 or 1 compared with more than 1), and disease involvement (visceral compared with non-visceral). The study investigators and an independent review committee assessed the tumour at baseline and then every 6 weeks until disease progressed according to the investigators' assessment. Patients continued to

receive study treatment until investigators established disease progression or unmanageable toxic effects developed.

3.3 TH3RESA enrolled patients with HER2-positive unresectable, locally advanced or metastatic breast cancer whose disease had progressed after at least 2 HER2-targeted regimens, including trastuzumab and lapatinib, and a taxane. Disease progression had to have occurred on both trastuzumab- and lapatinib-containing regimens (unless lapatinib was not tolerated by the patient). Patients were randomised 2:1 to trastuzumab emtansine (n=404) or treatment of physician's choice (n=198), which could be any of the following:

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

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

3.4 The co-primary efficacy end points in both EMILIA and TH3RESA were progression-free survival and overall survival. In EMILIA, progression-free survival was assessed by independent review (progression-free survival assessed by study investigators was a secondary end point), and in TH3RESA it was assessed by study investigators. Progression-free survival was defined as the time from randomisation to disease progression or death from any cause. The independent review committee in EMILIA and the study investigators in TH3RESA assessed disease progression based on Response Evaluation Criteria in Solid Tumours (RECIST). Overall survival was defined as the time from randomisation to death from any cause. Pre-specified secondary end points in both trials included objective response rate, duration of response, and time to

symptom progression (which was used as a proxy for health-related quality of life in EMILIA). TH3RESA collected EQ-5D utility data.

3.5 Patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 were eligible for inclusion in EMILIA. TH3RESA enrolled patients with an ECOG performance status of 0, 1 or 2 (6.2% of the trial's population had an ECOG performance status of 2). For patients randomised to trastuzumab emtansine in EMILIA, the median age was 53 years, 99.8% were female, and 57% had oestrogen- or progesterone-receptor-positive disease. EMILIA included patients whose disease had progressed on trastuzumab and a taxane received as an adjuvant treatment or as a treatment for locally advanced or metastatic disease. Because of this, patients received treatment as first- (12%), second- (36%), or third- or subsequent-line (52%) therapy for locally advanced or metastatic disease. In contrast, patients in TH3RESA had previously received, on average, 4 lines of therapy for locally advanced or metastatic disease. The company stated that patient and disease characteristics at baseline were well balanced between study groups in EMILIA and TH3RESA.

3.6 For EMILIA the company presented the primary analysis of progression-free survival and 2 interim analyses of overall survival that were performed 6 months apart. For TH3RESA it presented the primary analysis of progression-free survival and 1 interim analysis of overall survival. All efficacy end points in EMILIA and TH3RESA were assessed in the intention-to-treat population (that is, in all patients randomised at baseline). Patients in TH3RESA who initially received treatment of physician's choice but then switched to trastuzumab emtansine were included in the analyses as originally randomised.

3.7 In EMILIA, median follow-up was 13 months at the time of the primary analysis of progression-free survival and the first interim analysis of overall survival. Treatment with trastuzumab emtansine improved median progression-free survival as assessed by independent review by 3.2 months (trastuzumab emtansine 9.6 months, lapatinib plus capecitabine 6.4 months), with a hazard ratio stratified on randomisation factors of 0.65 (95% confidence interval [CI] 0.55 to 0.77, $p<0.001$). Investigator-assessed progression-free survival was similar (difference in median progression-free survival 3.6 months; hazard ratio 0.66, 95% CI 0.56 to 0.78). When the second interim analysis of overall survival was performed, median follow-up was 19 months. At that time, 149 (30%) and 182 (37%) of patients randomised to trastuzumab emtansine and lapatinib plus

capecitabine, respectively, had died. Trastuzumab emtansine increased median overall survival by 5.8 months (trastuzumab emtansine 30.9 months, lapatinib plus capecitabine 25.1 months), and the hazard ratio was 0.68 (95% CI 0.55 to 0.85, p<0.001). Estimated 1-year survival rates were 85.2% in the trastuzumab emtansine group compared with 78.4% in the lapatinib plus capecitabine group, and rates at 2 years were 64.7% in the trastuzumab emtansine group and 51.8% in the lapatinib plus capecitabine group. For the secondary end points, trastuzumab emtansine increased objective response rate by 12.7% and prolonged the duration of response by 6.1 months compared with lapatinib plus capecitabine.

3.8 In TH3RESA, a total of 44 patients (22.2%) switched from treatment of physician's choice to trastuzumab emtansine after their disease progressed. Of patients randomised to treatment of physician's choice, 83.2% received HER2-targeted regimens and 16.8% received single-agent chemotherapy. After 16 months of follow-up and 348 events of investigator-assessed disease progression (219 with trastuzumab emtansine, 129 with treatment of physician's choice), median progression-free survival was 6.2 months with trastuzumab emtansine and 3.3 months with treatment of physician's choice, a difference of 2.9 months (hazard ratio 0.53; 95% CI 0.42 to 0.66, p<0.0001). Median overall survival had not been established in the trastuzumab emtansine group by the time of the interim analysis (less than 50% of patients had died). The hazard ratio for overall survival was 0.55 (95% CI 0.37 to 0.83, p=0.0034), but the company did not consider it statistically significant because it had not crossed the stopping boundary (that is, the number of deaths that had accumulated at that time was not enough to come to a conclusion about overall survival).

3.9 Time to symptom progression was used as a proxy for health-related quality of life in EMILIA. It was defined as the time from randomisation to the first decrease of 5 points or more from baseline scores on the Trial Outcome Index of the patient-reported Functional Assessment of Cancer Therapy–Breast (FACT-B), which is scored from 0 to 92, with higher scores indicating a better quality of life. Trastuzumab emtansine delayed time to symptom progression by 2.5 months compared with lapatinib plus capecitabine (trastuzumab emtansine 7.1 months, lapatinib plus capecitabine 4.6 months; hazard ratio 0.796, p=0.0121). Of patients treated with trastuzumab emtansine or lapatinib plus capecitabine, 53.3% and 49.4% respectively had a clinically significant

improvement in symptoms from baseline (p=0.0842). TH3ERSA, which collected EQ-5D data, reported utility values of 0.71 and 0.69 for patients who received trastuzumab emtansine or treatment of physician's choice respectively. In response to the appraisal consultation document, the company provided further health-related quality of life data from EMILIA obtained using the FACT-B and Diarrhoea Assessment Scale tools. Patients in the trastuzumab emtansine group reported being 'less bothered' by side effects than those in the lapatinib plus capecitabine group. In addition, the number of patients reporting diarrhoea symptoms increased 1.5- to 2-fold during treatment with lapatinib plus capecitabine but remained near baseline levels during treatment with trastuzumab emtansine.

3.10 The company provided pre-specified subgroup analyses of EMILIA and TH3RESA for progression-free survival and overall survival. For patients who received study treatment as first, second, or third or subsequent line, the hazard ratios for overall survival were 0.61 (95% CI 0.32 to 1.16), 0.88 (95% CI 0.61 to 1.27) and 0.62 (95% CI 0.46 to 0.84) respectively. The company indicated that no subgroups were of particular clinical interest for this appraisal.

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

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

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

- Martin et al.: an open-label study of neratinib compared with lapatinib plus capecitabine for the second- or third-line treatment of HER2-positive locally advanced or metastatic breast cancer. Eligible patients had received up to 2 previous trastuzumab regimens and a taxane. Martin et al. did not report results for overall survival, so the company did not use this study for the analysis of overall survival.

- GBG26: a study in patients with HER2-positive, advanced breast cancer whose disease had progressed while being treated with trastuzumab. In this study, adding capecitabine to continued trastuzumab therapy was compared with capecitabine alone.

  The company did not include TH3RESA in the analysis, even though it was the only study that would have allowed the comparison of trastuzumab emtansine with trastuzumab plus vinorelbine (one of the comparators in the scope) received as a treatment of physician's choice. In response to a request for clarification from the ERG about why TH3RESA was not included, the company indicated that the treatment of physician's choice was determined after patients had been randomised and considering each patient's characteristics. The company explained that because of this, a comparison of trastuzumab emtansine with trastuzumab plus vinorelbine separately would break the randomisation in the trial and result in a biased comparison.

3.12 The company did a qualitative but not a statistical assessment of heterogeneity. It stated that the 5 included studies were comparable for age, ECOG performance status, disease stage and the number of sites with disease metastases. All studies apart from CEREBEL included patients who had received trastuzumab, of whom 71 to 95% received it for metastatic disease. In GBG26, only 70% of patients had received a taxane but the company considered this proportion large enough to include the study. The company stated that CEREBEL and Martin et al. seemed more heterogeneous than the other 3 trials. For CEREBEL, although the company used the subgroup of patients who had received trastuzumab, an unknown proportion of these patients could have received trastuzumab plus an anthracycline, which does not match the population specified in the decision problem. Furthermore, CEREBEL and Martin et al. had limited information on patient characteristics at baseline.

Because of this, the company presented the analysis with and without these 2 studies.

3.13 The company did the mixed treatment comparison from a Bayesian perspective using a fixed-effect model (that is, assuming that all trials estimate exactly the same treatment effect and that the variability between individual study results occurs by chance). It estimated hazard ratios and corresponding 95% credible intervals (CrI) for each pairwise comparison that was possible from the network of trials. The company also presented results using the Bucher method for the analysis that excluded CEREBEL and Martin et al. to compare the results obtained using different methods.

3.14 The trials used by the company allowed the comparison of trastuzumab emtansine with capecitabine and with trastuzumab plus capecitabine, but not with vinorelbine or with trastuzumab plus vinorelbine. In the analysis that included CEREBEL and Martin et al., the hazard ratio for progression-free survival was 0.39 (95% CrI 0.29 to 0.55) for trastuzumab emtansine relative to capecitabine, and 0.68 (95% CrI 0.50 to 0.91) for trastuzumab emtansine relative to trastuzumab plus capecitabine. For overall survival, the hazard ratio for trastuzumab emtansine was 0.55 (95% CrI 0.41 to 0.75) relative to capecitabine, and 0.68 (95% CrI 0.46 to 0.98) relative to trastuzumab plus capecitabine. Excluding CEREBEL and Martin et al. from the analysis resulted in trastuzumab emtansine being associated with a lower risk (lower hazard ratios) of both disease progression and death relative to capecitabine and to trastuzumab plus capecitabine than when the 2 studies were included. The results using the Bucher method were statistically significant and similar to those obtained using the Bayesian method.

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

3.16 In both EMILIA and TH3RESA, adverse events were analysed for a 'safety population', defined as patients who received at least 1 dose of study treatment. In addition, the company presented a pooled safety analysis of 884 patients who had received trastuzumab emtansine either in EMILIA or in 5 other phase I or II

studies. Trastuzumab emtansine caused grade 3 or above adverse events in 45.0% of these patients, serious adverse events in 19.8%, treatment discontinuation in 7.0% and death in 1.4%. The most common adverse events in the pooled analysis (occurring in 25% or more of patients) were fatigue (46.4%), nausea (43.0%), decreased platelet counts (29.6%), headache (29.4%), constipation (26.5%) and nosebleeds (25.2%). Serious adverse events reported by more than 5 patients were pneumonia (1.7%), fever (1.4%), cellulitis (1.1%), vomiting (0.9%), decreased platelet counts (0.9%), convulsion (0.8%), shortness of breath (0.8%), abdominal pain (0.7%), blood poisoning (0.7%), back pain (0.7%) and accumulation of fluid on the lungs (0.6%). The company considered that trastuzumab emtansine is well tolerated and that the additional toxicity can be managed.

Evidence Review Group critique and exploratory analyses

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

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

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

- Most patients in EMILIA and TH3RESA received study treatment as a third or subsequent line, whereas the company suggested that trastuzumab emtansine would be used second line in clinical practice.
- The ERG noted that because EMILIA and TH3RESA were international trials, not all patients would have received previous treatment according to UK practice.

- The ERG suggested that in clinical practice around one-third of patients would have an ECOG performance status of 2, whereas in EMILIA and TH3RESA, 0% and 6.2% of patients respectively had an ECOG performance status of 2.

3.20 The ERG noted the following differences between the trials used in the company's mixed treatment comparison:

- Not all patients had received a taxane in GBG26. The ERG's clinical experts believed that previous taxane therapy can modify the effect of subsequent treatment.
- The assessment of disease progression or time to progression was blinded to the intervention the patient had received in EMILIA and EGF100151 but not in the other trials included in the analysis.
- RECIST was used in EMILIA, EGF100151 and Martin et al. to assess disease progression, but it was unclear whether it was used in CEREBEL and GBG26.
- The sites of disease metastases differed between CEREBEL and the remaining studies because CEREBEL excluded patients with brain metastases.

3.21 The ERG agreed that it was appropriate for the company to have excluded TH3RESA from the mixed treatment comparison. However, it did not agree that using a fixed-effect model was appropriate because heterogeneity between trials was likely to exist. Therefore, the ERG requested that the company performs the analysis using a random-effects model (that is, a model that attempts to account for any unexplained variability between study results). However, when this was provided, the ERG stated that the company did not describe the analysis in sufficient detail, so the ERG repeated the analysis that included CEREBEL and Martin et al. using a random-effects model. It reported similar results to the company, but the ERG's results had wider credible intervals which crossed 1 (1 being the equivalent of no treatment effect). In the ERG's analysis, the probability of trastuzumab emtansine being the best treatment to reduce the risk of disease progression was 87%, and the probability of it being the best treatment to reduce the risk of death was 84%.

Cost-effectiveness evidence

3.22 The company submitted a de novo economic model to estimate the cost effectiveness of trastuzumab emtansine in adults with HER2-positive, unresectable, locally advanced or metastatic breast cancer who previously

received trastuzumab and a taxane, separately or in combination. The company conducted the analysis from the perspective of the NHS and personal social services. It chose a time horizon of 10 years and a cycle length of 1 week. Costs and health effects were discounted at an annual rate of 3.5%.

3.23 The company's model was a state-transition Markov cohort model simulating 3 states: progression-free, progressed disease and death. All patients entered the model in the progression-free state and received trastuzumab emtansine or one of its comparators either as first, second or third line (based on the proportions in EMILIA, see section 3.5). They could then remain in this state, move to the progressed-disease state or die. Once patients transitioned in the model, they could not return to their previous state. The company's model assumed that patients whose disease progressed stopped treatment and received capecitabine, vinorelbine or best supportive care, in line with advanced breast cancer: diagnosis and treatment (NICE guideline CG81).

3.24 The company obtained the clinical-effectiveness data for trastuzumab emtansine and the comparator lapatinib plus capecitabine from EMILIA. Progression-free survival in the model was based on the assessment by study investigators (secondary end point) rather than the assessment by independent review (primary end point). To model the clinical effectiveness of the comparators for which there was no head-to-head evidence, the company used the results of its Bayesian mixed treatment comparison that included CEREBEL and the study by Martin et al. It assumed that vinorelbine and trastuzumab plus vinorelbine, which could not be compared with trastuzumab emtansine in the mixed treatment comparison, were clinically equivalent to capecitabine and trastuzumab plus capecitabine respectively. This was because NICE guideline CG81 recommends capecitabine or vinorelbine as second- or third-line treatment for advanced breast cancer, and the All Wales Medicines Strategy Group recommends lapatinib plus capecitabine as an alternative to trastuzumab plus capecitabine or trastuzumab plus vinorelbine. The company suggested that this implies that capecitabine and vinorelbine, alone or in combination with trastuzumab, can be used interchangeably.

3.25 To estimate progression-free survival and overall survival for trastuzumab emtansine and lapatinib plus capecitabine, the company produced log-cumulative hazard plots to examine how the risks of disease progression and death change over time with each treatment. It then fitted alternative

parametric functions to Kaplan–Meier data for each of EMILIA's treatment groups, and extrapolated the curves beyond the end of the trial. The company chose the base-case survival functions for trastuzumab emtansine and lapatinib plus capecitabine based on statistical tests, on visually inspecting the curves' fit to the data and on the clinical plausibility of the extrapolation. It then applied the hazard ratios from the mixed treatment comparison to the survival function of trastuzumab emtansine to estimate progression-free survival and overall survival for each of the other comparators. The company's model assumed that the treatment effect of trastuzumab emtansine was maintained during the entire time horizon (that is, the hazard ratios for progression-free survival and overall survival remained below 1).

3.26 The company noted that the risk of disease progression with trastuzumab emtansine and lapatinib plus capecitabine was relatively constant during the first 17 months (72 weeks) after starting treatment, then started changing irregularly. It stated that although this might have a clinical explanation, it could be spurious because there were few patients at risk of developing disease progression after 17 months. According to statistical tests, the log-normal function provided the best fit to the Kaplan–Meier data for trastuzumab emtansine and lapatinib plus capecitabine. However, on visual inspection the company noted a poor fit. Because of this and the small effect progression-free survival had in the model compared with overall survival (see sections 3.33 and 3.34), the company chose to use in its base case the Kaplan–Meier data for each treatment group up to 17 months after starting treatment, the point at which the risk of disease progression starts changing irregularly, and fit the log-normal function beyond 17 months.

3.27 For overall survival, the log-logistic and gamma functions provided the best fit to the Kaplan–Meier data according to statistical tests. However, the company chose the gamma function, which it fitted to the entire curves to model overall survival. This was because the gamma function produced survival curves that were more biologically plausible and more comparable with the Kaplan–Meier curves and with external registry data than those produced by the log-logistic function. The difference in mean overall survival between trastuzumab emtansine and lapatinib plus capecitabine with the gamma function was 7.6 months.

3.28 The company could not transform the FACT-B Trial Outcome Index data collected from EMILIA to EQ-5D, and it did not use the utility values from TH3RESA because patients in TH3RESA received treatment as third- or subsequent-line therapy and would be expected to have a lower quality of life than patients with fewer recurrences. The company stated that the best available source of health-related quality of life data was a study by Lloyd et al., which has been used in previous NICE technology appraisals for metastatic breast cancer. The company used the model by Lloyd et al. to estimate treatment-specific utility values in the progression-free state based on the objective response rate reported for the treatment in trials. For trastuzumab emtansine and lapatinib plus capecitabine the company obtained response rates from EMILIA, estimating utility values of 0.78 and 0.74 respectively. It considered that the FACT-B and Diarrhoea Assessment Scale data from EMILIA and the favourable safety profile of trastuzumab emtansine support using a higher utility value for trastuzumab emtansine than for lapatinib plus capecitabine. The company estimated a utility value of 0.72 for capecitabine based on response rates from EGF100151 and a utility value of 0.73 for trastuzumab plus capecitabine based on response rates from GBG26. Because the company assumed clinical equivalence between capecitabine and vinorelbine (see section 3.24), it used the same utility value for vinorelbine as that for capecitabine (0.72) and the same value for trastuzumab plus vinorelbine as that for trastuzumab plus capecitabine (0.73). For the progressed-disease state, the company applied a single utility value of 0.50 for all patients, which it estimated based on the Lloyd et al. model. To capture the decrease in utility associated with adverse events, the company included utility decrements for 3 adverse events: diarrhoea and vomiting, fatigue and hand-foot syndrome. For capecitabine, trastuzumab plus capecitabine, vinorelbine, and trastuzumab plus vinorelbine, the company applied the same adverse events as for lapatinib plus capecitabine based on EMILIA, with the same frequency.

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

treatment the patient received in the progressed-disease state (capecitabine and/or vinorelbine) was received for 4.3 months, based on a study by Cameron et al. To capture the costs likely to be incurred at the end of life, the company incorporated a palliative care cost of £3916 per patient as a transition cost to the death state.

3.30 The company's deterministic base-case results (without the patient access scheme) suggested that trastuzumab emtansine was more costly and more effective than all of its comparators. In an incremental analysis, vinorelbine, trastuzumab plus capecitabine and trastuzumab plus vinorelbine were dominated and excluded from the analysis; that is, vinorelbine was more costly than capecitabine and equally effective, and trastuzumab plus capecitabine and trastuzumab plus vinorelbine were more costly and less effective than lapatinib plus capecitabine. Among the remaining alternatives, capecitabine was the cheapest, followed by lapatinib plus capecitabine, then trastuzumab emtansine. The incremental cost-effectiveness ratio (ICER) for lapatinib plus capecitabine compared with capecitabine alone was £49,798 per quality-adjusted life year (QALY) gained (incremental costs £20,997, incremental QALYs 0.42). The ICER for trastuzumab emtansine compared with lapatinib plus capecitabine was £167,236 per QALY gained (incremental costs £76,992, incremental QALYs 0.46). The company stated that lapatinib plus capecitabine should be excluded from the analysis because the ICER for lapatinib plus capecitabine compared with capecitabine alone is above the normally acceptable maximum ICER. In a pairwise comparison of trastuzumab emtansine with capecitabine the ICER was £111,095 per QALY gained (incremental costs £97,989, incremental QALYs 0.88).

3.31 In the company's base case, which used a 10-year time horizon, 3% of patients were alive at 10 years. In response to a request for clarification from the ERG, the company presented cost-effectiveness results using a 15-year time horizon. In an incremental analysis the ICER for trastuzumab emtansine compared with lapatinib plus capecitabine was £160,070 per QALY gained. At the end of the 15 years 1% of patients were alive.

3.32 The company presented 1-way sensitivity analyses in its base case that used a 10-year time horizon in which it varied most parameters to the lower and upper limit of their 95% confidence intervals. In addition, it explored alternative approaches to model progression-free survival and overall survival (see

sections 3.33 and 3.34). The company performed all these analyses only on the pairwise ICER for trastuzumab emtansine compared with capecitabine (£111,095 per QALY gained). It found that this ICER was most sensitive to the utility value applied for trastuzumab emtansine in the progression-free state. When the utility value varied, this resulted in ICERs ranging from £94,909 to £179,337 per QALY gained. The company stated that, compared with capecitabine, the cost effectiveness of trastuzumab emtansine was most sensitive to how progression-free survival and overall survival were extrapolated in the model, the hazard ratios estimated from the mixed treatment comparison, and the utility values used.

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

- Using the Kaplan–Meier data up to 17 months after starting treatment and fitting alternative parametric functions (Weibull, exponential, log-logistic and gamma) beyond 17 months instead of the log-normal function.
- Using the Kaplan–Meier data for each treatment group up to 3.5 months (14 weeks) after starting treatment, and fitting the exponential function to each group separately beyond 3.5 months. The company explored this approach because the risk of disease progression with trastuzumab emtansine and lapatinib plus capecitabine was similar during the first 3.5 months. The company stated that this might have biological plausibility, by which the true risk of disease progression with each treatment only becomes observed after 3.5 months.

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

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

- Fitting alternative parametric functions (Weibull, log-logistic and log-normal) instead of the gamma function to the entire survival curves.

- Using the Kaplan–Meier data for each treatment group up to 7.3 months (29 weeks) after starting treatment, and fitting the exponential function to each treatment group separately beyond 7.3 months. The company explored this approach because the risk of death with trastuzumab emtansine and lapatinib plus capecitabine was similar during the first 7.3 months.

- Using the Kaplan–Meier data for each treatment group up to 7.3 months (29 weeks) after starting treatment, and fitting the exponential function to each treatment group separately beyond 7.3 months, but assuming no treatment effect (hazard ratio of 1) beyond 23.8 months (95 weeks) after starting treatment. The company explored this approach because there were few patients at risk of dying after 23.8 months and the treatment effect of trastuzumab emtansine beyond that time was uncertain.

  The first analysis resulted in ICERs ranging from £111,004 per QALY gained (log-normal) to £151,208 per QALY gained (Weibull). The second and third analyses resulted in ICERs of £138,286 and £153,319 per QALY gained respectively.

3.35 To characterise the uncertainty in the base-case ICER the company performed a probabilistic sensitivity analysis, varying parameters simultaneously with values from a probability distribution. There was a 0% probability of trastuzumab emtansine being the most cost-effective treatment at a maximum acceptable ICER of £30,000 per QALY gained.

3.36 In response to the appraisal consultation document, the company submitted a patient access scheme. Including the confidential discount in the patient access scheme, the probability of trastuzumab emtansine being cost effective compared with lapatinib plus capecitabine at a maximum acceptable ICER of £30,000 per QALY gained remained 0%. Other cost-effectiveness estimates incorporating the patient access scheme are commercial in confidence and cannot be reported here because, having previously released the estimates without the patient access scheme, the estimates with the patient access scheme could reveal the confidential discount agreed between the company and the Department of Health. However, the estimates including the patient access scheme were fully taken into account during the appraisal.

Evidence Review Group critique and exploratory analyses

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

3.38 The ERG indicated that the company's modelling of progression-free survival and overall survival in the base case provided the most clinically plausible extrapolation. However, it noted that in the model the benefit of trastuzumab emtansine on progression-free survival and overall survival was assumed to be maintained during the entire time horizon (that is, the hazard ratio remained below 1). The ERG considered this subject to uncertainty and explored in a 1-way sensitivity analysis the conservative assumption of no treatment benefit with trastuzumab emtansine (hazard ratio of 1) beyond the time points at which the treatment effect was uncertain (see section 3.47).

3.39 The ERG stated that the utility values used in the model were consistent with values reported from a literature review of health-state utility values for breast cancer. In addition, the ERG's clinical advisers considered that it was reasonable to assume higher utility with trastuzumab emtansine than with its comparators because trastuzumab emtansine has a better safety profile.

3.40 The ERG noted that the model incorporated utility decrements for 3 adverse events only and costs for 2 adverse events only. It stated that this did not capture the decrease in utility and costs associated with many grade 3 or above adverse events that occurred frequently in EMILIA. The ERG included the costs of those adverse events in exploratory analyses (see section 3.45) and doubled the costs associated with adverse events in a 1-way sensitivity analysis (see section 3.47).

3.41 The company calculated the doses of trastuzumab emtansine, trastuzumab, capecitabine and vinorelbine based on the average body weight and body surface area of patients in EMILIA (this assumed that all patients receive the same treatment dose). The ERG indicated that the company, having assumed that any unused drug in a vial was discarded for trastuzumab emtansine and trastuzumab, calculated costs inaccurately. This was because patients' weight varies, so the combination of vial sizes patients would receive to administer the drug efficiently would also vary. In its exploratory analyses (see section 3.45),

the ERG applied alternative costs for trastuzumab emtansine, trastuzumab and capecitabine based on an approximated weight distribution, rather than an average weight, of patients with HER2-positive metastatic breast cancer to account for the variation in patients' body weight.

3.42 The ERG identified an error in the model relating to how the cost of administering trastuzumab plus vinorelbine was implemented, which it corrected in exploratory analyses (see section 3.45).

3.43 In the model, some patients remained in the progressed-disease state longer than others, depending on the treatment they had received in the progression-free state, but most patients who received treatment in the progressed-disease state (capecitabine or vinorelbine) received it for 4.3 months. The ERG noted that, in the company's model, patients who spent more time in the progressed-disease state incurred more treatment costs than those who spent less time despite receiving treatment for the same duration. The ERG corrected this in its exploratory analyses by calculating the average cost of each treatment received in the progressed disease-state independently (see section 3.45).

3.44 The company performed 1-way sensitivity analyses only on the pairwise ICER for trastuzumab emtansine compared with capecitabine. The ERG did not consider this to have established the robustness of the model or to have determined the key drivers of cost effectiveness. The ERG explained that it was important to include all the comparisons because the appropriate incremental comparison may change with each analysis. Furthermore, the ERG stated that the company did not present or justify the parameters it varied in the probabilistic sensitivity analysis, appeared to have selected the parameters arbitrarily and did not reflect the uncertainty around certain parameters.

3.45 To address its concerns about the company's model, the ERG performed the following exploratory analyses:

- Analysis 'a': including the costs of all adverse events that occurred in more than 2% of patients in either treatment group of EMILIA.
- Analysis 'b': correcting the error relating to how the cost of administering trastuzumab plus vinorelbine was implemented, and calculating the average cost of each treatment received in the progressed disease-state independently, together with analysis 'a'.

- Analysis 'c': applying the hazard ratios for progression-free survival and overall survival from the ERG's mixed treatment comparison that used a random-effects model, together with analysis 'b'.
- Analysis 'd': using a 15-year time horizon, together with analysis 'c'.
- Analysis 'e': calculating the cost of trastuzumab emtansine, trastuzumab and capecitabine based on an approximated weight distribution of patients with HER2-positive metastatic breast cancer, together with analysis 'd' (that is, applying all individual changes simultaneously).

3.46 In the above-listed analysis 'e' (hereafter 'the ERG's base case'), trastuzumab plus capecitabine, vinorelbine and trastuzumab plus vinorelbine were dominated and excluded from the analysis. In an incremental analysis, the ICER for trastuzumab emtansine compared with lapatinib plus capecitabine was £166,429 per QALY gained (incremental costs £80,971, incremental QALYs 0.49), which was very similar to the company's ICER of £167,236 per QALY gained. The ERG explained that this was because the changes it applied did not act on the ICER in the same direction (all changes, except applying revised drug costs, decreased the ICER). The incremental ICERs for trastuzumab emtansine compared with lapatinib plus capecitabine from the above-listed analyses were £167,229 per QALY for 'a', £166,701 for 'b', £166,701 for 'c' and £159,486 for 'd'.

3.47 Based on key areas of uncertainty it identified, the ERG repeated within its base case selected sensitivity analyses performed by the company. It also explored the following:

- Applying equal utility values of 0.74 for all treatments in the progression-free state, which was the value used for lapatinib plus capecitabine in the company's base-case analysis.
- Assuming that, compared with lapatinib plus capecitabine, trastuzumab emtansine had no effect on progression-free survival beyond 17.0 months after starting treatment and no effect on overall survival beyond 23.8 months after starting treatment (that is, beyond the points at which the treatment effect of trastuzumab emtansine was uncertain; see sections 3.33 and 3.34).
- Doubling the costs associated with adverse events.

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

  Compared with the ERG's base-case ICER of £166,429 per QALY gained for trastuzumab emtansine compared with lapatinib plus capecitabine, the ICERs from the above-listed analyses were £185,623, £449,554, £165,858 and £166,429 per QALY gained respectively. The ICER remained above £147,000 per QALY gained in all the other sensitivity analyses. The key drivers in the model were the relative treatment effect of trastuzumab emtansine on overall survival, the utility values, and the assumptions about drug wastage. The ERG indicated that, given the uncertainty in the results of its mixed treatment comparison, if any of the comparators were equally effective as trastuzumab emtansine, the comparator would dominate trastuzumab emtansine because it would be cheaper.

3.48 Full details of all the evidence are in the committee papers.

4 Consideration of the evidence

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of trastuzumab emtansine, having considered evidence on the nature of human epidermal growth factor receptor 2 (HER2) positive, unresectable locally advanced or metastatic breast cancer and the value placed on the benefits of trastuzumab emtansine by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

4.1 The Committee discussed with patient experts the nature of the condition and the perceived benefits of trastuzumab emtansine for patients. It heard that metastatic breast cancer is a debilitating condition that can affect women of all ages and leads to premature death. The Committee heard from the patient experts that patients and their families often highly value what may seem to others even relatively short extensions to life, as long as the person's quality of life is maintained. The Committee noted that patients are particularly concerned about unpleasant side effects associated with treatment. The clinical specialists explained that trastuzumab emtansine is both an effective treatment and also well tolerated, with fewer side effects than some of the other options. The Committee recognised that patients value the availability of more treatment options and that trastuzumab emtansine would be welcomed by patients and their families.

4.2 The Committee discussed with the clinical specialists the current clinical management of HER2-positive metastatic breast cancer. It was aware that NICE recommends trastuzumab plus paclitaxel as a first-line treatment for people who have not received chemotherapy for metastatic breast cancer and in whom anthracycline treatment is inappropriate (NICE technology appraisal guidance 34). After disease progression, NICE recommends second- and third-line treatment with non-targeted therapies such as capecitabine or vinorelbine, which can be combined with continued trastuzumab therapy if disease progression is within the central nervous system alone (NICE guideline CG81). The Committee heard from the clinical specialists that trastuzumab plus chemotherapy has become the standard first-line treatment in clinical practice, but more recently in England patients may receive pertuzumab in addition to trastuzumab and docetaxel, which is funded by the Cancer Drugs Fund. It further heard that after disease progression on trastuzumab (that is, in the second-line setting) clinical practice varies, but most patients will continue trastuzumab therapy combined with chemotherapy (capecitabine or

vinorelbine) or receive lapatinib plus capecitabine. The Committee noted that continued trastuzumab therapy was not offered by all cancer centres, and that lapatinib plus capecitabine was available in England through the Cancer Drugs Fund. The Committee heard from the clinical specialists that contrary to NICE guidance, single-agent chemotherapy (for example, capecitabine or vinorelbine) is not routinely used for patients whose disease progressed on first-line treatment. The Committee concluded that local access to treatments and the availability of treatments through the Cancer Drugs Fund led to some variation in clinical practice so that no single pathway of care could be defined.

4.3 The Committee considered the likely position of trastuzumab emtansine in the treatment pathway of HER2-positive, unresectable locally advanced or metastatic breast cancer and the key comparators for trastuzumab emtansine in clinical practice. It noted that the clinical specialists expect that trastuzumab emtansine would be used as second-line therapy (that is, instead of continued trastuzumab plus chemotherapy or lapatinib plus capecitabine) because trastuzumab emtansine had been shown to be more clinically effective than the alternative second-line agent, lapatinib plus capecitabine, in EMILIA. The Committee concluded that based on current clinical practice trastuzumab plus capecitabine, trastuzumab plus vinorelbine and lapatinib plus capecitabine were relevant comparators at that stage of the disease.

Clinical effectiveness

4.4 The Committee discussed which sources of trial data were appropriate for the place in therapy in which trastuzumab emtansine is likely to be used (that is, the second-line setting). The Committee was aware that 36% of patients in EMILIA and 0% of patients in TH3RESA received treatment as second-line therapy for locally advanced or metastatic disease. Given these proportions, the Committee concluded that EMILIA was the most relevant source of clinical evidence for its decision-making in this appraisal.

4.5 The Committee discussed whether the results from EMILIA were generalisable to clinical practice, noting that patients in England may receive pertuzumab plus trastuzumab plus docetaxel in the first-line setting. It heard from the company that 9.5% of patients in EMILIA had previously received pertuzumab therapy (10.3% of patients in the trastuzumab emtansine group, 8.7% of patients in the lapatinib plus capecitabine group) but the Committee considered this

proportion too small to determine whether the effect of trastuzumab emtansine differed in patients who had previously received pertuzumab. In addition, the Committee heard from the clinical specialists that there was no evidence on whether or not pertuzumab can modify the effect of subsequent treatment with trastuzumab emtansine. However, the clinical specialists indicated that trastuzumab emtansine demonstrated a clinical benefit after trastuzumab, and that trastuzumab and pertuzumab have similar mechanisms of action, so the effect of trastuzumab emtansine would not be expected to differ after trastuzumab or after pertuzumab plus trastuzumab. The Committee concluded that it was currently unknown whether previous pertuzumab would alter the clinical effectiveness of subsequent treatment with trastuzumab emtansine, but there was no positive evidence that this was the case.

4.6 The Committee also noted the Evidence Review Group's (ERG) concern that none of the patients in EMILIA had an Eastern Cooperative Oncology Group (ECOG) performance status of 2, whereas in clinical practice around one-third of patients would have an ECOG performance status of 2. The Committee appreciated that patients enrolled in clinical trials may be younger and with better performance status than those in routine clinical practice, and so might experience better outcomes. The Committee agreed that the population in EMILIA was otherwise reasonably representative of patients in the UK and concluded that the results of EMILIA were suitable for the assessment of the clinical effectiveness of trastuzumab emtansine in clinical practice.

4.7 The Committee considered the clinical effectiveness of trastuzumab emtansine as a second-line treatment. It was aware that in EMILIA, patients in the trastuzumab emtansine group experienced improved survival compared with patients in the lapatinib–capecitabine group, irrespective of the line of therapy. However, the Committee noted that subgroup analyses suggested a lesser benefit in patients who received second-line treatment (in whom the difference in effect was not statistically significant) than in the overall population (see section 3.10). The Committee was aware that the analysis may not have been powered to demonstrate a difference in treatment effect in the subgroup. In addition, the Committee heard from the clinical specialists that there is no biologically plausible reason for the effect to differ according to the number of previous treatments patients had received. The Committee concluded that the subgroup analysis was not reliable enough to inform a decision about the clinical effectiveness of trastuzumab emtansine as a second-line treatment.

4.8 The Committee took note of the patient expert's concern about the tolerability of treatment and discussed the adverse events in EMILIA that led patients to stop treatment, which it considered to be a reasonable proxy for tolerability. The Committee understood that fewer patients stopped treatment because of an adverse event in the trastuzumab emtansine group than in the lapatinib plus capecitabine group (5.9% and 17% of patients respectively). It also heard from the company that the most common adverse event that resulted in patients stopping trastuzumab emtansine was a decreased platelet count (2% of patients). The Committee concluded that trastuzumab emtansine had been shown to have a satisfactory adverse-event profile in EMILIA.

4.9 The Committee considered the Bayesian mixed treatment comparison used by the company to estimate hazard ratios for trastuzumab emtansine relative to the comparators for which no head-to-head evidence existed. The Committee agreed that CEREBEL and the study by Martin et al. should be included in the base-case analysis to use all available evidence and that the ERG's random-effects model would better reflect the heterogeneity between the trials than the company's fixed-effect model.

Cost effectiveness

4.10 The Committee considered the company's economic model used to estimate the cost effectiveness of trastuzumab emtansine and how it captured the main aspects of the condition. It noted that the company used a 3-state model and chose a time horizon of 10 years for its base case. The Committee agreed that the model structure was consistent with other models used for the same disease. The Committee noted that the ERG preferred a 15-year time horizon because a small proportion of patients were still alive at 10 years and data relating to these patients would not be included in a model with a 10-year horizon. The Committee agreed that in principle a lifetime horizon should be used to capture all long-term costs and health effects and concluded that the company's model was appropriate to estimate the cost effectiveness of trastuzumab emtansine, but that a 15-year time horizon should be used.

4.11 The Committee considered the utility values used in the company's model. It noted that in the progression-free state, the company applied a higher utility value for trastuzumab emtansine than for its comparators. The company considered that the favourable side effect profile of trastuzumab emtansine

supports using a distinct utility value for trastuzumab emtansine. The Committee questioned whether utility values should differ for each treatment because the clinical specialists indicated that most adverse events resolve within a few weeks, whereas in the model the utility values were applied throughout the entire progression-free state. In addition, the Committee considered that applying a higher utility value for trastuzumab emtansine could result in the benefit of treatment being double-counted and overestimated, because the utility decrements for adverse events already capture part of this benefit. In response to the appraisal consultation document, the company clarified that the utility decrements for adverse events were not applied separately in the model, but were incorporated into the utility values in the progression-free state, and therefore were applied only once. The Committee heard from the ERG that, although the modelling of adverse events had limitations (see section 3.40), the benefit of trastuzumab emtansine from reducing adverse events was not double-counted in the model. The Committee acknowledged the additional evidence submitted by the company in response to the appraisal consultation document (see section 3.9). It noted that the evidence suggested that in EMILIA, patients who received trastuzumab emtansine felt better and reported being less troubled by side effects than those who received lapatinib plus capecitabine. The Committee was aware that EMILIA was an open-label trial, which may have introduced bias in the outcomes reported by patients, but noted the additional evidence on wellbeing and side effects presented by the company. The Committee concluded that a marginally higher utility value for trastuzumab emtansine in the progression-free state could be accepted in this appraisal.

4.12 The Committee noted that in its cost-effectiveness analysis, the company assumed clinical equivalence between capecitabine and vinorelbine, and between trastuzumab plus capecitabine and trastuzumab plus vinorelbine. The Committee discussed with the clinical specialists whether this assumption was clinically plausible. The clinical specialists indicated that any chemotherapy would produce additional benefit when combined with trastuzumab. They stated that the precise clinical difference between capecitabine and vinorelbine had not been established in clinical trials, although in their opinion it would be reasonable to assume no difference. The Committee concluded that, although it would be preferable to base the comparison on data from well conducted clinical trials, the assumption of no difference between capecitabine- and vinorelbine-based regimens in the model could be justified for this appraisal.

4.13 The Committee considered the adverse events associated with trastuzumab emtansine in relation to the economic modelling. It noted that the model incorporated utility decrements for only 3 adverse events and costs for 2 adverse events. The Committee was concerned that this did not capture many adverse events associated with trastuzumab emtansine including decreased platelet counts. The Committee was aware that when the ERG included the costs of the adverse events that occurred frequently in EMILIA, this had little impact on the cost-effectiveness estimates. However, it concluded that the model should have incorporated both the decrease in utility and the increased costs associated with adverse events.

4.14 The Committee considered the cost-effectiveness results for trastuzumab emtansine. It noted the company's suggestion that lapatinib plus capecitabine should be excluded from the analysis because the incremental cost-effectiveness ratio (ICER) for lapatinib plus capecitabine compared with capecitabine alone was £49,800 per quality-adjusted life year (QALY) gained, which the company considered to be above the acceptable maximum ICER normally regarded by NICE to represent cost-effective treatments (see section 3.30). The Committee was aware that excluding a technology based on its cost effectiveness in relation to a maximum ICER does not comply with the NICE reference case, which recommends a fully incremental cost–utility analysis. The Committee agreed that there was no reason on this occasion to depart from the NICE reference case. It concluded that the cost effectiveness of trastuzumab emtansine should be evaluated in an incremental analysis comparing all technologies including lapatinib plus capecitabine.

4.15 The Committee discussed the most plausible ICERs for trastuzumab emtansine without the patient access scheme. It agreed that lapatinib plus capecitabine, trastuzumab plus capecitabine and trastuzumab plus vinorelbine were in routine use in clinical practice in the NHS and should be included in the analysis. It also agreed that the analysis should use a 15-year time horizon and incorporate the decrease in utility and increased costs associated with treating adverse events. The Committee noted that in both the company's and ERG's base case, trastuzumab plus capecitabine and trastuzumab plus vinorelbine were more costly and less effective than lapatinib plus capecitabine (that is, they were dominated). The company's base-case ICER for trastuzumab emtansine compared with lapatinib plus capecitabine was £167,200 per QALY gained. The Committee noted that the ERG's base-case ICER was very similar at £166,400

per QALY gained. At its first meeting, the Committee agreed that the most plausible ICER was above the ICER range that would normally be considered a cost-effective use of NHS resources.

4.16 At its second meeting, the Committee considered the revised cost-effectiveness results incorporating the patient access scheme submitted in response to the appraisal consultation document (which are commercial in confidence). It expressed disappointment that the patient access scheme did not reduce the ICER to a level close to one that could be accepted as a cost-effective use of NHS resources. The Committee concluded that the size of the discount in the patient access scheme meant that it was still unable to recommend trastuzumab emtansine for treating HER2-positive, unresectable locally advanced or metastatic breast cancer previously treated with trastuzumab and a taxane.

4.17 The Committee considered whether trastuzumab emtansine represents an innovative treatment. It acknowledged that trastuzumab emtansine is a novel antibody–drug conjugate combining the HER2-targeted anti-tumour activity of trastuzumab with a cytotoxic agent. It also noted that trastuzumab emtansine prolonged survival, with less toxicity than lapatinib plus capecitabine. However, the Committee considered that all benefits of a substantial nature relating to treatment with trastuzumab emtansine had been captured in the QALY calculation, including the favourable adverse-event profile and increased progression-free and overall survival.

4.18 The Committee considered supplementary advice from NICE that should be taken into account when appraising treatments that may extend the life of patients with a short life expectancy and that are licensed for indications that affect small numbers of people with incurable illnesses. For this advice to be applied, all the following criteria must be met.

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months.
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.
- The treatment is licensed or otherwise indicated for small patient populations.

In addition, when taking these criteria into account, the Committee must be persuaded

that the estimates of the extension to life are robust and that the assumptions used in the reference case of the economic modelling are plausible, objective and robust.

4.19 The Committee considered the criterion for short life expectancy. It agreed that the best estimate of expected survival using current standard NHS treatment was demonstrated in the control groups of the trials. The Committee noted that in EMILIA, the median overall survival of patients in the lapatinib plus capecitabine group was 25.1 months. The Committee noted the company's response to the appraisal consultation document suggesting that lapatinib plus capecitabine should not be considered a comparator in the context of life-extending treatments at the end of life because it is only available through the Cancer Drugs Fund. The Committee was aware that it should be guided by established practice in the NHS when identifying the appropriate comparators, irrespective of how these are funded. The Committee noted that lapatinib plus capecitabine was the comparator treatment in the EMILIA trial, and after discussion with clinical specialists the Committee had agreed that lapatinib plus capecitabine was a clinically relevant comparator in the second-line setting (see section 4.3). Lapatinib plus capecitabine was also the relevant comparator for trastuzumab emtansine in the incremental cost-effectiveness analysis. After further consideration, the Committee did not change its view that the evaluation of expected survival with current standard of care should be based on that of patients receiving lapatinib plus capecitabine. However, the Committee did note the comment from the company that if lapatinib plus capecitabine is to be a comparator, evidence on survival from sources other than the EMILIA trial should be taken into account. Specifically, the comment highlighted that in a clinical trial of lapatinib plus capecitabine compared with capecitabine alone (Cameron et al.) the median survival with lapatinib plus capecitabine was 75 weeks (18.8 months). The Committee considered evidence from this trial, together with other trials for lapatinib plus capecitabine in patients with advanced breast cancer. It noted that patients who received lapatinib plus capecitabine in EMILIA appeared to have lived longer than those who received it in other trials, in which median survival on this treatment generally fell below 24 months. However, the Committee did not have details of the patient characteristics at baseline in these trials, so it could not compare them directly with EMILIA or determine the extent to which they were generalisable to clinical practice. The Committee also noted that the mean survival with lapatinib plus capecitabine estimated by the company in its cost-effectiveness analysis was 30.4 months. The Committee found it difficult to evaluate this conflicting evidence, but after review of the reported median

survival from several trials of lapatinib plus capecitabine, it was prepared to accept that trastuzumab emtansine fulfilled this criterion. It also accepted that trastuzumab emtansine fulfilled the other 2 end-of-life criteria, namely a small patient population (approximately 1200) and a survival gain of at least 3 months. The Committee therefore concluded that trastuzumab emtansine fulfilled the criteria for end-of-life consideration.

4.20 Based on the considerations in section 4.19, the Committee discussed whether trastuzumab emtansine represents a cost-effective use of NHS resources. It agreed that, even taking into account additional weights applied to QALY benefits for a life-extending treatment at the end of life, the ICER incorporating the patient access scheme remained well above the range that could be considered a cost-effective use of NHS resources. The Committee concluded that trastuzumab emtansine could not be recommended for treating HER2-positive, unresectable locally advanced or metastatic breast cancer previously treated with trastuzumab and a taxane.

Pharmaceutical Price Regulation Scheme (PPRS)

4.21 The Committee met after an appeal against the Final Appraisal Determination (FAD) for this appraisal, which was upheld. The Appeal Panel had concluded that 'the 2014 PPRS should have been taken into account, or, alternatively and sufficiently for this appeal, that the possibility of the PPRS being relevant had not been sufficiently considered and its irrelevance established'. The Committee noted that, after this appeal, NICE had sought a view from the Department of Health about whether it should take account the payment mechanism set out in the 2014 PPRS agreement in its technology appraisals. In the Department of Health's view, 'the 2014 PPRS does not place obligations on, nor create expectations of, NICE other than where these are explicitly stated in that agreement'. The Department of Health noted paragraph 4.9 of the PPRS which states that 'the basic cost-effectiveness threshold used by NICE will be retained at a level consistent with the current range and not changed for the duration of the scheme', and stated that 'the PPRS contains no other provisions which require NICE to adopt a particular approach or method for technology appraisals, or to make an adjustment to its considerations to take account of the payment arrangements set out in the Scheme agreement'. The Committee understood that, in response to the appeal decision, NICE developed a position statement about the relevance of the 'PPRS Payment Mechanism' of the 2014

PPRS to assessing the cost effectiveness of new branded medicines. This took into account the views obtained from the Department of Health. It was subsequently refined in a targeted consultation with the Department of Health, the Association of the British Pharmaceutical Industry (ABPI), and NHS England. The NICE position statement concluded that 'the 2014 PPRS Payment Mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The Committee noted the response from the ABPI, an association with 57 pharmaceutical company members, which stated that the ABPI had no comments on the substance of the position statement, and welcomed the statement. The Committee also noted the ABPI comment that: 'Indeed, any other interpretation may increase the risk of legal challenge from other companies.' The Committee was, however, aware that the company continued to believe that it was 'unfair to disregard the consideration of PPRS payments within the appraisal process' and was 'deeply disappointed' by the conclusion of the position statement. Company representatives at the meeting stated that the company's opinion was that the NICE position statement should state that 'the 2014 PPRS Payment Mechanism *should*, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines', and that it should apply to all technology appraisals, not just to the appraisal of trastuzumab emtansine. The Committee concluded that the 2 sole negotiators for the PPRS, that is the Department of the Health and the ABPI, fully supported the NICE position statement, but that the company disagreed with it.

4.22 The Committee discussed what the NICE position statement meant for its consideration of cost effectiveness. It noted the company's suggestion that the failure of NICE to identify a solution was not sufficient reason for the Committee to disregard the impact of the 2014 PPRS on its appraisal of trastuzumab emtansine. The company representatives stated that the company's view was that the Committee should disregard the NICE position statement, and either accept the 'pragmatic solution' suggested in the company's formal response (see section 4.25), or itself devise some other mechanism to incorporate the PPRS into its evaluation of cost effectiveness. The Committee reminded itself that its role was limited to making recommendations to NICE about the clinical and cost effectiveness of treatments for use within the NHS, in line with the guide to the methods of technology appraisals (2013). This states that the Committee should not

recommend treatments that are not cost effective. It also recalled paragraph 6.4.14 of the guide to the methods of technology appraisal (2013), which states that: 'The potential budget impact of the adoption of a new technology does not determine the Appraisal Committee's decision.' The Committee concluded that it was not responsible for devising new methods for estimating cost effectiveness and, further, it had neither the remit nor the expertise to do so. Furthermore, it understood that the position statement had been issued as guidance to all NICE technology appraisal committees to ensure consistency of decision-making. It therefore took the view that the NICE position statement should not be disregarded without clear and coherent reasons for doing so.

4.23 The Committee discussed whether the PPRS could potentially be relevant to assessing opportunity costs that underlie a NICE appraisal; that is, would NHS adoption of trastuzumab emtansine, or other branded medicines that were not cost effective, come without additional cost to society, and without reducing spending on other more cost-effective treatments. It noted that the rationale for the NICE position statement was that it was not clear how payments made under the 2014 scheme were being applied in providing NHS services. The payments were not mandated to be allocated to local drug budgets and so would not automatically or routinely allow local commissioners or NHS England to revise their assessment of the opportunity costs of branded medicines. The Committee also noted NHS England's 'Question and Answer document for the NHS on the Pharmaceutical Price Regulation Scheme (PPRS)', which states that 'the agreement makes no provision for what happens to the PPRS payments, so there is no commitment for the DH [Department of Health] to make any additional payments to the NHS'. Moreover, the Committee was aware that any rebates for drug costs are paid quarterly, so even if the PPRS payments were repaid to the NHS, and directly to local commissioners, who have finite budgets, decisions would have to be made to temporarily reduce funding other health services until the PPRS payments are received, which would incur opportunity cost. In addition, there would be no rebate for administration or other follow-on medical costs incurred from introducing a new technology. The Committee also understood that, under the terms of the 2014 PPRS, when the allowed growth rate is exceeded, companies will make a cash payment of a percentage applied to sales covered by the PPRS payment during the relevant quarter (excluding products launched after 1 January 2014), and that percentage will be equal for all companies. Therefore, the Committee considered that the opportunity cost

would not only be borne by the NHS, but also by other companies who have joined the 2014 PPRS, and would have to contribute a larger share to the rebate based on how much the allowed spend was exceeded because of trastuzumab emtansine prescribing. The Committee concluded that, as it stands, the 2014 PPRS does not remove the opportunity cost from funding treatments that are not considered to be cost effective according to the normal methods of technology appraisals, and that the precise and full costs of introducing a new technology into the NHS were not covered or rebated via the PPRS.

4.24 The Committee noted that the essence of the position statement was that NICE did not consider that the 2014 PPRS enabled rebates to be transparently attributed to the acquisition cost of individual branded medicines at the time of the appraisal, and so could not identify a way in which the 2014 PPRS could fit within NICE's framework of appraising cost effectiveness. However, the statement did provide for potential exceptions to the general position of NICE. The Committee referred to the guidance in the guide to the methods of technology appraisal (2013) on considering prices for technologies in cost-effectiveness analyses. Specifically, it noted paragraph 5.5.2 which states that the public list prices for technologies should be used in the reference-case analysis or alternatively, and when nationally available, price reductions, provided that these are transparent and consistently available across the NHS, and the period for which the specified price is available is guaranteed. Because of the role of the Committee and the basis for the position statement, the Committee concluded that it would only be able to apply the exception provided for in the position statement if the PPRS mechanism could be shown to reduce the cost of the technology to the NHS, and still be in keeping with paragraph 5.5.2 of the guide to the methods of technology appraisal (2013).

4.25 The Committee discussed the company's proposal that the Committee issues positive guidance on trastuzumab emtansine conditional on the following:

- The company remains within the 2014 PPRS scheme.
- The spend level within the 2014 PPRS scheme remains above the agreed growth levels.
- Guidance is reviewed at the start of the 2019 PPRS scheme.

The Committee noted that the company's proposal did not show how the PPRS rebate

mechanism can be applied directly to the cost to the NHS of trastuzumab emtansine, in a way that could be incorporated into a cost-effectiveness analysis. It also heard from NICE that accepting this proposal would potentially be unlawful for a number of reasons. Firstly, the Committee would be over-riding current guidance on the assessment of the cost effectiveness of health technologies and, by not applying its published methods of technology appraisals, this implies that NICE would not be fulfilling its statutory functions. This would also be incongruous with the 2014 PPRS itself, which states that 'the basic cost-effectiveness threshold used by NICE will be retained at a level consistent with the current range and not changed for the duration of the scheme', indicating that NICE should continue to assess cost effectiveness. Secondly, accepting the proposal would potentially impact on the financial position of other pharmaceutical companies, with the potential legal implications referred to in the ABPI's response to consultation on the NICE position statement (see section 4.21). Thirdly, there is already a mechanism within the existing process for companies to propose special pricing arrangements to be taken into account in technology appraisals – Patient Access Schemes. These have to be approved by the Department of Health, which is also responsible for the 2014 PPRS. The Committee noted that the company could have used this mechanism to apply a price discount commensurate with what it believed would be the true cost of trastuzumab emtansine to the NHS, in the context of the 2014 PPRS. Accepting the company's proposal would, therefore, transcend the existing framework. In summary, the Committee was not satisfied that the company's proposal demonstrated that the impact of the PPRS rebate could be traced back to the opportunity cost of trastuzumab emtansine within the existing guide to the methods of technology appraisal (2013), and NICE's statutory functions. Because of this, the Committee concluded that the company's proposal did not represent an exception that might lead it to depart from the general position in the NICE statement.

4.26 In conclusion, the Committee did not hear anything that it could consider to be reasonable grounds to disregard the NICE position statement in this appraisal. The Committee agreed that it may consider the 2014 PPRS if specific proposals are put forward, if these fit within the methods and processes of technology appraisal and are consistent with NICE's statutory functions. However, it did not consider that such proposals had been put forward in this appraisal. Therefore, the Committee concluded that the 2014 PPRS did not affect its previous recommendations about trastuzumab emtansine.

Summary of Appraisal Committee's key conclusions

TA371	**Appraisal title: Trastuzumab emtansine for treating HER2-positive, unresectable locally advanced or metastatic breast cancer after treatment with trastuzumab and a taxane**	Section
Key conclusion		
Trastuzumab emtansine is not recommended, within its marketing authorisation, for treating adults with human epidermal growth factor receptor 2 (HER2) positive, unresectable locally advanced or metastatic breast cancer previously treated with trastuzumab and a taxane. The Committee agreed that the most plausible incremental cost-effectiveness ratio (ICER) for trastuzumab emtansine (without the patient access scheme) was above the ICER range that would normally be considered a cost-effective use of NHS resources. The Committee concluded that the size of the discount in the patient access scheme meant that it was still unable to recommend trastuzumab emtansine. The Committee agreed that trastuzumab emtansine fulfilled the criteria for end-of-life consideration. However, it agreed that, even taking into account additional weights applied to quality-adjusted life year (QALY) benefits for a life-extending treatment at the end of life and the patient access scheme, trastuzumab emtansine did not represent a cost-effective use of NHS resources. The Committee concluded that the 2014 Pharmaceutical Price Regulation Scheme (PPRS) did not affect its recommendations about trastuzumab emtansine.		1.1, 4.15, 4.16, 4.19, 4.20, 4.26
Current practice		
Clinical need of patients, including the availability of alternative treatments	The Committee recognised that patients value the availability of more treatment options and that trastuzumab emtansine would be welcomed by patients and their families. The Committee noted that some alternative treatments to trastuzumab emtansine were not offered by all cancer centres or were available in England through the Cancer Drugs Fund, which led to some variation in clinical practice so that no single pathway of care could be defined.	4.1, 4.2
The technology		

Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The Committee heard from the clinical specialists that trastuzumab emtansine is both an effective treatment and also well tolerated, with fewer side effects than some of the other options. The Committee acknowledged that trastuzumab emtansine is a novel antibody-drug conjugate combining the HER2-targeted anti-tumour activity of trastuzumab with a cytotoxic agent. It also noted that trastuzumab emtansine prolonged survival, with less toxicity than lapatinib plus capecitabine.	4.1, 4.17
What is the position of the treatment in the pathway of care for the condition?	The Committee noted that the clinical specialists expect that trastuzumab emtansine would be used second line (that is, instead of continued trastuzumab plus chemotherapy or lapatinib plus capecitabine).	4.3
Adverse reactions	The Committee concluded that trastuzumab emtansine had been shown to have a satisfactory adverse-event profile in EMILIA.	4.8
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The Committee discussed which sources of trial data were appropriate for the place in therapy in which trastuzumab emtansine is likely to be used (that is, the second-line setting). Because 36% of patients in EMILIA and 0% of patients in TH3RESA received treatment as second-line therapy, the Committee concluded that EMILIA was the most relevant source of clinical evidence for its decision-making in this appraisal.	4.4

Relevance to general clinical practice in the NHS	The Committee noted that patients in England may receive pertuzumab plus trastuzumab plus docetaxel in the first-line setting, and that 9.5% of patients in EMILIA had previously received pertuzumab therapy. It also noted the Evidence Review Group (ERG's) concern that none of the patients in EMILIA had an Eastern Cooperative Oncology Group (ECOG) performance status of 2, whereas in clinical practice around one-third of patients would have an ECOG performance status of 2. The Committee agreed that the population in EMILIA was otherwise reasonably representative of patients in the UK, concluding that the results of EMILIA were suitable for the assessment of the clinical effectiveness of trastuzumab emtansine in clinical practice.	4.5, 4.6
Uncertainties generated by the evidence	The Committee considered the clinical effectiveness of trastuzumab emtansine as a second-line treatment. It noted that subgroup analyses of EMILIA suggested a lesser benefit in patients who received second-line treatment (in whom the difference in effect was not statistically significant) than in the overall population. The Committee was aware that the analysis may not have been powered to demonstrate a difference in treatment effect in the subgroup, and that there is no biologically plausible reason for the effect to differ by the number of previous treatments received. The Committee concluded that the subgroup analysis was not reliable enough to inform a decision about the clinical effectiveness of trastuzumab emtansine as a second-line treatment.	4.7
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The Committee noted that the clinical specialists expect that trastuzumab emtansine would be used as a second-line therapy. In EMILIA, 36% of patients received treatment as second-line therapy for locally advanced or metastatic disease.	4.3, 4.4

Estimate of the size of the clinical effectiveness including strength of supporting evidence	The Committee concluded that EMILIA was the most relevant source of clinical evidence for its decision-making in this appraisal. In EMILIA, trastuzumab emtansine increased median overall survival by 5.8 months (trastuzumab emtansine 30.9 months, lapatinib plus capecitabine 25.1 months), and the hazard ratio was 0.68 (95% confidence interval 0.55 to 0.85, p<0.001).	3.7, 4.4
Evidence for cost effectiveness		
Availability and nature of evidence	The Committee concluded that the company's model was appropriate to estimate the cost effectiveness of trastuzumab emtansine but that, instead of the 10-year time horizon used in the company's base case, a 15-year time horizon should be used.	4.10
Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee noted that the company assumed clinical equivalence between capecitabine and vinorelbine, and between trastuzumab plus capecitabine and trastuzumab plus vinorelbine. It heard from the clinical specialists that in their opinion it would be reasonable to assume no difference. The Committee concluded that the assumption of no difference between capecitabine- and vinorelbine-based regimens in the model could be justified for this appraisal.	4.12

Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	The Committee noted that in the progression-free state, the company applied a higher utility value for trastuzumab emtansine than for its comparators. It noted that evidence from EMILIA suggested that in the trial, patients who received trastuzumab emtansine felt better and reported being less troubled by side effects than those who received lapatinib plus capecitabine. The Committee was aware that EMILIA was an open-label trial, which may have introduced bias in the outcomes reported by patients, but concluded that a marginally higher utility value for trastuzumab emtansine in the progression-free state could be accepted in this appraisal. The Committee noted that the model incorporated utility decrements for only 3 adverse events and costs for 2 adverse events. It concluded that the model should have incorporated the decrease in utility and the increased costs associated with the adverse events that occurred frequently in EMILIA.	4.11, 4.13
Are there specific groups of people for whom the technology is particularly cost effective?	There are no specific groups of people for whom the technology is particularly cost effective.	
What are the key drivers of cost effectiveness?	There were no specific Committee considerations on the key drivers of cost effectiveness.	
Most likely cost-effectiveness estimate (given as an ICER)	The Committee noted that, without the patient access scheme, the company's base-case ICER for trastuzumab emtansine compared with lapatinib plus capecitabine was £167,200 per QALY gained, and that the ERG's base-case ICER was very similar at £166,400 per QALY gained. It agreed that the most plausible ICER was above the ICER range that would normally be considered a cost-effective use of NHS resources, and that the patient access scheme did not reduce that ICER to a level close to one that could be accepted as a cost-effective use of NHS resources.	4.15, 4.16

Additional factors taken into account		
Patient access schemes (PPRS)	Roche has agreed a patient access scheme with the Department of Health. If trastuzumab emtansine had been recommended, this scheme would provide a simple discount to the list price of trastuzumab emtansine, with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Committee concluded that the proposals put forward by the company to take into account the PPRS did not represent an exception that might lead it to depart from the general position in the NICE statement.	2.3, 4.25
End-of-life considerations	Although the median survival of patients in the lapatinib plus capecitabine group of EMILIA was 25.1 months and the mean survival with lapatinib plus capecitabine was 30.4 months, review of the reported survival times from several trials other than EMILIA suggested that life expectancy on lapatinib plus capecitabine generally fell below 24 months. The Committee could not compare those trials directly with EMILIA or determine the extent to which they were generalisable to clinical practice but, based on the reported median survival on lapatinib plus capecitabine in them, it was prepared to accept that trastuzumab emtansine fulfilled the criterion for short life expectancy. It also accepted that trastuzumab emtansine fulfilled the other 2 end-of-life criteria (a small patient population and a survival gain of at least 3 months). However, it agreed that, even taking into account additional weights applied to QALY benefits for a life-extending treatment at the end of life and the patient access scheme, trastuzumab emtansine did not represent a cost-effective use of NHS resources.	4.19, 4.20
Equalities considerations and social value judgements	No equality issues relevant to the Committee's preliminary recommendations were raised.	

5 Review of guidance

5.1 The guidance on this technology will be considered for review 3 years after publication of the guidance. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Andrew Dillon
Chief Executive
December 2015

6 Appraisal Committee members and NICE project team

Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Jane Adam (Chair)
Consultant Radiologist, Department of Diagnostic Radiology, St George's Hospital, London

Professor Iain Squire (Vice-Chair)
Consultant Physician, University Hospitals of Leicester

Dr Gerardine Bryant
General Practitioner, Swadlincote, Derbyshire

Dr Andrew England
Senior Lecturer, Directorate of Radiography, University of Salford

Mr Adrian Griffin
Vice President, HTA & International Policy, Johnson & Johnson

Dr Anne McCune
Consultant Hepatologist, University Hospitals Bristol NHS Foundation Trust

Professor John McMurray
Professor of Medical Cardiology, University of Glasgow

Dr Mohit Misra
General Practitioner, Queen Elizabeth Hospital, London

Ms Pamela Rees
Lay Member

Dr Brian Shine
Consultant Chemical Pathologist, John Radcliffe Hospital, Oxford

Dr Eldon Spackman
Research Fellow, Centre for Health Economics, University of York

Mr David Thomson
Lay Member

Dr John Watkins
Clinical Senior Lecturer, Cardiff University; Consultant in Public Health Medicine, National Public Health Service Wales

Professor Olivia Wu
Professor of Health Technology Assessment, University of Glasgow

Dr Nerys Woolacott
Senior Research Fellow, Centre for Health Economics, University of York

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Ahmed Elsada
Technical Lead

Sally Doss and Zoe Charles
Technical Advisers

Bijal Joshi
Project Manager

7 Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by the School of Health and Related Research (ScHARR), The University of Sheffield:

- Squires H, Simpson EL, Harvey R, et.al. T-DM1 for treating HER2-positive, unresectable locally advanced or metastatic breast cancer after treatment with trastuzumab and a taxane: A Single Technology Appraisal, February 2014.

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to give their expert views. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I. Company:

- Roche Products

II. Professional/specialist and patient/carer groups:

- Breakthrough Breast Cancer
- Breast Cancer Campaign
- Breast Cancer Care
- Royal College of Nursing
- Royal College of Physicians (NCRI/RCP/RCR/ACP/JCCO)
- United Kingdom Oncology Nursing Society

III. Other consultees:

- Department of Health
- NHS England
- Welsh Government

IV. Commentator organisations (did not provide written evidence and without the right of appeal):

- Department of Health, Social Services and Public Safety for Northern Ireland
- GlaxoSmithKline (lapatinib)
- Healthcare Improvement Scotland
- Medicines and Healthcare products Regulatory Agency
- National Collaborating Centre for Cancer

C. The following individuals were selected from clinical specialist and patient expert nominations from the consultees and commentators. They gave their expert personal view on trastuzumab emtansine by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr Anne Armstrong, Consultant Medical Oncologist, nominated by organisation representing Royal College of Physicians (NCRI/RCP/RCR/ACP/JCCO) – clinical specialist
- Dr Gianfilippo Bertelli, Consultant / Honorary Senior Lecturer in Medical Oncology, nominated by organisation representing Royal College of Physicians (NCRI/RCP/RCR/ACP/JCCO) – clinical specialist
- Elisabeth Segal, nominated by organisation representing Breakthrough Breast Cancer – patient expert
- Tara Beaumont, nominated by organisation representing Breast Cancer Care – patient expert

D. Representatives from the following company attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Roche Products

About this guidance

NICE technology appraisal guidance is about the use of new and existing medicines and treatments in the NHS.

This guidance was developed using the NICE single technology appraisal process.

We have produced information for the public explaining this guidance. Information about the evidence it is based on is also available.

NICE produces guidance, standards and information on commissioning and providing high-quality healthcare, social care, and public health services. We have agreements to provide certain NICE services to Wales, Scotland and Northern Ireland. Decisions on how NICE guidance and other products apply in those countries are made by ministers in the Welsh government, Scottish government, and Northern Ireland Executive. NICE guidance or other products may include references to organisations or people responsible for commissioning or providing care that may be relevant only to England.

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Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

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