NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Trastuzumab emtansine for adjuvant treatment of HER2-positive early breast cancer [ID1516]

Committee Papers

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Trastuzumab emtansine for adjuvant treatment of HER2-positive early breast cancer [ID1516]

Contents:

The following documents are made available to consultees and commentators:

The **final scope and final stakeholder list** are available on the NICE website.

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   a. Professor Andrew Wardley – clinical expert Consultant & MAHSC Professor in Breast Medical Oncology, nominated by UK Breast Cancer Group
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Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Trastuzumab emtansine for adjuvant treatment of HER2-positive breast cancer (ID1516)

Document B

Company evidence submission

Roche Products Limited

September 2019

File name	Version	Contains confidential information	Date
ID1516_Trastuzumab emtansine_Document B_22-10-2019_REDACTED	1.0	Yes	22nd October, 2019

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Tables and figures

Tables

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Abbreviations

Abbreviation	Definitions
AC-T	Doxorubicin + cyclophosphamide followed by docetaxel
AC-TH	Doxorubicin + cyclophosphamide followed by docetaxel + trastuzumab
ADC	Antibody-drug conjugate
AE	Adverse event
AIC	Akaike Information Criterion
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BCS	Best case scenario
BIC	Bayesian Information Criterion
CI	Confidence interval
CNS	Central nervous system
CSR	Clinical study report
CT	Computerised tomography
DCIS	Ductal carcinoma *in situ*
DDFS	Distant disease-free survival
DFS	Disease-free survival
DRFI	Distant recurrence-free interval
DSU	Decision Support Unit
eBC	Early breast cancer
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
eMIT	Electronic market information tool
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	EuroQol-5 Dimension
ER	Oestrogen receptor
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
FAD	Final Appraisal Document
FDA	Food and Drug Administration
FEC	Fluorouracil + epirubicin + cyclophosphamide
FEC-THP	Fluorouracil + epirubicin + cyclophosphamide followed by pertuzumab + trastuzumab + taxane
GHS	Global health status
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUV	Health state utility value
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio

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Abbreviation	Definitions
IDFS	Invasive disease-free survival
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IV	Intravenous
LVEF	Left ventricular ejection fraction
MAIC	Match-adjusted indirect comparison
mBC	Metastatic breast cancer
MOS SF-36	Medical Outcomes Study Short Form Survey
MTA	Multiple technology appraisal
NCCN	National Comprehensive Cancer Network
NCRI	National Cancer Research Institute
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NYHA	New York Heart Association
OS	Overall survival
pCR	Pathological complete response
PFS	Progression-free survival
PH	Proportional hazards
PRO	Patient reported outcome
PSA	Probabilistic sensitivity analysis
PSSRU	Personal Social Services Research Unit
PTC	Pertuzumab + trastuzumab + chemotherapy
Q3W	Every 3 weeks
QALY	Quality-adjusted life year
QLQ-BR23	Breast Cancer-Specific Quality of Life Questionnaire
QLQ-C30	Quality of Life Questionnaire
QoL	Quality of life
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
RID	Residual invasive disease
SABCS	San Antonio Breast Cancer Symposium
SAE	Serious adverse event
SC	Subcutaneous
SLR	Systematic literature review
SMC	Scottish Medicine Consortium
SmPC	Summary of product characteristics
SoC	Standard of Care
STA	Single technology appraisal
STEEP	Standardized definitions for efficacy endpoints
TCH	Docetaxel + carboplatin + trastuzumab
TC-HP	Docetaxel + carboplatin + trastuzumab + pertuzumab

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Abbreviation	Definitions
tpCR	Total pathological complete response
TTO	Time trade-off
TTOT	Time-to-off treatment

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B.1 Table Decision problem, description of the technology and clinical care pathway

B.1.1 *Decision problem*

The submission covers the full anticipated marketing authorisation for adjuvant trastuzumab emtansine, [redacted]".

Overall, the decision problem addressed within this submission is consistent with the NICE final scope as outlined in Table 1, other than the patient population considered in this submission, which is slightly narrower than that specified in the final scope. The final scope does not specify that a patient's residual disease after neoadjuvant treatment must be invasive, therefore the final scope encompasses a broader population than this submission (i.e. the final scope includes patients with ductal carcinoma *in situ* [DCIS], which would not be considered RID according to most definitions of pathological complete response [pCR]). The narrower population considered in this submission has been chosen to align with both the pivotal clinical trial of trastuzumab emtansine in this indication, the KATHERINE trial, in which patients were required to have RID after neoadjuvant treatment, and with the anticipated marketing authorisation for the adjuvant use of trastuzumab emtansine.

In addition, NICE published a Final Appraisal Document (FAD) in February 2019 recommending the use of pertuzumab + trastuzumab + chemotherapy in the adjuvant treatment of patients with HER2-positive, node-positive eBC. Pertuzumab + trastuzumab + chemotherapy is therefore a relevant comparator to trastuzumab emtansine in a subgroup of the KATHERINE intention-to-treat (ITT) population: those patients with node-positive disease who received neoadjuvant therapy and still have RID at surgery. The economic analysis of this subgroup has been documented in Appendix M.

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Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with HER2-positive eBC who have residual disease following neoadjuvant therapy containing a taxane (with or without anthracycline) and HER2-targeted therapy.	Adult patients with HER2-positive eBC who have RID, in the breast and/or lymph nodes, after pre-operative systemic treatment that included HER2-targeted therapy.	The patient population considered in this submission is slightly narrower than that specified in the final scope, which does not specify that a patient's residual disease must be invasive. The broader population specified in the final scope may include patients with DCIS, which would not be considered RID in most definitions of pCR. The population considered in this submission is in line with the pivotal clinical trial for trastuzumab emtansine in this indication, the KATHERINE trial, in which patients were required to have RID after neoadjuvant treatment, and with the anticipated marketing authorisation for the adjuvant use of trastuzumab emtansine.
Intervention	Trastuzumab emtansine	Trastuzumab emtansine	N/A – in line with the NICE final scope.
Comparator(s)	Standard adjuvant therapies including trastuzumab. For people with node-positive disease, pertuzumab in combination with trastuzumab and chemotherapy.	This submission compares trastuzumab emtansine with trastuzumab in terms of both clinical efficacy and cost effectiveness, as per the final scope. For people with node-positive disease, exploratory results of a naïve clinical efficacy comparison between trastuzumab emtansine and pertuzumab + trastuzumab + chemotherapy, based on a Bucher analysis, are presented in Appendix M. The corresponding economic analysis is presented in Section B.3 and Appendix M as a subgroup analysis.	Comparison against standard adjuvant therapies including trastuzumab: in line with the final scope. Comparison against pertuzumab in combination with trastuzumab and chemotherapy in people with node-positive disease: no statistically robust comparisons were possible for the clinical efficacy of these regimens. Exploratory results based on a Bucher analysis are presented in order to best address the decision problem in this appraisal. However, these analyses are not endorsed by the Company because they are likely to lead to biased results and are not methodologically justified. The sizable limitations associated with the analyses mean that the results should be interpreted with caution. In terms of cost-effectiveness, this comparison has been presented as a subgroup analysis.

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	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Outcomes	The outcome measures to be considered include: • Overall survival • Disease-free survival • Adverse effects of treatment • Health-related quality of life	The following outcomes have been included within this submission: • Invasive disease-free survival • Distant recurrence-free interval • Overall survival • Disease-free survival • Adverse effects of treatment • Health-related quality of life	Invasive disease-free survival was the primary outcome of the pivotal phase III study for adjuvant trastuzumab emtansine in this indication – the KATHERINE study. Distant recurrence-free interval was a secondary outcome of the KATHERINE study.
Economic analysis	• The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. • The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. • Costs will be considered from an NHS and Personal Social Services perspective. • The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.	• The cost-effectiveness of trastuzumab emtansine vs the relevant comparators has been expressed in terms of incremental cost per quality-adjusted life year (• • •) gained. • A time horizon of 51 years has been chosen for the base case, which is considered an appropriate duration over which to fully capture meaningful differences in costs and health outcomes between trastuzumab emtansine and the comparators. • All costs have been considered from an NHS and Personal Social Services perspective. • The PAS/commercial access agreements for adjuvant trastuzumab emtansine, trastuzumab and pertuzumab have been taken into account.	N/A – in line with the NICE final scope.

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	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Subgroups to be considered	If evidence allows, the following subgroups will be considered separately: • Prior neoadjuvant therapy including trastuzumab (with no prior pertuzumab therapy). • Prior neoadjuvant therapy including pertuzumab with trastuzumab.	The following subgroups have been considered in the clinical section of this submission: • Prior neoadjuvant therapy including trastuzumab (with no prior pertuzumab therapy). • Prior neoadjuvant therapy including pertuzumab with trastuzumab. Patients with node-positive disease have also been included as a subgroup analysis of the economic model in Appendix M.	In the KATHERINE trial, the treatment effect of trastuzumab emtansine was consistent for patients who received prior neoadjuvant pertuzumab + trastuzumab + chemotherapy compared to patients who received trastuzumab + chemotherapy. No subgroup analysis was therefore conducted in the economic model based on whether patients received prior pertuzumab + trastuzumab + chemotherapy or trastuzumab + chemotherapy. In the economic analysis, a subgroup analysis considering node-positive patients specifically was conducted to facilitate a comparison of adjuvant trastuzumab emtansine with pertuzumab + trastuzumab + chemotherapy in these patients.
Special considerations including issues related to equity or equality	None specified.	None identified.	N/A – in line with the NICE final scope.

Abbreviations: DCIS: ductal carcinoma in situ; eBC: early breast cancer; HER2: human epidermal growth factor receptor 2; IDFS: invasive disease-free survival; N/A: not applicable; NHS: National Health Service; NICE: National Institute of Health and Care Excellence; PAS: patient access scheme; pCR: pathological complete response; QALY: quality-adjusted life year; RID: residual invasive disease.
Source: NICE Final Scope ID1516[1]

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B.1.2 *Description of the technology being appraised*

A summary of the mechanism of action, marketing authorisation status, costs and administration requirements associated with trastuzumab emtansine for the treatment of eBC is presented in Table 2.

Table 2. Technology being appraised

UK approved name and brand name	Trastuzumab emtansine (KADCYLA®)
Mechanism of action	• Trastuzumab emtansine is an antibody-drug conjugate (ADC) consisting of trastuzumab, a humanised IgG1 monoclonal antibody, and the microtubule inhibitor emtansine (DM1).[2] • Trastuzumab emtansine provides intracellular delivery of DM1 directly to HER2-overexpressing cells, while maintaining the HER2 receptor blocking and antibody-dependent cell-mediated cytotoxicity (ADCC) activity of trastuzumab.[2]
Marketing authorisation/CE mark status	• 2013: A European marketing authorisation was granted for trastuzumab emtansine in HER2-positive, unresectable locally advanced or metastatic breast cancer after treatment with trastuzumab and a taxane, separately or in combination.[2] • This represented the first approval of an ADC for the treatment of a prevalent solid tumour.[3, 4] Trastuzumab emtansine remains the only approved ADC for the treatment of HER2-positive breast cancer.[5] • 2019: A European marketing authorisation application to extend the use of trastuzumab emtansine to include "[redacted]", was submitted to the European Medicines Agency (EMA) on 4th February 2019 and a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) is expected in [redacted] 2019. • 2019: A US marketing authorisation was granted to extend the use of trastuzumab emtansine to include the adjuvant treatment of patients with HER2-positive eBC who have RID after neoadjuvant taxane and trastuzumab-based treatment. Trastuzumab emtansine was granted breakthrough therapy designation for this application.[6, 7]

Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	• Current indication: trastuzumab emtansine is indicated for use in HER2-positive, unresectable locally advanced or metastatic breast cancer after treatment with trastuzumab and a taxane, separately or in combination. Patients should have either:[2]
	  ○ Received prior therapy for locally advanced or metastatic disease, or
	  ○ Developed disease recurrence during or within six months of completing adjuvant therapy.
	• Contraindications include hypersensitivity to trastuzumab emtansine, succinic acid, sodium

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<table>
<tr><td></td><td>hydroxide, sucrose or polysorbate 20.[2]</td></tr>
<tr><td>Method of administration and dosage</td><td>

Trastuzumab emtansine is administered as an intravenous (IV) infusion at 3.6 mg/kg of body weight every 3 weeks (21 days) (eBC and mBC).[2]
Patients should be treated for 14 cycles (eBC), or until disease progression or unacceptable toxicity (eBC and mBC).[8]
Management of symptomatic adverse reactions (including increased AST/ALTs, hyperbilirubinemia, thrombocytopenia, left ventricular dysfunction or peripheral neuropathy) may require temporary interruption, dose reduction, or treatment discontinuation of trastuzumab emtansine, as outlined in the SmPC.[2] The dose reduction schedule is provided below:

<table>
<tr><th>Dose reduction schedule</th><th>Dose to be administered</th></tr>
<tr><td>First dose reduction</td><td>3 mg/kg</td></tr>
<tr><td>Second dose reduction</td><td>2.4 mg/kg</td></tr>
<tr><td>Requirement for further dose reduction</td><td>Discontinue treatment</td></tr>
</table>
</td></tr>
<tr><td>Additional tests or investigations</td><td>

It is standard clinical practice to test the HER2 status of tumours at the point of diagnosis.[9]
As such, no additional tests are required prior to the administration of trastuzumab emtansine.

</td></tr>
<tr><td>List price and average cost of a course of treatment</td><td>

The list price of trastuzumab emtansine is £1,641.01 per 100 mg vial and £2,625.62 per 160 mg vial.
The average cost of a course of treatment in the adjuvant setting is £50,699.32 (list price) – cost effectiveness model (ID1516).

</td></tr>
<tr><td>Patient access scheme (PAS) (if applicable)</td><td>

A PAS is in place between the Department of Health and Roche Products Ltd. for trastuzumab emtansine.
Trastuzumab emtansine (100 mg vial list price = £1,641.01 and 160 mg vial list price = £2,625.62) is offered at a discount of [redacted]% in both the adjuvant and second line metastatic settings (100 mg vial net price = £[redacted] and 160 mg vial net price = £[redacted]).

</td></tr>
</table>

Abbreviations: ADC: antibody drug conjugate; ADCC, antibody-dependent cell-mediated cytotoxicity; ALT: alanine transaminase; AST: aspartate transaminase; CHMP: Committee for Medicinal Products for Human Use; DM1: emtansine; eBC: early breast cancer; EMA: European Medicines Agency; HER2: human epidermal growth factor receptor 2; Ig: immunoglobulin; IV: intravenous; PAS: patient access scheme; RID: residual invasive disease; SmPC: summary of product characteristics.

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B.1.3 *Health condition and position of the technology in the treatment pathway*

Summary of health condition and the position of the technology

- Breast cancer was the most common type of cancer and the fourth most common cause of cancer death in the UK in 2016, accounting for 15% of all new cancer cases.[10]
- Approximately 14% of patients with eBC, in which the disease is still localised to the breast and regional lymph nodes, have HER2-positive disease.[11] If untreated, HER2-positive breast cancer is associated with increased tumour size, increased risk of disease recurrence and poorer clinical outcomes compared to HER2-negative disease.[12-16]
- The treatment goal in eBC is cure. Treating patients with the most effective regimens in the first instance is the best opportunity to prevent metastatic relapse. Metastatic breast cancer (mBC) is incurable (treatment is palliative with the goal of delaying progression) and is associated with high healthcare costs and societal burden.[17, 18] Treating eBC effectively to reduce the risk of metastatic relapse reduces the burden of breast cancer overall.
- Systemic HER2-targeted treatment is the standard of care (SoC) for HER2-positive eBC in the UK,[19] and has already transformed the treatment and prognosis of patients with HER2-positive eBC. Systemic treatment can be given in the neoadjuvant (pre-surgery) and adjuvant (post-surgery) settings as part of a complete eBC treatment regimen, to reduce the risk of disease recurrence.
- Neoadjuvant therapy may reduce the size of a tumour to the extent that no invasive tumour is detected in the surgically excised breast specimen (and axillary lymph node[s], depending on the definition), described as a pCR, whilst patients who do not achieve a pCR are described as having RID.
- Neoadjuvant HER2-targeted agents + chemotherapy have generated pCR rates of 29.0–66.2% in proof-of-concept clinical trials.[20-23] In current UK clinical practice the majority of patients with HER2-positive eBC eligible for neoadjuvant therapy receive neoadjuvant pertuzumab + trastuzumab + chemotherapy, which is associated with pCR rates of approximately 60%.[24-30] The 40% of patients who do not achieve pCR, and therefore have RID at surgery, are at high risk of recurrence and have been consistently demonstrated to have poorer prognosis than those who achieve a pCR.[31-34]
- Little guidance is available to inform the optimal treatment approach after surgery based on tumour response to neoadjuvant therapy, and adjuvant treatments for patients who may benefit from a change of systemic therapy are lacking. As a result, patients with RID at surgery currently receive the same adjuvant treatment as those achieving a pCR, despite their significantly poorer prognosis.[19]

B.1.3.1 Early breast cancer overview

Breast cancer is a malignant cancer that forms in tissues of the breast, usually the ducts or lobules. Breast cancer was the most common type of cancer and the fourth most common cause of cancer death in the UK in 2016, accounting for 15% of all new cancer cases.[10] Breast cancer is classified as eBC if it has not spread beyond the breast or axillary lymph nodes.

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The treatment goal in patients with eBC is preventing relapse with metastatic disease (also called advanced or secondary breast cancer), which is currently incurable, by giving the most effective available treatment early in the course of the disease. Improving the results of initial therapy, when the disease is localised to the breast and regional lymph nodes, offers patients the best chance of cure.

Approximately 14% of patients with eBC have HER2-positive disease,[11] in which the HER2 cell surface protein is overexpressed. The HER2 protein is a member of the epidermal growth factor receptor (EGFR) family that regulate normal cell growth, development and survival processes, and HER2 signalling may drive the growth of HER2-positive breast cancer. Importantly, the overexpression of HER2 is associated with an aggressive disease course and poor prognosis.[12, 35] If untreated, breast cancers that overexpress HER2 are associated with increased tumour size, increased risk of disease recurrence and poorer clinical outcomes compared to HER2-negative cancers.[12-16, 35] Patients diagnosed with HER2-positive breast cancer are on average around five years younger than the average breast cancer population,[36] and therefore more likely than patients in the general breast cancer population to still be in work, and/or have dependent children or relatives.

B.1.3.2 The burden of breast cancer

Breast cancer and its management have significant negative personal, social and economic effects on patients, their friends and families, and wider society, and these effects can persist in cancer survivors, who are at risk of disease recurrence and cardiovascular complications, infertility and neurocognitive problems.[37] Cancer survivors may also face a financial burden and employment discrimination even after treatment cessation.[37] Treating patients with eBC with the most effective treatment regimen in the first instance reduces the likelihood of progression to mBC, which is associated with a higher societal burden and healthcare costs, and may therefore reduce the burden of breast cancer overall.

Quality of life burden

Patients with eBC and their caregivers report lower health-related quality of life (HRQoL) compared to the general population, and this can persist following treatment cessation. In one Swedish study for example, patients with eBC of any subtype had a mean EuroQol-5 Dimension (EQ-5D) index value of 0.696 (95% confidence interval [CI], 0.634–0.747) in their first year after a primary breast cancer diagnosis, with 71% of patients reporting moderate to severe problems with pain and 65% of patients reporting moderate to severe problems with anxiety/depression.[38] Patients who progress to HER2-positive mBC in the UK have poorer health utility scores than patients with eBC receiving HER2 therapy + chemotherapy, reflecting the uncertainly associated with advanced disease.[39]

Caregiver and family member quality of life (QoL) is also negatively affected by the uncertain future associated with breast cancer, the life-threatening nature of the disease and the distressing treatment side effects that patients experience, resulting in a strain on the caregiver themselves and their families.[40, 41] For example, husbands of women with breast cancer of any stage who were receiving active breast cancer treatment were shown by Wagner (2006) to score significantly lower on general health, vitality, role-emotional and mental health subscales of the 36-item Medical Outcomes Study Short Form Survey (MOS SF-36) compared with spouses of healthy women.[42] The illness and premature death of patients with mBC has particularly severe psychological, social and economic implications for patients themselves as well as their spouses,

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children, other family and friends due to the relatively young average age at diagnosis of HER2-positive mBC (approximately 55 years).[40, 43]

Economic burden

Breast cancer also has an overarching impact on the UK economy through both direct and indirect costs. The gross national cost of incident mBC cases of any subtype in the UK has been estimated at £22 million annually (calculated in 2002 GBP),[44] and a National Cancer Research Institute (NCRI) report from 2012 stated that breast cancer of all subtypes and stages accounts for an annual economic cost of £1.5 billion in the UK.[45] The same study estimated that premature deaths, time off work and unpaid care by friends and family accounted for 64% of all UK cancer costs in 2009,[45] demonstrating the significance of both direct and indirect costs when considering the overall economic cost of breast cancer.

According to UK studies, a higher proportion of patients with HER2-positive mBC are unable to work and report significantly higher levels of activity impairment compared to patients with HER2-positive eBC.[18, 39] For example, the PURPOSE non-interventional study of patients with HER2-positive breast cancer found that significantly fewer patients with mBC (27.5%) were employed compared to patients with eBC (~50–51%, depending on whether patients were on treatment or post-treatment), and more patients with mBC reported being unable to work, reflecting the impact of advanced disease.[18] The estimated yearly total cost of absenteeism per patient (in employed patients and those reporting being unable to work) was £10,556 in patients receiving treatment for mBC.[18] The premature deaths of patients with mBC also has particularly severe social and economic implications, as many patients with HER2-positive mBC die at a relatively young age.

mBC also has substantial long-term cost and resource implications for the NHS. A 2016 study, including 359,771 patients with breast cancer in the UK, estimated that mean per-patient healthcare costs for a patient aged between 18–64 diagnosed with stage 3 or 4 cancer amounted to £39,353 over 9 years post-diagnosis (calculated in 2010 GBP).[46] Costs incurred for patients with HER2-positive mBC specifically are significant due to high levels of anti-cancer resource use in the initial management of the disease, the cost of available interventions, and the availability of effective treatments which extend life expectancy.[47, 48] For example, an interim analysis of the ESTHER non-interventional study (which follows UK patients from diagnosis of HER2-positive mBC or unresectable locally advanced breast cancer) found that 93.2% of 205 patients received systemic HER2-targeted therapies, 41% received bone-modifying agents, 22.9% received radiotherapy and 6.3% received metastatic ressection.[17] The cost of a year of treatment and supportive care for a patient with HER2-positive mBC who has progressed after first line treatment has been reported as in excess of £100,000 (when medicines are provided at list price), demonstrating the extent of this financial burden on the English healthcare system.[49]

Importance of effective treatments for eBC

It is therefore of the utmost importance to patients diagnosed with HER2-positive eBC in the UK, their families, society, and the healthcare system, to utilise the best possible treatment options at an early stage of the disease whilst the disease is still curable. Treating patients with eBC with the most effective treatment regimen in the first instance maximises the chance of a cure, and results in reduced patient, societal and economic burden through avoidance of disease progression to mBC.

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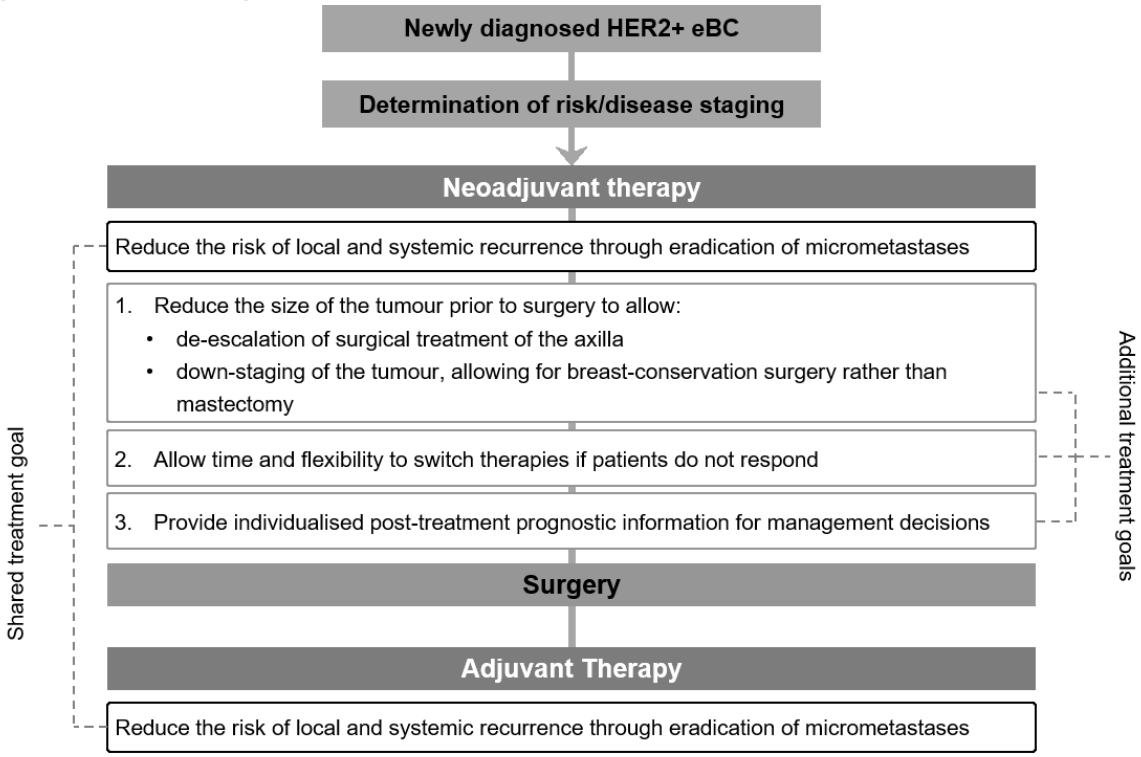
B.1.3.3 Principles of treatment in early breast cancer

The treatment goal in patients with eBC is preventing the development of incurable mBC, by giving the most effective available treatment early in the disease course. Current treatment for patients with HER2-positive eBC involves a combination of HER2-targeted therapy, chemotherapy, surgery, radiotherapy and hormone therapy (for patients with hormone receptor-positive disease), depending on the characteristics of the tumour.

As shown in Figure 1, systemic HER2-targeted therapy can be given neoadjuvantly (pre-surgery) and adjuvantly (post-surgery) as part of a complete eBC treatment regimen, with the goal of reducing the risk of both local and systemic recurrence.[50-53] In addition to this shared goal, initiating systemic treatment neoadjuvantly may also reduce the size of the tumour prior to surgery. This may reduce the morbidity of surgery by enabling down-staging of the surgical procedure in the breast, allowing for breast-conservation surgery rather than mastectomy, and reducing the extent of axillary surgery.[50-52] Patients in whom no invasive tumour is pathologically detected in the surgically excised breast specimen (and axillary lymph node[s], depending on the precise definition used) are described as having a pCR to neoadjuvant therapy, whilst those who do not achieve a pCR are described as having RID.

Figure 1. Treatment goals in eBC



Source: Cain *et al*. (2017);[52] Burstein *et al*. (2019).[53]
Abbreviations: eBC: early breast cancer; HER2: human epidermal growth factor receptor.

Current unmet need in the treatment of eBC

The use of HER2-targeted agents has already transformed the treatment and prognosis of patients with HER2-positive eBC, and as a result HER2-targeted agents + chemotherapy are now the SoC for the treatment of HER2-positive eBC in the UK.[19]

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A variety of regimens were originally used to test the principle of neoadjuvant HER2-targeted therapy, resulting in pCR rates ranging from 29.0% (for trastuzumab + chemotherapy) to 66.2% (for pertuzumab + trastuzumab + chemotherapy) in proof-of-principle clinical trials, as outlined in Table 3.

Table 3. pCR rates achieved with HER2-targeted therapy in proof-of-principle neoadjuvant clinical trials

Trial	Neoadjuvant regimen	Cycles of neoadjuvant HER2-targeted treatment	Number of patients	pCR rate (%)[a]	pCR definition[b]
NoAH[54]	TC	10	117	38	tpCR
NeoSphere[20]	PTC	4	107	45.8	pCR
	TC	4	107	29.0	
TRYPHAENA[21]	PTC	3–6	225	57.3–66.2	pCR
BERENICE[22]	PTC	4	400	60.7–61.8	tpCR
KRISTINE[55]	PTC	6	221	55.7	tpCR

Abbreviations: HER2: human epidermal growth factor receptor 2; pCR: pathological complete response; PTC: pertuzumab + trastuzumab + chemotherapy; TC: trastuzumab + chemotherapy; tpCR: total pathological complete response.
Footnotes: [a]pCR defined as the absence of invasive neoplastic cells at microscopic examination of the primary tumour at surgery, irrespective of DCIS; tpCR defined as the absence of invasive tumour in the breast and lymph nodes, irrespective of DCIS. [b]It is important to note that pCR rate was not the primary endpoint of the majority of these studies, and these studies therefore lack statistical power to make meaningful comparisons between treatment arms for this endpoint (with the exception of NeoSphere).

However, these trials were designed to provide proof-of-concept for neoadjuvant treatment rather than accurately reflecting current UK clinical practice, and some of the chemotherapy regimens investigated differ from those currently used in the UK. The majority of UK patients with HER2-positive eBC eligible for neoadjuvant treatment are currently treated with three to six cycles of neoadjuvant pertuzumab + trastuzumab + chemotherapy, which has resulted in pCR rates of approximately 60% in recent observational studies of UK clinical practice (Table 4).

pCR rates vary according to the number of cycles of neoadjuvant treatment and precise chemotherapy regimens used, with FEC-THP (fluorouracil + epirubicin + cyclophosphamide followed by pertuzumab + trastuzumab + taxane) or TC-HP (docetaxel + carboplatin + trastuzumab + pertuzumab) being the most commonly used neoadjuvant regimens in UK clinical practice today. A small proportion of patients may alternatively be treated with trastuzumab + chemotherapy (without pertuzumab), which is associated with pCR rates of approximately 29–52% in UK clinical practice (Table 4).

Table 4. pCR rates achieved with HER2-targeted therapy in UK clinical practice

Study	Neoadjuvant regimen	Number of patients	pCR rate (%)	pCR definition[a]
Battisti *et al.* (2018)[24] *The Royal Marsden*	PTC	143	56.6	tpCR
	TC	155	52.3	
McLean *et al.* (2019)[25] *Northern Centre for Cancer Care*	PTC	37	63.0	pCR
	TC	27	40.5	
Vatish *et al.* (2019)[26]	PTC	14	86	Unspecified

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Study	Neoadjuvant regimen	Number of patients	pCR rate (%)	pCR definition[a]
Royal Wolverhampton NHS Trust	TC	26	46	
Chambers *et al.* (2019)[27] *Three West Country oncology centres*	PTC	40	54.5	Unspecified
Kohli *et al.* (2019)[28] *Northern Centre for Cancer Care*	PTC	42	52	pCR
Sim *et al.* (2019)[29] *Kent Oncology Centre*	PTC	71	61	Unspecified
	TC	55	29	
Noble and Brady (2019)[30] *Dorset Cancer Network*	PTC	27	46.2	pCR

Footnotes: [a]pCR defined as the absence of invasive neoplastic cells at microscopic examination of the primary tumour at surgery, irrespective of DCIS; tpCR defined as the absence of invasive tumour in the breast and lymph nodes, irrespective of DCIS.
Abbreviations: pCR: pathological complete response; PTC: pertuzumab + trastuzumab + chemotherapy; TC: trastuzumab + chemotherapy; tpCR: total pathological complete response.

Association of pCR status with long-term outcomes

pCR is a significant predictor of long-term overall survival (OS), event-free survival (EFS) and distant disease-free survival (DDFS), particularly in HER2-positive breast cancer,[31, 32] and has become an established surrogate efficacy endpoint, including for regulatory/licensing purposes by both the EMA and FDA.[56-58] Patients with RID after completion of neoadjuvant therapy have been consistently demonstrated to have a significantly poorer prognosis and higher rates of recurrence than those who achieve a pCR across several meta-analyses and clinical trials of HER2-targeted agents.[31-34] Currently in the UK the approximately 40% of patients who have RID at surgery following neoadjuvant treatment including a HER2-targeted agent receive the same adjuvant therapy as those achieving a pCR, despite their poorer prognosis.[19, 24-30]

A meta-analysis of data from nearly 12,000 patients conducted by an FDA working-group demonstrated that overall, patients receiving neoadjuvant treatment for breast cancer who did not attain a total pathological complete response (tpCR) had substantially poorer long-term OS (Figure 2A) and EFS compared to patients who did achieve a tpCR. Not achieving a tpCR was also associated with poorer EFS in HER2-positive breast cancer specifically (Figure 2B).[32] A separate 2016 meta-analysis of 5,768 patients with HER2-positive breast cancer demonstrated that RID after neoadjuvant treatment was associated with both poorer EFS and poorer OS.[31] Patients who had RID at the time of surgery had approximately three times the hazard of experiencing an EFS or OS event, compared to patients who achieved a pCR.[31] The association with poorer EFS was most evident in patients who had received HER2-targeted neoadjuvant therapy.[31]

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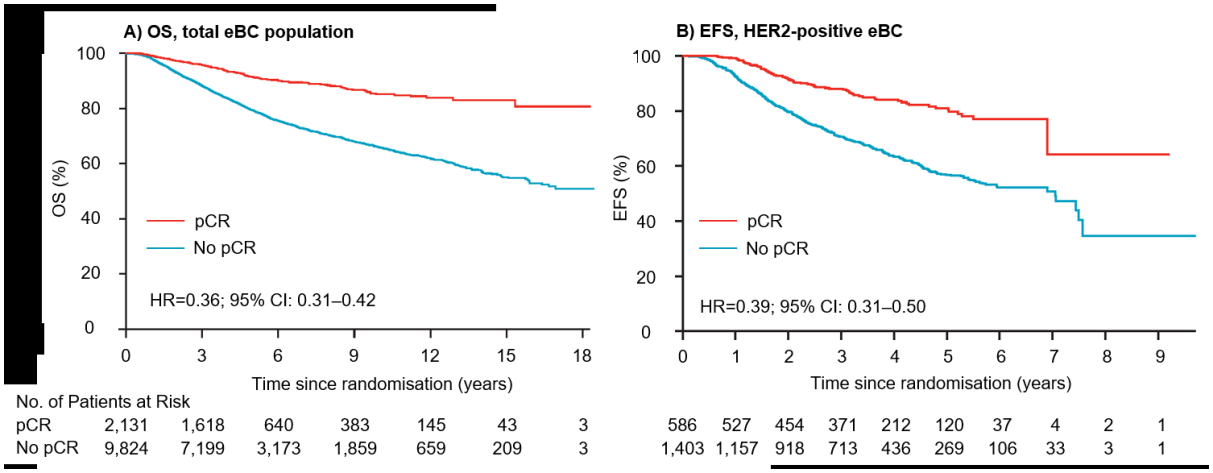
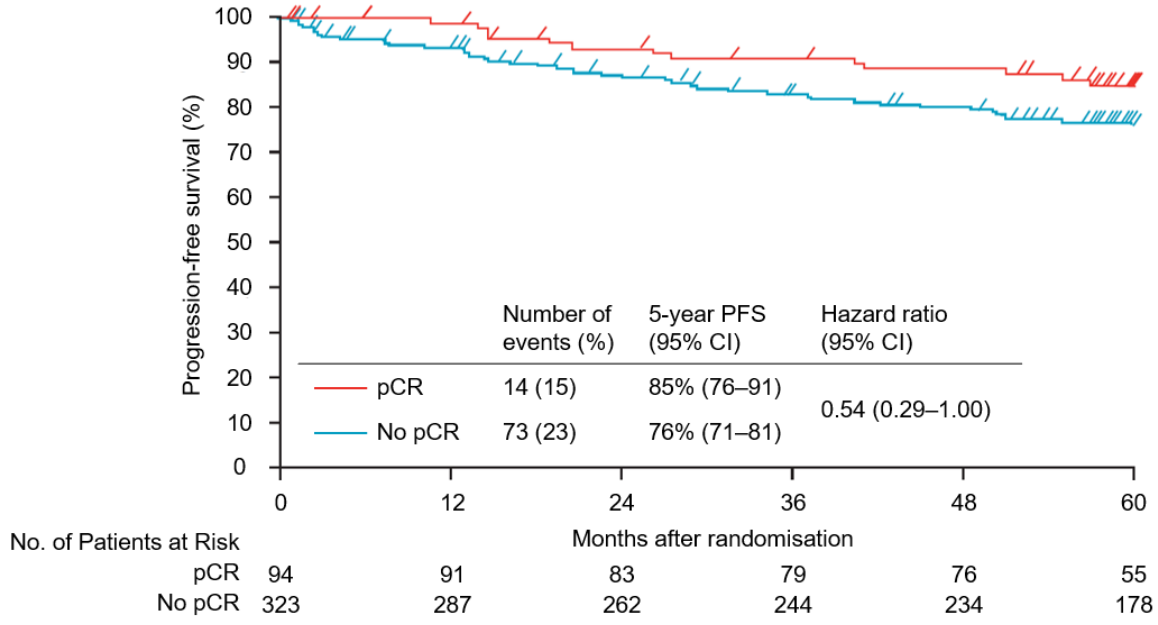
Figure 2. EFS and OS according to pCR[a] status



Footnotes: [a]pCR defined as absence of invasive cancer in the breast and axillary nodes, irrespective of DCIS (ypT0/is ypN0).
Abbreviations: CI: confidence interval; eBC: early breast cancer; EFS: event-free survival; HER2: human epidermal growth factor receptor 2; HR: hazard ratio; OS: overall survival; pCR: pathological complete response.
Source: Cortazar *et al*. (2014).[32]

Furthermore, exploratory subgroup analyses of the NeoSphere trial, which compared four neoadjuvant regimens containing HER2-targeted agents (with eligible patients going on to receive adjuvant trastuzumab + chemotherapy to complete one year of HER2-targeted treatment) demonstrated that the hazard of a progression-free survival (PFS) event at 5 years in patients with RID at the time of surgery ("no tpCR"; n=323) was approximately double that of patients who achieved a tpCR (n=94) when considering the trial population as a whole (Figure 3). However, it is important to note that these analyses were not powered for formal statistical hypothesis testing.[33]

Figure 3. PFS in the NeoSphere trial by pCR[a] status



Footnotes: [a]pCR defined as absence of invasive neoplastic cells at microscopic examination of the primary tumour at surgery. Remaining in-situ lesions were allowed.[20]
Abbreviations: CI: confidence interval; PFS: progression-free survival; tpCR: total pathological complete response.
Source: Gianni *et al*. (2016).[33]

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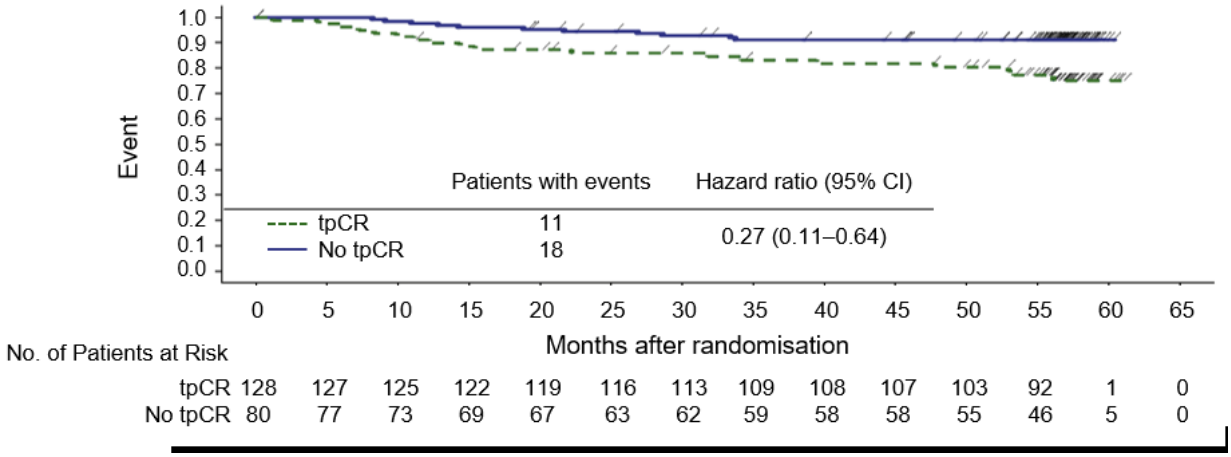
The TRYPHAENA long-term cardiac safety study, in which 208 patients were treated with pertuzumab + trastuzumab + standard neoadjuvant chemotherapy regimens and continued trastuzumab into the adjuvant setting to complete one year of treatment, was not powered to assess efficacy outcomes but also indicated that patients with RID ("no tpCR"; n=80) after neoadjuvant therapy had poorer disease-free survival (DFS) rates at 5 years compared to those who achieved a tpCR (n=128). 22.5% of patients with RID (18/80) experienced a DFS event compared to 8.6% of patients with a tpCR (11/128), and the hazard of a DFS event in patients with RID was three times greater than that for patients who achieved a pCR (Figure 4).[34]

Figure 4. Likelihood of a DFS event in patients with and without a tpCR[a] in TRYPHAENA



Footnotes: [a]pCR defined as the absence of invasive neoplastic cells in the breast and axilla (tpCR; ypT0/Tis, ypN0).
Abbreviations: CI: confidence interval; DFS: disease-free survival; tpCR: total pathological complete response.
Source: Schneeweiss *et al*. (2018).[34]

As presented above, there is considerable evidence that patients with HER2-positive disease who are treated neoadjuvantly, including with dual HER2-targeted therapy, and have RID after neoadjuvant treatment represent a group at greater risk of relapse compared to those who achieve a pCR, with a high level of unmet need.[59]

Despite this unmet need, there is a paucity of data on strategies for adapting treatment in the adjuvant setting depending on whether patients achieve a pCR or have RID. Little published data are available to guide whether patients should continue on the same treatment as they received neoadjuvantly or switch to a different treatment approach, and alternative treatments are not currently available for those who may benefit from a change of systemic treatment regimen. Consequently, completion of 1 year of HER2-targeted therapy (trastuzumab ± pertuzumab) is accepted practice for patients with HER2-positive eBC in England regardless of pathological response status.[19]

B.1.3.4 Current clinical pathway of care

NICE Guidance NG101 recommends that patients with HER2-positive eBC receive trastuzumab + chemotherapy in the neoadjuvant setting, with the addition of pertuzumab in patients "with HER2-positive, locally advanced, inflammatory or early stage breast cancer at high risk of recurrence".[19, 60] Patients treated with HER2-targeted therapy in the neoadjuvant setting continue treatment into the adjuvant setting, to complete up to one year (18 cycles) of treatment. Patients with clinical stage T1c and above HER2-positive disease receive adjuvant systemic HER2-targeted therapy with trastuzumab + pertuzumab if their disease is node-positive, or trastuzumab

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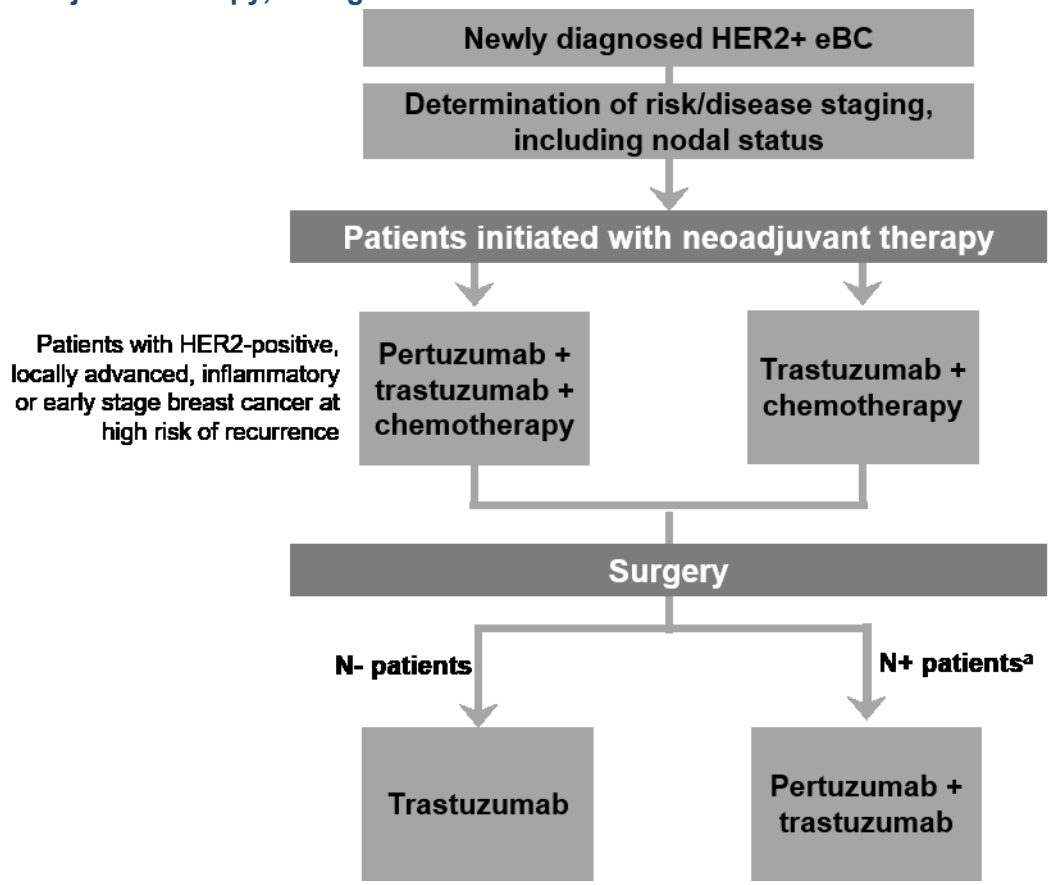
alone if node-negative, for one year or until disease recurrence (whichever is the shorter period).[19, 60] Patients with oestrogen receptor-positive breast cancer at medium to high risk of recurrence are also offered adjuvant endocrine therapy (usually an aromatase inhibitor).[19] The current clinical pathway of care for patients with HER2-positive eBC who are initiated with neoadjuvant therapy in England is summarised in Figure 5.

Figure 5. Current treatment pathway for patients with HER2-positive eBC, initiated with neoadjuvant therapy, in England



Footnotes: [a]node-positive pre-surgery, or evidence of prior node-positivity (i.e. fibrosis) found at surgery.
Abbreviations: eBC: early breast cancer; HER2: human epidermal growth factor receptor 2; N: node.

Currently in the UK, patients who receive neoadjuvant treatment including a HER2-targeted agent and have RID at surgery will receive the same adjuvant therapy as those achieving a pCR. However, many international guidelines for the systemic adjuvant treatment of patients with HER2-positive eBC have recently been updated following the publication of the KATHERINE trial, the pivotal trial for trastuzumab emtansine in the adjuvant setting, as shown in Table 5.

Table 5. Relevant guidelines for the systemic adjuvant treatment of HER2-positive eBC

Organisation	Date of issue/most recent update	Summary of recommendations
NICE (NG101,[19] TA569[60])	2018/2019	• In the adjuvant setting, trastuzumab, given at three-week intervals for one year should be offered to patients with T1c and above HER2-positive eBC in combination with chemotherapy and radiotherapy as appropriate. • Adjuvant trastuzumab can be considered in the same setting for patients with T1a/T1b HER2-positive eBC.

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Organisation	Date of issue/most recent update	Summary of recommendations
		• For patients with node-positive disease, adjuvant pertuzumab is recommended in combination with trastuzumab and chemotherapy, based on the results of the APHINITY trial.
ESMO[61]	2019	• Adjuvant trastuzumab is recommended for all patients with HER2-positive eBC who are not contraindicated, with the possible exception of cases with very low risk (e.g. T1aN0 tumours). • One year of dual blockade with pertuzumab + trastuzumab can be considered in patients with node-positive or ER-negative disease, starting before or after surgery. • Adjuvant trastuzumab should be replaced by adjuvant trastuzumab emtansine in cases of RID after completion of neoadjuvant chemotherapy combined with anti-HER2 therapy, once approved and where available.
St Gallen[53]	2019	• Decisions about optimal surgical, radiation therapy and medical approaches are increasingly tailored based on the initial response to neoadjuvant systemic treatment. • Adjuvant chemotherapy and anti-HER2 therapy is recommended for HER2-positive, stage 1 and higher breast cancers, with adjuvant trastuzumab for one year recommended for patients with node-negative disease. • Dual blockade with pertuzumab + trastuzumab in the adjuvant setting is recommended for node positive disease in cases of pCR after neoadjuvant treatment. • Adjuvant trastuzumab emtansine is recommended for women with RID after neoadjuvant treatment with HER2-targeted therapy combined with chemotherapy (single or dual HER2 blockade). • Extended treatment with neratinib is recommended following one year of trastuzumab in cases of node-positive, ER-positive HER2-positive breast cancers.
NCCN[62]	2019	• The NCCN guidelines support the continuation of HER2-targed therapy with pertuzumab + trastuzumab to complete one year of therapy in patients with node-positive, HER2-positive breast cancer post-surgery who have been treated with neoadjuvant systemic therapy. • For patients with HER2-positive RID after preoperative systemic therapy, adjuvant treatment with trastuzumab emtansine alone is recommended for 14 cycles.

Abbreviations: eBC: early breast cancer; ER: oestrogen receptor; ESMO: European Society for Medical Oncology; HER2: human epidermal growth factor receptor 2; NCCN: National Comprehensive Cancer Network; NICE: National Institute for Health and Care Excellence; RID: residual invasive disease.

B.1.3.5 Proposed use and positioning of adjuvant trastuzumab emtansine

The suggested positioning of trastuzumab emtansine for the adjuvant treatment of patients with HER2-positive eBC in England is shown in Figure 6. In summary, trastuzumab emtansine is expected to be used in line with its marketing authorisation: [redacted]

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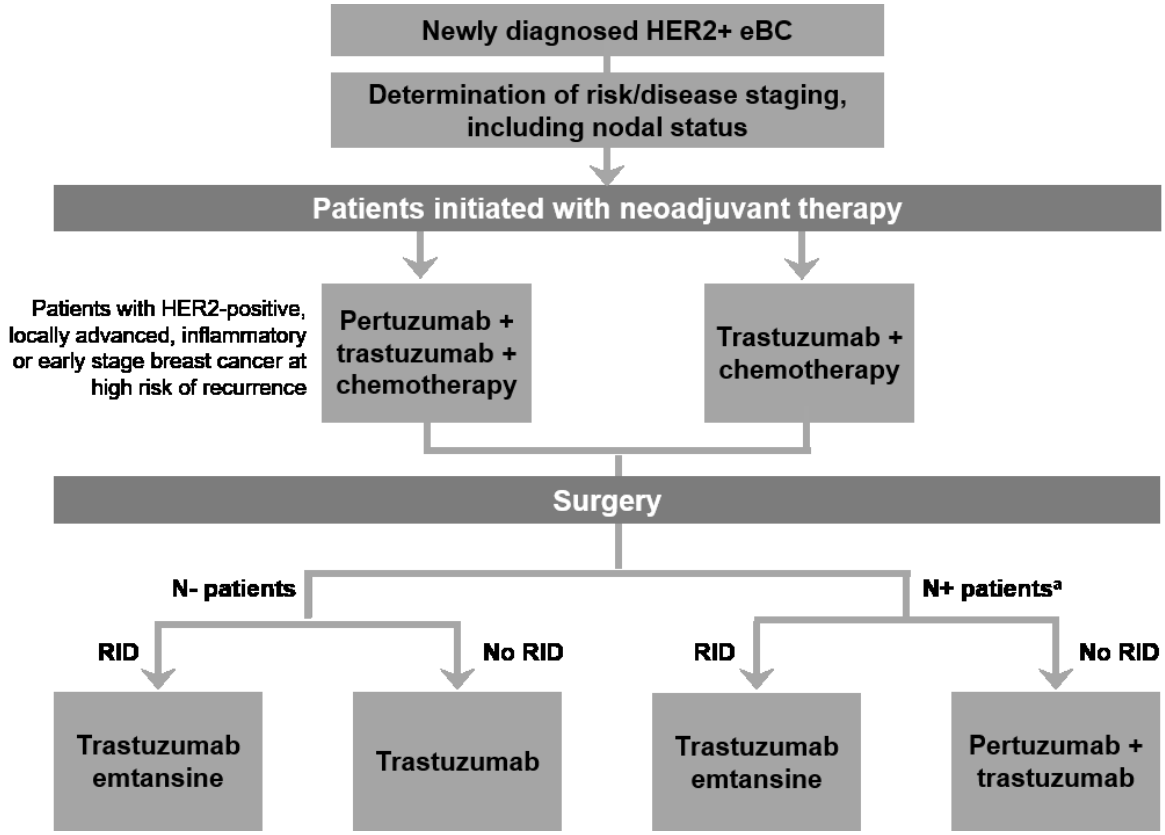
[redacted] The substantial margin of benefit observed in the KATHERINE study (as detailed in Section B.2) provides justification for the use of 14 cycles of trastuzumab emtansine for these patients.[8] This is reflected in the National Comprehensive Cancer Network (NCCN), European Society for Medical Oncology (ESMO) and St Gallen guidelines for the treatment of eBC, which have already been updated based on the results of the KATHERINE study and now recommend trastuzumab emtansine for patients with HER2-positive eBC who have RID following neoadjuvant systemic treatment which included HER2-targeted therapy.[53, 61, 62]

A positive recommendation in this setting would allow English patients with HER2-positive eBC and RID after neoadjuvant treatment that included HER2-targeted therapy to benefit from improved outcomes and a higher likelihood of achieving their treatment goals, and would provide the first opportunity to personalise adjuvant treatment for these patients based on tumour response to neoadjuvant therapy.

Figure 6. Anticipated positioning of trastuzumab emtansine, in patients with HER2-positive eBC initiated with neoadjuvant treatment



Footnotes: [a]Node-positive pre-surgery, or evidence of prior node-positivity (i.e. fibrosis) found at surgery.
Abbreviations: eBC: early breast cancer; HER2: human epidermal growth factor receptor 2; N: node; RID: residual invasive disease.

B.1.4 *Equality considerations*

No equality issues related to the use of adjuvant trastuzumab emtansine for the treatment of adults with HER2-positive eBC have been identified or are foreseen.

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B.2 Clinical effectiveness

Summary of clinical effectiveness

- One randomised controlled trial (RCT) was identified in a comprehensive systematic literature review (SLR) to find studies relevant to the decision problem: the pivotal phase III KATHERINE study, which evaluated the efficacy and safety of adjuvant trastuzumab emtansine (n=743) vs adjuvant trastuzumab (n=743) in patients with HER2-positive eBC who had RID in the breast and/or axilla after receiving neoadjuvant chemotherapy containing a taxane and HER2-targeted therapy.[8]
- A pre-specified interim analysis was conducted after 256 invasive-disease events had occurred (25th July 2018).[63] The interim analysis crossed the early reporting boundary of HR<0.732 or p<0.0124, and as such is presented in this submission.[8] The primary outcome of the study, invasive disease-free survival (IDFS), demonstrated the statistically and clinically significant benefit of adjuvant treatment with trastuzumab emtansine compared to trastuzumab:
    - Adjuvant trastuzumab emtansine significantly reduced the risk of an IDFS event by 50% vs trastuzumab (hazard ratio [HR]=0.50; 95% CI: 0.39–0.64; p<0.001).[8]
    - Estimates of IDFS at three years increased from 77.0% (95% CI: 73.8–80.3) for the trastuzumab arm to 88.3% (95% CI: 85.8–90.72) in the trastuzumab emtansine arm.[8, 63]
    - The median follow up duration in the ITT population was 41.4 months in the trastuzumab emtansine arm and 40.9 months in the trastuzumab arm.[8]
- Secondary efficacy endpoints were supportive of the substantial treatment benefit observed in the primary IDFS analysis: clear between-group differences in favour of trastuzumab emtansine were observed in IDFS (standardized definitions for efficacy endpoints [STEEP] definition), DFS and distant recurrence-free interval (DRFI).[8]
- OS data were immature at the cut-off date, but supportive of the IDFS analysis, with a separation of the survival curves from 30 months, continuing up to 60 months (HR=0.70; 95% CI: 0.47–1.05; p=0.0848).[8]
- Mean population change from baseline scores on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and EORTC Breast Cancer-Specific Quality of Life Questionnaire (QLQ-BR23) were small and similar in each treatment arm, indicating no clinically meaningful deterioration and suggesting that baseline functioning and HRQoL levels were maintained over the course of treatment.[64]
- Subgroup analyses were performed for the primary endpoint, IDFS, and were intended to assess consistency of the overall result in the ITT population.[8] IDFS improvements were observed across all clinically relevant subgroups analysed, demonstrating the internal consistency of the primary outcome across pre-specified patient subpopulations, and further demonstrating the robustness of the primary result.[8]
- No new safety signals for trastuzumab emtansine were observed in the KATHERINE study. As expected, adverse events (AEs) of any grade were more common in the trastuzumab emtansine arm than in the trastuzumab arm (98.8% vs 93.3%, respectively), as were AEs of ≥Grade 3 (25.7% vs 15.4%, respectively) and AEs leading to

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discontinuation (18.0% vs 2.1%, respectively).[8] However, the majority of AEs observed were reversible and could be well managed.[63]

B.2.1 *Identification and selection of relevant studies*

An SLR was conducted to identify relevant published clinical evidence pertaining the efficacy and safety of all licensed and investigational HER2-targeted pharmacological treatments in patients with eBC and RID after neoadjuvant therapy which included HER2-targeted treatment. An initial search was conducted in November 2018, followed by an update in June 2019 using the same search terms and eligibility criteria.

The initial (November 2018) database searches identified a total of 4,823 unique records, of which 4,610 were excluded following abstract review and 10 were excluded following full-text review. A further 24 records were identified from other sources (congress proceedings, reference list hand searching and health technology assessment [HTA] agency websites): hence 227 publications representing 89 unique trials were included in the initial SLR. In the update searches (June 2019), 42 additional publications were identified, representing 1 additional unique trial and 24 trials previously captured in the original SLR. Hence a total of 269 publications reporting on 90 unique trials were identified for inclusion across the original and update SLRs. A further 18 ongoing trials were identified as part of the trial registry searches, which were also included in the SLR.

The primary trials of interest were those aligned with the decision problem (trials categorised as adjuvant with prior HER2-targeted neoadjuvant therapy). Three relevant trials were identified and extracted in further detail (the KATHERINE study,[8] Peace 2017,[65] and NCT03674112 [trial currently ongoing][66]: Appendix D). Of these three studies, only one was a directly relevant RCT for trastuzumab emtansine in the adjuvant treatment of patients with HER2-positive eBC who had RID, in the breast and/or axillary lymph nodes, after pre-operative systemic treatment that included HER2-targeted therapy: the KATHERINE study.

Full details of the SLR search strategy, study selection process and results can be found in Appendix D.

B.2.2 *List of relevant clinical effectiveness evidence*

A summary of the KATHERINE study is presented in Table 6. One ongoing study is expected to provide additional safety evidence for adjuvant trastuzumab emtansine in the next 12 months (Section B.2.11).

Table 6. Clinical effectiveness evidence

Study	KATHERINE (NCT01772472, von Minckwitz *et al*. 2019)[8]
Study design	Phase III, open-label, randomised, prospective study involving 1,486 patients at 273 sites across 28 countries.
Population	Patients with HER2-positive eBC and RID in the breast and/or axillary lymph nodes at surgery, after completion of neoadjuvant chemotherapy plus HER2-targeted therapy.
Intervention(s)	Trastuzumab emtansine, with radiation and endocrine therapy per protocol and local guidelines.

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<table>
<tr><th>Study</th><th colspan="5">KATHERINE (NCT01772472, von Minckwitz et al. 2019)[8]</th></tr>
<tr><td>Comparator(s)</td><td colspan="5">Trastuzumab, with radiation and endocrine therapy per protocol and local guidelines.</td></tr>
<tr><td rowspan="2">Indicate if trial supports application for marketing authorisation</td><td>Yes</td><td>X</td><td rowspan="2">Indicate if trial used in the economic model</td><td>Yes</td><td>X</td></tr>
<tr><td>No</td><td></td><td>No</td><td></td></tr>
<tr><td>Rationale for use/non-use in the model</td><td colspan="5">The KATHERINE study is used in the economic model as it is the pivotal study submitted for the marketing authorisation of trastuzumab emtansine in this indication and provides directly relevant evidence for treatment effect of trastuzumab emtansine on outcomes important to the model. The KATHERINE study is the only study to assess the use of adjuvant trastuzumab emtansine treatment in patients with HER2-positive eBC that has results available at this time.</td></tr>
<tr><td>Reported outcomes specified in the decision problem</td><td colspan="5">• OS
• DFS
• Adverse effects of treatment
• HRQoL</td></tr>
<tr><td>All other reported outcomes</td><td colspan="5">• IDFS
• IDFS including second primary non-breast cancer (STEEP definition)
• DRFI</td></tr>
</table>

Abbreviations: DFS: disease-free survival; DRFI: distant recurrence-free interval; eBC: early breast cancer; HER2: human epidermal growth factor 2; HRQoL: health-related quality of life; IDFS: invasive disease-free survival; OS: overall survival; RID: residual invasive disease.
Source: NICE Final Scope ID1516;[1] von Minckwitz G *et al*. 2019.[8]

B.2.3 *Summary of methodology of the relevant clinical effectiveness evidence*

B.2.3.1 Trial design

The KATHERINE study is an ongoing, prospective, phase III, open-label, randomised, multicentre study to assess the efficacy and safety of adjuvant trastuzumab emtansine (n=743) compared with adjuvant trastuzumab (n=743) in patients with HER2-positive eBC who had RID in the breast and/or axillary lymph nodes at surgery, following neoadjuvant chemotherapy containing a taxane (with or without anthracycline) and trastuzumab ± a second HER2-targeted agent. Patients had to have completed at least six cycles (16 weeks) of neoadjuvant chemotherapy, containing a minimum of nine weeks of taxane-based therapy and nine weeks of trastuzumab (slightly shorter treatment durations were permitted for dose-dense regimens).[8]

An overview of the KATHERINE study design is presented in Figure 7.[8] Patients were randomised 1:1 to treatment with either adjuvant trastuzumab emtansine or trastuzumab every 3 weeks for 14 cycles. Randomisation and treatment occurred within 12 weeks after surgery. Patients were stratified by clinical stage at presentation, hormone receptor status, neoadjuvant HER2-targeted therapy type and pathological nodal status after neoadjuvant therapy.[8]

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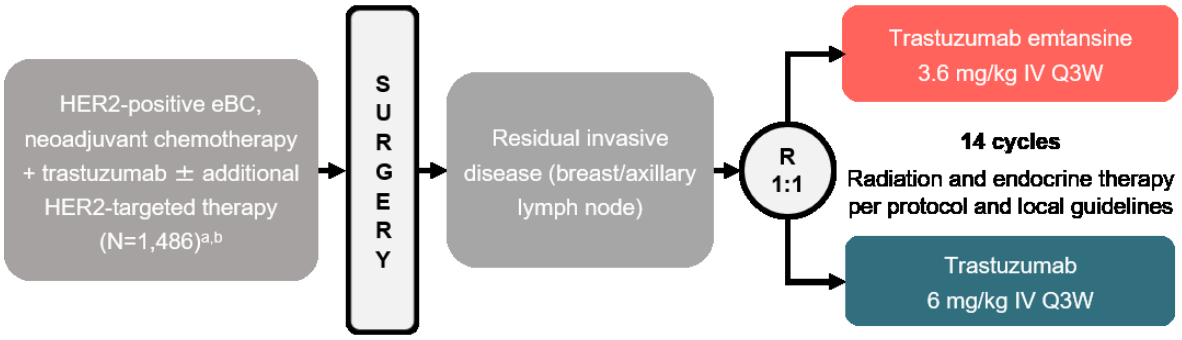
Figure 7. Overview of the KATHERINE study design



Footnotes: [a]Neoadjuvant systemic treatment was given for ≥6 cycles, with a total duration of ≥16 weeks, including ≥9 weeks of anti-HER2 therapy and ≥9 weeks of taxane-based chemotherapy (slightly shorter treatment durations were permitted for dose-dense regimens). [b]Dual anti-HER2 therapy was also permitted in the neoadjuvant setting.
Abbreviations: eBC: early breast cancer; HER2: human epidermal growth factor receptor 2; IV: intravenous; Q3W: every 3 weeks; R: randomised.
Source: von Minckwitz G *et al.* 2019.[8]

Trastuzumab emtansine was administered intravenously on Day 1 of a 3-week cycle at a dose of 3.6 mg/kg Q3W. Trastuzumab was administered intravenously on Day 1 of a 3-week cycle at a maintenance dose of 6 mg/kg, with a loading dose of 8 mg/kg if more than 6 weeks had passed since the last prior dose of trastuzumab. Treatment with trastuzumab emtansine could be reduced by a maximum of two dose levels (to 2.4 mg/kg) according to dose-modification guidelines. No dose reductions were permitted for trastuzumab. Radiation therapy and endocrine therapy were given concurrently according to institutional standards and the trial protocol. Patients who discontinued treatment with trastuzumab emtansine prior to 14 cycles were permitted to complete the duration of their study therapy with trastuzumab (up to a total 14 cycles of HER2-targeted therapy), if considered appropriate by the investigator. Following treatment discontinuation or completion, patients were followed for efficacy and safety objectives until the end of the study or patient withdrawal of consent.[8]

The primary objective of the KATHERINE study was to compare IDFS (excluding second primary non-breast cancers) between the trastuzumab emtansine and trastuzumab treatment arms.[63] Further details of both primary and secondary objectives are provided in Table 7.

B.2.3.2 Trial methodology

Table 7. Summary of trial methodology of relevant clinical trials

Trial name	KATHERINE (NCT01772472, von Minckwitz *et al.* 2019)[8]
Location	International: 273 sites across 28 countries, of which 14 were in the UK.
Trial design	Prospective, phase III, open-label, randomised, multicentre study.
Eligibility criteria for participants	A summary of key inclusion and exclusion criteria are provided below, with full details presented in Appendix L. **Key inclusion criteria** • Histologically confirmed HER2-positive invasive breast cancer (stage T1–4/N0–3/M0 except T1a/bN0). ○ HER2-positivity was confirmed by a central laboratory. • Pathological evidence of RID in the breast and/or axillary lymph nodes following completion of taxane-based neoadjuvant therapy administered with trastuzumab ±

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	additional HER2-targeted agents. ○ Patients must have completed ≥6 cycles (16 weeks) of neoadjuvant chemotherapy including ≥9 weeks of trastuzumab and ≥9 weeks of taxane-based therapy. • Surgical removal of all clinically evident disease in the breast and axillary lymph nodes. • Eastern Cooperative Oncology Group performance status (ECOG PS) 0–1. • LVEF ≥50% after neoadjuvant treatment and no decrease in LVEF by >15% from pre-neoadjuvant therapy LVEF. **Key exclusion criteria** • Stage IV (metastatic) breast cancer. • Gross residual disease remaining after mastectomy or positive margins after breast-conserving surgery. • Progressive disease during neoadjuvant therapy. • Cardiopulmonary dysfunction (heart failure of NYHA class II or higher or a history of a reduction in LVEF to <40% with previous therapy). • Current Grade ≥2 peripheral neuropathy (according to National Cancer Institute Common Terminology Criteria for Adverse Events, [NCI CTCAE]). • Any known active liver disease (e.g. due to hepatitis B virus [HBV], hepatitis C virus [HCV], autoimmune hepatic disorders or sclerosing cholangitis). • Treatment with anti-cancer investigational drugs within 28 days prior to commencing study treatment. • Exposure to cumulative doses of anthracyclines exceeding: ○ Doxorubicin: 240 mg/m^2 ○ Epirubicin or liposomal doxorubicin-hydrochloride: 480 mg/m^2 ○ Other anthracyclines: exposure equivalent to doxorubicin >240 mg/m^2
Method of study drug administration	• Trastuzumab emtansine (3.6 mg/kg) and trastuzumab (6 mg/kg) were administered intravenously every 3 weeks for 14 cycles. • A loading dose of trastuzumab (8 mg/kg) was administered if it had been more than 6 weeks since the preceding dose.
Permitted and disallowed concomitant medication	• The following medications were forbidden, or their intake was restricted, during the study: ○ Anticancer therapies including cytotoxic chemotherapy, radiotherapy (except for adjuvant radiotherapy for breast cancer after completion of chemotherapy), immunotherapy and biological or targeted (e.g. lapatinib or neratinib) anti-cancer therapy. ○ Any investigational agent (except those used for the purposes of the study). • Concomitant use of strong CYP3A4/5 inhibitors (e.g. ketoconazole or itraconazole) with trastuzumab emtansine was avoided, and patients were closely monitored for adverse reactions if a strong CYP3A4/5 inhibitor was used.
Primary outcomes	IDFS (excluding second primary non-breast cancers), defined as the time from randomisation to the first occurrence of one of the

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	following: ipsilateral invasive breast tumour recurrence, ipsilateral local-regional invasive breast cancer recurrence, distant recurrence, contralateral invasive breast cancer or death of any cause. • The KATHERINE definition of IDFS excludes second primary non-breast cancer tumours, based on the US FDA's recommended definition for a trial intended to support a regulatory filing. Inclusion of second primary non-breast cancer events in the IDFS definition has the disadvantage of including events not related to the cancer or the treatment under study, thereby potentially diluting any treatment effect. • As the STEEP criteria includes second primary non-breast cancer in the IDFS definition, this broader definition was included as a secondary outcome.
Secondary and other outcomes	A summary of the secondary outcomes is provided below: • IDFS (STEEP definition): defined as the time from randomisation to the first occurrence of one of the following: second primary non-breast cancer, ipsilateral invasive breast tumour recurrence, ipsilateral local-regional invasive breast cancer recurrence, distant recurrence, contralateral invasive breast cancer or death of any cause. • DFS, including non-invasive breast cancers: defined as the time from randomisation to first occurrence of an IDFS event including second primary non-breast cancer or contralateral or ipsilateral DCIS. • OS: defined as the time from randomisation to death of any cause. • DRFI: defined as the time from randomisation to date of distant breast cancer recurrence. • Incidence of cardiac events: defined as death from cardiac cause or severe chronic heart failure (NYHA Class III or IV). • Overall safety: defined as the incidence of AEs. • Patient reported outcomes (PROs): assessed using the EORTC QLQ-C30 and breast cancer specific (EORTC QLQ-BR23) questionnaires. Full details of domains assessed in the EORTC QLQ-C30 and EORTC QLQ-BR23 are presented in Appendix L.
Pre-planned subgroups	Subgroup analyses of IDFS were performed for randomisation stratification factors (underlined below) as well as other disease or patient related prognostic or predictive factors for the primary endpoint, as outlined below: • Hormone receptor status • Pathological nodal status after neoadjuvant therapy • Clinical stage at presentation • Neoadjuvant HER2-directed therapy type • Age • Race Subgroup analyses are planned based on the same factors for OS but have not been completed at this time.
Duration of study and follow-up	The study began on 3rd April 2013, with a primary completion date of 25th July 2018 and an estimated study completion date of 4th April 2023. For the analysis included in this submission, median follow-up duration in the ITT population was 41.4 months (range 0.1–62.7) in the trastuzumab emtansine arm and 40.9 months (range 0.1–62.6)

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	in the trastuzumab arm.

Abbreviations: AE: adverse event; CNS: central nervous system; CYP3A4/5: cytochrome P450 3A4/5; DCIS: ductal carcinoma *in situ*; DFS: disease-free survival; DRFI: distant recurrence-free interval; ECOG PS: Eastern Cooperative Oncology Group performance status; EORTC: European Organization for Research and Treatment of Cancer; FDA: food and drug administration; HBV: hepatitis B virus; HCV: hepatitis C virus; HER2: human epidermal growth factor receptor 2; HIV: human immunodeficiency virus; HR: hazard ratio; IDFS: invasive disease-free survival; IHC: immunohistochemistry; ISH: *in situ* hybridisation; ITT: intention-to-treat; LVEF: left ventricular ejection fraction; NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; NYHA: New York Heart Association; OS: overall survival; QLQ-BR23: Breast Cancer-Specific Quality of Life Questionnaire; STEEP: standardized definitions for efficacy endpoints; tpCR: total pathological complete response.
Source: von Minckwitz G *et al.* 2019;[8] Schneeweiss *et al.* 2019;[64] KATHERINE study CSR.[63]

B.2.3.3 Baseline characteristics

Key patient demographics and clinical characteristics of the patients enrolled in the KATHERINE study are presented in Table 8. Baseline characteristics were balanced between the two treatment arms,[63] and are consistent with those expected for the UK patient population with eBC. Median age was 49 years, with a majority of participants under 65 years of age. Most patients (72.3%) had hormone receptor-positive disease, approximately 75% presented with operable disease, and just under half of patients were node-positive after neoadjuvant therapy. The majority of patients (76.9%) had received an anthracycline-containing neoadjuvant chemotherapy regimen, and 19.5% of patients had received a second HER2-targeted agent in addition to trastuzumab during neoadjuvant therapy.[8] In the majority of cases, the additional HER2-targeted agent was pertuzumab.[63]

Table 8. Demographic and clinical characteristics of patients at baseline

Characteristics	Trastuzumab (N=743)	Trastuzumab emtansine (N=743)
Age, years		
Median (range)	49 (23–80)	49 (24–79)
Age group, n (%)		
<40	153 (20.6)	143 (19.2)
40–64	522 (70.3)	542 (72.9)
65–74	61 (8.2)	56 (7.5)
≥75	7 (0.9)	2 (0.3)
Region, n (%)		
North America	164 (22.1)	170 (22.9)
Western Europe	403 (54.2)	403 (54.2)
Rest of world	176 (23.7)	170 (22.9)
Race or ethnic group[a], n (%)		
American Indian[b] or Alaska Native	50 (6.7)	36 (4.8)
Asian	64 (8.6)	65 (8.7)
Black or African American	19 (2.6)	21 (2.8)
White	531 (71.5)	551 (74.2)
Multiple/Unknown/Other	79 (10.6)	70 (9.4)
Prior use of anthracycline, n (%)	564 (75.9)	579 (77.9)

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Characteristics	Trastuzumab (N=743)	Trastuzumab emtansine (N=743)
Clinical stage at presentation, n (%)		
Inoperable (Stage T4 Nx M0 or Tx N2–3 M0)	190 (25.6)	185 (24.9)
Operable (Stages T1–3 N0–1 M0)	553 (74.4)	558 (75.1)
Hormone receptor status, n (%)		
ER-negative and PR-negative or status unknown	203 (27.3)	209 (28.1)
ER-positive, PR-positive, or both	540 (72.7)	534 (71.9)
Menopausal status at screening, n (%)		
Pre-menopausal	413 (55.6)	399 (53.7)
Post-menopausal	330 (44.4)	344 (46.3)
Neoadjuvant HER2-targeted therapy, n (%)		
Trastuzumab alone	596 (80.2)	600 (80.8)
Trastuzumab + pertuzumab	139 (18.7)	133 (17.9)
Trastuzumab + other HER2-targeted therapy[c]	8 (1.1)	10 (1.3)
Primary tumour stage (at definitive surgery), n (%)		
ypT0, ypT1a, ypT1b, ypT1mic, ypTis	306 (41.2)	331 (44.5)
ypT1[d]/ypT1c	184 (24.8)	175 (23.6)
ypT2	185 (24.9)	174 (23.4)
ypT3	57 (7.7)	51 (6.9)
ypT4, ypT4a, ypT4b, ypT4c	9 (1.2)	7 (0.9)
ypT4d	1 (0.1)	5 (0.7)
ypTX	1 (0.1)	0
Regional lymph node stage (at definitive surgery), n (%)		
ypN0	335 (45.1)	344 (46.3)
ypN1	213 (28.7)	220 (29.6)
ypN2	103 (13.9)	86 (11.6)
ypN3	30 (4.0)	37 (5.0)
ypNX[e]	62 (8.3)	56 (7.5)
Pathological nodal status evaluated after neoadjuvant therapy, n (%)		
Node-positive	346 (46.6)	343 (46.2)
Node-negative/not done	397 (53.4)	400 (53.8)
RID ≤1 cm and negative axillary lymph nodes (ypT1a, ypT1b, ypT1mic and ypN0)	161 (21.7)	170 (22.9)

Footnotes: Please note that staging at initial diagnosis refers to clinical staging, staging at definitive surgery refers to pathologic staging. [a]Race or ethnic group was reported by the investigators. [b]Includes North, Central and South American Indians. [c]Other HER2-targeted agents were neratinib, dacomitinib, afatinib and lapatinib. [d]Five patients had ypT1 disease without further subspecification. [e]If extensive axillary evaluation was done prior to neoadjuvant therapy or if sentinel lymph nodes were evaluated before neoadjuvant therapy and were found not to involve tumour or had only micrometastases, further axillary evaluation was not required and the patient was classified as "not done" with respect to this variable.
Abbreviations: ER: oestrogen receptor; HER2: human epidermal growth factor receptor 2; PR: progesterone receptor; RID: residual invasive disease.
Source: von Minckwitz G *et al.* 2019;[8] KATHERINE study CSR.[63]

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B.2.4 *Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence*

B.2.4.1 Statistical analysis and study populations

A summary of the analysis populations for efficacy and safety outcomes for the KATHERINE study is presented in Table 9, while a summary of statistical analyses for the efficacy analyses is presented in Table 10. Details of the participant flow for the KATHERINE study are presented in Appendix D.

Table 9. Summary of analysis populations

	KATHERINE
Primary efficacy analysis and secondary analyses	The randomised (ITT) patient population (n=1,486)[a], including all patients who were randomised to the trastuzumab emtansine (n=743) or trastuzumab (n=743) arms, regardless of whether they received any study treatment. Patients discontinuing trastuzumab emtansine and switching to trastuzumab were included in the trastuzumab emtansine ITT population.
Safety analyses	The treated population who received at least one dose of trastuzumab emtansine (n=740) or trastuzumab (n=720), (n=1,460).[a] Patients receiving any dose of trastuzumab emtansine were included in the trastuzumab emtansine safety evaluable population, regardless of initial randomisation.

Footnotes: [a]One patient was randomised twice in error. The patient was first randomised to the trastuzumab arm but did not receive treatment and was included in the trastuzumab ITT population. The patient was then randomised to the trastuzumab emtansine arm and treated with trastuzumab emtansine. The patient was thus included in the trastuzumab emtansine safety population (n=740) based on treatment actually received. One patient was randomised to trastuzumab but was administered 13 cycles of trastuzumab and one cycle of trastuzumab emtansine in error so was included in the trastuzumab emtansine safety population. One patient was randomised to trastuzumab emtansine but was administered 9 cycles of trastuzumab in error and was thus included in the trastuzumab safety population.
Abbreviations: ITT: intention-to-treat.
Source: von Minckwitz G *et al.* 2019;[8] KATHERINE study CSR.[63]

Table 10. Summary of statistical analyses in KATHERINE

Trial	KATHERINE
Hypothesis objective	• The primary objective of KATHERINE was to compare IDFS in patients with HER2-positive eBC and RID in the breast and/or axillary lymph nodes, after neoadjuvant chemotherapy and HER2-directed therapy including trastuzumab followed by surgery between the two treatment arms. • The null hypothesis for the primary objective was that the survival distributions of IDFS in the two treatment arms were the same. The alternative hypothesis was that the survival distributions of IDFS in the treatment and the control arm were different: ○ H0: $S_{\text{trastuzumab emtansine}} = S_{\text{trastuzumab}}$ ○ H1: $S_{\text{trastuzumab emtansine}} \neq S_{\text{trastuzumab}}$.
Statistical analysis	• A stratified log-rank test was initially planned to compare IDFS between the two treatment arms, with an unstratified log-rank test planned as a sensitivity analysis. However, as the smallest strata per arm contained fewer than five patients, the unstratified log-rank test

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Trial	KATHERINE
	was used for the primary analysis to compare IDFS between the two treatment arms as robust stratified analyses could not be conducted. • The Kaplan-Meier approach was used to estimate 3-year IDFS rates and corresponding 95% CIs for each treatment arm. • A Cox proportional hazards model was used to estimate the HR between the two treatment arms (i.e. the magnitude of treatment effect) and its 95% CI. • Data from patients who did not have a documented event were censored at the date the patient was last known to be alive and event-free. • Secondary outcomes were analysed in a similar manner to estimate 3-year event rates for each treatment arm and the HR between arms with 95% CIs. • The final (event-driven) IDFS analysis is planned to be conducted when 384 invasive disease events have occurred. A single pre-specified interim analysis was also planned after approximately 67% of projected invasive disease events (~257) had occurred, with an early reporting boundary of HR<0.732 or p<0.0124 and an interim OS analysis planned if this boundary was crossed. ○ The overall two-sided type I error was controlled at 0.05 with the use of the Lan-DeMets alpha-spending function with an O'Brien-Fleming boundary. ○ The results of the interim IDFS analysis crossed the early reporting boundary for benefit of trastuzumab emtansine and are presented in the primary manuscript and in this submission. • The early reporting boundary for the first interim OS analysis (at the time of interim IDFS analysis) was set at p<0.0009 or observed HR<0.5826. • In addition to this first interim OS analysis triggered by the interim IDFS analysis crossing the early reporting boundary, two formal interim OS analyses and one final OS analysis are planned, with the overall two-sided type I error controlled at 0.05 with the use of the Lan-DeMets alpha-spending function with an O'Brien-Fleming boundary: ○ The second OS interim analysis will be conducted at the time of the final IDFS analysis, after approximately 5 years since enrolment of the first patient. ○ The third OS interim analysis will be conducted when ~279 deaths have occurred, approximately 2 years after the second OS interim analysis. ○ A final analysis when ~367 deaths have occurred, at the end of 10 years of follow up from the date of randomisation of the first patient.
Sample size, power calculation	• 384 invasive disease events and 1,484 patients were required for 80% power to detect a HR of 0.75 with a two-sided significance level of 5% for the primary analysis of IDFS. ○ This would correspond to a 6.5% improvement in 3-year IDFS from 70.0% in the trastuzumab arm to 76.5% in the trastuzumab emtansine arm. • A sample size of 1,484 patients and approximately 10 years of follow-up from the date of randomisation of the first patient gave this study 56% power to detect a HR of 0.80 in OS with a two-sided significance level of 5%.

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Trial	KATHERINE
	○ This would correspond to a 2.8% improvement in 3-year OS from 85.0% in the trastuzumab arm to 87.8% in the trastuzumab emtansine arm.
Data management, patient withdrawals	• The investigator could discontinue a patient from a study drug or withdraw a patient from the study at any time and patients could voluntarily discontinue a study drug or withdraw from the study at any time, for any reason. • Patient withdrawal was defined within three scenarios: ○ Discontinuation from study drug: patients were asked to attend a study treatment completion/early termination visit and undergo follow-up assessments. The primary reason for early discontinuation was documented on the appropriate electronic case report form (eCRF), and patients were not replaced. Patients who discontinued trastuzumab emtansine treatment prior to 14 cycles of study treatment could continue treatment with trastuzumab up to 14 cycles of HER2-directed treatment (unless discontinuation was due to trastuzumab-related toxicity), if considered appropriate by the investigator. ○ Withdrawal from the entire study: no further data were collected after the date of the patient's withdrawal from the study, but every effort was made to complete and report observations for the patient. The investigator had the responsibility to contact the patient or a legally authorised relative to complete a final evaluation and establish an explanation for the withdrawal. ○ Partial withdrawal from the study: all provisions regarding withdrawal from the entire study were applicable to partial withdrawal, except that the patient had to consent to be contacted for further information on recurrence as per the primary study outcome and survival status. Medical records were also reviewed for information on recurrence. It was documented in both the medical records and in the eCRF that the patient consented to be contacted for information on survival despite their withdrawal of informed consent. Information on AEs and concomitant medication was also collected during follow-up with these patients where possible. • If patients failed to attend scheduled visits, several attempts were made by the site to contact these patients for follow up information (i.e. at least three attempts within a reasonable amount of time). If contact was unsuccessful the patient's physician was contacted and asked to contact the patient or the patient's family to provide follow-up information. • If contact could not be established after sufficient attempts, the patient was declared "lost to follow-up".

Abbreviations: CI: confidence interval; eCRF: electronic case report form; HER2: human epidermal growth factor receptor 2; HR: hazard ratio; IDFS: invasive disease-free survival; ITT: intention-to-treat; OS: overall survival.
Source: von Minckwitz G *et al.* 2019;[8] KATHERINE study CSR.[63]

B.2.4.2 Analysis data cut-offs

The primary efficacy analysis took place after 256 IDFS events had occurred, in line with the pre-specified statistical analysis plan, because the early reporting boundary for the interim analysis

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was crossed. The clinical cut-off date for this analysis was 25th July 2018, at which point the median follow-up duration in the ITT population was 41.4 months (range 0.1–62.7) in the trastuzumab emtansine arm and 40.9 months (range 0.1–62.6) in the trastuzumab arm. The first interim analysis of OS was conducted at the same time, along with other analyses of safety and efficacy. The results from this first cut-off date are presented in this submission.[8, 63] One additional IDFS analysis, two additional interim OS analyses and a final OS analysis are planned in the future, with full details included in Table 10.[8, 63]

B.2.4.3 Participant disposition

A total of 1,925 patients were screened, of whom 1,486 patients were randomised 1:1 to receive trastuzumab emtansine (n=743) or trastuzumab (n=743).[8] Twenty-seven patients were randomised but did not receive their planned study medication (4 in the trastuzumab emtansine arm, 23 in the trastuzumab arm).[8]

Overall, 133 patients discontinued treatment due to AEs in the trastuzumab emtansine arm and 15 patients discontinued treatment due to AEs in the trastuzumab arm. Approximately half (n=71) of patients discontinuing treatment with trastuzumab emtansine went on to receive trastuzumab, of whom 63 completed a total of 14 cycles of HER2-targeted treatment.[8] At follow-up, 635 patients in the trastuzumab emtansine arm were alive and on study, compared with 597 patients in the trastuzumab arm.[8] A CONSORT diagram of patient disposition is presented in Appendix D.

B.2.5 *Quality assessment of the relevant clinical effectiveness evidence*

Quality (risk of bias) assessment of the KATHERINE RCT was conducted using the eight-criteria checklist provided in Section 2.5 of the NICE single technology appraisal user guide.[67] The results of the quality assessment are provided in Table 11. Overall, the KATHERINE study was well-designed, with appropriate randomisation and concealment of treatment allocation during randomisation. The study was funded by Roche.

Table 11. Quality assessment of the KATHERINE study

Study ID and publications	**KATHERINE (NCT01772472, von Minckwitz et al. 2019)[8, 63]**
Was the randomisation method adequate?	Yes – patients were randomised in a 1:1 ratio using a permuted-block randomisation scheme through an interactive voice response system/interactive web response system.[8]
Was the allocation adequately concealed?	Yes – an interactive voice response or interactive web response system was used.[8]
Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	Yes – baseline demographics and disease characteristics were similar between treatment groups.[8]
Were the care providers, participants and outcome assessors blind to treatment allocation?	No – open label study due to the distinctive differences in AE profiles between adjuvant trastuzumab emtansine and adjuvant trastuzumab. See Appendix D for discussion of the likely impact on the risk of bias.[8]

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Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No – 212 patients discontinued treatment with trastuzumab emtansine compared with 135 patients for trastuzumab. This was as expected given the targeted cytotoxic component of trastuzumab emtansine: a higher proportion of patients discontinued due to AEs in the trastuzumab emtansine arm (n=133) compared to the trastuzumab arm (n=15).[63]
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No – all predefined outcomes were reported.[8]
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes – the primary analysis was based on the ITT population. See Appendix D for methods used to account for missing data.[8]
Did the authors of the study publication declare any conflicts of interest?	Yes – the study was sponsored by F. Hoffmann–La Roche/Genentech, who developed the drug under investigation. Authors declared any other support that they received.[8]

Abbreviations: AE: adverse event; ITT; intention-to-treat.
Source: Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination).[68]

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B.2.6 *Clinical effectiveness results of the relevant trials*

Summary of clinical effectiveness results

- The KATHERINE study met its primary objective; trastuzumab emtansine reduced the risk of an IDFS event by 50% compared to trastuzumab (HR=0.50; 95% CI: 0.39–0.64; p<0.001) at a median follow up of 41.4 months in the trastuzumab emtansine arm and 40.9 months in the trastuzumab arm.[8]
- Estimates of IDFS at three years were 77.0% (95% CI: 73.8–80.3) for the trastuzumab arm and 88.3% (95% CI: 85.8–90.7) in the trastuzumab emtansine arm.[8, 63]
- Secondary efficacy outcomes were supportive of the substantial treatment benefit observed in the primary IDFS analysis: clear between-group differences in favour of trastuzumab emtansine were observed in IDFS (STEEP definition), DFS and DRFI. The OS data were immature at the clinical cut-off date, but are supportive of the IDFS analysis with a separation of the survival curves from 30 months, continuing up to 60 months (HR=0.70; 95% CI: 0.47–1.05; p=0.0848).[8]
- Mean population change from baseline scores on the EORTC QLQ-C30 and EORTC QLQ-BR23 were small and similar in each treatment arm, indicating no clinically meaningful deterioration and suggesting that baseline functioning and HRQoL levels were maintained over the course of treatment.[64]
- Subgroup analyses were performed for the primary outcome according to factors including clinical stage at presentation, hormone receptor status, neoadjuvant HER2-directed therapy type and pathological nodal status after neoadjuvant therapy.[8] These analyses demonstrated the consistency of the overall result across pre-specified patient subpopulations, further demonstrating the robustness of the primary result.[8]

B.2.6.1 Primary endpoint

The KATHERINE study met its primary objective of demonstrating a significant difference in IDFS between the two treatment arms: patients with HER2-positive eBC with RID in the breast and/or axillary lymph nodes after completion of neoadjuvant treatment containing a HER2-targeted agent experienced a statistically significant and clinically meaningful improvement in IDFS when treated with adjuvant trastuzumab emtansine compared with adjuvant trastuzumab.[63]

The early reporting efficacy boundary was crossed at the pre-specified interim analysis, which triggered full trial analysis at a median follow up of 41.4 months in the trastuzumab emtansine arm and 40.9 months in the trastuzumab arm.[8] At this analysis, in the ITT population, adjuvant trastuzumab emtansine significantly reduced the risk of an IDFS event by 50% compared to trastuzumab (HR=0.50; 95% CI: 0.39–0.64; p<0.001, Figure 8).[8] Invasive disease occurred in 91 patients (12.2%) in the trastuzumab emtansine arm and 165 patients (22.2%) in the trastuzumab arm.[8] The 3-year IDFS event free rates increased from 77.0% (95% CI: 73.8–80.3) for the trastuzumab arm to 88.3% (95% CI: 85.8–90.7) in the trastuzumab emtansine arm.[8] Distant recurrence was the first invasive-disease event for the majority of patients, and is discussed in more detail in Section B.2.6.2.

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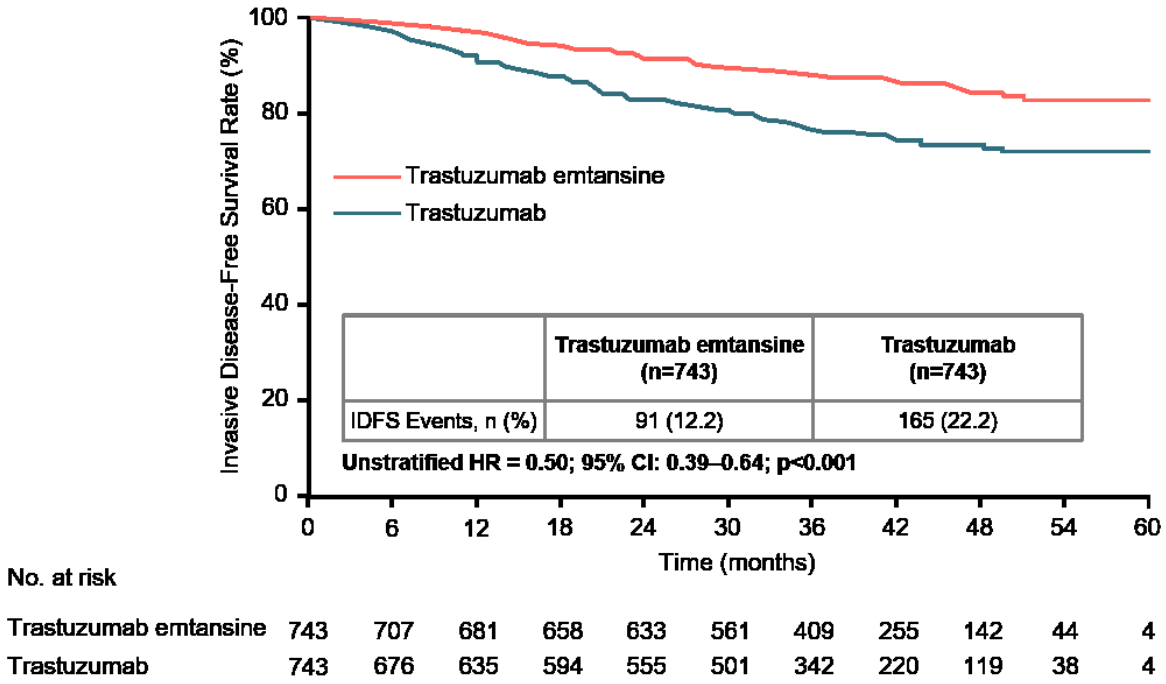
Figure 8. ITT primary endpoint analysis of IDFS



Abbreviations: CI: confidence interval; HR: hazard ratio; IDFS: invasive disease-free survival; ITT: intention-to-treat.
Source: von Minckwitz G *et al.* 2019.[8]

The robustness of the primary IDFS analysis was explored through two sensitivity analyses: censoring patients at the time they began a new anti-cancer therapy before experiencing an IDFS event and censoring patients at the time they discontinued study treatment for any reason before experiencing an IDFS event. Both analyses were consistent with the primary analysis, supporting the robustness of the primary IDFS analysis in the ITT population, and are not considered further in this submission.[63] Results of the IDFS (STEEP definition) and DFS analyses also served as sensitivity analyses for the primary analysis, and are discussed in further detail in Section B.2.6.2.

B.2.6.2 Secondary endpoints

Overall, secondary efficacy outcomes supported the clinical benefit of adjuvant trastuzumab emtansine seen on the primary outcome, IDFS. At the primary analysis there were clear between-arm differences in IDFS (STEEP definition, including second primary non-breast cancer events), DFS, DRFI and OS. A summary of secondary efficacy outcomes is presented in Table 12.[8]

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Table 12. Summary of secondary efficacy endpoints – unstratified analyses[a]

Secondary endpoint	Trastuzumab (N=743)	Trastuzumab emtansine (N=743)
IDFS (STEEP definition)		
Patients with an event, n (%)	167 (22.5)	95 (12.8)
3-year event-free rate, % (95% CI)	76.9 (73.7–80.1)	87.7 (85.2–90.2)
HR (95% CI)	0.51 (0.40–0.66)	
p-value (log-rank)	<0.0001	
DFS		
Patients with an event, n (%)	167 (22.5)	98 (13.2)
3-year event-free rate, % (95% CI)	76.9 (73.6–80.1)	87.4 (84.9–89.9)
HR (95% CI)	0.53 (0.41–0.68)	
p-value (log-rank)	<0.0001	
DRFI		
Patients with an event, n (%)	121 (16.3)	78 (10.5)
3-year event-free rate, % (95% CI)	83.0 (80.1–85.9)	89.7 (87.4–92.0)
HR (95% CI)	0.60 (0.45–0.79)	
p-value (log-rank)	0.0003	
OS		
Patients with an event, n (%)	56 (7.5)	42 (5.7)
HR (95% CI)	0.70 (0.47–1.05)	
p-value (log-rank)[b]	0.0848	

Footnotes: [a]No statistical adjustments were made for multiple comparisons. [b]The boundary for statistical significance in this prespecified interim analysis was p<0.000032 or HR<0.43.
Abbreviations: CI: confidence interval; DFS: disease-free survival; DRFI: distant recurrence-free interval; HR: hazard ratio; IDFS: invasive disease-free survival; OS: overall survival; STEEP: standardized definitions for efficacy endpoints.
Source: von Minckwitz G *et al.* 2019;[8] KATHERINE study CSR.[63]

Distant recurrence was the first invasive-disease event for the majority of patients, and occurred in fewer patients in the trastuzumab emtansine arm (n=78, 10.5%) than the trastuzumab arm (n=118, 15.9%) (Figure 9; HR=0.60; 95% CI: 0.45–0.79).[8] Trastuzumab emtansine reduced the incidence of non-central nervous system (CNS) recurrences (n=34, 4.6% in the trastuzumab emtansine arm vs n=86, 11.6% in the trastuzumab arm), rather than CNS recurrences (n=44, 5.9% in the trastuzumab emtansine arm vs n=32, 4.3% in the trastuzumab arm).[8, 63]

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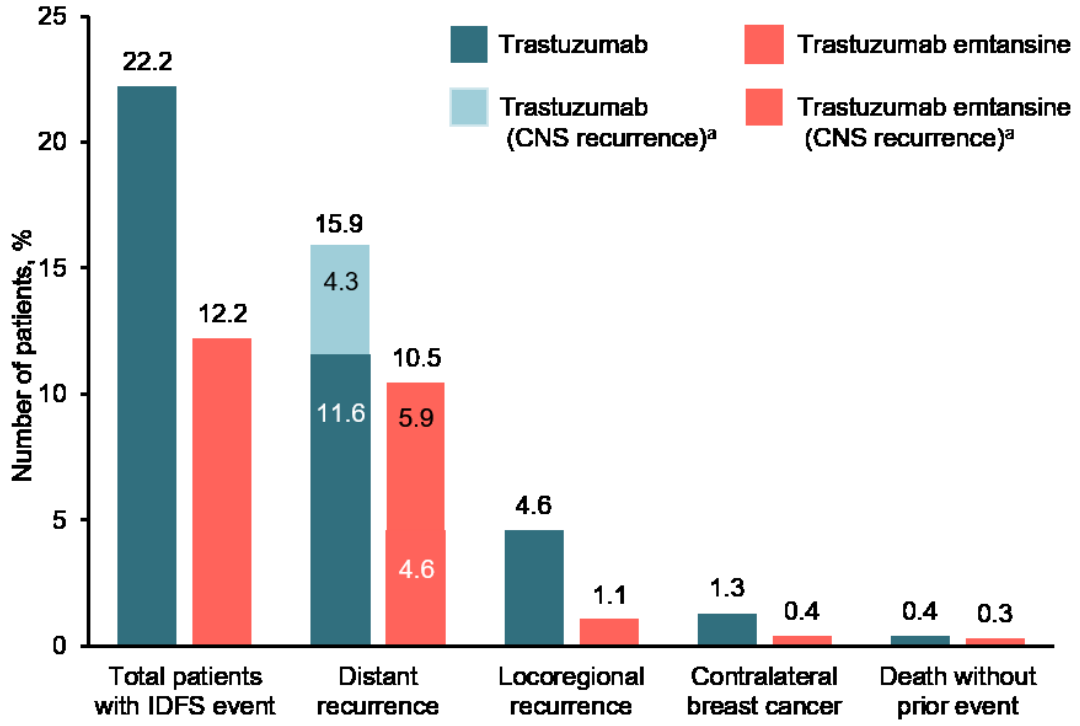
Figure 9. First recurrence of an IDFS event



Footnotes: [a]CNS metastases as component of distant recurrence (isolated or with other sites).
Abbreviations: CNS: central nervous system; IDFS: invasive disease-free survival.
Source: von Minckwitz G *et al.* 2019.[8]

The OS data were immature at the clinical cut-off date, with only 26.7% of the events required for the final analysis of OS having occurred (i.e. 98 deaths of the 367 deaths planned at the final OS analysis). The OS analysis did not cross the early reporting boundary, but is supportive of the IDFS analysis, with a separation of the curves from 30 months, continuing up to 60 months (HR=0.70, 95% CI: 0.47–1.05; p=0.0848; Figure 10). Three year OS rates were 95.2% for the trastuzumab emtansine arm compared with 93.6% for trastuzumab.[63] Any differences in OS may become more apparent in later analyses: a second interim OS analysis is planned at the time of final IDFS analysis, with a third interim analysis planned for when ~279 deaths have occurred (approximately two years after the second OS interim analysis). A final OS analysis will be performed at the end of 10 years of follow-up from the date of randomisation of the first patient, when ~367 deaths have occurred.[8]

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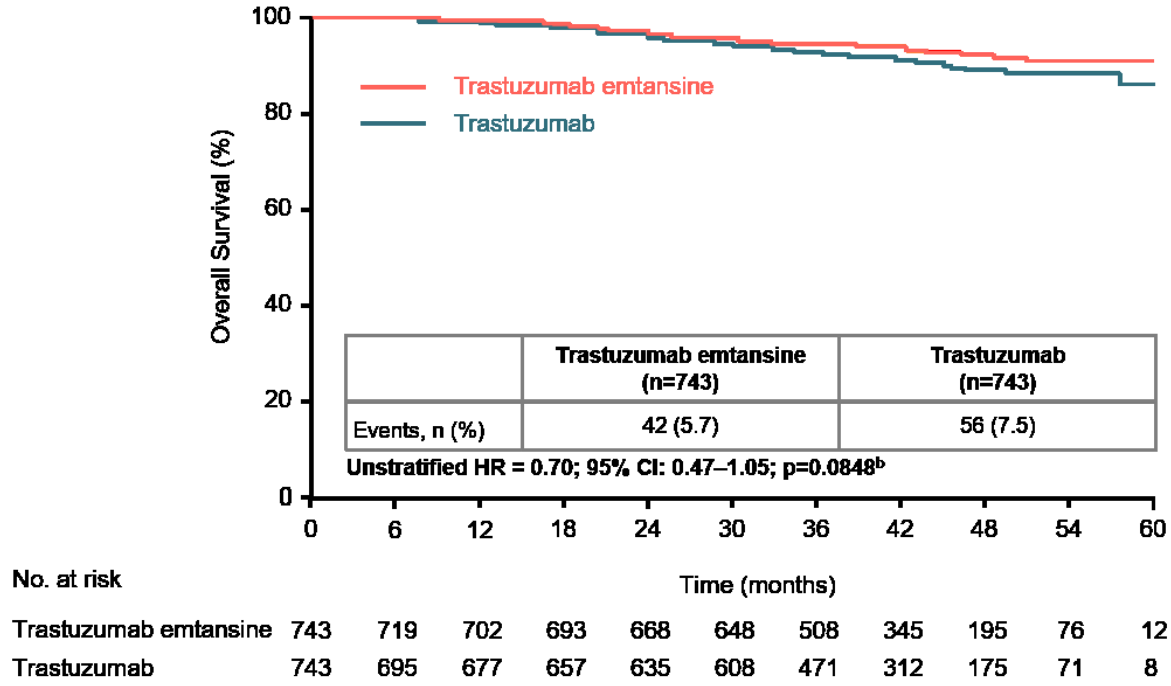
Figure 10. First interim analysis of OS[a]



Footnotes: [a]Up to three formal interim OS analyses are planned, in addition to the final OS analysis. Data presented here represent the first interim OS analysis (98 OS events; conducted when ~384 IDFS events had occurred); a second interim OS analysis is planned at the time of final IDFS analysis, with a third when ~279 deaths have occurred, and a final OS analysis at the end of 10 years of follow-up, when ~367 deaths have occurred. [b]Boundary for statistical significance: HR<0.43 or p<0.000032.
Abbreviations: CI: confidence interval; HR: hazard ratio; IDFS: invasive disease-free survival; OS: overall survival.
Source: von Minckwitz G *et al.* 2019.[8]

B.2.6.3 HRQoL

Completion rates for the EORTC QLQ-C30 and the QLQ-BR23 questionnaires were consistently high throughout the study (>70.0%) and were similar between the treatment arms.[64] A summary of the specific domains assessed by the questionnaires is provided in Appendix L. Overall, 640 (86%) patients in the trastuzumab emtansine arm and 612 (82%) patients in the trastuzumab arm had valid baseline and ≥1 post-baseline patient reported outcome (PRO) assessments and were included in the analysis.[64]

Baseline QLQ-C30 and QLQ-BR23 scale scores were similar in both treatment arms and consistent with normative scores reported for patients with stage I–II breast cancer.[64] Overall, similar mean changes from baseline in population scores for global health status (GHS, Figure 11), the five functioning scales (physical, social, role, cognitive and emotional) of the QLQ-C30, and the four functioning scales (body image, future prospect, sexual function and sexual enjoyment) of the QLQ-BR23 were observed in each treatment arm at most post-baseline assessments. Similar mean changes from baseline in population scores were also observed between treatment arms across the nine symptom scales (including financial difficulty) in the QLQ-C30 and the four symptom scales in the QLQ-BR23. While a numerical elevation over baseline on the symptom scales of appetite loss, constipation, pain, dyspnoea, nausea/vomiting, insomnia, fatigue and systemic therapy side effects was observed for population mean scores, these changes were less than the clinically meaningful differences for each scale (<10 points)

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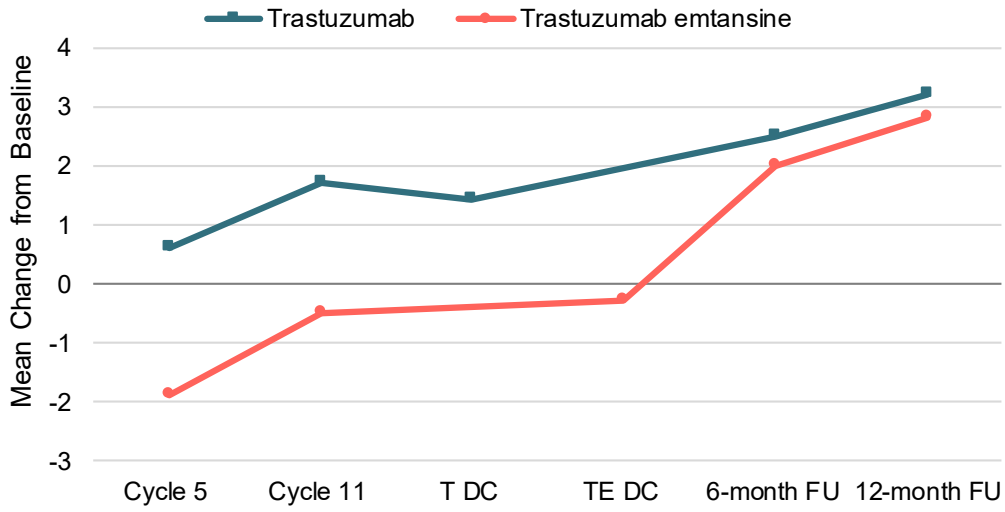
and the population mean scores generally returned to baseline levels after discontinuation of study treatment.[63, 64]

Figure 11. Mean change from baseline over time in EORTC QLQ-C30 GHS



Abbreviations: DC: discontinuation; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; FU: follow up; GHS: global health status; T: trastuzumab; TE: trastuzumab emtansine.
Source: Schneeweiss *et al.* 2019.[64]

In terms of individual patient results, a higher proportion of patients in the trastuzumab emtansine arm reported a clinically meaningful deterioration at any assessment during the study period in role functioning (49% vs 41%), appetite loss (38% vs 28%), constipation (47% vs 38%), fatigue (66% vs 61%), nausea/vomiting (39% vs 30%), and systemic therapy side effects (49% vs 36%) compared with patients in the trastuzumab arm. However, a lower proportion of patients in the trastuzumab emtansine arm reported clinically meaningful deterioration in diarrhoea at any point (22% vs 27%). By the 6-month follow-up assessment, proportions of patients reporting a clinically meaningful deterioration in symptoms was similar in each arm, though more patients in the trastuzumab emtansine arm still had a clinically meaningful deterioration in role functioning (17% vs 11%).[64]

There were no major differences (≥5%) in change from baseline between treatment arms in the five EQ-5D domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression).[69]

B.2.7 *Subgroup analysis*

Subgroup analyses were performed for the primary outcome, IDFS, and were intended to assess consistency of the overall result in the ITT population.[8] Subgroup analyses included age, race and stratification factors: clinical stage at presentation, hormone receptor status, neoadjuvant HER2-directed therapy type and pathological nodal status after neoadjuvant therapy.[8] IDFS improvements were observed in all clinically relevant subgroups analysed, providing evidence of internal consistency of the primary endpoint across pre-specified patient subpopulations, and further demonstrating the robustness of the primary result (Figure 12).[8]

In an exploratory analysis, clinical benefit was seen in 331 patients with RID ≤1 cm in the breast and negative axillary lymph nodes, with invasive-disease events in 17 patients in the

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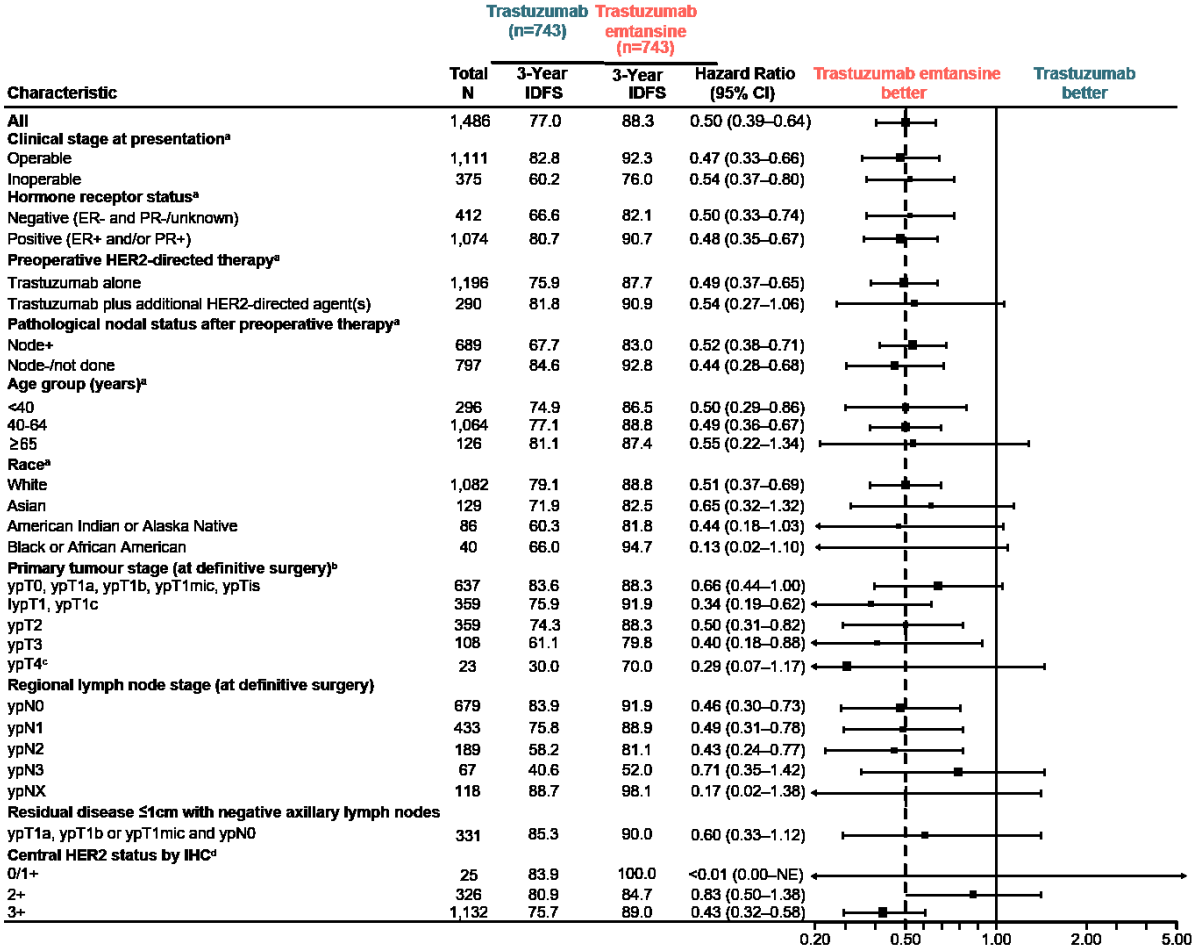
trastuzumab emtansine group (10.0%) and 25 patients in the trastuzumab group (15.5%) (HR=0.60; 95% CI: 0.33–1.12).[8]

Figure 12. Forest plot of IDFS for different subgroups in the ITT population



Footnotes: [a]Stratification factors. [b]Five patients with a ypT1 tumour stage had ypT1 disease without further sub-specification. [c]The ypT4 category includes all patients with ypT4 and one patient with ypTX. [d]Three patients had "unknown" HER2 IHC status. The size of the black squares corresponds to the number of patients.
Abbreviations: CI: confidence interval; ER: oestrogen receptor; HER2: human epidermal growth factor receptor 2; IDFS: invasive disease-free survival; IHC: immunohistochemistry; ITT: intention-to-treat; NE: not estimated; PR: progesterone receptor.
Source: Geyer CE *et al*. 2018.[70]

IDFS by neoadjuvant HER2-targeted therapy regimen

The addition of pertuzumab to neoadjuvant chemotherapy regimens was not standard practice during the recruitment period of the KATHERINE study, therefore the majority of patients received neoadjuvant trastuzumab + chemotherapy. However, 18.7% of patients (n=139) in the trastuzumab arm and 17.9% (n=133) in the trastuzumab emtansine arm received neoadjuvant pertuzumab + trastuzumab + chemotherapy, the current UK SoC in the neoadjuvant setting for patients with HER2-positive, locally advanced, inflammatory or early stage breast cancer at high risk of recurrence.[8]

Efficacy results in patients who received neoadjuvant pertuzumab + trastuzumab + chemotherapy and patients who received neoadjuvant trastuzumab + chemotherapy are displayed in Table 13.[8] Despite the low number of events, the results seen in this analysis show

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that the treatment effect of trastuzumab emtansine was consistent for patients who received neoadjuvant pertuzumab + trastuzumab, with near identical unstratified HRs for an IDFS event of 0.49 and 0.50, respectively.[8] As discussed in Section B.2.13.2, this is as expected given that there is no biological or clinical rationale why the addition of pertuzumab to the neoadjuvant treatment regimen would impact on the efficacy of trastuzumab emtansine in the adjuvant setting.

Table 13. Risk of first IDFS event by neoadjuvant HER2-targeted therapy

Neoadjuvant HER2-targeted therapy regimen	Trastuzumab (N=743)	Trastuzumab emtansine (N=743)
No prior pertuzumab		
Patients with an event,% (events/no. patients)	23.7 (141/596)	13.0 (78/600)
3-year event-free rate, %	75.9	87.7
Unstratified HR (95% CI)	0.49 (0.37–0.65)	
Prior pertuzumab		
Patients with an event, % (events/no. patients)	17.3 (24/139)	9.0 (12/133)
3-year event-free rate, %	80.9	91.4
Unstratified HR (95% CI)	0.50 (0.25–1.00)	

Abbreviations: CI: confidence interval; HER2: human epidermal growth factor receptor 2; HR: hazard ratio; IDFS: invasive disease-free survival.
Source: von Minckwitz G *et al.* 2019.[8]

B.2.8 *Meta-analysis*

As no further RCTs studying the efficacy and safety of trastuzumab emtansine as adjuvant treatment of HER2-positive eBC were found, no meta-analysis was conducted.

B.2.9 *Indirect and mixed treatment comparisons*

In February 2019, NICE published a FAD recommending the use of pertuzumab + trastuzumab + chemotherapy in the adjuvant treatment of patients with HER2-positive, node-positive eBC, based on the results of the APHINTY clinical trial.[71] Patients with node-positive, HER2-positive eBC who are treated neoadjuvantly with pertuzumab + trastuzumab + chemotherapy can now continue treatment into the adjuvant setting to complete 18 cycles of pertuzumab + trastuzumab, and this continuation of treatment has become the SoC for patients with node-positive, HER2-positive eBC.

As is documented in Section B.1, the Company is expecting to receive a licence for trastuzumab emtansine for the adjuvant treatment of "[redacted]". This results in a population overlap between the recommended indication of pertuzumab + trastuzumab + chemotherapy and the expected licence of trastuzumab emtansine. In summary, patients with HER2-positive and node-positive disease who still have RID following neoadjuvant therapy could be eligible for trastuzumab emtansine or pertuzumab + trastuzumab + chemotherapy. This ultimately means that pertuzumab + trastuzumab + chemotherapy should be included as a relevant comparator, for the node-positive subgroup, in this appraisal – as per the final scope.

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The design phase of the KATHERINE trial predates the APHINITY regimen becoming the SoC for UK patients with node-positive, HER2-positive eBC. A pertuzumab + trastuzumab + chemotherapy arm was not included in the KATHERINE study. A lack of head-to-head data in this subgroup of interest necessitated an indirect treatment comparison (ITC).

The following subsections outline the clinical SLR and feasibility assessment associated with this ITC.

B.2.9.1 Summary of SLR of clinical evidence

An SLR was performed to capture all relevant evidence in order to fully inform an ITC. The SLR captured published clinical evidence on the efficacy and safety of anti-HER2 therapies in the treatment of patients with HER2-positive eBC.

Full details of the methods associated with this SLR, including search strategy and study selection process, can be found in Appendix D. The results of the review have been summarised below:

A total of 90 unique trials across the original (November 2018) and updated (June 2019) searches met the criteria for inclusion in the review. In addition to these 90 published trials an additional 18 ongoing trials (identified as part of the trial registry searches) were also captured. The included trials represent all studies investigating anti-HER2 agents in patients with HER2-positive eBC. All included trials (completed and ongoing) were classified according to the following trial design categories:

- **Neoadjuvant only – (64 unique trials):** trials where patients are randomised to neoadjuvant therapy and the randomised therapy ends prior to surgery. Following completion of the randomised neoadjuvant treatment and subsequent surgery, all patients may receive adjuvant therapy at the discretion of the physician, or all patients could receive SoC trastuzumab for up to 1 year. Any adjuvant therapy received is not part of randomisation and all patients across all arms of the trial receive the same treatment.
- **Neoadjuvant-to-adjuvant – (14 unique trials):** trials in which patients are randomised to neoadjuvant therapy and after surgery randomisation is maintained for adjuvant therapy (i.e. the randomised treatment begins in the neoadjuvant setting and continues after surgery). In these studies, the chemotherapy component of the randomised regimen in the neoadjuvant setting is dropped from the adjuvant treatment post-surgery, but the neoadjuvant HER2-targeted agent is continued.
- **Adjuvant (with prior neoadjuvant HER2 therapy) – (3 unique trials):** represents trials in which patients are randomised to adjuvant therapy after surgery. Enrolled patients have also received HER2-targeted agents (± chemotherapy) in the neoadjuvant setting.
- **Adjuvant (no prior neoadjuvant HER2 therapy) – (27 unique trials):** represents trials in which patients are randomised to adjuvant therapy after surgery. The enrolled patients have not received HER2-targeted agents in the neoadjuvant setting, but they may have received chemotherapy.
- **Extended adjuvant – (1 unique trial):** represents trials in which, following adjuvant HER2-targeted therapy, patients are randomised to additional HER2-targeted therapy. Note that in this category patients may or may not have received HER2-targeted therapy and/or chemotherapy in the neoadjuvant setting.

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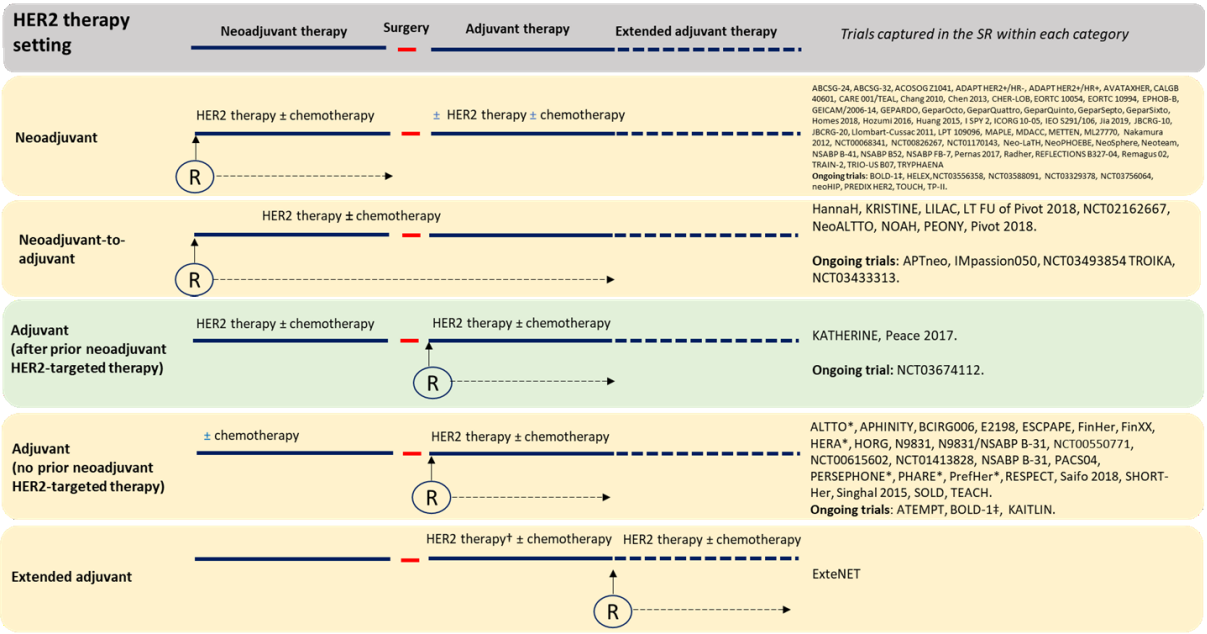
One on-going trial (BOLD-1) was classified as 'neoadjuvant only' or 'adjuvant (no prior neoadjuvant HER2)' and is therefore included in both categories. A breakdown of all captured trials and how they are classified is presented in Figure 13.

Figure 13. Classification of trials captured in the clinical SLR



Footnotes: *Indicates patients in the trials could have received neoadjuvant chemotherapy. †Standard of care adjuvant treatment contains trastuzumab or trastuzumab and pertuzumab. ‡The BOLD-1 trial ITT and subset population could be in either the neoadjuvant only or adjuvant only groups as patients were randomised to neoadjuvant or adjuvant therapy.
Abbreviations: FU: follow-up; HER2: human epidermal growth factor receptor 2; LT: long-term; RCT: randomised controlled trial; SR: systematic review.

B.2.9.2 Feasibility assessment

Objective

The objective of the network meta-analysis feasibility assessment is to summarise the potential outcome-specific networks to allow for comparisons of trastuzumab emtansine with comparators of interest in patients with eBC with RID after HER2-targeted therapy in the neoadjuvant setting.

A robust meta-analysis feasibility assessment is crucial to the relevance and credibility of any statistical analyses for decision making. To achieve this, a transparent, step-wise, and reproducible methodology is employed (Figure 14).

Methodology & results

Overview

The feasibility assessment is composed of three components. The first step is to explore the connectivity (a "mapping") of the identified trials based on the interventions of the trial. This exercise results in a "best-case" scenario (BCS) evidence network. Trials included in the BCS network then undergo a heterogeneity assessment. The designs and patient characteristics of the trials included in the network will be explored. At this stage, trials may be excluded due to

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insufficient homogeneity. The final step of this assessment is to generate an outcome-specific evidence network. Once again, studies may be excluded if the reported outcomes are insufficiently similar to the KATHERINE study in terms of definition and timing of assessment. Ideally, the feasibility assessment will result in a series of trials with the same design, similar patient characteristics, common interventions and comparable outcome measures.

Figure 14. Summary of approach taken in feasibility assessment

Abbreviations: SLR: systematic literature review.

The methodology and results associated with each step of the feasibility assessment are outlined in detail below:

1. Best case scenario evidence network

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The trials of interest for this assessment are those classified as adjuvant trials, where patients had received anti-HER2 neoadjuvant therapy prior to surgery and randomisation (i.e. the same design as the KATHERINE trial). Only two potentially relevant RCTs (excluding the KATHERINE trial) were captured in the SLR – see Figure 13. These two trials form what can be described as the BCS evidence network. A brief discussion of both these trials is provided below:

- **NCT03674112:** An ongoing phase II, cross-over RCT with a nine-week treatment period prior to cross-over (three cycles of three weeks). The primary objective of this study is to evaluate patient preference and satisfaction of subcutaneous (SC) administration of pertuzumab and trastuzumab fixed-dosed combination (primary outcome is the proportion of participants who preferred the fixed-dose SC administration of pertuzumab and trastuzumab vs intravenous administration).[66]
- **Peace 2017:** A phase II RCT investigating a trastuzumab in combination with an anti-HER2 vaccine in low-expressing HER2-positive eBC patients. The primary objective of this study was to assess the safety of the vaccine in combination with trastuzumab.[65]

2. Heterogeneity assessment

The heterogeneity assessment of these two trials was severely impeded by data availability.

NCT03674112[66] is an ongoing trial (estimated completion date March 2020) and no formal publication of results yet exists. The only information on patient characteristics are available via the inclusion/exclusion criteria stated on ClinicalTrials.gov. Based on this information the populations in the KATHERINE trial and NCT03674112 seem broadly comparable (see Table 14).

The Peace *et al.* trial is published as an abstract only.[65] Unsurprisingly, information on population characteristics is sparse. Nevertheless, the information that is publicly available once again appears to signal that the populations in the KATHERINE trial and the Peace *et al.* study are broadly comparable.

In summary, no trials were excluded from the network based on the heterogeneity assessment. For completeness, Table 14 details the study details and inclusion criteria for each of the three trials.

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Table 14. Summary of trial design, eligibility criteria, and treatment regimens for RCTs aligned with the KATHERINE trial

	KATHERINE[8]	NCT03674112[66] (ongoing trial)	Peace 2017[65]
Study details	• Full publication (interim analysis) • Open-label, phase III RCT • Multicentre, international (28 countries) • NCT01772472	• Clinical trial registry page only • Phase II, open-label cross-over RCT • Multicentre, international • NCT03674112	• Abstract publication • Single-blind, phase II RCT
Inclusion criteria	• Early or locally advanced HER2-positive breast cancer • ECOG 0 or 1 • Completion of ≥6 cycles neoadjuvant chemotherapy and HER2-targeted (≥9 weeks trastuzumab) treatment • ≤12 weeks between surgery and randomisation	• HER2-positive inflammatory, locally advanced or early breast cancer • Received neoadjuvant pertuzumab and trastuzumab and have completed neoadjuvant chemotherapy and subsequently undergone surgery for breast cancer • ECOG 0 or 1 • ≤9 weeks between last systemic neoadjuvant therapy and randomisation	• Stage I-III HER2-positive breast cancer • At high risk for recurrence; no complete response after trastuzumab neoadjuvant therapy or those undergoing up-front surgery with any node positive disease • Undergone standard of care surgery, radiation and neoadjuvant/adjuvant chemotherapy with approved trastuzumab-containing regimen
Randomised adjuvant therapy	• Trastuzumab emtansine 6 mg/kg q3w; 14 cycles (IV)	• FD combination of SC pertuzumab (600 mg) and trastuzumab (600 mg) – 3 cycles (SC) then cross-over to loose combination administration of the formulations for 3 cycles (IV)	• Trastuzumab and NeuVax
	• Trastuzumab 6 mg/kg q3w; 14 cycles (IV)	• Loose combination of pertuzumab (420 mg) and trastuzumab (6 mg/kg) – 3 cycles (IV) then cross-over to FD combination of the formulations for 3 cycles (SC)	• Trastuzumab and GM-CSF

Abbreviations: ECOG: Eastern Cooperative Oncology Group; FD: fixed dose; GM-CSF: granulocyte-macrophage colony-stimulating factor; HER2: human growth factor receptor 2; IV: intravenous; q3w: every three weeks; RCT: randomised controlled trial; SC: subcutaneous.
Sources: von Minckwitz G *et al*. 2019,[8] ClinicalTrials.gov,[66] Peace et al 2017[65].

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3. Outcome-specific evidence network

The final step is to construct a network of outcome specific evidence. Unfortunately, due to the nature of the two trials (phase II), the outcomes of the NCT03674112 and Peace *et al.* are not sufficiently aligned to construct a network of outcome-specific evidence.

The objective of the NCT03674112 study was to evaluate patient preference and satisfaction with SC administration of a fixed-dosed combination of pertuzumab + trastuzumab. Therefore, the primary outcome was the proportion of participants who preferred the fixed-dose SC administration. Naturally, this is insufficiently comparable with the primary outcome of the KATHERINE trial (IDFS).

Although the Peace *et al*. publication is primarily concerned with the safety associated with a vaccine, the trial does include a control arm of adjuvant trastuzumab. Despite the inclusion of a trastuzumab arm, several issues preclude its inclusion in an outcome-specific evidence network. First, the primary efficacy outcome is DFS. While the difference between DFS and IDFS is not insurmountable, this difference represents further misalignment and additional uncertainty. Further, the abstract reports results from an interim analysis of a phase IIb study. These efficacy results are therefore based on few events from limited patient numbers. Finally, and perhaps most crucially, the issue of lack of data availability is the main issue precluding the inclusion of this study in the outcome-specific network. As was previously mentioned, the write-up of this study is reported in abstract form – available in the Reference Pack for this submission. Consequently, details on population characteristics, trial design, and efficacy are not readily available.

Key excluded studies

Many well-known trials in the HER2-positive breast cancer space have been captured as part of the SLR. The Company appreciates that it may not be immediately clear as to why some of the more prominent trials cannot be used to inform a comparison of trastuzumab emtansine vs pertuzumab + trastuzumab in the adjuvant setting. For completeness, a brief discussion around why it is inappropriate to directly use certain key studies to inform the comparison has been included below:

APHINITY study[72]

The APHINITY study is an ongoing, randomised, placebo-controlled phase III trial comparing pertuzumab + trastuzumab + chemotherapy vs placebo + trastuzumab + chemotherapy in the adjuvant treatment of patients with HER2-positive eBC.

The APHINITY study includes the intervention of interest for this ITC (pertuzumab + trastuzumab) and also measures the same primary outcome as the KATHERINE study (IDFS) in the treatment setting of interest (adjuvant treatment). However, differences in trial design result in incomparable study populations – see below:

- **pCR and presence of RID:** Patients included in the KATHERINE study are only those who did not achieve a pCR following neoadjuvant treatment, and therefore had RID in the breast and/or axillary lymph nodes. This “residual invasive or non-pCR subgroup” is not reproducible in the APHINITY study population simply because patients were not pre-treated in APHINITY (therefore an assessment of pCR was not possible).

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- **Pre-treatment:** Patients in the KATHERINE study were pre-treated with neoadjuvant HER2-targeted treatment + chemotherapy whereas patients in the APHINITY trial were treatment-naïve. This means that patient baseline risk was different across the studies.
- **Treatment exposure:** Efficacy results in the KATHERINE study represent the effect of 14 cycles of adjuvant treatment, compared to the 18 cycles of adjuvant treatment received in APHINITY. (Although patients in the KATHERINE study received neoadjuvant HER2-targeted therapy prior to enrollment, only adjuvant treatment was administered as part of the study.)
- **Contrasting study objectives:** Patients in the KATHERINE study were pre-treated with neoadjuvant therapy. The neoadjuvant therapy eradicated tumour cells sensitive to standard chemotherapy and trastuzumab-based agents (including dual-blockade) while the invasive cells that remained in the breast and/or axillary lymph nodes likely developed "escape mechanisms" to neoadjuvant treatment that can be overcome by the change of the therapy.[73] The main rationale for the KATHERINE study was to investigate if a change of adjuvant treatment could improve efficacy in pre-selected patients with unique treatment biology. However, this objective is not possible to achieve in a situation where patients were not treated prior to surgery and RID therefore cannot be assessed, such as in the APHINITY trial.

For the reasons called out above, any ITC of KATHERINE vs APHINITY is likely to yield biased results and is not methodologically justified.

KRISTINE study[23]

The KRISTINE study is a randomised, open-label phase III trial investigating the safety and efficacy of trastuzumab + pertuzumab + chemotherapy vs trastuzumab emtansine + pertuzumab in the neoadjuvant treatment of HER2-positive eBC. Despite being a neoadjuvant study, data were also collected in the adjuvant setting as part of the follow-up period in this trial.

At first glance, the KRISTINE study seems suitable as a data source to help inform the ITC. However, upon further exploration, it became clear that the differences in the trial design were insurmountable and it was subsequently deemed inappropriate from a methodological standpoint to use the KRISTINE data as a source of comparative evidence. These limitations are detailed below:

- **Difference in primary outcome:** KRISTINE was principally designed as a neoadjuvant study and therefore the primary endpoint is pCR. In contrast, the KATHERINE study is an adjuvant trial and the primary endpoint is IDFS. Please note; IDFS was collected in KRISTINE – as a secondary endpoint. Naturally, statistical powering is therefore a challenge here. It is also important to note that the KRISTINE study did not meet its primary endpoint, meaning that any secondary endpoint analyses would be descriptive in nature.
- **Number of patients with RID in the pertuzumab + trastuzumab arm of KRISTINE:** 221 patients were randomised to the pertuzumab + trastuzumab arm of the KRISTINE study. Of those, only 98 patients had RID following neoadjuvant therapy. Given these low event numbers and insufficient IDFS powering, any ITC using these data would be incredibly uncertain and the likelihood of unbiased analysis and conclusions would be very low indeed.
- **Timing of patient recruitment and randomisation:** In the KATHERINE study, patients were recruited and randomised following surgery (i.e. in the adjuvant setting), whereas in

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KRISTINE patients were recruited and randomised prior to initiation of neoadjuvant therapy. This leads to differences in reported baseline characteristics, patient follow-up time and data collection points for long-term endpoints across the two trials.

- **No common comparator arm –** KRISTINE and KATHERINE are not connected in a network by a common comparator. When a connected network exists (through a common comparator arm) we can compare the relative effects of the treatments using hazard ratios (i.e. there is a correction for study-specific treatment effects). Without a common comparator, the single arms from different studies must be used. In this case, we are actually comparing the absolute effect in each of these cohorts – thereby leading to biased conclusions. We could use patient-level data to circumvent this bias, however, it would require patient matching. The issues documented in bullets two and three, would preclude the conducting of a matching exercise in this situation.
- **Differences in reporting milestones:** Any population-adjustment methods would be extremely challenging due to the different timing of reported patient baseline characteristics. This difference links back to the differences in trial design and the timing of randomisation (KATHERINE patients randomised following surgery; KRISTINE patients randomised prior to neoadjuvant therapy). For clarity, in the KRISTINE study, patient characteristics were not collected again following surgery.

The limitations listed above mean that any indirect comparison based on the results of this trial would be extremely uncertain – it was therefore deemed inappropriate from a methodological perspective.

BERENICE study[22]

BERENICE (NCT02132949) is a non-randomised, phase II, open-label study in patients with normal cardiac function. In the neoadjuvant period, cohort A patients received four cycles of dose-dense doxorubicin + cyclophosphamide, then 12 doses of standard paclitaxel plus four standard trastuzumab + pertuzumab cycles. In cohort B patients received four standard fluorouracil/epirubicin/cyclophosphamide cycles, then four docetaxel cycles with four standard trastuzumab + pertuzumab cycles. This study was captured as part of the SLR but excluded at the title/abstract screening stage. The reason for exclusion was the lack of randomisation – patients were assigned to the two different cohorts based on investigator choice.

- As stated above, this study is still ongoing. The IDFS data from this study are not yet available – study completion is estimated for Q4 2020. The primary objective of this trial is to evaluate cardiac safety when comparing two different chemotherapy regiments when in combination with pertuzumab + trastuzumab. Therefore, tpCR and IDFS were only collected as secondary endpoints. Regardless, there is no trastuzumab emtansine arm or trastuzumab arm in this study. It is therefore not possible to include in a connected evidence network with the KATHERINE trial.

Conclusion of feasibility assessment

Results of the assessment showed that a connected network, among trials with the same design as the KATHERINE study, was not feasible. This was due to limitations in terms of data availability, differences in study designs and study populations and differences in outcomes being explored.

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Further, any comparison utilising key studies in the HER2-positive eBC space is likely to be accompanied by significant uncertainty and methodological limitations.

Proposed approach

Given the inclusion of pertuzumab + trastuzumab as a relevant comparator (in the node-positive population) in the final scope for this appraisal, the Company acknowledges that some form of comparison between trastuzumab emtansine and pertuzumab + trastuzumab in this setting must be presented.

Despite the trial design and population differences, it was deemed most appropriate to use the APHINITY trial data to inform the comparison. The APHINITY study was judged to be most appropriate since it includes a large sample size, the comparator of interest (pertuzumab + trastuzumab), and the same primary outcome as the KATHERINE study (IDFS). A Bucher analysis has subsequently been performed by the Company.

The Bucher methodology is a relatively straightforward analysis and was performed as outlined in Bucher *et al.*[74] This simpler approach was preferred over more complex analyses such as a match-adjusted indirect comparison (MAIC). Despite the availability of patient-level data in both the KATHERINE and the APHINITY trial, a robust MAIC was not possible. This was principally due to the inability to match the populations in the two trials (no assessment of RID in APHINITY). Furthermore, applying complex ITC methodology to an already limited data set would only serve to further amplify any uncertainty.

Greater detail on the methodology associated with the chosen analysis is provided in Appendix M. It is crucial to note here that despite providing this analysis, the population differences and the limitations listed above still persist. The Bucher analysis is a naïve comparison and makes no attempt to adjust for population differences.

The Company is fully aware of the limitations associated with the chosen methodology, however given the current evidence base, it appears to be the most appropriate approach. There is no doubt that a high degree of uncertainty exists around the outputs of this analysis, effort has therefore been made to include extensive scenario analyses (Appendix M).

In summary, a robust ITC comparing trastuzumab emtansine to pertuzumab + trastuzumab in this setting is not possible. A Bucher analysis using the APHINITY trial data was therefore commissioned. These analyses are not endorsed by the Company because they are likely to lead to biased results and are not methodologically justified. The exploratory analyses have simply been provided in order to best address the Decision Problem in this appraisal. The sizable limitations associated with the analyses mean that the results should be interpreted with caution.

B.2.9.3 Uncertainties in the indirect and mixed treatment comparisons

Please see Appendix M for greater detail on the methodology behind the trastuzumab emtansine vs pertuzumab + trastuzumab comparison.

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B.2.10 *Adverse reactions*

Summary of adverse reactions

- No new safety signals for trastuzumab emtansine were identified in the KATHERINE study.[8]
- AEs of any grade were more common in the trastuzumab emtansine arm than in the trastuzumab arm (98.8% vs 93.3%, respectively), as were AEs leading to discontinuation (18.0% vs 2.1%, respectively), although the majority of AEs observed were reversible and could be well managed.[8, 63] The most common AEs in either the trastuzumab emtansine arm or trastuzumab arm were fatigue (366 patients [49.5%] vs 243 patients [33.8%], respectively) and nausea (308 patients [41.6%] vs 94 patients [13.1%], respectively).[8]
- AEs of Grade 3 or higher were more common in the trastuzumab emtansine arm than in the trastuzumab arm (25.7% vs 15.4%, respectively). The most common AEs of Grade 3 or higher in the trastuzumab emtansine arm were a decreased platelet count and hypertension (42 patients [5.7%] and 15 patients [2.0%], respectively), and hypertension and radiation-related skin injury in the trastuzumab arm (nine patients [1.2%] and seven patients [1.0%], respectively).[8]
- The number of patients with ≥1 AE of cardiac dysfunction was higher in the trastuzumab arm than in the trastuzumab emtansine arm (40 patients [5.6%] vs 23 patients [3.1%], as was the number of patients with any cardiac event (27 patients [3.8%] vs 19 patients [2.6%], respectively).[63]
- There was one death due to an AE (intracranial haemorrhage), in the trastuzumab emtansine arm.[8]

Patients who received at least one dose of study treatment (trastuzumab emtansine or trastuzumab) were included in safety analyses (Table 9). The safety analysis population included 740 patients who were treated with at least one dose of trastuzumab emtansine and 720 patients who received trastuzumab but no trastuzumab emtansine.[8] Cardiac events and potential cases of hepatic dysfunction were adjudicated by an independent clinical-events committee.

B.2.10.1 Treatment duration, dose interruptions and dose modifications

A summary of treatment exposure during the KATHERINE study is provided in Table 15. In total, 528/740 patients (71.4%) who received trastuzumab emtansine and 583/720 (81.0%) patients who received trastuzumab completed all 14 cycles of treatment.[8] Patients in both treatment arms received a median of 14 cycles of treatment (range 1–14), corresponding to a median treatment duration of 10 months.[63] In the trastuzumab emtansine arm, 77 patients (10.4%) had one dose-level reduction, and 29 patients (3.9%) had a second dose-level reduction. No patients in the trastuzumab arm had any dose-level reductions.[8] Of 133 patients who discontinued trastuzumab emtansine early due to AEs, 71 switched to trastuzumab, of whom 63 (88.7%) completed a total of 14 cycles of HER2-targeted treatment. Fifteen patients discontinued treatment with trastuzumab due to AEs.[8]

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Table 15. Study treatment exposure

Patients, n (%)	Trastuzumab (N=720)	Trastuzumab emtansine (N=740)
Cycles of trastuzumab/trastuzumab emtansine completed		
7 cycles	664 (92.2)	637 (86.1)
14 cycles	583 (81.0)	528 (71.4)
Dose reduction level		
No dose reduction	N/A	634 (85.7)
Dose reduction by one level (3.0 mg/kg)	N/A	77 (10.4)
Dose reduction by two levels (2.4 mg/kg)	N/A	29 (3.9)

Abbreviations: N/A: not applicable.
Source: von Minckwitz G *et al*. 2019.[8]

B.2.10.2 Safety results

Safety summary

A summary of all patients experiencing AEs in the KATHERINE study is presented in Table 16. Overall, the safety profile of trastuzumab emtansine in this study was consistent with prior experience, and trastuzumab emtansine was generally well tolerated.[8]

Table 16. Safety summary

Event, n (%)	Trastuzumab (N=720)	Trastuzumab emtansine (N=740)
Any AE	672 (93.3)	731 (98.8)
Grade ≥3 AE	111 (15.4)	190 (25.7)
AE leading to death	0	1 (0.1)[a]
SAE	58 (8.1)	94 (12.7)
SAE related to study treatment	8 (1.1)	39 (5.3)
AE leading to discontinuation of trial drug	15 (2.1)	133 (18.0)

Footnotes: [a]One patient with a platelet count of 55,000 per cubic millimetre fell at home and died of an intracranial haemorrhage.
Abbreviations: AE: adverse event; SAE: serious adverse event.
Source: von Minckwitz G *et al*. 2019[8] and KATHERINE study CSR.[63]

AEs of any grade were more common in the trastuzumab emtansine arm than in the trastuzumab arm (98.8% vs 93.3%, respectively).[63] The most common AEs in either treatment arm were fatigue (366 patients [49.5%] in the trastuzumab emtansine arm, 243 patients [33.8%] in the trastuzumab arm) and nausea (308 patients [41.6%] in the trastuzumab emtansine arm, 94 patients [13.1%] in the trastuzumab arm), as outlined in Table 17.[63] AEs of any grade occurring in ≥10% more patients receiving trastuzumab emtansine than receiving trastuzumab were: fatigue, nausea, dry mouth, headache, peripheral sensory neuropathy, aspartate aminotransferase (AST) increased, platelet count decreased, alanine aminotransferase (ALT) increased, and epistaxis. No events occurred in 10% more patients receiving trastuzumab than trastuzumab emtansine.[63]

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Table 17. All AEs of any grade occurring with incidence ≥10% in either treatment arm

MedDRA Preferred Term, n (%)	Trastuzumab (N=720)	Trastuzumab emtansine (N=740)
Any AE	672 (93.3)	731 (98.8)
Fatigue	243 (33.8)	366 (49.5)
Nausea	94 (13.1)	308 (41.6)
Platelet count decreased	17 (2.4)	211 (28.5)
AST increased	40 (5.6)	210 (28.4)
Headache	122 (16.9)	210 (28.4)
Arthralgia	148 (20.6)	192 (25.9)
Radiation skin injury	199 (27.6)	188 (25.4)
ALT increased	41 (5.7)	171 (23.1)
Epistaxis	25 (3.5)	159 (21.5)
Peripheral sensory neuropathy	50 (6.9)	138 (18.6)
Constipation	59 (8.2)	159 (21.5)
Myalgia	80 (11.1)	138 (18.6)
Vomiting	37 (5.1)	108 (14.6)
Insomnia	86 (11.9)	101 (13.6)
Cough	86 (11.9)	100 (13.5)
Dry mouth	9 (1.3)	100 (13.5)
Influenza-like illness	87 (12.1)	100 (13.5)
Hot flush	146 (20.3)	95 (12.8)
Pain	92 (12.8)	93 (12.6)
Diarrhoea	90 (12.5)	91 (12.3)
Pain in extremity	70 (9.7)	86 (11.6)
Stomatitis	27 (3.8)	80 (10.8)
Pyrexia	29 (4.0)	77 (10.4)
Anaemia	60 (8.3)	74 (10.0)

Abbreviations: AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; MedDRA: Medical Dictionary for Regulatory Activities.
Source: von Minckwitz G *et al*. 2019.[8]

AEs of Grade 3 or higher

AEs of Grade 3 or higher were more common in the trastuzumab emtansine arm than in the trastuzumab arm (25.7% vs 15.4%, respectively).[63] As shown in Table 18, the most common AEs of Grade 3 or higher in the trastuzumab emtansine arm were a decreased platelet count and hypertension (42 patients [5.7%] and 15 patients [2.0%], respectively), and hypertension and radiation-related skin injury in the trastuzumab arm (nine patients [1.3%] and seven patients [1.0%], respectively).[63] Of the 42 patients in the trastuzumab emtansine arm for which platelet count decreased, 40 patients' events had resolved and two patients had recovering/resolving AEs at the clinical cut-off date.[63]

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Table 18. AEs of Grade 3 or higher by treatment arm

Event, n (%)	Trastuzumab (N=720)	Trastuzumab emtansine (N=740)
Any Grade ≥3 AE	111 (15.4)	190 (25.7)
Decreased platelet count	2 (0.3)	42 (5.7)
Decreased neutrophil count	5 (0.7)	9 (1.2)
Radiation-related skin injury	7 (1.0)	10 (1.4)
Hypertension	9 (1.3)	15 (2.0)
Peripheral sensory neuropathy	0	10 (1.4)
Hypokalaemia	1 (0.1)	9 (1.2)
Fatigue	1 (0.1)	8 (1.1)
Anaemia	1 (0.1)	8 (1.1)

Abbreviations: AE: adverse event.
Source: von Minckwitz G *et al*. 2019.[8]

SAEs

SAEs occurred in 94 patients (12.7%) who received trastuzumab emtansine and 58 patients (8.1%) who received trastuzumab.[63] The total number of SAEs was 114 in the trastuzumab emtansine arm and 70 in the trastuzumab arm.[63] A summary of SAEs occurring in ≥0.5% of patients in either the trastuzumab emtansine or the trastuzumab arm are shown in Table 19.[63]

Table 19. Serious AEs occurring in ≥0.5% of patients in either treatment arm

MedDRA Preferred Term, n (%)	Trastuzumab (N=720)	Trastuzumab emtansine (N=740)
Mastitis	6 (0.8)	8 (1.1)
Device related infection	0	6 (0.8)
Platelet count decreased	0	10 (1.4)
Hypersensitivity	0	4 (0.5)

Abbreviations: AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities.
Source: KATHERINE study CSR.[63]

AEs leading to discontinuation

The incidence of AEs leading to discontinuation was higher in the trastuzumab emtansine arm than in the trastuzumab arm (18.0% vs 2.1%, respectively).[63] The most common AEs leading to treatment discontinuation (in ≥1% of patients) in the trastuzumab emtansine arm were laboratory abnormalities (platelet count decreased [4.2%], elevated blood bilirubin [2.6%], elevated AST [1.6%], ALT increased [1.5%]), peripheral sensory neuropathy (1.5%) and ejection fraction decreased (1.2%).[63] The most common AE leading to treatment discontinuation (in ≥1% of patients) in the trastuzumab arm was ejection fraction decreased (1.4%).[63] The majority of AEs leading to discontinuation were Grade 1–2 and most had resolved or were resolving by the clinical cut-off date.[63] A total of 198 AEs leading to discontinuation were reported by 133 patients in the trastuzumab emtansine arm, and approximately half (n=71) of patients discontinuing trastuzumab emtansine received subsequent trastuzumab, of whom 63 completed 14 cycles of HER2-targeted treatment.[63]

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AEs leading to dose reduction or interruption

In the trastuzumab emtansine arm, 90 patients (12.2%) had ≥1 AE leading to dose reduction. Dose reductions were not permitted in the trastuzumab arm.[63] The most common AEs leading to dose reductions (in ≥1% of patients) in the trastuzumab emtansine arm were platelet count decreased (3.1%), blood bilirubin increased (2.7%), ALT increased (1.9%), AST increased (1.5%) and fatigue (1.1%).[63]

The incidence of AEs leading to dose interruption was higher in the trastuzumab emtansine arm than in the trastuzumab arm (14.3% vs 5.1%, respectively).[63] The most common AEs leading to dose interruption (in ≥1% of patients) in the trastuzumab emtansine arm were platelet count decreased (1.9%), AST increased (1.6%) and neutrophil count decreased (1.2%).[63] In the trastuzumab arm, the only AE leading to dose interruption in ≥1% of patients was ejection fraction decreased (1.5%).[63]

AEs leading to death

A total of 98 deaths occurred during the study (Table 20; 42 patients [5.7%] in the trastuzumab emtansine arm vs 56 patients [7.8%] in the trastuzumab arm), which were mostly due to breast cancer (39 patients [5.3%] vs 52 patients [7.2%]).[63] In the trastuzumab emtansine arm, one patient who had a decreased platelet count of 55,000/mm^3 died from an intracranial haemorrhage that occurred after a fall, which the investigator assessed to be related to treatment with trastuzumab emtansine.[63]

Table 20. Summary of deaths

Cause of death	Trastuzumab (N=720)	Trastuzumab emtansine (N=740)
Total deaths, n (%)	56 (7.8%)	42 (5.7%)
Cause of death, n (%)		
Breast cancer	52 (7.2%)	39 (5.3%)
AE	1 (0.1%)[a]	1 (0.1%)
Other[b]	3 (0.4%)	2 (0.3%)

Footnotes: [a]One patient in the trastuzumab arm died due to encephalitis infection which occurred outside the protocol-specified reporting period for AEs of 30 days, and was not related to study treatment or study procedure. This event was therefore not reportable as an AE, but was erroneously marked as a death due to an AE on the eCRF instead of under "other", and therefore appears in the CSR (and this table) under the AE category. The physician assessed the encephalitis infection to be not related to trastuzumab, but related to disease under study and concomitant medication (dexamethasone) that may have increased susceptibility to infection.
[b]Five patients died with reason reported as "other" (terms reported were: pneumonia [n=2], and cerebrovascular event [n=1] in the trastuzumab arm; cerebrovascular event with renal insufficiency [n=1] and death after osteosynthesis [n=1] in the trastuzumab emtansine arm). Per protocol, these were non-reportable AEs because they occurred >30 days after last study treatment and were not related to study treatment or study procedures.
Abbreviations: AE: adverse event; eCRF: electronic case report form.
Source: von Minckwitz G *et al*. 2019;[8] KATHERINE study CSR.[63]

Selected AEs

Selected AEs for additional analysis were chosen on the basis of prior experience with trastuzumab emtansine. As expected, a higher incidence of these selected AEs (thrombocytopenia, peripheral neuropathy, haemorrhage, hepatotoxicity, infusion-related reactions/hypersensitivity, and pulmonary toxicity) was observed in the trastuzumab emtansine arm than the trastuzumab arm. However, the trastuzumab emtansine arm had a numerically lower rate of cardiac AEs and adjudicated cardiac events, compared with trastuzumab.[8]

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Cardiac safety

Cardiac events were defined as death from a cardiac cause, heart failure of New York Heart Association (NYHA) class III or IV, or a substantial decrease in left ventricular ejection fraction (LVEF), defined as a decrease of at least 10% from baseline and to below 50% or cardiac death.[8]

The incidence of patients with ≥1 AEs of cardiac dysfunction was numerically higher in the trastuzumab arm than in the trastuzumab emtansine arm (40 patients [5.6%] vs 23 patients [3.1%]), as was the number of patients with any cardiac event (27 patients [3.8%] vs 19 patients [2.6%], respectively).[63] Substantial decrease in LVEF occurred in 28 patients in the trastuzumab arm, compared with 23 patients in the trastuzumab emtansine arm.[63] Recovery from LVEF decrease was achieved in the majority of patients in both treatment arms (22 patients [84.6%] in the trastuzumab arm vs 14 patients [73.7%] in the trastuzumab emtansine arm).[63] Excluding patients with subsequent cardiac death, four patients (15.4%) in the trastuzumab arm and five patients (26.3%) in the trastuzumab emtansine arm had not recovered from LVEF decrease at the clinical cut-off date.[63]

Adjudicated cardiac events were also higher in the trastuzumab arm compared with the trastuzumab emtansine arm (four patients [0.6%] vs one patient [0.1%], respectively), and nine patients (1.3%) in the trastuzumab arm and four patients (0.5%) in the trastuzumab emtansine arm had ≥1 Grade 3 AE of cardiac dysfunction.[8, 63] One patient in the trastuzumab arm died due to cerebrovascular event, which occurred after the patient had stopped treatment and was not considered related to the study drug.[63]

Hepatotoxicity

Hepatotoxicity events were more common in the trastuzumab emtansine arm than in the trastuzumab arm (276 patients [37.3%] vs 76 patients [10.6%], respectively).[63] The most common hepatotoxicity-related AEs occurring in ≥2% patients in either arm were AST increased (210 patients [28.4%] in the trastuzumab emtansine arm vs 40 patients [5.6%] in the trastuzumab arm), ALT increased (171 patients [23.1%] vs 41 patients [5.7%]), blood alkaline phosphatase increased (61 patients [8.2%] vs 13 patients [1.8%]), blood bilirubin increased (49 patients [6.6%] vs two patients [0.3%]) and gamma glutamyltransferase increased (27 patients [3.6%] vs four patients [0.6%]).[63] Four protocol defined hepatic events were positively adjudicated by the Hepatic Review Committee in the trastuzumab emtansine arm.[63]

Hepatotoxicity-related AEs were mostly Grade 1 or 2 in severity, with Grade ≥3 AEs reported for 12 patients (1.6%) in the trastuzumab emtansine arm and three patients (0.4%) in the trastuzumab arm.[63] At the time of the clinical cut-off in the trastuzumab emtansine arm, Grade ≥3 AEs had resolved in seven patients (58.3%) and were recovering in three patients (25.0%).[63] In the trastuzumab arm at clinical cut-off, Grade ≥3 AEs had resolved in one patient (33.3%).[63] Two patients (0.3%) had Grade 3 AEs of nodular regenerative hyperplasia in the trastuzumab emtansine arm, which occurred in the treatment-free follow up phase.[63] Grade 4 or 5 AEs of hepatotoxicity were not reported in either arm.[63]

Pulmonary toxicity

A higher incidence of pulmonary toxicity was observed in the trastuzumab emtansine arm compared with the trastuzumab arm (21 patients [2.8%] vs six patients [0.8%], respectively).[63] The most common AEs of pulmonary toxicity (≥1% patients in either arm) were radiation pneumonitis (11 patients [1.5%] in the trastuzumab emtansine arm vs five patients [0.7%] in the

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trastuzumab arm) and pneumonitis (eight patients [1.1%] vs one patient [0.1%]).[63] Three patients in the trastuzumab emtansine arm had Grade ≥3 pulmonary toxicity events compared with no patients in the trastuzumab arm, all of which were resolved at clinical cut-off date.[63]

Thrombocytopenia

A higher incidence of thrombocytopenia AEs was observed in the trastuzumab emtansine arm compared with the trastuzumab arm. Two hundred and eleven patients (28.5%) experienced a platelet count decrease in the trastuzumab emtansine arm vs 17 patients (2.4%) in the trastuzumab arm. Forty-four events were classified as Grade ≥3 (42 in the trastuzumab emtansine arm vs two in the trastuzumab arm).[63] The majority (40/42) of trastuzumab emtansine-treated patients with Grade ≥3 AEs were reported to have their AEs resolved at clinical cut-off date, and two patients had events that were recovering/resolving.[63]

Haemorrhage

A higher incidence of AEs of haemorrhage was observed in the trastuzumab emtansine arm compared with the trastuzumab arm (216 patients [29.2%] vs 69 patients [9.6%], respectively).[63] However, percentages of patients with haemorrhage of Grade ≥3 were similar between treatment arms. In the trastuzumab emtansine arm, three patients (0.4%) experienced at least one Grade ≥3 haemorrhage AE compared with two patients (0.3%) in the trastuzumab arm.[63] At clinical cut-off date, two patients in each arm were reported to have resolved AEs.[63]

Infusion-related reactions/hypersensitivity

There was a higher incidence of infusion-related reactions/hypersensitivity AEs observed in the trastuzumab emtansine arm compared with the trastuzumab arm (57 patients [7.7%] vs 19 patients [2.6%], respectively).[63] The majority of events in both arms were of Grade 1 or 2 in severity (98.8%), with one patient in the trastuzumab emtansine arm reporting a Grade ≥3 hypersensitivity event which was reported to have resolved at clinical cut-off date.[63]

Peripheral neuropathy

Patients with pre-existing Grade 1 neuropathy were allowed to enrol in the KATHERINE study.[8] There was a higher incidence of peripheral neuropathy observed in the trastuzumab emtansine arm compared with the trastuzumab arm (239 patients [32.3%] vs 122 patients [16.9%], respectively).[63] The most frequently reported AE of peripheral neuropathy (≥1% patients in either arm) was peripheral sensory neuropathy (138 patients [18.6%] in the trastuzumab emtansine arm vs 50 patients [6.9%] in the trastuzumab arm).[63] At clinical cut-off date, neuropathy had resolved in 103 of 138 patients in the trastuzumab emtansine group (74.6%).[8] Grade 3 peripheral neuropathy was reported in 10 patients in the trastuzumab emtansine arm (1.4%), of which six patients had their AEs resolved and two patients were recovering/resolving at clinical cut-off date.[63]

B.2.11 *Ongoing studies*

Patients in the KATHERINE study will be followed for approximately 10 years from the date of randomisation of the first patient (3rd April 2013).[63] More mature data for all study outcomes are anticipated over the coming years. The final analysis of IDFS is expected in 2020, at which time a further interim analysis of OS will be conducted, and the final analysis of OS is expected in 2023.[63] One other study (ATEMPT) that includes a trastuzumab emtansine arm in the adjuvant

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treatment of eBC is also currently ongoing and will provide additional safety evidence for this indication in the next 12 months.

Furthermore, several ongoing studies will provide evidence for pertuzumab + trastuzumab + chemotherapy, a relevant comparator in this appraisal for patients with node-positive disease. However, as outlined in B.2.9, comparisons between the KATHERINE study and these studies are of limited usefulness.

B.2.11.1 ATEMPT (NCT01853748)[66]

The US-based, randomised, phase II, open-label ATEMPT trial (N=512) is currently ongoing and will provide additional data on the safety profile of trastuzumab emtansine in the adjuvant setting in the next 12 months. The ATEMPT patient population has a very different risk profile to those included in the KATHERINE study, as these patients have stage I HER2-positive disease and as such were not treated neoadjuvantly. In contrast, KATHERINE enrolled patients who had been treated neoadjuvantly and had RID after neoadjuvant therapy, thus had particularly high-risk disease. Comparisons of efficacy evidence between ATEMPT and KATHERINE are therefore of limited value. However, the ATEMPT trial will assess clinically relevant toxicities experienced with one year of adjuvant trastuzumab emtansine compared to one year of adjuvant trastuzumab + paclitaxel, and will therefore provide relevant safety evidence in this indication.

In this study, patients with stage I HER2-postitive disease who have not previously received trastuzumab or paclitaxel are treated with:

- Trastuzumab emtansine every three weeks by IV infusion for 17 treatments (total of 51 weeks), or
- Trastuzumab + paclitaxel once per week by IV infusion for 12 weeks, followed by trastuzumab only by IV injection every three weeks for 13 treatments.

The primary outcome of the study is DFS in patients treated with trastuzumab emtansine at two years, with secondary outcomes including DFS in subgroups of patients defined by tumour size, OS, cardiac dysfunction, and rates of thrombocytopenia and amenorrhea. Results are likely to be reported after the estimated primary completion date in January 2020, although the exact publication date is unknown at this time.

B.2.11.2 BERENICE (NCT02132949)[22]

The BERENICE study is a non-randomised, open-label, multinational, phase II cardiac safety study to evaluate the safety of pertuzumab + trastuzumab + standard neoadjuvant anthracycline or taxane-based chemotherapy in 401 patients with HER2-positive, locally advanced, inflammatory, or eBC (with primary tumours >2 cm in diameter or node-positive disease). This study reflects current clinical practice for the neoadjuvant and adjuvant treatment of HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence (pertuzumab + trastuzumab + chemotherapy), and will provide exploratory efficacy evidence for this treatment regimen in the next 12 months.

In this study, patients are treated neoadjuvantly (i.e. pre-surgery) with:

- Dose-dense doxorubicin and cyclophosphamide, followed by paclitaxel, with pertuzumab + trastuzumab given from the start of paclitaxel (Cohort A), or

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- FEC, followed by docetaxel, with pertuzumab + trastuzumab given from the start of docetaxel (Cohort B).

Following surgery, patients resume treatment with pertuzumab + trastuzumab to receive up to one year of pertuzumab + trastuzumab. The BERENICE trial, which began in 2014, is primarily a safety study, with primary outcome measures including the percentage of participants with NYHA Class III and IV heart failure during the neoadjuvant treatment period and the percentage of participants with a drop in LVEF of at least 10% from baseline and to below 50% during the neoadjuvant treatment period. Secondary outcome measures look at treatment efficacy, such as EFS determined by the investigator according to the Response Evaluation Criteria in Solid Tumours (RECIST), IDFS and OS (all assessed until ~6.5 years). The efficacy results for BERENICE will be reported in Q4 2020, although it is important to note that BERENICE is first and foremost a safety study, thus this efficacy evidence will be of limited value to this submission.

B.2.11.3 NCT03674112

NCT03674112 (N=140, predicted) is an ongoing phase II, cross-over RCT in adult patients who have completed neoadjuvant chemotherapy with neoadjuvant pertuzumab + trastuzumab and have undergone surgical treatment of HER2-positive eBC, with no evidence of residual disease at surgery. This study in the adjuvant setting consists of a nine-week treatment period, followed by a cross-over period. During the treatment period, patients are treated with:[66]

- Arm A: pertuzumab IV + trastuzumab IV for 3 cycles (one cycle is 21 days), followed by pertuzumab + trastuzumab fixed-dose combination SC for 3 cycles.
- Arm B: pertuzumab + trastuzumab fixed-dose combination SC for 3 cycles, followed by pertuzumab IV + trastuzumab IV for 3 cycles.

On completion of the treatment period, patients choose one of the two treatment regimens to receive in the cross-over period for the remaining treatment cycles (18 cycles in total, including pre-study neoadjuvant treatment). The primary objective of this study is to evaluate patient preference and satisfaction with SC administration of pertuzumab + trastuzumab compared to IV administration. The primary outcome is the proportion of participants who prefer the fixed-dose SC administration. Secondary outcome measures include HRQoL, the proportion of patients who experience AEs, and efficacy outcomes such as IDFS and OS.[66] This study may therefore provide exploratory efficacy evidence for pertuzumab + trastuzumab in the adjuvant setting in the next 12 months. However, comparisons between the results of this trial and the KATHERINE study will be of limited value due to the exploratory nature of these analyses and the very different risk profile of the included patients, who do not have RID. The estimated primary completion date of this study is the 31st March 2020.[66]

B.2.11.4 APHINITY (NCT01358877)

The APHINITY study (N=4,805) is an ongoing, randomised, placebo-controlled, phase III trial comparing 18 cycles of pertuzumab + trastuzumab + chemotherapy vs placebo + trastuzumab + chemotherapy in the adjuvant treatment of patients with operable HER2-positive eBC.[72] [redacted], and will provide further efficacy evidence for pertuzumab + trastuzumab + chemotherapy in this setting. However, as discussed

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in Section B.2.9, differences in patient population between the KATHERINE and APHINITY studies limit the usefulness of any comparisons between the two trials.

B.2.12 *Innovation*

Currently in England, the most effective neoadjuvant and adjuvant therapies for the treatment of patients with HER2-positive eBC consist of single or dual HER2 blockade with trastuzumab ± pertuzumab in combination with chemotherapy. While multiple studies have demonstrated the effectiveness of these agents, approximately 40% of UK patients have RID at the time of surgery even when treated with dual HER2 blockade.[24-30] Trastuzumab emtansine is the first treatment to be rigorously studied in patients with HER2-positive eBC and RID in the breast and/or axillary lymph nodes following neoadjuvant therapy with a HER2-targeted agent, and the KATHERINE study is the first robust phase III trial to specifically investigate adapting breast cancer treatment in the adjuvant setting based on response to neoadjuvant therapy.[8] The introduction of adjuvant trastuzumab emtansine therefore represents the first opportunity to achieve an as yet unrealised objective of neoadjuvant treatment: to adapt subsequent treatment on the basis of tumour response to neoadjuvant therapy.

The ADC trastuzumab emtansine is well placed to address the urgent need for new, effective treatments in these patients at the highest risk of relapse following neoadjuvant treatment, due to its novel mechanism of action. Trastuzumab emtansine was the first ADC to be approved for the treatment of prevalent solid tumours, and is the only ADC licensed for treating HER2-positive breast cancer.[3, 5] The stable linker which binds trastuzumab to DM1 is broken down within HER2-overexpressing tumour cells following receptor-mediated internalisation to release DM1,[2] maximising the targeted intracellular delivery of a cytotoxic agent to HER2-overexpressing tumour cells whilst minimising systemic exposure and cytotoxic effects on normal tissue.[2, 4, 75]

Trastuzumab emtansine's novel mechanism of action has been previously shown to produce a dramatic improvement in outcomes in patients with HER2-positive mBC compared to the previous standard of care. A similar step-change in the efficacy of treatment for patients with HER2-positive eBC who have RID in the breast and/or axillary lymph nodes following neoadjuvant HER2-targeted therapy has been demonstrated in the KATHERINE study.[8] The margin of benefit demonstrated (11.3% improvement in IDFS at 3 years) been described by UK clinicians as clear and practice-changing, and has resulted in updates to the NCCN, ESMO and St Gallen guidelines for the treatment of eBC to incorporate this novel adjuvant treatment option (Table 5).[53, 61, 62]

This dramatic increase in efficacy is particularly important for patients treated in the curative setting. Patients with eBC only have one chance for a disease cure, making it essential to provide these patients with the best possible treatments. The significant positive impact of this innovative therapy and resulting change in the treatment paradigm for eBC has been recognised by the FDA, which has approved trastuzumab emtansine for treating patients with HER2-positive eBC who have RID after neoadjuvant treatment with a taxane and trastuzumab. Trastuzumab emtansine received breakthrough therapy designation for this indication.[6]

Overall, trastuzumab emtansine offers an effective treatment option in the adjuvant setting over and above existing treatments that have already shown substantial benefit for patients with HER2-positive eBC, and addresses the urgent need for new, effective treatments for patients at the highest risk of relapse following neoadjuvant treatment.

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B.2.13 *Interpretation of clinical effectiveness and safety evidence*

B.2.13.1 Principal findings from the clinical evidence base

Trastuzumab emtansine is the first treatment to be rigorously studied in patients with HER2-positive eBC and RID in the breast and/or axillary lymph nodes, following neoadjuvant therapy that included a HER2-targeted agent. The results of the randomised, prospective phase III KATHERINE study demonstrate that treatment with 14 cycles of trastuzumab emtansine can significantly improve outcomes for these patients.[8] The substantial margin of benefit observed at the interim analysis of the KATHERINE study (a 50% reduction in risk of an IDFS event compared to trastuzumab, HR=0.50; 95% CI: 0.39–0.64; p<0.001)[8] is comparable to the margin of benefit observed in the HERA trial, the pivotal and practice-changing study of one year of trastuzumab compared with observation, in patients with HER2-positive eBC, which demonstrated a 46% reduction in the risk of a DFS event at two years (HR=0.54; 95% CI: 0.43–0.67; p<0001).

As discussed in Section B.1.3.3, patients who have RID in the breast and/or axillary lymph nodes after completion of neoadjuvant therapy are at considerably higher risk of relapse and mortality than patients who achieve a pCR,[24, 31, 32] and published data to guide the most appropriate adjuvant therapy for these patients are currently lacking. The option to personalise treatment for a patient based on their tumour response in the neoadjuvant setting presents a crucial opportunity to improve treatment outcomes for patients while the disease is localised to the breast and regional lymph nodes, which can maximise the chance of a cure and prevent progression to incurable mBC.

The results of the secondary outcomes of the KATHERINE study are supportive of the primary outcome of IDFS. Although there is no statistical difference in terms of OS at this interim analysis, this is likely due to the relatively short-term follow-up of the study so far; i.e. because the data are immature (only 26% [98 of 367] of the events required for the final planned OS analysis had occurred).[63] A separation of the OS curves was already observed from 30 months, increasing up to 60 months, and so any differences in OS may become apparent in later analyses.[63] Recent meta-analyses have shown that surrogate endpoints (including IDFS and DFS) have high, individual-level associations with OS in the adjuvant breast cancer setting,[76, 77] suggesting that the statistically and clinically significant IDFS benefits observed in the KATHERINE study could be indicative of OS benefits in the long-term.

Subgroup analyses of the KATHERINE study showed a consistent benefit irrespective of age, race, hormone receptor status, pathological nodal status after neoadjuvant therapy, clinical stage at presentation and type (single or dual) of HER2-targeted therapy in the neoadjuvant regimen.[8] Treatment benefit of trastuzumab emtansine was also consistent regardless of primary tumour stage at definitive surgery (i.e. the extent of RID): clinical benefit was observed in patients with RID ≤1 cm in the breast and negative axillary lymph nodes, demonstrating that even a relatively small amount of RID in the breast, with disease-free axillary lymph nodes, can negatively impact disease prognosis, and that patients with any level of RID can benefit from treatment with adjuvant trastuzumab emtansine.[8] Additionally, the KATHERINE study showed that trastuzumab emtansine had a similar IDFS benefit for patients who received neoadjuvant trastuzumab + chemotherapy (HR=0.49; 95% CI: 0.37–0.65) and patients who received neoadjuvant pertuzumab + trastuzumab + chemotherapy (HR=0.50; 95% CI: 0.25–1.00), the current SoC in

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the neoadjuvant setting for patients with HER2-positive, locally advanced, inflammatory or early stage breast cancer at high risk of recurrence.[8]

The safety profile of trastuzumab emtansine in the KATHERINE study was consistent with that observed in previous studies, and the majority of AEs observed were Grade 1–2, and/or reversible and could be well managed.[63] As expected given the targeted cytotoxic component of trastuzumab emtansine, a higher percentage of patients experienced AEs in the trastuzumab emtansine group compared with the trastuzumab group. Adverse events of Grade 3 or higher occurred in 25.7% of patients in the trastuzumab emtansine group and in 15.4% of those in the trastuzumab group.[8] More patients in the trastuzumab emtansine arm discontinued treatment (28.5%) than in the trastuzumab arm (18.2%), largely due to AEs.[63] This was in part driven by an increase in AEs associated with laboratory parameters, including ALT increased, AST increased, bilirubin increased, and platelet count decreased. The majority of AEs leading to discontinuation were Grade 1–2 and had resolved by the clinical cut-off date.[63] The reversibility of these AEs is an important finding in this patient population, as enduring AEs are of particular importance in the treatment of patients with eBC. Cardiac event rates were low in both treatment arms, and trastuzumab emtansine could be administered for up to 14 cycles without evidence of significant cardiac toxicity or clinically significant LVEF decline, with a numerically lower rate of cardiac AEs compared with trastuzumab.[63]

The greater incidence of AEs observed with trastuzumab emtansine compared to trastuzumab appeared to have a minimal impact on patient-reported quality of life and tolerability of treatment. Mean change from baseline scores for GHS and all functioning and symptom scales of the EORTC QLQ-C30 and EORTC QLQ-BR23 were similar in each treatment arm and were not clinically meaningful.[64] Although a higher proportion of patients in the trastuzumab emtansine arm reported a clinically meaningful deterioration at one or more assessments for the majority of symptom scales compared to the trastuzumab arm, these proportions were generally similar by the 6-month follow-up assessment.[64]

B.2.13.2 Strengths and limitations of the clinical evidence base

The clinical evidence base for trastuzumab emtansine in patients with HER2-positive eBC and RID after neoadjuvant treatment comes from the phase III KATHERINE study. The KATHERINE study is a robust, large, randomised, phase III trial, that included 14 trial sites in the UK, and baseline characteristics of the patients enrolled in the study are consistent with those expected for the UK patient population with eBC.[63]

The majority of patients received neoadjuvant trastuzumab + chemotherapy, which was reflective of the SoC when the study was recruiting. However, 18.7% of patients (n=139) in the trastuzumab arm and 17.9% (n=133) in the trastuzumab emtansine arm received neoadjuvant pertuzumab + trastuzumab + chemotherapy, the current SoC in the neoadjuvant setting for patients with HER2-positive, locally advanced, inflammatory or early stage breast cancer at high risk of recurrence.[8] There is no biological or clinical rationale why the addition of pertuzumab to the neoadjuvant treatment regimen would impact on the efficacy of trastuzumab emtansine in the adjuvant setting. As expected, the treatment effect of trastuzumab emtansine was consistent regardless of HER2-targeted neoadjuvant treatment received (HR=0.50; 95% CI 0.25–1.00 for patients receiving neoadjuvant pertuzumab, vs HR=0.49; 95% CI: 0.37–0.65 for patients who did not receive neoadjuvant pertuzumab), although the absolute percentage of events was lower in patients treated with neoadjuvant pertuzumab, demonstrating the added benefit of neoadjuvant

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pertuzumab treatment (Section B.2.7).[8] The addition of pertuzumab to the neoadjuvant treatment regimen therefore does not impact the efficacy of trastuzumab emtansine in the adjuvant setting.

At the time that the KATHERINE study was recruiting, trastuzumab was the SoC in the adjuvant treatment of HER2-positive eBC and the only appropriate comparator to adjuvant trastuzumab emtansine. However, treatment of patients with HER2-positive eBC has progressed since the KATHERINE study was designed and was enrolling patients, and given the recent positive NICE recommendation for pertuzumab in the adjuvant treatment of patients with HER2-positive, lymph node-positive eBC, based on data from the APHINITY trial, pertuzumab + trastuzumab + chemotherapy is now the SoC in the adjuvant treatment of this population.[60, 72] Direct comparisons between trastuzumab emtansine and pertuzumab + trastuzumab + chemotherapy in this patient population are not possible based on currently available evidence. However, the results of a naïve comparison between trastuzumab emtansine and pertuzumab + trastuzumab + chemotherapy are discussed in Appendix M.

The KATHERINE study confirms that 14 cycles of trastuzumab emtansine in the eBC setting provides a valuable treatment option for UK patients with HER2-positive eBC who have RID in the breast and/or axillary lymph nodes after neoadjuvant treatment, and are therefore at high risk of recurrence. By reducing the risk of disease relapse and development of mBC, trastuzumab emtansine offers improved outcomes for patients with HER2-positive eBC in the UK and can be expected to reduce the high clinical and economic burden associated with mBC. The positive KATHERINE data build on the results of the TH3RESA and EMILIA studies of trastuzumab emtansine in patients with mBC, indicating that trastuzumab emtansine provides benefit for patients with various stages of HER2-positive breast cancer.[47, 78] Most importantly, the data are supportive of trastuzumab emtansine as the treatment of choice to address the unmet need in patients with eBC who have RID in the breast and/or axillary lymph nodes at surgery, and are therefore at a particularly high risk of disease recurrence.

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B.3 Cost effectiveness

B.3.1 *Published cost-effectiveness studies*

No published studies were found that assessed the cost-effectiveness of adjuvant treatment with trastuzumab emtansine in patients with HER2-positive eBC. Please see Appendix G for a full description of the cost-effectiveness SLR and results.

B.3.2 *Economic analysis*

The economic analysis described below evaluates the use of trastuzumab emtansine in the adjuvant setting. The model upon which the analysis is predicated is believed to accurately reflect the disease pathway in this therapeutic area. Furthermore, the structure is in line with previous HTA submissions and published cost-effectiveness analyses evaluating anti-HER2 therapy in eBC.[71, 79, 80]

B.3.2.1 Patient population

The ITT population in the pivotal KATHERINE trial is aligned with the patient population outlined in the final scope of this appraisal. Following recent regulatory discussions, the Company expects to receive a European Marketing Authorisation in this population. The anticipated label for trastuzumab emtansine in eBC is expected to read as follows:

“[redacted].”

This economic analysis will focus on the ITT population of the KATHERINE trial and is therefore aligned with the anticipated label, though is slightly narrower than the final scope of this appraisal as described in Section B.1.1.

In February of 2019, NICE published a FAD recommending the use of pertuzumab + trastuzumab + chemotherapy (PTC) in the adjuvant treatment of patients with node-positive, HER2-positive eBC.[71] This means that PTC is a relevant comparator to trastuzumab emtansine in patients who are node-positive, have received neoadjuvant therapy, and still have RID in the breast and/or axillary lymph nodes at the time of surgery – a subgroup of the KATHERINE ITT population. Due to methodological limitations of implementing an ITC vs PTC, the economic analysis for this subgroup has been documented as a scenario analysis in a supplementary appendix. For clarity, economic analyses included in this submission are set out as follows:

- Trastuzumab emtansine vs trastuzumab – Base case – below
- Trastuzumab emtansine vs PTC – Scenario analysis – Appendix M

Clinical parameters of the model for the base case analysis were primarily populated using data from the pivotal KATHERINE trial. Section B.3.3 describes the sourcing and implementation of clinical data in the model. Full details of the KATHERINE study characteristics are described in Section B.2.3 of this document.

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The methodology used in the comparison of trastuzumab emtansine vs PTC is described in full in Section B.2.9 and Appendix M.

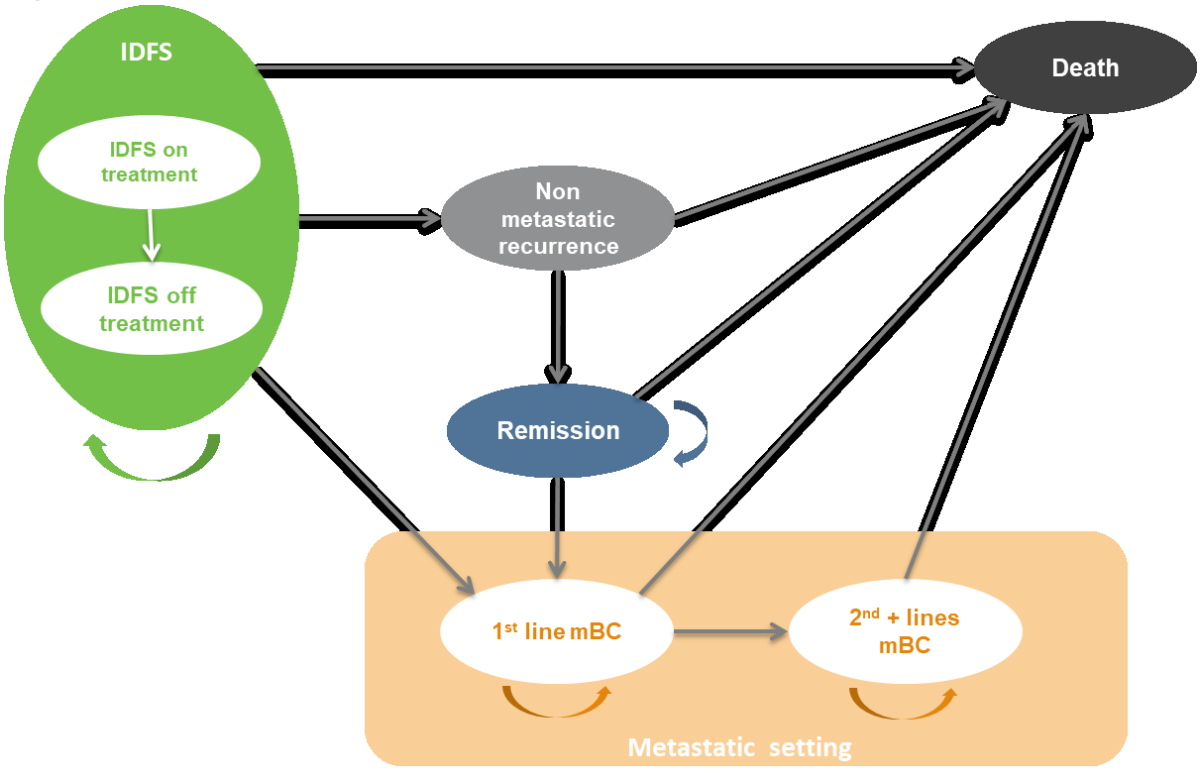
B.3.2.2 Model structure

A Markov model was developed in Microsoft Excel® with the following seven health states: 'IDFS – on treatment', 'IDFS – off treatment', 'Non-metastatic recurrence', 'Remission', 'First-line treatment for mBC (First-line mBC)', 'Subsequent treatment lines for mBC (Second+ line mBC)', and 'Death', see Figure 15.

The cycle length of the model is one month, with the proportion of patients in each health state calculated every 30.4 days. A half cycle correction has been applied in the model. Costs and quality-adjusted life-years (QALYs) have been discounted at a rate of 3.5% per annum, as is recommended in the NICE Reference Case, 2013.[81]

This type of model was considered appropriate for the decision problem. Both the structure and health states are in-line with the clinical pathway outlined in Section B.1.3. The chosen approach is consistent with previous NICE technology appraisals in this disease area (TA107,[82] TA424,[79] and TA569[71]) as well as the economic studies identified in the SLR (Section B.3.1). Furthermore, the model structure was discussed and validated by an independent UK advisory board held in September 2017, see Section B.3.10.

Figure 15. Model structure schematic for HER2-positive breast cancer



Abbreviations: IDFS, invasive disease-free survival; mBC, metastatic breast cancer.

Transition between health states

Patients enter the model in the IDFS health state and remain there until recurrence (non-metastatic or metastatic) or death. The non-metastatic recurrence health state includes various

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types of non-distant recurrence, including locoregional and contralateral recurrences. This classification is consistent with the definition of the primary endpoint (IDFS) in the KATHERINE study. No distinction was made in terms of the type of non-metastatic recurrence in this analysis. All types of non-metastatic recurrence were believed to be similar in terms of the associated resource use, QoL and mortality – this assumption was validated during the recent NICE appraisal of adjuvant pertuzumab.[71]

The possible transitions between each of the health states are described briefly below. Please see Section B.3.3 for full details of how the probabilities of these transitions were derived.

Non-metastatic recurrence pathway

- **IDFS on-treatment to off-treatment health state:** Patients receive a maximum of 14 cycles of trastuzumab emtansine in the intervention arm or a maximum of 14 cycles of trastuzumab in the comparator arm (IDFS – on-treatment). Once patients discontinue their eBC assigned regimen they transition to the IDFS off-treatment state.
- **IDFS to non-metastatic recurrence health state:** Patients who experience a non-distant recurrence transition to the non-metastatic recurrence health state. Patients entering this health state will be subject to 12 months of additional adjuvant therapy. In this context, the non-metastatic recurrence health state is a one year “tunnel state”. Upon completion of the additional adjuvant treatment, all patients are assumed to be in remission.
- **Remission to first-line mBC health state:** Once in remission, if a patient’s disease returns, it is assumed they would progress to the (first-line mBC) health state (i.e. the event is assumed to be metastatic).

Metastatic recurrence pathway

- **IDFS to first-line mBC health state:** Patients who experience a distant recurrence when in the IDFS health state transition to the first-line mBC state. In this state, first-line treatment for mBC is administered.
- **First-line mBC to subsequent lines for mBC health state:** Once in the first-line mBC health state, patients are at risk of disease progression and transitioning to the metastatic – progressed health state (second+ line mBC). In this state patients are administered subsequent lines of treatment for their progressed mBC.
- **Transition to death:** Death is an absorbing state. Patients can transition to death from any health state in the model.

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Table 21. Comparison of economic analyses in past NICE appraisals

	Previous appraisals			Current appraisal	
	TA107 – Trastuzumab for the adjuvant treatment of early-stage HER2-positive breast cancer[82]	**TA424** – Pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer[79]	**TA569 –** Pertuzumab for adjuvant treatment of HER2-positive early stage breast cancer[71]	**Chosen values**	**Justification**
Time horizon	45 years (lifetime)	50 years (lifetime)	52 years (lifetime)	52 years (lifetime)	In accordance with NICE Reference Case[81]
Treatment waning effect	Effect maintained for ten years. Two-thirds of this benefit is seen until year 45	No waning. Treatment effect set equal after seven years	Effect maintained for four years before waning to null at seven years	Effect maintained for four years before waning to null at seven years	Full justification explained in Section 0
Source of utilities	Published literature	Published literature	eBC health states *- EQ-5D data from the APHINITY trial* mBC health states *- Lloyd, 2006*	eBC health states *- EQ-5D data from the KATHERINE trial* mBC health states *- Lloyd, 2006*	In accordance with NICE Reference Case[81]
Source of costs	MEDTAP study, ABACUS study, HERA database, and MIMS	NHS reference costs, BNF, published literature, and expert opinion	Published literature and expert opinion	Published literature and expert opinion	In accordance with NICE Reference case[81]

Abbreviations: ABACUS: Awareness and Beliefs about Cancer; BNF: British National Formulary; EQ-5D: EuroQol 5-Dimension; HER2: human epidermal growth factor receptor 2; NHS: National Health Service; NICE: National Institute for Health and Care Excellence.

B.3.2.3 Intervention technology and comparators

This analysis evaluates the cost-effectiveness of trastuzumab emtansine (intervention arm) vs trastuzumab (comparator arm) in the adjuvant treatment of patients with HER2-positive eBC. The intervention and comparators are in line with the decision problem set out in the final scope of this appraisal.

The remainder of this subsection outlines the basic dosing schedules of the primary treatment options in the KATHERINE study. Further details around the acquisition costs, administration

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schedule, and real-world usage applied in the cost-effectiveness model are available in Section B.3.5.

Trastuzumab emtansine: Trastuzumab emtansine was administered on Day 1 of a three-week cycle (q3w) at a dose of 3.6 mg/kg. All doses were given as intravenous (IV) infusions.

Trastuzumab: Trastuzumab was administered on Day 1 of a 3-week cycle (q3w) at a maintenance dose of 6 mg/kg. All doses were given as IV infusions.

Please note that whilst branded trastuzumab (Herceptin®) IV was the comparator in the KATHERINE trial, subcutaneous (SC) branded trastuzumab and trastuzumab biosimilar have also been included in this economic analysis – see Section B.3.5.1 for more details.

Please refer to Section B.3.5.1 for further information on the costs and resource use associated with the intervention and comparators in this analysis.

B.3.3 *Clinical parameters and variables*

The primary data source used to populate the clinical elements of the cost-effectiveness model was the pivotal KATHERINE trial. KATHERINE is a phase III study evaluating trastuzumab emtansine compared to trastuzumab.[63] In situations where the KATHERINE data were insufficient, additional evidence from various sources was utilised. These sources included published literature, expert advice and assumptions.

Expert opinion noted that the ITT trial population observed in KATHERINE is representative of patients with RID who could expect to receive adjuvant trastuzumab emtansine in the UK (see Section B.2.3.2). As a result, responses and outcomes seen in this study are assumed to be reflective of UK clinical practice.

The main body of the submission outlines the analysis and implementation of the comparison against trastuzumab. Other analyses, including those comparing to pertuzumab + trastuzumab, are documented in the appendices of this submission.

B.3.3.1 Modelling of IDFS

Patients remain in the IDFS health state as long as they remain disease-free, as defined by the study protocol (see Section B.2), and alive. The probability of remaining in the IDFS health state is derived from patient-level data in the KATHERINE study. The median follow-up period in the ITT population was 41.43 months and 40.94 months in the trastuzumab emtansine and trastuzumab arms, respectively. At the time of the primary analysis of IDFS (data cut-off 25th July 2018), only 91 (12.2%) and 165 (22.2%) IDFS events had occurred in the trastuzumab emtansine and trastuzumab arms, respectively. The lack of completeness of this data, and the truncated follow-up period in KATHERINE, meant that extrapolation techniques were essential to model IDFS over a lifetime time horizon (52 years).

Modelling of IDFS was informed using patient-level data from the KATHERINE study. Parametric functions were then applied to this data to facilitate extrapolation beyond the follow-up period, as per NICE Decision Support Unit (DSU) guidance.[83] The selected parametric function was subsequently adjusted to produce a more clinically accurate and robust extrapolation. Empirical

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evidence was used to help inform this adjustment and create IDFS curves that are reflective of longer-term outcomes in this indication.

Since trastuzumab emtansine is not yet licensed in the adjuvant eBC setting, empirical data only exist for the comparator arm (trastuzumab). Therefore, data from long-term studies of trastuzumab (HERA[84] and BCIRG 006[85] trials) were used to inform the adjustment of the extrapolations.

The modelling of IDFS over the time horizon of the model can be broken down into three discrete periods:

- **Time period 1** – Zero to three years
- **Time period 2** – From year three to year ten
- **Time period 3** – From year ten until the end of the time horizon (year 52)

For each of these time periods, different data and assumptions were incorporated to produce accurate extrapolations. The methodology involved in generating the IDFS curves is detailed in the following subsections.

Time period 1 (zero to three years) – Patient-level data from the KATHERINE study

In accordance with standard practice, a parametric extrapolation function was fitted to the Kaplan-Meier data from the KATHERINE study. Several candidate distributions were fitted to the IDFS data and assessed for "goodness of fit". The selected distribution provided the basis of the extrapolation beyond the observed period of the trial. Additional adjustment of this distribution, using empirical data, dictated the final shape of the IDFS curves used in the model (see subsection relating to "Time period 2"). The following parametric functions were fitted to the trial-data: Exponential, Weibull, Log-logistic, Log-normal, Gamma and Gompertz.

The selection process of the most appropriate distribution is outlined below. A criterion-based guide was used to facilitate the accurate extrapolation and justification of survival estimates. Methodology employed during this selection process is in accordance with the NICE DSU Technical Report.[83]

Assessment of the proportional hazards assumption

Prior to deciding on the most appropriate parametric distribution, it was important to check the existence of proportional hazards (PH). The PH assumption states that the hazard in one group (arm A) is a constant proportion of the hazard in the other group (arm B). This proportion is the hazard ratio. That is, although the hazard may vary with time, the ratio of the hazard rates is constant.

The PH assumption can be tested graphically, using log-cumulative hazard plots. These graphs plot log(time) on the x-axis vs log(–log(S(time))) on the y-axis, where S(time) is the survival time. The PH assumption can be assumed to hold if the gradient of the two curves is found to be reasonably constant (i.e. they do not obviously diverge, converge or intersect). The log of the survival probabilities plotted with the log of time for the arms in the KATHERINE trial are shown in Figure 16.

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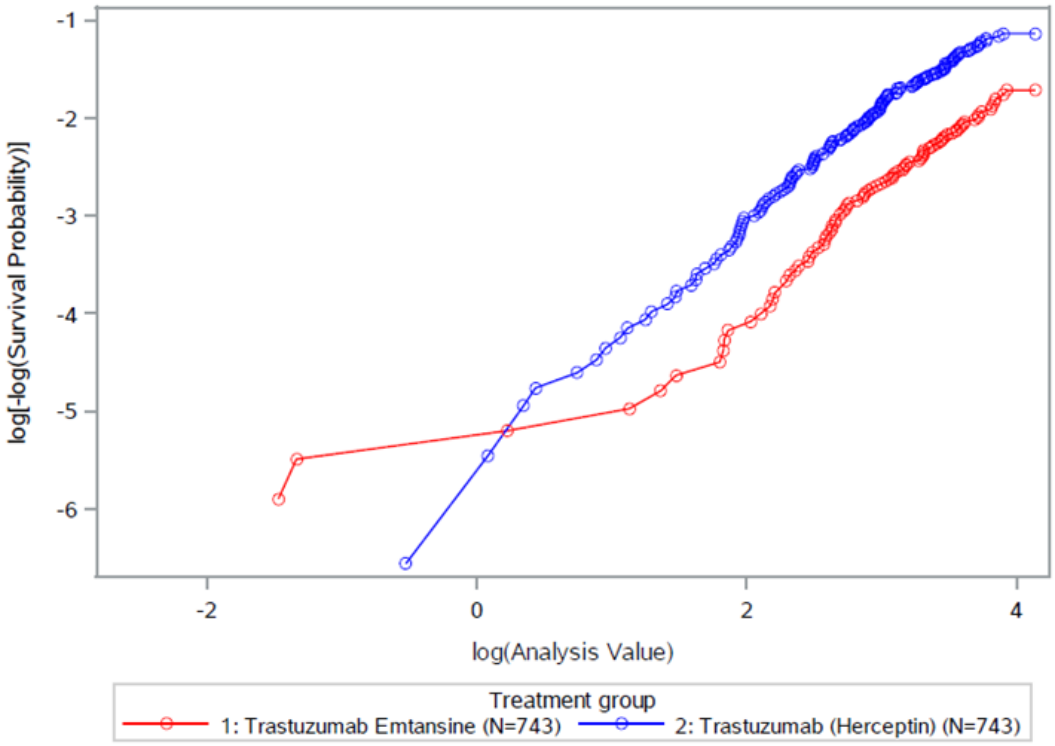
Figure 16. Log of negative log of estimated survivor functions – IDFS endpoint from the KATHERINE study



As shown in Figure 16, the two curves cross, which signals that the PH assumption may not hold. However, this crossing takes place at a time when minimal events have occurred, and the curve is therefore associated with a lot of uncertainty. Consequently, this crossing should not be over-emphasised. After crossing, the curves can be seen to remain parallel thereafter. In summary, evidence of PH is not conclusively given by this plot alone.

To further assess the existence of PH, a plot of the Schoenfeld residuals has also been generated (Figure 17). In the presence of PH, the line on the graph should be horizontal – thereby proving that the residuals are independent of time. It is clear that the regression line on the graph has a slightly negative slope. This once again signals that the PH assumption may not hold.

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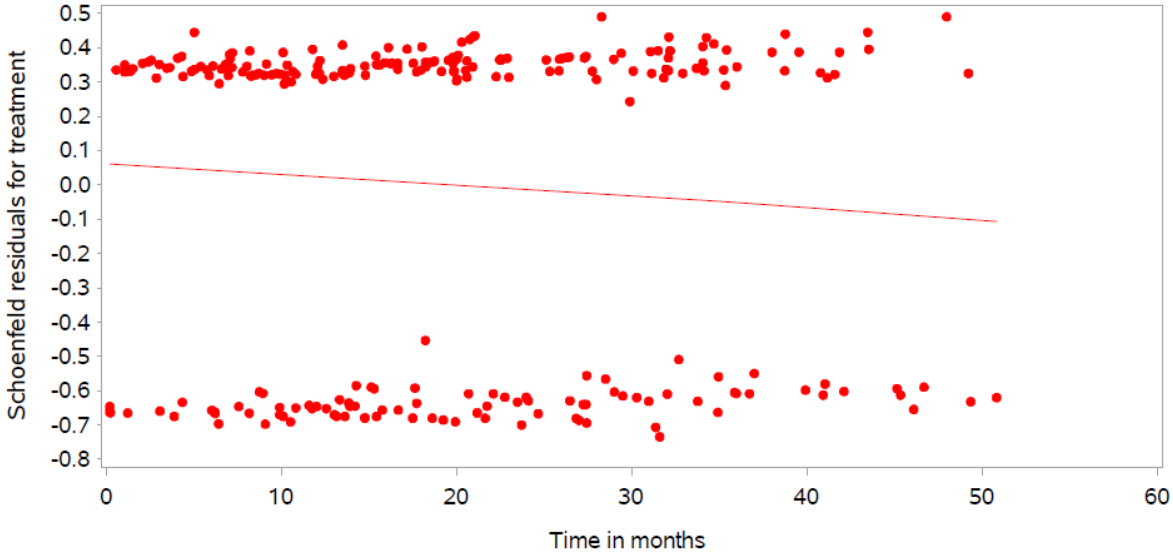
Figure 17. Plot of Schoenfeld residuals



It is important to note here that IDFS results projected by the extrapolations are relatively insensitive to whether or not proportional hazards is assumed. Table 22 presents landmark IDFS figures from extrapolations that have assumed proportional and non-proportional hazards.

Table 22. Landmark IDFS – PH vs Non-PH – Averages across all candidate distributions[a]

	TE arm		Trastuzumab arm		Δ		
	PH	Non-PH	PH	Non-PH	PH	Non-PH	PH vs non-PH
Median IDFS	32.07	32.04	24.25	24.56	7.82	7.49	**0.33**
Mean IDFS	27.41	27.37	22.25	22.36	5.16	5.02	**0.14**
Landmark IDFS							
12 months	96.04%	96.04%	91.79%	91.75%	4.25%	4.29%	**-0.04%**
24 months	92.14%	92.20%	84.52%	84.42%	7.61%	7.78%	**-0.17%**
36 months	88.45%	88.52%	78.11%	78.02%	10.34%	10.50%	**-0.16%**
48 months	85.22%	85.25%	72.81%	72.79%	12.42%	12.47%	**-0.05%**
60 months	82.59%	82.54%	68.68%	68.73%	13.91%	13.81%	**0.10%**
120 months	75.34%	75.11%	59.54%	59.82%	15.81%	15.28%	**0.52%**
480 months	26.82%	26.82%	21.21%	21.38%	5.61%	5.44%	**0.17%**

Footnotes: [a]The figures reported in the table above are averages from extrapolations using the Exponential, Weibull, Log-Normal, Generalized Gamma, Log-Logistic, and Gompertz distributions.
Abbreviations: IDFS: invasive disease-free survival; non-PH: non-proportional hazards; PH: proportional hazards; TE: trastuzumab emtansine.

At all key time points, the difference in IDFS between the PH and non-PH extrapolation is <1%. This marginal difference is expected to translate into a negligible impact on overall cost-effectiveness results.

It is difficult to conclusively prove that it is appropriate to apply the PH assumption to this data. In light of the evidence presented above, it has been assumed that PH do not exist between the two treatment arms. Therefore, "stratified" models were used (i.e. curves were fitted separately to each treatment arm) to extrapolate IDFS over the time horizon, as per the NICE DSU guidance.[83] This approach is conservative and is likely to result in less-favourable cost-effectiveness results

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when comparing trastuzumab emtansine to trastuzumab in the adjuvant setting, compared to if the PH assumption had been used.

Akaike Information Criterion (AIC) / Bayesian Information Criterion (BIC) Goodness of fit

Parametric distributions were assessed for their goodness of fit to the observed data using the AIC. Lower values for AIC indicate a better mathematical assessment of the fit to the actual data. BIC values have also been calculated and reported in this submission. As the approach taken here is Frequentist, as opposed to Bayesian, the BIC values do not factor into the decision-making process when selecting a distribution, and have instead been included for completeness.

Table 23 presents the AIC and BIC values for the extrapolation of IDFS data. The relative ranking of goodness of fit is shown in brackets, with one indicating the best fit and six the worst, i.e. lowest and highest AIC values, respectively.

Table 23. IDFS extrapolation – AIC and BIC values (relative ranking of goodness of fit shown in brackets)

	AIC		BIC	
	Trastuzumab emtansine arm	**Trastuzumab arm**	**Trastuzumab emtansine arm**	**Trastuzumab arm**
Exponential	**718.91 (1)**	1105.56 (4)	723.52 (1)	1110.17 (2)
Weibull	720.52 (3)	1107.55 (5)	729.74 (3)	1116.77 (5)
Log-normal	725.23 (6)	**1098.36 (1)**	734.45 (5)	1107.58 (1)
Gamma	722.49 (5)	1099.83 (2)	736.33 (6)	1113.67 (4)
Log-logistic	720.35 (2)	1104.06 (3)	729.57 (2)	1113.28 (3)
Gompertz	720.82 (4)	1107.56 (6)	730.04 (4)	1116.78 (6)

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion.

According to the AIC values, the Exponential and Log-normal functions provide the best (statistical) fit to the observed data in the trastuzumab emtansine arm and the trastuzumab arm, respectively. Despite these functions being the “best-fitting”, it is worth noting that there was only a difference in AIC value of 1.7 and 7.2 across the four best fitting functions in the trastuzumab emtansine and trastuzumab arms, respectively. For context, parametric models with a difference in AIC/BIC of ≤5 can be broadly considered to produce negligible differences in terms of fit.

The NICE DSU technical support document, developed by Latimer *et al.*, states that the same parametric function should be used across both treatment arms (where feasible).[83] Using the same type of function ensures consistency and limits potential problems such as the crossing of the curves. Although curve crossing was not an issue in this instance it was considered best practice to adhere as closely as possible to the recommendations set out in Latimer *et al.*[83] When considering the fit across the two arms jointly, the best fitting extrapolation is produced by either the Exponential or the Log-logistic function.

Mathematical measures such as the AIC and BIC are designed to show how well a parametric function fits to the Kaplan-Meier data, relative to the other functions in question. In other words, the AIC (BIC) values say nothing of the appropriateness of the extrapolation beyond the Kaplan-Meier data. As the degree of immaturity and censoring are high in the KATHERINE data, the AIC and BIC values quoted here should be interpreted with caution.

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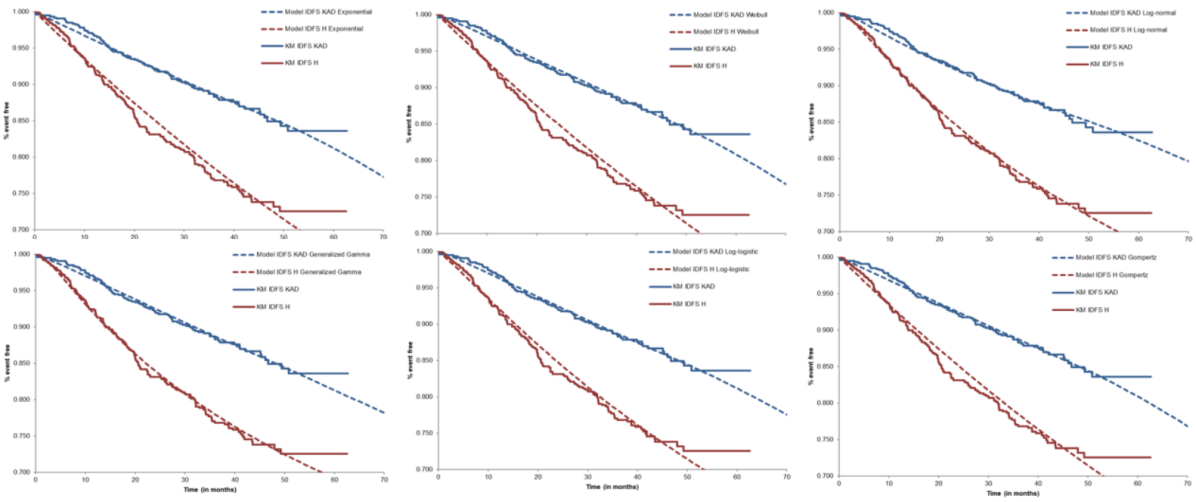
These limitations in the goodness of fit statistics necessitate the exercises laid in out in the following subsections (visual inspection and external validation) when selecting the most appropriate function on which to base the extrapolation of IDFS.

Visual inspection

In addition to Goodness of Fit statistics, all candidate distributions were also assessed for visual fit to the Kaplan-Meier data. The visual fit of each distribution to the Kaplan-Meier of the primary analysis is provided in Figure 18.

Figure 18. Visual inspection of IDFS extrapolations[a]



Footnotes: [a]Y-axes have been manipulated in order to magnify curves.
Abbreviations: IDFS: invasive disease-free survival; H: trastuzumab; KAD: trastuzumab emtansine; KM: Kaplan-Meier.

All distributions appeared to fit the Kaplan-Meier data well, especially in the trastuzumab emtansine arm. In the trastuzumab arm, all extrapolations overestimated IDFS compared to the Kaplan-Meier data from the primary analysis. This should be taken into account when evaluating the cost-effectiveness analysis results.

In summary, the Log-logistic and the Generalized gamma appear to be the best fitting functions across both treatment arms. It is important to note that this conclusion is subjective and all of the distributions can be seen to fit the data reasonably well.

Landmark IDFS rates

The AIC and BIC statistics serve to illustrate the relative fit of a parametric function. When selecting an appropriate extrapolation, it is also important to take the absolute fit to the Kaplan-Meier data into consideration. To quantify this, a simple comparison of IDFS events at different timepoints was undertaken. Table 24 presents the proportion of patients who did not experience an IDFS event at one, two, three and four years according to the parametric extrapolations and Kaplan-Meier data.

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Table 24. IDFS events at 12, 24, 36 and 48 months

Timepoint	Parametric function	Trastuzumab emtansine arm	Trastuzumab arm	Trastuzumab emtansine vs trastuzumab	Δ vs KM data	
					Trastuzumab emtansine arm	Trastuzumab arm
12 months	KM data	96.64%	92.11%	4.53%	0.00%	0.00%
	Exponential	95.90%	91.93%	3.97%	-0.74%	-0.18%
	Weibull	96.20%	92.00%	4.20%	-0.44%	-0.11%
	Log-normal	95.74%	91.51%	4.23%	-0.90%	-0.60%
	Gen. gamma	96.19%	91.26%	4.93%	-0.45%	-0.85%
	Log-logistic	96.18%	91.88%	4.30%	-0.46%	-0.23%
	Gompertz	96.04%	91.93%	4.11%	-0.60%	-0.18%
24 months	KM data	92.05%	83.11%	8.94%	0.00%	0.00%
	Exponential	92.13%	84.80%	7.32%	0.08%	1.69%
	Weibull	92.37%	84.85%	7.52%	0.32%	1.74%
	Log-normal	91.79%	83.92%	7.87%	-0.26%	0.81%
	Gen. gamma	92.34%	83.65%	8.68%	0.29%	0.54%
	Log-logistic	92.29%	84.46%	7.83%	0.24%	1.35%
	Gompertz	92.28%	84.80%	7.48%	0.23%	1.69%
36 months	KM data	88.26%	76.79%	11.47%	0.00%	0.00%
	Exponential	88.50%	78.23%	10.27%	0.24%	1.44%
	Weibull	88.57%	78.23%	10.34%	0.31%	1.44%
	Log-normal	88.40%	77.79%	10.62%	0.14%	1.00%
	Gen. gamma	88.55%	77.75%	10.80%	0.29%	0.96%
	Log-logistic	88.50%	77.88%	10.62%	0.24%	1.09%
	Gompertz	88.57%	78.23%	10.34%	0.31%	1.44%
48 months	KM data	84.27%	73.19%	11.08%	0.00%	0.00%
	Exponential	85.01%	72.16%	12.86%	0.74%	-1.03%
	Weibull	84.85%	72.12%	12.73%	0.58%	-1.07%
	Log-normal	85.45%	72.70%	12.75%	1.18%	-0.49%
	Gen. gamma	84.87%	72.99%	11.88%	0.60%	-0.20%
	Log-logistic	84.89%	72.09%	12.80%	0.62%	-1.10%
	Gompertz	84.90%	72.16%	12.74%	0.63%	-1.03%

Abbreviations: KM: Kaplan-Meier; Δ: difference.

Overall, all functions across both treatment arms proved to be a good absolute fit to the Kaplan-Meier IDFS data. At all timepoints, incremental differences between the extrapolations and the Kaplan-Meier data were below 2%. It can be reasonably assumed that differences in the absolute fit of the parametric function extrapolations are negligible.

Based on the assessment and selection process described above, the Log-logistic distribution has been deemed to be the best fitting function and is therefore used for the IDFS extrapolation in years zero to three (time period 1) in both treatment arms. This distribution also provides the basis for the adjusted curves from year three onwards. The choice of function for IDFS extrapolation has been varied as part of the sensitivity analyses for this submission – please refer to Section B.3.8.

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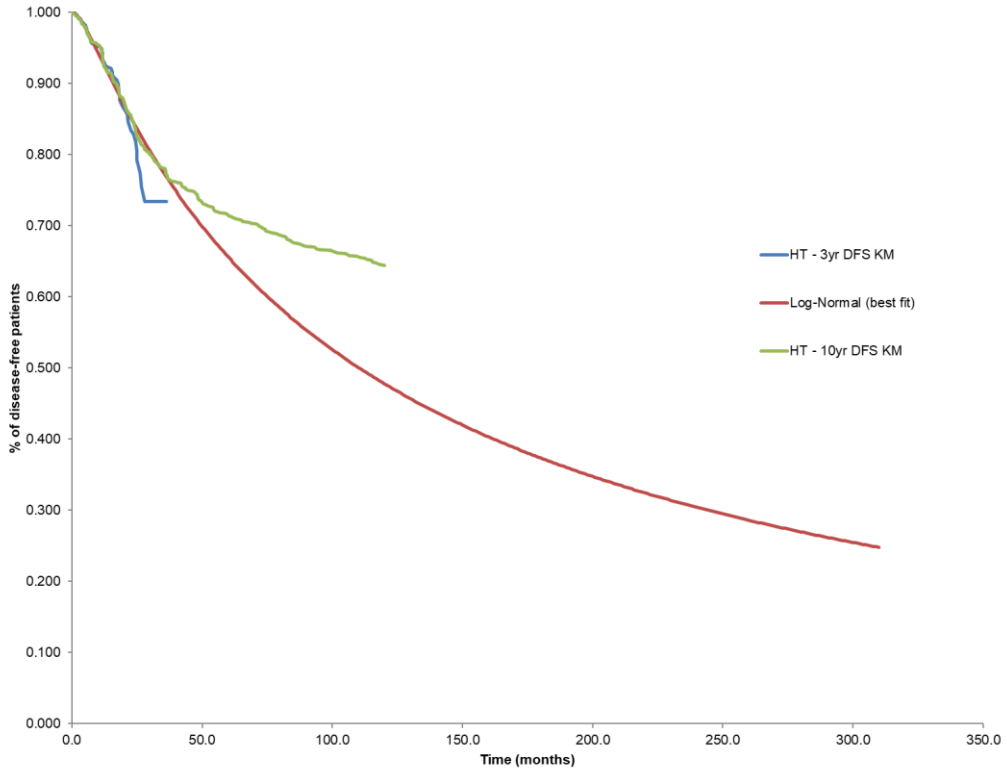
Time period 2 (year three to year ten) – empirical data

At the time of this submission, the KATHERINE trial has a follow-up period of approximately four years. Published literature shows that the underlying risk of recurrence in the first four years for a patient with eBC is not representative of the risk of recurrence at a later date.[84, 85] Patients in the IDFS state are exposed to a far greater risk of recurrence in the first three to five years, although this risk eventually decreases over time. Ultimately, the extrapolation parameter estimates that have been calculated based on KATHERINE data correspond to a time period with a high risk of recurrence. This results in extrapolations which overestimate the rate of recurrence at later timepoints. These conclusions are reflected in the evidence reported in both the BCIRG 006 and HERA trials, which are long-term studies of trastuzumab therapy.[84, 85]

Figure 19 shows the extrapolation of DFS based on the three-year data cut of the HERA trial and the actual Kaplan-Meier curve seen at year 11 of the same trial.[84] It is apparent that the extrapolation based on the three-year data-cut vastly underestimates the actual DFS estimates seen at year ten. A similar situation is expected to be observed in the KATHERINE data, thus indicating that an adjustment of the underlying risk (i.e. IDFS curve) is required.

Figure 19. Comparison of 3-year HERA data extrapolation and latest HERA data cut (ten-years) (node-positive population – one year of trastuzumab therapy cohort)



Abbreviations: DFS: disease-free survival; HT: trastuzumab + chemotherapy; KM: Kaplan-Meier; yr: year.

A three-year DFS data cut was not available for the BCIRG 006 trial, therefore only the HERA study has been included in Figure 19. Though it may have been possible to construct an extrapolation based on BCIRG 006 Kaplan-Meier data at year three, this was deemed inappropriate from a methodological point of view.

Adjustment of the extrapolation based on external data

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Two external long-term trastuzumab studies have been used to examine the relationship between time in IDFS/DFS and the underlying risk of recurrence. It is important to note that the same data sources, rationale, and adjustments outlined below were also used, and subsequently accepted, in the NICE appraisal of pertuzumab in the adjuvant treatment of HER2-positive breast cancer (TA569).[71]

The first study, HERA, is a randomised, open-label, multicentre, phase III trial investigating the efficacy of trastuzumab therapy over one and two years after standard neoadjuvant chemotherapy, adjuvant chemotherapy, or both, in patients with HER2-positive eBC.[84]The HERA trial provides longer term follow-up data on DFS in patients with eBC. These data can be used as an additional source to inform the long-term extrapolation of IDFS in the KATHERINE study. It should be noted however that the primary outcome in HERA was DFS, compared to IDFS in the KATHERINE study.

The second study, BCIRG 006, was also a randomised phase III trial of patients with node-positive or high-risk node-negative eBC, and compared doxorubicin + cyclophosphamide followed by docetaxel (AC-T); AC-T + trastuzumab (AC-TH); and a non-anthracycline-containing arm, docetaxel + carboplatin + trastuzumab (TCH). The final ten-year analyses of the BCIRG 006 were also recently published.[85]

The ITT populations in both the BCRIG 006 and HERA trials have a far better prognosis than those patients included in the KATHERINE study. The node-positive populations in these trials represent a higher risk population and are believed to be a more appropriate proxy to patients with RID following neoadjuvant therapy (KATHERINE population). The node-positive populations in the long-term trastuzumab trials have therefore been used as an analogue in the following subsections to justify and validate the adjustments to the IDFS extrapolation made in the KATHERINE CEM.

Analyses of the long-term data from the HERA and BCIRG 006 studies show that recurrence rate starts off relatively high before sharply decreasing and finally stabilising (at approximately 120 months). A clear change in the incidence of events is observed after 36 months of follow-up (Figure 20). Following randomisation up until 36 months, the recurrence rate is maintained at a high level in both trials. After 36 months, the recurrence rate begins to decrease with time. In essence, the follow-up data from these trials illustrates that the number of additional DFS events decreased with time from 36 months onwards. Much like the APHINITY trial, this trend is also assumed to be evident in the KATHERINE data.

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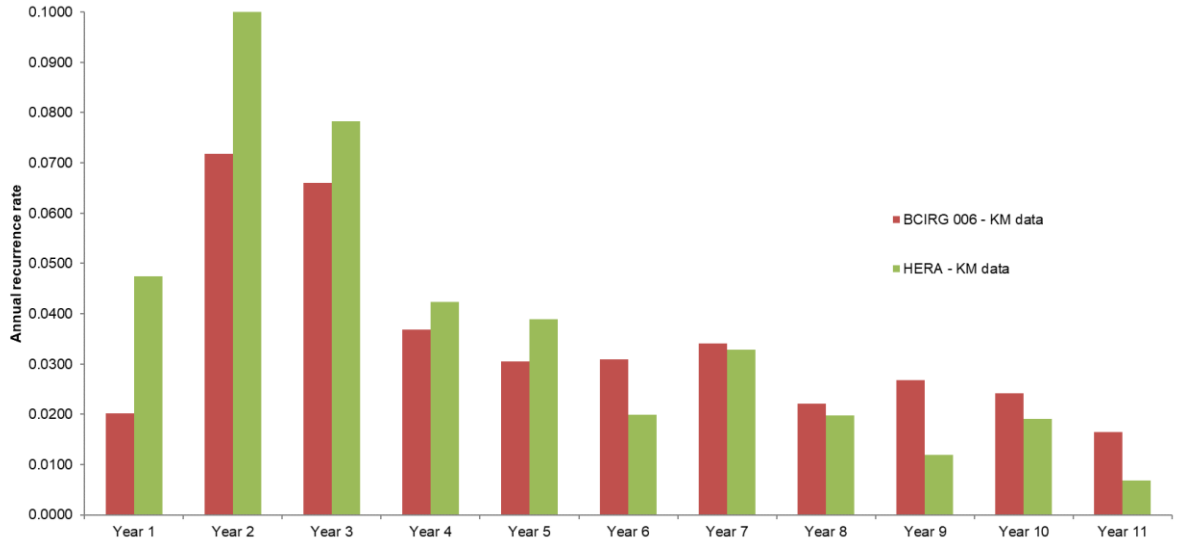
Figure 20. Annual recurrence rate (DFS endpoint) from the HERA and BCIRG 006 clinical trials – node-positive population



The trend seen in Figure 20 and described above has been replicated in the economic analysis by assuming that from 36 months onwards, the proportion of patients being "cured" (no longer at risk of recurrence and only subject to background mortality) linearly increases with time from 0% at 36 months to 95% at 120 months.

Thirty-six months was selected as the start point of the cure model because the evidence base (Figure 20) appears to show a clear change in the hazard rate from this timepoint. This start point was also the preference of the Appraisal Committee in TA569.[71]

An *ad-hoc* literature search was also carried out as part of the adjuvant pertuzumab appraisal. This search captured a case study report published by Takeuchi *et al.*[86] This report examined the incidence of very late disease recurrence in 1,114 Japanese patients with surgically treated breast carcinoma. In the Takeuchi study, only ~1.10% of patients (12/1,114 = 1.07%) experienced a disease recurrence after 10 years. When using 95% as the "maximum cure rate", this model predicts that 1.42% of patients will experience a disease recurrence after 10 years in IDFS in the trastuzumab arm. This maximum cure rate therefore leads to model projections that are closely aligned to the Takeuchi *et al.* publication. The proximity of the late recurrence estimates from Takeuchi *et al.* and the model also provides further support for the Company's preferred choice of extrapolation function in the base case analysis. Furthermore, this cure rate was also used for decision-making in the adjuvant pertuzumab appraisal (TA569).[71]

This adjustment results in IDFS curves that are broadly reflective of the long-term trend in recurrence rate in the HERA trial – See Figure 21 and Figure 22.

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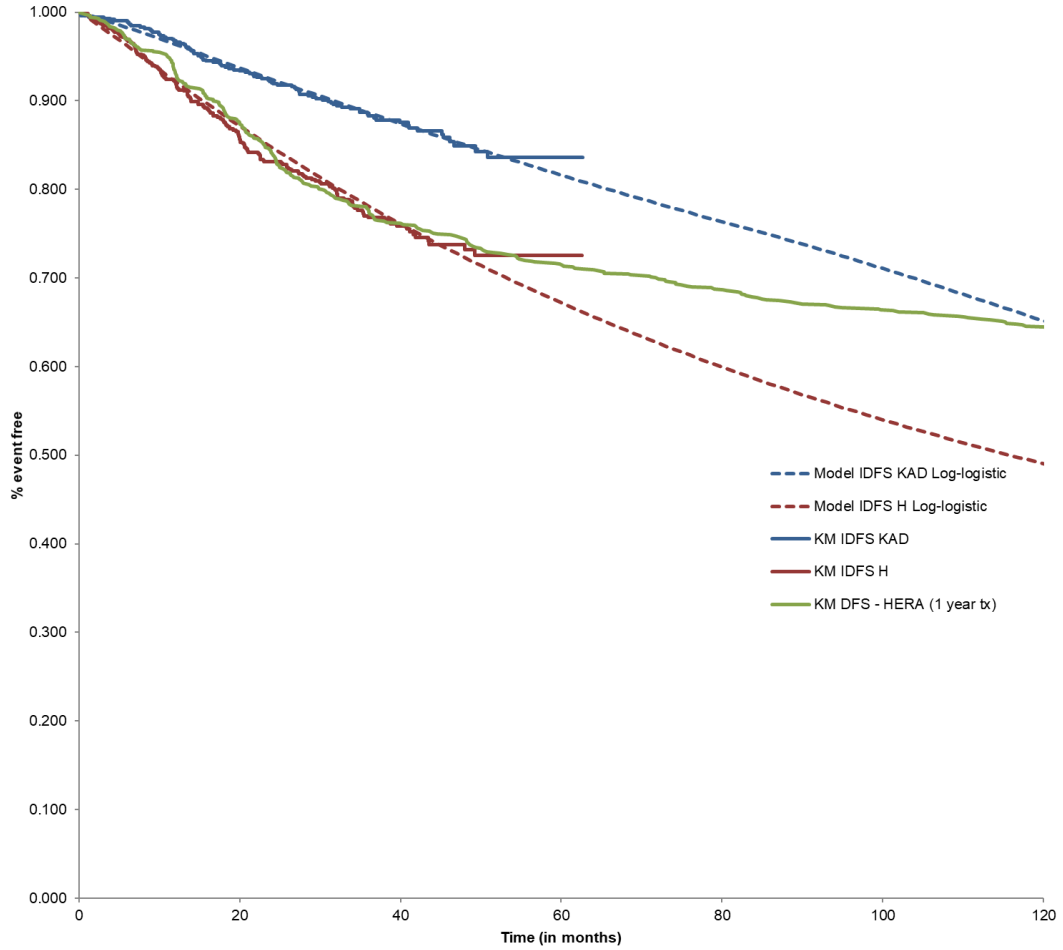
Figure 21. Unadjusted KATHERINE IDFS extrapolation vs HERA 10-year Kaplan-Meier data (0% cure proportion)



Abbreviations: DFS: disease-free survival; H: trastuzumab; IDFS: invasive disease-free survival; KAD: trastuzumab emtansine; KM: Kaplan-Meier; tx: treatment.

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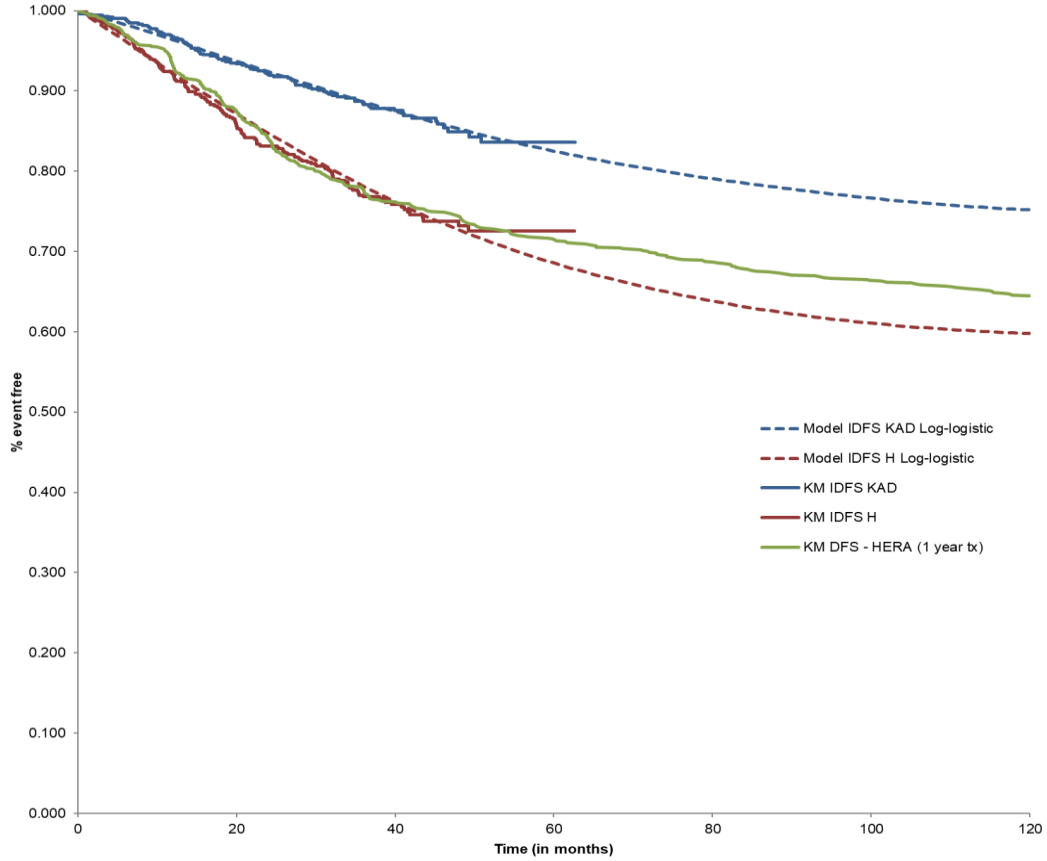
Figure 22. Adjusted KATHERINE IDFS extrapolation vs HERA 10-year Kaplan-Meier data (95% cure proportion, 36 –120 months)



Abbreviations: DFS: disease-free survival; H: trastuzumab; IDFS: invasive disease-free survival; KAD: trastuzumab emtansine; KM: Kaplan-Meier; tx: treatment.

Validation of the trastuzumab + chemotherapy extrapolation

Following the aforementioned adjustments, it is important to validate the final extrapolations with the longer-term data. Figure 23 shows the recurrence rate in the trastuzumab arm of the model, and the pooled observed recurrence rate of both trastuzumab arms in the BCIRG 006 study.

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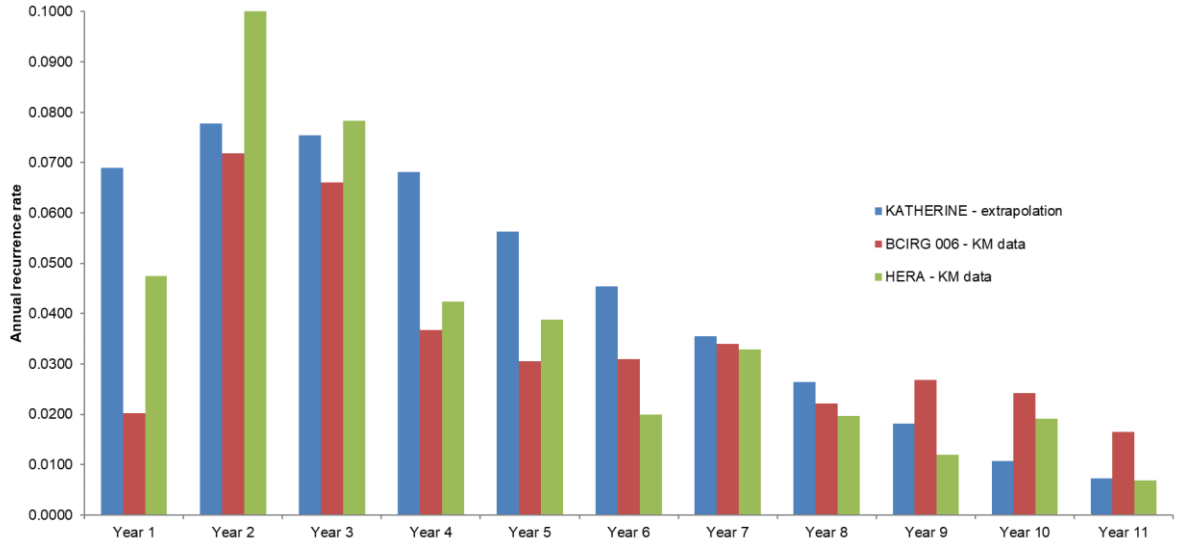
Figure 23. Annual recurrence rate observed in the trastuzumab arms of the BCIRG 006* & HERA* trials compared to modelled recurrence rate in trastuzumab arm of KATHERINE**



Footnotes: * node-positive population; **, ITT population.
Abbreviations: KM: Kaplan Meier.

The difference in recurrence rate seen in the first four years is driven by the results from the respective trials. From year four to year ten the recurrence rates observed in BCIRG 006 are broadly similar to the modelled recurrence rate in the economic analysis. This similarity confirms that the adjustments are reasonable and appropriately reflect the long-term risk of eBC patients.

It is important to note here that the KATHERINE trial used a different primary endpoint (IDFS) to the BCIRG 006 study (DFS). The IDFS and DFS endpoints are similar in terms of their definitions and hence results across the two measures are assumed comparable.

The adjustments made to the IDFS extrapolation were in-line with those made in the recent adjuvant pertuzumab NICE appraisal. These adjustments were judged to be appropriate and the resulting extrapolation used for decision-making.

Duration of incremental treatment effect

In the base case analyses, it is assumed that the treatment effect of trastuzumab emtansine will be maintained for 84 months (seven years) before gradually decreasing to be null at 120 months (ten years). The assumption of maintenance of treatment effect beyond the KATHERINE study follow-up period is based on observations from long-term trastuzumab studies.

Evidence of a persisting treatment effect can be found by examining the hazard ratios in the long term trastuzumab trials (HERA and BCIRG 006). Much like trastuzumab emtansine, trastuzumab is also an anti-HER2 molecule and therefore a suitable analogue regarding long term treatment patterns. Hazard ratios between year 7 and year 10 of the HERA and BCIRG 006 trials are shown to be 0.803 and 0.801, respectively. The fact that this hazard ratio is still below 1.00 across this time period can be interpreted as evidence of a long-term treatment effect. However, an important caveat to this point is that ~52% of patients randomised to the placebo arm in the HERA trial cross over to the intervention arms of the study. Naturally, the outcomes seen in the placebo arm of the trial were greatly improved once patients began receiving trastuzumab and as a result the treatment effect at later timepoints is vastly underestimated.[84]

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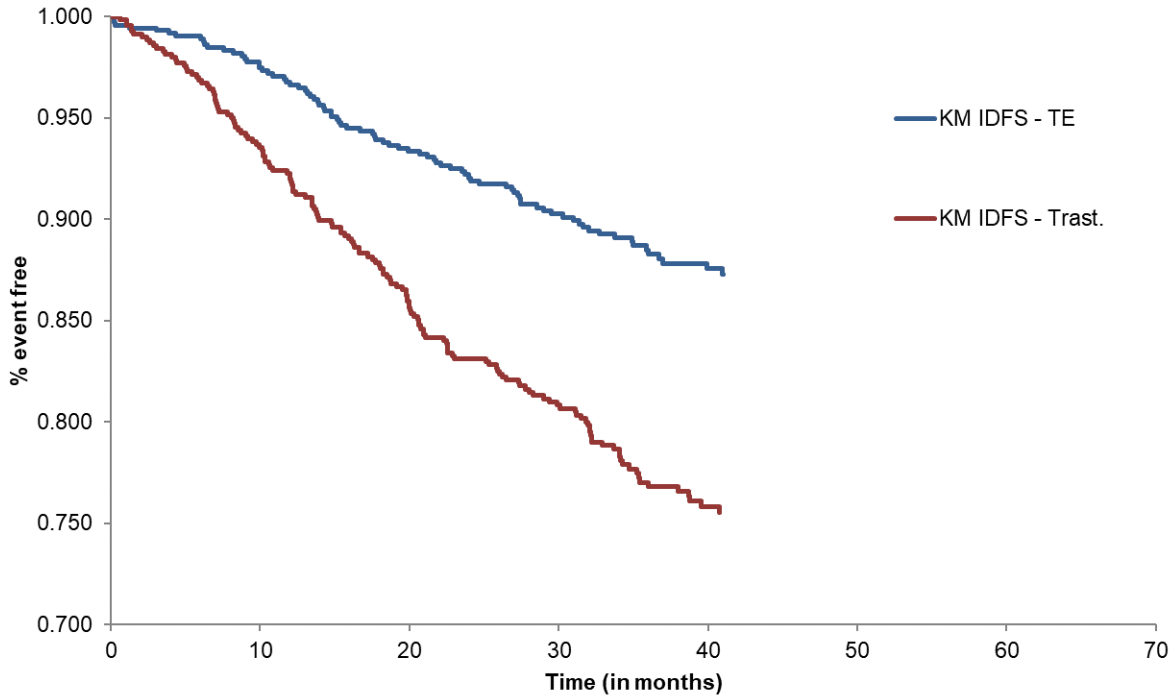
The Company's base case treatment effect assumptions are also aligned to TA424 (appraisal of pertuzumab in the neoadjuvant treatment of HER2-positive eBC) – where a treatment effect duration of seven years was adopted. This assumption was validated by a clinical advisory board and subsequently accepted by the Evidence Review Group (ERG). In this submission, the Company has also assumed an incremental treatment effect duration of seven years, before decreasing linearly and then ceasing completely at ten years. This addition of the waning effect is assumed because patients will receive a total of 14 cycles of in the adjuvant setting, as opposed to only four to six in the neoadjuvant setting.

Furthermore, if the KATHERINE study Kaplan-Meier IDFS curves are capped at median follow-up (~41 months), before the bulk of the censoring occurs, we see that the greatest separation in the curves occurs at this time point – Figure 24. It could be argued that the largest separation of the curves should be interpreted as an increasing treatment effect.

Figure 24. IDFS Kaplan-Meier curves capped to median follow-up[a]



Footnotes: [a]Please note, y-axis has been adjusted in order to magnify the curves.
Abbreviations: IDFS: invasive disease-free survival; KM: Kaplan-Meier; TE: trastuzumab emtansine; Trast: trastuzumab.

The proposed assumptions around treatment effect are aligned to the Company's base case during the adjuvant pertuzumab appraisal. The ERG for TA569 preferred to assume that the treatment effect will be maintained for only 48 months (4 years) before ceasing completely at 84 months (seven years). Though accepted by the Committee, these assumptions were believed to be overly conservative and unreflective of clinical practice by both the Manufacturer and the clinical expert in attendance at the meetings. The OS interim analysis (2nd analysis of IDFS) from the APHINITY trial is expected to read out in [redacted] (i.e. during the course of this appraisal). The Company expects that the second data cut from the APHINITY trial will prove the ERG's assumptions in TA569 to be overly conservative.

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The Company acknowledges the inherent uncertainty around this aspect of the model. In attempt to quantify this uncertainty, extensive scenario analyses were conducted around the treatment effect duration parameters – see Section B.3.8.3.

Time period 3 (year 10 to year 52)

The hazard rate observed in the eleventh year of the HERA trial appears similar to that of the UK mortality table, when assuming the patient is 65 years old.[84] It has therefore been reasonably assumed that 95% of patients are no longer at risk of recurrence beyond 120 months and are only exposed to death thereafter. This assumption will be tested in a scenario analysis.

The model assumes the following for each treatment arm:

- **Trastuzumab:** Only 5% of patients are assumed to be at risk of recurrence. For this 5% of patients, the risk of recurrence is derived from the KATHERINE data. The remaining 95% of patients are subject to the background mortality rate of the age-adjusted UK population only.
- **Trastuzumab emtansine:** No more treatment effect is assumed beyond the seven years, which means that the hazard rate of recurrence from the trastuzumab arm is applied to the trastuzumab emtansine arm of the model.

Empirical data pertaining to this time period does not exist in this indication. This makes it difficult to validate the IDFS curves beyond the ten-year time point.

Modelling of death in the IDFS health state

Whilst in the IDFS state, patients are at risk of both recurrence and death. The risk of death applied here is the superior value between the risk of dying without recurrence (as observed in the KATHERINE study) and background mortality in the age-adjusted UK population.

The risk of dying without recurrence is derived from the KATHERINE trial. In the ITT population, there were a total of 5 deaths without prior events (two and three in the trastuzumab emtansine and trastuzumab arm, respectively). A constant weekly probability was calculated. Too few death events (5/1,486 = 0.34%) were observed to accurately and robustly extrapolate this parameter dependent of time. This probability was therefore assumed to be constant for the entirety of the time horizon.

In actuality, the weekly probability of disease-related death (without first experiencing an IDFS event) in the KATHERINE trial is so low (0.0001) that the UK weekly background mortality rates are superior from cycle one of the time horizon. Consequently, in the base case analysis the risk of death that IDFS patients are exposed to is always equal to that of the age-adjusted UK population (background mortality).

Summary of IDFS curve construction

A summary of the methodology involved in extrapolating the KATHERINE IDFS curves is given below. Figure 25 displays the data sources used to construct the curves in each of the time periods. Figure 26 shows IDFS extrapolations as per the model base case (ITT, Log-logistic).

- **Time period 1 (0–3 years)** – KATHERINE trial data are used to estimate the recurrence rate.

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- **Time period 2 (3–10 years)** – Extrapolated recurrence rate is adjusted to more accurately reflect the trend in the recurrence rate observed in the long-term trastuzumab studies.
- **Time period 3 (10–51 years)** – Based on evidence from long-term trastuzumab studies, 95% of patients are assumed to be "cured" and are no longer at risk of recurrence, only background mortality applies.

Figure 25. Summary of the construction of IDFS curves and timing of treatment effect

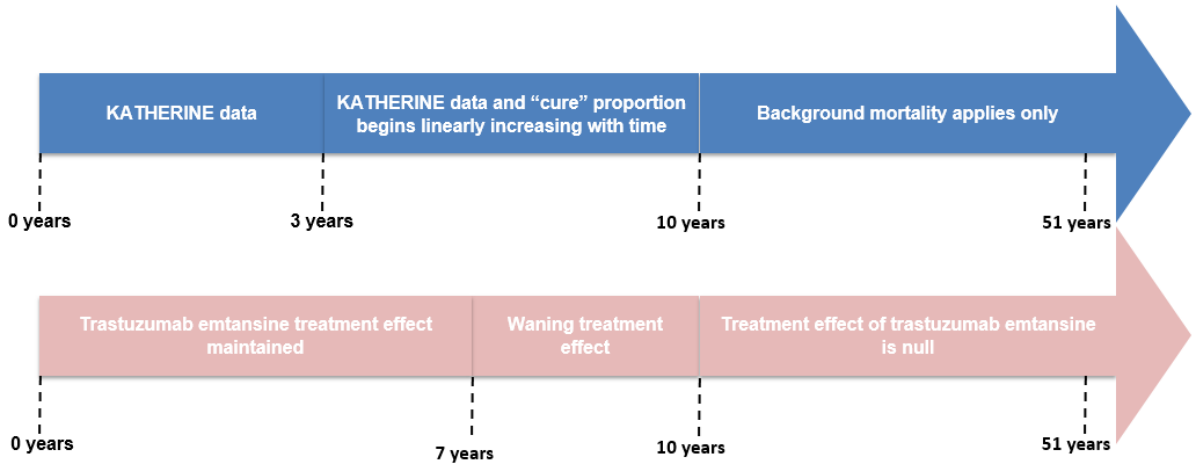

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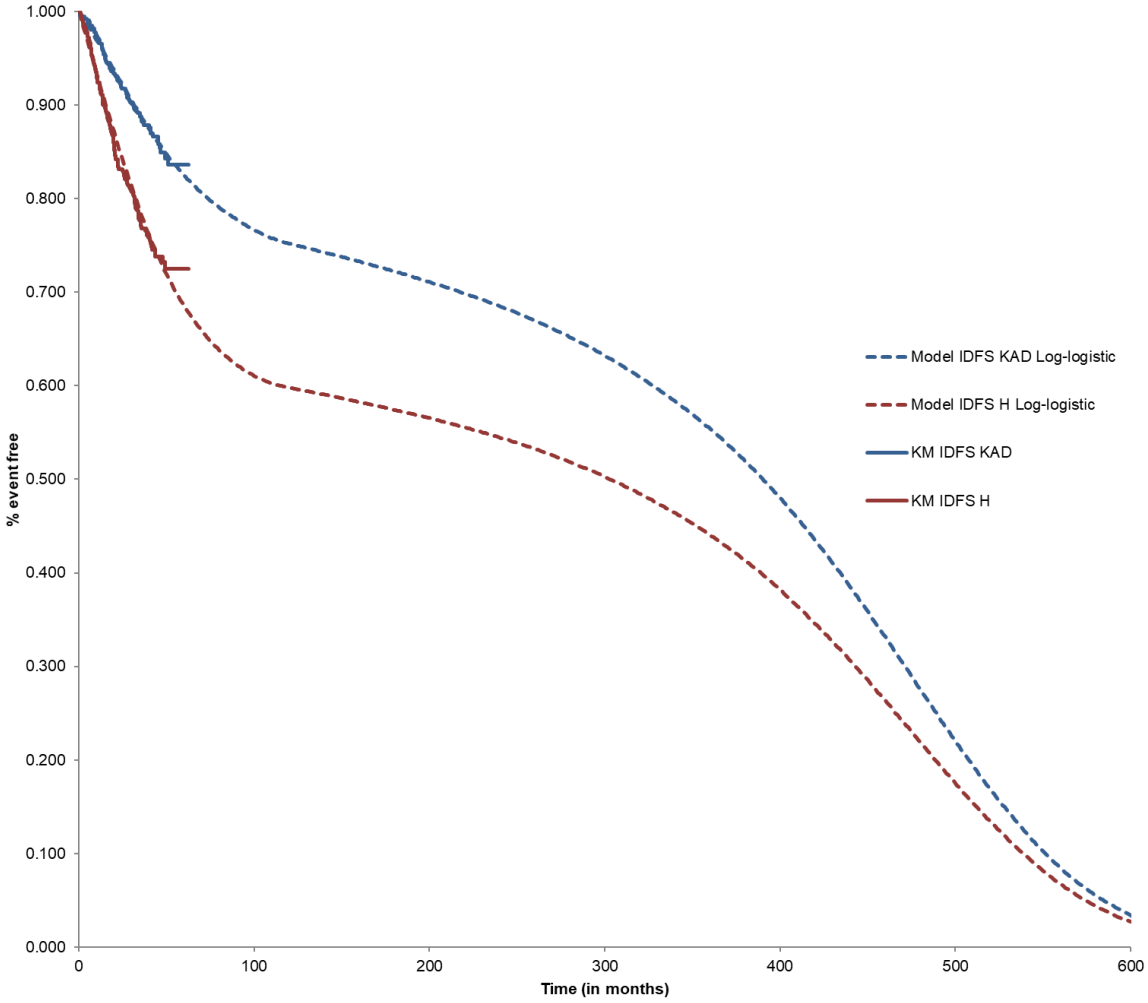
Figure 26. Base case IDFS extrapolation – Log-logistic



Abbreviations: H, trastuzumab; IDFS: invasive disease-free survival; KAD: trastuzumab emtansine; KM: Kaplan-Meier.

B.3.3.2 Modelling of recurrences

As per Figure 15, patients in the IDFS health state can experience either a metastatic (transition to “first-line mBC” health state) or non-metastatic (transition to the “non-metastatic recurrence” health state) recurrence. The probabilities for these transitions have been derived from the IDFS events observed in the KATHERINE study.

Table 25 provides a breakdown of IDFS events observed in each treatment arm of the ITT population. It should be noted that deaths were not included as an IDFS event when calculating the proportion of metastatic and non-metastatic recurrences. Deaths in the IDFS health state are accounted for separately in the model.

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Table 25. Types of IDFS event observed within the KATHERINE study

	Trastuzumab emtansine (n=743)	Trastuzumab (n=743)	Both arms
IDFS event, n	91	165	256
Deaths without prior event, n (%)	2 (2.20%)	3 (1.82%)	5 (1.95%)
IDFS event excluding deaths, n	89	162	251
Distant recurrence, n (%)	78 (87.64%)	118 (72.84%)	196 (78.09%)
Other types of recurrence, n (%)	11 (12.36%)	44 (27.16%)	55 (21.91%)

Abbreviations: IDFS: invasive disease-free survival.

The difference in the proportion IDFS events which were metastatic was not formally tested therefore claims of statistical significance cannot be made. However, there is a non-trivial difference (14.80%) between the two treatment arms. In light of this difference the company has applied treatment-specific proportions in the base case analysis (as opposed to applying pooled values across both arms). For completeness, results generated when using the pooled values have also been included as a scenario analysis – please see B.3.8.3.

Definition and modelling of disease recurrence

Incorporating the timing of relapse into the model was recommended by clinical experts. These experts explained that patients who relapse early tend to have more aggressive disease which does not respond well to treatment, and so are on later lines of therapy for a relatively short duration. However, patients who relapse later tend to have less aggressive disease which is more amenable to treatment, so are on later lines of treatment for a longer amount of time, and therefore have much higher total treatment costs. It was decided that early vs late relapses should be considered in the model because of the impact that the timing of relapse has on treatment outcomes and costs.

Figure 27 displays the survival of patients who experienced a disease recurrence in the HERA study. The “early” curve represents the survival of those patients who experienced a metastatic event within 18 months of adjuvant treatment initiation. The “late” curve represents the same information but for those patients who experienced a metastatic event after 18 months of adjuvant treatment initiation. There is a clear difference in post-progression survival between these two populations. Patients who progress on adjuvant therapy, or shortly after completion (within six months), clearly have a worse prognosis than those who progress after 18 months. This difference in curves provides further justification for stratifying according to timing of relapse in the model.

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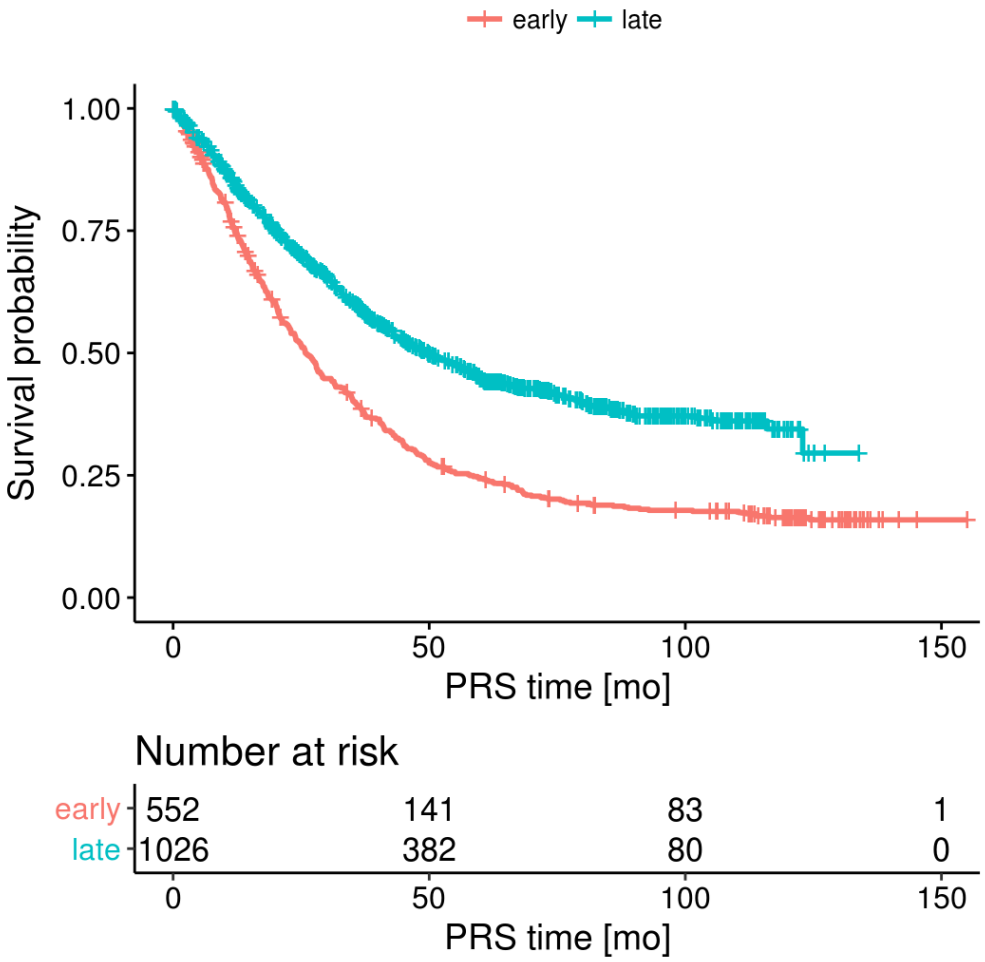
Figure 27. Post-progression survival of patients with disease recurrence in the HERA study ("early" vs "late" relapsers)



Abbreviations: mo: months; PRS: post-recurrence survival.

In addition, patients in the UK may be eligible for differing treatments depending on when their disease progresses. For example, patients who experience a metastatic disease recurrence within 18 months of beginning adjuvant initiation ("early" relapsers) can be treated with trastuzumab emtansine.

In the model, these "early relapser" patients have a poorer prognosis and will therefore receive a more aggressive treatment. Survival estimates derived from a subgroup of the EMILIA study (patients who had a metastatic recurrence within 18 months of adjuvant treatment initiation) are used to model the progression (to second line [2L] mBC) and survival of patients who experience a metastatic recurrence within the first 18 months after adjuvant treatment initiation. In the EMILIA study, the corresponding population was selected to estimate the risk of disease progression (PFS) and the risk of death following progression (post-progression survival). Outcomes from both treatment arms were pooled (i.e. analysed as a single treatment group) to increase the number of events thereby generating more robust survival estimates.

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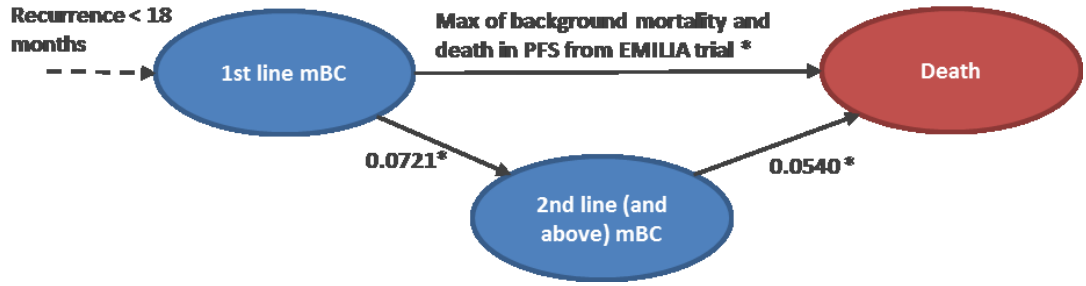
Figure 28. Summary of monthly transition probability sources in the metastatic setting following early relapse (within 18 months)



Footnotes: *All data derived from the EMILIA study are based on the "early relapsers" sub-population.
Abbreviations: mBC: metastatic breast cancer; PFS: progression-free survival.

Non-metastatic recurrence pathway

Patients in the IDFS state can experience either a non-metastatic recurrence or a metastatic recurrence. The non-metastatic recurrence pathway consists of two health states: "Non-metastatic recurrence" and "Remission". The transitions and associated probabilities to and from these states are described below.

Non-metastatic recurrence

Patients transition from the IDFS state to the non-metastatic recurrence health state based on the percentage observed in the KATHERINE study – see Table 26. The model assumes that all patients who experience a non-metastatic recurrence would undergo one year of additional adjuvant therapy. Following this treatment, all patients would then enter the remission health state. In this context, the non-metastatic recurrence health state acts as a "tunnel-state". The assumption that all patients transition to remission following additional adjuvant therapy is perhaps not realistic. The Company acknowledges that, in reality, some patients may incur a metastasis during this 12-month treatment period. However, clinical experts consulted by Roche suggested that very few patients would progress or die during the first 12 months following a non-metastatic recurrence. Thus, this assumption is unlikely to significantly impact on the overall cost-effectiveness results.

As stated above, this model structure was used for in the recent NICE appraisal of adjuvant pertuzumab. The assumptions made regarding transitions to and from the non-metastatic health state were judged to be appropriate by both the ERG and Committee of that appraisal.

Table 26. Proportion of recurrences which are non-metastatic by treatment arm in the "early" and "late" relapser population

	Trastuzumab emtansine (n=743)	Trastuzumab (n=743)
IDFS event, n	91	165
Deaths without prior event, n (%)	2 (2.20%)	3 (1.82%)
IDFS event excluding deaths, n	89	162
"Early" relapser – pre-18 months[a]		
Metastatic recurrence, n (%)	36 (85.71%)	60 (72.29%)

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	Trastuzumab emtansine (n=743)	Trastuzumab (n=743)
Non-metastatic recurrence, n (%)	6 (14.29%)	23 (27.71%)
"Late" relapser – post-18 months[a]		
Metastatic recurrence, n (%)	42 (89.36%)	58 (73.42%)
Non-metastatic recurrence, n (%)	5 (10.64%)	21 (26.58%)

Footnotes: [a]Deaths are not counted as IDFS events in these figures. Death is accounted for separately in the model.
Abbreviations: IDFS: invasive disease-free survival.

Patients are also at risk of death during their year in the non-metastatic recurrence health state. This risk of death applied here is the superior value between the risk of dying without recurrence (as observed in the KATHERINE study) and background mortality in the age-adjusted UK population. When background mortality is applied, the risk of breast cancer-related death is zero. This methodology is applied for the following transitions:

- IDFS to death
- Non-metastatic recurrence to death
- Remission to death

The number of deaths without disease recurrence in the KATHERINE study is low. As a result, the general population mortality risk exceeds the risk of death (without recurrence) in the KATHERINE study at cycle one of the model.

Remission

Following the adjuvant therapy received during the non-metastatic recurrence state, patients who are still alive automatically transition to the remission state. When in remission, patients can either die or experience another recurrence.

Risk of death in the remission health state is assumed to be the same as in IDFS. Once background mortality exceeds this value, the patients observe the death risk of the age-adjusted UK population. This is the same methodology used for the transition to death from the IDFS state and the non-metastatic recurrence health state (see above).

A patient in remission will have already experienced a non-metastatic recurrence; this analysis assumes that any additional recurrence would be metastatic in nature. In other words, a patient would transition directly from the remission state to the metastatic – first-line mBC state. The probability of this transition has been sourced from a study by Hamilton *et al.*[87] This study included a cohort of 12,836 patients with eBC and reported the estimated risk of incurring a second malignancy following adjuvant therapy.

Recurrence rate from the remission health state was assumed to remain constant over time. Therefore, an exponential distribution was used to derive a constant transition probability. The Hamilton study reports a mean time until progression of 7.6 years (91.2 months);[87] this value was converted into a monthly transition probability of 0.00760 using Equation 1. There are several differences between the populations being evaluated in this analysis and the one in the Hamilton *et al.* publication, as described below.

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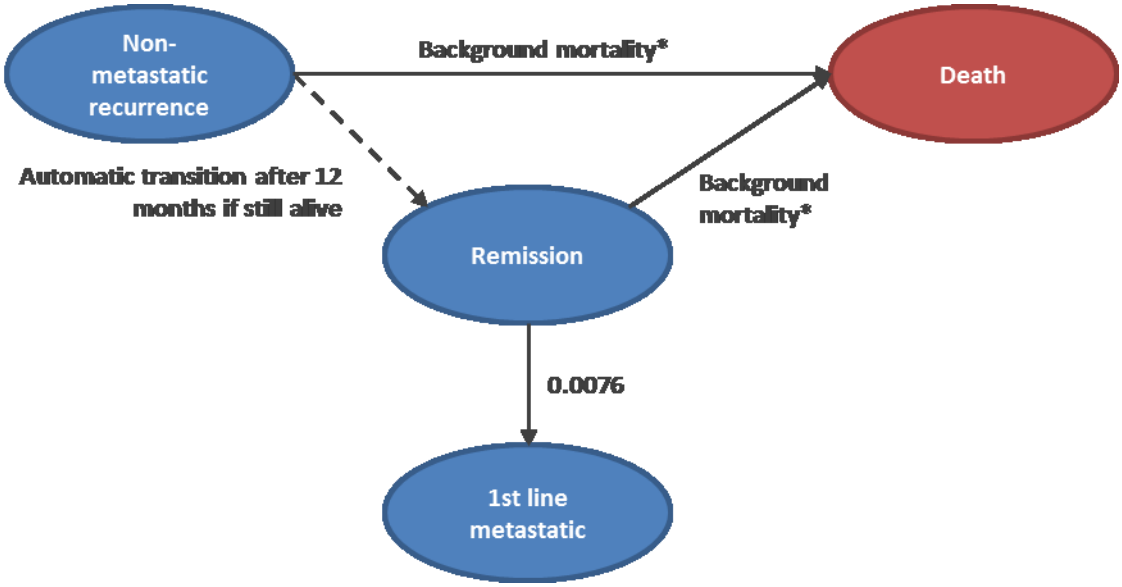
Equation 1: Calculation of remission to first line mBC transition probability

$$S(t) = e^{-\varphi t}$$

The population in the Hamilton *et al.* study was heterogeneous, as it included stage I/II female patients with BC (HER2-positive, negative or unknown status), ranging between 20 to 79 years of age, diagnosed between 1989 and 2005. Furthermore, all patients were treated with adjuvant chest-wall radiation and were from one institution in Canada. This concern was originally raised by the ERG in the appraisal of pertuzumab in the neoadjuvant setting. Nevertheless, the committees in both the adjuvant and neoadjuvant pertuzumab appraisals accepted the use of this source as it was believed to be the best available evidence at the time of writing, a fact which is also believed to be true here. This parameter was manipulated extensively during sensitivity analysis (please see Section B.3.8) as a result of the associated uncertainty.

Transition probabilities in the non-metastatic recurrence pathway are summarised in Figure 29.

Figure 29. Summary of monthly transition probability sources in the non-metastatic recurrence pathway



Footnotes: *This risk of death applied here is the superior value between the risk of dying without recurrence (as observed in KATHERINE) and background mortality in the age-adjusted UK population. The number of deaths without disease recurrence in KATHERINE is low. As a result, the general population mortality risk exceeds the risk of death (without recurrence) in KATHERINE from cycle one of the model time horizon.

Metastatic recurrence pathway

The metastatic recurrence pathway is comprised of two health states: i) First line (1L) mBC treatment and ii) subsequent treatment lines for mBC (2L+ mBC).

1L mBC progression and survival probabilities

Patients can arrive in this health state from the IDFS or remission health states (see above). Once in this state, patients can either die or their metastatic recurrence can progress.

The risk of progression in the mBC setting has evolved substantially over the past five years. The advent of certain transformative therapies means that, on average, patients are remaining

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progression-free for longer than ever before. Consequently, it has been assumed that the patients in the mBC setting today would experience different progression rates than those seen in the KATHERINE trial.

In the first line metastatic setting, three treatment regimens are available to patients in the UK: pertuzumab + trastuzumab + chemotherapy, trastuzumab + chemotherapy, and chemotherapy. The probability of metastatic progression has therefore been derived from available evidence relating to these treatment regimens.

- **Pertuzumab + trastuzumab + chemotherapy and trastuzumab + chemotherapy** – risk of disease progression derived from the CLEOPATRA trial data.[48]
- **Chemotherapy** – risk of disease progression derived from the M77001 trial.[88]

The rate of metastatic progression would be expected to vary over time. This would ordinarily warrant the use of time-dependent transition probabilities. However, one of the flaws of a Markov model is its "memoryless" feature. There is no easy way of tracking when a patient enters a health state or knowing how long they remain there for (unless they enter the model in said health state). This limitation makes the introduction of time-dependent transition probabilities in the 1L metastatic health state problematic. To avoid the use of time-dependent transition probabilities and thus a vastly more complex modelling approach, the Kaplan-Meier data from the trials above have been extrapolated using an exponential distribution. An exponential extrapolation assumes constant hazards over time and therefore produces transition probabilities that are independent of time.

The final transition probability associated with metastatic progression is a weighted average of the probabilities from the three possible metastatic treatment regimens (see Table 27). Treatment usage data presented in Table 27 has been taken from market research commissioned by the Company, which looks at treatment usage in patients with HER2-positive BC in the UK.[89]

Table 27. Summary of monthly metastatic progression transition probabilities

Transition	Treatment regimen	Treatment usage	Data source	Monthly probability	Data source
First line mBC to 2+ line mBC	Pertuzumab + trastuzumab + chemotherapy	75%	Market research	0.0317	CLEOPATRA[48]
	Trastuzumab + chemotherapy	16%	Market research	0.0470	CLEOPATRA[48]
	Chemotherapy	9%	Market research	0.0694	M77001[88]
	Metastatic prog.	**100%**	**Total**	**0.0373**	**Weighted avg.**

Abbreviations: mBC: metastatic breast cancer.

The transition to death from the first-line mBC state is modelled using the number of deaths (without progression events) observed in the CLEOPATRA and M77001 studies. In practice, the general population mortality is higher because patients usually progress before dying from the disease.

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≥2nd line mBC survival probabilities

Following metastatic progression, only one further transition is possible (subsequent lines for mBC treatment to death). The risk of death in the 2L+ metastatic setting has been estimated according to the therapies a UK 2L mBC patient can receive today (see Table 28). Post-progression (post first-line) survival probabilities have been derived using the same methodology as the metastatic progression probabilities.

- **Pertuzumab + trastuzumab + chemotherapy and trastuzumab + chemotherapy** – Post-progression survival probabilities have been derived from the CLEOPATRA trial data.
- **Chemotherapy** – Post-progression survival probabilities have been derived from the M77001 trial.
- **Trastuzumab emtansine** – Post-progression survival probabilities have been assumed equal to those of trastuzumab + chemotherapy.

Once again, the Kaplan-Meier data from these trials have been extrapolated using an exponential distribution to circumvent the use of complex time-dependent transition probabilities. Similarly to the metastatic progression probability, this value is also an average weighted by the treatment usage percentages seen in Table 27.

Table 28. Summary of monthly risk of death in progressed metastatic (2L mBC) disease

Transition	Treatment regimen	Treatment usage	Data source	Monthly probability	Data source
First line mBC to 2+ line mBC	Pertuzumab + trastuzumab + chemotherapy	10%	Market research	0.0273	CLEOPATRA
	Trastuzumab + chemotherapy	7%	Market research	0.0315	CLEOPATRA
	Chemotherapy	5%	Market research	0.0598	M77001
	Trastuzumab emtansine	78%	Market research	0.0315	CLEOPATRA
	Metastatic death	**100%**	**Total**	**0.0325**	**Weighted avg.**

Abbreviations: mBC: metastatic breast cancer.

Validation of Exponential extrapolation of mBC transition probabilities

As shown by the figures reported in Table 29, the average progression-free (1L mBC) and post-progression (2L+ mBC) survival predicted by the exponential extrapolations are similar to the estimates seen in the CLEOPATRA and M77001 trials.

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Table 29. Metastatic recurrence pathway – Comparison of Kaplan-Meier and extrapolated (exponential) estimates

Health state	Transition	Kaplan-Meier estimates (months)	Exponential (months)	Data source
1st-line mBC	PFS – pertuzumab	28.0	28.4	CLEOPATRA
	PFS – trastuzumab	20.8	21.1	CLEOPATRA
	PFS – chemotherapy	14.9	15.6	M77001
2nd+ line mBC	PPS – pertuzumab	29.9	30.7	CLEOPATRA
	PPS – trastuzumab	19.4	18.6	CLEOPATRA
	PPS – chemotherapy	13.9	15.3	M77001

Abbreviations: mBC: metastatic breast cancer; PFS: progression-free survival; PPS: post-progression survival.

In reality, the treatment option chosen in the second line mBC setting would impact on a patient's survival (i.e. patients receiving trastuzumab emtansine could expect greater survival than patients receiving lapatinib + capecitabine, according to results of the EMILIA study). The following rationale justifies why the analysis described here does not account for the survival impact imposed by treatment choice in the 2L mBC setting.

- **First-line treatment choice has a greater impact on OS than second-line treatment choice –** Receiving pertuzumab + trastuzumab + chemotherapy as opposed to trastuzumab + chemotherapy in first-line mBC offers a 15.7-month OS benefit, whereas trastuzumab emtansine instead of lapatinib + capecitabine in the second-line mBC setting provides an OS benefit of five months.
- **Data limitations –** No data are currently available on the sequential use of pertuzumab + trastuzumab + chemotherapy and trastuzumab emtansine in mBC. To reduce the uncertainty, second-line options impact only costs and not survival.

Because of these limitations, it was preferred to derive survival data in mBC for pertuzumab + trastuzumab and trastuzumab only from a single trial (CLEOPATRA study). Using a single data source helped to avoid various issues with population comparability across trials.

Summary of transition probabilities

Figure 30 displays an updated model diagram which includes labels of the various possible transitions. Table 30 lists these transitions along with their values, sources, and the subsection in which they are fully described.

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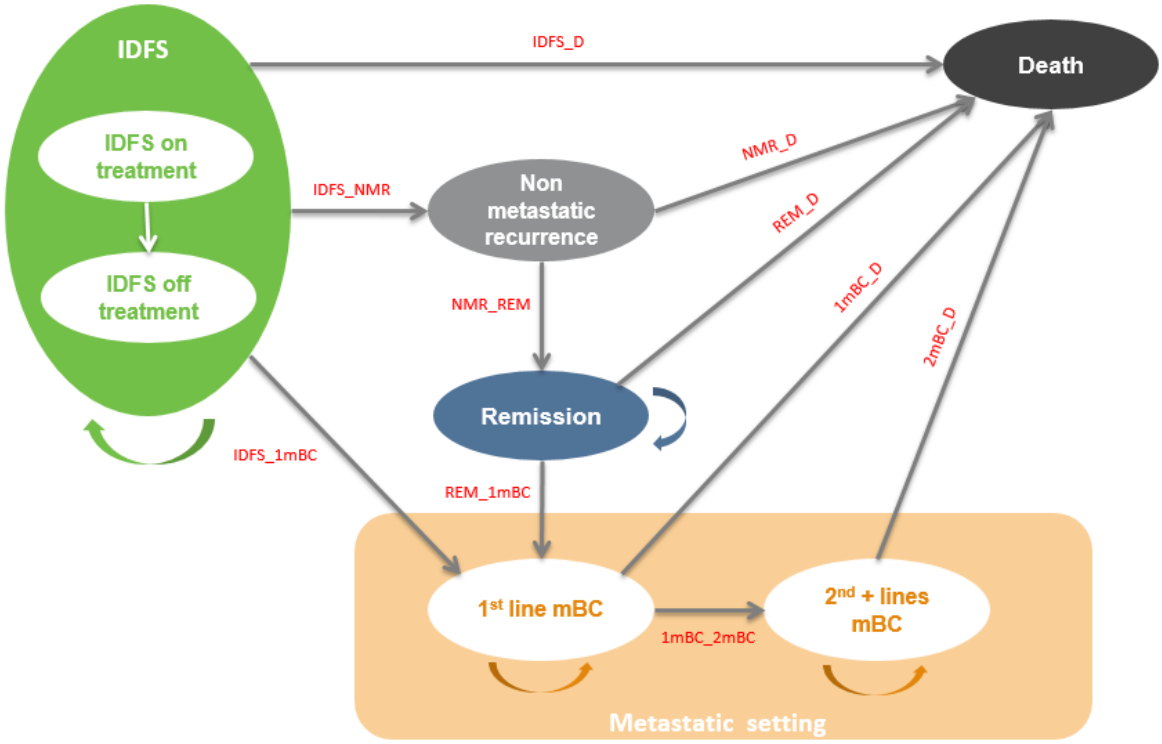
Figure 30. Summary of transition probabilities



Abbreviations: BC: breast cancer; IDFS: invasive disease-free survival; mBC: metastatic breast cancer; NMR: non-metastatic recurrence. Transition probabilities defined in Table 30

Table 30. Summary of transition probabilities

Starting state	Destination state	Transition name	Value	Source
IDFS	Non-metastatic recurrence	IDFS_NMR	Adjusted Log-logistic extrapolation	KATHERINE[63]
	Metastatic recurrence	IDFS_1mBC	Adjusted Log-logistic extrapolation	KATHERINE[63]
	Death	IDFS_D	Maximum of BGM or IDFS death rate	UK life tables, KATHERINE[63]
Non-metastatic recurrence	Remission	NMR_REM	1.00	Assumption
	Death	NMR_D	Max of BGM or IDFS death rate	UK life tables, KATHERINE[63]
Remission	First-line mBC	REM_1mBC	0.0076	Hamilton *et al.*[87]
	Death	REM_D	Max of BGM or IDFS death rate	UK life tables, KATHERINE[63]
First-line mBC – *Early relapser*	2nd + line mBC	N/A	0.0721	EMILIA (pooled treatment arms)[78]
	Death	N/A	Max of BGM or PFS in relevant trial	UK life tables, or EMILIA (pooled treatment arms)[78]

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Starting state	Destination state	Transition name	Value	Source
First-line mBC	2nd + line mBC	1mBC_2mBC	0.0373	Weighted average of post-progression survival in various trials
	Death	1mBC_D	Max of BGM or PFS in relevant trial	UK life tables, CLEOPATRA,[48] or M77001[88]
Second+ line mBC – *Early relapser*	Death	N/A	0.0540	EMILIA (pooled treatment arms)[78]
Second+ line mBC	Death	2mBC_D	0.0325	Weighted average of risk of death in various trials

Abbreviations: BGM: background mortality; IDFS: invasive disease-free survival; mBC: metastatic breast cancer; N/A: not applicable; NMR: non-metastatic recurrence; PFS: progression-free survival; REM: remission.

B.3.3.3 Modelling of overall survival

The submitted cost-effectiveness model is a seven-state Markov model. When adopting this approach, it is difficult to explicitly model OS. A notable flaw in the Markov approach is that although death events can be accounted for, the origin of the patient who died is difficult to ascertain (i.e. a patient may die, but it is difficult to tell which health state the patient was in at the time of death).

In theory, it is possible to conduct survival analysis on the KATHERINE OS data and subsequently fit parametric functions to the Kaplan-Meier curves. However, the immaturity of the OS data means that a substantial amount of uncertainty would be introduced to the model. Only 98 deaths occurred across both treatment arms in the ITT population of KATHERINE, which means approximately 93% of the population are still alive at the end of follow-up. This number of events was judged to be insufficient to robustly extrapolate OS parametrically over a 51-year time horizon.

The limitations associated with the parametric extrapolation of OS meant that OS is instead modelled by accounting for the risk of death in each individual health state. Background mortality applies in all health states and is the main reason for death in the IDFS, non-metastatic recurrence, and remission states. The risk of death is significantly higher in the mBC health states. For mBC patients, the risk of death is modelled according to trial data on therapies available to current UK patients – see 0 for more details on this methodology.

B.3.3.4 Treatment duration

In the KATHERINE study, patients in both arms were expected to receive treatment for a maximum of 14 cycles. It was possible for treatment to be discontinued because of unacceptable toxicity or disease progression. Treatment duration in the model was derived from time-to-off-treatment (TTOT) data observed in the KATHERINE trial.

In the KATHERINE study, most patients in the Safety Evaluable population (81.0% in the trastuzumab arm and 71.4% in the trastuzumab emtansine arm) completed 14 cycles of the

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assigned regimen (i.e. they did not discontinue due to toxicity or progression – Table 31). As documented in the KATHERINE clinical study report (CSR), patients who discontinued trastuzumab emtansine were permitted to complete the duration of their study therapy with trastuzumab if appropriate based on toxicity considerations. Consequently, a total of 593 patients (80.1%) receiving trastuzumab emtansine completed the 14 cycles of any study treatment (trastuzumab emtansine or trastuzumab emtansine plus trastuzumab if a switch patient), see Table 31.[63]

Seventy-one patients switched to trastuzumab from trastuzumab emtansine therapy during the course of the study. Of these 71 switch patients, a total of 63 patients (88.7%) completed 14 cycles of trastuzumab emtansine and trastuzumab.[63]

Table 31. Treatment discontinuation in the KATHERINE study[63]

		Trastuzumab (n=740)	Trastuzumab emtansine (n=740)
Total treatment duration (median)		10 months	10 months
Number of cycles (median)		14	14
Number (%) of patients completing at least a total of X cycles of assigned treatment:	*1 cycle*	720 (100.0%)	740 (100.0%)
	4 cycles	683 (94.9%)	677 (91.5%)
	7 cycles	664 (92.2%)	637 (86.1%)
	11 cycles	618 (85.8%)	579 (78.2%)
	14 cycles	583 (81.0%)	528 (71.4%)
Number (%) of patients completing at least a total of X cycles of all study treatment:	*1 cycle*	N/A	740 (100.0%)
	4 cycles	N/A	698 (94.3%)
	7 cycles	N/A	673 (90.9%)
	11 cycles	N/A	639 (86.4%)
	14 cycles	N/A	593 (80.1%)

The model incorporates two options for modelling treatment duration. The first option, and the Company's base case, is the actual treatment duration as seen in the KATHERINE study. When this option is selected, the treatment duration is calculated by using the actual proportion of patients that receive the drug at each treatment cycle in the trial. In the cost-effectiveness model, TTOT data in the trastuzumab emtansine arm includes patients who remained on trastuzumab emtansine therapy and patients who switched to trastuzumab therapy. Trastuzumab emtansine costs are then used for all patients in all treatment cycles (i.e. no adjustments are made to the costs to account for patients switching treatments). Trastuzumab emtansine is [redacted], taking this approach therefore gives a conservative view of the cost-effectiveness of trastuzumab emtansine compared to trastuzumab in this population. In Section B.3.8, the cost-effectiveness impact of this conservative approach is fully evaluated. The TTOT used in each arm of the base case analysis is given in Table 32 below.

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Table 32. Time-to-off-treatment data used in the base case analysis

Cycle number	Trastuzumab arm (trastuzumab only)	Trastuzumab emtansine arm (Any study treatment)
1	99.9%	100.0%
2	97.9%	97.8%
3	96.3%	95.9%
4	94.7%	94.3%
5	93.9%	92.7%
6	93.1%	91.9%
7	92.1%	90.9%
8	90.6%	90.0%
9	89.7%	88.8%
10	88.5%	87.7%
11	85.8%	86.4%
12	83.9%	84.7%
13	82.5%	82.4%
14	81.0%	80.1%

The second option for modelling treatment duration allows treatment duration to be modelled as per the KATHERINE protocol or the summary of product characteristics (SmPC) label. This option essentially sets the proportion of patients on treatment equal to the proportion of patients in the IDFS health state until the maximum of 14 treatment cycles have elapsed. When treatment duration is modelled using this option, it is assumed that patients only discontinue treatment due to progression (treatment switching is therefore not relevant to this scenario). In other words, discontinuations due to toxicity are assumed not to occur. This assumption is obviously clinically implausible and therefore this option is only included for completeness, as part of the scenario analyses.

Dose reductions

Dose reductions were permitted during the KATHERINE trial for patients receiving trastuzumab emtansine – see Section B.2.10.1. However, no dose reductions were accounted for in the economic analysis.

As per Table 15, the vast majority (85.7%) of patients in the trastuzumab emtansine arm did not require any dose modification. Consequently, it was decided not to further complicate the model by attempting to account for a minority of patients who had a dose reduction.[63]

The assumption that no dose modifications took place is not likely to significantly impact the overall cost-effectiveness results. Further, this approach can be judged to be conservative. By accounting for dose reductions, we would essentially be reducing the costs in the intervention arm of the model, thereby decreasing the incremental cost-effectiveness ratio (ICER).

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B.3.4 *Measurement and valuation of health effects*

B.3.4.1 Health-related quality-of-life data from clinical trials

Patients in the KATHERINE trial reported HRQoL, eBC symptoms and health status using the EORTC QLQ-C30, EORTC QLQ-BR23 and EQ-5D-3L.

EORTC QLQ-C30 and EORTC QLQ-BR23

The EORTC QLQ-C30 is a 30-item questionnaire which includes five functional scales (physical, role, emotional, cognitive and social), three symptom scales (fatigue, nausea & vomiting and pain) and a global health status/QoL scale. Furthermore, it contains six single items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties).The EORTC QLQ-BR23 is a breast-specific supplement to the EORTC QLQ-C30 that comprises 23 questions to assess body image, sexual functioning, sexual enjoyment, future perspective, systemic therapy side effects, breast symptoms, arm symptoms and being upset by hair loss.[90]

Both the EORTC QLQ-C30 and the BR23 supplement were completed at the following timepoints of the KATHERINE study: screening, during treatment (cycle 5 and cycle 11), and every six months for one year after the study completion visit, as described in the Schedule of Assessments in the KATHERINE .[63]

Given that EQ-5D-3L measurements were also taken during the trial, it was decided that the EORTC data would not be incorporated into the cost-effectiveness analysis.

EQ-5D-3L[91]

Patients provided data on eBC symptoms and functioning using the EQ-5D-3L. The EQ-5D-3L was administered on the same schedule as the EORTC QLQ-C30 and the BR23 supplement. Responses were collected at: screening, during treatment (cycle 5 and cycle 11), and every six months for one year after the study completion visit.

The EQ-5D is NICE's preferred instrument for the measurement of HRQoL in adults. This data was therefore used to derive the health state utility values (HSUVs) in the cost-effectiveness analysis. This methodology is consistent with the guidance given in the NICE Reference Case.[81]

B.3.4.2 Mapping

According to the NICE reference case, EQ-5D is the preferred measure of HRQoL in adults.[81] Given that EQ-5D-3L data were collected during the KATHERINE study, no mapping techniques were required.

B.3.4.3 Health-related quality-of-life studies

An SLR was conducted to identify HRQoL evidence in patients treated in the adjuvant setting for HER2-positive eBC. Detailed descriptions of the search strategy and extraction methods are provided in Appendix H.

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Summary of identified studies and results

The SLR identified a total of 25 studies, all reporting HRQoL data; no studies were identified that reported utility values that could directly inform the cost-effectiveness model. Given this, and the availability of EQ-5D data from the KATHERINE trial for eBC health states, none of the HRQoL studies identified by the SLR were considered further for the submission. A summary of the 25 identified HRQoL studies is provided in Appendix H.

B.3.4.4 Adverse reactions

Almost all patients experienced at least one AE during the treatment period (98.9% of patients in the trastuzumab emtansine arm vs 93.3% of patients in the trastuzumab arm) in the KATHERINE study. More than 95% of the AEs in both treatment arms were Grade 1 or 2 in severity.

The most frequently reported AEs (occurring in ≥20% of patients in either arm) were as follows: (expressed in the trastuzumab arm vs trastuzumab emtansine arm): fatigue (33.8% vs 49.5%), nausea (13.1% vs 41.6%), radiation skin injury (27.6% vs 25.4%), arthralgia (20.6% vs 25.9%), headache (16.9% vs 28.4%), aspartate aminotransferase increased (5.6% vs 28.4%) and hot flush (20.3% vs 12.8%).[63]

Adverse event data used in the model were taken directly from the KATHERINE study. There were two approaches that could have been adopted when quantifying AE impacts on HRQoL:

- **"Double-counting"** – Any disutility resulting from AEs will have been captured in the trial-collected HRQoL data. These data were used to derive the health state utilities in the base case economic analysis. It can therefore be assumed that incorporating an additional disutility can be considered double-counting.

- **Underestimation** – It can be assumed that trial derived utilities typically underestimate disutility associated with AEs. It is therefore reasonable to apply an additional disutility in the model.

In this analysis, it is assumed that any disutility resulting from treatment-related AEs is reflected in the EQ-5D responses from the KATHERINE study. This assumption was also utilised in TA569 (adjuvant pertuzumab).[71] It is possible that this approach underestimates the disutility associated with the AEs – particularly in the trastuzumab emtansine arm. Despite this, the difference in incidence of treatment-related Grade ≥3 AEs between the treatment arms is negligible. Ultimately, the omission of AE disutility does not significantly impact the overall cost-effectiveness results.

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

Utility has been applied cyclically in the model. The differing levels of utility across health states meant that HRQoL is not assumed constant over time. The section below outlines the utility sources used both in the base case setting and in the accompanying scenario analyses.

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Base case analysis

In the base case analysis, model health states have been categorised into "eBC" and "mBC" states. Table 33 shows the classification of health states. A different combination of data sources has been used to derive utilities for the eBC and mBC groups.

Table 33. Classification of eBC and mBC health states

eBC	mBC
• IDFS • Non-metastatic recurrence • Remission	• 1st line mBC • ≥2nd line mBC

Abbreviations: eBC: early breast cancer; IDFS: invasive disease-free survival; mBC: metastatic breast cancer.

eBC health state utilities

In accordance with the NICE reference case, utility estimates in the IDFS health state were derived from EQ-5D responses in the KATHERINE study. The UK tariff[92] was then applied directly to these responses in order to derive the utilities. Values for the non-metastatic recurrence and remission health states are predicated on assumptions, which are fully explained below.

No significant difference was found in the EQ-5D results of the two treatment arms in the KATHERINE study. This was because the schedule of EQ-5D administration was designed to capture differences in QoL across the various stages of disease, not between treatment arms. No obvious rationale exists for why HRQoL would radically differ depending on the treatment being received. This, in addition to the lack of a statistically significant difference, meant that EQ-5D responses from both treatment arms could be pooled. Pooling the responses increased the number of observations and consequently produced more robust utility estimates. These estimates were then applied across both arms of the model, regardless of whether a patient initially received trastuzumab emtansine or trastuzumab. For the sake of completeness, cost-effectiveness results have also been generated using utilities derived from the treatment-specific EQ-5D responses. This analysis is described in greater detail below and the results are available in Section B.3.8.3 of this submission.

In the IDFS health state, patients can be either "on" or "off" treatment. Treatment-related AEs mean that QoL can be expected to vary depending on whether or not a patient is receiving therapy. To account for this difference, specific utilities have been applied depending on whether or not a patient is in the "IDFS – on treatment" or "IDFS – off treatment" health state.

The EQ-5D-3L questionnaire was not administered to patients who had progressed in the KATHERINE study. As a result, no EQ-5D-3L data were available to derive utility estimates for the non-metastatic recurrence and remission health states. In the base case analysis, Non-metastatic recurrence and Remission utilities were assumed equal to "IDFS – on treatment" and "IDFS – off treatment", respectively. Similar equivalencies were also assumed in the neoadjuvant and adjuvant pertuzumab appraisals and were subsequently accepted by the NICE Committee.[71, 79] Nevertheless, these assumptions have been examined during the sensitivity/scenario analysis process. Results of these analyses are available in Section B.3.8.3.

The base case utilities for the eBC health states are reported in Table 34.

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mBC health state utilities

As mentioned above, the EQ-5D-3L was not administered to patients who had progressed in the KATHERINE study. It was therefore not possible to use KATHERINE-derived utility estimates for the mBC health states in the model. Base case utilities in the mBC health states have therefore been taken from a publication by Lloyd *et al.*[93]

Lloyd *et al.* report the results of 100 participants asked to value various health states and side-effects associated with mBC using the Standard Gamble technique. An overall value for PFS is found, and then deviations from this value (such as response to treatment and progression of disease) are reported as incremental changes from this baseline utility value. The utility values from this study have been used in various NICE Technology Appraisals in breast cancer.[71, 79, 80] Despite differences in patient population, the estimates reported in the Lloyd *et al.* publication are thought to be the best available evidence at the time of writing.

The utilities used in the base case analysis for both the early and metastatic health states are reported in Table 34.

Table 34. Summary of utility values used in the base case analysis

State	Utility (SE)	95% CI	Source	Reference in submission	Justification
Health state utilities – base case					
IDFS – On treatment	0.775 (0.009)	N/A	EQ-5D data from KATHERINE (pooled)	Section B.3.4.5	Derived from KATHERINE EQ-5D data. In-line with NICE reference case
IDFS – Off treatment	0.788 (0.010)	N/A			
Non metastatic recurrence	0.775 (0.009)	N/A	Assumption		
Remission	0.788 (0.010)	N/A			
First-line mBC	0.773 (0.004)	N/A	Lloyd *et al.*		Well-established source of utilities. Used in previous TAs in this disease area
Second+ line mBC	0.520 (0.004)	N/A			

Abbreviations: CI: confidence interval; eBC: early breast cancer; EQ-5D: EuroQol 5-Dimension questionnaire; IDFS: invasive disease-free survival; mBC: metastatic breast cancer; NICE: National Institute for Health and Care Excellence; SE: standard error; TA: Technology Assessment.

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Scenario analyses

Health state utility estimates in patients with HER2-positive BC are available from a range of published sources. To present a more complete evaluation, utilities from these sources have also been included here as scenario analyses. A brief description of these sources is given below, along with an overview of how the estimates were incorporated into the model.

eBC – the KATHERINE study EQ-5D (per treatment arm)

Pooled EQ-5D data were used to derive eBC utilities in the base case analysis. As mentioned above, no statistically significant difference was detected between the EQ-5D results of the two treatment arms. Nevertheless, a scenario analysis using treatment-specific EQ-5D data is included for completeness. The utility estimates used in this scenario are reported in Table 40.

eBC – Hedden *et al.*[94]

The publication by Hedden *et al.* is a cost-effectiveness analysis of the real-world effectiveness of adjuvant trastuzumab in Canada. The analysis centres on a HER2-positive population. This population is broadly in line with the population being evaluated in this appraisal. No estimates were reported according to presence of RID.

Health states in the Hedden *et al.* model differ slightly from the *de novo* analysis in this submission. Despite the differences, the health state definitions between the two analyses were deemed similar enough not to require any further adjustment of the utilities. Table 35 illustrates how the Hedden values have been applied in this analysis.

Table 35. eBC health state utilities used in the Hedden *et al.* analysis and de novo analysis

Health state in *de novo* analysis	Health state in Hedden *et al.*	Utility reported
IDFS – On chemotherapy	Post-surgical with adjuvant treatment	0.970
IDFS – On treatment/off chemotherapy	Post-surgical with adjuvant treatment	0.970
IDFS – Off treatment	Relapse-free survival	0.990
Non metastatic recurrence	Local relapse	0.750
Remission	Relapse-free survival	0.990

Abbreviations: IDFS: invasive disease-free survival.

eBC – Lidgren *et al.*[38]

The aim of this study was to describe HRQoL in different BC disease states using preference-based measures. A total of 361 consecutive patients with BC attending the BC outpatient clinic at Karolinska University Hospital, Solna, Sweden for outpatient visits between April and May 2005 were included in the study. The EQ-5D self-classifier and a direct time trade-off (TTO) question were used to estimate the HRQoL in different BC disease states.

The resultant EQ-5D values from this study are reported below, along with how they were assigned to the health states used in this analysis. Once again, no further adjustment was deemed necessary.

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Table 36. eBC health state utilities used in the Lidgren *et al.* analysis and de novo analysis

Health state in *de novo* analysis	Health state in Lidgren *et al.*	Utility reported
IDFS – On chemotherapy	First year after primary breast cancer	0.696
IDFS – On treatment/off chemotherapy	First year after primary breast cancer	0.696
IDFS – Off treatment	Second and following years after primary breast cancer/recurrence	0.779
Non metastatic recurrence	Second and following years after primary breast cancer/recurrence	0.779
Remission	Second and following years after primary breast cancer / recurrence	0.779

Abbreviations: IDFS: invasive disease-free survival.

mBC – Hedden *et al.*[94]

The Hedden *et al.* publication (cited above) also includes utility estimates for metastatic health states. As can be seen in Table 37, the mBC health states included in this model and in the Hedden *et al.* publication are almost equivalent.

Table 37. mBC health state utilities used in the Hedden *et al.* analysis and de novo analysis

Health state in *de novo* analysis	**Health state in Hedden *et al.***	**Utility reported**
First-line mBC	Non-progressive metastatic disease with or without trastuzumab	0.650
Second+ line mBC	Progressive metastatic disease	0.290

Abbreviations: mBC: metastatic breast cancer.

mBC – Lidgren *et al.*[38]

Much like the Hedden publication, the Lidgren study also reported utilities in both the eBC and mBC setting – see Table 38.

A single value has been reported for metastatic disease. In essence, the Lidgren study does not distinguish between first and second-line (non-progressed/progressed) metastatic disease. When this source is selected during scenario analysis, the utility associated with 2+ line mBC is assumed equal to the utility associated with first-line mBC.

Table 38. mBC health state utilities used in the Lidgren *et al.* analysis and de novo analysis

Health state in *de novo* analysis	**Health state in Lidgren *et al.***	**Utility reported**
First-line mBC	Metastatic disease	0.650
Second+ line mBC		0.290

Abbreviations: mBC: metastatic breast cancer.

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mBC – Paracha *et al*.[95]

This study analysed data from a large (n=906), repeated measure (11,451 observations), EQ-5D-3L dataset from the MARIANNE trial to estimate HSUVs. Patient responses to the EQ-5D-3L were used to derive utility values using the UK tariff. At the time of the analysis, 336 patients had experienced disease progression; whereas 354 deaths were observed in the trial. Two mixed models (random-coefficient) using an unstructured covariance structure were fitted to predict utility values according to baseline patient characteristics and key clinical outcomes. Time was included as a random effect. Key sets of variables considered for the multivariable mixed regression models were included. Table 39 reports the utilities quoted in this study and how they are applied to the health states in this analysis.

Table 39. mBC health state utilities used in the Paracha *et al.* analysis and de novo analysis

Health state in *de novo* analysis	Health state in Paracha *et al.*	Utility reported
First-line mBC	mBC - Stable disease with no toxicity	0.806
Second-line mBC	mBC progression	0.536

Abbreviations: mBC: metastatic breast cancer.

Age adjustment

As the population ages, HRQoL and utility are expected to decline because of an increased number of comorbidities. To reflect this trend, all health state utilities (base case and scenario analyses) have been adjusted over the time horizon to reflect the modelled patient's age. This adjustment prevents the health state utilities exceeding those of the age-matched UK population. The data used to perform this adjustment was taken from Ara *et al.*[96] Table 40 shows how the utilities have been assigned in the respective health state in the model.

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Table 40. Summary of utility values used in the cost-effectiveness analysis

State	Utility (SE)	95% CI	Source	Reference in submission	Justification
Health state utilities – base case					
IDFS – On treatment	0.775 (0.009)	N/A	EQ-5D from KATHERINE (pooled)	Section B.3.4.5	Derived from KATHERINE EQ-5D data. In-line with NICE reference case
IDFS – Off treatment	0.788 (0.010)	N/A			
Non metastatic recurrence	0.775 (0.009)	N/A	Assumption		
Remission	0.788 (0.010)	N/A			
First-line mBC	0.765 (0.004)	N/A	Lloyd *et al.*		Well-established source of utilities. Used in previous TAs in this disease area
Second+ line mBC	0.508 (0.004)	N/A			
eBC health state utilities – Scenario analysis					
IDFS – On treatment	TE = 0.774 (0.009) Trast. = 0.776 (0.010)	N/A	EQ-5D from KATHERINE (per treatment arm)	Section B.3.4.5	Utilities derived from KATHERINE EQ-5D data. In-line with NICE reference case
IDFS – Off treatment	TE = 0.784 (0.010) Trast. = 0.791 (0.010)	N/A			
Non metastatic recurrence	TE = 0.774 (0.009) Trast. = 0.776 (0.010)	N/A	Assumption		
Remission	TE = 0.784 (0.010) Trast. = 0.791 (0.010)	N/A			
eBC health state utilities – Scenario analysis					
IDFS – On chemo	0.97 (0.026)	0.94-0.99	Hedden *et al.*	Section B.3.4.5	Well-established source of utilities. Used in previous TAs in this disease area
IDFS – On treatment/off chemotherapy	0.97 (0.026)	0.94-0.99			
IDFS – Off treatment	0.99 (0.010)	0.98-1.00			
Non metastatic recurrence	0.75 (0.194)	0.56-0.94			
Remission	0.99 (0.010)	0.98-1.00			

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State	Utility (SE)	95% CI	Source	Reference in submission	Justification
eBC health state utilities – Scenario analysis					
IDFS – On chemo	0.696	0.63-0.75	Lidgren *et al.*	Section B.3.4.5	Well-established source of utilities. Used in previous TAs in this disease area
IDFS – On treatment/off chemotherapy	0.696	0.63-0.75			
IDFS – Off treatment	0.779	0.75-0.81			
Non metastatic recurrence	0.779	0.75-0.81			
Remission	0.779	0.75-0.81			
mBC health state utilities – Scenario analysis					
First-line mBC	0.65	0.50-0.80	Hedden *et al.*	Section B.3.4.5	Well-established source of utilities. Used in previous TAs in this disease area
Second+ line mBC	0.29	0.16-0.41			
mBC health state utilities – Scenario analysis					
First-line mBC	0.685	0.620-0.735	Lidgren *et al.*	Section B.3.4.5	Well-established source of utilities. Used in previous TAs in this disease area
Second+ line mBC	0.685	0.620-0.735			
mBC health state utilities – Scenario analysis					
First-line mBC	0.806	0.645-0.967	Paracha *et al.*	Section B.3.4.5	Well-established source of utilities. Used in previous TAs in this disease area
Second+ line mBC	0.536	0.423-0.643			

Abbreviations: CI: confidence interval; eBC: early breast cancer; EQ-5D: EuroQol 5-Dimension questionnaire; IDFS: invasive disease-free survival; mBC: metastatic breast cancer; NICE: National Institute for Health and Care Excellence; SE: standard error; TA: Technology Assessment; TE: trastuzumab emtansine; Trast: trastuzumab.

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B.3.5 *Cost and healthcare resource use identification, measurement and valuation*

B.3.5.1 Intervention and comparators' costs and resource use

Drug acquisition costs – Intervention and comparator

Trastuzumab emtansine

Trastuzumab emtansine is available as 100 mg and 160 mg vials with list prices of £1,641.01 and £2,625.62, respectively.[97] The recommended dose of trastuzumab emtansine is 3.6 mg/kg, administered as an IV infusion (no loading doses are required). Trastuzumab emtansine is administered on Day 1 of a 3-week cycle (q3w) for a maximum of up to 14 cycles.

Trastuzumab emtansine, in the adjuvant and metastatic settings, is subject to a confidential PAS between the Department of Health and Roche Products Ltd. Trastuzumab emtansine (100 mg vial list price = £1,641.01 and 160 mg vial list price = £2,625.62) is offered at a simple discount of [redacted]

Trastuzumab

There are three different forms of trastuzumab included in this economic analysis:

- Trastuzumab IV: branded trastuzumab (Herceptin) administered as an IV infusion
- Trastuzumab SC: branded trastuzumab (Herceptin) administered as an SC injection
- Trastuzumab biosimilar: trastuzumab biosimilar administered as an IV infusion

Branded trastuzumab (Herceptin) IV

The list price of branded trastuzumab IV is £407.40 for a 150 mg vial. The recommended initial loading dose of trastuzumab is 8 mg/kg, followed every three weeks thereafter by a maintenance dose of 6 mg/kg body weight.[98]

Trastuzumab SC

Trastuzumab SC is available as a 600 mg vial for a list price of £1,222.20. The SC form of trastuzumab is given as a fixed dose of 600 mg, no loading dose is necessary.[98]

Herceptin (trastuzumab) is also subject to a confidential CAA. [redacted]

Trastuzumab biosimilar

Trastuzumab biosimilars are now readily available in the UK. The biosimilars are administered intravenously at a dosing and treatment schedule identical to that of branded trastuzumab (Herceptin IV).[98]

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The list price of trastuzumab biosimilars is now public knowledge (see Table 41). It should be noted however that these products underwent a national tendering process in Q3 of 2018. As part of this tendering process, companies were able to offer confidential discounts to the NHS. The net price of these drugs was a main driver of cost-effectiveness in the recent NICE appraisal of pertuzumab in the adjuvant treatment of HER2-positive early breast cancer. Consequently, this issue was discussed at length during the appraisal consultation documents and committee meetings. Market intelligence provided by the Company and Professor Clark (Clinical lead for the Cancer Drugs Fund) allowed the Appraisal Committee to rule that the average discount offered on these products is 70.00% off the list price of branded trastuzumab (Herceptin) IV. This figure was incorporated into the Committee's preferred assumptions and subsequently used for the purposes of decision making.

Table 41. List price of trastuzumab biosimilars available in the UK[98]

Brand name	Manufacturer	List price
Herzuma	Napp Pharmaceuticals Ltd	£366.66
Kanjinti	Amgen Ltd.	
Ontruzant	MSD Ltd.	
Trazimera	Pfizer Ltd.	

Abbreviations: MSD: Merck Sharp & Dohme.

The base case settings of this analysis will reflect the UK market at the time of submission (September 2019). Trastuzumab biosimilars will be costed at a discount of 70.00% of the branded trastuzumab (Herceptin) IV list price (net price = £122.22 per 150 mg vial). This approach is also consistent with the decision-making in TA569 (NICE appraisal of pertuzumab for the adjuvant treatment of HER2-positive early stage breast cancer).[71]

Trastuzumab usage in the comparator arm of the cost-effectiveness model

As mentioned above, there are three forms of trastuzumab currently available in the UK. The technology acquisition cost in the comparator arm is a weighted average of the prices and market shares of each of these forms of trastuzumab.

The price differential between trastuzumab biosimilars and branded (Herceptin) trastuzumab IV is such that there is no plausible reason as to why a physician would prescribe Herceptin instead of a biosimilar. As a result, there is no usage of branded trastuzumab (Herceptin) IV in the base case analysis. This assumption was also validated during TA569 and was incorporated into decision-making.

In TA569, 95% of the trastuzumab monotherapy market was assumed to be Herceptin SC (March 2019). This figure was first suggested by Professor Clark and subsequently ratified by the Appraisal Committee. Following the advent of trastuzumab biosimilars, obvious cost-savings can be realised through the prescription of these products rather than Herceptin SC. To date, there has been no mandate to treat patients with the cheaper biosimilars rather than the more expensive SC formulation. Instead, the choice of trastuzumab formulation is still at the discretion of patients. The strong patient preference for a SC formulation (rather than IV) has resulted in limited erosion of the Herceptin SC market share, a fact which is also reflected in recent market research collected by the Company. In conclusion, the original assumption (market share of subcutaneous trastuzumab = 95%) used in TA569 is also utilised in the base case analysis.[71]

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For clarity, trastuzumab usage in the base case economic analysis is presented below (see Table 42).

Table 42. Trastuzumab usage in the base case setting of the economic model

Treatment arm	Form of trastuzumab	Proportion of patients	Reference
Comparator	Branded SC	95.00%	TA569[71]
	Biosimilar IV	5.00%	

Abbreviations: IV: intravenous; SC: subcutaneous; TA: technology appraisal.

The launch of biosimilars and the conclusion of the tendering process occurred in Q2 and Q3 of 2018, respectively. It is therefore the belief of the Company that these shares can reasonably be assumed to reflect a market in "steady state". No major evolution of these figures is expected in the near future. Assumptions around trastuzumab biosimilar market share have been examined as part of the scenario analyses of this submission.

Drug acquisition costs – Subsequent treatments

Upon experiencing a recurrence, patients are assumed to receive additional treatment. A variety of different therapies are available to UK patients, and which treatment they receive depends on the disease setting (i.e. non-metastatic recurrence, first-line mBC, or second+ line mBC).

The acquisition costs of subsequent therapies included in the model are detailed below in Table 43. As mentioned above, trastuzumab emtansine, trastuzumab IV and trastuzumab SC are subject to confidential discounts. Roche also offers a CAA on pertuzumab, which equates to a 58.00% discount on list price in the metastatic setting.

Please note: docetaxel, paclitaxel, lapatinib, and capecitabine are available in various vial compositions/pack sizes in the UK. In the case of lapatinib and capecitabine (tablet form) only the best value options (i.e. cheapest price per mg) have been included in the model. Paclitaxel and docetaxel are administered intravenously. The two most frequently prescribed compositions (according to eMIT) have been incorporated into the model.[99]

Table 43. Drug acquisition costs (subsequent treatments)

Drug	Concentration/amount	Cost per pack/vial	Source
Pertuzumab – mBC	420 mg/14 ml	[redacted]	BNF – 2019
Trastuzumab biosimilar IV	150 mg	£122.22	BNF – 2019
Trastuzumab SC	600 mg / 5 ml	[redacted]	BNF – 2019
Trastuzumab emtansine	100 mg	[redacted]	BNF – 2019
	160 mg	[redacted]	
Docetaxel	20 mg/1 ml	£11.61	eMIT – June, 2018
	80 mg/4 ml	£28.48	
Paclitaxel	30 mg/5 ml	£8.62	eMIT – June, 2018
	100 mg/16.7 ml	£9.49	
Lapatinib	250 mg (105 tablets)	£1,206.45	BNF – 2019

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Drug	Concentration/amount	Cost per pack/vial	Source
Capecitabine	150 mg (60 tablets)	£30.00	BNF – 2019

Abbreviations: BNF: British National Formulary; eMIT: electronic market information tool; IV: intravenous; mBC: metastatic breast cancer; SC, subcutaneous.

The total costs of these subsequent lines of treatment are calculated as a weighted average based on current market shares in the UK. Table 44 details the market shares, and the average treatment duration in each health state. The quoted market shares have been primarily ascertained through internal market research conducted by the Company. In situations where market share data were not available, assumptions (detailed below) have been utilised. In terms of the duration of treatment data, these have been primarily taken from economic models in previous NICE appraisals.

Table 44. Subsequent therapy treatment durations and market shares

Health state	Treatment regimen	# cycles	Source	Market share	Source
Non-metastatic recurrence	Trastuzumab biosimilar IV + docetaxel	18	Assumption	95.00%	Equal to H arm in IDFS
	Trastuzumab SC + docetaxel	18	Assumption	5.00%	
First-line mBC – Early recurrence	Pertuzumab + trastuzumab + chemotherapy	37.39	TA509 – P in mBC	Trastuzumab emtansine arm = 75.00% Trast. Arm = 0.00%	Market research & assumptions
	Trastuzumab biosimilar IV + chemotherapy	23.65	TA509 – P in mBC	Trastuzumab emtansine arm = 4.00% Trast. Arm = 4.00%	
	Trastuzumab SC + docetaxel	23.65	TA509 – P in mBC	Trastuzumab emtansine arm = 13.00% Trast. Arm = 13.00%	
	Trastuzumab emtansine	19.3	Assumed equal to TA458 – K in 2L mBC	Trastuzumab emtansine arm = 0.00% Trast. Arm = 75.00%	
	Chemotherapy	6.0	Assumption	Trastuzumab emtansine arm = 8.00% Trast. Arm = 8.00%	
First-line mBC	Pertuzumab + trastuzumab biosimilar IV + docetaxel	37.39	TA509 – P in mBC	75.00%	Market research
	Trastuzumab biosimilar IV + docetaxel	23.65	TA509 – P in mBC	4.00%	
	Trastuzumab SC + docetaxel	23.65	TA509 – P in mBC	13.00%	
	Chemotherapy	6.00	Assumption	8.00%	Assumption

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Health state	Treatment regimen	# cycles	Source	Market share	Source
Second + line mBC – Early recurrence	Pertuzumab + trastuzumab biosimilar IV + docetaxel	9.36	Assumed equal to Trast. + chemo	10.00%	Market research
	Trastuzumab biosimilar IV + chemotherapy	9.36	TA458 – K in 2L mBC	4.00%	
	Trastuzumab SC + chemotherapy	9.36	TA458 – K in 2L mBC	3.00%	
	Trastuzumab emtansine	19.33	TA458 – K in 2L mBC	78.00%	
	Chemotherapy	6.00	Assumption	4.00%	Assumption
Second + line mBC	Pertuzumab + trastuzumab biosimilar IV + docetaxel	9.36	Assumed equal to Trast. + chemo	10.00%	Market research
	Trastuzumab biosimilar IV + capecitabine	9.36	TA458 – K in 2L mBC	4.00%	
	Trastuzumab SC + capecitabine	9.36	TA458 – K in 2L mBC	3.00%	
	Trastuzumab emtansine	19.33	TA458 – K in 2L mBC	78.00%	
	Lapatinib	12.29	TA458 – K in 2L mBC	1.00%	
	Chemotherapy	6.00	Assumption	8.00%	Assumption

Abbreviations: IV: intravenous; K: trastuzumab emtansine; mBC: metastatic breast cancer; NHSE: National Health Service England; P: pertuzumab; SC: subcutaneous.

Key subsequent therapy assumptions

In order to bridge data gaps or avoid unnecessary complexity, some key assumptions have been utilised during the costing of subsequent therapies. These assumptions are briefly detailed below:

i) Trastuzumab biosimilar vs branded trastuzumab IV – It has been assumed that all IV trastuzumab used in the supportive care setting is biosimilar. This is aligned with the assumption in the IDFS health state.

Additionally, pertuzumab is not commissioned in combination with Herceptin SC (only trastuzumab IV) in the UK, therefore it has been assumed that all pertuzumab is also used in combination with trastuzumab biosimilar IV.

ii) First-line mBC – early relapser – Expert opinion elicited by the Company signals that physicians would not re-challenge patients with trastuzumab emtansine in the 1st-line mBC setting after trastuzumab emtansine therapy in the adjuvant setting. Supportive care in the 1L mBC – early relapser health state has therefore been stratified according to treatment received in the adjuvant setting. It has been assumed that in the trastuzumab emtansine arm, patients would expect to receive pertuzumab + trastuzumab + chemotherapy instead of trastuzumab emtansine.

iii) Pertuzumab + trastuzumab + chemotherapy usage in ≥2L mBC – Pertuzumab + trastuzumab + chemotherapy is only reimbursed in patients who have not had prior anti-HER2 therapy for

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their metastatic disease. The market research in 1L mBC showed that a small proportion of generic chemotherapy was being used, therefore there is some usage of pertuzumab + trastuzumab + chemotherapy in the 2L setting. The duration of treatment in this setting has been assumed equal to that of the trastuzumab arm in the trastuzumab emtansine in 2L mBC cost-effectiveness model (TA458).[100]

iv) Chemotherapy – In cases where generic chemotherapy was used, the specific therapy was not always reported in the market research. Chemotherapy has therefore been costed as docetaxel.

It is important to highlight here that the market shares and costings of subsequent therapies are not a major driver of cost-effectiveness results. The effect of these assumptions should not be overemphasised.

Administration and pharmacy costs

Administration costs associated with each technology have been sourced using the National Tariff for Chemotherapy Regimens list 2017–2018, the NHS reference costs schedule 2017/18, and the Personal Social Services Research Unit (PSSRU) costs 2017 document.[101, 102]

Much like TA569, this appraisal is evaluating the use of anti-HER2 therapies in the adjuvant treatment of early HER2-positive breast cancer. TA569 was therefore used as a guide when calculating the administration costs in this analysis. The costs and assumptions used in TA569 were judged to be comprehensive and reasonable by both the ERG and the Appraisal Committee.[71]

According to the National Tariff of chemotherapy regimens, the administration of the initial dose of trastuzumab emtansine IV and trastuzumab biosimilar IV should be costed using code SB14Z in the NHS reference costs schedule 2017/18 (Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance [chemotherapy delivery: day case]) whereas the administration cost for subsequent (maintenance) cycles should equate to SB13Z of the reference schedule (Deliver more Complex Parenteral Chemotherapy at First Attendance (chemotherapy delivery: day case)). Despite the lack of loading doses, differing costs have been used for the initial and subsequent doses. This is designed to reflect the difference in delivery time. Both trastuzumab emtansine and trastuzumab IV initial doses should comprise of a 90-minute IV infusion. If the initial dose is well tolerated, subsequent doses can then be given as 30-minute infusions.[2, 103] The costs quoted above are applied to all treatments that are administered via IV infusion.

The cost of a subcutaneous administration of trastuzumab is assumed equivalent to SB12Z (Deliver Simple Parenteral Chemotherapy at First Attendance [chemotherapy delivery: day case]) according to the National Tariff of chemotherapy regimens.[101]

An additional administration cost has been included in the model to account for the pharmacist's time during the prescription and preparation of treatments. It has been assumed that each administration will require 12 minutes of a pharmacist's time, as per Millar *et al*.[104] This cost is applied to every administration, regardless of treatment or treatment arm. When a medication is administered orally, the pharmacy cost is the only administration cost applied. A full breakdown of administration costs applied in the model is given in Table 45.

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As stated above, the codes and assumptions outlined in this subsection were also applied in TA569 and were subsequently accepted by the ERG and the Appraisal Committee.

Table 45. Drug administration costs

Drug	First cycle			Subsequent cycles		
	NHS reference code	Cost per admin.	Source	NHS reference code	Cost per admin.	Source
IV delivery	SB14Z[a]	£374.52	NHS ref. costs 2017/18	SB13Z[b]	£309.22	NHS ref. costs 2017/18
H SC delivery	SB12Z[c]	£247.74	NHS ref. costs 2017/18	SB12Z[c]	£247.74	NHS ref. costs 2017/18
Pharmacy cost	N/A	£9.27[d]	PSSRU 2018	N/A	£9.27[d]	PSSRU 2018

Footnotes: [a]Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance – day case. [b]Deliver more Complex Parenteral Chemotherapy at First Attendance – day case. [c]Deliver Simple Parenteral Chemotherapy at First Attendance - day case. [d]Average hourly cost of "Hospital-based health care staff (band 6) – 12 minutes of time.
Abbreviations: admin: administration; IV: intravenous; N/A: not applicable; NHS: National Health Service; PSSRU: Personal and Social Services Research Unit; ref.: reference; SC: subcutaneous.

B.3.5.2 Health-state unit costs and resource use

Health state costs have been applied cyclically and irrespective of treatment arm throughout the duration of the model time horizon. The cost and resource use required in each health state is outlined below.

The supportive care regimens and assumptions used here are aligned to those used in the pertuzumab adjuvant appraisal. These regimens and assumptions have been validated by numerous clinical experts, and have consequently been accepted by the ERG and appraisal committee.

IDFS health state

Resource use and supportive care regimens are expected to differ depending on how long a patient has remained in the IDFS health state. Specific supportive care costs have been derived and applied in the following time periods:

- Year 1
- Years 2–5
- Years ≥5

Patients can remain on adjuvant treatment in the IDFS health state for a maximum of 14 cycles (42 weeks, ~9.5 months). Typically, not all patients will complete the full 14 cycles of therapy, a proportion may discontinue treatment due to, for example, safety concerns. As a result, the IDFS health state in the first year of the model time horizon will contain two different subpopulations: i) IDFS – on treatment and ii) IDFS – off treatment. Although resource use and supportive care is expected to be minimal in this health state, the supportive care provided would be expected to differ between these two populations. This difference in supportive care regimens has not been

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reflected in the model. The Company acknowledges that theoretically this approach would be more accurate. However, the incremental difference in discontinuation of anti-HER2 therapy by IDFS patients between the two arms in the first year is considered minimal (19% and 19.9% in trastuzumab and trastuzumab emtansine arm, respectively). This would ultimately translate into a negligible impact on overall cost-effectiveness results.

The resource use assumed here is in line with the "IDFS" health state of the adjuvant pertuzumab appraisal. The cyclical costs applied in the EFS and IDFS states are still very much comparable.

Table 46. IDFS health state – resource use and supportive care costs

Resource	Unit cost	Source	% of patients	Frequency per year		
				Year 1	Years 2–5	Years ⩾5
Oncologist visit	£130.00	NHS ref. 2017/18 – 800	100%	2	0	0
GP visit	£37.00	PSSRU 2018 – page 162	100%	0	1	1
Mammogram	£11.34	TA767 – NHS BSP (inflated)	100%	1	1	0
ECHO scan	£70.36	NHS ref. 2017/18 – RD51A	70%	4	0	0
MUGA scan	£249.00	NHS ref. 2017/18 – RN22Z	30%			
Total base case cost per (four-week) cycle:				£63.93	£7.11	£3.08

Abbreviations: BSP: breast screening programme; ECHO: echocardiogram; GP: general practitioner; MUGA: multigated acquisition; NHS: National Health Service; PSSRU: Personal and Social Services Research Unit.

Non-metastatic recurrence

Patients who experience a non-metastatic recurrence undergo an additional 12 months of adjuvant therapy. The supportive care regimen in this state is assumed equal to that of year one in IDFS (on treatment). In addition, it has also been assumed that 75% of patients will receive a computerised tomography (CT) scan to facilitate the monitoring of the recurrence (Table 47). This assumption has been validated by expert clinicians at a Roche advisory board. Assumed resource use in this health state is also aligned with the adjuvant pertuzumab submission.

Table 47. Non-metastatic recurrence state – resource use and supportive care costs

Resource	Unit cost	Source	Proportion of patients (%)	Frequency per year	Cost per cycle
Oncologist visit	£132.10	NHS ref. 2017/18 – WF01A-800	100%	2	£22.02
Mammogram	£11.83	TA767 – NHS BSP (inflated)	100%	1	£0.99
ECHO scan	£107.84	NHS ref. 2017/18 – RD51A	70%	4	£53.52
MUGA scan	£283.61	NHS ref. 2017/18 – RN22Z	30%		

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Resource	Unit cost	Source	Proportion of patients (%)	Frequency per year	Cost per cycle
CT scan	£90.47	NHS ref. - 2017/18 – RD20A	75%	2	£11.31
Total base case cost per (monthly) cycle: £87.83					

Abbreviations: BSP: breast screening programme; CT: computerised tomography; ECHO: echocardiogram; GP: general practitioner; MUGA: multigated acquisition; NHS: National Health Service.

Remission

In the NICE appraisal of pertuzumab in the neoadjuvant setting (TA424) it was assumed that patients in remission would incur the same health state costs as those in year 1–2 of EFS. Patients in remission in this model receive an identical supportive care regimen to those patients who are in year 2–5 of IDFS (see Table 46). This updated assumption is aligned to the approach taken in the recent appraisal of adjuvant pertuzumab (TA569).

Metastatic (first-line mBC and 2nd + line mBC)

In the metastatic health states, response to treatment is assessed using outpatient visits, CT scans, cardiac monitoring, and health care practitioner time. Furthermore, in clinical trials a CT scan is typically conducted every three months to assess whether a person's disease has progressed. Advice from clinicians indicated that the frequency of CT scans may vary depending on treatment centre. In light of this, and the assumptions made in previous NICE multiple technology appraisals (MTAs) and Scottish Medicine Consortium (SMC) submissions, the model applies a conservative estimate of one CT scan per year in the first-line mBC health state.

Costs and assumptions described here are in line with those used in the appraisals of pertuzumab in the neoadjuvant and adjuvant setting.[71, 79] A full breakdown of the supportive care costs for the mBC health states are summarised in Table 48 and Table 49. Please note that mBC resource use is not assumed to vary according to the timing of recurrence. The costs quoted in the tables below have been applied equally to both "early" and "late" relapsers.

Table 48. First-line mBC state – resource use and supportive care costs

Items	Frequency (yearly)	Unit cost per contact	Proportion of patients	Cost sources	Resource use sources
Cycle costs					
GP visit	12	£37.40	100%	PSSRU 2018 – page 127	Assumption
ECHO Scan	2	£107.84	70%	NHS ref. 2017/18 – RD51A	CG81
MUGA Scan	2	£283.61	30%	NHS ref. 2017/18 – RN22Z	CG81
Clinical nurse specialist	12	£77.98	100%	NHS ref. 2017/18 – N09AF	CG81

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Items	Frequency (yearly)	Unit cost per contact	Proportion of patients	Cost sources	Resource use sources
District Nurse (home visit)	22	£38.45	100%	NHS ref. 2017/18 - N02AF	CG81
CT Scan	One off cost	£90.47	75%	NHS ref. 2017/18 – RD20A	Ad. board (03/2013); CG81
Social worker	One off cost	£84.00	100%	PSSRU 2018 – 11.1 – page 139	CG81
Total base case cost per (monthly) cycle = £231.70					

Abbreviations: CT: computerised tomography; ECHO: echocardiogram; GP: general practitioner; MUGA: multigated acquisition; NHS: National Health Service; PSSRU: Personal and Social Services Research Unit.

Table 49. Second + line mBC state – resource use and supportive care costs

Items	Frequency (yearly)	Unit cost per contact	Proportion of patients	Cost sources	Resource use sources
GP visit	12	£37.40	100%	PSSRU 2018 – page 127	Assumption
Clinical nurse specialist	12	£77.98	100%	NHS ref. 2017/18 – N09AF	CG81
District Nurse (home visit)	24	£38.45	100%	NHS ref. 2017/18 – N02AF	CG81
Average monthly supportive care cost = £192.28					

Abbreviations: GP: general practitioner; NHS: National Health Service; PSSRU: Personal and Social Services Research Unit.

Validation of health state costs and resource use

Given the model structures used, similar health state costs have been included in both the adjuvant and neoadjuvant appraisals of pertuzumab. Cyclical supportive care costs used in all three models are reported in Table 50.

Table 50. Comparison of health state costs in the neoadjuvant and adjuvant appraisals

TA424 – pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer[79]		TA569 – pertuzumab for the adjuvant treatment of HER2-positive breast cancer[71]		ID1516 - Trastuzumab emtansine for adjuvant treatment of HER2-positive early breast cancer	
Health state	**Cycle cost**	**Health state**	**Cycle cost**	**Health state**	**Cycle cost**
EFS	Year 1–2 = £67.85 Year 3–5 = £15.11 ≥5 years = £3.83	IDFS	Year 1-2 (on treatment) = £63.93 Year 3–5 = £7.11 ≥5 years = £3.08	IDFS	Year 1-2 =£76.57 Year 3-5 = £4.12 ≥5 years = £3.12

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TA424 – pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer[79]		TA569 – pertuzumab for the adjuvant treatment of HER2-positive breast cancer[71]		ID1516 - Trastuzumab emtansine for adjuvant treatment of HER2-positive early breast cancer	
Health state	**Cycle cost**	**Health state**	**Cycle cost**	**Health state**	**Cycle cost**
Locoregional recurrence	£73.97	Non-metastatic recurrence	£76.80	Non-metastatic recurrence	£87.88
Remission	£67.85	Remission	£7.11	Remission	£4.15
mBC – non-progressed	£232.00	First-line mBC	£214.78	First-line mBC	£231.70
mBC – progressed	£185.00	Second+ line mBC	£180.85	Second+ line mBC	£192.28

Abbreviations: EFS: event-free survival; HER2: human epidermal growth factor receptor 2; IDFS: invasive disease-free survival; mBC: metastatic breast cancer.

Table 50 illustrates that the cyclical costs reported in this appraisal are in close proximity to those used in the neoadjuvant and adjuvant submissions.

B.3.5.3 Adverse reaction unit costs and resource use

IDFS

Following the guidance received in recent technology appraisals in this disease area,[71, 79, 80] the criteria used for the inclusion/exclusion of an AE in the model are outlined below:

- **Only AEs of Grade ≥3:** Typically, clinicians will only intervene and treat an AE if it is severe enough to be classified as Grade 3 or above. The costs and HRQoL effects associated with Grade 1 and 2 events are therefore assumed to be negligible and hence omitted from this analysis.
- **Occur in ≥2% of patients:** A reasonable assumption was made that an AE must have occurred in at least 2% of the study population to be included in the model.

The data used to inform this aspect of the analysis were taken directly from the KATHERINE trial. The frequency and cost of treating these AEs are reported in Table 51. The principal source of cost information was the NHS reference cost schedule 2016–2017. Specific costs for treating these AEs were not reported in the most recent version of the schedule (2017/2018), therefore costs were taken from the 2016-2017 edition and inflated in order to reflect the current price year.

Table 51. List of adverse events and costs included in the economic model

Adverse events	Frequency		Treatment	Event cost	Source
	Trastuzumab emtansine (n=740)	Trastuzumab (n=720)			
Platelet count decreased	42 (5.68%)	0 (0.00%)	Platelet disorder drugs – Band 1 – Total HRG activity	£1,712.99[a]	NHS Ref. 2016/17 – XD43Z

Footnotes: [a]Equal to £1,641.93 in 2016 before being inflated to reflect the 2019 price year.
Abbreviations: CC: Casemix companion; NHS: National Health Service.

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For ease of implementation, these costs have been applied to patients in cycle one of the model. In reality, AEs can occur at any point while a patient receives treatment. The application of the costs at this timepoint in the analysis is expected to result in an overestimation of AE costs in the analysis. Nevertheless, both treatment-related side-effect profiles are relatively mild and the costs associated with AEs is thought to have a negligible impact on the overall cost-effectiveness results.

The methodology used to quantify the cost impact of AEs is analogous to the methodology used in the adjuvant pertuzumab appraisal.[71]

Subsequent therapies

As per Section B.3.5.1, patients will receive subsequent therapies following progression. The cost of managing treatment-related AEs on these subsequent therapies is also accounted for as part of "supportive care". The primary source of these management costs are cost-effectiveness models from previous NICE appraisals in which the regimens were evaluated as either interventions or comparators.

Many of these costings were calculated several years ago, therefore these costs have been inflated in order to reflect the current price year. In Table 52, weekly management costs (per patient) are given for each subsequent therapy included in this analysis.

Table 52. Adverse event management costs for subsequent therapies (per patient, per week)

Regimen	Original cost	Original price year	Inflated cost	Reference
Trastuzumab[a] + docetaxel	£13.51	2015	£14.85	T arm in PT + chemo in mBC appraisal – TA509[80]
Pertuzumab + trastuzumab[a] + docetaxel	£15.09	2015	£16.59	PT + chemo arm in PH in mBC appraisal – TA509[80]
Chemotherapy	£1.28	2017	£1.34	Capecitabine arm in trastuzumab emtansine in mBC appraisal – TA458[100]
Trastuzumab emtansine	£2.12	2017	£2.21	Trastuzumab emtansine arm in trastuzumab emtansine in mBC appraisal – TA458[100]
Lapatinib + capecitabine	£7.21	2017	£7.52	Lap + cap arm in trastuzumab emtansine in mBC appraisal – TA458[100]

Footnotes: [a]Applies to all types of trastuzumab in the analysis – branded IV, branded SC, and biosimilar.
Abbreviations: cap: capecitabine; lap: lapatinib; mBC: metastatic breast cancer; PT + chemo: pertuzumab + trastuzumab + chemotherapy; T: trastuzumab.

B.3.5.4 Miscellaneous unit costs and resource use

No other costs and resource use have been identified as suitable for inclusion in this analysis. All relevant inputs have been described and justified in the preceding sections.

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B.3.6 *Summary of base-case analysis inputs and assumptions*

B.3.6.1 Summary of base-case analysis inputs

Table 53 summarises all key variables applied in the base case of the economic model.

Table 53. Summary of variables applied in the base case setting of the economic model

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
General model parameters			
Time horizon	51 years	Fixed	Section B.3.2
Discount rate – efficacy	3.50%	Fixed	
Discount rate – costs	3.50%	Fixed	
Age	49 years	Fixed	Section B.2.3.3
Body weight	71.42 kg	Fixed	
Height	163.10 cm	Fixed	
Body surface area	1.77 cm	Fixed	
Average serum creatinine	0.85	Fixed	
Clinical parameters			
Treatment duration	Trial-observed	Fixed	Section B.3.3
IDFS parametric distribution	Log-logistic	Fixed	
% of metastatic recurrences – Early relapser	Trastuzumab emtansine = 85.71% Trast. = 72.29%	Fixed	
% of non-metastatic recurrences – Early relapser	Trastuzumab emtansine = 14.29% Trast. = 27.71%	Fixed	

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Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
% of metastatic recurrences	Trastuzumab emtansine = 89.36% Trast. = 73.42%	Fixed	
% of non-metastatic recurrences	Trastuzumab emtansine = 10.64% Trast. = 26.58%	Fixed	
Incremental treatment effect begins to wane	4 years (48 months)	Fixed	
Incremental treatment effect ceases	7 years (84 months)	Fixed	
“Cure” proportion is applied	3 years (36 months)	Fixed	
Maximum cure is reached	10 years (120 months)	Fixed	
Maximum “cure” proportion	95.00%	Fixed	
Definition of “early relapser” (ER)	Recurrence within 18 months of adjuvant therapy initiation	Fixed	
Transition probabilities	Section B.3.3	Multivariate normal	
Treatment share in first-line metastatic setting			
Pertuzumab + trastuzumab + chemotherapy	75.00%	Fixed	
Trastuzumab SC	13.00%	Fixed	
Trastuzumab biosimilar	4.00%	Fixed	
Chemotherapy	8.00%	Fixed	
Treatment share in second-line metastatic setting			
Trastuzumab emtansine	78.00%	Fixed	
Trastuzumab SC	3.00%	Fixed	
Trastuzumab biosimilar	4.00%	Fixed	
Lapatinib	1.00%	Fixed	
Pertuzumab + trast. bx + chemo	10.00%	Fixed	
Chemotherapy	4.00%	Fixed	

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Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Utilities – base case			
IDFS – on treatment	0.775	Gamma	Section B.3.4.5
IDFS – off treatment	0.788	Gamma	
Non-metastatic recurrence	0.775	Gamma	
Remission	0.788	Gamma	
First-line metastatic recurrence	0.765	Gamma	
Second + line metastatic recurrence	0.508	Gamma	
Technology acquisition costs (unit costs)			
Trastuzumab emtansine (100 mg)	[redacted]	Fixed	Section B.3.5
Trastuzumab emtansine (160 mg)	[redacted]	Fixed	
Branded trastuzumab IV (150 mg)	[redacted]	Fixed	
Trastuzumab biosimilar (150 mg)	£122.22	Fixed	
Trastuzumab SC (600 mg)	[redacted]	Fixed	
Pertuzumab (420 mg) – mBC	[redacted]	Fixed	
Docetaxel (20 mg / 1 ml)	£11.61	Fixed	
Docetaxel (160 mg / 8 ml)	£25.59	Fixed	
Paclitaxel (30 mg / 5 ml)	£8.62	Fixed	
Paclitaxel (100 mg / 16.7 ml)	£9.49	Fixed	
Lapatanib (250 x 84 mg)	£965.16	Fixed	
Capecitabine (120 x 500 mg)	£26.71	Fixed	
Trastuzumab usage			
Trastuzumab IV market share (trastuzumab arm)	00.00%	Fixed	Section B.3.5
Trastuzumab SC market share (trastuzumab arm)	95.00%	Fixed	

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Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Biosimilar market share (both arms)	5.00%	Fixed	
Administration costs			
IV administration cost – First cycle	£374.52	Gamma (£280.89-£468.15)	Section B.3.5
IV administration cost – subsequent cycles	£309.22	Gamma (£231.92-£386.53)	
SC administration cost – all cycles	£247.74	Gamma (£185.81-£309.68)	
Pharmacy preparation	£9.27	Gamma (£6.95-£11.58)	
Health state supportive care costs - cyclical costs only (±25%)			
IDFS – year 1	£76.52	Log Normal (£57.39-£95.66)	Section B.3.5
IDFS – year 2-5	£4.10	Log Normal (£3.08-£5.13)	
IDFS – ≥5 years	£3.12	Log Normal (£2.34-£3.90)	
Non-metastatic recurrence	£87.83	Log Normal (£65.87-£109.79)	
Remission	£4.10	Log Normal (£3.08-£5.13)	
First-line metastatic recurrence	£231.70	Log Normal (£173.78-£289.63)	
Second + line metastatic recurrence	£192.28	Log Normal (£144.21-£240.36)	
Adverse event management costs (per event) – IDFS			
Platelet count decreased	£1,712.99	Gamma (£1,284.74-£2,141.24)	Section B.3.5
Adverse event management costs (per event) – Subsequent therapies			
Trastuzumab + chemotherapy	£14.85	Fixed	Section B.3.5
Trastuzumab emtansine	£2.21	Fixed	
Pertuzumab + trastuzumab + docetaxel	£16.59	Fixed	
Chemotherapy	£1.28	Fixed	

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Abbreviations: CI: confidence interval; eBC: early breast cancer; ER: early relapser; IDFS: invasive disease-free survival; IV: intravenous; mBC: metastatic breast cancer; SC: subcutaneous; 5-FU: 5-fluorouracil.

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B.3.6.2 Assumptions

Table 54. Key assumptions used in the economic model (base case)

Area	Assumption	Justification
Time horizon	51 years	Fifty-one years is believed to be long enough to reflect all important differences in costs or outcomes between the technologies being compared. This value is also in line with previous appraisals in this disease area.
Clinical inputs	Treatment duration as observed in KATHERINE	Treatment duration in the model has been derived from the TTOT data that were collected during the KATHERINE trial. This is considered to reflect the actual use of trastuzumab emtansine and trastuzumab in UK clinical practice, should the trastuzumab emtansine become commercially available in this indication.
	Incremental treatment effect duration	The incremental treatment effect will be applied for seven years (84 months) before waning and ceasing completely at ten years (120 months). Long-term follow-up in trastuzumab studies have shown maintenance of treatment effect. See B.3.3.1 for full details on the rationale behind this assumption. In addition, a seven-year treatment effect duration has been assumed in a previous appraisal of the combination of pertuzumab + trastuzumab + chemotherapy in the neoadjuvant breast cancer setting.
	"Cure" proportion assumptions	1. "Cured" patients are assumed to be at risk of death from other causes ("background mortality") and no longer at risk of disease recurrence or breast cancer-related death 2. The point at which a proportion of patients start to be "cured" is 36 months. The selection of this time point is predicated on data available from the APHINITY and KATHERINE trials and the Committee's preferences from TA569. Please see Section B.3.3.1 for a full explanation of this assumption. 3. Maximum "cured" proportion is reached at ten years. Much like 2), this assumption is based on observations from long term historical studies of trastuzumab. Further details are provided in Section B.3.3.1. 4. Maximum "cured" proportion is 95% (i.e. 5% of patients would never be "cured"). 95% of the IDFS population at 10 years remain cured for the duration of the time horizon. It was deemed clinically implausible to assume a 100% "cure" rate. The 95% cure rate aligns with a publication

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Area	Assumption	Justification
		by Takeuchi *et al.* This maximum cure rate was also accepted by the Committee in TA569. 5. "Cured" proportion between starting point (36 months) and maximum (120 months) is assumed to linearly increase with time. Assumption that everyone will be "cured" after a time point is less appropriate, therefore a linear relationship between time and "cured" proportion seems more reasonable, i.e. the more patients stay on IDFS the more likely are to be "cured".
	Fast or early relapse vs late relapser	1. Patients who experience a recurrence in under 18 months from commencing adjuvant therapy are classed as "Fast relapsers". Fast relapsers are assumed to have a worse prognosis. This assumption is based on data from the HERA trial (See Figure 27). 2. Fast relapser survival estimates were derived from the EMILIA study. Transitions from first-line mBC to second+ line mBC and death probabilities from first-line and second-line mBC follow an exponential rate (Markov property). See 0.
	Probability from remission to first-line mBC	Monthly probability of subsequent metastatic recurrence has been derived from Hamilton *et al*. There are several differences between the populations evaluated in the model and the one described in the publication. Nevertheless, the same probability has been used in previous appraisals in eBC.
	Late relapse probabilities	Slow relapsers are assumed to receive the three most commonly used therapies in the UK: • Pertuzumab + trastuzumab + taxane, • Trastuzumab + taxane, • Chemotherapy For pertuzumab + trastuzumab + taxane, and trastuzumab + taxane, adjustment to the survival curve was based on the CLEOPATRA study, while for chemotherapy adjustment was based on M77001 study. These were used to model three transitions: from first-line mBC to second-line mBC, first-line mBC to death and second-line mBC to death. A weighted average probability (probabilities weighted by their market shares) was used for each transition. The CLEOPATRA and M77001 studies did not include patients with adjuvant pertuzumab + trastuzumab + chemotherapy, as the combination was not available at that time.

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Area	Assumption	Justification
		Prior adjuvant therapy with chemotherapy, anthracyclines, hormone therapy and radiotherapy was used in most of patients in M77001, and in CLEOPATRA adjuvant or neoadjuvant trastuzumab was allowed.
HRQoL	Pooled utilities across treatment arms	No statistically significant difference was detected in EQ-5D results between the two treatment arms. Therefore, EQ-5D results were pooled and health state utilities have been applied across both treatment arms in the model.
	Utilities for the "non-metastatic recurrence" and "remission" health states have been assumed equal to "IDFS – on chemotherapy" and "IDFS – off treatment", respectively	EQ-5D data were not collected following recurrence in the KATHERINE study. As a result, it was not possible to estimate utilities for post-recurrence health states. A variety of published utilities have been included as scenario analyses. This assumption was also made in the NICE appraisal of pertuzumab in the neoadjuvant and adjuvant settings.[71, 79]
	AE disutilities are not applied in the model	The disutility associated with AEs was assumed to have been captured in the EQ-5D responses in KATHERINE. See Section B.3.4.4.
Costs and resource use	Post-recurrence treatments	In the KATHERINE study, post-recurrence treatments were not robustly captured. Usage of various treatment regimens in the mBC health states has been estimated using market research commissioned by the Company.
	Remission health state costs are assumed equal to IDFS (off-treatment)	Clinically plausible and in line with the methodology used in TA424 and TA569.
	Trastuzumab biosimilar vs branded trastuzumab IV use in subsequent therapies	It has been assumed that all IV trastuzumab used in the supportive care setting is biosimilar. This is aligned with the assumption in the IDFS health state.
	Trastuzumab emtansine usage in first-line mBC – early relapser patients	First-line mBC – early relapser: Expert opinion elicited by the Company signals that physicians would not re-challenge patients with trastuzumab emtansine in the 1st-line mBC setting after trastuzumab emtansine therapy in the adjuvant setting. Supportive care in the first-line mBC – early relapser health state has therefore been stratified according to treatment received in the adjuvant setting. It has been assumed that in the trastuzumab emtansine arm, patients would expect to receive pertuzumab + trastuzumab + chemotherapy instead of trastuzumab emtansine.
	Pertuzumab + trastuzumab + chemotherapy usage in ≥ 2L mBC	Pertuzumab + trastuzumab + chemotherapy is only reimbursed in patients who have not had prior anti-HER2 therapy for their metastatic disease. The market research in 1L mBC showed that a small proportion of generic chemotherapy was being used, therefore there

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Area	Assumption	Justification
		is some usage of pertuzumab + trastuzumab + chemotherapy in the second-line setting. The duration of treatment in this setting has been assumed equal to that of the trastuzumab arm in the trastuzumab emtansine in second-line mBC cost-effectiveness model (TA458).
	Chemotherapy as a subsequent treatment	In cases where generic chemotherapy was used, the specific therapy was not always reported in the market research. Chemotherapy has therefore been costed as docetaxel.

B.3.7 *Base-case results*

B.3.7.1 Base-case incremental cost-effectiveness analysis results

Base case results of the economic model are presented below. Only results pertaining to the comparison with trastuzumab are featured here. Please see the supplementary appendix for the results specific to the trastuzumab emtansine vs pertuzumab + trastuzumab analysis.

Trastuzumab emtansine provided a QALY gain of [redacted] and a life-year gain of 16.99, at a total overall cost of £[redacted]. In contrast, trastuzumab provided a QALY gain of [redacted] and a life-year gain of 15.02, at a total cost of £[redacted]. The resulting base case ICER when comparing trastuzumab emtansine to trastuzumab is £1,293/QALY gained.

See Table 55 for a top-line summary of the base case cost-effectiveness results.

Table 55. Base case cost-effectiveness results (confidential discounts applied)

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Trastuzumab	[redacted]	15.02	[redacted]	[redacted]	1.97	1.60	£1,293
Trastuzumab emtansine	[redacted]	16.99	[redacted]				

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

B.3.8 *Sensitivity analyses*

B.3.8.1 Probabilistic sensitivity analysis

To assess the uncertainty surrounding the variables included in the cost-effectiveness model, a probabilistic sensitivity analysis (PSA) was undertaken using 1,000 samples. The mean values, distributions around the means, and sources used to estimate the parameters are detailed in Section B.3.6.1.

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The PSA results produced a mean ICER of £1,127/QALY gained when trastuzumab emtansine was compared with trastuzumab. Results of the PSA compared to the base case analysis are presented in Table 56. Figure 31 and Figure 32 show the cost-effectiveness plane and acceptability curve, respectively.

The analyses below have been conducted using medication prices with confidential discounts applied.

Table 56. PSA results compared to base case (confidential discounts applied)

	Costs		QALYs		ICERs (£/QALY)	
	Base case	PSA	Base case	PSA	Base case	PSA
Trastuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£1,293	£1,127
Trastuzumab emtansine	[redacted]	[redacted]	[redacted]	[redacted]		

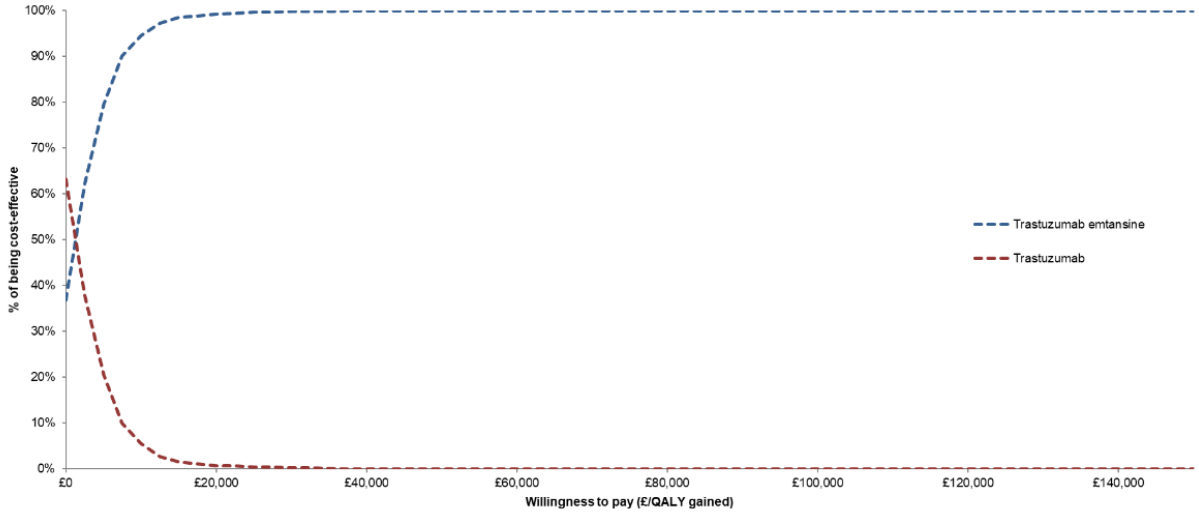
Abbreviations: ICER: incremental cost-effectiveness ratio; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year.

Figure 31. Cost-effectiveness plane

REDACTED

Abbreviations: Inc: incremental; Inc. QALYs: incremental quality-adjusted life years.

Figure 32. Cost-effectiveness acceptability curve



Abbreviations: QALY: quality-adjusted life year.

B.3.8.2 Deterministic sensitivity analysis

The choice of parameters to include in the univariate analysis was considered a priori, and was further informed by the results in Section B.3.7. For each parameter, the lower and upper values used in the univariate analysis were ±25% of the base case value.

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The values featured in the univariate analysis are given in Table 57. Please note, clinical parameters were not varied during univariate sensitivity analyses but were instead considered in the probabilistic sensitivity analysis and the scenario analyses subsections. For presentation purposes, only the ten most sensitive of analyses have been included in the Tornado diagram (Figure 33).

Table 57. Parameter values for univariate sensitivity analysis

Parameter	Base case value	Lower value	Upper value
AE management cost per patient – KAD	£106.48	£79.86	£133.10
Administration cost – First cycle – KAD	£383.78	£287.84	£479.73
Administration cost – First cycle – H	£383.78	£287.84	£479.73
Administration cost – First cycle – H (SC)	£257.01	£192.76	£321.26
Administration cost – Subsequent cycle – KAD	£318.49	£238.87	£398.11
Administration cost – Subsequent cycle – H	£318.49	£238.87	£398.11
Administration cost – Subsequent cycle – H (SC)	£257.01	£192.76	£321.26
Monthly supportive care cost in IDFS – Year 1 & 2	£76.57	£57.43	£95.71
Monthly supportive care cost in IDFS – Year 3 to 5	£4.15	£3.11	£5.18
Monthly supportive care cost in IDFS – Year 6 onwards	£3.12	£2.34	£3.90
Monthly supportive care cost in remission	£4.15	£3.11	£5.18
Monthly supportive care cost in locoregional recurrence	£1,909.32	£1,431.99	£2,386.65
Monthly supportive care cost in 1st line early metastatic setting – KAD	£2,550.69	£1,913.02	£3,188.36
Monthly supportive care cost in 1st line early metastatic setting – H	£3,618.67	£2,714.00	£4,523.33
Monthly supportive care cost in 1st line metastatic setting	£2,550.69	£1,913.02	£3,188.36
Monthly supportive care cost in 2nd line metastatic setting	£3,796.32	£2,847.24	£4,745.40
Utility in IDFS on treatment – KAD	0.775	0.581	0.969
Utility in IDFS off treatment – KAD	0.788	0.591	0.984
Utility in NMR – KAD	0.775	0.581	0.969
Utility in remission – KAD	0.788	0.591	0.984
Utility in IDFS on treatment – H	0.775	0.581	0.969
Utility in IDFS off treatment – H	0.788	0.591	0.984
Utility in locoregional recurrence – H	0.775	0.581	0.969
Utility in remission – H	0.788	0.591	0.984
Utility in metastatic setting	0.765	0.574	0.956
Utility in progressed metastatic setting	0.508	0.381	0.635

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Abbreviations: AE: adverse event; H: trastuzumab; IDFS: invasive disease-free survival: KAD: trastuzumab emtansine; NMR: non-metastatic recurrence; SC: subcutaneous.

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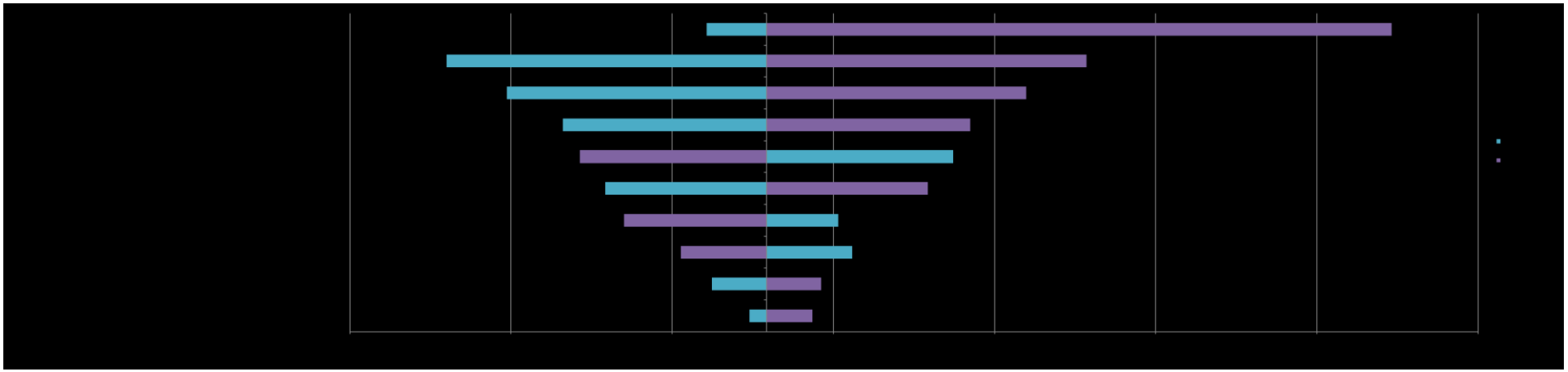
Figure 33. Tornado diagram



Abbreviations: H: trastuzumab; ICER: incremental cost-effectiveness ratio; IDFS: invasive disease-free survival; KAD: trastuzumab emtansine; mBC: metastatic breast cancer; QALY: quality-adjusted life year.

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B.3.8.3 Scenario analysis

Scenario analyses were conducted to assess uncertainty around model structure and parameters. The list below outlines the areas of the model that were evaluated. Key results are shown in Table 58 and Table 59.

- Model settings
  - Time horizon
  - Patient weight
- Clinical inputs
  - IDFS parametric distribution
  - Duration of treatment effect
  - Proportion of recurrences that are metastatic
  - Definition of “early” relapsers
- Health state utilities
  - Age adjustment of utilities
  - Source of eBC health state utilities
  - Source of mBC health state utilities
- Costs and resource use
  - Drug dosing assumptions
  - Trastuzumab SC market share (Biosimilar market share = 0%)
  - Selected health state costs

Table 58. Results from scenario analyses – costs and utilities

	Value	Trastuzumab emtansine			Trastuzumab			Trastuzumab emtansine vs. trastuzumab			
		Life Years	QALYs	Costs	Life Years	QALYs	Costs	Life Years	QALYs	Costs	ICER (£/QALY)
Treatment duration option	Observed treatment duration	16.99	[redacted]	[redacted]	15.02	[redacted]	[redacted]	1.97	1.60	[redacted]	£1,293
Treatment duration option	Until disease recurrence (per label)	16.99	[redacted]	[redacted]	15.02	[redacted]	[redacted]	1.97	1.60	[redacted]	£2,734
Utilities in eBC	EQ-5D from KATHERINE (per treatment arm)	16.99	[redacted]	[redacted]	15.02	[redacted]	[redacted]	1.97	1.57	[redacted]	£1,318

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	Value	Trastuzumab emtansine			Trastuzumab			Trastuzumab emtansine vs. trastuzumab			
		Life Years	QALYs	Costs	Life Years	QALYs	Costs	Life Years	QALYs	Costs	ICER (£/QALY)
Utilities in eBC	EQ-5D from KATHERINE (pooled)	16.99	[redacted]	[redacted]	15.02	[redacted]	[redacted]	1.97	1.60	[redacted]	£1,293
Utilities in eBC	Heden et al.	16.99	[redacted]	[redacted]	15.02	[redacted]	[redacted]	1.97	1.62	[redacted]	£1,273
Utilities in eBC	Lidgren et al.	16.99	[redacted]	[redacted]	15.02	[redacted]	[redacted]	1.97	1.60	[redacted]	£1,291
Utilities in mBC	Heden et al.	16.99	[redacted]	[redacted]	15.02	[redacted]	[redacted]	1.97	1.60	[redacted]	£1,293
Utilities in mBC	Lidgren et al.	16.99	[redacted]	[redacted]	15.02	[redacted]	[redacted]	1.97	1.60	[redacted]	£1,293
Utilities in mBC	Lloyd et al.	16.99	[redacted]	[redacted]	15.02	[redacted]	[redacted]	1.97	1.60	[redacted]	£1,293
Utilities in mBC	Paracha et al.	16.99	[redacted]	[redacted]	15.02	[redacted]	[redacted]	1.97	1.60	[redacted]	£1,293
Dosing scenarios	Planned dose without vial sharing	16.99	[redacted]	[redacted]	15.02	[redacted]	[redacted]	1.97	1.60	[redacted]	£1,297
Dosing scenarios	Planned dose with vial sharing	16.99	[redacted]	[redacted]	15.02	[redacted]	[redacted]	1.97	1.60	[redacted]	£1,104
Dosing scenarios	Actual dose without vial sharing	16.99	[redacted]	[redacted]	15.02	[redacted]	[redacted]	1.97	1.60	[redacted]	£1,293
Dosing scenarios	Actual dose with vial sharing	16.99	[redacted]	[redacted]	15.02	[redacted]	[redacted]	1.97	1.60	[redacted]	£729
Herceptin SC market share	70%	16.99	[redacted]	[redacted]	15.02	[redacted]	[redacted]	1.97	1.60	[redacted]	£2,407
Herceptin SC market share	75%	16.99	[redacted]	[redacted]	15.02	[redacted]	[redacted]	1.97	1.60	[redacted]	£2,184
Herceptin SC market share	80%	16.99	[redacted]	[redacted]	15.02	[redacted]	[redacted]	1.97	1.60	[redacted]	£1,961
Herceptin SC market share	85%	16.99	[redacted]	[redacted]	15.02	[redacted]	[redacted]	1.97	1.60	[redacted]	£1,738
Herceptin SC market share	90%	16.99	[redacted]	[redacted]	15.02	[redacted]	[redacted]	1.97	1.60	[redacted]	£1,516
Herceptin SC	95%	16.99	[redacted]	[redacted]	15.02	[redacted]	[redacted]	1.97	1.60	[redacted]	£1,293

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	Value	Trastuzumab emtansine			Trastuzumab			Trastuzumab emtansine vs. trastuzumab			
		Life Years	QALYs	Costs	Life Years	QALYs	Costs	Life Years	QALYs	Costs	ICER (£/QALY)
market share											
Herceptin SC market share	100%	16.99	[redacted]	[redacted]	15.02	[redacted]	[redacted]	1.97	1.60	[redacted]	£1,070

Table 59. Results from scenario analyses – clinical parameters and efficacy

	Value	Trastuzumab emtansine			Trastuzumab			Trastuzumab emtansine vs trastuzumab			
		Life Years	QALYs	Costs	Life Years	QALYs	Costs	Life Years	QALYs	Costs	ICER (£/QALY)
Distribution IDFS – TE	Exponential	16.83	[redacted]	[redacted]	14.75	[redacted]	[redacted]	2.07	1.69	[redacted]	£379
Distribution IDFS – TE	Weibull	16.74	[redacted]	[redacted]	14.74	[redacted]	[redacted]	2.00	1.63	[redacted]	£1,009
Distribution IDFS – TE	Log-normal	17.32	[redacted]	[redacted]	15.29	[redacted]	[redacted]	2.03	1.65	[redacted]	£918
Distribution IDFS – TE	Generalized Gamma	17.02	[redacted]	[redacted]	15.41	[redacted]	[redacted]	1.61	1.30	[redacted]	£5,314
Distribution IDFS – TE	Log-logistic	16.99	[redacted]	[redacted]	15.02	[redacted]	[redacted]	1.97	1.60	[redacted]	£1,293
Distribution IDFS – TE	Gompertz	16.73	[redacted]	[redacted]	14.75	[redacted]	[redacted]	1.97	1.60	[redacted]	£1,158
Duration of treatment effect	Effect is maintained over time	17.07	[redacted]	[redacted]	15.02	[redacted]	[redacted]	2.05	1.66	[redacted]	£601
Duration of treatment effect	Effect is limited in time (effect to 7 years, wane to 10 years)	16.99	[redacted]	[redacted]	15.02	[redacted]	[redacted]	1.97	1.60	[redacted]	£1,293
Proportion of recurrences which are metastatic	Average	17.10	[redacted]	[redacted]	14.92	[redacted]	[redacted]	2.18	1.77	[redacted]	£668
Proportion of recurrences which are metastatic	Individual arm data	16.99	[redacted]	[redacted]	15.02	[redacted]	[redacted]	1.97	1.60	[redacted]	£1,293
Time horizon	10	7.95	[redacted]	[redacted]	7.51	[redacted]	[redacted]	0.45	0.42	[redacted]	£13,625
Time horizon	20	12.56	[redacted]	[redacted]	11.42	[redacted]	[redacted]	1.14	0.99	[redacted]	£2,967

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	Value	Trastuzumab emtansine			Trastuzumab			Trastuzumab emtansine vs trastuzumab			
		Life Years	QALYs	Costs	Life Years	QALYs	Costs	Life Years	QALYs	Costs	ICER (£/QALY)
Time horizon	30	15.33	[redacted]	[redacted]	13.68	[redacted]	[redacted]	1.65	1.38	[redacted]	£1,653
Time horizon	40	16.68	[redacted]	[redacted]	14.77	[redacted]	[redacted]	1.91	1.56	[redacted]	£1,342
Time horizon	50	16.98	[redacted]	[redacted]	15.01	[redacted]	[redacted]	1.97	1.60	[redacted]	£1,293
Time horizon	60	17.00	[redacted]	[redacted]	15.02	[redacted]	[redacted]	1.97	1.60	[redacted]	£1,292
Definition of "Early" relapsers (months)	6	17.07	[redacted]	[redacted]	15.27	[redacted]	[redacted]	1.80	1.47	[redacted]	£910
Definition of "Early" relapsers (months)	12	17.03	[redacted]	[redacted]	15.14	[redacted]	[redacted]	1.89	1.54	[redacted]	£1,132
Definition of "Early" relapsers (months)	18	16.99	[redacted]	[redacted]	15.02	[redacted]	[redacted]	1.97	1.60	[redacted]	£1,293
Definition of "Early" relapsers (months)	24	16.95	[redacted]	[redacted]	14.90	[redacted]	[redacted]	2.05	1.66	[redacted]	£1,405
Incremental tx effect begins to decrease	48	16.70	[redacted]	[redacted]	15.02	[redacted]	[redacted]	1.68	1.36	[redacted]	£3,889
Incremental tx effect begins to decrease	60	16.84	[redacted]	[redacted]	15.02	[redacted]	[redacted]	1.82	1.48	[redacted]	£2,555
Incremental tx effect begins to decrease	72	16.93	[redacted]	[redacted]	15.02	[redacted]	[redacted]	1.91	1.55	[redacted]	£1,755
Incremental tx effect begins to decrease	84	16.99	[redacted]	[redacted]	15.02	[redacted]	[redacted]	1.97	1.60	[redacted]	£1,293
Incremental tx effect begins to decrease	96	17.02	[redacted]	[redacted]	15.02	[redacted]	[redacted]	2.00	1.62	[redacted]	£1,054
Incremental tx effect begins to decrease	108	17.03	[redacted]	[redacted]	15.02	[redacted]	[redacted]	2.02	1.64	[redacted]	£944
Incremental tx effect	120	17.04	[redacted]	[redacted]	15.02	[redacted]	[redacted]	2.02	1.64	[redacted]	£893

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	Value	Trastuzumab emtansine			Trastuzumab			Trastuzumab emtansine vs trastuzumab			
		Life Years	QALYs	Costs	Life Years	QALYs	Costs	Life Years	QALYs	Costs	ICER (£/QALY)
begins to decrease											
Maximum "cure" proportion	0%	14.61	[redacted]	[redacted]	13.07	[redacted]	[redacted]	1.54	1.23	[redacted]	£5,744
Maximum "cure" proportion	20%	15.03	[redacted]	[redacted]	13.41	[redacted]	[redacted]	1.62	1.30	[redacted]	£4,726
Maximum "cure" proportion	40%	15.48	[redacted]	[redacted]	13.78	[redacted]	[redacted]	1.71	1.37	[redacted]	£3,751
Maximum "cure" proportion	60%	15.98	[redacted]	[redacted]	14.19	[redacted]	[redacted]	1.80	1.45	[redacted]	£2,819
Maximum "cure" proportion	80%	16.54	[redacted]	[redacted]	14.64	[redacted]	[redacted]	1.89	1.53	[redacted]	£1,931
Maximum "cure" proportion	100%	17.15	[redacted]	[redacted]	15.15	[redacted]	[redacted]	2.00	1.62	[redacted]	£1,086
"Cure" proportion begins to increase	36	16.99	[redacted]	[redacted]	15.02	[redacted]	[redacted]	1.97	1.60	[redacted]	£1,293
"Cure" proportion begins to increase	48	16.83	[redacted]	[redacted]	14.82	[redacted]	[redacted]	2.01	1.63	[redacted]	£928
"Cure" proportion begins to increase	60	16.69	[redacted]	[redacted]	14.64	[redacted]	[redacted]	2.04	1.65	[redacted]	£664
"Cure" proportion begins to increase	72	16.55	[redacted]	[redacted]	14.49	[redacted]	[redacted]	2.06	1.66	[redacted]	£489
"Cure" proportion begins to increase	84	16.42	[redacted]	[redacted]	14.35	[redacted]	[redacted]	2.07	1.67	[redacted]	£411
"Cure" proportion begins to increase	96	16.28	[redacted]	[redacted]	14.23	[redacted]	[redacted]	2.05	1.65	[redacted]	£461
"Cure" proportion begins to increase	108	16.15	[redacted]	[redacted]	14.12	[redacted]	[redacted]	2.02	1.63	[redacted]	£627
"Cure" proportion	120	16.02	[redacted]	[redacted]	14.03	[redacted]	[redacted]	1.99	1.60	[redacted]	£861

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	Value	Trastuzumab emtansine			Trastuzumab			Trastuzumab emtansine vs trastuzumab			
		Life Years	QALYs	Costs	Life Years	QALYs	Costs	Life Years	QALYs	Costs	ICER (£/QALY)
begins to increase											

Abbreviations: ICER: incremental cost-effectiveness ratio; IDFS: invasive-disease free survival; QALY: quality-adjusted life year; TE: trastuzumab emtansine.

B.3.8.4 Summary of sensitivity analyses results

PSA results are compared to the base case in Table 56. The PSA simulations produced a mean ICER of £1,127/QALY gained. This value is close to the base case value of £1,293/QALY gained. Furthermore, the cost-effectiveness acceptability curve showed that the trastuzumab emtansine regimen had a ~99.30% probability of being the most cost-effective treatment at a £20,000 willingness-to pay-threshold.

The results of the univariate sensitivity analysis show that the model drivers were the utilities in the IDFS health state and the supportive care costs in the metastatic setting. The lowest ICER produced was £300/QALY gained. This result was generated using the upper value (£4,745.40) for the monthly supportive care cost in the 2nd line setting. When using the lower value for the utility in IDFS – off treatment state (trastuzumab emtansine arm), the highest ICER was generated (£3,232/QALY gained). The analysis around the utility value in IDFS – off treatment (trastuzumab emtansine arm) also produced the largest range in ICERs (£1,107–£3,232/QALY gained).

Many scenario analyses were conducted as part of this submission. The parameters varied included those pertaining to the model settings, clinical parameters, health state utilities, and cost and resource use. ICERs produced by the scenario analysis ranged from £379/QALY gained (use of Exponential function for the extrapolation of IDFS in both treatment arms) to £13,625/QALY gained (10-year time horizon)

This economic analysis was limited by the availability of relevant data. To compensate for the shortfall in data, assumptions and expert opinion were utilised. These factors introduced a degree of uncertainty into the analysis. The Company is aware of this uncertainty, hence the extensive sensitivity analysis that has been documented in this section.

B.3.9 *Subgroup analysis*

The analysis and results described above pertain to the comparison of trastuzumab emtansine vs trastuzumab in the ITT population of the KATHERINE trial. As stated in Section B.3.2.1, an analysis in a subgroup of the expected label population (patients with node-positive disease, have been pre-treated with an anti-HER2 therapy, have RID and are therefore eligible for pertuzumab + trastuzumab + chemotherapy) has also been conducted as part of this appraisal. The methodology and results associated with this analysis are available in Appendix M.

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B.3.10 *Validation*

B.3.10.1 Validation of cost-effectiveness analysis

The modelling approach and structure described in this submission is consistent with various other oncology models and previous submissions to NICE in the breast cancer therapy area.[71, 79, 80] The methodology described above has broadly adhered to the guidelines stipulated in the NICE reference case. Instances in which the Company has deviated from this guide have been highlighted and justified.

The general modelling approach and inputs were cross referenced with previous technology appraisals and subsequently validated by external health economists and UK clinical experts. The purpose of this validation was to ensure the model was both theoretically sound and reflective of clinical practice.

Clinical data have been incorporated into the model from the KATHERINE study and long-term clinical trial data. This methodology is described fully in Section B.3.3. Clinical outcomes in both arms of the model have been extensively compared and validated against relevant evidence to assess the accuracy of modelled IDFS outcomes (see Appendix J).

This analysis took the perspective of the UK NHS. The health states included in this evaluation are similar to those of the adjuvant and neoadjuvant pertuzumab appraisals. Consequently, health state cost and resource use used here mirrors that of those submissions. A comparison of the of health state costs across the three analyses can be found in Table 50.

A formal quality assessment and validation of model outcomes was conducted by an independent assessor prior to submission. A technical cell by cell verification of formulae, functions and coding was performed as part of this process. In addition, a number of ‘pressure tests’ were conducted, often using extreme values. The results of the model using these values were then compared to expected outputs to assess functional accuracy.

B.3.11 *Interpretation and conclusions of economic evidence*

This economic evaluation focused on assessing the cost-effectiveness of trastuzumab emtansine for the adjuvant treatment of patients with HER2-positive eBC from a UK health system perspective.

The model draws upon clinical data from the KATHERINE study: an ongoing, phase III, randomised, placebo-controlled study in patients with RID following neoadjuvant therapy. The focus of the economic analysis was the comparison trastuzumab emtansine vs trastuzumab, justification of this approach has been provided in Section B.3.2. The baseline characteristics of the patients in KATHERINE have been validated by clinical experts and can be considered broadly representative of the corresponding population in the UK. This evaluation can therefore be considered relevant to clinical practice in England and Wales.

The EQ-5D questionnaire was administered as part of the KATHERINE trial. No clinically significant difference was observed between responses of the two treatment arms. Therefore, EQ-5D data were pooled and health state utilities, irrespective of treatment arm, were derived and applied as such in the model. This methodology is in-line with the guidance stipulated in the NICE Reference Case.

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A UK NHS perspective was taken with respect to the costs and resource use quantified in the model. All costs were taken from published UK sources or previous NICE technology appraisals in this disease area. Once again, this methodology is in accordance with that of the NICE Reference Case.

As reported in Section B.3.7, the trastuzumab emtansine arm was associated with a gain of 16.99 life-years, an increase of 1.97 compared to the trastuzumab arm. Trastuzumab emtansine is also associated with an incremental QALY gain of 1.60. Given the modelling approach, this differential is driven by the time to recurrence benefit seen in the trastuzumab emtansine arm.

The base case ICER when comparing trastuzumab emtansine to trastuzumab is £1,293/QALY gained. Please note that this ICER has been generated when incorporating confidential discounts on the list prices of trastuzumab emtansine, trastuzumab SC, trastuzumab biosimilars, and pertuzumab.

Extensive sensitivity and scenario analyses have been conducted to test the robustness of model results when parameter values were manipulated, alternative approaches implemented, and different data sources utilised. Complete results of these analyses can be found in Section B.3.8. Main drivers of the cost-effectiveness results were found to be the IDFS health state utilities and supportive care costs in the metastatic setting.

The key strengths associated with the presented cost-effectiveness analysis surround its use of the best available evidence to inform the model:

- Clinical effectiveness data taken from a randomised placebo-controlled trial (KATHERINE) which included one of the relevant UK comparators in the control arm.
- Health state utilities derived directly from EQ-5D data collected in the population of interest during the KATHERINE study.
- Costs and resource use data taken from well-established UK sources and previous NICE technology appraisals.
- Extensive sensitivity and scenario analyses conducted to quantify uncertainty and identify major drivers of cost-effectiveness results.
- Comprehensive external validation undertaken using TA569, TA424, ID523, and available evidence from long-term clinical studies.

Limitations associated with this analysis are analogous to those seen across recent economic evaluations in general. Major uncertainties stem from the lack of observed data pertaining to trastuzumab emtansine in this setting, particularly in the mid to long term.

The analysis presented here could be strengthened principally through a greater cache of clinical data documenting trastuzumab emtansine therapy in patients with eBC. The KATHERINE trial is still ongoing, therefore the uncertainty associated with extrapolations and treatment effect duration in the medium term is likely to be lessened somewhat with later data read-outs.

Ultimately, the methodology detailed in this document is believed to have produced a robust base case analysis. Particular attention should be paid to the resulting ICER value (£1,293/QALY

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gained). This is testament to the practice-changing efficacy profile seen in the results of the KATHERINE trial.

The approach and assumptions use in the base case analysis can broadly be considered to be conservative, with the exception of the function used to extrapolate IDFS (Log-logistic) and the duration of treatment effect (full effect to seven years before waning and ceasing completely at ten years). When employing the most conservative function for the extrapolation of IDFS (Generalized gamma) and the conservative assumptions on the treatment effect duration that were used in the TA569 appraisal, the ICER is £5,834/QALY gained. This ICER can be considered the "plausible worst-case" scenario.

Both the base case and plausible worst-case scenario ICERs are significantly below the threshold at which NICE routinely approves technologies. Trastuzumab emtansine in the adjuvant setting can therefore be conclusively judged to be a cost-effective use of scarce NHS resources.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Trastuzumab emtansine for adjuvant treatment of HER2-positive early breast cancer [ID1516]

Clarification questions

October, 2019

File name	Version	Contains confidential information	Date
"ID1516_TE in eBC_CQs_Main body_11-11-2019_REDACTED"		**Yes**	**11th November, 2019**

Section A: Clarification on effectiveness data

Literature searches

A1. Priority question: Regarding Appendix D 'Identification, selection and synthesis of clinical evidence' and Appendix G 'Published cost-effectiveness', the ERG is currently unable to fully critique these searches due to the lack of hits per line for each strategy. Please provide full strategies including hits per line as reported in Appendix I.

The full strategies have been provided as a supplementary appendix to this response.

A2. Regarding the clinical effectiveness searches:

A. Table 3 reports a search of EBM Reviews, which included CDSR, DARE, CENTRAL, HTA and NHS EED databases. Please provide the number of results for each database within the EBM Reviews suite of resources.

When the original and updated search strategy was run in EBM Reviews, the number of citations identified from each of the component databases was not recorded (only the total number of potentially relevant citations (Figure 1 and 2, Appendix D) . It was felt that these data were not critical as all identified citations were screened against the pre-approved eligibility criteria detailed in Table 10 of Appendix D.

B. Tables 7-9 report searches of conference proceedings, clinical trials registries and organisational websites. The PRISMA flowcharts (Figures 1 & 2) do not include any of the results from these resources. Please provide details of the number of results for each resource, and how they were considered within the flowchart.

The 24 citations identified from other sources included:

- Clinical trial registries, n=3
- Conference proceedings, n=13
- Hand searching of reference lists of included studies/previous reviews, n=8

They are considered in the PRISMA Flowchart (Figure 1) under the Category "Additional records identified through other sources (n=24)".

C. Please confirm whether any searches were conducted specifically to identify adverse events.

No searches were conducted to specifically identify adverse events. No terms for any outcomes were included in the clinical effectiveness searches. Any adverse event data of interest reported in RCTs meeting the predefined eligibility criteria (Table 10, Appendix D) were considered for inclusion.

A3. Regarding the cost-effectiveness searches:

A. Please confirm which database hosts were used to search Medline and Embase (Appendix G).

Embase was searched via Embase.com; Medline and Medline-in-process have been searched via PubMed.

B. Please clarify whether the strategies presented in Table 15 and 16 were used for both the original searches in November 2017 as well as the update searches in February 2019.

The same strategies have been used since the original SLR was conducted in 2014. All subsequent updates used the same databases and search strings

C. Neither the Medline nor Embase search strategies (tables 15 & 16) appear to contain any MeSH or Emtree indexing terms to identify costs or economic concepts. As only title and abstract terms for cost and economics were searched for, please can the company explain what impact this may have had on the overall recall of results.

Since the original search strategy was first developed in 2014, better established and validated search filters for the identification of economic evaluations have indeed been developed. While it is true that more comprehensive use of MeSH/ EMTREE terms could have been used, the Company would like to point out that both search strategies are comprehensive. In Medline, the use of "Technology Assessment, Biomedical"[MeSH] would have identified key studies, especially in combination with free text terms for economic evaluations. Furthermore, it should be noted that the Embase search string does contain the EMTREE term for economic evaluations ('economic evaluation'/exp) which has been supplemented by free-text terms. It should also be noted that Embase.com does contain and index the content of Medline, which essentially provides an additional level of assurance that relevant publications have been captured. Finally, extensive cross-referencing against previously published reviews of models in the same indication as well as previous technology appraisals (including NICE submissions) has been conducted. While we

acknowledge that the search string could have been more sensitive, we believe that the risk of omitting key publications is low.

D. The cost-effectiveness searches were limited to English language publications only, which best practice guidance recommends against. Please clarify whether potentially relevant references were missed due to this limit.

Limiting the search terms to English resulted in the exclusion of only 3.5% of identified citations (<100 citations). Additionally, it is overwhelmingly likely that the primary publications of the economic models would have been published in peer-reviewed journals which are typically in English. We therefore believe that the risk of omitting relevant publications is rather low.

E. The cost-effectiveness searches do not include terms for the intervention or comparators. Please justify this restriction and clarify whether potentially relevant references were missed due to this limit.

Omitting a description of interventions and comparators should not be considered a restriction. In fact, not excluding publications based on intervention and comparator terms can be considered less restrictive than if those had been added.

A4. Regarding Health-related quality-of-life studies:

The submission reports HRQOL studies were identified using the cost searches in Appendix G. The Medline and Embase strategies (Tables 15 and 16) do not contain any MeSH or Emtree indexing terms for any of the Short Form instruments. Please justify these omissions and clarify whether potentially relevant references were missed due to this.

With respect to the Medline search string, the Company would like to point out that MeSH terms for Short Form do not exist due to the general indexing of the database. In Embase, EMTREE terms for Short Form do exist and indeed could have been added for completeness. To address the concern of the ERG, the search strategy was also tested with the EMTREE terms added. It should be noted that due to the highly comprehensive description of the instruments as well as the concepts related to “quality of life” through free-text words, the addition of the EMTREE terms had no substantial impact on the final number of citations captured. With that in mind and considering the complete cross-referencing and hand searching conducted as part of the overall systematic review process, we are confident that no studies of interest have been omitted.

A5. Regarding Cost and healthcare resource identification, measurement and valuation:

A. The searches detailed in Appendix I were run in October 2017. Please confirm whether updated searches were conducted. If so, please provide full search strategies for all updates.
B. If updated searches were not conducted, please explain the rationale for this and check whether more current, relevant references were missed. Please clarify how applicable these results are to current clinical practice

Updated searches were run in June 2019 and were omitted from the submitted Appendices in error. The full methodology and results of these searches have now been added to the Appendices Document.

A6. According to Table 27 of Appendix I of the CS, the SLR excluded non-English language studies.

A. How many studies were rejected solely on this basis?
B. Please provide the references rejected solely for this reason at full paper screening.

Cost and healthcare resource use data identified in the systematic literature review detailed in Appendix I must be relevant to the UK NHS and PSS. It is therefore very unlikely that publications in other languages would be relevant. However, a top-line review of records excluded on the basis of "study design/publication type, geographic setting or language" in both the original SLR (2017) and SLR update (2019) has been conducted for completeness and has found that:

- At the title/abstract screening stage, of the 396 records excluded based on "study design/publication type, geographic setting or language" in the original SLR and the 105 records excluded on this basis in the updated SLR, no publications were excluded solely on the basis of being in a non-English language.
- These records were all excluded based on geographic setting, publication type or study design.
- At the full text screening stage, of the 13 records excluded based on "study design/publication type, geographic setting or language" in the original SLR and 5 records excluded on this basis in the updated SLR, none were in a language other than English.

Health Condition

A7. Please provide estimates of the absolute prevalence and incidence of patients in England (or the UK) who fit the description of the population addressed in the scope.

This information has already been provided as part of the Company's original submission. The epidemiology information used in the budget impact assessment has been provided in Table 1 below.

Table 1. Eligible population for trastuzumab emtansine in the adjuvant treatment of HER2-positive eBC

	Eligible patients (proportion, %)	2019	2020	2021	2022	2023	2024	Source
		N	N	N	N	N	N	
1	Annual incidence of breast cancer in the UK (100%)	59,783	60,567	61,309	62,022	62,730	63,391	*CRUK*
2	Patients with eBC in the UK (94.24%)	56,343	57,081	57,780	58,452	59,120	59,743	*CRUK*
3	Number of patients with HER2-positive eBC in the UK	8,057	8,163	8,263	8,359	8,454	8,543	*Rakha et al.*
4	Total number patients with of HER2-positive eBC in England	6,768	6,857	6,941	7,021	7,101	7,176	*Office for National Statistics*
		Neoadjuvant treatment rates						
5	Number of patients with HER2-positive eBC treated neoadjuvantly	3,113	3,291	3,470	3,511	3,551	3,588	*Market research - Q2 2019*
		RID rates by nodal status						
6	Number of neoadjuvantly treated patients who are node-negative (26%)	809	856	902	913	923	933	*Roche Market research – Q2 2019*
7	Number of node-negative patients with RID following neoadjuvant therapy (28%)	227	240	253	256	258	261	*Roche Market research – Q2 2019*
8	Number of neoadjuvantly treated patients who are node-positive (74%)	2,304	2,435	2,568	2,598	2,628	2,655	*Roche Market research – Q2 2019*
9	Number of node-positive patients with RID following neoadjuvant therapy (34%)	783	828	873	883	893	903	*Roche Market research – Q2 2019*
10	Total number of patients eligible for trastuzumab emtansine in England	1,010	1,068	1,126	1,139	1,152	1,164	*7 + 9*

Abbreviations: CRUK: Cancer research UK; eBC: early breast cancer; pCR: pathological complete response; RID: residual invasive disease.

A8. The company states on page 14 of the CS that, “It is standard clinical practice to test the HER2 status of tumours at the point of diagnosis. As such, no additional tests are required prior to the administration of trastuzumab emtansine”. The population being targeted in this submission is, “Adult patients with HER2-positive early breast cancer who have residual invasive disease (RID) in the breast and/or lymph nodes after pre-operative systemic treatment that included HER2-targeted therapy”. Could the company comment further on the mechanism through which they expect tumours that have not previously responded to a HER2 therapy to respond to a HER2-targeted antibody-drug conjugate upon repeat treatment? And if the residual tumours have not previously responded to a HER2 therapy (i.e. patients do not achieve a pathological complete response), can it be assumed that these tumours are HER2 positive without re-biopsy? HER2 status (positive or negative) can differ between the primary tumour and any lymph node metastases, please clarify how this will be dealt with?

It is not reflective to say that patients in the KATHERINE study had tumours that did not respond to HER2 therapy, as many would have experienced a response such as tumour regression. Rather, it is that the neoadjuvant therapy they received did not eliminate all the invasive disease.

Given the differing mechanisms of action of trastuzumab emtansine as compared with trastuzumab (with or without pertuzumab) the anti-tumour effects of these agents are not fully overlapping. The binding of trastuzumab (and pertuzumab) to the HER2 receptor reduces downstream cellular proliferation signalling via several mechanisms and also induces antibody-dependent cellular cytotoxicity (ADCC).[i] While the trastuzumab component of trastuzumab emtansine also exerts these anti-tumour effects, internalization and degradation of the HER2 receptor/trastuzumab emtansine complex allows intracellular release of the emtansine component. Once released, emtansine can exert its cytotoxic effects. It is the addition of this cytotoxic element that is hypothesized to be responsible for the superior efficacy seen for trastuzumab emtansine as compared with trastuzumab in the KATHERINE study. Likewise, clinical trials in the metastatic setting have shown trastuzumab emtansine to be efficacious in patients who’s tumours have become resistant to trastuzumab.[ii,iii]

Furthermore as the KATHERINE protocol did not require surgical excisions to be re-tested for HER2, it is reasonable to expect that the magnitude of benefit seen in the trial will be replicated in UK clinical practice where re-biopsy in this situation is not standard.

Given the magnitude of benefit in the KATHERINE study, and the HER2 targeted mechanism of action of trastuzumab emtansine, it is reasonable to expect that loss of HER2 expression is not a concern in this patient population.
Finally, in UK clinical practice, once HER2 expression has been found in a tumour it is standard practice to continue with anti-HER2 treatment at least initially e.g. continuation to a year of trastuzumab (with or without pertuzumab) regardless of response to neoadjuvant treatment. This technology replaces that treatment with one that has a broader mechanism of action.

Included Studies

A9. Please clarify the dates of the analyses in the KATHERINE study. On page 37 of the CS it is stated: "The clinical cut-off date for this analysis was 25th July 2018, …. The first interim analysis of OS was conducted at the same time, along with other analyses of safety and efficacy. … One additional IDFS analysis, two additional interim OS analyses and a final OS analysis are planned in the future, …" However, in Table 10, it is stated that the "The second OS interim analysis will be conducted at the time of the final IDFS analysis, after approximately 5 years since enrolment of the first patient." The first patient was enrolled in April 2013 (CS, page 31); therefore, 5 years later would be April 2018.

A. Please provide estimated calendar dates for the following analyses:
- First interim OS analysis / interim IDFS analysis: 25 July 2018
- Second interim OS analysis / final IDFS analysis:
- Third OS interim analysis:
- Final analysis:

- First interim OS analysis / interim IDFS analysis: 25 July, 2018

- Second interim OS analysis / final IDFS analysis: This should be per protocol after 384 IDFS events and 206 OS events have occurred -- this is currently projecting to approximately **Q2, 2021**.

- Third OS interim analysis: This should be per protocol after 279 OS events have occurred -- this is currently projecting to be approximately **Q2, 2025**.

- Final analysis: This should be per protocol after 367 OS events have occurred -- this is currently projecting to approximately **Q1, 2029**

Please note; these analyses are event-driven. There is a degree of uncertainty surrounding these dates. The Company will continue to monitor the event rate and will update NICE/ERG if necessary.

Clarification questions

B. If there are more recent analyses from the KATHERINE study, please provide the data. If not, please indicate when follow-up data will be available.

No additional analyses have taken place. Please see part “a” of this response for information on when follow-up data will be available from the KATHERINE trial.

A10. Please clarify how many patients in each arm of the KATHERINE study were from the UK. Please also clarify how many patients in each arm of the APHINITY study were from the UK.

KATHERINE (71 total)

- Trastuzumab emtansine - 33
- Trastuzumab - 38

APHINITY (224 total)

- Pertuzumab-Trastuzumab - 109
- Trastuzumab – 115

A11. Priority question: Please provide the CSR for the APHINITY study and please provide all publications from the APHINITY study.

These documents have been provided as supplementary appendices to this response.

A12. Please clarify whether the definition for DFS in the KATHERINE study (CS, page 31: “DFS, including non-invasive breast cancers: defined as the time from randomisation to first occurrence of an IDFS event including second primary non-breast cancer or contralateral or ipsilateral DCIS”) is in line with the FDA definition: “DFS is defined as the time from randomization until disease recurrence or death from any cause”.[1] In addition, please provide a table comparing the FDA definition and the Definition for the Assessment of Time-to-event Endpoints in CANcer trials (DATECAN) guidelines IDFS definition with definitions used in KATHERINE and APHINITY trials.

We can confirm that the definition is in line with the FDA definition. Please see Table 2.

Table 2. Endpoint definitions across clinical trials of interest

Trial	Invasive-disease–free survival (IDFS) definition	DFS definition
FDA Definition	Not defined	DFS is defined as the time from randomization until disease recurrence or death from any cause
CANcer trial (DATECAN)[iv]	Defined as including invasive ipsilateral breast tumour recurrence/progression, Local invasive recurrence/Progression, Regional invasive recurrence/progression (M+: regional progression), invasive contralateral breast cancer, Appearance/occurrence of metastasis/distant recurrence, second primary invasive cancer (non-breast cancer), Ipsilateral DCIS, Contralateral DCIS and death from breast cancer, non-breast cancer, related to protocol treatment, any cause and unknown cause.	As stated in the paper DFS was deemed ambiguous and renamed by the experts as invasive DFS (iDFS).
KATHERINE[v]	(STEEP DEFINTION – **secondary endpoint**) Defined as the time from randomisation to the first occurrence of one of the following: second primary non-breast cancer, ipsilateral invasive breast tumour recurrence, ipsilateral local-regional invasive breast cancer recurrence, distant recurrence, contralateral invasive breast cancer or death of any cause*	Defined as the time from randomisation to first occurrence of an IDFS event including second primary non-breast cancer or contralateral or ipsilateral DCIS
APHINITY[vi]	(STEEP DEFINTION – **secondary endpoint**) Defined as time from randomisation until the date of first occurrence of one of: recurrence of ipsilateral invasive breast tumour, recurrence of ipsilateral locoregional invasive disease, a distant disease recurrence, contralateral invasive BC, second primary non-breast cancers or death from any cause*	Defined as time between randomisation and the date of the first occurrence of an IDFS event including second primary non-breast cancer event or contralateral or ipsilateral DCIS.

*Please note the KATHERINE and APHINITY studies used a modified IDFS definition for the primary outcome. This definition of IDFS excluded second primary non-breast cancer tumours, based on the US FDA's recommended definition for a trial intended to support a regulatory filing. Inclusion of second primary non-breast cancer events in the IDFS definition has the disadvantage of including events not related to the cancer or the treatment under study, thereby potentially diluting any treatment effect.

A13. Please clarify why 133 patients discontinued treatment due to AEs in the trastuzumab emtansine arm compared to only 15 patients in the trastuzumab arm (CS, page 37).

Please see Table 49 of the KATHERINE CSR for a more detailed breakdown of the adverse events causing treatment discontinuation for both the trastuzumab emtansine study arm and the trastuzumab study arm.

Due to the cytotoxic element of trastuzumab emtansine, trastuzumab and trastuzumab emtansine have different side effect profiles. As seen in Table 49, the majority of AEs leading to treatment discontinuation in the trastuzumab arm were due to cardiac toxicity (ejection fraction decreased: 10 out of 15, 66%), whereas the AEs leading to treatment discontinuation in the trastuzumab emtansine arm were predominantly those resulting from the cytotoxic (emtansine) element in addition to some cardiac toxicity (laboratory abnormalities (platelet count decreased [4.2%], elevated blood bilirubin [2.6%], elevated AST [1.6%], ALT increased [1.5%]), peripheral sensory neuropathy (1.5%) and ejection fraction decreased (1.2%).

Thus, the addition of a cytotoxic element to the treatment (albeit a targeted one) leads to a different adverse event profile and a higher treatment discontinuation rate. This is consistent with what is known from the use of trastuzumab emtansine in the metastatic breast cancer setting.

A14. Please clarify why 23 randomised patients did not receive trastuzumab, compared to only 4 patients not receiving trastuzumab emtansine (Appendix D, Figure 3, page 39).

KATHERINE was an open label study and hence patients were aware of which arm they had been randomized to. It is expected that this led to higher dropout rates in the control arm. The reasons why patients did not receive treatment are given below:

Trastuzumab arm (n=23):

- Withdrawal by subject (n=17)
    - This was likely driven due to the fact that the KATHERINE trial was an open-label study and patients may have been dissatisfied being randomised to the control arm
- Protocol violation (n=4)
- Other (n=2): pt was re-randomized into other arm of study and treated with trastuzumab emtansine; pt did not have adequate venous access

Trastuzumab emtansine arm (n=4):

- Withdrawal by subject (n=2)
- Other (n=1) not eligible
- Recurrence noted prior to first dose of study drug (n=1)

A15. Priority question: Please provide full baseline characteristics for the node-positive subgroups from the KATHERINE and APHINITY trials by treatment arm.

This information has been provided as a supplementary appendix to this response.

A16. Priority question: Please provide full baseline characteristics and separate results for all outcomes from the KATHERINE trial for the node-negative population.

This information has been provided as a supplementary appendix to this response.

A17. Priority question: Could the company clarify how the patients who required a trastuzumab emtansine dose reduction to 3.0mg/kg (n=77) or 2.4mg/kg (n=29) were dealt with in the analysis? Specifically, could the company provide a subgroup analysis for these patients (3.6 mg/kg vs. 3.0 mg/kg vs. 2.4 mg/kg) across OS, DFS, IDFS, distant recurrence-free survival, HRQoL and adverse event outcomes?

This information has been provided as a supplementary appendix to this response.

A18. Could the company provide details on how many patients who discontinued trastuzumab emtansine therapy crossed over to complete study treatment with trastuzumab in the KATHERINE study and vice versa? And at what stage of the trastuzumab emtansine/trastuzumab therapy they made the cross over (e.g. at which cycle number (between 1 and 13 cycles) and how many cycles they received in total?

In the KATHERINE study, patients are only able to switch from trastuzumab emtansine therapy to trastuzumab (one way). There are 71 patients that switched from TDM1 to Trastuzumab, of which 63 completed 14 cycles (trastuzumab emtansine + trastuzumab) – Table 9 CSR.

As discussed on the teleconference, please refer to Table 40, 41 and 42 of the CSR for more information.

A19. Could the company describe how they anticipate the adverse events that are reported to be more frequent in the trastuzumab emtasine arm will be managed in the clinic, particularly with regards to low platelet counts, haemorrhage, increased aspartate aminotransferase/alanine aminotransferase levels and peripheral neuropathy? If these are managed with other drugs/clinical approaches, could the company comment on how or if these costs are addressed in the economic model?

Overall, the majority of adverse events (AE's) from trastuzumab emtasine were grade I, II, and laboratory abnormalities as oppose to a symptomatic burden to patients. In the event of higher-grade abnormalities, there is clear guidance in the summary of product characteristics (SmPC), which discusses a dose reduction schedule and dose modification for AE's such as increased transaminases (AST/ALT), thrombocytopenia or peripheral neuropathy.

Most events were considered transient and self-limiting:

- **Thrombocytopenia –** The majority of these events were grade I and II (n=169). These were deemed to have minimal clinical consequence and can be successfully monitored through standard blood tests. In addition, platelet count typically increases before the next scheduled dose.
- **Increase AST/ALT –** The majority of these events were grade I and II (n=206/168). These were deemed to have minimal clinical consequence and can be successfully monitored through standard blood tests. In addition, these findings were generally transient.
- **Haemorrhage -** The majority of these events were grade I and II. These are typically self-limiting or controlled through local measures. Grade III haemorrhage were similar between treatment arms.
- **Peripheral Neuropathy –** Patients were eligible to enrol with Grade I neuropathy. All patient had received a form of taxane therapy and this is known to cause peripheral neuropathy.[vii] Generally, there is no treatment to address this AE, but at the time of data cut off almost 75% of peripheral neuropathy cases had been resolved.[v]

The adverse events highlighted are known effects of using trastuzumab emtansine. As this treatment is used in other indications, such as in the metastatic setting, it is expected that breast cancer units have experience in the management of these effects. Additionally, some of these adverse events demonstrated in other breast

cancer therapy treatments, such as taxanes, thus reinforcing the common nature of these events and therefore the widespread experience in dealing with them.

In summary, the adverse events highlighted in this question will not typically warrant active clinical intervention. Nevertheless, the cost and HRQoL impacts associated with these events have been incorporated in the economic model as part of a scenario analysis. Please see the response to B30 for further information.

A20. Please clarify the definition of, 'clinically meaningful improvement' on Page 39 of the CS.

We use the term "clinically meaningful improvement" to describe not only a statistically significant clinical trial outcome, but an advance that will change the treatment of this group of patients. We understand from a group of UK breast cancer experts that the magnitude of benefit seen in this study is considered transforming, clear and practice changing. The KATHERINE study showed a 50% reduction in risk of IDFS events (HR=0.50) with trastuzumab emtasine compared to trastuzumab and an 11.3% difference between groups, favouring trastuzumab emtasine, in the 3-year IDFS event free rates (88.3% vs 77%). Treatment guidelines such as NCCN, ESMO and St.Gallen have already been updated to recommend the use of trastuzumab emtansine, demonstrating a change in clinical practice. Furthermore, we have received numerous requests for compassionate access from both clinicians and patients.

Indirect comparison

A21. Priority question:

A. Please provide full Bucher indirect comparison results for the outcomes OS, DFS, recurrence/death probabilities and the incidence of the main AEs that are included in the economic model (in line with question B30), using scenarios A, B and C (as in Appendix M of the CS).

The requested Bucher analyses have been conducted using the same methodology as documented in Appendix M of the original submission. The results of these analyses are presented below in Table 3-Table 5.

Please note, it is not immediately clear to the Company what is meant by the ERG's "recurrence/death probabilities" request. We assume that the provision of the Bucher analyses on IDFS (recurrence probabilities), DFS (recurrence probabilities), and OS (death probabilities) endpoints, as below, satisfies this request.

Table 3. Hazard ratios from Bucher analysis – DFS endpoint

Scenario	APHINITY			KATHERINE			ITC	
	Population	HR (95% CI)	Log HR (±SE)	Population	HR (95% CI)	Log HR (±SE)	Log HR (±SE)	HR (95% CI)
A	Node-positive	0.77 (0.62-0.95)	-0.26 (0.11)	Node-positive	0.55 (0.40-0.75)	-0.60 (0.16)	-0.34 (0.19)	0.71 (0.49-1.04)
B	Node-positive	0.77 (0.62-0.95	-0.26 (0.11)	ITT	0.53 (0.41-0.68)	-0.63 (0.13)	-0.37 (0.17)	0.69 (0.49-0.96)
C	ITT	0.82 (0.68-0.99)	-0.20 (0.10)	ITT	0.53 (0.41-0.68)	-0.63 (0.13)	-0.44 (0.16)	0.65 (0.47-0.89)

Abbreviations: 95% CI: 95% confidence interval; HR: hazard ratio; ITC: indirect treatment comparison; ITT: intention to treat.

Table 4. Hazard ratios from Bucher analysis – OS

Scenario	APHINITY			KATHERINE			ITC	
	Population	HR (95% CI)	Log HR (±SE)	Population	HR (95% CI)	Log HR (±SE)	Log HR (±SE)	HR (95% CI)
A	Node-positive	0.85 (0.61-1.18)	-0.16 (0.17)	Node-positive	0.66 (0.41-1.06)	-0.42 (0.24)	-0.25 (0.30)	0.78 (0.43-1.39)
B	Node-positive	0.85 (0.61-1.18)	-0.16 (0.17)	ITT	0.70 (0.47-1.05)	-0.36 (0.21)	-0.19 (0.27)	0.82 (0.49-1.39)
C	ITT	0.91 (0.67-1.23)	-0.09 (0.15)	ITT	0.70 (0.47-1.05)	-0.36 (0.21)	-0.26 (0.26)	0.77 (0.46-1.27)

Abbreviations: 95% CI: 95% confidence interval; HR: hazard ratio; ITC: indirect treatment comparison; ITT: intention to treat.

Table 5. Odds ratios from Bucher analysis – platelet count decrease*

Scenario	APHINITY			KATHERINE			ITC	
	Population	OR (95% CI)	Log OR (±SE)	Population	OR (95% CI)	Log OR (±SE)	Log OR (±SE)	OR (95% CI)
A	Node-positive	0.43 (0.22-2.19)	-0.84 (0.59)	Node-positive	48.61 (0.33-87.96)	3.88 (1.42)	4.73 (1.54)	113.05 (5.52-2316.24)
B	Node-positive	0.43 (0.22-2.19)	-0.84 (0.59)	ITT	86.59 (0.43-113.0)	4.46 (1.42)	5.31 (1.54)	201.37 (9.89-4099.00)
C	ITT	2.81 (0.50-4.92)	1.03 (0.58)	ITT	86.59 (0.43-113.0)	4.46 (1.42)	3.43 (1.54)	30.82 (1.52-625.87)

Abbreviations: 95% CI: 95% confidence interval; HR: hazard ratio; ITC: indirect treatment comparison; ITT: intention to treat.
* Zero events in trastuzumab arm of KATHERINE arm was changed to 0.5 events in order to be able to derive an odds ratio

Please note, there is a high degree of variability in the results of the Bucher safety analysis. This is principally due to there being zero events in the trastuzumab arm of the KATHERINE study.

Clarification questions

B. Please also provide the comparison results above obtained from Bayesian MCMC analysis with posterior outcomes, incorporated in the economic model.

The methodology and results associated with this analysis have been provided as a supplementary appendix to this response. Please see below for a brief overview of the methodology and interpretation of the results:

A Bayesian ITC was performed using MCMC to compare the treatment effects of trastuzumab emtansine versus pertuzumab + trastuzumab. The same input data from APHINITY and KATHERINE trials were used as in the previously presented Bucher analysis. The analysis was performed using the GEMTC R package which implements consistency models for Evidence Synthesis using JAGS as described in NICE TSD series on Evidence Synthesis (specifically the framework described in TSD 2). Two analyses were performed: A fixed effects analysis and a random effects analysis (allowing for between study variance). Given there are only 2 trials included in the evidence base it was necessary to use an informative prior for between study variance in the random effects analysis. These informative priors for between study variance were chosen from Table 4 of Turner *et al* with the suggested prior for Pharmacological vs pharmacological comparisons being taken (OS was considered a "Mortality" outcome type and IDFS a "Internal/external structure-related outcomes (e.g. radiograph outcomes)" outcome type per the groupings presented in that paper. [viii]

The results of the fixed effects analysis are consistent with the Bucher analysis. The random effects analysis results in effect estimates that are similar but with wider 95% credible intervals. This is unexpected but of limited utility for decision-making as the estimate of between study variance is solely driven by choice of prior distribution given the limited data included in the analysis.

As the fixed effects analysis was consistent with the Bucher analysis it has not been implemented in the model. Given the additional uncertainty generated by use of a Random effects model with only 2 studies and therefore no data to inform the estimate of between study heterogeneity it has also not been implemented in the model but could be implemented by replacing the estimates from the Bucher analysis included on the Sheet “Model Inputs” and Cell I186:I188.

C. Please also provide the comparison results above obtained from IPD meta-regression and incorporate them in the economic model.

Unfortunately, after extensive further investigation, the Company has reached the conclusion that it is not possible to conduct this analysis in a robust way.

Clarification questions

As highlighted in Document B, the inability to conduct this analysis primarily stems from the differences in the study populations of the APHINITY and KATHERINE trials. Patients included in the KATHERINE study are only those who did not achieve a pCR following neoadjuvant treatment, and therefore had RID in the breast and/or axillary lymph nodes. This “residual invasive or non-pCR subgroup” is not reproducible in the APHINITY study population simply because patients were not pre-treated in APHINITY (therefore an assessment of pCR was not possible).

This difference in the patient populations across the trials has proved irreconcilable. It is not clear to the Company which variables to include/exclude as covariates in the IPD meta-regression. Additionally, it is not known whether this inclusion/exclusion is likely to increase or decrease clinical heterogeneity e.g. for node-positivity: is node-positivity after neoadjuvant treatment comparable to node-positivity in treatment-naïve patients? For “Tumour size at baseline”, the tumour size after neoadjuvant pre-treatment (KATHERINE) is different from tumour size in treatment naïve patients APHINITY). Equivalent values in “tumour size at baseline” does not mean the same, clinically speaking, in the KATHERINE and APHINITY studies because the tumour is expected to shrink following pre-treatment. Using these covariates to try to explain the heterogeneity between the two trials does not seem appropriate, as, although they have similar names, they are not measuring the same characteristics of disease.

In conclusion, the methodological flaws resulting from the lack of clinical comparability of both the covariates and the study populations are likely to lead to uninterpretable and biased results which are not informative or useful for the purposes of decision-making.

A22. Priority question: In the company submission it is stated that the indirect comparison analyses “are not endorsed by the Company because they are likely to lead to biased results and are not methodologically justified (CS, page 55). The main difference between the two trials is that the KATHERINE study included pre-treated patients and the APHINITY study included treatment-naïve patients. Please provide published evidence that the relative effect of pertuzumab versus trastuzumab and the relative effect of trastuzumab emtansine versus trastuzumab is likely to be different in pre-treated and treatment-naïve patients. Or, in the absence of published evidence, please provide expert opinion that there are likely to be differences – in that case please provide details (number of experts for each statement and their qualifications as experts) of the experts consulted.

Given the results from the CTNeoBC meta-analysis, we know that residual invasive disease in HER2-positive patients following neoadjuvant treatment confers an especially poor prognosis.[xi] Thus, the pre-treated patients in KATHERINE are a very different patient population to the treatment naive patients in APHINITY (60% of whom could be expected to achieve pCR had their treatment been initiated pre surgery). Therefore, to compare outcomes across the two studies is to look at two different patient populations (as evidenced by comparison of the control arms of each study, which differs only by timing of treatment initiation). Hence why we believe the results of an indirect treatment comparison are biased and not methodologically sound.
Please see below the requested expert opinions.

Expert statement 1

Dr. M B Mukesh MBBS, FRCR, MSc, MD
Consultant Clinical Oncologist
East Suffolk & North Essex NHS Foundation Trust
mmukesh@nhs.net

"APHINITY study looked at the addition of adjuvant pertuzumab for high risk Her2 positive breast cancer patients. The high risk was based on node positive disease or primary tumour size of >1cm. The addition of pertuzumab reduced the risk of invasive cancer recurrence especially in the node positive group and its use is supported by NICE.[ix]

KATHERINE study randomized Her-2 positive BC patients who had residual invasive disease after neo-adjuvant chemotherapy (NACT) with Her-2 directed therapy between adjuvant trastuzumab with trastuzumab emtansine. Patients with residual invasive cancer after neo-adjuvant treatment are considered as high risk of developing recurrent invasive disease.[xi] The study results showed clinical and statistical significant reduction in risk of recurrent breast cancer and death in the trastuzumab emtansine arm.

To my knowledge, there is no published data looking at the "relative effect of pertuzumab & trastuzumab versus trastuzumab and relative effect of trastuzumab emtansine versus trastuzumab" in early breast cancer setting. The indirect comparison between APHINITY and KATHERINE study is not appropriate as both study looked at a very different patient population with different interventions. The APHINITY study did not include patients receiving NACT and the high risk was defined based on baseline node positivity. There was no information about tumour sensitivity to treatment. The study included addition of pertuzumab to trastuzumab in adjuvant setting for more effective Her-2 pathway blockade. KATHERINE study was based on patients who had received NACT and Her-2 directed therapy and had residual disease post neo-adjuvant treatment. The study did not select patients

based on baseline tumour size or nodal status but included patients who had demonstrated in vivo resistance to chemotherapy and Her-2 directed therapy (80% trastuzumab and 20% with trastuzumab & pertuzumab). The high risk feature was residual disease post neo-adjuvant therapy. The study looked at switching adjuvant Her-2 directed antibodies (trastuzumab ± pertuzumab) with antibody drug conjugate (trastuzumab emtansine) in patients with residual disease."

Expert statement 2:

Dr Duncan Wheatley Clinical Oncologist Clinical Lead for Peninsula cancer research network, Member of NIHR breast clinical studies group and executive member of the UK breast cancer Group. Recruiter to TRYPHAENA, APHINITY, KAITLIN, and KATHERINE Studies.

"In the aphinity study, her2+ breast cancer patients were post surgically treated with adjuvant chemotherapy and trastuzumab and randomised to receive a year of pertuzumab/placebo. At 3 years the invasive event free survival was 94.1% for those receiving pertuzumab vs 93.2% for those who didn't. In the slightly higher risk node positive population (63% of trial population), the invasive cancer event rate was 92% vs 90.2%. These differences were statistically significant , but small. 40% of the patients in Aphinity had small, less than 2cm tumours and 47% were node negative. Therefore overall these patients in Aphinity were a good prognostic group, as seen by the excellent 3 year survival of both groups. However further follow up is needed to see if the long term benefits change over time. Certainly more patients will relapse over time.

However we know the main prognostic guide , probably even over stage at diagnosis, is response to neoadjuvant treatment. Her2+ breast cancer patients who achieve a pathological complete response to neoadjuvant treatment with chemotherapy and her2 directed antibodies, have an excellent long term survival compared to those who don't. This could not be assessed in the Aphinity trial as all patients were treated after surgery in the adjuvant setting. However some patients would have achieved a pathological CR with neoadjuvant her2 based chemotherapy and some wouldn't. Therefore this trial generally contains a high proportion of patients with lower risk disease, and many patients who would have achieved a pathological CR, if they had received neoadjuvant chemotherapy, and achieved an excellent long term survival. This is evidenced by the excellent, albiet only at 3 year, survival of both groups.

In the Katherine study, the hypothesis was that we already knew that patients who don't achieve a pathological complete response have a worse outcome, switching to alternative her2 based therapy might give them a better outcome. The bigger the residual cancer burden after neoadjuvant therapy, the higher the risk of relapse. Therefore the patients in Katherine study were biologically predetermined to be a much higher risk group than in Aphinity. This is both because they had residual

disease after her2 antibody containing chemotherapy (some with trastuzumab, some (19%) with 2 her2 containing regimes, mainly pertuzumab) and because patients receiving neoadjuvant chemotherapy will usually have a much higher stage at diagnosis than most of the patients in aphinity. Patients who have pertuzumab added to trastuzumab, have almost double the chance of achieving a pathological complete response, so those with residual disease will be rarer and presumably even more resistant. Pathological CR is more likely in the er- her2+ subgroup than the er+her2+ group (as shown by the fact 25% of patients in Katherine study were er-, 75% er+, whereas overall there is a 50/50 split for er-/er+ patients in her2+ breast cancer populations).
In the results of Katherine, overall the event rate for relapses is higher than Aphinity because of these facts, that a poorer prognostic group had been selected via higher initial stage and resistance to standard her2 based chemotherapy. The 3 year event free survival was 88.3% for the T-DM1 group, versus 77.0% for those continuing with trastuzumab, with a hazard ratio of 0.50.
The standard of care for most larger (over 2cm/node positive) her2+ breast cancer patients would be neoadjuvant chemotherapy with pertuzumab and trastuzumab, as per NICE guidance. For those with nodal involvement, adjuvant pertuzumab and trastuzumab would be the standard of care adjuvantly. The addition of pertuzumab neoadjuvantly roughly doubles the path cr rate, so would half the number of patients not achieving a pathological cr, and therefore potential candidates for Kadcyla. I would therefore strongly support neoadjuvant dual antibody containing neo adjuvant chemotherapy for these patients, with kadcyla for those not achieving a pathological complete response. This would be instead of the much less effective therapy of continuing the antibodies (as per standard of care) post surgery, with their costs anyway."

Expert statement 3:

Mr Henry Cain,
Consultant Oncoplastic Breast Surgeon,
Royal Victoria Infirmary

"To answer to this question it must be appreciated that these trials have been undertaken in 2 dramatically different patient populations. The patients in the Katherine trial, pre recruitment and randomisation to the trial, have been identified as a high risk of poor outcome by the fact that they had residual disease (failed pCR) following neo-adjuvant therapy. This is not the case in the Aphinity study which includes a relatively unselected group of treatment naive patients.

It is accepted that the oncological outcome of a patient is not affected by starting systemic treatment pre or post-surgery i.e. there has never been a survival advantage shown by completing a proportion of your systemic treatment in the pre-operative setting.

Clarification questions

Accepting this, if the populations of the 2 studies were the same then the outcome of the control arm of the Aphinity trial who received a year of Herceptin should be identical to the control arm of the Katherine trial who also received a year of Herceptin with up to 6 cycles given in the pre-operative setting with the remainder of the cycles of Herceptin given in the post-operative period.

The IDF of the control arm of the Aphinity trial was 90.6% compared with the IDF of the control arm in Katherine of 77%. This clearly demonstrates that the 2 trial populations are entirely different. By using pre-operative treatment of the tumour the Katherine study filtered out the patients who were going to do well (had achieved a pCR) that contributed to the excellent outcome seen in the control arm of the Aphinity study and focused treatment adaption on the patient with most to gain. Due to these different patient groups in the 2 studies it is inappropriate to make a direct cross study comparison between the patient groups."

Section B: Clarification on cost-effectiveness data

Clinical inputs

B1. Priority question: Please provide all details of the communication between the company and the clinical experts. Please include anonymised information about the clinical experts, detailed minutes of the face-to-face meeting and/or teleconference, list of expert recommendations and justifications for clinical assumptions and inputs used in the model. In particular, please indicate the following:

a. How many experts provided information for each of the following: model structure, identification of subsequent treatments and their estimated shares in clinical practice, health state resource use and costs, modelling of IDFS, recurrence and duration of treatment effect? In each case, please provide more detail of the clinical/working setting and experience of included experts.

Please see Table 6 below.

Table 6. Expert validation breakdown

Study	Expert background	Forum and justification
Model structure	Consultant in Medical Oncology, The Christie NHS Foundation Trust, Manchester	Feedback on the modelling structure was sought as part of a HTA advisory board that took place as part of TA569. Given that TA569 also evaluated an anti-HER2 therapy in the adjuvant treatment of HER2+ eBC it was deemed reasonable to use the same structure here.
	Consultant Medical Oncologist, Northern Centre for Cancer Care, Newcastle	
	The Christie NHS Foundation Trust, Manchester	
	London School of Hygiene and Tropical Medicine, London	
	London School of Hygiene and Tropical Medicine, London	
	Institute for Health Services Research University of Exeter Medical School, Exeter	
	Senior Research Fellow, Centre for Health Economics, York	
Subsequent treatments and market shares	61 medical or clinical oncologists practicing in breast cancer across the UK.	This information was collected as part of market research conducted by the Company (readout = August, 2019). A summary of this research has been submitted as an appendix to this response.

Health state costs and resource use	Not applicable	Resource use frequencies in this analysis are identical to those in the TA569 (pertuzumab in adjuvant treatment of HER2+ breast cancer) which were in turn based upon those used in TA424 (appraisal of neoadjuvant pertuzumab in HER2+ breast cancer). The resource usage in these appraisals is not expected to have changed over time. Additionally, this appraisal focuses on the same disease area (early HER2+ breast cancer) and the same type of therapy (anti-HER2). Consequently, there appears to be no clear rationale to deviate from the accepted values used in TA569. Please see the response to B29.
Modelling of IDFS, recurrence, and Treatment effect duration	Consultant in Medical Oncology, The Christie NHS Foundation Trust, Manchester Consultant Medical Oncologist, Northern Centre for Cancer Care, Newcastle The Christie NHS Foundation Trust, Manchester London School of Hygiene and Tropical Medicine, London London School of Hygiene and Tropical Medicine, London Institute for Health Services Research University of Exeter Medical School, Exeter Senior Research Fellow, Centre for Health Economics, York	Feedback on these aspects were discussed as part of the HTA advisory board that took place for TA569. The approach and the assumptions taken in that analysis were judged appropriate for decision-making by the appraisal Committee. Given the similarity in disease area (HER2+ eBC), therapy class (anti-HER2), and data availability there appeared to be no clear rationale to deviate from the methodology accepted as part of the TA569.

b. Please provide further details of the opinions given by experts in relation to each of aspects of the model listed in part a of this question and provide details regarding the extent to which these opinions were included in the model or justification of why they were not included.

The minutes from the HTA advisory board and a summary of the market research conducted by the Company have been provided as supplementary appendices to this response.

Model structure and implementation

B2. Priority question: Please provide all input parameters for the model based on the node-negative population, include them in the model and provide additional cost-effectiveness analyses for the node-negative population based on this set of input parameters.

The methodology and results of this analysis have been provided as part of a supplementary appendix to this response.

IDFS modelling

B3. The sources used beyond the follow-up from KATHERINE trial were not obtained from systematic review. Please conduct targeted reviews for the inputs used in the model that were obtained from sources other than the KATHERINE trial and incorporate the findings of these targeted systematic reviews into the economic model.

All clinical inputs used in the period beyond the KATHERINE follow-up have been derived from trials evaluating anti-HER2 therapies in HER2-positive metastatic breast cancer setting (with the exception of the Hamilton *et al.* study – see B17). As these trials evaluated drugs owned by Roche Products Ltd, patient-level data has been available to the Company when developing this economic analysis.
It is very unlikely that a targeted review is likely to yield clinical sources any more appropriate than the patient-level data sets, in the exact population of interest, that are already used in the analysis.

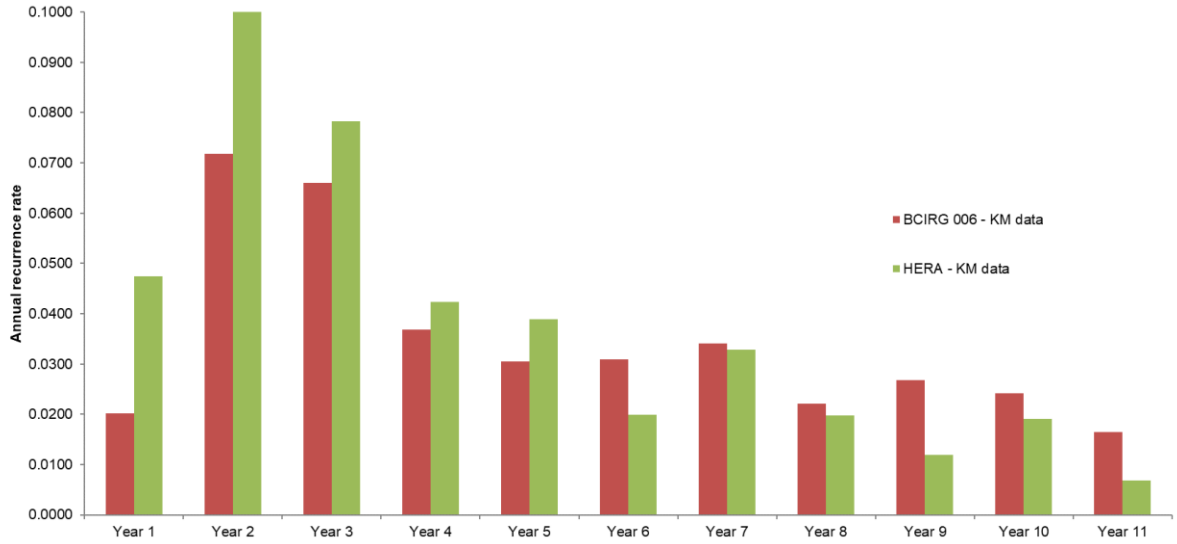
It is also important to note that the Company has conducted four extensive systematic literature reviews during the development of this dossier. Additionally, the sources used were also used in TA569 and were deemed appropriate for decision-making by both the ERG and Appraisal Committee.

B4. Priority question: Please explain why the first cut-off point for modelling IDFS was set to 3 years.

- Page 80 says “Published literature shows that the underlying risk of recurrence in the first four years for a patient with eBC is not representative of the risk of recurrence at a later date”.

This statement should say, “Published literature shows that the underlying risk of recurrence in the first three years for a patient with eBC is not representative of the risk of recurrence at a later date”.
This is evolution of risk is displayed in Figure 20 of Document B (presented below). The annual recurrence rate in both BCIRG 006 and HERA appears to almost halve from year three to four.

Figure 1. Annual recurrence rate (DFS endpoint) from the HERA and BCIRG 006 clinical trials – node-positive population



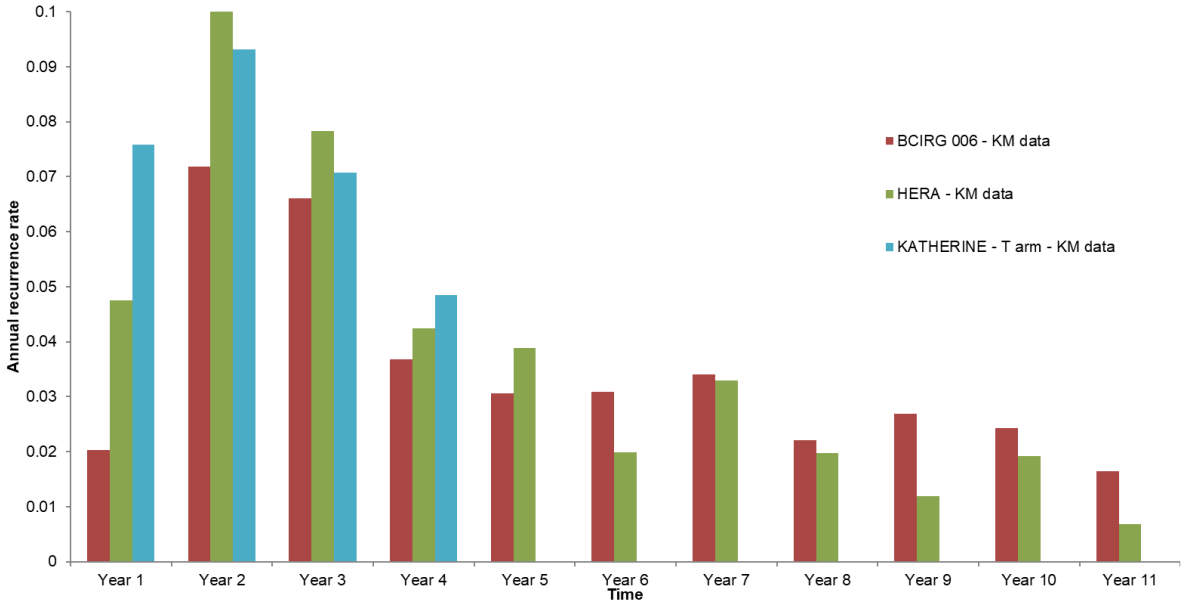
- Page 37 says: “The clinical cut-off date for this analysis was 25th July 2018, at which point the median follow-up duration in the ITT population was 41.4 months (range 0.1–62.7) in the trastuzumab emtansine arm and 40.9 months (range 0.1–62.6) in the trastuzumab arm”. Does this mean that not all available data from KATHERINE was used for modelling IDFS?

No. Survival analysis was conducted on all IDFS data collected from the first analysis of the KATHERINE trial. The entirety of the IDFS data was used to generate the extrapolation parameters seen in the cost-effectiveness model.

- If the risk of recurrence drops after year 3, this should have been observed in the trial. Please provide the evidence to confirm this statement. This should at least include a new Figure 20 with additional bars for KATHERINE as observed in the trial (year 1 until end of the observation period – not extrapolations as in Figure 23).

An adapted Figure 20 (containing the trastuzumab arm IDFS data from the KATHERINE trial) is presented below.

Figure 2. Annual recurrence rate from the KM data in the trastuzumab arms of the HERA, BCIRG 006 and KATHERINE clinical trials[a]



[a] Year 5 data point has been omitted due to low event numbers (n=2)

Naturally, censoring is an issue with the KATHERINE KM data. There is therefore a degree of uncertainty associated with all of these annual recurrence rates. This is especially pertinent to the "Year 4" and "year 5" data points. Median follow-up was ~41 months in the trastuzumab arm (i.e. in the middle of the "Year 4" timepoint) and only two events occur during the "Year 5" time period. Caution should therefore be taken when interpreting this data.

Despite this uncertainty, the sizable drop in the recurrence rate from year 3 to year 4 in the KATHERINE KM data can be used as supportive evidence of beginning the "cure model" at year 3 in the extrapolation of IDFS in the economic analysis.

B5. Priority question: Page 81 of the company submission says: "The node-positive populations in these trials represent a higher risk population and are

believed to be a more appropriate proxy to patients with RID following neoadjuvant therapy (KATHERINE population)". Please provide evidence to justify this statement.

The Company is unaware of any evidence to support this statement. It is a reasonable assumption that has been made.

Patients with residual invasive disease following neoadjuvant therapy are at a higher risk of disease recurrence. Similarly, patients in which disease has spread to the lymph nodes (node-positive) are also at a higher risk of disease recurrence. Both RID following neoadjuvant therapy[x,xi,xii,xiii,xiv] and node-positivity[xv,xvi,xvii] are well-documented risk factors.

The statement made on page 81 of the CS was simply designed to highlight that it was more appropriate to compare between two higher risk populations (RID in KATHERINE and node-positive in HERA) rather than a high risk population (RID patients in KATHERINE) and a lower risk population (ITT population in HERA).

B6. Page 82 of the company submission says: "The trend seen in Figure 20 and described above has been replicated in the economic analysis by assuming that from 36 months onwards, the proportion of patients being "cured" (no longer at risk of recurrence and only subject to background mortality) linearly increases with time from 0% at 36 months to 95% at 120 months". Please explain why a linear trend was assumed, why increases up to 95% and why up to 120 months. Please include in the model an alternative option for the linear trend.

There are several alternatives to a linear trend. During the mid-point teleconference, the ERG did not specify which option they would like to see as an alternative. Instead, they suggested that the Company should provide an explanation as to why they used the linear trend. The Company has addressed this below:

A linear trend was used as it is both simple to integrate into the model structure and intuitive to the end user. To apply alternative trends would require re-structuring the current economic model and the introduction of a significant amount of complexity into the overall modelling approach.

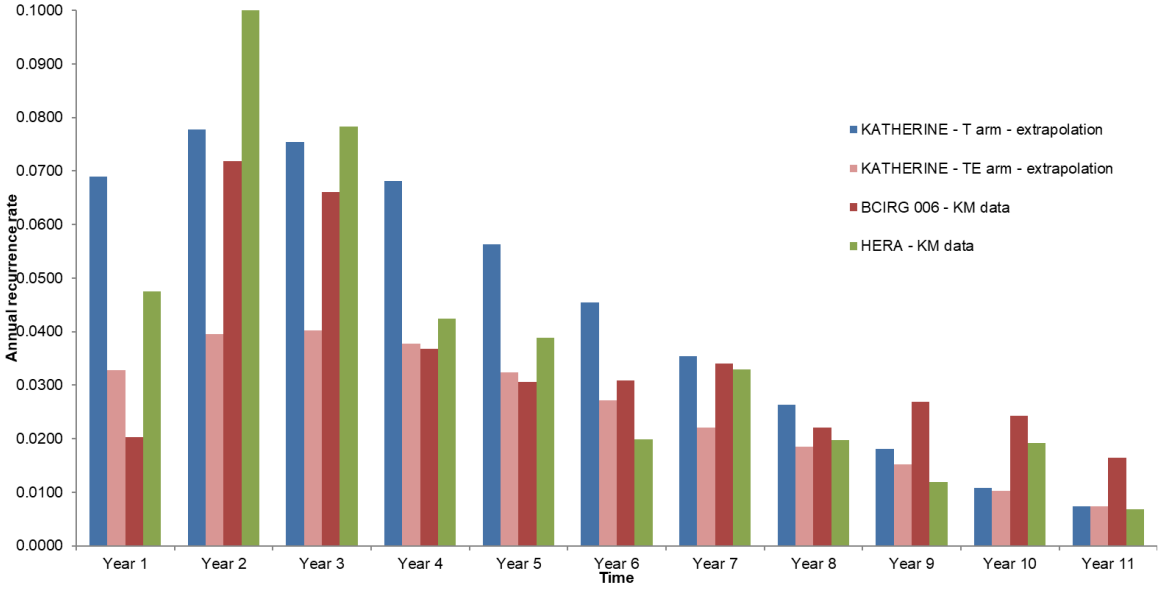
The cure model is currently applied equivalently across both treatment arms. By applying alternative functions it is likely that we will be in a situation in which different trends are being used for different the arms in the model. There is no clinical rationale to support this.

Clarification questions

B7. Based on Figure 23, the company concluded the following: “The difference in recurrence rate seen in the first four years is driven by the results from the respective trials. From year four to year ten the recurrence rates observed in BCIRG 006 are broadly similar to the modelled recurrence rate in the economic analysis”. The ERG does not consider this evident. In both HERA and BCIRG the drop at year 4 is much larger than the drop observed in the model. Please include the modelled TE arm in Figure 23.

An updated Figure 23 from Document B is presented below.

Figure 3. Annual recurrence rate observed in the trastuzumab arms of the BCIRG 006* & HERA* trials compared to modelled recurrence rate in trastuzumab and trastuzumab emtansine arms of KATHERINE - cure model begins at month 36**



Footnotes: * node-positive population; **, ITT population.
Abbreviations: KM: Kaplan Meier; T, trastuzumab; TE, trastuzumab emtansine

The Company agrees that there is a larger drop in the annual hazard rate in year 4 of the HERA and BCIRG 006 trials compared to the extrapolation of the trastuzumab arm in the model. However, it is important to note that this overestimation of the hazard persists only between year four and six. From year seven onwards the hazard rate seen in the extrapolation is broadly reflective of those seen in the longer term KM data of the KATHERINE and BCIRG 006 trials. An overestimation of the comparator arm hazard in 3 years of a 51-year analysis (6%) is unlikely to have a significant impact on the overall cost-effectiveness results seen in the Company CS. To quantify this impact, the Company has conducted an exploratory scenario analysis.

Clarification questions

When beginning the cure model from month zero, the overestimation of the hazard in the trastuzumab arm of the model is significantly lessened - see Figure 4. The cost-effectiveness results of this scenario analysis are reported below.

Figure 4. Annual recurrence rate observed in the trastuzumab arms of the BCIRG 006* & HERA* trials compared to modelled recurrence rate in trastuzumab and trastuzumab emtansine arms of KATHERINE - cure model begins at month zero**

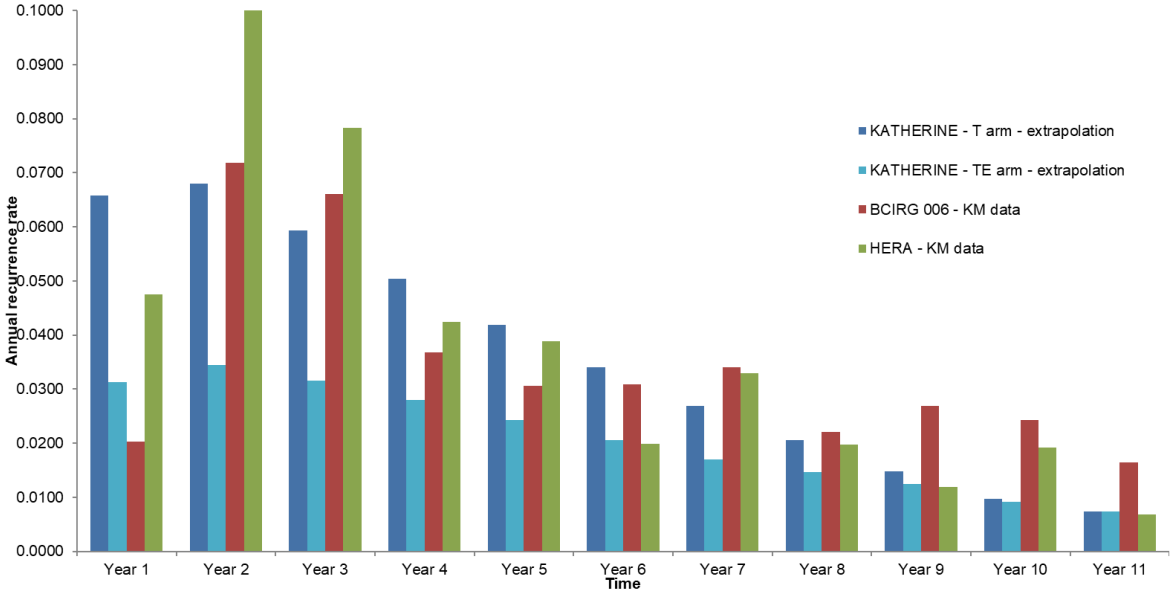


Table 7. Cost-effectiveness results when starting the cure model from month zero

Technologies	Total costs	Total LYG	Total QALYs	Δ costs	Δ LYG	Δ QALYs	ICER (£/QALY)	Δ from base case ICER
Cure model begins at 36 months (Base case analysis)								
Trastuzumab	[redacted]	15.02	[redacted]	[redacted]	1.97	1.60	£1,293	£0
Trastuzumab emtansine	[redacted]	16.99	[redacted]					
Cure model begins a 0 months (Scenario analysis)								
Trastuzumab	[redacted]	16.04	[redacted]	[redacted]	1.54	1.26	£3,481	+£2,188
Trastuzumab emtansine	[redacted]	17.59	[redacted]					

It is important to note here that there is no clinical rationale for beginning the cure model at month zero. This is simply an illustrative example designed to show the limited impact that the overestimation of the hazard in year 4-6 of the trastuzumab extrapolation has on the overall cost-effectiveness results. Additionally, there appears to be a significant underestimation of the hazard in year 2 and 3 of the

extrapolation (Figure 4) therefore the impact on the cost-effectiveness of this scenario analysis is likely to be overstated.

B8. Priority question: In Table 9 it is mentioned that "Patients discontinuing trastuzumab emtansine and switching to trastuzumab were included in the trastuzumab emtansine ITT population". Please clarify whether the estimation of the survival curves to extrapolate IDFS in the TE arm accounts for this switching. Please explain how treatment discontinuation (in both arms) is operationalized in the model.

During the KATHERINE study, 71 patients switched to trastuzumab treatment from trastuzumab emtansine therapy. This equates to less than 10% of patients in the intervention arm. Given that only a small minority of patients were affected, it was decided not to introduce additional uncertainty into the analysis by performing any crossover adjustments. It is important to note here that the approach of not adjusting the IDFS curves for treatment switching is a conservative approach with respect to the cost-effectiveness of trastuzumab emtansine.

First, the proportion of patients who switched from trastuzumab emtansine to trastuzumab therapy is so small that it should not have a large effect on the efficacy profiles seen in the trial. Additionally, based on the ITT principle, this switching leads to an underestimation of the trastuzumab emtansine treatment effect (patients who switched [received less trastuzumab emtansine] are still analysed as though they are in the trastuzumab emtansine arm). Finally, as noted in Document B, TTOT data in the trastuzumab emtansine arm includes patients who remained on trastuzumab emtansine therapy and patients who switched to trastuzumab therapy. Trastuzumab emtansine costs are used for all patients in all treatment cycles of the intervention arm (i.e. even when patients switched to the less costly comparator [trastuzumab], they are captured in the analysis using the more expensive treatment [trastuzumab emtansine] costs).

Ultimately, the factors outlined in the previous paragraph combine to result in an analysis that potentially underestimates the efficacy and overestimates the costs in the trastuzumab emtansine arm of the model. The lack of crossover adjustment is therefore an incredibly conservative analysis with respect to the cost-effectiveness of trastuzumab emtansine.

B9. Page 81 in the company submission says: "It should be noted however that the primary outcome in HERA was DFS, compared to IDFS in the KATHERINE study".

Please explain the similarities and differences between IDFS and DFS and how using one end point or the other is expected to affect the cost effectiveness results.

The similarities and differences between the definition of DFS used in the HERA trial and the definition of IDFS used in the KATHERINE trial are given below in Table 8.

Table 8. Definitions of the primary endpoints used in the HERA and KATHERINE trials

Study	Primary endpoint	Definition
HERA	DFS	Defined as time from randomization to the first occurrence of any of the following disease-free–survival events: • Recurrence of breast cancer at any site; • The development of ipsilateral or contralateral breast cancer, including ductal carcinoma in situ but not lobular carcinoma in situ; • Second nonbreast malignant disease other than basal-cell or squamous-cell carcinoma of the skin or carcinoma in situ of the cervix; • Or death from any cause without documentation of a cancer-related event.
KATHERINE	IDFS	Defined as the time from randomization until the date of the first occurrence of one of the following events (hereafter referred to as invasive-disease events): • Recurrence of ipsilateral invasive breast tumor, • Recurrence of ipsilateral locoregional invasive breast cancer, • Contralateral invasive breast cancer, • A distant disease recurrence, • Or death from any cause.

Commenting precisely on how the use of a different endpoint will impact the overall cost-effectiveness results is not a straightforward task. However, the trastuzumab emtansine treatment effect is shown to be consistent across both the IDFS and DFS analyses. The efficacy results in the DFS analysis from the KATHERINE trial have been given below. Please refer to page 110-112 of the trial CSR for more details.

> *At the CCOD, DFS events had occurred in 167 patients (22.5%) in the trastuzumab arm compared with 98 patients (13.2%) in the trastuzumab emtansine arm. Treatment with trastuzumab emtansine resulted in an improvement in DFS as compared with trastuzumab (unstratified HR = 0.53, 95% CI: 0.41, 0.68) (Table 28). Estimates of the DFS event-free rates at 3 years were 76.89% vs. 87.41% in the trastuzumab and trastuzumab emtansine arms, respectively.*

The Kaplan-Meier plot of DFS is consistent with the curves observed in the primary IDFS analysis. A clear and persistent early separation of the curves between the two arms was observed after randomization.

Given this consistency in efficacy profile, the choice of primary endpoint is expected to negligibly impact the overall cost-effectiveness results reported in the CS.

B10. Priority question: Please explain why the second cut-off point for modelling IDFS was 10 years. Please include in the model the possibility of changing this and the first cut-off (3 years) so that it is possible to test these assumptions in scenario analyses.

In TA569 (appraisal of adjuvant pertuzumab), the maximum cure rate (95%) is reached at 120 months (i.e. at 120 months, 95% of patients still in the IDFS health state have zero risk of recurrence – they are assumed to be "cured"). This timepoint was chosen because the DFS hazard rate observed in the 11th year of the HERA trial is similar to that of the UK mortality for patients aged 62 (the age at which patients in the hypothetical cohort of the economic analysis would be after 10 years had elapsed).

The same rationale was also used in this analysis in order to justify a "second cut-off point" of 10 years. The average age of the KATHERINE cohort is 49 in cycle one of the cost-effectiveness model. After 10 years, the average age of the cohort is 59. The UK mortality rate for a 59-year-old female is 0.005, whereas the annual hazard rate in the 11th year (120 months – 132 months) of the HERA trial was (0.007). The difference between these two rates is minimal and not thought to significantly affect the cost-effectiveness results – see Table 9.

The submitted model already contains the requisite functionality to conduct scenario analyses on the start and end point of the cure model. Indeed, scenario analyses on the cure model assumptions were provided as part of the original submission. For completeness, additional analyses around the second cut-off point have been included below.

Table 9. Scenario analyses on timepoint at maximum cure rate is reached*

Modelled patient age, Point at which maximum cure rate is reached	ICER (/QALY gained)	Change from base case ICER (£)
57 years old, 96 months (8 years)	£1,758	£466
58 years old, 108 months (9 years)	£1,452	£159

Clarification questions

59 years old, 120 months (10 years)	**£1,293**	**£0**
60 years old, 132 months (11 years)	£1,252	-£41
61 years old, 144 months (12 years)	£1,287	-£6

* The cure rate start point and maximum cure rate used in these analyses are the same as the base (i.e. 36 months and 95%, respectively)

Results in Table 9 shows that the timepoint at which the maximum cure rate is reached has a negligible impact on the ICER. This is principally due to the fact that the cure model is applied equivalently across both arms of the model.

Duration of treatment effect

B11. Priority question: Page 85 of the company submission says: “it is assumed that the treatment effect of trastuzumab emtansine will be maintained for 84 months (seven years) before gradually decreasing to be null at 120 months (ten years). The assumption of maintenance of treatment effect beyond the KATHERINE study follow-up period is based on observations from long-term trastuzumab studies”. These statements require further explanation. Please consider answering at least the following questions:

a. How is the “maintained” treatment effect operationalised in the model (e.g. what does it mean in terms of hazard rates or survival probabilities)? Please provide hazard rates obtained from the modelled iDFS and OS curves

The “maintained” treatment effect is operationalized by letting the extrapolation of the KM curve persist unmodified through time until the "gradually decreased” treatment effect is operationalized (see part b).

Please note; although the cure model begins to adjust the extrapolation from 36 months, this adjustment is applied equivalently to both treatment arms and is therefore independent of this issue.

b. How is the “gradually decreased” treatment effect operationalised in the model (e.g. what does it mean in terms of hazard rates or survival probabilities)?

Hazard rates in the trastuzumab emtansine arm of the model increase linearly until they are equivalent to those in the trastuzumab arm of the model at the

corresponding timepoint. Please see columns U to Y in the “K” sheet of the economic model for further information on the mechanics behind this effect.

c. Is the treatment effect defined up to the point where general population hazard rates apply?

It is not immediately clear to the Company what this question is referring to. Nevertheless, some additional explanation has been provided below.

In the base case, a treatment effect is defined until month 120 (10 years). At 10 years, the hazard rates are equal in both arms of the model (i.e. hazard ratio = 1).

Please note, the model is set-up in such a way that the survival rates in the analysis cannot exceed that of the general age-adjusted population.

d. “Maintained” would be based on a constant hazard ratio at the end of the KATHERINE trial? If that is the case then please provide that hazard ratio.

This is incorrect. The model is not driven by a constant hazard ratio observed at the end of the KATHERINE trial. In fact the hazard ratio is evolving year-by-year until the “treatment effect ceases” – See Figure 8.

Please see part “a.” of this question for an explanation of how the treatment effect is “maintained” in the model.

e. In Table 21, Document B it is stated for treatment effect waning that “Full justification explained in Section 0”. Please provide the full justification for treatment waning assumptions in the current appraisal and provide the location of this justification in the report.

The justification of the treatment effect duration assumed in the base case analysis is given in Section B.3.3.1 of Document B (page 85-87).

B12. Page 85 of the company submission says: “Hazard ratios between year 7 and year 10 of the HERA and BCIRG 006 trials are shown to be 0.803 and 0.801,

respectively". Please provide the HR simulated by the model and compare. Please include in the model the option of setting that HR = 1.

The hazard ratios between year 7 and 10 of HERA, BCIRG-006, and KATHERINE (model) are given in Table 10 below.

Table 10. Hazard ratio between year 7 and year 10 of HERA, BCIRG-006 and KATHERINE (model)

Study	Hazard ratio
HERA	0.803
BCIRG 006	0.801
KATHERINE (model)	0.798

The hazard ratio between year 7 and year 10 projected by the IDFS extrapolation in the model is broadly aligned to the figures derived from the long term HERA and BCIRG 006 data.

The model, already submitted by the company, includes the ability to set the HR to 1. This can be done using the "Treatment effect null at:" field (Cell I147) on the "Model inputs" sheet. Once the timepoint specified in this cell is reached, the hazard rates in the trastuzumab arm are then applied to the trastuzumab emtansine arm. The equivalence in hazard rates between the two arms results in a HR = 1.

B13. Priority question:

A. Based on the IDFS KM curves, please provide a plot of the IDFS hazard rates over time for both arms, and based on these hazard rates, please provide a plot of the IDFS hazard ratio over time.

Please see Figure 5 and Figure 6 below.

Figure 5. Annual recurrence rate over time in KATHERINE KM data

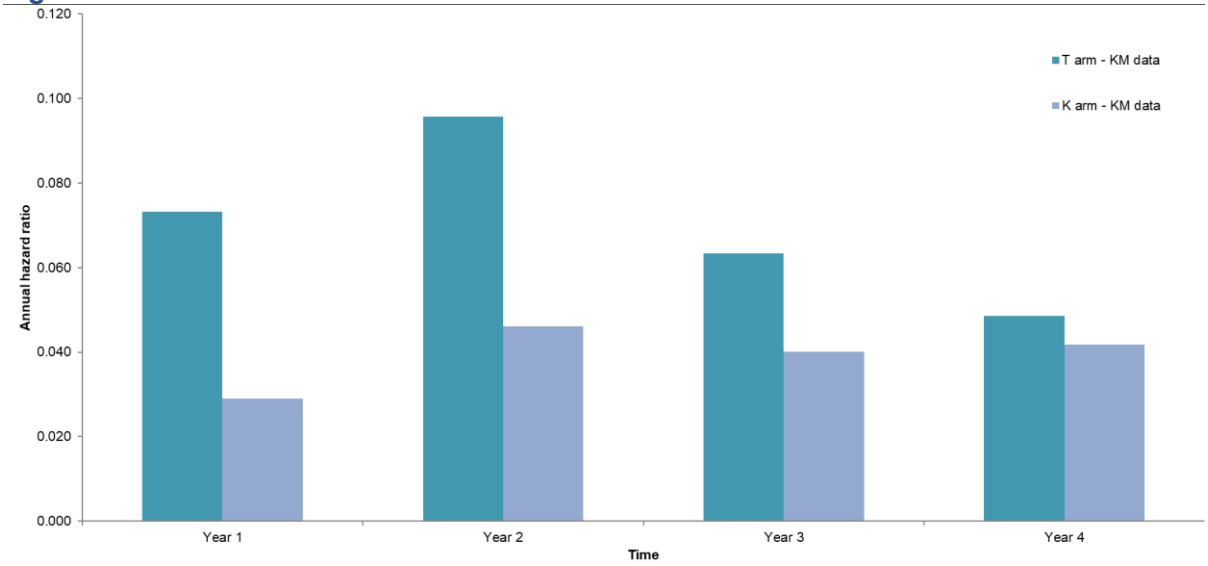
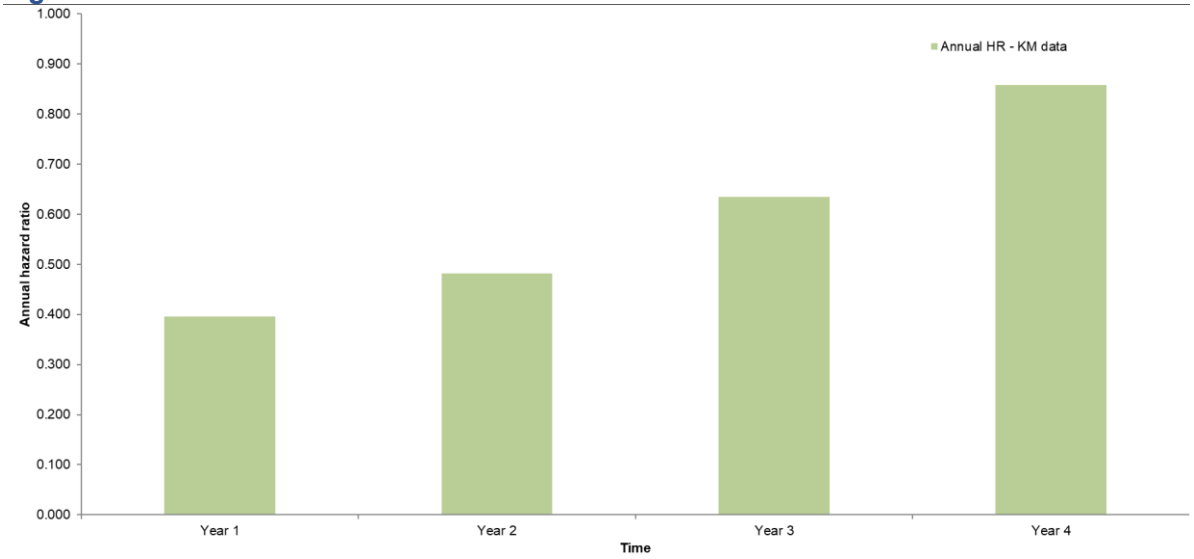


Figure 6. Annual hazard ratio over time in KATHERINE KM data



It is important to caveat the presentation of these graphs with a note on censoring. Table 11 presents the percentage of patients at risk and event numbers over time in the KM data.

Table 11. Patients at risk and event numbers in the KATHERINE trial*

Time	Trastuzumab arm			Trastuzumab emtansine arm		
	Patients at risk at start of year (%)	Patients at risk at end of year (%)	Number of IDFS events	Patients at risk at start of year (%)	Patients at risk at end of year (%)	Number of IDFS events
Year 1 (0-11 months)	743 (100.00%)	635 (85.46%)	53	743 (100.00%)	685 (92.19%)	21
Year 2 (12-23 months)	635 (85.46%)	555 (74.70%)	63	682 (91.79%)	640 (86.14%)	32
Year 3 (24-35 months)	555 (74.70%)	350 (47.11%)	33	633 (85.20%)	443 (59.62%)	24
Year 4 (36-47 months)	350 (47.11%)	110 (16.02%)	14	409 (55.05%)	170 (22.88%)	12
Year 5 (48-59 months)[a]	110 (16.02%)	0 (0.00%)	2	170 (22.88%)	0 (0.00%)	2

*Discrepancies exist in the "patients at risk…" categories due to the non-uniform time intervals in KM data.
[a] Year 5 has been omitted from Figure 5 and Figure 6 due to low event numbers

The data and graphs presented in response to this sub-question should be interpreted with caution. Median follow-up in both arms is ~41 months. Therefore, there is substantial censoring in the "Year 4" data point. This, coupled with the limited event numbers, results in significant levels of uncertainty in the observed hazard rates in this time period.

B. Based on the IDFS extrapolated curves, please provide a plot of the IDFS hazard rates over time for both arms, and based on these hazard rates, please provide a plot of the IDFS hazard ratio over time.

Please see Figure 7 and Figure 8 below.

Figure 7. Annual recurrence rate over time in IDFS extrapolations of KATHERINE data

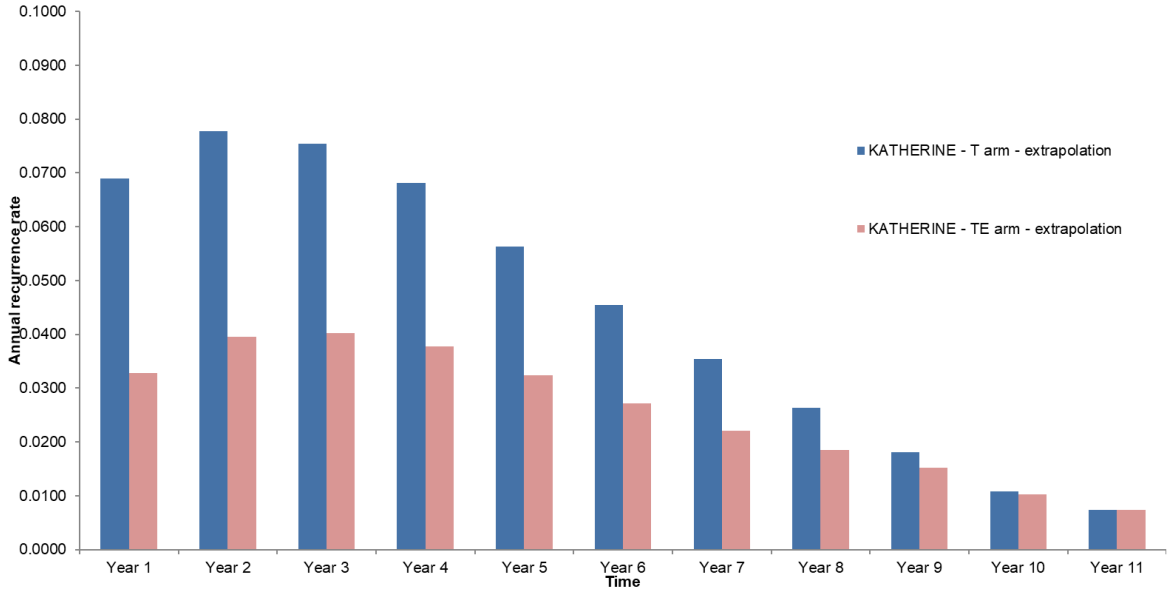
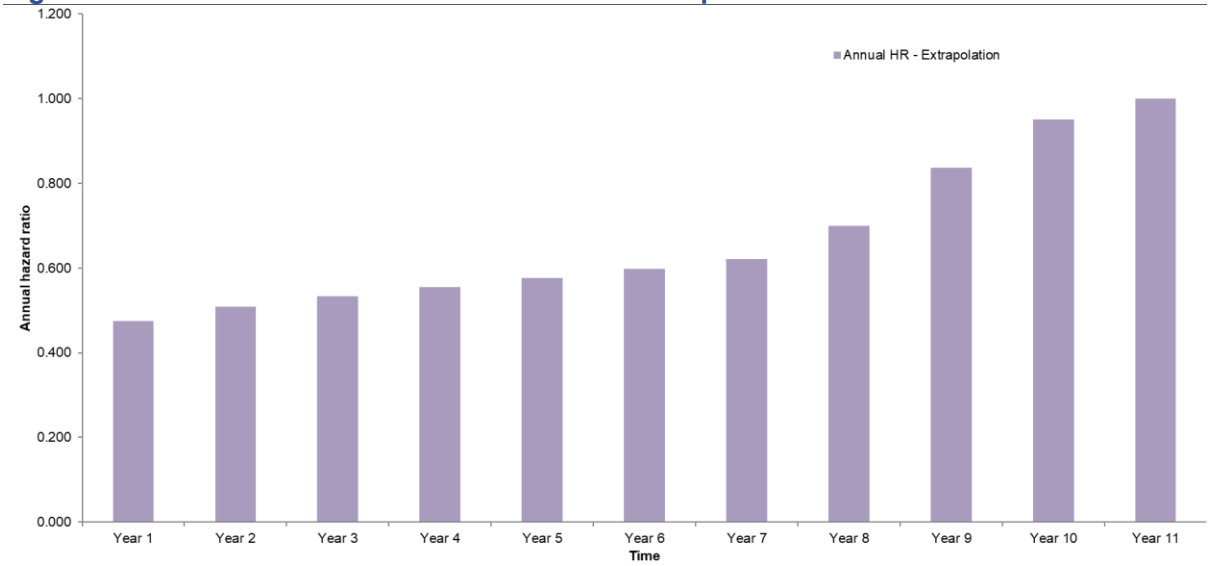


Figure 8. Annual hazard ratio over time in IDFS extrapolations of KATHERINE data



Disease recurrence

B14. Please justify the choice of 18 months as cut-off point for early relapse.

Incorporating the timing of relapse into the economic model was suggested by a clinical expert during a HTA advisory board that took place as part of TA569. The following is an excerpt from the minutes of that meeting:

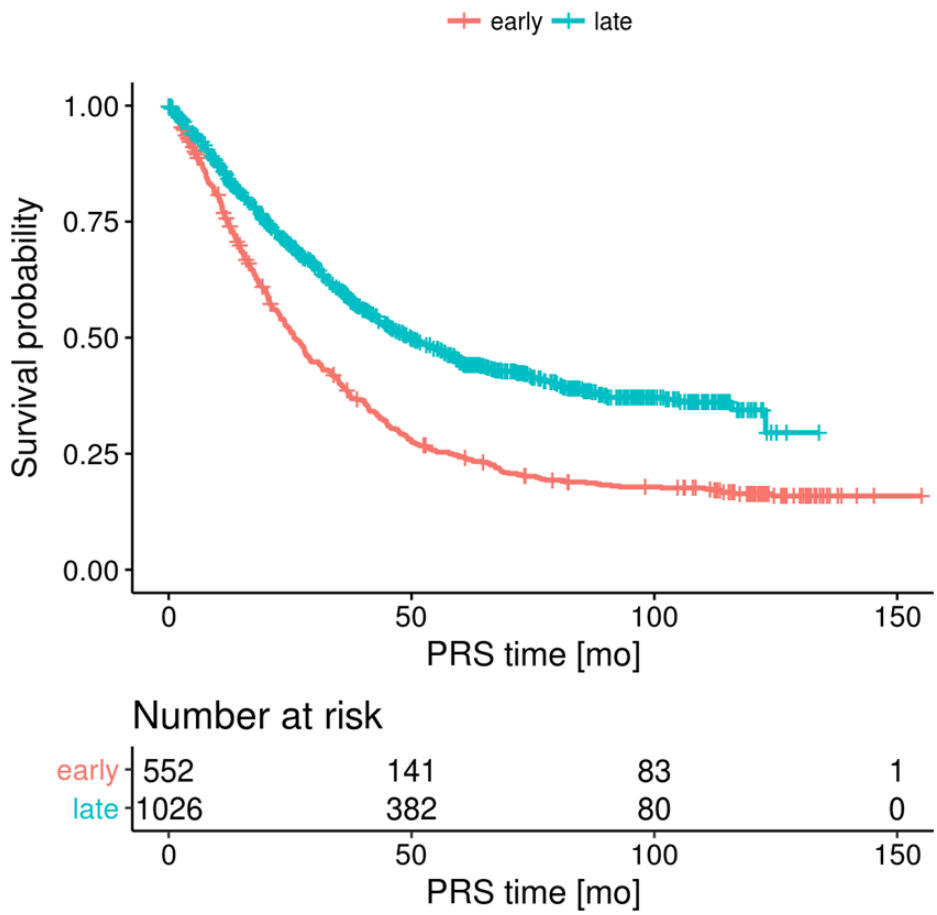
Incorporating the timing of relapse into the model. XX explained that patients who relapse early tend to have more aggressive disease which does not respond well to treatment, and so are on later-lines of therapy for a relatively short duration. However, patients who relapse later tend to have less aggressive disease which is

more amenable to treatment, so are on later lines of treatment for a longer amount of time, and therefore have much higher total treatment costs.

- *It was felt that early (≤1 year) versus late (>1 year) relapses should be considered in the model because of the impact that the timing of relapse has on treatment outcomes and costs.*

The EMILIA study (trastuzumab emtansine in mBC) contained a subpopulation (~12% of patients in each arm) which had received prior systemic treatment for early breast cancer but had relapsed within 6 months of completing treatment (18-months from treatment initiation). Given the availability of this patient-level data set, it was decided to use 18-months (from initiation) as the cut-off point for early relapse in the TA569 analysis. An additional analysis of the HERA trial confirmed that there is a clear difference in prognosis for patients who experience a recurrence less than 18-months from adjuvant initiation compared to those who experience a recurrence more than 18-months from adjuvant initiation – see Figure 9.

Figure 9. PPS of patients with a disease recurrence in the HERA study (progression within or after 18 months)



The use of an 18-month "cut-off" point was judged reasonable by the ERG and appraisal Committee during TA569 and was therefore also adopted here.

Clarification questions

B15. Priority question: Please justify why it is appropriate to use survival estimates from EMILIA to model early relapse. Please include in the model the option of selecting these estimates separately per treatment arm (as opposed to pooled, as it is now).

The EMILIA study (trastuzumab emtansine in mBC) contained a subpopulation (~12% of patients in each arm) which had received prior systemic treatment for early breast cancer but had relapsed within 6 months of completing treatment (18-months from treatment initiation). Given the availability of this patient-level data set, it was decided to use the EMILIA study in order to derive the survival estimates in the early relapse setting.

The Company decided to pool the PFS estimates across treatment arms of the EMILIA early-relapser population. This was primarily due to notion that more patients would result in more event numbers which in turn would result in more robust transition probabilities. Deriving treatment-specific transition probabilities from the EMILIA population is inappropriate. In this population, there were only 34 PFS events and 27 PFS events in the lapatinib + capecitabine and trastuzumab emtansine arms, respectively. Such few events mean that any treatment-specific transition probabilities are likely to be associated with large confidence intervals and a great deal of uncertainty. This issue is amplified when attempting to derive survival probabilities (14 and 11 OS events in the lapatinib + capecitabine and the trastuzumab emtansine arms, respectively).

The Company maintains that the original approach (pooled) provides the most robust transition probability estimates in this population. For Completeness, the ability for the user to modify the transition probabilities in the early relapser population in each arm of the model has been included.

Remission

B16. Priority question: Please explain the main differences between the IDFS and remission health states in the model. In particular, please indicate why patients in these health states are assumed to have the same utility and the same probability to transitioning to the death health state but patients in remission have a different probability of transitioning to first line mBC. Please include in the model the option to increase this risk to test this assumption in a scenario analysis.

Patients in remission are assumed to have experienced a non-metastatic recurrence. Data to inform transition probabilities and utilities were not collected in patients who had experienced a recurrence in the KATHERINE study. Therefore, assumptions had to made.

Patients in remission are not actively experiencing a recurrence and are therefore assumed to be invasive disease-free and no longer receiving treatment. A reasonable assumption was made that patients in this state could expect the same quality of life as patients in the IDFS – off treatment health state. This was the approach also taken in TA569 and was subsequently judged to be reasonable by both the ERG and the appraisal Committee. Nevertheless, a basic scenario analysis has been conducted to and the results are presented in Table 12. In the scenario analysis, it is assumed that patients in remission would have a 10% worse health state utility compared to patients in the IDFS – off treatment health state.

Table 12 Cost-effectiveness results when assuming a different utility in the Remission and IDFS - off treatment health states

Technologies	Total costs	Total LYG	Total QALYs	Δ costs	Δ LYG	Δ QALYs	ICER (£/QALY)	Δ from base case ICER
Remission HSUV is equal to IDFS – off treatment HSUV (Base case analysis)								
Trastuzumab	[redacted]	15.28	[redacted]	[redacted]	1.77	1.44	£1,247	£0
Trastuzumab emtansine	[redacted]	17.05	[redacted]					
Remission HSUV is 90% of IDFS – off treatment HSUV (Scenario analysis)								
Trastuzumab	[redacted]	15.28	[redacted]	[redacted]	1.77	1.48	£1,215	-£33
Trastuzumab emtansine	[redacted]	17.05	[redacted]					

Health state utilities are applied independent of treatment in the model. Therefore, as expected, there is almost no effect on the ICER (-£33). In fact, it could be argued that the approach taken in the Company base case is actually conservative.

As discussed above, transition probabilities were not available for “Remission” patients in the KATHERINE study. The risk of disease-related death in eBC is very small – as evidenced by the low number of deaths in the KATHERINE (91/1,480 = 6.12%) study. Unfortunately, no further information on these disease-related deaths is available, however, it is expected that the vast majority of these would have occurred because of a metastatic event. A reasonable assumption was made that unless a patient had metastatic disease their risk of death would be equal to

background mortality. The same approach was taken in TA569 and was judged to be reasonable. Further the cost-effectiveness results are not expected to be sensitive to this assumption because once again, the same approach has been applied across both treatment arms.

A key structural assumption in the model is that patients can only experience one non-metastatic recurrence (i.e. once they are in remission, they can only transition to either first-line mBC or death). Given that patients in remission have already experienced a non-metastatic recurrence, it is therefore assumed that they will be at slightly higher risk of another recurrence. The ability to alter the transition probability from the remission health state to 1st-line mBC is available in the original model submitted by the Company (cell L251 "Model Inputs" sheet). A simplistic scenario analysis has been presented below. In the scenario analysis, the remission to first-line mBC transition probability has been varied by ±10%.

Table 13. Cost-effectiveness results when varying the Remission to 1st-line mBC transition probability

Technologies	Total costs	Total LYG	Total QALYs	Δ costs	Δ LYG	Δ QALYs	ICER (£/QALY)	Δ from base case ICER
Remission to 1st-line mBC transition probability is 0.0076 (Base case analysis)								
Trastuzumab	[redacted]	15.28	[redacted]	[redacted]	1.77	1.44	£1,247	£0
Trastuzumab emtansine	[redacted]	17.05	[redacted]					
Remission to 1st-line mBC transition probability is 0.0068 (scenario analysis)								
Trastuzumab	[redacted]	15.32	[redacted]	[redacted]	1.74	1.42	£1,459	+£211
Trastuzumab emtansine	[redacted]	17.06	[redacted]					
Remission to 1st-line mBC transition probability is 0.0084 (scenario analysis)								
Trastuzumab	[redacted]	15.25	[redacted]	[redacted]	1.80	1.46	£1,070	-£178
Trastuzumab emtansine	[redacted]	17.04	[redacted]					

Again, the absolute impact on the ICER is minimal.

B17. A monthly transition probability from Hamilton et al. has been used for transitioning from remission to first line mBC. Please justify the choice of Hamilton et al. to model the transition from the remission state to the metastatic – first-line mBC state confirm that there are no other data from KATHERINE to inform this probability.

Clarification questions

Kindly compare the abovementioned probability with the transition probabilities derived from the trial data from IDFS to first line mBC. Please add in the model the option to replace the transition probability from Hamilton et al. by the transition probability from IDFS to first line mBC.

Justification of the use of Hamilton *et al.*

A patient in remission will have already experienced a non-metastatic recurrence; this analysis assumes that any additional recurrence would be metastatic in nature. In other words, a patient would transition directly from the remission state (after having a non-metastatic recurrence) to the metastatic – first-line mBC state. The probability of this transition was taken from the Hamilton *et al* study. This study included a cohort of 12,836 patients with eBC and reported the estimated risk of incurring a second malignancy following adjuvant therapy.

Recurrence rate from the remission health state was assumed to remain constant over time. Therefore, an exponential distribution was used to derive a constant transition probability. The Hamilton study reports a mean time until progression of 7.6 years (91.2 months); this value was converted into a monthly transition probability of 0.00760 using Equation 1. There are several differences between the populations being evaluated in this analysis and the one in the Hamilton *et al.* publication, as described below.

Equation 1: Calculation of remission to first line mBC transition probability

$$S(t) = e^{-\varphi t}$$

The population in the Hamilton *et al.* study was heterogeneous, as it included stage I/II female patients with BC (HER2-positive, negative or unknown status), ranging between 20 to 79 years of age, diagnosed between 1989 and 2005. Furthermore, all patients were treated with adjuvant chest-wall radiation and were from one institution in Canada. This concern was originally raised by the ERG in the appraisal of pertuzumab in the neoadjuvant setting. Nevertheless, the committee accepted the use of this source as it was believed to be the best available evidence at the time of writing, a fact which is also believed to be true here.

KATHERINE data availability

Following disease recurrence, the follow-up assessments in the KATHERINE study are less frequent – see below:

> *"In the cases of disease recurrence, diagnosed at any time during the study, patients were out of the study schedule and were only followed up once a year (starting 1 year after first relapse) for approximately 10 years from the*

Clarification questions

date of randomization of the first patient for survival and new relapse events as per secondary endpoints" - Page 62-63 of the KATHERINE CSR

Consequently, data on those patients who experienced a non-metastatic recurrence and have then gone on to experience a metastatic recurrence is not available. It is also worth noting here that only 55 non-metastatic recurrences occurred (Table 25 of Document B) across both treatment arms in KATHERINE. The proportion of those 55 who would then have gone on to have metastatic recurrence in the follow-up period (~62 months) is unknown, yet thought to be minimal. For this reason, the transition probability from remission (following a non-metastatic recurrence) to 1st-line mBC cannot be calculated from the current KATHERINE data cut.

IDFS to 1st-line mBC transition probability from KATHERINE

The probability of experiencing an IDFS event (includes metastatic and non-metastatic recurrences) is derived from the IDFS extrapolations in the model. The probability a patient would have a metastatic or non-metastatic recurrence is then calculated by weighting the probability of having an IDFS event by the proportion of recurrences that were non-metastatic/metastatic as seen in the KATHERINE study (Table 26 of Document B).

As the IDFS extrapolations are time-dependent, there is no single transition probability for IDFS to 1st-line mBC. It is therefore not possible to replace the Hamilton *et al.* transition probability with a IDFS to 1st-line mBC transition probability from KATHERINE.

Additionally, the Hamilton *et al.* transition probability is applied to patients who have already experienced a non-metastatic recurrence and are then transitioning from the remission health state to the 1st-line mBC health state. Therefore, the probability of transitioning directly from IDFS to the 1st-line mBC health state using KATHERINE data is not representative of the same transition as the Hamilton *et al.* probability.

Finally, the submitted model already incorporates the ability to override the Hamilton *et al.* probability and conduct sensitivity analyses on this parameter (Cell L251 – "Model Inputs" sheet).

Recurrence

B18. Please justify the assumption that the risk of death in the non-metastatic recurrence health state is the same as in IDFS (i.e. background mortality). Please include in the model the option to increase this risk to test this assumption in a scenario analysis.

The risk of disease-related death in this setting is very small – as evidenced by the low number of breast cancer-related deaths in the KATHERINE (91/1,480 = 6.12%)

Clarification questions

study. Unfortunately, no further information on these deaths is available, however, it is expected that the vast majority of these would have occurred because of a metastatic event. A reasonable assumption was made that unless a patient had metastatic disease their risk of death would be equal to background mortality. The same approach was taken in TA569 and was judged to be reasonable. Further the cost-effectiveness results are not expected to be sensitive to this assumption because once again, the same approach has been applied across both treatment arms.

The option to increase the risk of death in the non-metastatic recurrence health state has been included in the revised economic model.

Mortality

B19. Priority question: On page 99, Document B, it is stated "For mBC patients, the risk of death is modelled according to trial data on therapies available to current UK patients – see 0 for more details on this methodology." Please provide the full details of the methodology and provide the location of this description in the report.

"See 0" should say "see Section B.3.3.2". The full methodology has been provided below.

<u>≥2nd line mBC survival probabilities</u>
Following metastatic progression, only one further transition is possible (subsequent lines for mBC treatment to death). The risk of death in the 2L+ metastatic setting has been estimated according to the therapies a UK 2L mBC patient can receive today (see Table 14). Post-progression (post first-line) survival probabilities have been derived using the same methodology as the metastatic progression probabilities.

- **Pertuzumab + trastuzumab + chemotherapy and trastuzumab + chemotherapy** – Post-progression survival probabilities have been derived from the CLEOPATRA trial data.
- **Chemotherapy** – Post-progression survival probabilities have been derived from the M77001 trial.
- **Trastuzumab emtansine** – Post-progression survival probabilities have been assumed equal to those of trastuzumab + chemotherapy.

Once again, the Kaplan-Meier data from these trials have been extrapolated using an exponential distribution to circumvent the use of complex time-dependent transition probabilities. Similarly to the metastatic progression probability, this value is also an average weighted by the treatment usage percentages seen in Table 14.

Table 14. Summary of monthly risk of death in progressed metastatic (2L mBC) disease

Clarification questions

Transition	Treatment regimen	Treatment usage	Data source	Monthly probability	Data source
First line mBC to 2+ line mBC	Pertuzumab + trastuzumab + chemotherapy	10%	Market research	0.0273	CLEOPATRA
	Trastuzumab + chemotherapy	7%	Market research	0.0315	CLEOPATRA
	Chemotherapy	5%	Market research	0.0598	M77001
	Trastuzumab emtansine	78%	Market research	0.0315	CLEOPATRA
	Metastatic death	**100%**	**Total**	**0.0325**	**Weighted avg.**

Abbreviations: mBC: metastatic breast cancer.

Please refer to the "2nd line data" sheet of the cost-effectiveness model for more information on the exact methodology behind the extrapolations and the derivation of the individual trial probabilities.

HRQoL

B20. Priority question: Please present any evidence from the literature which supports the assumptions that HRQoL in non-metastatic recurrence and remission is equivalent to HRQoL in IDFS-on treatment and IDFS-off treatment, respectively.

This assumption was made due to the absence of robust data and in order to simplify the analysis. The company is unaware of any published literature which comments on this specific issue.
It is important to note that this assumption was also used in the recent NICE appraisal of pertuzumab in the adjuvant treatment of HER2-positive, node-positive, early breast cancer patients. The ERG and Committee for that appraisal both deemed this assumption to be reasonable.
Finally, this assumption applies to all treatment arms included in the economic analysis. It is therefore unlikely to significantly impact the incremental cost-effectiveness results.

B21. In Table 38 of the company submission, the values presented are inconsistent with the Lidgren model values. Please clarify which are the intended values.

A corrected version of Table 36 (Table 15) and 38 (Table 16) of Document B are given below:

Table 15. eBC health state utilities used in the Lidgren et al. analysis and de novo analysis

Health state in de novo analysis	Health state in Lidgren et al.	Utility reported (95% CI)
IDFS – On treatment	First year after primary breast cancer (State P)	0.696 (0.63-0.75)
IDFS – Off treatment	Second and following years after primary breast cancer/recurrence (State S)	0.779 (0.75-0.81)
Non metastatic recurrence	First year after recurrence (State R)	0.779 (0.70-0.85)
Remission	Second and following years after primary breast cancer / recurrence (State S)	0.779 (0.75-0.81)

Abbreviations: CI, Confidence interval; IDFS: invasive disease-free survival.

Table 16. mBC health state utilities used in the Lidgren *et al.* analysis and de novo analysis

Health state in de novo analysis	Health state in Lidgren *et al.*	Utility reported (95% CI)
First-line mBC	Metastatic disease (State M)	0.685 (0.62-0.74)
Second+ line mBC		

Abbreviations: mBC: metastatic breast cancer.

The scenario analyses in which these utilities are incorporated have been re-ran. Topline cost-effectiveness results have been presented below.

Table 17. Corrected cost-effectiveness results for Lidgren et al. scenario analyses

	Technologies	Total costs	Total LYG	Total QALYs	Δ costs	Δ LYG	Δ QALYs	ICER (£/QALY)	Δ from base case ICER
Base case	Trastuzumab	[redacted]	15.28	[redacted]	[redacted]	1.77	1.44	£1,247	£0
	Trastuzumab emtansine	[redacted]	17.05	[redacted]					
Lidgren utilities for eBC states	Trastuzumab	[redacted]	15.28	[redacted]	[redacted]	1.77	1.44	£1,250	+£3
	Trastuzumab emtansine	[redacted]	17.05	[redacted]					
Lidgren utilities for mBC states	Trastuzumab	[redacted]	15.28	[redacted]	[redacted]	1.77	1.42	£1,268	+£21
	Trastuzumab emtansine	[redacted]	17.05	[redacted]					
Lidgren utilities for all states	Trastuzumab	[redacted]	15.28	[redacted]	[redacted]	1.77	1.42	£1,270	+£23
	Trastuzumab emtansine	[redacted]	17.05	[redacted]					

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

B22. Priority question: No additional disutilities due to AEs are applied in the model, under the assumption that these are captured in the trial HRQoL data. However, the base-case also assumes equal utility between treatment arms, which will not account for differences in AE profiles and their impact on HRQoL. Please include an option in the model which allows for the disutility of any AEs included in the model to be applied.

The ability to include disutility for AEs is included in the originally submitted model. Please see the “AEs” worksheet.

Resource use and costs

B23. Please confirm that trastuzumab biosimilars are only available in IV form but not SC and whether it is expected that SC biosimilars will be available soon.

Trastuzumab SC will lose exclusivity in March, 2024. At the time of writing, the company is unaware of any SC biosimilars currently in clinical development.

B24. Page 112 in the company submission says “Trastuzumab biosimilars will be costed at a discount of 70.00% of the branded trastuzumab (Herceptin) IV list price (net price = [redacted] per 150 mg vial)”. However, a discount of 66.67% is used in the model for trastuzumab biosimilars.

a) Please clarify the assumed trastuzumab biosimilar discount.

The 70.00% value in Document B refers to an assumed discount on the list price of BRANDED TRASTUZUMAB (HERCEPTIN) IV. The 66.67% value in the model is applied to the list price of trastuzumab biosimilars. The list price of biosimilars has a list price that is 10% lower than that of Herceptin IV.
Applying a 66.67% discount on the trastuzumab biosimilar list price results in a net price equal to applying a 70% discount on branded trastuzumab (Herceptin) IV list price.

Page 113 of CS: “Roche also offers a CAA on pertuzumab, which equates to a [redacted] discount on list price in the metastatic setting.” However, a 53.00% discount is used in the model.

b) Please clarify the pertuzumab discount.

As explained in Document B, pertuzumab is subject to a Commercial Access Agreement with NHS England. [redacted]
On the “Cost inputs” sheet (Cell J17[redacted] On the “supportive Care Costs” sheet (Cell G80),[redacted]

B25. Priority question: Please provide evidence to support the statement on page 112 of the company submission: “The strong patient preference for a SC formulation (rather than IV) has resulted in limited erosion of the Herceptin SC market share, a fact which is also reflected in recent market research collected by the Company”. This statement does not seem to apply after recurrence, where the market shares shown in Table 44 indicate a strong preference for IV over SC. If that is the case, please explain why.

The Market shares detailed in the non-metastatic recurrence row of the table are incorrect. The corrected table, which includes the market shares used in the base case analysis, is given below.

Table 18. Subsequent therapy treatment durations and market shares

Health state	Treatment regimen	# cycles	Source	Market share	Source
Non-metastatic recurrence	Trastuzumab biosimilar IV + docetaxel	18	Assumption	5.00%	Equal to H arm in IDFS
	Trastuzumab SC + docetaxel	18	Assumption	95.00%	
First-line mBC – Early recurrence	Pertuzumab + trastuzumab + chemotherapy	37.39	TA509 – P in mBC	Trastuzumab emtansine arm = 75.00% Trast. Arm = 0.00%	Market research & assumptions
	Trastuzumab biosimilar IV + chemotherapy	23.65	TA509 – P in mBC	Trastuzumab emtansine arm = 4.00% Trast. Arm = 4.00%	
	Trastuzumab SC + docetaxel	23.65	TA509 – P in mBC	Trastuzumab emtansine arm = 13.00% Trast. Arm = 13.00%	
	Trastuzumab emtansine	19.3	Assumed equal to TA458 – K in 2L mBC	Trastuzumab emtansine arm = 0.00% Trast. Arm = 75.00%	
	Chemotherapy	6.0	Assumption	Trastuzumab emtansine arm = 8.00% Trast. Arm = 8.00%	
First-line mBC	Pertuzumab + trastuzumab biosimilar IV + docetaxel	37.39	TA509 – P in mBC	75.00%	Market research
	Trastuzumab biosimilar IV + docetaxel	23.65	TA509 – P in mBC	4.00%	
	Trastuzumab SC + docetaxel	23.65	TA509 – P in mBC	13.00%	
	Chemotherapy	6.00	Assumption	8.00%	Assumption
Second + line mBC – Early recurrence	Pertuzumab + trastuzumab biosimilar IV + docetaxel	9.36	Assumed equal to Trast. + chemo	10.00%	Market research
	Trastuzumab biosimilar IV + chemotherapy	9.36	TA458 – K in 2L mBC	4.00%	
	Trastuzumab SC + chemotherapy	9.36	TA458 – K in 2L mBC	3.00%	

Health state	Treatment regimen	# cycles	Source	Market share	Source
	Trastuzumab emtansine	19.33	TA458 – K in 2L mBC	78.00%	
	Chemotherapy	6.00	Assumption	4.00%	Assumption
Second + line mBC	Pertuzumab + trastuzumab biosimilar IV + docetaxel	9.36	Assumed equal to Trast. + chemo	10.00%	Market research
	Trastuzumab biosimilar IV + capecitabine	9.36	TA458 – K in 2L mBC	4.00%	
	Trastuzumab SC + capecitabine	9.36	TA458 – K in 2L mBC	3.00%	
	Trastuzumab emtansine	19.33	TA458 – K in 2L mBC	78.00%	
	Lapatinib	12.29	TA458 – K in 2L mBC	1.00%	
	Chemotherapy	6.00	Assumption	8.00%	Assumption

Abbreviations: IV: intravenous; K: trastuzumab emtansine; mBC: metastatic breast cancer; NHSE: National Health Service England; P: pertuzumab; SC: subcutaneous.

B26. Priority question: In the company submission, it is stated that the market share related inputs (e.g. Table 44 from the company submission) were partially based on market research study conducted by the company. However, the details of the market research study (and its results) were not provided. Please provide all the details of the market research conducted by the company. Please provide evidence to support the choice of all market shares assumed throughout Section B.3.5. Please confirm whether any other additional evidence was searched or any other research organisation was contacted to determine the market share between Herceptin IV and Herceptin SC at different pathways of care settings (e.g. neo-adjuvant, local-recurrence and 1st and 2nd line mBC?

The write-up pertaining to this market research has been provided as part of a supplementary appendix to these responses. No additional research was conducted.

B27. Priority question: Please verify that none of the patients in the KATHERINE study received trastuzumab or trastuzumab emtansine more than 14 cycles. If they did, please provide the complete TTOT curves.

No patient received more than 14 cycles of either trastuzumab or trastuzumab emtansine in the KATHERINE trial (see Table 40 and Table 41 of the KATHERINE Clinical Study Report).

Clarification questions

B28. Priority question: It is assumed that after disease recurrence, trastuzumab and trastuzumab emtansine arms receive different treatments in post-IDFS states. For instance, patients from the trastuzumab arm might receive trastuzumab emtansine in post-IDFS states, whereas patients from trastuzumab emtansine arm are assumed to receive other treatments than trastuzumab emtansine. The impact of different treatments received in post-IDFS states was not reflected in the disease prognosis. Please incorporate in the model:

a. A scenario in which both arms receive the same treatments

b. A scenario in which the prognosis of different treatments received in post-IDFS states is sufficiently reflected in the model.

Patients can only expect to receive different supportive care treatments in the "1st-line mBC – Early disease recurrence" health state. The base case assumes that all treatment arms experience the same transition probabilities (part "a" of the request). To address part "b", functionality has been added into the model whereby the user is able to modify the inputs in the 1st-line mBC – early disease recurrence state to create treatment arm-specific probabilities. Please see the row 216-231 of the "Model Inputs" sheet in the economic model.

B29. Please provide sources to validate resource use frequencies reported in Table 46, 47 and 49.

Validation of the health state costs is documented at the end of Section B.3.5.2. Table 50 from Document B has been presented below for completeness.

Table 19. Comparison of health state costs in the neoadjuvant and adjuvant appraisals (Table 50 of Document B)

TA424 – pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer		TA569 – pertuzumab for the adjuvant treatment of HER2-positive breast cancer		ID1516 - Trastuzumab emtansine for adjuvant treatment of HER2-positive early breast cancer	
Health state	**Cycle cost**	**Health state**	**Cycle cost**	**Health state**	**Cycle cost**
EFS	Year 1–2 = £67.85 Year 3–5 = £15.11	IDFS	Year 1-2 (on treatment) = £63.93 Year 3–5 = £7.11	IDFS	Year 1-2 =£76.57 Year 3-5 = £4.12

Clarification questions

TA424 – pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer		TA569 – pertuzumab for the adjuvant treatment of HER2-positive breast cancer		ID1516 - Trastuzumab emtansine for adjuvant treatment of HER2-positive early breast cancer	
Health state	**Cycle cost**	**Health state**	**Cycle cost**	**Health state**	**Cycle cost**
	≥5 years = £3.83		≥5 years = £3.08		≥5 years = £3.12
Locoregional recurrence	£73.97	Non-metastatic recurrence	£76.80	Non-metastatic recurrence	£87.88
Remission	£67.85	Remission	£7.11	Remission	£4.15
mBC – non-progressed	£232.00	First-line mBC	£214.78	First-line mBC	£231.70
mBC – progressed	£185.00	Second+ line mBC	£180.85	Second+ line mBC	£192.28

Abbreviations: EFS: event-free survival; HER2: human epidermal growth factor receptor 2; IDFS: invasive disease-free survival; mBC: metastatic breast cancer.

Resource use frequencies in this analysis are identical to those in the TA569 (pertuzumab in adjuvant treatment of HER2+ breast cancer) which were in turn based upon those used in TA424 (appraisal of neoadjuvant pertuzumab in HER2+ breast cancer). In both appraisals the health state costs were judged to be appropriate for decision-making by both the ERG and the Appraisal Committees. The resource usage in these appraisals is not expected to have changed over time. Additionally, this appraisal focuses on the same disease area (early HER2+ breast cancer) and the same type of therapy (anti-HER2). Consequently, there appears to be no clear rationale to deviate from the accepted values used in TA569.
For clarity, a series of tables from Document B of TA569 have been included as a supplementary appendix to this response.

Adverse events

B30. Please explain why hypertension was not included as an adverse event (AE) in the model (as the incidence is 2%). Please make sure to include in the model all AEs which met the modelling inclusion criteria and those mentioned in Question – A19. Please include these AEs also in "subsequent therapies".

The AE data outlined in Section B.2.10 of the CS pertain to any AE reported during the KATHERINE study. As outlined later in Document B, only those AEs deemed to be "treatment-related" have been included in the economic analysis.
Data on the (treatment-related) incidence of hypertension, low platelet counts, haemorrhage, increased aspartate aminotransferase/alanine aminotransferase levels and peripheral neuropathy are detailed in Table 20, below. The complete data set on the incidence of grade ≥3, treatment-related AEs is available on the "AEs" sheet of the cost-effectiveness model.

Table 20. Incidence of select treatment-related grade ≥3 AEs reported in the KATHERINE trial

Adverse events	Frequency	
	Trastuzumab emtansine (n=740)	Trastuzumab (n=720)
Hypertension	5 (0.68%)	2 (0.28%)
Platelet count decreased*	46 (5.68%)	0 (0.00%)
Haemorrhage	1 (0.14%)	0 (0.00%)
Increased asp. AT/ ala. AT	4 (0.54%)	1 (0.14%)
Peripheral neuropathy	12 (1.62%)	0 (0.00%)

Abbreviations: ala., asp., Aspartate; AT, Aminotransferase; Alanine; N/R, not reported.
* Corrected values

The company acknowledges that the AEs highlighted by the ERG will be costly and detrimental to a patient's health-related quality of life (HRQoL). Despite this, the inclusion of these events in the analysis is unlikely to have a significant impact on the overall cost-effectiveness results. Treatment-related AEs are only likely to occur during the treatment period i.e. the first year of the time horizon. The costs and disutilities accrued here are likely to be negligible in the context of the total costs and quality-adjusted life years (QALYs) accrued over the entire 51-year time horizon.

Irrespective of these objections, the company has provided some analyses in which the ERG's requested AEs have been included.

Table 21 below reports an updated list of costs that have been added into the model.

Table 21. Updated list of adverse events and costs included in the model

Adverse events	Frequency		Treatment	Event cost	Source
	Trastuzumab emtansine (n=740)	Trastuzumab (n=720)			
Hypertension	5 (0.68%)	2 (0.28%)	Hypertension – Total HRG	£659.95	NHS Ref. 2017/18 – EB04Z
Platelet count decreased	46 (5.68%)	0 (0.00%)	Platelet disorder drugs – Band 1 – Total HRG activity	£1,712.99[a]	NHS Ref. 2016/17 – XD43Z
Haemorrhage	1 (0.14%)	0 (0.00%)	Haemorrhagic Cerebrovascular disorders[b] – Total HRG activity	£2,985.08	NHS Ref. 2017/18 – AA23C-G
Increased asp. AT/ ala. AT	4 (0.54%)	1 (0.14%)	Liver failure disorders[b] – Total HRG activity	£2,412.54	NHS Ref. 2017/18 – GC01C-F
Peripheral neuropathy[c]	12 (1.62%)	0 (0.00%)	Muscular, Balance, Cranial or Peripheral Nerve Disorders, Epilepsy or Head Injury[b] – Total HRG activity	£1,292.75	NHS Ref. 2017/18 – AA26C-H

Abbreviations: CC, Casemix companion; NHS, National Health Service.
Footnotes: a. Equal to £1,641.93 in 2016 before being inflated to reflect the 2019 price year.
b, A weighted average of the costs for all casemix companion codes were used to generate the event cost. i.e. the cost for a CC code was weighted by the "Activity" value reported in the schedule.
c. Includes events classed as "peripheral neuropathy", "peripheral motor neuropathy", and "peripheral sensory neuropathy"

Unfortunately, disutilities were not readily available for the adverse events included in Table 21, the values used had to be estimated by the company in order to conduct this scenario analysis. The company assumed a disutility of -0.5 for all events. This value is extreme and believed to be far in excess of the actual disutility a patient could expect from any of these events. Such a conservative value was chosen to illustrate the limited impact this analysis would have on the overall cost-effectiveness results originally presented in the company submission.

Table 22. Adverse event disutilities included in the model – node-positive population

Clarification questions

Adverse events	Frequency		Duration of adverse event	Disutility
	Trastuzumab emtansine (n=740)	Trastuzumab (n=720)		
Hypertension	5 (0.68%)	2 (0.28%)	10.64 months*	-0.5
Platelet count decreased	46 (5.68%)	0 (0.00%)	10.64 months*	-0.5
Haemorrhage	1 (0.14%)	0 (0.00%)	10.64 months*	-0.5
Increased asp. AT/ ala. AT	4 (0.54%)	1 (0.14%)	10.64 months*	-0.5
Peripheral neuropathy	12 (1.62%)	0 (0.00%)	10.64 months*	-0.5

*10.64 months is the safety duration (14 cycle episode of care + 30 days)

The results of this analysis (incorporating the updated costs and disutilities) are displayed alongside the results presented in the original submission below. Despite this conservative analysis, only a modest increase in the ICER was observed (+£62 from base case).

Table 23. Results when incorporating the ERG's selected adverse event costs and disutilities

Technologies	Total costs	Total LYG	Total QALYs	Δ costs	Δ LYG	Δ QALYs	ICER (£/QALY)	Δ from base case ICER
Base case analysis								
Trastuzumab	[redacted]	15.28	[redacted]	[redacted]	1.77	1.44	£1,247	£0
Trastuzumab emtansine	[redacted]	17.05	[redacted]					
Analysis including ERGs selected AE costs and disutilities								
Trastuzumab	[redacted]	15.28	[redacted]	[redacted]	1.77	1.40	£1,309	+£62
Trastuzumab emtansine	[redacted]	17.05	[redacted]					

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

Base case input parameters

B31. Priority question: Many relevant parameters (e.g. patient weight, market shares etc.) were not included in the probabilistic and one-way sensitivity analysis.

a. Please provide the selection criteria for the parameters to be included in the probabilistic and one-way sensitivity analysis.

b. Please provide a new probabilistic and one-way sensitivity analysis where all relevant parameters are included alongside a description of the selection criteria for relevant parameters. In particular, please make the following parameters probabilistic and re-run the PSA:

- Patient weight/BSA: the variability of patient weight/ BSA should be properly reflected, using either bootstrapping from individual patient level data or fitting a distribution (e.g. normal distribution) to trial/population level data using standard deviation instead of standard error, in line with the publication: (https://www.sciencedirect.com/science/article/pii/S1098301516304387)
- Percentages of recurrence (4 parameters): each of them modelled as a Beta distribution.
- Transition probabilities: instead of a multivariate normal distribution, a Dirichlet distribution should be used to avoid values above 1 and below 0.
- Treatment market shares should be modelled using a Dirichlet distribution.
- Utilities should be modelled according to a Beta distribution, not a Gamma.
- It seems inconsistent to use a Gamma distribution for modelling some cost parameters and a log-normal for other parameters. Please justify the choice of the most appropriate distribution and consider modelling costs in a consistent way.
- Please include AE costs in the PSA (either Gamma or log-normal distribution)

See Table 24 with list of parameters included in PSA (with associated distribution) and OWSA. Table 2 provides a list of parameters not included in the PSA and OWSA.

Regarding the transition probabilities, the sum of all probabilities leaving a specific health state will not be above one with current data inputs. We have created a worksheet named “Transition probabilities” in which we calculate, based on the 1,000 simulations, the maximum probability of cumulative transitions per node (= sum of the maximum values generated in 1,000 simulations for each transition probability pertaining to the respective node). We can conclude that the sum is never above one with current data inputs.

Table 24 Parameters included in the PSA, OWSA and Scenario analyses

PSA	OWSA
Demographics	
• Demographics (weight, height) – Normal	
Utilities	
• Utility in IDFS on treatment, IDFS off treatment, recurrence, remission for KAD, H, PH – Beta • Utility in metastatic and progressed metastatic health states – Beta	• Utility in iDFS on treatment, iDFS off treatment, recurrence, remission for KAD, H, PH • Utility in metastatic and progressed metastatic health states
Clinical data	

• HR K vs PH – Lognormal
• Parameters of parametric distributions –Normal
• Probability of IDFS and remission to death – Beta
• Probability of non-metastatic recurrence to death - Beta
• Proportion of metastatic recurrences (early relapse and post early relapse for KAD, H, PH) - Beta
• Probability of metastatic recurrence from remission state - Beta
• In case of early recurrence (for KAD, H, PH),
  ○ probability 1st line metastatic to 2nd line metastatic - Normal
  ○ probability 1st line metastatic to death - Beta
  ○ probability 2nd line metastatic to death - Normal
• In case of post early recurrence (for KAD, H, PH),
  ○ treatment mix in 1st line metastatic setting – Dirichlet
  ○ risk of progression in 1st line metastatic disease for each 1st line metastatic treatment– Normal
	• HR Kadcyla vs Perjeta
	• Probability of IDFS and remission to death
	• Probability of non-metastatic recurrence to death
	• Proportion metastatic recurrences (early relapse and post early relapse for KAD, H, PH)
	• Probability of metastatic recurrence from remission state
	• In case of early recurrence,
	  ○ probability 1st line metastatic to 2nd line metastatic (KAD, H, PH)
	  ○ Probability 1st line metastatic to death (KAD, H, PH)
	  ○ probability 2nd line metastatic to death (KAD, H, PH)
	• In case of post early recurrence,
	  ○ Weighted (for treatment mix) probability 1st line metastatic to 2nd line metastatic (KAD, H, PH)
	  ○ Weighted (for treatment mix) probability 1st line metastatic to death (KAD, H, PH)
	  ○ Weighted (for treatment mix) probability 2nd line metastatic to death (KAD, H, PH)

○ risk of death in 1st line metastatic disease for each 1st line metastatic treatment – Beta ○ treatment mix in 2nd line metastatic setting – Dirichlet ○ risk of death in 2nd line metastatic disease for each 2nd line metastatic treatment except KAD (sheet 'Model inputs' cell I344) – Normal	
Costs	
• Administration costs – Lognormal • AE unit costs, except for PH ('Sheet Cost inputs' cell H109 – Lognormal • Occurrence of AE – Lognormal • Supportive care costs – Lognormal	• AE cost per patient (KAD, H, PH) • Administration cost first cycle and subsequent cycle (KAD, H, H(SC), PH) • Monthly supportive care costs in the different health states (IDFS year 1&2, IDFS years 3 to 5, iDFS years 6+, remission, recurrence, 1st line early metastatic (KAD, H, PH), 1st line and 2nd line late metastatic

Table 25: Parameters not included in PSA, OWSA and Scenario analyses:

PSA	OWSA
• Drug costs • Age	• Drug costs • Demographics (age, weight, height)

Please note: user-modified values are not included in the PSA.

Updated PSA and OWSA results are provided below.

Probabilistic sensitivity analysis

Trastuzumab emtansine vs. trastuzumab

The PSA results produced a mean ICER of £1,436/QALY gained when trastuzumab emtansine was compared with trastuzumab. Results of the PSA compared to the base case analysis are presented in Table 26. Figure 10 and Figure 11 show the cost-effectiveness plane and acceptability curve, respectively.

The analyses below have been conducted using medication prices with confidential discounts applied.

Table 26. PSA results compared to base case (confidential discounts applied)

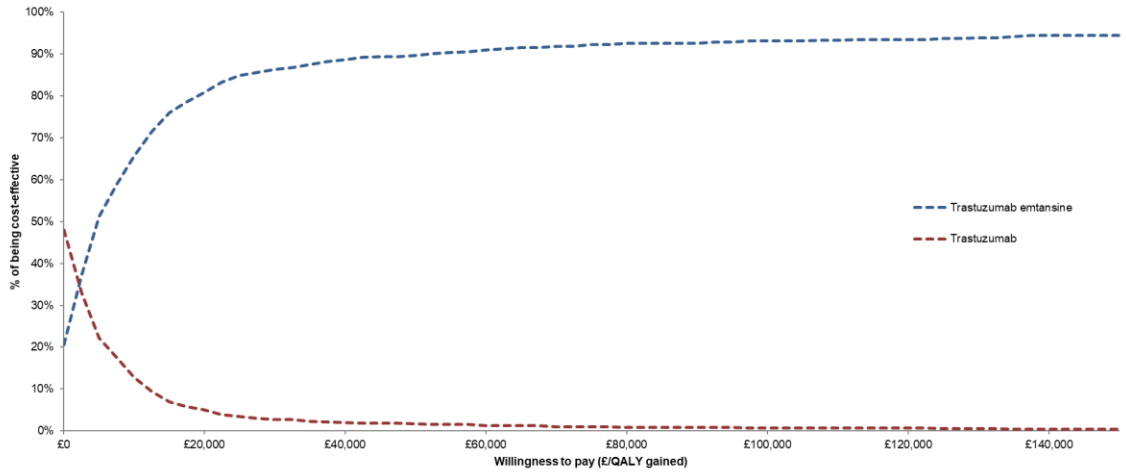
	Costs		QALYs		ICERs (£/QALY)	
	Base case	PSA	Base case	PSA	Base case	PSA
Trastuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£1,247	£1,436
Trastuzumab emtansine	[redacted]	[redacted]	[redacted]	[redacted]		

Abbreviations: ICER: incremental cost-effectiveness ratio; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year.

Figure 10. Cost-effectiveness plane – trastuzumab emtansine vs. trastuzumab

REDACTED

Figure 11. Cost-effectiveness acceptability curve - trastuzumab emtansine vs. trastuzumab



Trastuzumab emtansine vs. pertuzumab + trastuzumab

The PSA results showed that trastuzumab emtansine was dominant when compared to compared with pertuzumab + trastuzumab. Results of the PSA compared to the analysis in the node-positive population are presented in Table 26. Figure 10 and Figure 11 show the cost-effectiveness plane and acceptability curve, respectively. The analyses below have been conducted using medication prices with confidential discounts applied.

Table 27. PSA results compared to node-positive analysis scenario analysis – trastuzumab emtansine vs. trastuzumab

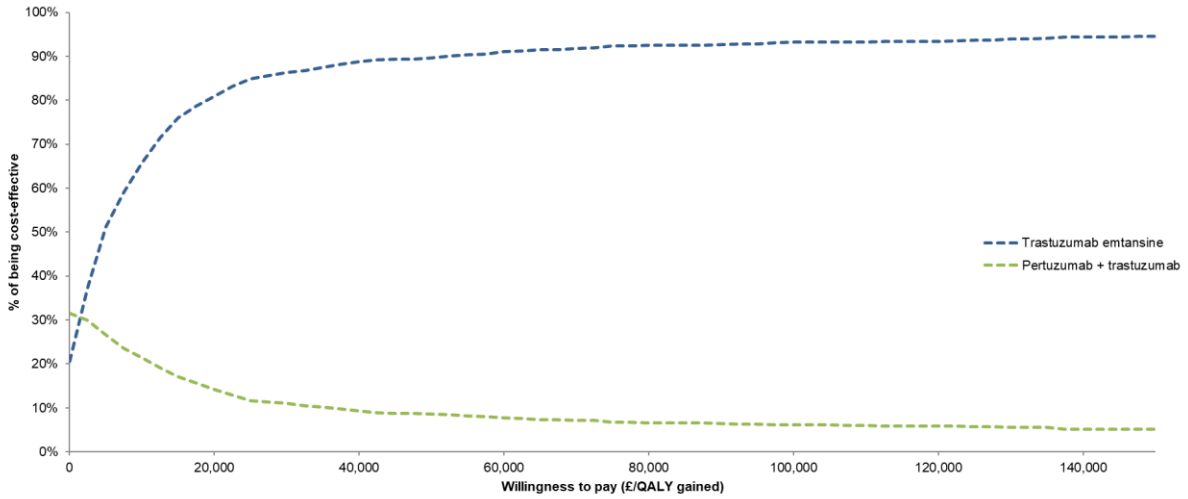
	Costs		QALYs		ICERs (£/QALY)	
	Base case	PSA	Base case	PSA	Base case	PSA
Pertuzumab + trastuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£303	Dominant
Trastuzumab emtansine	[redacted]	[redacted]	[redacted]	[redacted]		

Abbreviations: ICER: incremental cost-effectiveness ratio; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year.

Figure 12. Cost-effectiveness plane – trastuzumab emtansine vs. pertuzumab + trastuzumab

REDACTED

Figure 13. Cost-effectiveness acceptability curve - trastuzumab emtansine vs. pertuzumab + trastuzumab



One-way (deterministic) sensitivity analysis

The parameters considered in the OWSA are given in Table 24. Please see the "UDSA" sheet of the economic model for a full breakdown of the lower and upper values used in the analysis.

The Tornado diagrams for trastuzumab emtansine versus trastuzumab and trastuzumab emtansine versus pertuzumab + trastuzumab are given below. For presentation purposes, only the ten most sensitive of analyses have been included in the Tornado diagram. Please see the "UDSA" sheet of the model for the entirety of the results.

Figure 14. Tornado diagram - trastuzumab emtansine versus trastuzumab

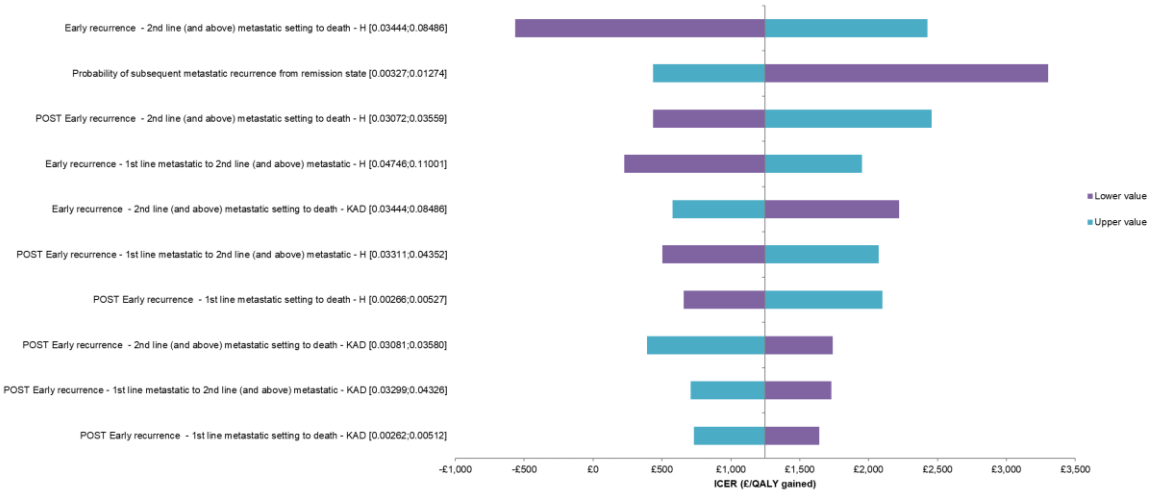
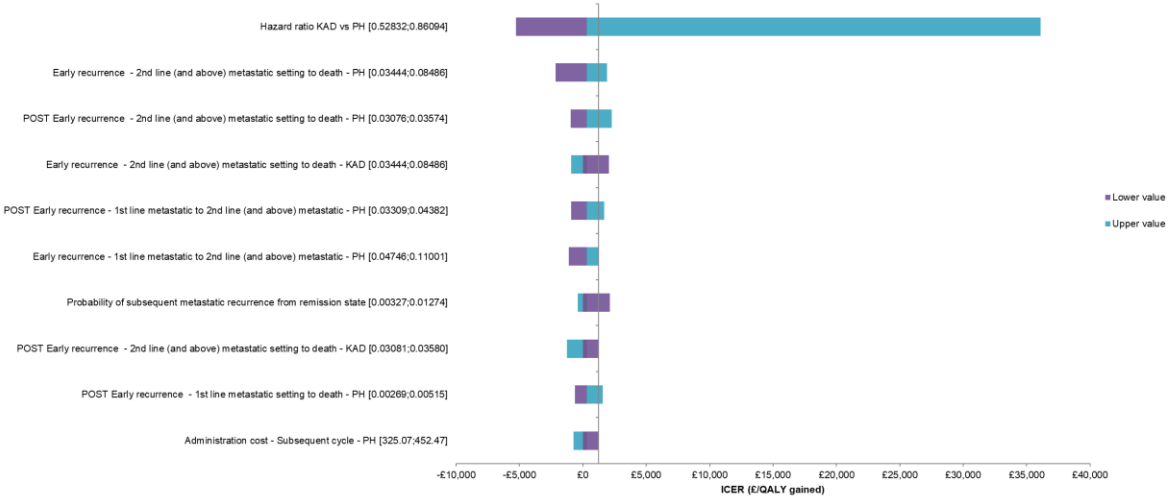


Figure 15. Tornado diagram - trastuzumab emtansine versus. pertuzumab + trastuzumab



B32. Priority question: Please confirm that the demographic parameters used in the model (age, body weight, height, body surface area, average serum creatinine) are representative for the UK. If they are not, please provide appropriate parameters.

Please see Table 28. Please note, the average serum creatinine cell in the model does not impact the analysis and is simply presented for completeness. The UK-specific value of this parameter has not been presented in Table 28.

Table 28. Baseline characteristics of UK-specific KATHERINE population compared to the ITT KATHERINE population

Parameter	KATHERINE ITT		KATHERINE UK population	
	N (pooled)	Mean (SD)	N (pooled)	Mean (SD)

Baseline age, (years)	1486	49.10 (10.65)	71	47.73 (9.47)
Baseline weight, (kg)	1470	70.91 (15.15)	71	73.47 (13.16)
Baseline height, (cm)	1470	163.10 (7.17)	71	164.00 (5.99)
BSA, (m2)	1470	1.77 (NR)	71	1.79 (0.15)

Abbreviations: BSA, Body surface area; ITT, Intention-to-Treat; SD, Standard deviation

Despite minor differences across the parameters, the baseline characteristics of UK patients in the KATHERINE study are broadly in-line with those of the ITT population. It can therefore be assumed that the cost-effectiveness results provided in the original submission are generalizable to a UK-specific population.

For completeness, revised cost-effectiveness results using the UK-specific values have been presented below. The original approach taken by the Company is conservative and perhaps an underestimation of the cost-effectiveness of trastuzumab emtansine in the UK.

Table 29. Cost-effectiveness results when incorporating UK-specific baseline characteristics

Technologies	Total costs	Total LYG	Total QALYs	Δ costs	Δ LYG	Δ QALYs	ICER (£/QALY)	Δ from base case ICER
ITT baseline characteristics analysis (Base case)								
Trastuzumab	[redacted]	15.02	[redacted]	[redacted]	1.97	1.60	£1,293	£0
Trastuzumab emtansine	[redacted]	16.99	[redacted]					
UK-specific baseline characteristics analysis								
Trastuzumab	[redacted]	15.23	[redacted]	[redacted]	2.02	1.65	£210	-£1,083
Trastuzumab emtansine	[redacted]	17.25	[redacted]					

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

Validation

B33. Priority question: Please provide details about what validation efforts were performed in Section B.3.10 of the company submission and the results of these validation efforts. This could be presented for example (but not necessarily) with the

help of the validation tool AdViSHE (https://advishe.wordpress.com/author/advishe/). Please confirm whether black-box tests to detect modelling errors were conducted. If not, please include these steps as well.

- Validation of the key aspects of the methodology used has been described in Table 6 of this response.
- Validation of the predicted model results have been cross-checked against the long-term adjuvant trastuzumab trials (HERA and BCIRG 005) in Appendix J of the original submission
- Technical validation of the economic model was conducted by an external vendor (write-up provided as supplementary appendix). Core themes included in this review were:
    - Functionality
    - Clarity
    - Accuracy
    - Consistency

Section C: Textual clarification and additional points

C1. Please confirm that the treatment waning effect assumed for this appraisal is **not** the one mentioned in Table 21 of the company submission ("Effect maintained for four years before waning to null at seven years").

There is an error in Table 21 of Document B. In the base case analysis, it is assumed that the treatment effect of trastuzumab emtansine is maintained for seven years before waning to null at 10 years.

C2. In several parts of the company submission there are references to Section 0. Please correct this and indicate the appropriate section.

Table 30 below identifies all instances of this, along with the correct cross references.

Table 30 Instances of incorrect cross-referencing in Document B

Subsection, page number	Sentence	Correct cross reference
B.3.2.2, page 72	"Full justification explained in Section 0"	B.3.3.1
B.3.3.3, page 99	"The risk of death is significantly higher in the mBC health states. For mBC patients, the risk of death is modelled according to trial data on therapies available to current UK	B.3.3.2

Subsection, page number	Sentence	Correct cross reference
	patients – see 0 for more details on this methodology."	
B.3.6.2, page 128	"2. Fast relapser survival estimates were derived from the EMILIA study. Transitions from first-line mBC to second+ line mBC and death probabilities from first-line and second-line mBC follow an exponential rate (Markov property). See 0."	B.3.3.2

C3. Please answer the following questions about Table 31:

a. Total treatment duration and number of cycles reported are total or median? It might simply be that the median is missing.

Table 31 in Document B has been adapted from Table 40 and 41 of the KATHERINE CSR. The values in the "Total Treatment duration (median)" row of Table 31 refer to the median treatment duration in each arm of the study.

b. The number of patients in the trastuzumab arm is 720 or 740?

There are 720 patients in the safety evaluable population of the trastuzumab arm of the KATHERINE study.

c. Please explain the differences between "Number (%) of patients completing at least a total of X cycles of assigned treatment" and "Number (%) of patients completing at least a total of X cycles of all study treatment".

"Number (%) of patients completing at least a total of X cycles of assigned treatment" = The number (%) of patients completing at least a total of X cycles of trastuzumab emtansine

"Number (%) of patients completing at least a total of X cycles of all study treatment" = The number (%) of patients completing at least a total of X cycles of either trastuzumab emtansine OR trastuzumab. i.e. This column includes patients who discontinued trastuzumab emtansine therapy and completed the remaining 14 cycles of therapy with trastuzumab.

C4. Please explain Table 32. The caption says TTOT but the table presents percentages.

Table 32 reports the percentage of patients on treatment in both treatment arms at each of the 14 cycles

C5. Please confirm the market shares for non-metastatic recurrence shown in Table 44.

Table 44 in Document B contains an error. The correct market shares, as used in the base case analysis are reported in
Table 31 below.

Table 31 Subsequent therapy market shares in Non-metastatic recurrence health state

Health state	Treatment regimen	Market share
Non-metastatic recurrence	Trastuzumab biosimilar IV + docetaxel	5.00%
	Trastuzumab SC + docetaxel	95.00%

Abbreviations: IV, intravenous; SC, Subcutaneous.

C6. Please provide Figure 18 in the company submission with the parametric curves extrapolated to more than 70 months.

Please see Figure 16 and Figure 17 below.

Figure 16. Visual inspection of IDFS extrapolations - Cure model adjustment applied

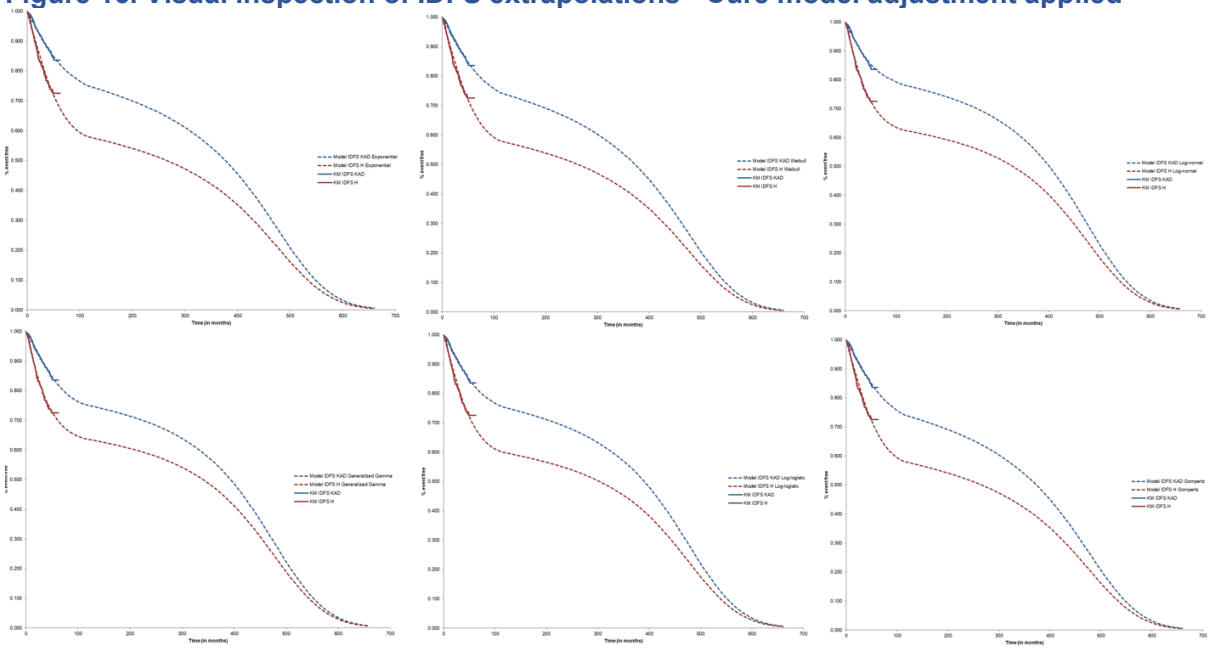
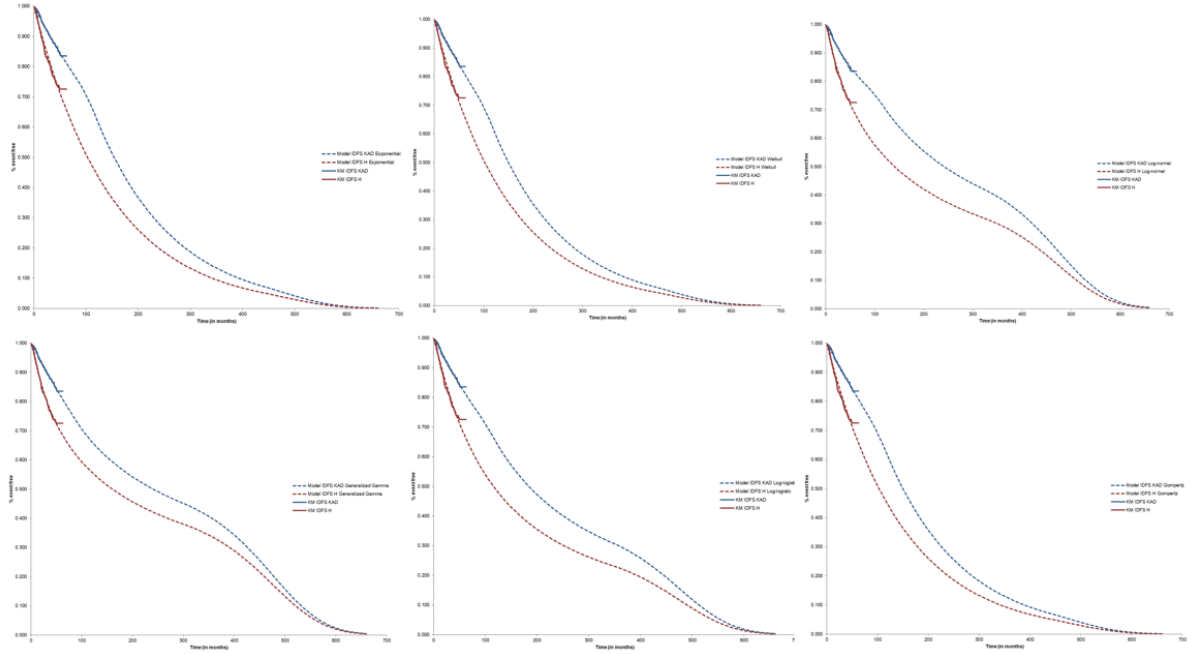


Figure 17. Visual inspection of IDFS extrapolations - No cure model adjustment applied



Please note, these graphs have been provided in one image for convenience. The individual graphs have also been supplied as a supplementary appendix to these responses.

C7. Throughout section B3.5.2 there is confusion regarding whether IDFS costs are differentiated as

a. year 1, years 2-5 and year 5 onwards (p117 and p118) or

b. years 1-2, years 3-5 and year 5 onwards (Table 50).

Please clarify which was the intended separation

The separation, as used in the base case analysis, is as follows:

- Years 1-2
- Years 3-5
- Years ≥5

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[vi] Von Minckwitz, Gunter & Procter, Marion & Azambuja, Evandro & Zardavas, Dimitrios & Benyunes, Mark & Viale, Giuseppe & Suter, Thomas & Arahmani, Amal & Rouchet, Nathalie & Clark, Emma & Knott, Adam & Láng, István & Levy, Christelle & Yardley, Denise & Bines, Jose & Gelber, Richard & Piccart, Martine & Baselga, Jose. (2017). Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. New England Journal of Medicine. 377. 10.1056/NEJMoa1703643.

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ID 1516 – Trastuzumab emtansine for adjuvant treatment of early HER2-positive breast cancer

Company response to the ERG's clarification questions - Appendix

30th October, 2019

A Clarification on effectiveness data

Question A1. Priority question: Regarding Appendix D 'Identification, selection and synthesis of clinical evidence' and Appendix G 'Published cost-effectiveness', the ERG is currently unable to fully critique these searches due to the lack of hits per line for each strategy. Please provide full strategies including hits per line as reported in Appendix I.

Database search terms (2018 SLR)

Table 1. Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946 to 29th November 2018: accessed 30th November 2018

#	Searches	Results
1	exp Breast Neoplasms/	269564
2	((breast or mammary) adj5 (tumour$ or tumor$ or cancer$ or neoplasm$ or adenocarcinoma$ or carcinoma$)).mp.	384556
3	1 or 2	384562
4	exp Receptor, ErbB-2/ or exp Receptor, Epidermal Growth Factor/	55538
5	(epidermal growth factor receptor or HER*).mp.	2203477
6	4 or 5	2221436
7	exp TRASTUZUMAB/	5965
8	(trastuzumab or herceptin* or ogivri*).mp.	10358
9	(perjeta* or omnitarg* or pertuzumab).mp.	836
10	kadcyla*.mp.	81
11	(tyverb* or lapatinib).mp.	2409
12	(nerlynx* or neratinib).mp.	202
13	(gilotrif* or afatinib).mp.	1046
14	7 or 8 or 9 or 10 or 11 or 12 or 13	12830
15	randomized controlled trial.pt.	472060
16	controlled clinical trial.pt.	92771
17	randomi#ed.ab.	511722
18	placebo.ab.	193548
19	randomly.ab.	301094
20	clinical trials as topic.sh.	185394
21	trial.ti.	190649
22	15 or 16 or 17 or 18 or 19 or 20 or 21	1216325
23	3 and 6 and 14 and 22	1269
24	exp animals/ not humans.sh.	4519948
25	23 not 24	1265

Table 2. Embase 1974 to 29th November 2018: accessed 30th November 2018

#	Searches	Results
1	exp breast tumor/	478139
2	((breast or mammary) adj5 (tumour$ or tumor$ or cancer$ or neoplasm$ or adenocarcinoma$ or carcinoma$)).mp.	558111
3	1 or 2	563149
4	exp epidermal growth factor receptor/	69044
5	(epidermal growth factor receptor or HER*).mp.	2805256
6	4 or 5	2805256
7	(trastuzumab or herceptin* or ogivri*).mp.	36291
8	exp trastuzumab/	34015
9	(perjeta* or omnitarg* or pertuzumab).mp.	3969
10	exp pertuzumab/	3820
11	exp trastuzumab emtansine/ or kadcyla*.mp.	2093
12	(tyverb* or lapatinib).mp.	11127
13	exp lapatinib/	10838
14	(nerlynx* or neratinib).mp.	1276
15	exp neratinib/	1213
16	(gilotrif* or afatinib).mp.	4075
17	exp afatinib/	3945
18	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17	44764
19	random*.ti,ab.	1356116
20	factorial*.ti,ab.	33893
21	(crossover* or cross over*).ti,ab.	96725
22	((doubl* or singl*) adj blind*).ti,ab.	213137
23	(assign* or allocat* or volunteer* or placebo*).ti,ab.	935112
24	crossover procedure/	57468
25	double blind procedure/	155706
26	single blind procedure/	33223
27	randomized controlled trial/	525561
28	19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27	2078181
29	3 and 6 and 18 and 28	2570

Table 3. EBM Reviews – Cochrane Database of Systematic Reviews 2005 to 21st November 2018, EBM Reviews – ACP Journal Club 1991 to October 2018, EBM Reviews – Database of Abstracts of Reviews of Effects 1st Quarter 2016, EBM Reviews – Cochrane Clinical Answers November 2018, EBM Reviews – Cochrane Central Register of Controlled Trials October 2018, EBM Reviews – Cochrane Methodology Register 3rd Quarter 2012, EBM Reviews – Health Technology Assessment 4th Quarter 2016, EBM Reviews – NHS Economic Evaluation Database 1st Quarter 2016: accessed 30th November 2018

#	Searches	Results
1	exp Breast Neoplasms/	11936
2	((breast or mammary) adj5 (tumour$ or tumor$ or cancer$ or neoplasm$ or adenocarcinoma$ or carcinoma$)).mp.	31704
3	1 or 2	31704

#	Searches	Results
4	exp Receptor, ErbB-2/ or exp Receptor, Epidermal Growth Factor/	1143
5	(epidermal growth factor receptor or HER*).mp.	60688
6	4 or 5	60899
7	exp TRASTUZUMAB/	0
8	(trastuzumab or herceptin* or ogivri*).mp.	2037
9	(perjeta* or omnitarg* or pertuzumab).mp.	373
10	kadcyla*.mp.	7
11	(tyverb* or lapatinib).mp.	595
12	(nerlynx* or neratinib).mp.	75
13	(gilotrif* or afatinib).mp.	264
14	7 or 8 or 9 or 10 or 11 or 12 or 13	2582
15	3 and 6 and 14	1703

Database search terms (2019 SLR update)

Table 4. Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946 to 4th June 2019: accessed 5th June 2019

#	Searches	Results
1	exp Breast Neoplasms/	276586
2	((breast or mammary) adj5 (tumour$ or tumor$ or cancer$ or neoplasm$ or adenocarcinoma$ or carcinoma$)).mp.	395492
3	1 or 2	395498
4	exp Receptor, ErbB-2/ or exp Receptor, Epidermal Growth Factor/	57994
5	(epidermal growth factor receptor or HER*).mp.	2295776
6	4 or 5	2314467
7	exp TRASTUZUMAB/	6222
8	(trastuzumab or herceptin* or ogivri*).mp.	10871
9	(perjeta* or omnitarg* or pertuzumab).mp.	914
10	kadcyla*.mp.	86
11	(tyverb* or lapatinib).mp.	2505
12	(nerlynx* or neratinib).mp.	238
13	(gilotrif* or afatinib).mp.	1170
14	7 or 8 or 9 or 10 or 11 or 12 or 13	13527
15	randomized controlled trial.pt.	483099
16	controlled clinical trial.pt.	93095
17	randomi#ed.ab.	532165
18	placebo.ab.	198191
19	randomly.ab.	312030
20	clinical trials as topic.sh.	187183
21	trial.ti.	199599
22	15 or 16 or 17 or 18 or 19 or 20 or 21	1252190
23	3 and 6 and 14 and 22	1331

#	Searches	Results
24	exp animals/ not humans.sh.	4585406
25	23 not 24	1327
26	limit 25 to yr="2018 -Current"	140

Table 5. Embase 1974 to 4th June 2019: accessed June 5th 2019

#	Searches	Results
1	exp breast tumor/	495002
2	((breast or mammary) adj5 (tumour$ or tumor$ or cancer$ or neoplasm$ or adenocarcinoma$ or carcinoma$)).mp.	577807
3	1 or 2	583037
4	exp epidermal growth factor receptor/	71907
5	(epidermal growth factor receptor or HER*).mp.	2931533
6	4 or 5	2931533
7	(trastuzumab or herceptin* or ogivri*).mp.	37778
8	exp trastuzumab/	35320
9	(perjeta* or omnitarg* or pertuzumab).mp.	4300
10	exp pertuzumab/	4133
11	exp trastuzumab emtansine/ or kadcyla*.mp.	2283
12	(tyverb* or lapatinib).mp.	11477
13	exp lapatinib/	11157
14	(nerlynx* or neratinib).mp.	1412
15	exp neratinib/	1338
16	(gilotrif* or afatinib).mp.	4446
17	exp afatinib/	4298
18	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17	46744
19	random*.ti,ab.	1414360
20	factorial*.ti,ab.	35262
21	(crossover* or cross over*).ti,ab.	99803
22	((doubl* or singl*) adj blind*).ti,ab.	219292
23	(assign* or allocat* or volunteer* or placebo*).ti,ab.	968531
24	crossover procedure/	59316
25	double blind procedure/	161015
26	single blind procedure/	35236
27	randomized controlled trial/	551382
28	19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27	2159483
29	3 and 6 and 18 and 28	2737
30	limit 29 to yr="2018 -Current"	347

Table 6. EBM Reviews – Cochrane Database of Systematic Reviews 2005 to 31st May 2019, EBM Reviews – ACP Journal Club 1991 to May 2019, EBM Reviews – Database of Abstracts of Reviews of Effects 1st Quarter 2016, EBM Reviews – Cochrane Clinical Answers May 2019, EBM Reviews – Cochrane Central Register of Controlled Trials April 2019, EBM Reviews –

Cochrane Methodology Register 3rd Quarter 2012, EBM Reviews – Health Technology Assessment 4th Quarter 2016, EBM Reviews – NHS Economic Evaluation Database 1st Quarter 2016: accessed 5th June 2019

#	Searches	Results
1	exp Breast Neoplasms/	12382
2	((breast or mammary) adj5 (tumour$ or tumor$ or cancer$ or neoplasm$ or adenocarcinoma$ or carcinoma$)).mp.	38705
3	1 or 2	38705
4	exp Receptor, ErbB-2/ or exp Receptor, Epidermal Growth Factor/	786
5	(epidermal growth factor receptor or HER*).mp.	73757
6	4 or 5	73872
7	exp TRASTUZUMAB/	0
8	(trastuzumab or herceptin* or ogivri*).mp.	2681
9	(perjeta* or omnitarg* or pertuzumab).mp.	485
10	kadcyla*.mp.	16
11	(tyverb* or lapatinib).mp.	740
12	(nerlynx* or neratinib).mp.	94
13	(gilotrif* or afatinib).mp.	384
14	7 or 8 or 9 or 10 or 11 or 12 or 13	3422
15	3 and 6 and 14	2220
16	limit 15 to yr="2018 -Current" [Limit not valid in DARE; records were retained]	250

Question A5. Regarding Cost and healthcare resource identification, measurement and valuation:

A. The searches detailed in Appendix I were run in October 2017. Please confirm whether updated searches were conducted. If so, please provide full search strategies for all updates.

B. If updated searches were not conducted, please explain the rationale for this and check whether more current, relevant references were missed. Please clarify how applicable these results are to current clinical practice

Please find a corrected version of Appendix I below. Additional full text references resulting from the correction of this appendix have been included as supplementary appendices.

Cost and healthcare resource identification, measurement and valuation

Objective

An SLR and SLR update were conducted to identify recent studies (published since 2012) presenting novel cost and resource use data relevant to the adjuvant treatment of HER2-positive

early breast cancer, including the management of recurrence and/or metastatic disease in the longer-term.

Methods

The SLR and SLR update were performed in accordance with the methodological principles of conduct for systematic reviews as detailed in the University of York Centre for Reviews and Dissemination's "Guidance for Undertaking Reviews in Health Care".1

Electronic databases

The following electronic databases were searched:

MEDLINE, including MEDLINE Daily, MEDLINE In-Process and Epub Ahead of Print; 1946 to present

Embase; 1974 to 2017 October 25, 1974 to 2019 June 11

The Cochrane Library, specifically the following:

NHS Economic Evaluation Database (NHS-EED); Issue 2 of 4, April 2015

MEDLINE and Embase were initially searched separately via the Ovid SP platform on 26th October 2017 and updated on 12th June 2019. The Cochrane Library database was searched via the Wiley Online platform on 26th October 2017, however this database was not searched during the update as NHS-EED is no longer being updated and no records were added since the date of the previous searches. Results of the SLR update searches were manually de-duplicated against the results of the original SLR to identify new records since the original searches were conducted on 26th October 2017.

Manual congress searches

The conference proceedings of the following major oncology congresses were manually searched to identify any recent economic evidence that may not have been published as full-text journal articles at the time of the database search. Searches were performed on congresses held over the prior two years (since 2015) as any high-quality studies reported in abstract form before that time were expected to have since been published as full-text articles.

European Society for Medical Oncology (ESMO) Congress

American Society of Clinical Oncology (ASCO) Annual Meeting

San Antonio Breast Cancer Symposium (SABCS)

International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Annual European and Annual International meetings

Grey literature searching

The NICE website was manually searched for previous, relevant HTA submissions from the last 10 years (since 2007), which were then reviewed to identify any further relevant data.

Reference list searching

Finally, the bibliographies of all relevant SLRs, meta-analyses, HTA submissions and economic evaluations identified through the electronic database searches were also manually searched to identify any additional studies of relevance.

Search strategy

A list of search terms used in the MEDLINE, MEDLINE Daily, MEDLINE In-Process and Epub Ahead of Print electronic databases for the original SLR and SLR update are provided in Table 7 and Table 8. Search terms used in the Embase database are presented in Table 9 and Table 10, while search terms used in the Cochrane Library database are presented in Table 11. Search terms used in the manual congress searching are provided in Table 13.

Search terms for cost and resource use studies were based on the “economic studies” search filter developed by the Scottish Intercollegiate Guidance Network (SIGN), which is an adaptation of the strategy designed by the NHS Centre for Reviews and Dissemination at the University of York.111 The search terms for geographic region were based on the strategy developed by NICE.112 During the SLR update, the geographic region search terms were updated in line with the latest UK search filter developed by NICE.113, 114 A date limit restricting the electronic database searches to those published in the last 5 years (since 2012) was applied, with the rationale that studies published more than 5 years ago may no longer be applicable to current clinical practice, and that those more recently published may not yet have been considered for use in published economic models in this therapeutic area.

Table 7. Search terms for use in MEDLINE databases (searched via the Ovid SP platform on 26th October 2017)

Term group	#	Terms	# Hits
Breast cancer	1	((breast or mammary) adj5 (malignan$ or tumour$ or tumor$ or cancer$ or neoplasm$ or adenocarcinoma$ or carcinoma$)).ti,ab.	325031
	2	exp Breast Neoplasms/	274664
	3	exp breast tumor/	274664
	4	exp breast cancer/	274664
	5	or/1-4	382011
Adjuvant	6	exp Chemotherapy, Adjuvant/	38149
	7	exp Radiotherapy, Adjuvant/	21357
	8	(adjuvant$ or operable$ or early$ or "locally advanced").ti,ab.	1527540
	9	or/6-8	1550502

Term group	#	Terms	# Hits
Recurrence / metastatic	10	exp metastasis/	194870
	11	exp neoplasm metastasis/	194870
	12	exp neoplasm recurrence, local/	109664
	13	(metasta$ or recur$ or secondar$ or disseminat$ or relaps$ or advance$ or inoperab$ or terminal or incurable or late stage or stage 3a or stage 3b or stage 3c or stage 3 or stage iii or stage 4a or stage 4b or stage 4 or stage iv).ti,ab.	2661710
	14	or/10-13	2736860
Cost and resource use	15	Economics/	27432
	16	"costs and cost analysis"/	47699
	17	Cost allocation/	2051
	18	Cost-benefit analysis/	75982
	19	Cost control/	21727
	20	Cost savings/	10862
	21	Cost of illness/	24188
	22	Cost sharing/	2350
	23	"deductibles and coinsurance"/	1645
	24	Medical savings accounts/	524
	25	Health care costs/	36102
	26	Direct service costs/	1180
	27	Drug costs/	15063
	28	Employer health costs/	1101
	29	Hospital costs/	10100
	30	Health expenditures/	17553
	31	Capital expenditures/	2007
	32	Value of life/	5803

Term group	#	Terms	# Hits
	33	exp economics, hospital/	23283
	34	exp economics, medical/	14356
	35	Economics, nursing/	3992
	36	Economics, pharmaceutical/	2972
	37	exp "fees and charges"/	29780
	38	exp budgets/	13516
	39	(low adj cost).mp.	42928
	40	(high adj cost).mp.	11897
	41	(health?care adj cost$).mp.	8536
	42	(fiscal or funding or financial or finance).tw.	128584
	43	(cost adj estimate$).mp.	2019
	44	(cost adj variable).mp.	41
	45	(unit adj cost$).mp.	2235
	46	(economic$ or pharmacoeconomic$ or price$ or pricing).tw.	254454
	47	((health care or healthcare or health-care or drug$ or medication$ or treatment$ or physician$ or nurse$ or nursing or hospital$) adj2 cost$).tw.	61901
	48	((resource$ or healthcare$ or health care or health-care or service$) adj3 (use$ or utilis$ or utiliz$ or consume$ or consuming or consumption$)).tw.	102976
	49	or/15-48	736606
Geographic region	50	exp Great Britain/	362849
	51	(national health service$ or nhs$).ti,ab,in.	158563
	52	(english not ((published or publication$ or translat$ or written or language$ or speak$ or literature or citation$) adj5 english)).ti,ab.	92493
	53	(gb or "g.b." or britain$ or (british$ not "british columbia") or uk or "u.k." or united kingdom$ or (england$ not "new england") or northern ireland$ or	1920720

Term group	#	Terms	# Hits
		northern irish$ or scotland$ or scottish$ or ((wales or "south wales") not "new south wales") or welsh$).ti,ab,jw,in.	
	54	(London or Birmingham or Leeds or Glasgow or Sheffield or Bradford or Edinburgh or Liverpool or Manchester or Bristol or Wakefield or Cardiff or Coventry or Nottingham or Leicester or Sunderland or Belfast or Newcastle upon Tyne or Brighton or Hull or Plymouth or Stoke-on-Trent or Wolverhampton or Derby or Swansea or Southampton or Salford or Aberdeen or Westminster or Portsmouth or York or Peterborough or Dundee or Lancaster or Oxford or Newport or Preston or St Albans or Norwich or Chester or Cambridge or Salisbury or Exeter or Gloucester or Lisburn or Chichester or Winchester or Londonderry or Carlisle or Worcester or Bath or Durham or Lincoln or Hereford or Armagh or Inverness or Stirling or Canterbury or Lichfield or Newry or Ripon or Bangor or Truro or Ely or Wells or St Davids).ti,ab,in.	2164766
	55	or/50-54	3118336
	56	(exp africa/ or exp americas/ or exp antarctic regions/ or exp arctic regions/ or exp asia/ or exp oceania/) not (exp great britain/ or europe/)	2647488
	57	55 not 56	2909510
Exclusion terms	58	(Comment or editorial or letter or "case reports").pt.	3441858
	59	(case stud$ or case report$).ti.	261113
	60	Letter/ or historical article/	1373194
	61	exp Animals/ not exp Humans/	4682051
	62	or/58-61	8431072
Totals	63	9 or 14	3949482
	64	5 and 63	159087
	65	64 and 49	4496
	66	65 and 57	773

Term group	#	Terms	# Hits
	67	66 not 62	749
	68	limit 67 to yr="2012 -Current"	303

Table 8. Search terms for use in MEDLINE databases (searched via the Ovid SP platform on 12th June 2019)

Term group	#	Terms	# Hits
Breast cancer	1	((breast or mammary) adj5 (malignan$ or tumour$ or tumor$ or cancer$ or neoplasm$ or adenocarcinoma$ or carcinoma$)).ti,ab.	333218
	2	exp Breast Neoplasms/	276867
	3	exp breast tumor/	276867
	4	exp breast cancer/	276867
	5	or/1-4	389902
Adjuvant	6	exp Chemotherapy, Adjuvant/	38356
	7	exp Radiotherapy, Adjuvant/	21307
	8	(adjuvant$ or operable$ or early$ or "locally advanced").ti,ab.	1563892
	9	or/6-8	1586759
Recurrence / metastatic	10	exp metastasis/	194073
	11	exp neoplasm metastasis/	194073
	12	exp neoplasm recurrence, local/	110377
	13	(metasta$ or recur$ or secondar$ or disseminat$ or relaps$ or advance$ or inoperab$ or terminal or incurable or late stage or stage 3a or stage 3b or stage 3c or stage 3 or stage iii or stage 4a or stage 4b or stage 4 or stage iv).ti,ab.	2751471
	14	or/10-13	2824795
Cost and resource use	15	Economics/	27046
	16	"costs and cost analysis"/	47296

Term group	#	Terms	# Hits
	17	Cost allocation/	1997
	18	Cost-benefit analysis/	76714
	19	Cost control/	21366
	20	Cost savings/	11217
	21	Cost of illness/	25163
	22	Cost sharing/	2430
	23	"deductibles and coinsurance"/	1712
	24	Medical savings accounts/	528
	25	Health care costs/	36981
	26	Direct service costs/	1165
	27	Drug costs/	15321
	28	Employer health costs/	1088
	29	Hospital costs/	10355
	30	Health expenditures/	18817
	31	Capital expenditures/	1987
	32	Value of life/	5647
	33	exp economics, hospital/	23615
	34	exp economics, medical/	14102
	35	Economics, nursing/	3986
	36	Economics, pharmaceutical/	2862
	37	exp "fees and charges"/	29742
	38	exp budgets/	13515
	39	(low adj cost).mp.	50297
	40	(high adj cost).mp.	13137
	41	(health?care adj cost$).mp.	55192

Term group	#	Terms	# Hits
	42	(fiscal or funding or financial or finance).tw.	133437
	43	(cost adj estimate$).mp.	2107
	44	(cost adj variable).mp.	146
	45	(unit adj cost$).mp.	2348
	46	(economic$ or pharmacoeconomic$ or price$ or pricing).tw.	274235
	47	((health care or healthcare or health-care or drug$ or medication$ or treatment$ or physician$ or nurse$ or nursing or hospital$) adj2 cost$).tw.	66410
	48	((resource$ or healthcare$ or health care or health-care or service$) adj3 (use$ or utilis$ or utiliz$ or consume$ or consuming or consumption$)).tw.	111318
	49	or/15-48	777143
Geographic region	50	exp Great Britain/	353205
	51	(national health service$ or nhs$).ti,ab,in.	172643
	52	(english not ((published or publication* or translat* or written or language* or speak* or literature or citation*) adj5 english)).ti,ab.	91686
	53	(gb or "g.b." or britain* or (british* not "british columbia") or uk or "u.k." or united kingdom* or (england* not "new england") or northern ireland* or northern irish* or scotland* or scottish* or ((wales or "south wales") not "new south wales") or welsh*).ti,ab,jw,in.	1932994
	54	(bath or "bath's" or ((birmingham not alabama*) or ("birmingham's" not alabama*) or bradford or "bradford's" or brighton or "brighton's" or bristol or "bristol's" or carlisle* or "carlisle's" or (cambridge not (massachusetts* or boston* or harvard*)) or ("cambridge's" not (massachusetts* or boston* or harvard*)) or (canterbury not zealand*) or ("canterbury's" not zealand*) or chelmsford or "chelmsford's" or chester or "chester's" or chichester or "chichester's" or coventry or "coventry's" or derby or "derby's" or (durham not (carolina* or nc)) or ("durham's" not (carolina* or nc)) or ely or "ely's" or exeter or "exeter's" or gloucester or "gloucester's" or	1291854

Term group	#	Terms	# Hits
		hereford or "hereford's" or hull or "hull's" or lancaster or "lancaster's" or leeds* or leicester or "leicester's" or (lincoln not nebraska*) or ("lincoln's" not nebraska*) or (liverpool not (new south wales* or nsw)) or ("liverpool's" not (new south wales* or nsw)) or ((london not (ontario* or ont or toronto*)) or ("london's" not (ontario* or ont or toronto*)) or manchester or "manchester's" or (newcastle not (new south wales* or nsw)) or ("newcastle's" not (new south wales* or nsw)) or norwich or "norwich's" or nottingham or "nottingham's" or oxford or "oxford's" or peterborough or "peterborough's" or plymouth or "plymouth's" or portsmouth or "portsmouth's" or preston or "preston's" or ripon or "ripon's" or salford or "salford's" or salisbury or "salisbury's" or sheffield or "sheffield's" or southampton or "southampton's" or st albans or stoke or "stoke's" or sunderland or "sunderland's" or truro or "truro's" or wakefield or "wakefield's" or wells or westminster or "westminster's" or winchester or "winchester's" or wolverhampton or "wolverhampton's" or (worcester not (massachusetts* or boston* or harvard*)) or ("worcester's" not (massachusetts* or boston* or harvard*)) or (york not ("new york*" or ny or ontario* or ont or toronto*)) or ("york's" not ("new york*" or ny or ontario* or ont or toronto*))))).ti,ab,in.	
	55	(bangor or "bangor's" or cardiff or "cardiff's" or newport or "newport's" or st asaph or "st asaph's" or st davids or swansea or "swansea's").ti,ab,in.	50276
	56	(aberdeen or "aberdeen's" or dundee or "dundee's" or edinburgh or "edinburgh's" or glasgow or "glasgow's" or inverness or (perth not australia*) or ("perth's" not australia*) or stirling or "stirling's").ti,ab,in.	192784
	57	(armagh or "armagh's" or belfast or "belfast's" or lisburn or "lisburn's" or londonderry or "londonderry's" or derry or "derry's" or newry or "newry's").ti,ab,in.	23640
	58	or/50-57	2492940
	59	(exp africa/ or exp americas/ or exp antarctic regions/ or exp arctic regions/ or exp asia/ or exp oceania/) not (exp great britain/ or europe/)	2712368
	60	58 not 59	2357753

Term group	#	Terms	# Hits
Exclusion terms	61	(Comment or editorial or letter or "case reports").pt.	3551395
	62	(case stud$ or case report$).ti.	274415
	63	Letter/ or historical article/	1375015
	64	exp Animals/ not exp Humans/	4587805
	65	or/61-64	8435168
Totals	66	9 or 14	4064087
	67	5 and 66	161913
	68	67 and 49	3931
	69	68 and 60	578
	70	69 not 65	559
	71	limit 70 to yr="2012 -Current"	288

Table 9. Search terms for use in the Embase database (searched via the Ovid SP platform on 26th October 2017)

Term group	#	Terms	# Hits
Breast cancer	1	((breast or mammary) adj5 (malignan$ or tumour$ or tumor$ or cancer$ or neoplasm$ or adenocarcinoma$ or carcinoma$)).ti,ab.	421763
	2	exp Breast Neoplasms/	459742
	3	exp breast tumor/	459742
	4	exp breast cancer/	393008
	5	or/1-4	530185
Adjuvant	6	exp adjuvant therapy/	132794
	7	(adjuvant$ or operable$ or early$ or "locally advanced").ti,ab.	1923355
	8	6 or 7	1975363
	9	exp metastasis/	530522

Term group	#	Terms	# Hits
Recurrence / metastatic	10	exp neoplasm metastasis/	530522
	11	exp neoplasm recurrence, local/	50161
	12	exp cancer recurrence/	115539
	13	exp advanced cancer/	68843
	14	(metasta$ or recur$ or secondar$ or disseminat$ or relaps$ or advance$ or inoperab$ or terminal or incurable or late stage or stage 3a or stage 3b or stage 3c or stage 3 or stage iii or stage 4a or stage 4b or stage 4 or stage iv).ti,ab.	3328066
Cost and resource use	15	or/9-14	3461838
	16	Economic aspect/	110696
	17	Cost-benefit analysis/	76342
	18	Cost control/	60767
	19	Cost of illness/	17196
	20	Health care cost/	165775
	21	Hospital cost/	18226
	22	Cost effectiveness analysis/	129382
	23	Cost minimization analysis/	3088
	24	Financial management/	110047
	25	Health care financing/	12617
	26	Health economics/	35493
	27	(fiscal or funding or financial or finance).tw.	150381
	28	(cost adj estimate$).mp.	2805
	29	(cost adj variable).mp.	53
	30	(unit adj cost$).mp.	3613
	31	socioeconomics/	130090

Term group	#	Terms	# Hits
	32	((health care or healthcare or health-care or drug$ or medication$ or treatment$ or physician$ or nurse$ or nursing or hospital$) adj2 cost$).tw.	90347
	33	((resource$ or healthcare$ or health care or health-care or service$) adj3 (use$ or utilis$ or utiliz$ or consume$ or consuming or consumption$)).tw.	130266
	34	or/16-33	935903
Geographic region	35	United Kingdom/	387806
	36	(national health service$ or nhs$).ti,ab,in,ad.	268696
	37	(english not ((published or publication$ or translat$ or written or language$ or speak$ or literature or citation$) adj5 english)).ti,ab.	33699
	38	(gb or "g.b." or britain$ or (british$ not "british columbia") or uk or "u.k." or united kingdom$ or (england$ not "new england") or northern ireland$ or northern irish$ or scotland$ or scottish$ or ((wales or "south wales") not "new south wales") or welsh$).ti,ab,jw,in,ad.	2829878
	39	(London or Birmingham or Leeds or Glasgow or Sheffield or Bradford or Edinburgh or Liverpool or Manchester or Bristol or Wakefield or Cardiff or Coventry or Nottingham or Leicester or Sunderland or Belfast or Newcastle upon Tyne or Brighton or Hull or Plymouth or Stoke-on-Trent or Wolverhampton or Derby or Swansea or Southampton or Salford or Aberdeen or Westminster or Portsmouth or York or Peterborough or Dundee or Lancaster or Oxford or Newport or Preston or St Albans or Norwich or Chester or Cambridge or Salisbury or Exeter or Gloucester or Lisburn or Chichester or Winchester or Londonderry or Carlisle or Worcester or Bath or Durham or Lincoln or Hereford or Armagh or Inverness or Stirling or Canterbury or Lichfield or Newry or Ripon or Bangor or Truro or Ely or Wells or St Davids).ti,ab,in,ad.	3453728
	40	or/35-39	4444463
	41	(exp "arctic and antarctic"/ or exp oceanic regions/ or exp western hemisphere/ or exp africa/ or exp asia/) not (united kingdom/ or europe/)	2576089

Term group	#	Terms	# Hits
	42	40 not 41	4190560
Exclusion terms	43	("conference abstract" or "conference paper").pt.	3495481
	44	limit 43 to yr="1974-2014"	2624741
	45	(editorial or letter).pt.	1546935
	46	(case stud$ or case report$).ti.	312902
	47	Letter/ or historical article/	948811
	48	exp Animals/ not exp Humans/	4754858
	49	or/44-48	8907921
Totals	50	8 or 15	4947844
	51	5 and 50	242271
	52	51 and 34	7550
	53	52 and 42	1731
	54	53 not 49	1343
	55	limit 54 to yr="2012 -Current"	672

Table 10. Search terms for use in the Embase database (searched via the Ovid SP platform on 12th June 2019)

Term group	#	Terms	# Hits
Breast cancer	1	((breast or mammary) adj5 (malignan$ or tumour$ or tumor$ or cancer$ or neoplasm$ or adenocarcinoma$ or carcinoma$)).ti,ab.	461661
	2	exp Breast Neoplasms/	495915
	3	exp breast tumor/	495915
	4	exp breast cancer/	432628
	5	or/1-4	572825
Adjuvant	6	exp adjuvant therapy/	147982

Term group	#	Terms	# Hits
	7	(adjuvant$ or operable$ or early$ or "locally advanced").ti,ab.	2111123
	8	6 or 7	2166618
	9	exp metastasis/	578831
Recurrence / metastatic	10	exp neoplasm metastasis/	578831
	11	exp neoplasm recurrence, local/	52955
	12	exp cancer recurrence/	154314
	13	exp advanced cancer/	89064
	14	(metasta$ or recur$ or secondar$ or disseminat$ or relaps$ or advance$ or inoperab$ or terminal or incurable or late stage or stage 3a or stage 3b or stage 3c or stage 3 or stage iii or stage 4a or stage 4b or stage 4 or stage iv).ti,ab.	3690063
Cost and resource use	15	or/9-14	3822274
	16	Economic aspect/	109760
	17	Cost-benefit analysis/	80996
	18	Cost control/	65198
	19	Cost of illness/	18260
	20	Health care cost/	178918
	21	Hospital cost/	20054
	22	Cost effectiveness analysis/	141810
	23	Cost minimization analysis/	3329
	24	Financial management/	110129
	25	Health care financing/	13000
	26	Health economics/	31865
	27	(fiscal or funding or financial or finance).tw.	175756
	28	(cost adj estimate$).mp.	3140

Term group	#	Terms	# Hits
	29	(cost adj variable).mp.	238
	30	(unit adj cost$).mp.	4157
	31	socioeconomics/	132343
	32	((health care or healthcare or health-care or drug$ or medication$ or treatment$ or physician$ or nurse$ or nursing or hospital$) adj2 cost$).tw.	104934
	33	((resource$ or healthcare$ or health care or health-care or service$) adj3 (use$ or utilis$ or utiliz$ or consume$ or consuming or consumption$)).tw.	152003
	34	or/16-33	1009159
Geographic region	35	exp United Kingdom/	401091
	36	(national health service* or nhs*).ti,ab,in,ad.	315178
	37	(english not ((published or publication* or translat* or written or language* or speak* or literature or citation*) adj5 english)).ti,ab.	38835
	38	(gb or "g.b." or britain* or (british* not "british columbia") or uk or "u.k." or united kingdom* or (england* not "new england") or northern ireland* or northern irish* or scotland* or scottish* or ((wales or "south wales") not "new south wales") or welsh*).ti,ab,jx,in,ad.	2985892
	39	(bath or "bath's" or ((birmingham not alabama*) or ("birmingham's" not alabama*) or bradford or "bradford's" or brighton or "brighton's" or bristol or "bristol's" or carlisle* or "carlisle's" or (cambridge not (massachusetts* or boston* or harvard*)) or ("cambridge's" not (massachusetts* or boston* or harvard*)) or (canterbury not zealand*) or ("canterbury's" not zealand*) or chelmsford or "chelmsford's" or chester or "chester's" or chichester or "chichester's" or coventry or "coventry's" or derby or "derby's" or (durham not (carolina* or nc)) or ("durham's" not (carolina* or nc)) or ely or "ely's" or exeter or "exeter's" or gloucester or "gloucester's" or hereford or "hereford's" or hull or "hull's" or lancaster or "lancaster's" or leeds* or leicester or "leicester's" or (lincoln not nebraska*) or ("lincoln's" not nebraska*) or (liverpool not (new south wales* or nsw)) or ("liverpool's" not (new south wales* or	2285703

Term group	#	Terms	# Hits
		nsw)) or ((london not (ontario* or ont or toronto*)) or ("london's" not (ontario* or ont or toronto*)) or manchester or "manchester's" or (newcastle not (new south wales* or nsw)) or ("newcastle's" not (new south wales* or nsw)) or norwich or "norwich's" or nottingham or "nottingham's" or oxford or "oxford's" or peterborough or "peterborough's" or plymouth or "plymouth's" or portsmouth or "portsmouth's" or preston or "preston's" or ripon or "ripon's" or salford or "salford's" or salisbury or "salisbury's" or sheffield or "sheffield's" or southampton or "southampton's" or st albans or stoke or "stoke's" or sunderland or "sunderland's" or truro or "truro's" or wakefield or "wakefield's" or wells or westminster or "westminster's" or winchester or "winchester's" or wolverhampton or "wolverhampton's" or (worcester not (massachusetts* or boston* or harvard*)) or ("worcester's" not (massachusetts* or boston* or harvard*)) or (york not ("new york*" or ny or ontario* or ont or toronto*)) or ("york's" not ("new york*" or ny or ontario* or ont or toronto*))))).ti,ab,in,ad.	
	40	(bangor or "bangor's" or cardiff or "cardiff's" or newport or "newport's" or st asaph or "st asaph's" or st davids or swansea or "swansea's").ti,ab,in,ad.	93024
	41	(aberdeen or "aberdeen's" or dundee or "dundee's" or edinburgh or "edinburgh's" or glasgow or "glasgow's" or inverness or (perth not australia*) or ("perth's" not australia*) or stirling or "stirling's").ti,ab,in,ad.	316147
	42	(armagh or "armagh's" or belfast or "belfast's" or lisburn or "lisburn's" or londonderry or "londonderry's" or derry or "derry's" or newry or "newry's").ti,ab,in,ad.	41975
	43	or/35-42	3636718
	44	(exp "arctic and antarctic"/ or exp oceanic regions/ or exp western hemisphere/ or exp africa/ or exp asia/ or exp "australia and new zealand"/) not (exp united kingdom/ or europe/)	2885946
	45	43 not 44	3439886
Exclusion terms	46	("conference abstract" or "conference paper").pt.	4188576

Term group	#	Terms	# Hits
	47	limit 46 to yr="1974-2016"	3373194
	48	(editorial or letter).pt.	1673200
	49	(case stud$ or case report$).ti.	334327
	50	Letter/ or historical article/	1014779
	51	exp Animals/ not exp Humans/	4450604
	52	or/47-51	9436267
Totals	53	8 or 15	5436868
	54	5 and 53	266795
	55	54 and 34	8633
	56	55 and 45	1535
	57	56 not 52	1136
	58	limit 57 to yr="2012 -Current"	594

Table 11. Search terms for use in the NHS-EED database (searched via The Cochrane Library, via the Wiley Online platform on 26th October 2017)

Term group	#	Terms	# Hits
Breast cancer	#1	((breast or mammary) near/5 (malignan* or tumour* or tumor* or cancer* or neoplasm* or adenocarcinoma* or carcinoma*)):ti,ab	23558
	#2	[mh "Breast Neoplasms"]	10371
	#3	#1 or #2	24741
	#4	[mh "Chemotherapy, Adjuvant"]	3880
	#5	[mh "Radiotherapy, Adjuvant"]	1033
Adjuvant	#6	(adjuvant* or operable* or early* or "locally advanced"):ti,ab	92620
	#7	#4 or #5 or #6	94093
	#8	[mh "neoplasm metastasis"]	4503

Term group	#	Terms	# Hits
	#9	(metasta* or recur* or secondar* or relaps* or advance* or inoperab* or terminal or incurable or "late stage" or "stage 3a" or "stage 3b" or "stage 3c" or "stage 3" or "stage iii" or "stage 4a" or "stage 4b" or "stage 4" or "stage iv"):ti,ab	170800
Recurrence / metastatic	#10	#8 or #9	171748
	#11	#7 or #10	237162
	#12	#3 and #11	16208
	#13	#12 Publication Year from 2012 to 2017, in Economic Evaluations	60

Results from the database searches were downloaded into an EndNote® database and manually de-duplicated against the results of the original SLR before being transferred into a bespoke web-based platform for record screening.

Study selection

To be included in the cost and resource use SLR, articles had to meet pre-defined eligibility criteria which are detailed in Table 12. The citations found through the searches were first assessed against the eligibility criteria by two independent reviewers based on abstract and title. Where the applicability of the inclusion criteria was unclear, the article was included at this stage in order to ensure that all potentially relevant studies were captured. Full-text copies of publications potentially meeting the eligibility criteria were then obtained and reviewed against the same eligibility criteria by two independent reviewers. In cases where the article did not give enough information to be sure it met the inclusion criteria at the full-text screening stage, the article was excluded to ensure that only relevant articles were ultimately included in the review.

At both the title/abstract and full-text review stages, any disagreements between the reviewers were resolved by discussion until a consensus was met, with a third independent reviewer making the final decision if necessary. For studies meeting the eligibility criteria after the second (full-text) screening stage, data were extracted by a single reviewer into a pre-specified data extraction grid and verified by a second independent individual.

Table 12. Eligibility criteria for the cost and resource use SLR

Domain	Inclusion Criteria	Exclusion Criteria
Population	Patients with breast cancer receiving treatment at the adjuvant stage (i.e. after initial surgery) or later in the disease pathway (i.e. for metastatic disease)	Patients without breast cancer Patients with breast cancer receiving neoadjuvant treatment

Domain	Inclusion Criteria	Exclusion Criteria
Intervention(s)	Any or none	-
Comparator(s)	Any or none	-
Outcomes	Direct cost or resource use data collected since 2007 Data must be relevant to the UK NHS and PSS, and of relevance to the adjuvant treatment of HER2-positive early breast cancer	Studies not presenting relevant cost/resource use data for the population of interest (e.g. presenting indirect costs only), or studies presenting data collected prior to 2007
Study design/ publication type	Any original research study published as a journal article in 2012 or later, HTA submissions published since 2007, or congress abstracts published in the last 2 years (since 2015), including: Randomised controlled trials Budget impact models Cost-of-illness studies Comparative economic evaluations such as cost-effectiveness, cost-utility, cost-benefit, cost-consequence or cost-minimisation analyses	Publications other than SLRs not reporting original research Journal articles published prior to 2012, HTA submissions published prior to 2007 or congress abstracts published prior to 2015 Case reports/case series
	Systematic reviews and meta-analyses will be included at the title/abstract screening stage and used for the identification of additional primary studies not identified through other searches. They will then be excluded during the full-text review stage	
Geographic setting	UK	Regions outside of the UK or, in the case of pooled data, where data from the UK has not been presented separately
Other considerations	Full-text or abstract in English If the full-text is non-English, the abstract must contain enough data to be eligible for inclusion in its own right Human subjects	Non-English language articles Studies not on human subjects

Abbreviations: HTA: Health Technology Assessment; NHS: National Health Service; PSS: Personal Social Services; SLR: Systematic Literature Review; UK: United Kingdom.

Grey literature searches

The search terms used in the grey literature and NICE website searches are provided in Table 13. During the original SLR, congress searches and searches of the NICE website were conducted on 9th November 2017. During the SLR update, congress searches were conducted on 24th June 2019 and searches of the NICE website were conducted on 26th June 2019.

Table 13. Search strategies used in manual congress searching

Congress	Link	Search strategy	Total unique hits	Relevant results
ESMO Congress 2016 2017 2018	2016: https://academic.oup.com/annonc/issue/27/suppl_6 2017: Abstract book PDF 2018: https://academic.oup.com/annonc/search-results?q=cost&f_IssueNo=suppl_8&f_Volume=29&fl_SiteID=5262&qb=%7B%22q%22:%22cost%22%7D&page=1	2016: Using the ctrl-F function, the abstract titles listed on the abstract book webpage were screened for the terms “cost”, “resource” and “economic”. 2017: The PDF was opened and the terms “cost”, “resource”, and “economic” were searched for using the ctrl-F function. 2018: Using the ctrl-F function, the abstract titles listed on the abstract book webpage were screened for the terms “cost”, “resource” and “economic”.	2016: 43 2017: 374 2018: 133	2016: 0 2017: 0 2018: 0

Congress	Link	Search strategy	Total unique hits	Relevant results
ASCO Annual Meeting 2016 2017 2018 2019	2016: Abstract book PDF 2017: Abstract book PDF 2018: https://meetinglibrary.asco.org/ 2019: https://meetinglibrary.asco.org/	2016: The PDF was opened and the terms “cost”, “resource”, and “economic” were searched for using the ctrl-F function. 2017: The PDF was opened and the terms “cost”, “resource”, and “economic” were used using the ctrl-F function. 2018: “Search 2018 ASCO Annual Meeting” was selected and the terms “cost”, “resource” and “economic” were searched separately using the ‘Basic Search’ function. 2019: “Search 2019 ASCO Annual Meeting” was selected and the terms “cost”, “resource” and “economic” were searched separately using the ‘Basic Search’ function.	2016: 288 2017: 272 2018: 543 2019: 470	2016: 0 2017: 0 2018: 0 2019: 0

Congress	Link	Search strategy	Total unique hits	Relevant results
SABCS 2015 2016 2017 2018	Abstract book PDFs	2015: The PDF was opened and the terms “cost”, “resource”, and “economic” were searched for using the ctrl-F function. 2016: The PDF was opened and the terms “cost”, “resource”, and “economic” were searched for using the ctrl-F function. 2017: The PDF was opened and the terms “cost”, “resource”, and “economic” were searched for using the ctrl-F function. 2018: The PDF was opened and the terms “cost”, “resource”, and “economic” were searched for using the ctrl-F function.	2015: 130 2016: 156 2017: 269 2018: 213	2015: 0 2016: 0 2017: 0 2018: 0

Congress	Link	Search strategy	Total unique hits	Relevant results
ISPOR Annual International Meeting 2016 2017 2018 2019	https://www.ispor.org/heor-resources/presentations-database/search	2016: The conference "ISPOR Annual International Meeting 2016" was selected and the term "breast" was entered into the keyword search box with the 'abstract' search option selected. 2017: The conference "ISPOR Annual International Meeting 2017" was selected and the term "breast" was entered into the keyword search box with the 'abstract' search option selected. 2018: The conference "ISPOR Annual International Meeting 2018" was selected and the term "breast" was entered into the keyword search box with the 'abstract' search option selected. 2019: The conference "ISPOR Annual International Meeting 2019" was selected and the term "breast" was entered into the keyword search box with the 'abstract' search option selected.	2016: 68 2017: 71 2018: 47 2019: 29	2016: 0 2017: 0 2018: 0 2019: 0

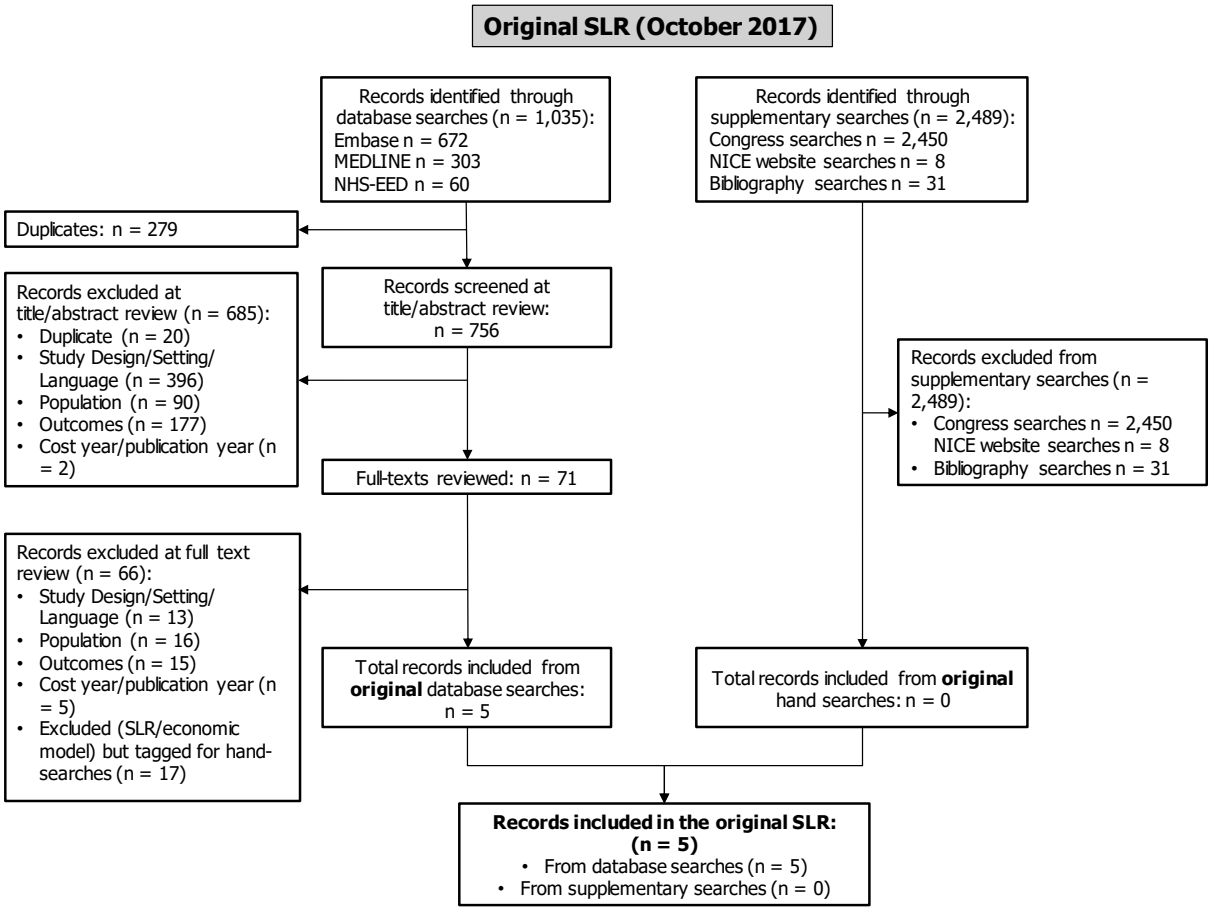
Congress	Link	Search strategy	Total unique hits	Relevant results
ISPOR Annual European meeting 2016 2017 2018	https://www.ispor.org/heor-resources/presentations-database/search	2016: The conference "ISPOR Europe 2016" was selected and the term "breast" was entered into the keyword search box with the 'abstract' search option selected. 2017: The conference "ISPOR Europe 2017" was selected and the term "breast" was entered into the keyword search box with the 'abstract' search option selected. 2018: The conference "ISPOR Europe 2018" was selected and the term "breast" was entered into the keyword search box with the 'abstract' search option selected.	2016: 68 2017: 77 2018: 80	2016: 0 2017: 0 2018: 0
NICE website*	www.nice.org.uk	2017: "Cancer" was entered into the search box and 'search' was clicked. The results were then limited to 'technology appraisal guidance'. Only those from 2007 onwards were hand-searched for relevant studies. 2019: "Breast Cancer" was entered into the search box and 'search' was clicked. The results were then limited to 'technology appraisal guidance'. Only those from November 2017 onwards were hand-searched for relevant studies.	2017 original SLR: 8 2019 SLR update: 9	2017 original SLR: 0 2019 SLR update: 1

Abbreviations: ASCO: American Society of Clinical Oncology; ESMO: European Society for Medical Oncology; ISPOR: International Society for Pharmacoeconomics and Outcomes Research; NICE: National Institute of Health and Care Excellence; SABCS: San Antonio Breast Cancer Symposium; SLR: systematic literature review. *During the original SLR, identified TAs include TA458, TA421, TA424, TA263, TA257, TA239, TA214 and TA116. During the SLR update, identified TAs include TA579, TA569, TA563, TA515, TA509, TA501, TA503, TA495 and TA496.

Results

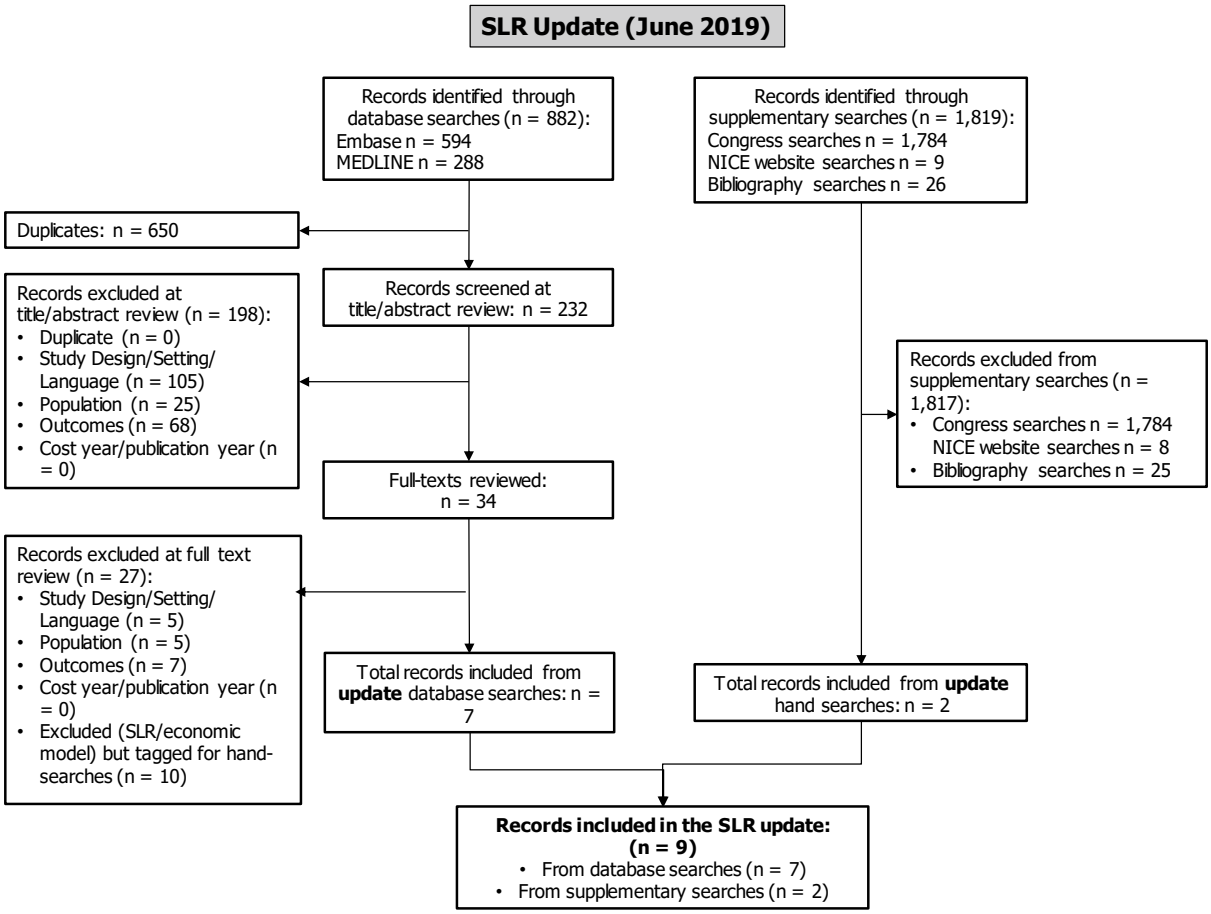
In the original SLR conducted on 26th October 2017, a total of 756 unique records were identified from the electronic database searches and reviewed at the title/abstract review stage. After title/abstract review, 71 records were reviewed at the full-text stage with 5 records ultimately meeting the inclusion criteria. No additional records were identified and included through the congress searching, NICE website searching or through hand searching of bibliographies. In the SLR update conducted on 12th June 2019, 232 unique records were identified from the electronic database searches and reviewed at the title/abstract review stage. After title/abstract review, 34 records were reviewed at the full-text stage with 7 records ultimately meeting the inclusion criteria. The NICE website searching resulted in one record for inclusion, and one additional record was identified and included through the hand searching of bibliographies. No additional relevant records were identified through the congress searching. The flow of studies through the systematic review process is presented in Figure 1 for the original SLR and in Figure 2 for the SLR update.

Figure 1. PRISMA flowchart for the cost and resource use original SLR



Abbreviations: NHS-EED: National Health Service Economic Evaluation Database; NICE: National Institute of Health and Care Excellence; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR: systematic literature review.

Figure 2. PRISMA flowchart for the cost and resource use SLR update



Abbreviations: NICE: National Institute of Health and Care Excellence; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR: systematic literature review.

Details and results of the relevant studies identified in the cost and resource use SLR are presented below in Table 14. Details of the studies excluded at the full-text review stage can be found in Table 15.

Table 14. Summary of included studies in the cost and resource use SLR

<table>
<tr><th>Study</th><th>Objective</th><th>Country and cost year</th><th>Patient population</th><th>Valuation methods</th><th>Technology and other costs</th><th>Resource use</th><th>Applicability to clinical practice in England</th></tr>
<tr>
<td>Holt et al. 2013115</td>
<td>To examine the implications of routine Oncotype DX testing in patients with oestrogen receptor (ER)-positive, node-negative or pNImi breast cancer who were assessed for adjuvant chemotherapy</td>
<td>United Kingdom (UK) (Wales)

Cost year 2010</td>
<td>Recruitment was via one cancer centre in West Wales.

Women with excised ER-positive (Allred score ⩾3/8 by immunohistochemistry [IHC]) and node-negative (pN0, pN0i+) invasive breast cancer or minimal node involvement (pN1mi) were identified at multidisciplinary team (MDT) meetings as being suitable for testing.

Oncologists were encouraged to include patients even if initial assessment suggested they were at very low risk of recurrence, so as to best reflect testing of this whole cohort.

Women aged <18 years, pregnant, unable to comprehend the details of the trial, unable to complete the documentation in English or who had a</td>
<td>All patients were asked to complete a diary of medical interactions over the 6 months following inclusion in the study.

Hospital notes and electronic chemotherapy prescription records were used to estimate the total cost of chemotherapy. All other treatment costs were derived from UK-specific sources and inflated where necessary to 2010 Great British Pounds (GBP) using the Hospital and Community Health Services pay and price inflation index.</td>
<td>Summary of treatment/management costs for patients receiving chemotherapy and those not receiving chemotherapy

<table>
<tr><th rowspan="2">Resource</th><th colspan="2">Cost, GBP [mean (SD)]</th></tr>
<tr><th>Chemo (n=35)</th><th>No Chemo (n=107)</th></tr>
<tr><td>General Practitioner (GP) cost</td><td>67 (94)</td><td>68 (107)</td></tr>
<tr><td>GP home visit cost</td><td>3 (20)</td><td>1 (12)</td></tr>
<tr><td>GP phone consultation cost</td><td>1 (4)</td><td>1 (6)</td></tr>
<tr><td>GP nurse cost</td><td>4 (19)</td><td>23 (120)</td></tr>
<tr><td>District nurse cost</td><td>398 (721)</td><td>29 (151)</td></tr>
<tr><td>Hospital nurse cost</td><td>53 (200)</td><td>15 (68)</td></tr>
<tr><td>Lymphoedema clinic cost</td><td>16 (52)</td><td>38 (117)</td></tr>
<tr><td>Hospital doctor cost</td><td>236 (246)</td><td>218 (294)</td></tr>
<tr><td>Counsellors cost</td><td>0 (0)</td><td>11 (85)</td></tr>
<tr><td>Physiotherapist cost</td><td>1 (6)</td><td>3 (14)</td></tr>
<tr><td>Plastic surgeon cost</td><td>14 (46)</td><td>8 (46)</td></tr>
</table>
</td>
<td>35 patients received chemotherapy and 107 patients did not receive chemotherapy.

Decision impact results

Initially, 57 (40.14%) of the 142 patients were recommended chemotherapy and hormone therapy. In 26 of these 57 patients (45.61%), treatment was revised to hormone therapy alone after the recurrence score (RS) (from Oncotype DX) was made available. The remaining 85 (59.86%) patients were initially advised that hormone therapy alone would be sufficient, but, after review of the recurrence score, 12 (14.12%) of these were advised chemotherapy as well.

<table>
<tr><th>Decision</th><th>Patient Number</th><th>Percentage of Patients</th></tr>
<tr><td>Hormone therapy only unchanged</td><td>73</td><td>51.41</td></tr>
<tr><td>Hormone therapy changed to hormone therapy + chemotherapy</td><td>12</td><td>8.45</td></tr>
<tr><td>Chemotherapy + hormone therapy unchanged</td><td>31</td><td>21.83</td></tr>
</table>
</td>
<td>Data were collected in the UK (Wales) and costs have been given in GBP.

Data were collected from a single centre, enrolling near consecutive patients, a number of whom would not be expected to receive the test were it introduced in the National Health Service (NHS).</td>
</tr>
</table>

<table>
<tr><th>Study</th><th>Objective</th><th>Country and cost year</th><th>Patient population</th><th>Valuation methods</th><th colspan="3">Technology and other costs</th><th colspan="3">Resource use</th><th>Applicability to clinical practice in England</th></tr>
<tr><td></td><td></td><td></td><td>previous history of breast cancer treatment were excluded.

146 patients were enrolled and 142 patients were evaluable for the final analysis.

Of these 35 patients received chemotherapy and 107 patients did not receive chemotherapy.</td><td></td><td colspan="3"><table>
<tr><td>Hospital stay cost</td><td>596 (1,689)</td><td>90 (482)</td></tr>
<tr><td>Herceptin cost</td><td>2,241 (8,509)</td><td>0 (0)</td></tr>
<tr><td>Consultant cost</td><td>79 (107)</td><td>82 (95)</td></tr>
<tr><td>Computerised tomography simulation (CT SIM) planning cost</td><td>1,312 (1,158)</td><td>1,212 (1,065)</td></tr>
<tr><td>Radiotherapy cost</td><td>6,987 (4,171)</td><td>6,680 (4,286)</td></tr>
<tr><td>Radiotherapy review cost</td><td>138 (89)</td><td>135 (103)</td></tr>
<tr><td>Radiotherapy boosts cost</td><td>1,433 (2,299)</td><td>768 (1,799)</td></tr>
<tr><td>Mould room cost</td><td>6 (21)</td><td>5 (20)</td></tr>
<tr><td>Fluorouracil, epirubicin, cyclophosphamide (FEC) cost</td><td>1119 (892)</td><td>0 (0)</td></tr>
<tr><td>Docetaxel, doxorubicin, cyclophosphamide (TAC) cost</td><td>1,465 (2,116)</td><td>0 (0)</td></tr>
<tr><td>Pre-chemo assessment cost</td><td>60 (44)</td><td>0 (0)</td></tr>
<tr><td>Pre-chemo bloods cost</td><td>27 (8)</td><td>0 (0)</td></tr>
<tr><td>Oncologist appointment</td><td>157 (150)</td><td>0 (0)</td></tr>
</table></td><td colspan="3"><table>
<tr><td>Chemotherapy + hormone therapy changed to hormone therapy only</td><td>26</td><td>18.31</td></tr>
</table>
Decision impact results by (RS) subgroup

In the low RS group, 26 of 79 patients were initially recommended for chemotherapy, of which 23 were then recommended against (-88.4%). In the intermediate RS group, 16 of 39 patients were initially advised chemotherapy, which was increased to 19 on receipt of the results (+18.6%). In the high RS group, 15 of 24 patients were initially recommended chemotherapy, which was increased to 21 (+40%). The final chemotherapy recommendations were 3 of 79 (3.7%) in the low RS group, 19 of 39 (48.7%) in the intermediate RS group and 21 of 24 (87.5%) in the high RS group.</td><td></td></tr>
</table>

<table>
<tr><th>Study</th><th>Objective</th><th>Country and cost year</th><th>Patient population</th><th>Valuation methods</th><th>Technology and other costs</th><th>Resource use</th><th>Applicability to clinical practice in England</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td><table>
<tr><td>cost</td><td></td><td></td></tr>
<tr><td>Multi-gated acquisition scan (MUGA) cost</td><td>4 (16)</td><td>0 (0)</td></tr>
<tr><td>Echocardiogram (ECHO) cost</td><td>9 (28)</td><td>0 (0)</td></tr>
<tr><td>Chemotherapy day unit (CDU) doctor cost</td><td>46 (84)</td><td>0 (0)</td></tr>
<tr><td>CDU triage nurse cost</td><td>42 (71)</td><td>0 (0)</td></tr>
<tr><td>Bone scan cost</td><td>26 (64)</td><td>56 (84)</td></tr>
<tr><td>GCSF cost</td><td>3,510 (8,246)</td><td>0 (0)</td></tr>
<tr><td>Total cost</td><td>20,418 (13,052)</td><td>9,568 (6,087)</td></tr>
</table></td><td></td><td></td></tr>
<tr><td>Loncaster et al. 2017116</td><td>To evaluate the impact of Oncotype DX Breast Recurrence Score testing on adjuvant chemotherapy decision-making in routine clinical practice in patients with newly diagnosed, ER-positive, human epidermal growth factor receptor 2 (HER2)-</td><td>UK (Greater Manchester)

Cost year Not reported (NR)</td><td>Analysis includes 201 patients: 82 patients from a prospective pilot study plus 119 patients from an audit beyond the pilot study.

Inclusion criteria included: females with newly diagnosed invasive breast cancer who underwent breast and axillary surgery with curative intent; a decision to refer the</td><td>The study was prospective registration with analysis retrospectively following treatment decisions made based on standard clinicopathological data and the RS result.

During the study period, data on clinicopathological factors, RS</td><td>NR</td><td>74 patients (36.8%) received chemotherapy. The remaining 127 patients (63.2%) received endocrine therapy as their only systemic treatment.

Treatment by patient group in relation to the RS result
<table>
<tr><th></th><th>Chemo</th><th>No Chemo</th></tr>
<tr><td colspan="3">Overall population (n=201)</td></tr>
<tr><td>Low RS</td><td>4 (2.0%)</td><td>82 (40.8%)</td></tr>
</table></td><td>Data were collected in the UK and costs have been given in GBP.

Data have been collected in a real-world setting during routine clinical practice.</td></tr>
</table>

Study	Objective	Country and cost year	Patient population	Valuation methods	Technology and other costs	Resource use	Applicability to clinical practice in England
	negative, invasive breast cancer who underwent breast surgery with curative intent.		patient to an oncologist for chemotherapy made at a breast cancer MDT meeting; ER-positive (Quick score ⩾5/8) and HER2 0, 1+ or non-amplified; axillary lymph node-negative or node-positive (post-menopausal females only); at least intermediate risk disease (personal response determinants in cancer therapy [PREDICT] overall survival benefit from chemotherapy estimated to be >3% at 10 years). In addition, patients had to be considered fit for chemotherapy.	results and subsequent chemotherapy usage were collected.		Intermediate RS: 48 (23.9%); 41 (20.4%) High RS: 22 (10.9%); 4 (2.0%) Total: 74 (36.8%); 127 (63.2%) **Node-negative (n=136)** Low RS: 3 (4.6%); 37 (56.9%) Intermediate RS: 12 (18.5%); 7 (10.8%) High RS: 5 (7.7%); 1 (1.5%) Total: 20 (30.8%); 45 (69.2%) **Node-positive (n=65)** Low RS: 1 (0.7%); 45 (33.1%) Intermediate RS: 36 (26.5%); 34 (25.0%) High RS: 17 (12.5%); 3 (2.2%) Total: 54 (39.7%); 82 (60.3%) RS: low, <18; intermediate, 18–30; high, ⩾31.	Only node-negative patients would be expected to receive the test were it introduced in the NHS and so the node-positive results may not be applicable.
Picot et al. 2017117	To assess the clinical effectiveness and cost-effectiveness of INTRABEAM Photo Radiotherapy	UK Cost year 2013	Patients with early operable breast cancer. The patient population included in the economic model	The study was prospective registration with analysis retrospectively following treatment decisions made	Additional staff resources required for use of INTRABEAM assumed by economic model	Model parameter values for clinical pathway Proportion of INTRABEAM patients having mastectomy at local recurrence: 0.8 (a range of 0.7-0.8 was given by the experts but the latter was used within the model)	Economic model. Cost data were derived from

<table>
<tr><th>Study</th><th>Objective</th><th>Country and cost year</th><th>Patient population</th><th>Valuation methods</th><th>Technology and other costs</th><th>Resource use</th><th>Applicability to clinical practice in England</th></tr>
<tr>
<td></td>
<td>System for the adjuvant treatment of early breast cancer during surgical removal of the tumour.</td>
<td></td>
<td>reflects the patient population in the pre-pathology stratum of the targeted intraoperative radiotherapy-alone (TARGIT-A) trial.

The TARGIT-A study recommends INTRABEAM concurrent with lumpectomy as an alternative to post-operative whole-breast external beam radiation therapy (WB-EBRT) but does not recommend the use of post-operative INTRABEAM as an alternative to WB-EBRT.</td>
<td>based on standard clinicopathological data and the RS result.

During the study period, data on clinicopathological factors, RS results and subsequent chemotherapy usage were collected.

Staff time was costed using the NHS staff pay bands – hourly costs were taken from the Personal Social Services (PSS) Research Unit's Unit Costs of Health and Social Care 2013.

Radiotherapy and clinical expert opinion was used to identify activities and estimate the staff time required at each band. Two experts were consulted and the cost of each activity shown</td>
<td>
<table>
<tr><th>Frequency of cost</th><th>Activity</th><th>Cost, £</th></tr>
<tr><td>One off</td><td>INTRABEAM operating procedure development</td><td>757.00</td></tr>
<tr><td>One off</td><td>Initial INTRABEAM training</td><td>5,227.00</td></tr>
<tr><td>Annual</td><td>Technical commissioning</td><td>2,271.00</td></tr>
<tr><td>Annual</td><td>Technical commissioning sign off</td><td>275.00</td></tr>
<tr><td>Annual</td><td>Refresher training on radiation protection</td><td>920.00</td></tr>
<tr><td>Per treatment</td><td>Pre-treatment quality control (QC) check</td><td>25.00</td></tr>
<tr><td>Per treatment</td><td>Planning INTRABEAM dose in operating theatre</td><td>25.00</td></tr>
<tr><td>Per treatment</td><td>Delivering INTRABEAM dose in operating theatre</td><td>83.00</td></tr>
<tr><td>Per treatment</td><td>Additional time required by medical physicist in support of INTRABEAM use</td><td>76.00</td></tr>
</table>
</td>
<td>INTRABEAM device lifetime and resource-use assumptions in model base case

From manufacturer and radiotherapy expert opinion, the working lifetime of an INTRABEAM device is assumed to be 10 years.</td>
<td>UK sources and resource use data presented here are from expert clinical opinion in the UK. Costs are reported in GBP.</td>
</tr>
</table>

Study	Objective	Country and cost year	Patient population	Valuation methods	Technology and other costs	Resource use	Applicability to clinical practice in England
				was derived using the unit costs.			
Round et al. 2015118	The aim of the study was to estimate the total direct and indirect costs provided to lung, colorectal, breast and prostate cancer patients in England and Wales during the end-of-life period.	England and Wales Cost year 2013/14	Breast cancer patients during their end-of-life period. End-of-life period was defined as the point at which a patient begins the use of strong opioids. (Note that this is different from the National Institute for Health and Care Excellence (NICE) definition of end-of-life: a person is approaching the end of life when it is considered by health care professionals that they are likely to die within the next 12 months.)	A systematic literature review (SLR) was performed to find cost and resource use of end-of-life patients. A model was built to estimate the costs per patient. This was calculated by summing the resources used during the end of life period and multiplying by the unit cost of the resource. Both direct and indirect costs are considered in the study. Direct costs are those borne directly by the health or social care services. The key indirect cost included in this study relates to value of the provision of informal care. This has been valued using the	Mean estimated cost per patient, with Bayesian credible intervals (95% confidence interval [CI]):* Health care: £4,346 (£395, £12,545) Social care: £2,843 (£84, £10,170) Charity care: £480 (£7, £1,845) Informal care: £4,868 (£18, £21,818) Total: £12,663 (£1,249, £38,712) *Based on 10,000 Monte Carlo simulations	NR	End of life definition does not follow that set out by NICE and therefore the data may not be applicable. Cost and resource data were derived from UK sources and costs were reported in GBP. The wide 95% credible intervals of the mean estimated cost per patient indicate the results are highly uncertain. The uncertainty was driven by highly uncertain resource use estimates and that, in many

Study	Objective	Country and cost year	Patient population	Valuation methods	Technology and other costs	Resource use	Applicability to clinical practice in England
				human capital approach.			cases, it was not possible to find data specific to patients at the end of life.
Vaidya et al. 2016119	To study the clinical and cost-effectiveness of targeted intraoperative radiotherapy (TARGIT) versus WB-EBRT in breast cancer patients after undergoing breast-conserving surgery.	UK Cost year 2013/14	Patients receiving external beam radiation therapy (EBRT).	Hospital transportation data was collected using a short survey at two sites in England (n=37).	NR	13.5% (n/N=5/37) of patients reported using hospital transport to travel to hospital for EBRT.	Resource data were derived from UK sources. Analysis was undertaken from a NHS and PSS perspective. Patient characteristics were not given for the hospital transportation survey and so this data may not be applicable. It was also a very small sample.
Britton et al. 2019120	To investigate the experience of Great Western Hospital, Swindon in using 21-gene	UK Cost year NR	Patients with lymph node-positive breast cancer at Great Western Hospital, who underwent Oncotype DX testing	All data submitted for Oncotype DX testing in lymph node-positive patients by Great Western Hospital were	NR	5 patients ultimately underwent both chemotherapy and hormone therapy.	Resource use data were collected from a single centre in the UK.

Study	Objective	Country and cost year	Patient population	Valuation methods	Technology and other costs	Resource use	Applicability to clinical practice in England
	Oncotype DX testing to help guide decisions about adjuvant chemotherapy for patients with lymph node-positive breast cancer.		as part of the PONDX trial (N=20). Following Oncotype DX testing, 12 patients had a RS of <18, 4 patients had a RS of 18-30 and 4 patients had a RS of >30.	retrospectively analysed for all patients up to August 2018.		Decision impact results Prior to Oncotype DX testing, all 20 patients were recommended chemotherapy and hormone therapy. In 14 of these 20 patients, treatment was revised to hormone therapy only after the RS (from Oncotype DX) was made available.	
Wardley et al. 2018121	To describe first line resource usage for patients with advanced HER2-positive breast cancer.	UK Cost year NR	Patients with HER2-positive metastatic, unresectable locally advanced breast cancer, who were part of the UK ESTHER study (N=205). Patients had a median age of 57 years (range 29-96). 71% of patients had ER/ progesterone receptor (PgR)-positive disease. 188 patients (91.7%) had baseline metastases: 60% of these patients had visceral involvement and 6.3% had central nervous system (CNS) metastases.	An interim analysis from the ESTHER disease register was conducted, with data extracted on 22nd February 2017.	NR	Of 205 patients, 191 (93.2%) received a HER2-targeted agent, with 144 patients (70.2%) receiving pertuzumab with trastuzumab. 29 patients (14%) received hormone therapy alongside or following HER2-agent and chemotherapy. First-line advanced breast cancer anti-cancer resource use (N=205) Resource use — % of full population Systemic anti-cancer therapies Pertuzumab + trastuzumab + docetaxel — 63.4% Pertuzumab + trastuzumab + paclitaxel — 6.8%	Resource use data were collected from 26 UK clinical centres as part of an ongoing study conducted by Roche UK.

Study	Objective	Country and cost year	Patient population	Valuation methods	Technology and other costs	Resource use		Applicability to clinical practice in England
						Trastuzumab + chemotherapy	19.5%	
						Trastuzumab emtansine	3.4%	
						Chemotherapy (no HER2 agent)	1.0%	
						Hormone therapy (no HER2 agent)	5.9%	
						Bone-modifying agents		
						Bon-modifying agent	44.0%	
						Denosumab	22.4%	
						Bisphosphonates	19.0%	
						Surgical interventions		
						Breast surgery	6.8%	
						Metastatic resection	6.3%	
						Brain	2.1%	
						Other	4.2%	
						Radiotherapy		
						Radiotherapy	22.9%	
Green et al. 2019122	To make an assessment of the impact of Oncotype DX results in terms of numbers of patients receiving	UK Cost year NR	All patients who had undergone Oncotype DX testing since its routine introduction in clinical practice at a single UK centre in October 2015.	Patients were identified retrospectively using the Oncotype DX requesting programme.	NR	Overall, a total 113 patients underwent Oncotype DX testing and received hormone therapy, with 101 patients ultimately eligible for inclusion in the study.		Data were collected in the UK. Data were collected in a

<table>
<tr><th>Study</th><th>Objective</th><th>Country and cost year</th><th>Patient population</th><th>Valuation methods</th><th>Technology and other costs</th><th>Resource use</th><th>Applicability to clinical practice in England</th></tr>
<tr><td></td><td>chemotherapy and whether it is cost-effective.</td><td></td><td>Patients had ER-positive, HER2-negative, N0 or N1mi breast cancer with a Nottingham Prognostic Index (NPI) of 3.4 – 5.4, were treated on the NHS and could not have received prior neoadjuvant treatment (N=101).

Patients had a mean age of 56.8 years (median 57 years, range 41-72 years).</td><td>Further data were collected via electronic case note review and NPI scores were calculated.

Oncology case notes were also reviewed to identify factors influencing decisions regarding chemotherapy.

Decisions around whether patients were offered adjuvant treatment were made at the MDT meeting.</td><td></td><td>Treatment by patient group in relation to the RS result

<table><tr><th>RS group</th><th>Chemotherapy, n (%)</th></tr><tr><td>Low RS (n=56)</td><td>3 (5.4)</td></tr><tr><td>Intermediate RS (n=37)</td><td>13 (35.1)</td></tr><tr><td>High RS (n=8)</td><td>8 (100)</td></tr><tr><td>Total (N=101)</td><td>24 (23.8)</td></tr></table>
RS: low, <18; intermediate, 18–30; high, >30.

15 of those 24 patients receiving chemotherapy would have been offered chemotherapy based on the criteria used prior to routine Oncotype DX testing.</td><td>real-world setting during routine clinical practice.</td></tr>
<tr><td>Hinde et al. 2019123</td><td>To evaluate the cost-effectiveness of EndoPredict in patients with indeterminate risk classification, and to aid adjuvant chemotherapy decision-making</td><td>UK

Cost year 2016</td><td>The analysis was based on a small scale, manufacturer sponsored study of EndoPredict conducted across eight sites in the UK between July 2015 and September 2016, in patients with breast cancer (N=149).</td><td>Patients identified as being in the intermediate risk group came to a provisional treatment decision regarding

the use of chemotherapy. They received the</td><td>Chemotherapy cost analysis results

<table><tr><th></th><th>Mean standard tools only cost (Standard Deviation [SD])</th><th>Mean EndoPredict and standard tools decision cost (SD)</th></tr></table></td><td>With EndoPredict:

There was an increase in the number of chemotherapy cycles prescribed per patient (0.15 cycles more with EndoPredict, 4.52 vs 4.68)

28 patients who would have had no chemotherapy using standard criteria had their treatment plan changed to receive chemotherapy</td><td>All costs were measured in 2016 GBP.

The analysis took the perspective of the NHS, such that only the</td></tr>
</table>

Study	Objective	Country and cost year	Patient population	Valuation methods	Technology and other costs	Resource use	Applicability to clinical practice in England
	for patients with an intermediate risk score using standardised risk tools, while considering both the potential for short term cost saving and long tern cost effectiveness.		Patients were at first presentation of early breast cancer with all known disease surgically removed, ER-positive and HER2-negative, with no clear decision on whether chemotherapy should be given as an adjunct based on current prognostic criteria as preferred by the clinical team. Patients with either lymph node-positive (n=141) or lymph node-negative (n=8) disease were included. The mean age of patients was 56.5 years (range 25.9 – 77.2 years).	relevant regimen, dose and cycle length, using standard clinical-pathological criteria constituting the standard practice of the oncologist. If the patients consented, a tissue sample was sent for EndoPredict testing prior to re-consultation within two weeks, at which point the results were discussed and an updated treatment regimen decided. No trial follow up was planned beyond the second consultation, as such the primary outcome is the impact of EndoPredict to change the initial treatment decision.	Cost of the acquisition and delivery of chemotherapy, per patient: £4,687 (5,074) over 61 patients; £4,836 (5,261) over 62 patients Total short term cost (chemotherapy costs plus cost of EndoPredict to all follow-up): £1,919 (3,972); £3,512 (4,138) Cost-effectiveness analysis results Screening decision — Expected costs (discounted) per patient, £ Standard tools only — £7,228 EndoPredict and standard tools — £8,710 With EndoPredict, there was a small increase in the mean per patient cost of acquisition and provision of chemotherapy to the NHS (£149, p=0.4366). This occurred due to a decrease in the cost per cycle (£982 for the EndoPredict arm vs £983.	27 patients who would have had chemotherapy using standard criteria had their treatment changed from chemotherapy to no chemotherapy	costs directly incurred by the NHS were included. Chemotherapy cost data were calculated using the results of a trial conducted across eight sites in the UK.

Study	Objective	Country and cost year	Patient population	Valuation methods	Technology and other costs	Resource use	Applicability to clinical practice in England
				Where available evidence from the trial was used to inform micro-costing analysis (e.g. chemotherapy costs), if no such evidence was available then evidence from the wider literature and reference cost resources were used. The cost of each chemotherapy regimen was estimated at a patient level from the trial data, both before and after the EndoPredict decision. For the cost analysis, details on the selected regimen, dose, number of cycles and body surface area were combined with the unit cost of each regimen drawn from the British National Formulary (BNF), and the estimated laboratory and	When the cost of providing EndoPredict to all patients (N=149) was included in the cost-effectiveness analysis, the expected cost difference was statistically significant at £1593 (p=0.0004).		

<table>
<tr><th>Study</th><th>Objective</th><th>Country and cost year</th><th>Patient population</th><th>Valuation methods</th><th>Technology and other costs</th><th>Resource use</th><th>Applicability to clinical practice in England</th></tr>
<tr><td></td><td></td><td></td><td></td><td>human resource costs of delivery, applied as a fixed cost per cycle of £139.39.</td><td></td><td></td><td></td></tr>
<tr><td>TA501124</td><td>To evaluate the clinical and cost-effectiveness of the INTRABEAM photon radiotherapy system for adjuvant treatment of early breast cancer during surgical removal of the tumour.</td><td>UK

Cost year 2012-13</td><td>Data were included if it was relevant to patients with early operable breast cancer in the adjuvant treatment stage.</td><td>Treatment unit costs, the time required and associated staff costs of INTRABEAM therapy were obtained from clinical expert opinion (n=2) and Carl Zeiss UK (INTRABEAM manufacturer).

Cost of 1 hour in the operating theatre was informed by University Hospitals Southampton Finance Department, January 2014.</td><td>Additional staff costs for use of INTRABEAM used in the economic model, informed by expert opinion

<table><tr><th>Frequency of cost</th><th>Activity</th><th>Cost (£)</th></tr><tr><td>One-off (every ten years in the base case)</td><td>INTRABEAM operating procedure development</td><td>757</td></tr><tr><td>One-off (every ten years in the base case)</td><td>Initial INTRABEAM training</td><td>5,227</td></tr><tr><td>Annual</td><td>Technical commissioning</td><td>2,271</td></tr><tr><td>Annual</td><td>Technical commissioning sign off</td><td>275</td></tr><tr><td>Annual</td><td>Refresher training on radiation protection</td><td>920</td></tr><tr><td>Per treatment</td><td>Pre-treatment QC</td><td>25</td></tr></table></td><td>Additional staff resources required for use of INTRABEAM used in the economic model, informed by expert opinion

<table><tr><th>Activity</th><th>No. of staff</th><th>Time required</th></tr><tr><td>INTRABEAM operating procedure development</td><td>1</td><td>2 days</td></tr><tr><td>Initial INTRABEAM training</td><td>6</td><td>2 days</td></tr><tr><td>Technical commissioning</td><td>2</td><td>3 days</td></tr><tr><td>Technical commissioning sign off</td><td>1</td><td>0.5 days</td></tr><tr><td>Refresher training on</td><td>15</td><td>1 hour</td></tr></table></td><td>All costs were measured in 2012-13 GBP.

The economic model took the perspective of the NHS and PSS in the UK, such that only the costs directly incurred by the NHS were included.

Cost and resource use data were obtained from UK clinical expert opinion, the UK INTRABEAM manufacturing company and a hospital finance department based in the UK.</td></tr>
</table>

<table>
<tr><th>Study</th><th>Objective</th><th>Country and cost year</th><th>Patient population</th><th>Valuation methods</th><th>Technology and other costs</th><th>Resource use</th><th>Applicability to clinical practice in England</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>
check
Planning
Per treatment INTRABEAM dose in operating theatre 25
Delivering
Per treatment INTRABEAM dose in operating theatre 83
Additional time required by medical physicist in support of INTRABEAM use 76
Cost of consumables required for use of INTRABEAM, informed by Carl Zeiss UK
<table>
<tr><th>Description</th><th>Cost per unit (£)</th><th>Number of treatments</th><th>Cost per treatment (£)</th></tr>
<tr><td>Spherical applicator</td><td>3,170</td><td>100</td><td>31.70</td></tr>
</table>
</td><td>
radiation protection
Pre-treatment QC check 1 30 minutes
Planning
INTRABEAM dose in operating theatre 3 6 minutes
Delivering
INTRABEAM dose in operating theatre 2 33 minutes
Additional time required by medical physicist in support of INTRABEAM use 1 1.5 hours
</td><td></td></tr>
</table>

Study	Objective	Country and cost year	Patient population	Valuation methods	Technology and other costs	Resource use	Applicability to clinical practice in England
					Radiation protection shields, pack of 10: 1,041 — 5 — 208.20 Sterile plastic drapes, pack of 5: 96 — 5 — 19.20 Other costs used in the economic model, informed by Carl Zeiss UK Description / Cost (£) INTRABEAM device capital cost: 435,000 Annual maintenance INTRABEAM device: 35,000 INTRABEAM device equivalent annual cost*: 53,025 *Calculation from capital cost and one-off costs using device lifetime of 10 years and discount rate of 3.5%. A cost for one hour in the operating theatre at Southampton General Hospital is £569, which includes nurse cost but does not include any medical staff or anaesthetist cost.		

<table>
<tr><th>Study</th><th>Objective</th><th>Country and cost year</th><th>Patient population</th><th>Valuation methods</th><th>Technology and other costs</th><th>Resource use</th><th>Applicability to clinical practice in England</th></tr>
<tr>
<td>Cheeseman et al. 2018125</td>
<td>To characterise treatment patterns and resource use for patients with metastatic hormone receptor (HR)-positive/HER2-negative breast cancer treated at Leeds Cancer Centre prior to the approval of cyclin-dependent kinase (CDK) 4/6 therapies.</td>
<td>UK

Cost year NA</td>
<td>Female patients ≥18 years old with metastatic or locally advanced HR-positive/HER2-negative breast cancer, who were diagnosed between January 2012 and March 2018 (N=243).

The total sample included 33 (14%) pre/peri-menopausal patients, 204 (84%) post-menopausal patients and 6 patients (2%) with menopausal status unknown.

124 (51%) patients had progressed to metastatic disease from a previous diagnosis, 72 (30%) were diagnosed with metastatic disease, and 47 (19%) were diagnosed with locally advanced disease.

Patients enrolled in clinical trials, with operable local recurrence as only disease site, incomplete treatment</td>
<td>Structured hospital electronic medical records (EMR) including coded data, unstructured text and clinical review of patients were retrospectively reviewed for patient characteristics, systemic therapies (by treatment intent), surgery, radiotherapy, use of supportive treatments, monitoring and use of healthcare resources.

Expert review of clinical notes was also undertaken.

Patients were followed until the date of the last record, death or the end of the study time period, whichever came first.</td>
<td>NR</td>
<td>Overall, 238 patients (98%) received treatment at some point during follow up, including 34 patients (13%) with locally advanced disease who were treated with curative intent. 5 patients received no treatment at all.

Median non-curative line of treatment was 2 per patient (range 1–9).

Median treatment duration for first line of treatment was 128 days (range 1–1,708).

Healthcare resource use

<table>
<tr><th>Resource</th><th>No. of patients, n (%)</th></tr>
<tr><td>Systemic anti-cancer treatment (SACT)</td><td>NR (98%)</td></tr>
<tr><td>Chemotherapy</td><td>NR (47%)</td></tr>
<tr><td>Radiotherapy</td><td>32 (13%)</td></tr>
<tr><td>Targeted therapy</td><td>NR (21%)</td></tr>
<tr><td>Endocrine therapy</td><td>NR (92%)</td></tr>
</table>
</td>
<td>Data were collected in a real-world setting during routine clinical practice.

Resource use data were collected from a single centre in the UK.</td>
</tr>
</table>

Study	Objective	Country and cost year	Patient population	Valuation methods	Technology and other costs	Resource use	Applicability to clinical practice in England
			records, receiving treatments not currently reimbursed in the UK or with significant secondary malignancies were excluded. Patients had a median age of 67 (range 33–95 years).	Healthcare resource use data included numbers of overnight inpatient stays, day case inpatient admissions (not including routine clinic appointments) and outpatient visits. Crude healthcare resource rates were calculated for all hospitalisations (including overnight, day case and outpatient visits) and 95% CI derived from Poisson estimates. The median length of follow up was 34 months (interquartile range [IQR] 17–58; range <1 – 77).		Endocrine therapy (non-curative treatment, at first line of treatment) NR (70%) Single line of endocrine therapy NR (28%) Letrozole NR (13%) Anastrozole NR (8%) Exemestane NR (6%) Healthcare resource use for patients with metastatic breast cancer at presentation (n=75) Resource — No. of patients, n (%) Letrozole NR (56%) Anastrozole NR (29%) Exemestane NR (28%) Tamoxifen NR (28%) Capecitabine NR (17%) ⩾2 lines of letrozole-exemestane NR (64%)	

Study	Objective	Country and cost year	Patient population	Valuation methods	Technology and other costs	Resource use		Applicability to clinical practice in England
						Healthcare resource use for post-menopausal patients (n=204)		
						Resource	n (95% CI)	
						First line of treatment		
						Total hospitalisation rate per patient, in visits per year	19.2 (18.6–19.8)	
						Day case inpatient rate per patient (for patients using endocrine therapy), in admissions per year	6.5 (6.0–5.9)	
						Overnight inpatient hospitalisation rate per patient (for patients using endocrine therapy), in stays per year	1.5 (1.3–1.9)	
						Third line of treatment		
						Total hospitalisation rate per patient, in visits per year	26.7 (25.1–28.4)	
						Day case inpatient rate per patient (for patients using endocrine therapy), in admissions per year	8.8 (7.5–10.1)	
						Overnight inpatient hospitalisation rate per patient (for patients using endocrine therapy), in stays per year	2.1 (1.3–2.9)	

Study	Objective	Country and cost year	Patient population	Valuation methods	Technology and other costs	Resource use	Applicability to clinical practice in England
Twelves et al. 2018126	To characterise treatment patterns and overall survival for patients with metastatic HR-positive/HER2-negative breast cancer treated at Leeds Cancer Centre prior to the approval of CDK 4/6 therapies.	UK Cost year NR	Female patients ≥18 years old with metastatic or locally advanced HR-positive/HER2-negative breast cancer, who were treated from January 2012 to March 2018 (N=253). 84% of patients identified as post-menopausal. Overall, 47 patients (19%) had locally advanced disease, 75 patients (30%) had metastatic breast cancer at initial presentation and 131 patients (52%) had metastatic breast cancer at first recurrence. Patients enrolled in clinical trials, with operable local recurrence as only disease site, incomplete treatment records or significant secondary malignancy were excluded. Patients had a median age of 67	Anonymised retrospective data was extracted for the cohort directly from structured hospital electronic medical records and by expert review of clinical notes. Patients were followed until the date of the last record, death or the end of the study time period (June 2018), whichever came first. Median follow-up was 24 months (IQR 8.8–51.4; range <1–76) for progressed metastatic patients, and 32 months (IQR 18.2–50.6; range <1 –70) for newly diagnosed metastatic patients.	NR	Healthcare resource use (at some point during follow up) Resource — No. of patients, n (%) SACT — 192 (98%) Radiotherapy — 19 (10%) Salvage surgery — 17 (9%) Opioid analgesics — NR (58%) Anti-emetics — NR (44%) Bisphosphonates — NR (25%) Median SACT line of therapy was 2 per patient (range 1–9). Healthcare resource use for patients with metastatic breast cancer at initial presentation (n=75) Resource — No. of patients, n (%) Chemotherapy — NR (35%) Endocrine therapy — NR (93%)	Data were collected in a real-world setting during routine clinical practice. Resource use data were collected from a single centre in the UK.

Study	Objective	Country and cost year	Patient population	Valuation methods	Technology and other costs	Resource use		Applicability to clinical practice in England
			(IQR 56–76; range 33–92).			Targeted therapy (e.g. everolimus)	NR (7%)	
						First line of treatment		
						Letrozole	NR (47%)	
						Anastrozole	NR (23%)	
						Epirubicin cyclophosphamide	NR (11%)	
						Second line of treatment		
						Exemestane	NR (19%)	
						Healthcare resource use for patients with recurring metastatic breast cancer (n=131)		
						Resource	No. of patients, n (%)	
						Chemotherapy	NR (50%)	
						Endocrine therapy	NR (93%)	
						Targeted therapy	NR (27%)	
						First line of treatment		
						Letrozole	NR (20%)	

<table>
<tr><th>Study</th><th>Objective</th><th>Country and cost year</th><th>Patient population</th><th>Valuation methods</th><th>Technology and other costs</th><th>Resource use</th><th>Applicability to clinical practice in England</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td>Exemestane (single agent) NR (15%)
Anastrozole NR (14%)
Everolimus (with exemestane) NR (11%)
Paclitaxel NR (9%)
Second line of treatment
Fulvestrant NR (13%)</td><td></td></tr>
<tr><td>Tramonti et al. 2018127</td><td>To determine decision impact and budget impact of a 21-gene expression assay (Oncotype DX) used to refine prognostication of ER-positive, HER2- and node-negative early breast cancer and help guide treatment decisions based on the likely benefit of adjuvant chemotherapy.</td><td>UK

Cost year 2016-2017</td><td>Between 2016 and 2017 at the Edinburgh Breast Unit, early breast cancer patients were tested using Oncotype DX (N=36), with 575 controls also identified.</td><td>Oncotype DX, a 21-gene expression panel, was adopted in the Edinburgh Breast Unit in January 2016 for 36 ER-positive, HER2- and node-negative breast cancer patients.

As the 36 patients tested with Oncotype DX experienced a relative reduction in the probability of receiving chemotherapy of 13% (p=0.079), this estimation of the relative reduction in the probability of receiving</td><td>Costs used in simulation of a representative Scottish cohort of breast cancer patients (N=600)

Resource — Cost per patient (£)
Chemotherapy 4,159
Oncotype DX 2,500

With Oncotype DX testing of 35 patients, 5 patients would have avoided chemotherapy, providing a cost saving of £20,795. Balancing test costs against chemotherapy savings, the net modelled cost of testing was £66,705 at listing price, reaching cost neutrality at an illustrative cost of £595 per test.</td><td>Number of patients given chemotherapy with and without Oncotype DX testing (N=600)

With Oncotype DX testing of 35 patients, n — Without Oncotype DX testing, n
Given Chemotherapy 73 78
Not given Chemotherapy 527 522</td><td>A simulation of a representative Scottish cohort of breast cancer patients was used to calculate cost data.

The estimation of the relative reduction in the probability of receiving chemotherapy used in the simulation was calculated using data from 36 patients tested at a Scottish Breast Unit.</td></tr>
</table>

Study	Objective	Country and cost year	Patient population	Valuation methods	Technology and other costs	Resource use	Applicability to clinical practice in England
				chemotherapy was used in a simulation of a representative Scottish cohort (n=600) to determine the budget impact of Oncotype DX. The simulation used the observed rates of treatment and testing, and the estimated reduction in the probability of receiving chemotherapy if tested with Oncotype DX. A novel before- and after-adoption logistic regression based method was used to determine decision impact and budget impact. Adjustment was made for time varying case-mix			

<table>
<tr><th>Study</th><th>Objective</th><th>Country and cost year</th><th>Patient population</th><th>Valuation methods</th><th>Technology and other costs</th><th>Resource use</th><th>Applicability to clinical practice in England</th></tr>
<tr><td></td><td></td><td></td><td></td><td>and clinical risk in matched before- and after- cohorts between 2010 and 2017.</td><td></td><td></td><td></td></tr>
<tr><td>Kurosky et al. 2015128</td><td>To describe the demographic profile, clinical characteristics, and real-world treatment patterns, including type of therapy administered, duration of treatment, and reason for stopping treatment, of postmenopausal women with ER-positive/HER2-negative metastatic breast cancer in the UK.</td><td>UK

Cost year NR</td><td>Included patients were women with histologically or cytologically confirmed metastatic ER-positive/HER2-negative breast cancer in the UK (N=209).

Most patients had naturally occurring menopause (92.8%).

Patients either presented with de novo stage IV disease or had a diagnosis of earlier-stage breast cancer that later progressed to metastatic disease, were postmenopausal (natural or induced) at the time of metastatic diagnosis, had received at least 2 lines of systemic treatment for metastatic disease; discontinued second-line treatment</td><td>In 2015, 41 oncologists and gynaecologists from across the UK selected eligible patients (N=209) retrospectively and abstracted data from the patients' medical records into a secure web-based case report form.</td><td>NR</td><td>Treatment patterns for patients diagnosed before metastatic disease (n=66)

<table><tr><th>Treatment received</th><th>Proportion of patients (%)</th></tr><tr><td>Surgery</td><td>90.9</td></tr><tr><td>Adjuvant endocrine therapy</td><td>89.4</td></tr><tr><td>Radiation therapy</td><td>87.8</td></tr><tr><td>Adjuvant chemotherapy</td><td>59.1</td></tr></table>
Among all patients, endocrine therapy (85.7%) and chemotherapy (74.6%) were the most common treatments in the metastatic setting.

Patients received a mean (SD) of 2.7 (0.8) lines of systemic treatments. Among patients who were not actively receiving systemic therapy at the time of abstraction, the median total duration of systemic treatment was 15.1 months.</td><td>Medical record abstraction of 209 UK breast cancer patients was carried out by 41 physicians from across the UK, with 43.9% and 31.7% of physicians practising in the Greater London/South East region and in the Midlands/East region, respectively.

As convenience sampling was used, generalisability of the study results may be limited. The abstracted data were limited to the information recorded and available in</td></tr>
</table>

Study	Objective	Country and cost year	Patient population	Valuation methods	Technology and other costs	Resource use	Applicability to clinical practice in England
			between January 1, 2008, and August 31, 2014, and had received care from a participating physician from the time of metastatic diagnosis to the last available encounter in their medical record. Patients with other concurrent malignancies (except adequately treated non-melanoma skin cancer or other non-invasive neoplasms) and patients who had participated in a breast cancer-related clinical trial or interventional study for any treatment in the metastatic setting were excluded. Mean (SD) age at metastatic diagnosis was 62.3 (9.5) years.			Endocrine therapy was the most common treatment received for both first- (49.3%) and second-line (54.1%) therapy and was administered for a median duration of 11.6 and 7.2 months, respectively. Chemotherapy was the most common treatment received for third-line therapy (53.5%) and was administered for a median duration of 5.1 months.	patients' medical records held by participating physicians.

Abbreviations: BNF: British National Formulary; CDK: cyclin-dependent kinase; CDU: chemotherapy day unit; CI: confidence interval; CNS: central nervous system; CT SIM: computerised tomography simulation; EBRT: external-beam radiation therapy; ECHO: echocardiogram; EMR: electronic medical records; ER: oestrogen receptor; FEC: fluorouracil, epirubicin, cyclophosphamide; GBP: Great British Pounds; GP: general practitioner; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; IHC: immunohistochemistry; IQR: interquartile range; MDT: multidisciplinary team; MUGA: multi-gated acquisition scan; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; NPI: Nottingham Prognostic Index; NR: not reported; PgR: progesterone receptor; PREDICT: personal response determinants in cancer therapy; PSS: Personal Social Services; QC: quality control; RS: recurrence score; SACT: systemic anti-

cancer treatment; SD: standard deviation; SLR; systematic literature review; TAC: docetaxel, doxorubicin, cyclophosphamide; TARGIT: targeted intraoperative radiotherapy; TARGIT-A: targeted intraoperative radiotherapy-alone; UK: United Kingdom; WB-EBRT: whole breast external-beam radiation therapy.

Table 15. Articles excluded from the cost and resource use SLR at full-text stage

No.	Article excluded	Reason for exclusion
Original SLR (26th October 2017)		
1	Caldeira R, Scazafave M. Real-World Treatment Patterns for Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer in Europe and the United States. Oncology & Therapy. 2016;4(2):189-197.	Study design / setting (e.g. geographic region) / language
2	Colomer R, Hall P, Szkultecka-Debek M, Bondi R, Flinois A, Le Cleach J. Response to targeted therapy and healthcare resource utilization (HRU): A european retrospective chart review study in patients with HER2+ metastatic breast cancer. Value in Health. 2016;19(7):A742.	Study design / setting (e.g. geographic region) / language
3	Cressman S, Browman GP, Hoch JS, Kovacic L, Peacock SJ. A time-trend economic analysis of cancer drug trials. Oncologist. 2016;20(7):729-736.	Study design / setting (e.g. geographic region) / language
4	Duran I, Fink MG, Bahl A, Hoefeler H, Mahmood A, Luftner D, Ghazal H, Wei R, Chung KC, Hechmati G, Green J, Atchison C. Health resource utilisation associated with skeletal-related events in patients with bone metastases secondary to solid tumours: regional comparisons in an observational study. European Journal of Cancer Care. 2017;26;e12452.	Study design / setting (e.g. geographic region) / language
5	Eiermann W, Rezai M, Kummel S, Kuhn T, Warm M, Friedrichs K, Schneeweiss A, Markmann S, Eggemann H, Hilfrich J, Jackisch C, Witzel I, Eidtmann H, Bachinger A, Hell S, Blohmer J. The 21-gene recurrence score assay impacts adjuvant therapy recommendations for ER-positive, node-negative and node-positive early breast cancer resulting in a risk-adapted change in chemotherapy use. Annals of Oncology. 2013;24(3):618-624.	Study design / setting (e.g. geographic region) / language
6	Exner R, Bago-Horvath Z, Bartsch R, Mittlboeck M, Retel VP, Fitzal F, Rudas M, Singer C, Pfeiler G, Gnant M, Jakesz R, Dubsky P. The multigene signature MammaPrint impacts on multidisciplinary team decisions in ER+, HER2- early breast cancer. British Journal of Cancer. 2014;111(5):837-842.	Study design / setting (e.g. geographic region) / language
7	Hequet D, Huchon C, Baffert S, Alran S, Reyal F, Nguyen T, Combes A, Trichot C, Alves K, Berseneff H, Rouzier R. Preoperative clinical pathway of breast cancer patients: Determinants of compliance with EUSOMA quality indicators. British Journal of Cancer. 2017;116(11):1394-1401.	Study design / setting (e.g. geographic region) / language
8	Jarrett N, Scott I, Addington-Hall J, Amir Z, Brearley S, Hodges L, Richardson A, Sharpe M, Stamataki Z, Stark D, Siller C, Ziegler L, Foster C. Informing future research priorities into the psychological and social problems faced by cancer survivors: a rapid review and synthesis of the literature. European Journal of Oncology Nursing. 2013;17(5):510-520.	Study design / setting (e.g. geographic region) / language
9	Naidoo S, Friedman ML, Paly VF, Hansen R, Sidhu MK, Smith I. Targeted literature review of advanced/metastatic triple-negative breast cancer burden of illness. Value in Health. 2017;20(5):A94-A95.	Study design / setting (e.g. geographic region) / language
10	Philip J, Collins A, Burchell J, Krishnasamy M, Mileshkin L, McLachlan SA, Le B, Millar J, Currow D, Hudson P, Sundararajan V. Integration of palliative care for patients with metastatic breast cancer: Have we achieved quality end-of-life care?. Journal of Pain and Symptom Management. 2016;52(6):e152.	Study design / setting (e.g. geographic region) / language
11	Sivendran S, Holliday R, Guittar R, Cox, C, Newport K. The impact of a nurse practitioner-led symptom clinic on Emergency department use in cancer patients. Journal of Community and Supportive Oncology. 2016;14(6):268-272.	Study design / setting (e.g. geographic region) / language

No.	Article excluded	Reason for exclusion
12	Skedgel C, Rayson D, Younis T. Is febrile neutropenia prophylaxis with granulocyte-colony stimulating factors economically justified for adjuvant TC chemotherapy in breast cancer?. Supportive Care in Cancer. 2016;24(1):387-394.	Study design / setting (e.g. geographic region) / language
13	Thorat T, Chambers J, Neumann PJ. Understanding qaly gains across different types of cancers and cancer-related interventions. Value in Health. 2015;18(3):A192.	Study design / setting (e.g. geographic region) / language
14	Hall PS, Hamilton P, Hulme CT, Meads DM, Jones H, Newsham A, Marti J, Smith AF, Mason H, Velikova G, Ashley L. Costs of cancer care for use in economic evaluation: a UK analysis of patient-level routine health system data. British journal of cancer. 2015;112(5):948-956.	Population
15	Himelstein AL, Qin R, Novotny PJ, Seisler DK, Khatcheressian JL, Roberts JD, Grubbs SS, O'Connor T, Weckstein D, Loprinzi CL, Shapiro CL. CALGB 70604 (Alliance): A randomized phase III study of standard dosing vs. longer interval dosing of zoledronic acid in metastatic cancer. Journal of Clinical Oncology. Conference. 2015;33(15 Supplement 1):9501.	Population
16	Hoefeler H, Duran I, Hechmati G, Rodriguez CG, Lüftner D, Ashcroft J, Bahl A, Atchison C, Wei R, Thomas E, Lorusso V. Health resource utilization associated with skeletal-related events in patients with bone metastases: Results from a multinational retrospective–prospective observational study–a cohort from 4 European countries. Journal of bone oncology. 2014;3(2):40-48.	Population
17	Jones L, FitzGerald G, Leurent B, Round J, Eades J, Davis S, Gishen F, Holman A, Hopkins K, Tookman A. Rehabilitation in advanced, progressive, recurrent cancer: a randomized controlled trial. Journal of pain and symptom management. 2013;46(3):315-325.	Population
18	Lafranconi A, Bramesfeld A, Rigau D, Lerda D, Sola I, Pylkkänen L, Neamțiu L, Posso M, Martinez-Zapata MJ, Alonso-Coello P, Deandrea S. Intensive follow-up for women with breast cancer: review of clinical, economic and patient's preference domains through evidence to decision framework. Health and Quality of Life Outcomes. 2017;15(1):206.	Population
19	Luengo-Fernandez R, Leal J, Gray A, Sullivan R. Economic burden of cancer across the European Union: a population-based cost analysis. The lancet oncology. 2013;14(12):1165-1174.	Population
20	Manchanda R. Brca testing in high-risk populations. Clinical Cancer Research. Conference: 10th Biennial Ovarian Cancer Research Symposium. United States. 2015;21(16 Supplement 1).	Population
21	Miquel-Cases A, Teixeira S, Retèl V, Steuten L, Olmos RV, Rutgers E, Van Harten WH. Cost-effectiveness of 18F-FDG PET/CT for screening distant metastasis in stage II/III breast cancer patients of the UK, the United States and the Netherlands. Value in health. 2015;18(7):A337.	Population
22	Muhibullah N, Gutteridge E, Whisker L, Khout H. Clinical impact of Oncotype Dx assay after integration in breast MDT. European Journal of Surgical Oncology. 2016;42(5):S56.	Population
23	Robertson S, Summerhayes C, Laws S, Rainsbury D. P037. The cost of risk reducing mastectomy and immediate reconstruction versus surveillance. European Journal of Surgical Oncology. 2015;41(6):S37.	Population
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26	Schelenz S, Giles D, Abdallah S. Epidemiology, management and economic impact of febrile neutropenia in oncology patients receiving routine care at a regional UK cancer centre. Annals of oncology. 2011;23(7):1889-1893.	Population
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42	Smieliauskas F, Chien CR, Shen C, Geynisman DM, Shih YC. Cost-effectiveness analyses of targeted oral anti-cancer drugs: a systematic review. Pharmacoeconomics. 2014;32(7):651-680.	Outcomes
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No.	Article excluded	Reason for exclusion
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62	Morton R, Sayma M, Sura MS. Economic analysis of the breast cancer screening program used by the UK NHS: should the program be maintained?. Breast Cancer: Targets and Therapy. 2017;9:217-225.	Study design; tagged for reference list hand-searches
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No.	Article excluded	Reason for exclusion
66	Whear R, Abdul-Rahman AK, Boddy K, Thompson-Coon J, Perry M, Stein K. The clinical effectiveness of patient initiated clinics for patients with chronic or recurrent conditions managed in secondary care: a systematic review. PLoS One. 2013;8(10):e7477.	Study design; tagged for reference list hand-searches
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1	Borowiack E, Marzec M, Nowotarska A, et al. Chance of reimbursement for ADD-ON therapies in Poland and in the world - review of the reimbursement recommendations. Przeglad epidemiologiczny 2018;72:99-109.	Study design / setting (e.g. geographic region) / language
2	Duran I, Fink MG, Bahl A, et al. Health resource utilisation associated with skeletal-related events in patients with bone metastases secondary to solid tumours: regional comparisons in an observational study. European journal of cancer care 2017;26.	Study design / setting (e.g. geographic region) / language
3	Koleva-Kolarova RG, Greuter MJW, Feenstra TL, et al. Molecular imaging with positron emission tomography and computed tomography (PET/CT) for selecting first-line targeted treatment in metastatic breast cancer: A cost-effectiveness study. Oncotarget 2018;9:19836-19846	Study design / setting (e.g. geographic region) / language
4	McGuire A, Brown JAL, Joyce DP, et al. Evaluating the cost effectiveness of trastuzumab in the neoadjuvant setting. Irish Journal of Medical Science 2018;187 (Supplement 4):S138	Study design / setting (e.g. geographic region) / language
5	Rahbar SA, Shu A, Kirby A. Decreasing adjuvant chemotherapy use in patients >50 years of age with earlystage breast cancer: A single-institution application of the TAILORx Study findings. Annals of Surgical Oncology 2019;26 (2 Supplement):238	Study design / setting (e.g. geographic region) / language
6	Bhamidipati K, Ali A, Skaria B, et al. Cost effectiveness of simpson's biplane method & early predictors of left ventricular dysfunction in breast cancer patients treated with trastuzumab. Cardiology (Switzerland) 2018;140 (Supplement 1):386.	Population
7	De Silva T, Russell V, Henry F, et al. Outcomes in unilateral breast cancer patients following unilateral mastectomy and reconstruction versus bilateral mastectomy reconstruction. European Journal of Surgical Oncology 2018;44 (6):911-912.	Population
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10	Rashid MU, Kabeer KK, Jafferbhoy S, et al. P141. Further investigations during follow up of breast cancer patients treated with curative intent. European Journal of Surgical Oncology 2019;45 (5):921.	Population
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12	Bermingham S, Schmid P, Forster F, et al. Societal costs of ER+/HER2-advanced or metastatic breast cancer in post-menopausal women in the United Kingdom. Value in Health 2017;20 (9):A427.	Outcomes
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No.	Article excluded	Reason for exclusion
14	Hulme C, Hall P, Shinkins B, et al. Cost effectiveness analyses of 6 versus 12 months of adjuvant trastuzumab in patients with HER2 positive early breast cancer: Results from the PERSEPHONE trial. British Journal of Cancer 2018;119 (1):49	Outcomes
15	O'Connell RL, Rattay T, Dave RV, et al. The impact of immediate breast reconstruction on the time to delivery of adjuvant therapy: the iBRA-2 study. British Journal of Cancer 2019;120:883-895.	Outcomes
16	Ong H, Campbell C, Weller D. Use of Theoretical Domains Framework to identify psychosocial determinants associated with adjuvant hormonal treatment adherence among breast cancer population: Mixed method systematic review. British Journal of Cancer 2018;119 (1):43-44.	Outcomes
17	Tailor J, Panesar S, Gullan R, et al. The implications of rising cerebral metastases incidence on a large-volume neuro-oncology multidisciplinary team (MDT). Neuro-Oncology 2017;19 (Supplement 1):i29.	Outcomes
18	Andronis L, Goranitis I, Bayliss S, et al. Cost-Effectiveness of Treatments for the Management of Bone Metastases: A Systematic Literature Review. Pharmacoeconomics 2018;36:301-322.	Study design; tagged for reference list hand-searches
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21	Hinde S, Theriou C, May S, et al. The cost-effectiveness of EndoPredict to inform adjuvant chemotherapy decisions in early breast cancer. Annals of Oncology 2017;28 (Supplement 5):v399.	Study design; tagged for reference list hand-searches
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23	Livings C, Jones N, Bertranou E, et al. Cost effectiveness of fulvestrant 500 mg in endocrine therapy-naive women with hormone receptor-positive advanced breast cancer in the UK. Value in Health 2017;20 (9):A435.	Study design; tagged for reference list hand-searches
24	Pouwels X, Ramaekers BLT, Joore MA. Reviewing the quality, health benefit and value for money of chemotherapy and targeted therapy for metastatic breast cancer. Breast Cancer Research & Treatment 2017;165:485-498.	Study design; tagged for reference list hand-searches
25	Silva C, Caramelo O, Almeida-Santos T, et al. Factors associated with ovarian function recovery after chemotherapy for breast cancer: a systematic review and meta-analysis. Human reproduction (Oxford, England) 2016;31:2737-2749.	Study design; tagged for reference list hand-searches
26	Sun L, Legood R, Dos-Santos-Silva I, et al. Global treatment costs of breast cancer by stage: A systematic review. PLoS ONE [Electronic Resource] 2018;13:e0207993.	Study design; tagged for reference list hand-searches
27	Telford C, Bertranou E, Large S, et al. Cost-Effectiveness Analysis of Fulvestrant 500 mg in Endocrine Therapy-Naive Postmenopausal Women with Hormone Receptor-Positive Advanced Breast Cancer in the UK. PharmacoEconomics Open 2019;25:25.	Study design; tagged for reference list hand-searches

Section B: Clarification of cost-effectiveness data

Question B2. Priority question: Please provide all input parameters for the model based on the node-negative population, include them in the model and provide additional cost-effectiveness analyses for the node-negative population based on this set of input parameters.

General approach

In the KATHERINE study, patients were classified as being node-positive or node-negative/not tested (N-/ND). The analysis and results presented in response to this question are predicated on the data collected in the N-/ND population.

As previously communicated, this request is tantamount to an entirely new economic analysis. Timeline constraints have meant that a pragmatic approach has been taken in the Company's response. A reasonable assumption has been made that costs and HRQoL of a patient would not be expected to vary depending on nodal status. Additionally, the post-IDFS transition probabilities used in the ITT analysis have been derived irrespective of nodal status. Consequently, these inputs have also been assumed appropriate for this analysis. For clarity, the parameters varied for this analysis are specified below:

- **Key demographic characteristics have been re-calculated using the N-/ND data**
    - **Age, weight, height**
- **IDFS Extrapolation parameters have been re-calculated using the N-/ND data**
- **IDFS event breakdown in the "Early" and "Late" relapser populations have been re-calculated using the N-/ND data**

The methodology and results of this analysis have been outlined below. Situations in which the methodology/parameters differentiated from the ITT analysis have been highlighted.

Clinical Parameters and Variables

Modelling of IDFS

Patients remain in the IDFS health state as long as they remain disease-free, as defined by the study protocol (see Section B.2 of Document B), and alive. The probability of remaining in the IDFS health state is derived from patient-level data in the KATHERINE study. At the time of the primary analysis of IDFS (data cut-off 25th July 2018), only 29 (7.25%) and 62 (15.62%) IDFS events had occurred in the N-/ND subpopulation of the trastuzumab emtansine and trastuzumab arms, respectively. The lack of completeness of this data, and the truncated follow-up period in KATHERINE, meant that extrapolation techniques were essential to model IDFS over a lifetime time horizon (51 years).

Modelling of IDFS was informed using patient-level data from the KATHERINE study. Parametric functions were then applied to this data to facilitate extrapolation beyond the follow-up period, as

per NICE Decision Support Unit (DSU) guidance. The selected parametric function was subsequently adjusted to produce a more clinically accurate and robust extrapolation. Empirical evidence was used to help inform this adjustment and create IDFS curves that are reflective of longer-term outcomes in this indication.

Since trastuzumab emtansine is not yet licensed in the adjuvant eBC setting, empirical data only exist for the comparator arm (trastuzumab). Therefore, data from long-term studies of trastuzumab (HERA84 and BCIRG 00685 trials) were used to inform the adjustment of the extrapolations.

The modelling of IDFS over the time horizon of the model can be broken down into three discrete periods:

- Time period 1 – Zero to three years
- Time period 2 – From year three to year ten
- Time period 3 – From year ten until the end of the time horizon (year 52)

For each of these time periods, different data and assumptions were incorporated to produce accurate extrapolations. The methodology involved in generating the IDFS curves is detailed in the following subsections.

Time period 1 (zero to three years) – Patient-level data from the KATHERINE study

In accordance with standard practice, a parametric extrapolation function was fitted to the Kaplan-Meier data from the KATHERINE study. Several candidate distributions were fitted to the IDFS data and assessed for "goodness of fit". The selected distribution provided the basis of the extrapolation beyond the observed period of the trial. Additional adjustment of this distribution, using empirical data, dictated the final shape of the IDFS curves used in the model (see subsection relating to "Time period 2"). The following parametric functions were fitted to the trial-data: Exponential, Weibull, Log-logistic, Log-normal, Gamma and Gompertz.

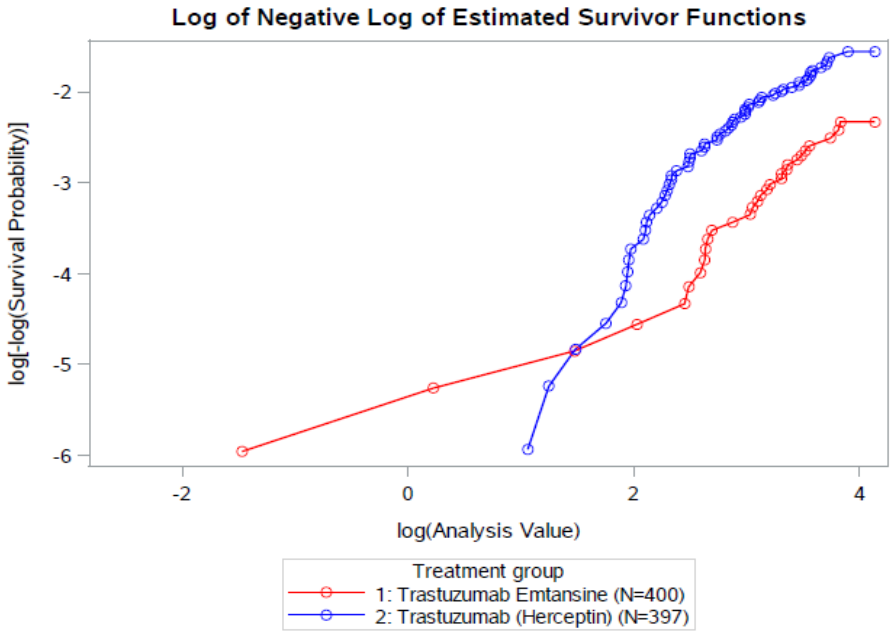
The selection process of the most appropriate distribution is outlined below. A criterion-based guide was used to facilitate the accurate extrapolation and justification of survival estimates. Methodology employed during this selection process is in accordance with the NICE DSU Technical Report.

Assessment of the proportional hazards assumption

Prior to deciding on the most appropriate parametric distribution, it was important to check the existence of proportional hazards (PH). The PH assumption states that the hazard in one group (arm A) is a constant proportion of the hazard in the other group (arm B). This proportion is the hazard ratio. That is, although the hazard may vary with time, the ratio of the hazard rates is constant.

The PH assumption can be tested graphically, using log-cumulative hazard plots. These graphs plot log(time) on the x-axis vs log(–log(S(time))) on the y-axis, where S(time) is the survival time. The PH assumption can be assumed to hold if the gradient of the two curves is found to be reasonably constant (i.e. they do not obviously diverge, converge or intersect). The log of the survival probabilities plotted with the log of time for the arms in the N-/ND population of the KATHERINE trial are shown in Figure 3.

Figure 3. Log of negative log of estimated survivor functions – IDFS endpoint from the KATHERINE study - node-negative/not done population



As shown in Figure 16, the two curves cross, which signals that the PH assumption may not hold. However, this crossing takes place at a time when minimal events have occurred, and the curve is therefore associated with a lot of uncertainty. Consequently, this crossing should not be over-emphasised.

It is important to note here that IDFS results projected by the extrapolations are relatively insensitive to whether or not proportional hazards is assumed. Table 16 presents landmark IDFS figures from extrapolations that have assumed proportional and non-proportional hazards.

Table 16. Landmark IDFS – PH vs Non-PH – Averages across all candidate distributions[a] – node-negative/not done population

	TE arm		Trastuzumab arm		Δ		
	PH	Non-PH	PH	Non-PH	PH	Non-PH	PH vs non-PH
Median IDFS (years)	34.68	34.69	31.17	31.57	3.51	3.12	-0.39
Mean IDFS (years)	30.59	30.61	26.18	26.78	4.41	3.83	-0.58
Landmark IDFS							
12 months	97.79%	97.72%	94.73%	95.34%	3.05%	2.38%	-0.67%
24 months	95.47%	95.48%	89.77%	90.81%	5.70%	4.67%	-1.03%
36 months	93.21%	93.27%	85.21%	86.53%	8.01%	6.74%	-1.26%
48 months	91.18%	91.26%	81.31%	82.81%	9.88%	8.45%	-1.42%
60 months	89.46%	89.54%	78.17%	79.78%	11.30%	9.76%	-1.53%

120 months	84.14%	84.15%	70.69%	72.41%	13.44%	11.74%	-1.71%
480 months	31.18%	31.23%	26.21%	26.90%	4.98%	4.33%	-0.64%

Footnotes: [a]The figures reported in the table above are averages from extrapolations using the Exponential, Weibull, Log-Normal, Generalized Gamma, Log-Logistic, and Gompertz distributions.
Abbreviations: IDFS: invasive disease-free survival; non-PH: non-proportional hazards; PH: proportional hazards; TE: trastuzumab emtansine.

At all key time points, the difference in IDFS between the PH and non-PH extrapolation is <2%. This marginal difference is expected to translate into a negligible impact on overall cost-effectiveness results.

It is difficult to conclusively prove that it is appropriate to apply the PH assumption to this data. In light of the evidence presented above, it has been assumed that PH do not exist between the two treatment arms. Therefore, "stratified" models were used (i.e. curves were fitted separately to each treatment arm) to extrapolate IDFS over the time horizon, as per the NICE DSU guidance.

Akaike Information Criterion (AIC) / Bayesian Information Criterion (BIC) Goodness of fit

Parametric distributions were assessed for their goodness of fit to the observed data using the AIC. Lower values for AIC indicate a better mathematical assessment of the fit to the actual data. BIC values have also been calculated and reported in this submission. As the approach taken here is Frequentist, as opposed to Bayesian, the BIC values do not factor into the decision-making process when selecting a distribution, and have instead been included for completeness.

Table 17 presents the AIC and BIC values for the extrapolation of IDFS data. The relative ranking of goodness of fit is shown in brackets, with one indicating the best fit and six the worst, i.e. lowest and highest AIC values, respectively.

Table 17. IDFS extrapolation – AIC and BIC values (relative ranking of goodness of fit shown in brackets) in N-/ND population of KATHERINE trial – node-negative/not done population

	AIC		BIC	
	Trastuzumab emtansine arm	Trastuzumab arm	Trastuzumab emtansine arm	Trastuzumab arm
Exponential	**261.53747 (1)**	460.47561 (3)	265.52893 (1)	464.45954 (3)
Weibull	263.42979 (2)	462.34148 (5)	271.41272 (2)	470.30935 (5)
Log-logistic	263.43422 (3)	460.89237 (4)	271.41715 (3)	468.86024 (4)
Log-Normal	265.40783 (5)	455.32283 (2)	273.39076 (5)	463.2907 (2)
Gamma	265.42237 (6)	**447.95434 (1)**	277.39676 (6)	459.90615 (1)
Gompertz	263.4536 (4)	462.47561 (6)	271.43653 (4)	470.44348 (6)

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion.

According to the AIC values, the Exponential and Gamma functions provide the best (statistical) fit to the observed data in the trastuzumab emtansine arm and the trastuzumab arm, respectively.

The NICE DSU technical support document, developed by Latimer et al., states that the same parametric function should be used across both treatment arms (where feasible). Using the same type of function ensures consistency and limits potential problems such as the crossing of the curves. Although curve crossing was not an issue in this instance it was considered best practice to adhere as closely as possible to the recommendations set out in Latimer et al. When

considering the fit across the two arms jointly, the best fitting extrapolation is produced by either the Exponential function.

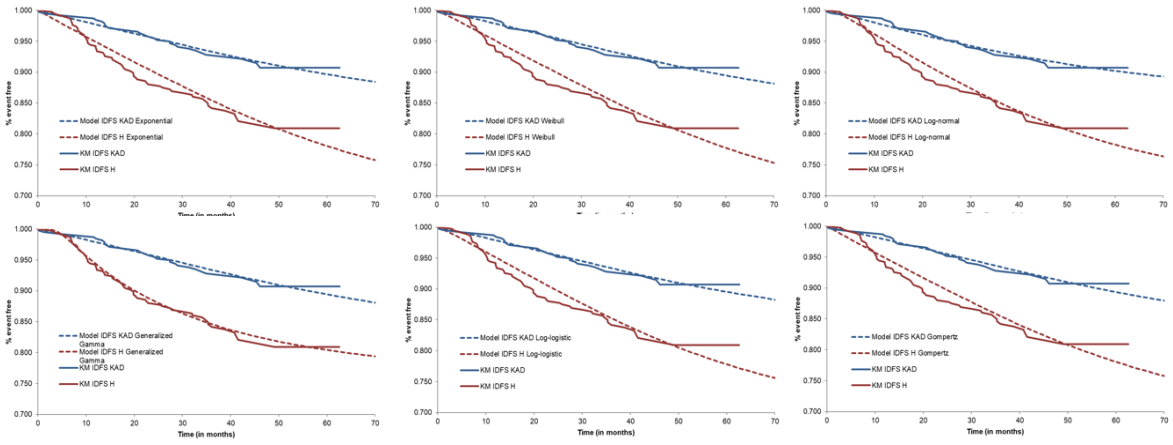
Mathematical measures such as the AIC and BIC are designed to show how well a parametric function fits to the Kaplan-Meier data, relative to the other functions in question. In other words, the AIC (BIC) values say nothing of the appropriateness of the extrapolation beyond the Kaplan-Meier data. As the degree of immaturity and censoring are high in the KATHERINE data, the AIC and BIC values quoted here should be interpreted with caution.

These limitations in the goodness of fit statistics necessitate the exercises laid in out in the following subsections (visual inspection and external validation) when selecting the most appropriate function on which to base the extrapolation of IDFS.

Visual inspection

In addition to Goodness of Fit statistics, all candidate distributions were also assessed for visual fit to the Kaplan-Meier data. The visual fit of each distribution to the Kaplan-Meier of the primary analysis is provided in Figure 4. Please see the cost-effectiveness model for separate images.

Figure 4. Visual inspection of IDFS extrapolations[a]



Footnotes: [a]Y-axes have been manipulated in order to magnify curves.
Abbreviations: IDFS: invasive disease-free survival; H: trastuzumab; KAD: trastuzumab emtansine; KM: Kaplan-Meier.

None of the extrapolations fit the data particularly well. In the trastuzumab arm (red), nearly all of the extrapolations overestimate IDFS when compared to the KM data.

Landmark IDFS rates

The AIC and BIC statistics serve to illustrate the relative fit of a parametric function. When selecting an appropriate extrapolation, it is also important to take the absolute fit to the Kaplan-Meier data into consideration. To quantify this, a simple comparison of IDFS events at different timepoints was undertaken. Table 18 presents the proportion of patients who did not experience an IDFS event at one, two, three and four years according to the parametric extrapolations and Kaplan-Meier data.

Table 18. IDFS events at 12, 24, 36 and 48 months

Timepoint	Parametric function	Trastuzumab emtansine arm	Trastuzumab arm	Trastuzumab emtansine vs trastuzumab	Δ vs KM data	
					Trastuzumab emtansine arm	Trastuzumab arm
12 months	KM data	98.70%	94.19%	4.50%	0.00%	0.00%
	Exponential	97.63%	94.69%	2.94%	-1.07%	0.50%
	Weibull	97.80%	94.96%	2.84%	-0.90%	0.77%
	Log-normal	97.52%	94.99%	2.53%	-1.18%	0.80%
	Gen. gamma	97.80%	94.04%	3.76%	-0.90%	-0.15%
	Log-logistic	97.80%	94.91%	2.88%	-0.90%	0.72%
	Gompertz	97.77%	94.69%	3.08%	-0.93%	0.50%
24 months	KM data	95.75%	88.02%	7.73%	0.00%	0.00%
	Exponential	95.41%	89.86%	5.55%	-0.34%	1.84%
	Weibull	95.55%	90.07%	5.48%	-0.20%	2.05%
	Log-normal	95.21%	89.61%	5.60%	-0.54%	1.59%
	Gen. gamma	95.57%	88.22%	7.34%	-0.18%	0.20%
	Log-logistic	95.53%	89.87%	5.67%	-0.22%	1.85%
	Gompertz	95.58%	89.86%	5.72%	-0.17%	1.84%
36 months	KM data	92.80%	84.57%	8.22%	0.00%	0.00%
	Exponential	93.25%	85.28%	7.97%	0.45%	0.71%
	Weibull	93.30%	85.33%	7.96%	0.50%	0.76%
	Log-normal	93.18%	84.90%	8.28%	0.38%	0.33%
	Gen. gamma	93.30%	84.51%	8.79%	0.50%	-0.06%
	Log-logistic	93.28%	85.09%	8.18%	0.48%	0.52%
	Gompertz	93.33%	85.28%	8.05%	0.53%	0.71%
48 months	KM data	90.68%	82.06%	8.62%	0.00%	0.00%
	Exponential	91.27%	81.25%	10.03%	0.59%	-0.81%
	Weibull	91.20%	81.11%	10.09%	0.52%	-0.95%
	Log-normal	91.50%	81.08%	10.41%	0.82%	-0.98%
	Gen. gamma	91.19%	82.04%	9.16%	0.51%	-0.02%
	Log-logistic	91.22%	80.98%	10.24%	0.54%	-1.08%
	Gompertz	91.19%	81.25%	9.94%	0.51%	-0.81%

Abbreviations: KM: Kaplan-Meier; Δ: difference.

Overall, all functions across both treatment arms proved to be a reasonable absolute fit to the Kaplan-Meier IDFS data. At all timepoints, incremental differences between the extrapolations and the Kaplan-Meier data were below 2.5%. It can be reasonably assumed that differences in the absolute fit of the parametric function extrapolations are negligible.

Based on the assessment and selection process described above, the Exponential distribution has been deemed to be the best fitting function and is therefore used for the IDFS extrapolation in years zero to three (time period 1) in both treatment arms. This distribution also provides the basis for the adjusted curves from year three onwards.

Time period 2 (year three to year ten) – empirical data

The approach to the modelling of IDFS in this time period has not changed from the analysis in the ITT population. See Section B.3.3.1 of Document B.

Time period 3 (year 10 to year 52)

The approach to the modelling of IDFS in this time period has not changed from the analysis in the ITT population. See Section B.3.3.1 of Document B.

Modelling of death in IDFS health state

Whilst in the IDFS state, patients are at risk of both recurrence and death. The risk of death applied here is the superior value between the risk of dying without recurrence (as observed in the KATHERINE study) and background mortality in the age-adjusted UK population.

The risk of dying without recurrence is derived from the KATHERINE trial. In the node-negative/not done population, there were a total of 4 deaths without prior events (two in the trastuzumab emtansine and two in the trastuzumab arm). A constant weekly probability was calculated. Too few death events (4/797= 0.5%) were observed to accurately and robustly extrapolate this parameter dependent of time. This probability was therefore assumed to be constant for the entirety of the time horizon.

In actuality, the weekly probability of disease-related death (without first experiencing an IDFS event) in the KATHERINE trial is so low (<0.0001) that the UK weekly background mortality rates are superior from cycle one of the time horizon. Consequently, in the base case analysis the risk of death that IDFS patients are exposed to is always equal to that of the age-adjusted UK population (background mortality).

Summary of IDFS curve construction

Broadly speaking, the approach to the construction of the IDFS curves in this subgroup analysis has not varied from the approach in the ITT population. For clarity, a summary of the methodology is given below. Figure 5 displays the data sources used to construct the curves in each of the time periods. Figure 5 shows IDFS extrapolations used in this analysis (node-negative/not done, Exponential).

- **Time period 1 (0–3 years)** – KATHERINE trial data are used to estimate the recurrence rate.
- **Time period 2 (3–10 years)** – Extrapolated recurrence rate is adjusted to more accurately reflect the trend in the recurrence rate observed in the long-term trastuzumab studies.
- **Time period 3 (10–51 years)** – Based on evidence from long-term trastuzumab studies, 95% of patients are assumed to be “cured” and are no longer at risk of recurrence, only background mortality applies.

Figure 5. Summary of the construction of IDFS curves and timing of treatment effect

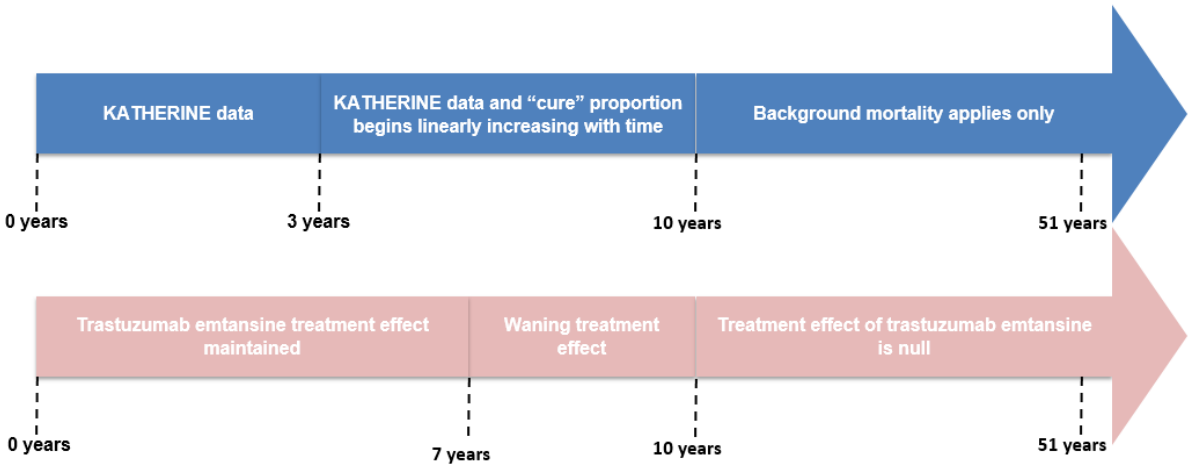
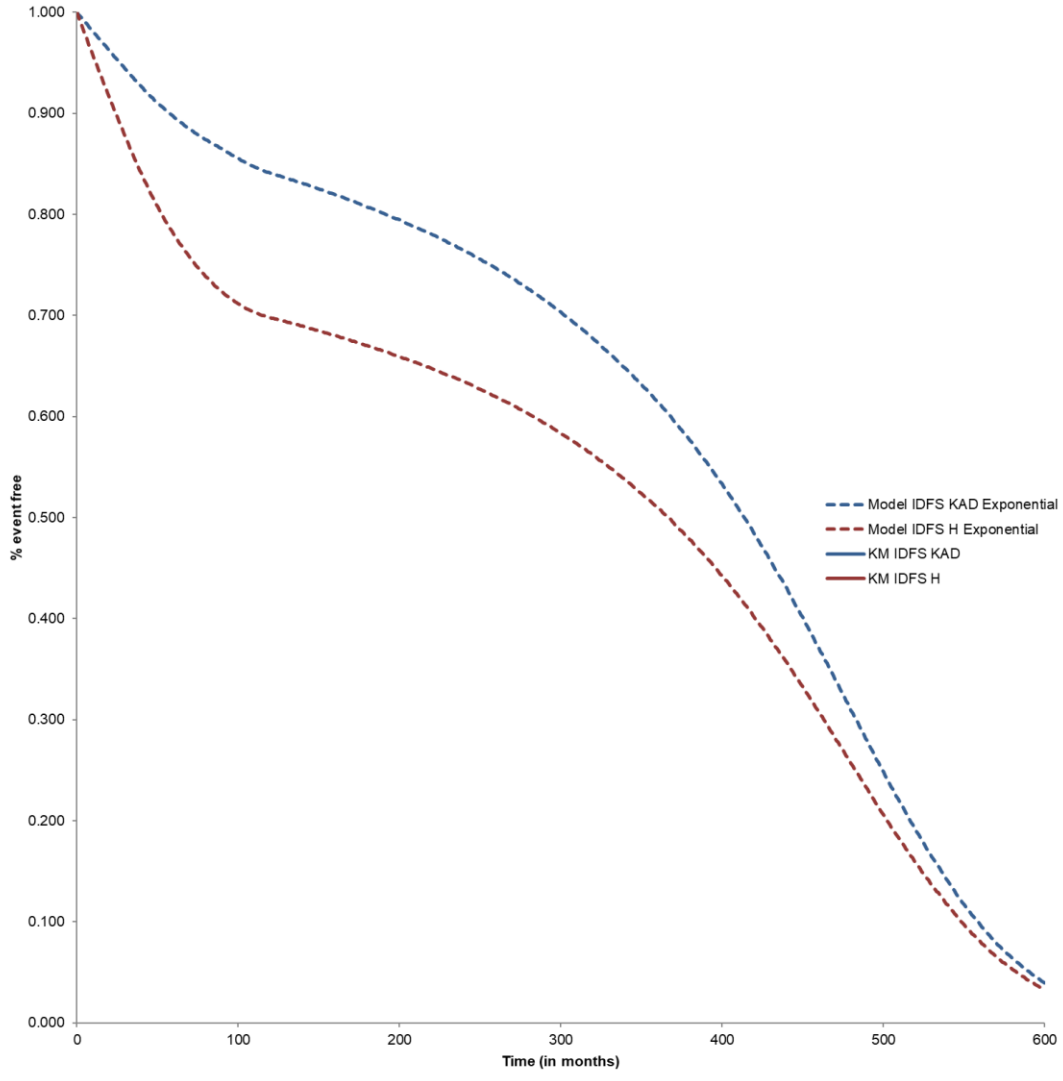


Figure 6. IDFS extrapolation - Exponential - N-/ND population



Modelling of recurrences

The same methodology and assumptions used to model recurrence in the ITT analysis have also been utilised here. There is however a notable exception. This exception refers to the split of metastatic/non-metastatic recurrences in both the "early" and "late" relapser populations. The IDFS event breakdown used in the ITT analysis has been given below in Table 19 (Table 26 from Document B).

Table 19. Proportion of recurrences which are non-metastatic by treatment arm in the "early" and "late" relapser population – ITT population

	Trastuzumab emtansine (n=743)	Trastuzumab (n=743)
IDFS event, n	91	165
Deaths without prior event, n (%)	2 (2.20%)	3 (1.82%)
IDFS event excluding deaths, n	89	162
"Early" relapser – pre-18 months[a]		
Metastatic recurrence, n (%)	36 (85.71%)	60 (72.29%)
Non-metastatic recurrence, n (%)	6 (14.29%)	23 (27.71%)
"Late" relapser – post-18 months[a]		
Metastatic recurrence, n (%)	42 (89.36%)	58 (73.42%)
Non-metastatic recurrence, n (%)	5 (10.64%)	21 (26.58%)

Footnotes: [a]Deaths are not counted as IDFS events in these figures. Death is accounted for separately in the model.
Abbreviations: IDFS: invasive disease-free survival.

An equivalent breakdown, derived from data observed in the N-/ND population, is presented below in Table 20.

Table 20. Proportion of recurrences which are non-metastatic by treatment arm in the "early" and "late" relapser population – N-/ND population

	Trastuzumab emtansine (n=400)	Trastuzumab (n=397)
IDFS event, n	29	62
Deaths without prior event, n (%)	2 (0.5%)	2 (0.5%)
IDFS events excluding deaths, n	27	60
"Early" relapser – pre-18 months[a]		
Metastatic recurrence, n (%)	9 (81.82%)	24 (68.33%)
Non-metastatic recurrence, n (%)	2 (22.22%)	9 (31.67%)
"Late" relapser – post-18 months[a]		
Metastatic recurrence, n (%)	12 (75.00%)	17 (62.96%)
Non-metastatic recurrence, n (%)	4 (25.00%)	10 (37.04%)

Footnotes: [a]Deaths are not counted as IDFS events in these figures. Death is accounted for separately in the model.
Abbreviations: IDFS: invasive disease-free survival.

The difference in the proportion of IDFS events which were metastatic was not formally tested therefore claims of statistical significance cannot be made. However, there is a non-trivial difference between the two treatment arms in both the "early" and "late" relapser sub-populations. In light of this difference the company has applied treatment-specific proportions in the base case analysis (as opposed to applying pooled values across both arms). This approach is aligned with the approach taken in the ITT analysis.

Modelling of overall survival

The methodology used to model overall survival in the ITT analysis has also been used here. See Section B.3.3.3 of Document B.

Treatment duration

Treatment duration is not expected to vary depending on nodal status. Therefore, the same time to off-treatment data used in the ITT analysis has also been used here. This assumption can be verified through examining Table 21. Across all treatment cycles there is <1% difference between the ITT data and the N-/ND data.

Table 21. Treatment discontinuation in the KATHERINE study – ITT vs. N-/ND populations

		ITT population		Node-negative / not done population	
		Trastuzumab (n=740)	Trastuzumab emtansine (n=740)	Trastuzumab (n=389)	Trastuzumab emtansine (n=400)
Total treatment duration (median)		10 months	10 months	10 months	10 months
Number of cycles (median)		14	14	14	14
Number (%) of patients completing at least a total of X cycles of assigned treatment:	*1 cycle*	720 (100.0%)	740 (100.0%)	389 (100.0%)	400 (100.0%)
	4 cycles	683 (94.9%)	677 (91.5%)	374 (96.1%)	365 (91.3%)
	7 cycles	664 (92.2%)	637 (86.1%)	367 (94.3%)	345 (86.3%)
	11 cycles	618 (85.8%)	579 (78.2%)	345 (88.7%)	311 (77.8%)
	14 cycles	583 (81.0%)	528 (71.4%)	323 (83.0%)	288 (72.0%)
Number (%) of patients completing at least a total of X cycles of all	*1 cycle*	N/A	740 (100.0%)	N/A	400 (100.0%)
	4 cycles	N/A	698 (94.3%)	N/A	374 (93.5%)
	7 cycles	N/A	673 (90.9%)	N/A	362 (90.5%)

study treatment:	*11 cycles*	N/A	639 (86.4%)	N/A	343 (85.8%)
	14 cycles	N/A	593 (80.1%)	N/A	322 (80.5%)

Measurement and valuation of health effects

Health-related quality of life is not expected to vary depending on nodal status. Therefore the same health state utilities used in the base case analysis of the ITT population have also been used here. See Section B.3.4 of Document B.

Cost and healthcare resource use

Costs associated with medicine acquisition, administration, AEs, and supportive care are not expected to vary according to nodal status. Therefore the same costs used in the base case analysis of the ITT population have also been assumed here. See Section B.3.5 of Document B.

Summary of inputs and assumptions

Summary of base case analysis inputs

The majority of inputs used in this analysis are identical to those used in the base case analysis of the ITT population (see Table 53 of Document B). Any deviation from this has been documented in the "Clinical parameters and variables" subsection of this response and have also been presented in Table 22 below for completeness.

Table 22. Summary of alternative inputs used in node-negative/not done economic analysis

Variable	Value used in ITT analysis	Value used in N-/ND analysis
Demographic parameters (pooled across tx arms)		
Age	49.10 (SD = 10.65)	48.85 (SD = 10.80)
Body weight (kg)	70.91 (SD = 15.15)	70.05 (SD = 14.71)
Height (cm)	163.10 (SD = 7.17)	163.36 (SD = 7.17)
Clinical parameters		
IDFS parametric distribution	Log-logistic	Exponential
% of metastatic recurrences – Early relapser	Trastuzumab emtansine = 85.71% Trast. = 72.29%	Trastuzumab emtansine = 81.82% Trast. = 72.73%
% of non-metastatic recurrences – Early relapser	Trastuzumab emtansine = 14.29% Trast. = 27.71%	Trastuzumab emtansine = 18.18% Trast. = 27.27%

Variable	Value used in ITT analysis	Value used in N-/ND analysis
% of metastatic recurrences	Trastuzumab emtansine = 89.36% Trast. = 73.42%	Trastuzumab emtansine = 75.00% Trast. = 62.96%
% of non-metastatic recurrences	Trastuzumab emtansine = 10.64% Trast. = 26.58%	Trastuzumab emtansine = 25.00% Trast. = 37.04%

Assumptions

The assumptions made in this economic analysis are identical to those in the base case analysis of the KATHERINE ITT population (see Table 54, Document B).

Top-line cost-effectiveness results

Trastuzumab emtansine provided a QALY gain of [redacted] and a life-year gain of 18.35, at a total overall cost of £[redacted]. In contrast, trastuzumab provided a QALY gain of [redacted] and a life-year gain of 16.74, at a total cost of £[redacted]. The resulting ICER when comparing trastuzumab emtansine to trastuzumab in the N-/ND population is £2,634/QALY gained.

See Table 23 for a top-line summary of the base case cost-effectiveness results.

Table 23. Top-line cost-effectiveness results (confidential discounts applied) - N-/ND subpopulation

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Trastuzumab	[redacted]	16.74	[redacted]	[redacted]	1.61	1.32	£2,634
Trastuzumab emtansine	[redacted]	18.35	[redacted]				

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

Sensitivity analyses

Probabilistic sensitivity analysis

To assess the uncertainty surrounding the variables included in the cost-effectiveness model, a probabilistic sensitivity analysis (PSA) was undertaken using 1,000 samples. See Table 24 for the list of parameters included in PSA (with associated distribution) and OWSA. Table 25 provides a list of parameters not included in the PSA and OWSA.

Regarding the transition probabilities, the sum of all probabilities leaving a specific health state will not be above one with current data inputs. We have created a worksheet named “Transition probabilities” in which we calculate, based on the 1,000 simulations, the maximum probability of cumulative transitions per node (= sum of the maximum values generated in 1,000 simulations for

each transition probability pertaining to the respective node). We can conclude that the sum is never above one with current data inputs.

Table 24. Parameters included in the PSA, OWSA and Scenario analyses - N-/ND subpopulation

PSA	OWSA
Demographics	
• Demographics (weight, height) – Normal	A1.
Utilities	
• Utility in IDFS on treatment, IDFS off treatment, recurrence, remission for KAD, H, PH – Beta • Utility in metastatic and progressed metastatic health states – Beta	• Utility in iDFS on treatment, iDFS off treatment, recurrence, remission for KAD, H, PH • Utility in metastatic and progressed metastatic health states
Clinical data A2.	

• HR K vs PH – Lognormal
• Parameters of parametric distributions – Normal
• Probability of IDFS and remission to death – Beta
• Probability of non-metastatic recurrence to death - Beta
• Proportion of metastatic recurrences (early relapse and post early relapse for KAD, H, PH) - Beta
• Probability of metastatic recurrence from remission state - Beta
• In case of early recurrence (for KAD, H, PH),
  ○ probability 1st line metastatic to 2nd line metastatic - Normal
  ○ probability 1st line metastatic to death - Beta
  ○ probability 2nd line metastatic to death - Normal
• In case of post early recurrence (for KAD, H, PH),
  ○ treatment mix in 1st line metastatic setting – Dirichlet
  ○ risk of progression in 1st line metastatic disease for each 1st line metastatic treatment– Normal
  ○ risk of death in 1st line metastatic disease for each 1st line metastatic treatment – Beta
  ○ treatment mix in 2nd line metastatic setting – Dirichlet
  ○ risk of death in 2nd line metastatic disease for each 2nd line metastatic treatment except KAD (sheet 'Model inputs' cell I344) – Normal
	• HR Kadcyla vs Perjeta
	A3.
	• Probability of IDFS and remission to death
	• Probability of non-metastatic recurrence to death
	• Proportion metastatic recurrences (early relapse and post early relapse for KAD, H, PH)
	• Probability of metastatic recurrence from remission state
	• In case of early recurrence,
	  ○ probability 1st line metastatic to 2nd line metastatic (KAD, H, PH)
	  ○ Probability 1st line metastatic to death (KAD, H, PH)
	  ○ probability 2nd line metastatic to death (KAD, H, PH)
	• In case of post early recurrence,
	  ○ Weighted (for treatment mix) probability 1st line metastatic to 2nd line metastatic (KAD, H, PH)
	  ○ Weighted (for treatment mix) probability 1st line metastatic to death (KAD, H, PH)
	  ○ Weighted (for treatment mix) probability 2nd line metastatic to death (KAD, H, PH)

A4. **Costs**	
• Administration costs – Lognormal • AE unit costs, except for PH ('Sheet Cost inputs' cell H109 – Lognormal	• AE cost per patient (KAD, H, PH) • Administration cost first cycle and subsequent cycle (KAD, H, H(SC), PH)

• Occurrence of AE – Lognormal • Supportive care costs – Lognormal	• Monthly supportive care costs in the different health states (IDFS year 1&2, IDFS years 3 to 5, iDFS years 6+, remission, recurrence, 1st line early metastatic (KAD, H, PH), 1st line and 2nd line late metastatic

Table 25: Parameters not included in PSA, OWSA and Scenario analyses:

PSA	OWSA
• Drug costs • Age	• Drug costs • Demographics (age, weight, height)

The PSA results produced a mean ICER of £2,811/QALY gained when trastuzumab emtansine was compared with trastuzumab. Results of the PSA compared to the base case analysis are presented in Table 26. Figure 7 and Figure 8 show the cost-effectiveness plane and acceptability curve, respectively.

The analyses below have been conducted using medication prices with confidential discounts applied.

Table 26. PSA results compared to base case (confidential discounts applied) - N-/ND subpopulation

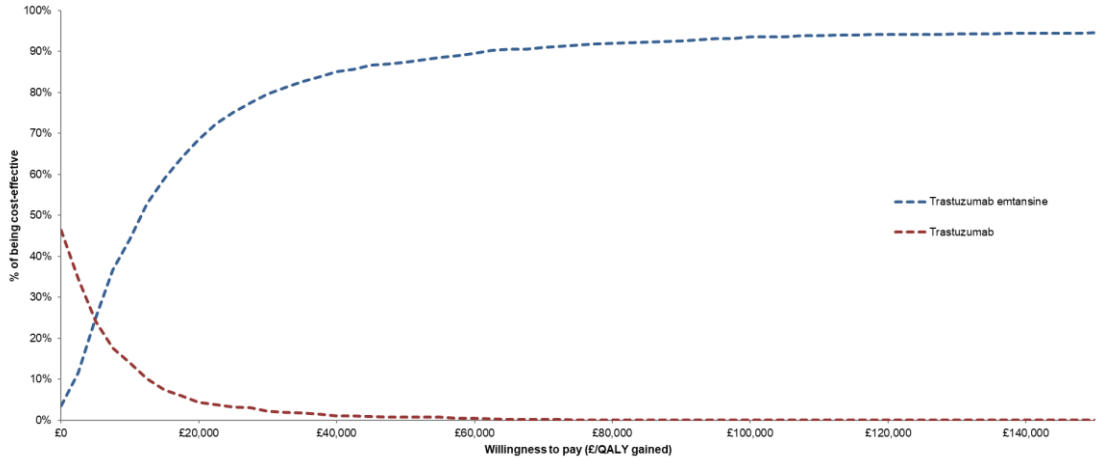
	Costs		QALYs		ICERs (£/QALY)	
	Base case	PSA	Base case	PSA	Base case	PSA
Trastuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£2,634	£2,811
Trastuzumab emtansine	[redacted]	[redacted]	[redacted]	[redacted]		

Abbreviations: ICER: incremental cost-effectiveness ratio; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year.

Figure 7. Cost-effectiveness plane - N-/ND subpopulation

REDACTED

Figure 8. Cost-effectiveness acceptability curve – N-/ND subpopulation



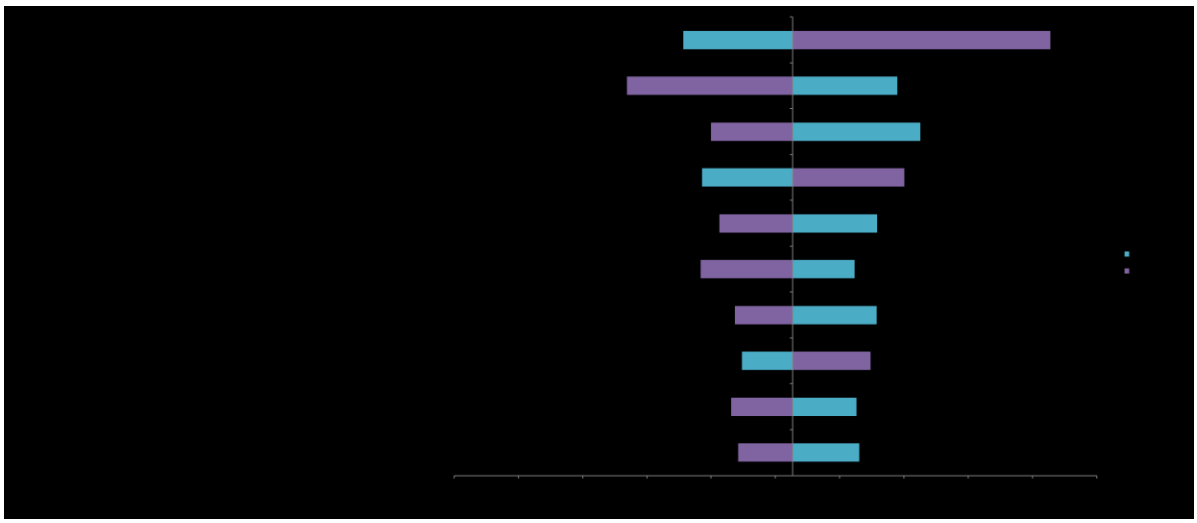
Abbreviations: QALY: quality-adjusted life year.

Deterministic sensitivity analysis

The choice of parameters to include in the univariate analysis was considered a priori, and was further informed by the results in Section B.3.7. For each parameter, the lower and upper values used in the univariate analysis were ±25% of the base case value. Please see the "UDSA" sheet of the economic model for a full breakdown of the lower and upper values used in the analysis.

The values featured in the univariate analysis are given in Table 24. For presentation purposes, only the ten most sensitive of analyses have been included in the Tornado diagram (Figure 33).

Figure 9. Tornado diagram - trastuzumab emtansine versus trastuzumab – N-/ND population



Scenario analyses

Please see the economic model for a full breakdown of the scenario analyses results in this subgroup.

Summary of sensitivity analyses results

PSA results are compared to the base case in Table 26. The PSA simulations produced a mean ICER of £2,811/QALY gained. This value is close to the base case value of £2,634/QALY gained. Furthermore, the cost-effectiveness acceptability curve showed that the trastuzumab emtansine regimen had a ~95% probability of being the most cost-effective treatment at a £20,000 willingness-to pay-threshold.

The results of the univariate sensitivity analysis show that the model drivers were the utilities in the probability of subsequent metastatic recurrence from remission state and the probability of metastatic death in the "early" relapser subpopulation of the trastuzumab arm. The lowest ICER produced was £1,345/QALY gained. This result was generated using the upper value (0.084) for the probability of metastatic death in the "early" relapser subpopulation of the trastuzumab arm. When using the lower value for the probability of subsequent metastatic recurrence from remission state, the highest ICER was generated (£4,637/QALY gained). The analysis around the probability of subsequent metastatic recurrence from remission state also produced the largest range in ICERs (£1,781–£4,637/QALY gained).

Interpretation and conclusions of economic evidence

The analysis presented here aligns closely with the analysis of the ITT population presented in the original submission. As documented in the "general approach" section, it has been assumed that costs and HRQoL would not be expected to vary according to a patient's nodal status. The difference between this analysis and the ITT analysis primarily centres on the derivation of the clinical inputs, specifically:

- Key demographic parameters
    - Weight, height, age
- IDFS KM data (upon which the IDFS extrapolations in the model are based)
- IDFS event breakdown

The limitations outlined in Section B.3.11 of the original submission also persist here. However, a more prominent limitation in this analysis compared to the ITT analysis is the limited patient numbers. In the N-/ND population of KATHERINE, there are only 797 patients (trastuzumab arm = 397 and trastuzumab emtansine arm = 400). Additionally, there were only 29 and 62 IDFS events in the trastuzumab emtansine and trastuzumab arms, respectively. This is a very small number of events upon which to base an extrapolation that runs for approximately 50 years. Consequently, there is a sizable degree of uncertainty associated with both the extrapolations and the proportions for metastatic/non-metastatic recurrence. Uncertainty in these aspects of the analysis will likely translate to uncertainty in the overall cost-effectiveness results of this analysis.

Despite the more favourable efficacy profile in the N-/ND population versus ITT (HR=0.42 vs 0.50), the ICER has increased in this analysis. This is most likely due to the *de novo* extrapolation parameters that have been calculated for this population. Once again, it is

important to note the uncertainty associated with the extrapolations and indeed the metastatic/non-metastatic recurrence proportions in this subgroup. Regardless of this uncertainty, much like the ITT results, the ICER in the N-/ND subgroup is significantly below the threshold at which NICE routinely approves technologies. Trastuzumab emtansine in the adjuvant setting can therefore be conclusively judged to be a cost-effective use of scarce NHS resources.

Question B29. Please provide sources to validate resource use frequencies reported in Table 46, 47 and 49.

Please see below a series of tables detailing the resource use frequency values used in TA569 (appraisal of adjuvant pertuzumab in the treatment of HER2+ breast cancer).

Table 27. IDFS health state – resource use and supportive care costs

Resource	Unit cost	Source	% of patients	Frequency per year		
				Year 1	Years 2–5	Years ≥5
Oncologist visit	£130.00	NHS ref. 2016/17 - 800	100%	2	0	0
GP visit	£37.00	PSSRU 2017 - page 162	100%	0	1	1
Mammogram	£11.34	TA767 - NHS BSP (inflated)	100%	1	1	0
ECHO scan	£70.36	NHS ref. 2016/17 – RD51A	70%	4	0	0
MUGA scan	£249.00	NHS ref. 2016/17 – RN22Z	30%			
Total base case cost per (four-week) cycle:				£63.93	£7.11	£3.08

Abbreviations: ECHO, echocardiogram; GP, general practitioner; MUGA, multigated acquisition; NHS, National Health Service; PSSRU, Personal and Social Services Research Unit.

Table 28. Non-metastatic recurrence state – resource use and supportive care costs

Resource	Unit cost	Source	Proportion of patients (%)	Frequency per year	Cost per cycle
Oncologist visit	£130.00	NHS ref. 2016/17 - 800	100%	2	£21.67
Mammogram	£11.34	TA767 - NHS BSP (inflated)	100%	1	£0.95
ECHO scan	£70.36	NHS ref. 2016/17 – RD51A	70%	4	£41.32
MUGA scan	£249.00	NHS ref. 2016/17 – RN22Z	30%		

Resource	Unit cost	Source	Proportion of patients (%)	Frequency per year	Cost per cycle
CT scan	£103.00	NHS ref. schedule - 2016/17 - RD20A	75%	2	£12.88
Total base case cost per (4-week) cycle: £76.80					

Abbreviations: CT, computerised tomography; ECHO, echocardiogram; GP, general practitioner; MUGA, multigated acquisition; NHS, National Health Service.

Remission

In the NICE appraisal of pertuzumab in the neoadjuvant setting it was assumed that patients in remission would incur the same health state costs as those in year 1–2 of EFS. Patients in remission in this model receive an identical supportive care regimen to those patients who are in year 2–5 of IDFS (see Table 27).

Table 29. First-line mBC state – resource use and supportive care costs

Items	Frequency (yearly)	Unit cost per contact	Proportion of patients	Cost sources	Resource use sources
Cycle costs					
GP visit	12	£37.00	100%	PSSRU 2017 - page 162	Assumption
ECHO Scan	2	£70.36	70%	NHS ref. 2016/17 – RD51A	CG81
MUGA Scan	2	£249.00	30%	NHS ref. 2016/17 – RN22Z	CG81
Clinical nurse specialist	12	£69.85	100%	NHS ref. - 2016/17 – N09AF	CG81
District Nurse (home visit)	22	£37.00	100%	NHS ref. - 2016/17 - N02AF	CG81
CT Scan	One off cost	£103.00	75%	NHS ref. 2016/17 - RD20A	Ad. board (03/2013); CG81
Social worker	One off cost	£82.00	100%	PSSRU 2017 - 11.2 - page 174	CG81
Total base case cost per (4-week) cycle = £214.78					

Abbreviations: CT, computerised tomography; ECHO, echocardiogram; GP, general practitioner; MUGA, multigated acquisition; NHS, National Health Service; PSSRU, Personal and Social Services Research Unit.

Table 30. Second + line mBC state – resource use and supportive care costs

Items	Frequency (yearly)	Unit cost per contact	Proportion of patients	Cost sources	Resource use sources
GP visit	12	£37.00	100%	PSSRU 2017 - page 162	Assumption
Clinical nurse specialist	12	£69.85	100%	NHS ref. - 2016/17 – N09AF	CG81
District Nurse (home visit)	24	£37.00	100%	NHS ref. - 2016/17 - N02AF	CG81
Average monthly supportive care cost = £180.85					

Abbreviations: GP, general practitioner; NHS, National Health Service; PSSRU, Personal and Social Services Research Unit.

Section C – Textual clarification

Question 6: Please provide Figure 18 in the company submission with the parametric curves extrapolated to more than 70 months.

Figure 10. Visual inspection of IDFS curves - Cure model adjustment applied - Exponential

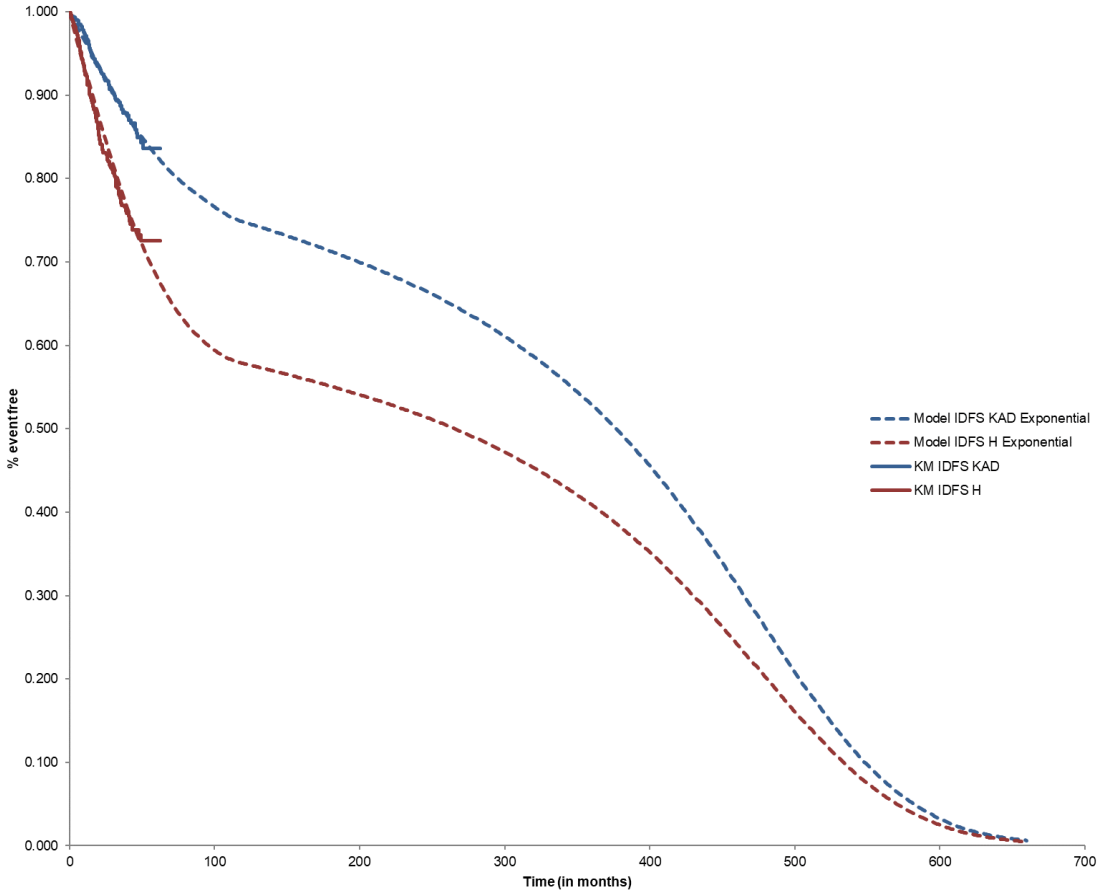


Figure 11. Visual inspection of IDFS curves - Cure model adjustment applied - Weibull

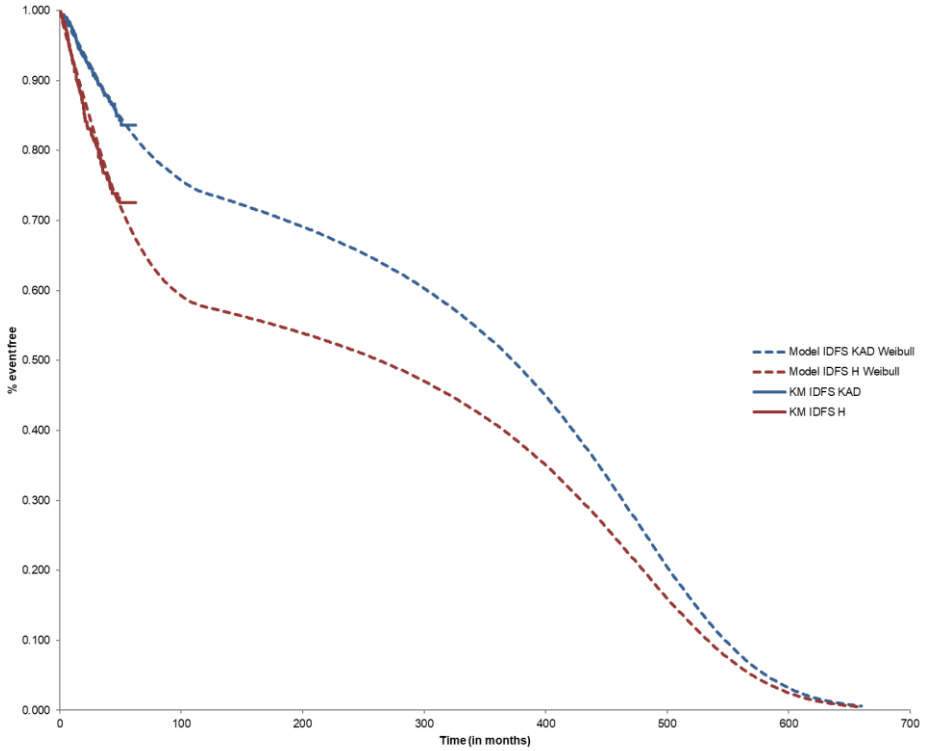


Figure 12. Visual inspection of IDFS curves - Cure model adjustment applied – Log-normal

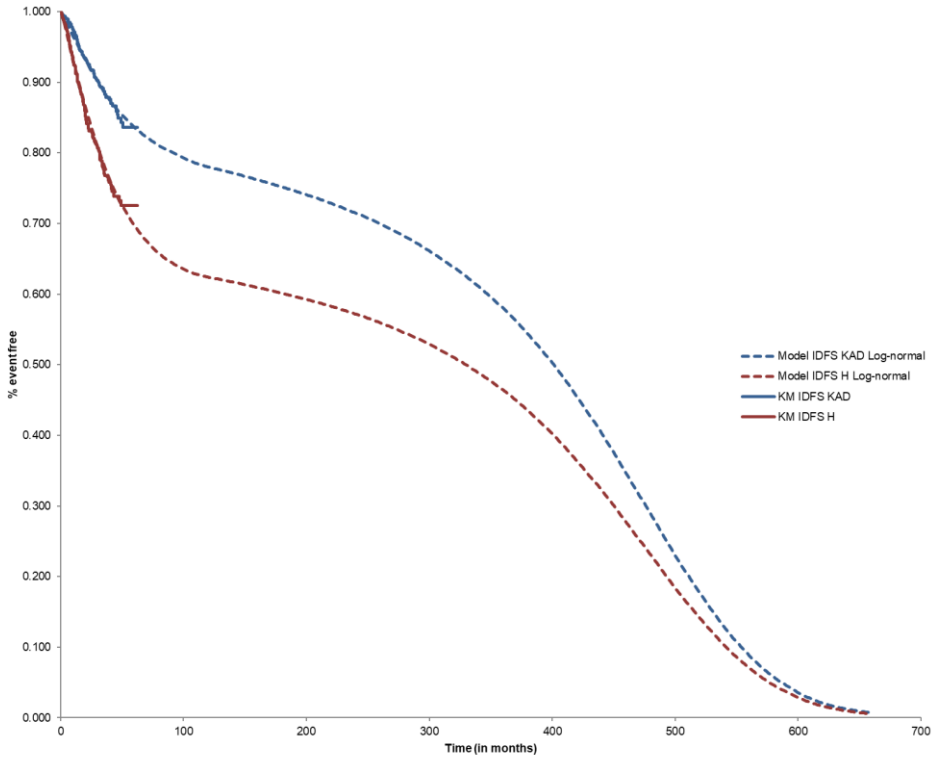


Figure 13. Visual inspection of IDFS curves - Cure model adjustment applied – Gamma

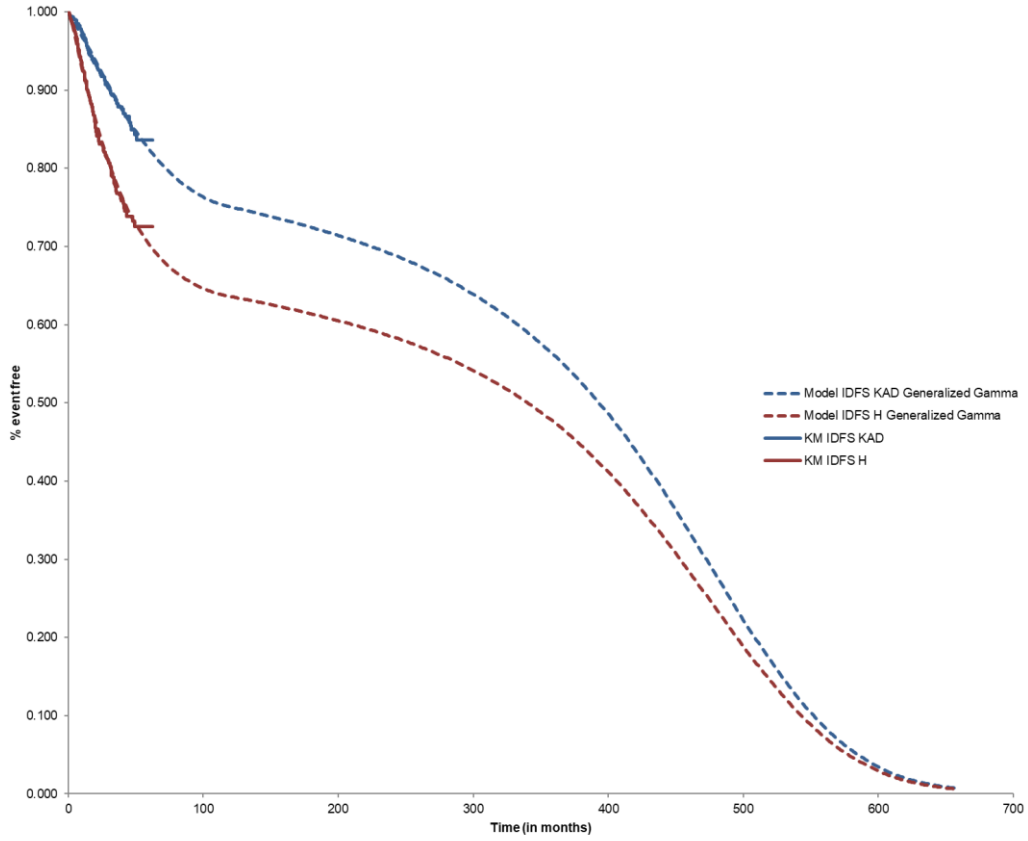


Figure 14. Visual inspection of IDFS curves - Cure model adjustment applied – Log-logistic

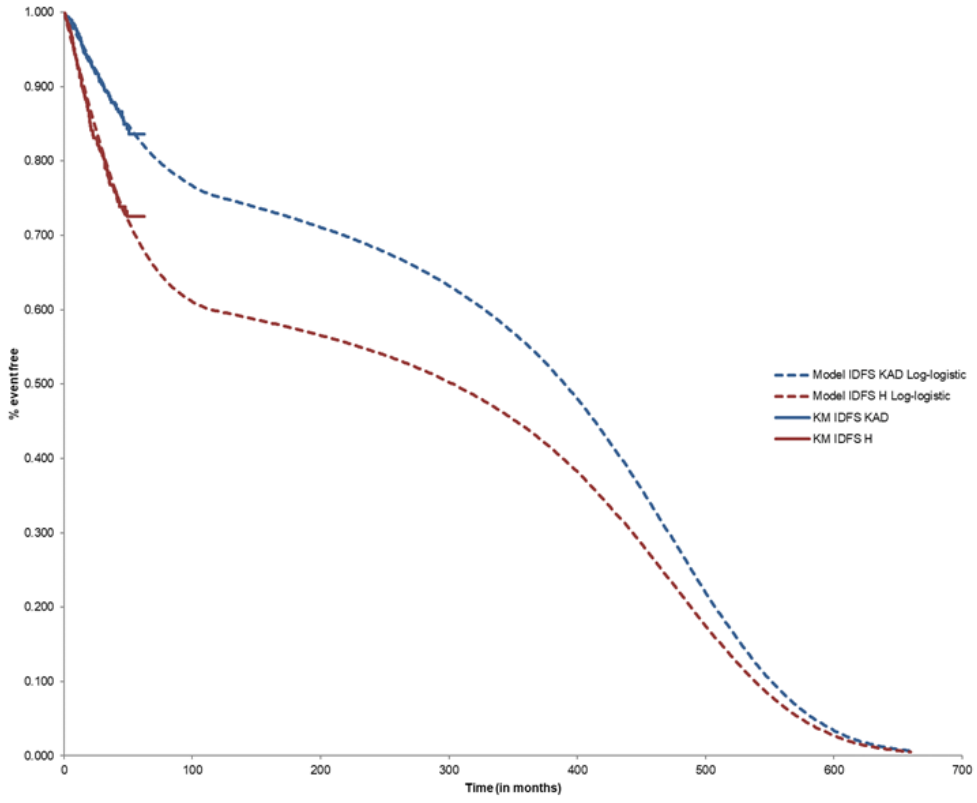


Figure 15. Visual inspection of IDFS curves - Cure model adjustment applied – Gompertz

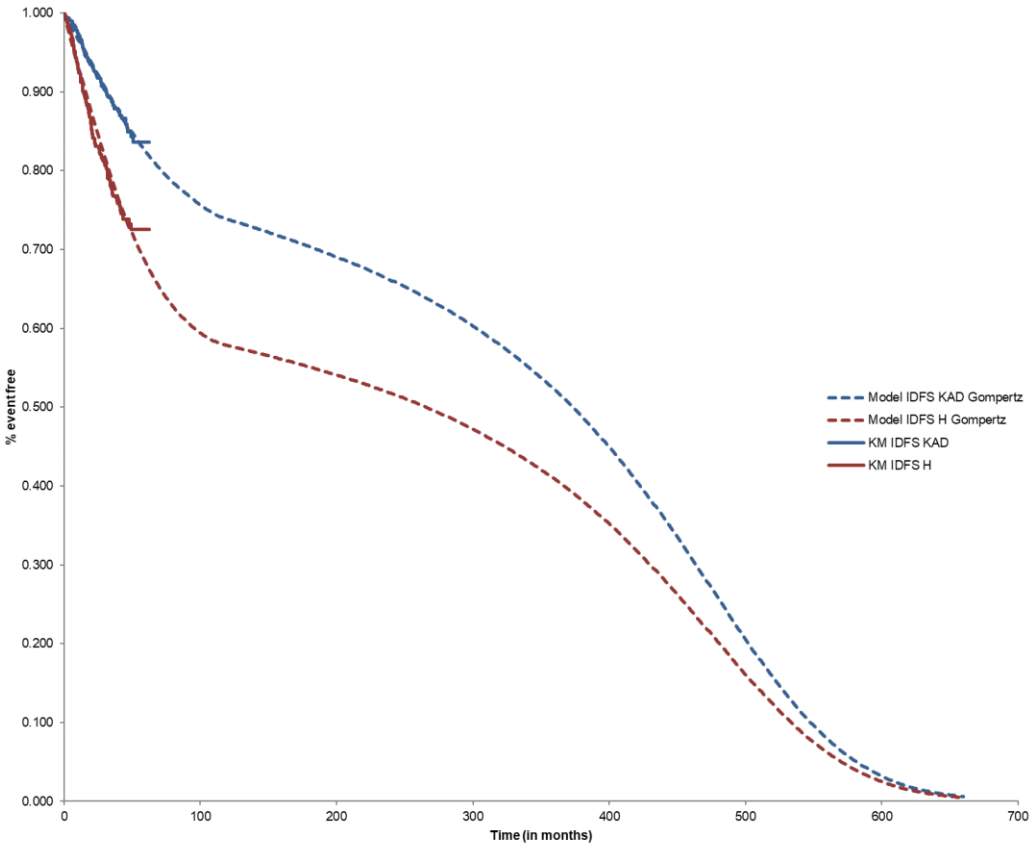


Figure 16. Visual inspection of IDFS curves – No cure model adjustment applied – Exponential

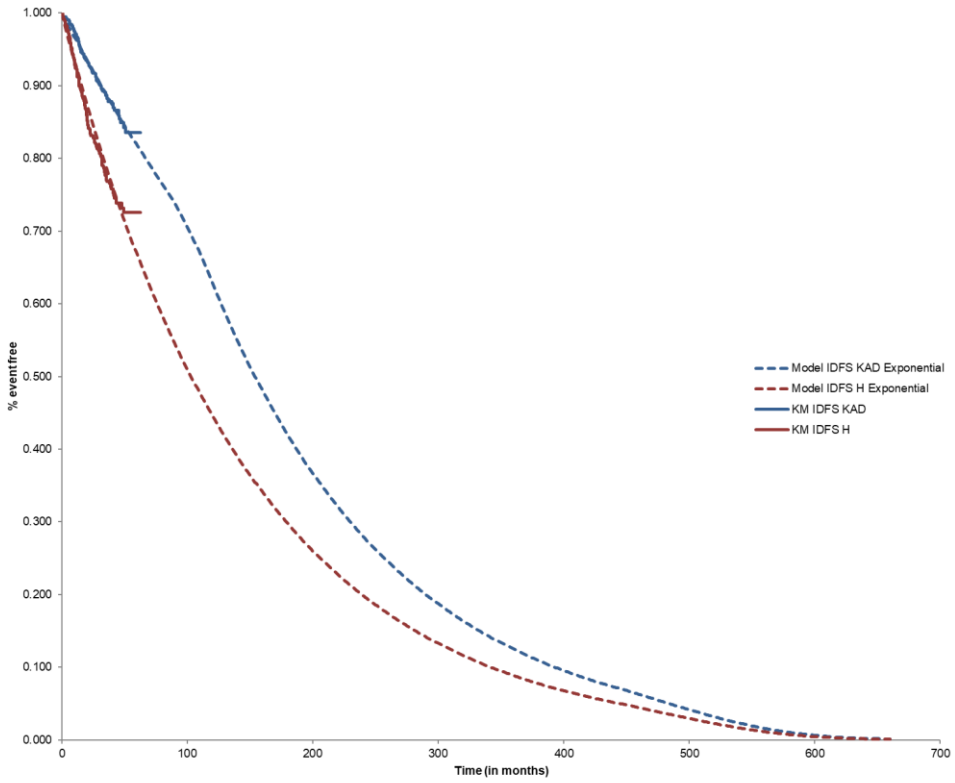


Figure 17. Visual inspection of IDFS curves – No cure model adjustment applied – Weibull

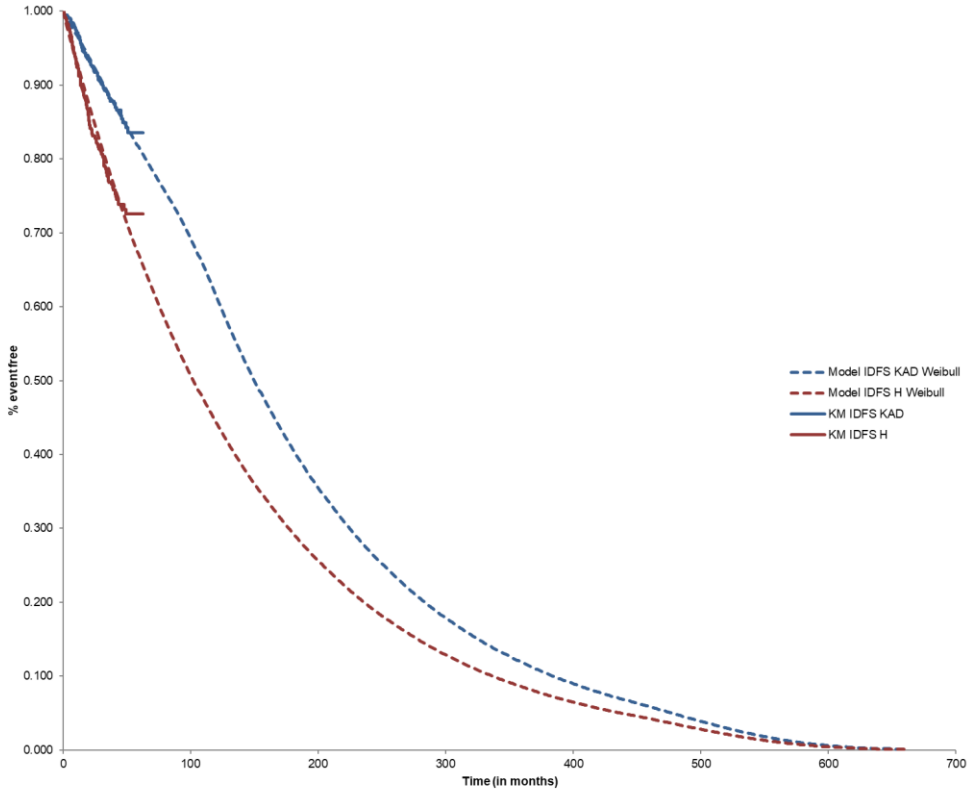


Figure 18. Visual inspection of IDFS curves – No cure model adjustment applied – Log-normal

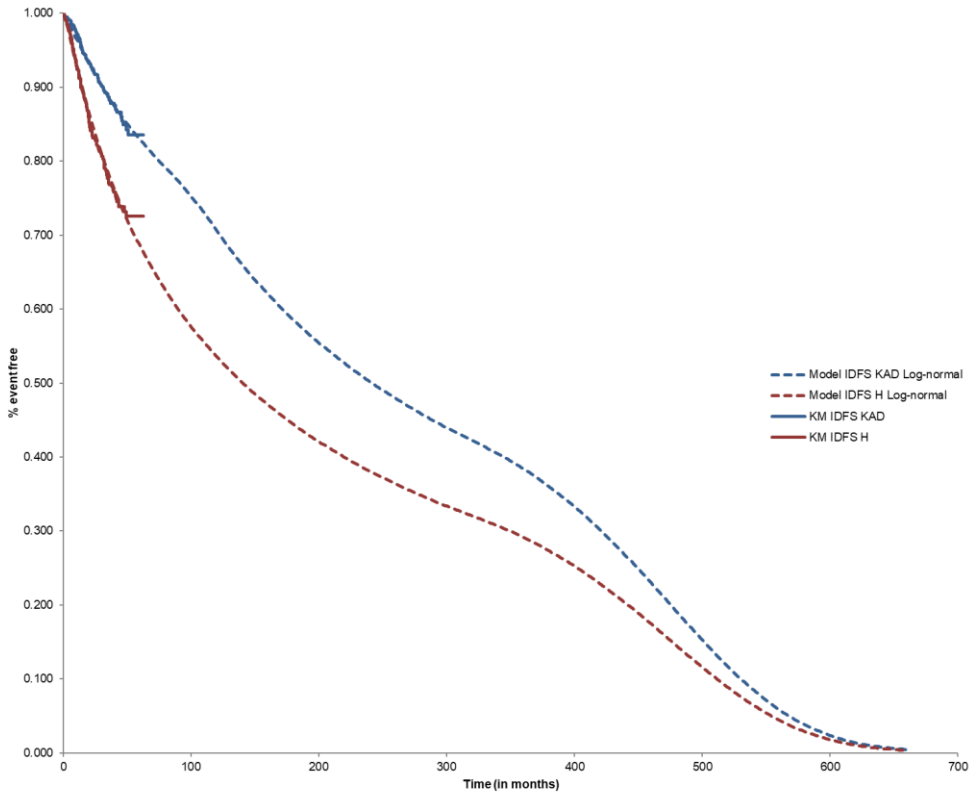


Figure 19. Visual inspection of IDFS curves – No cure model adjustment applied – Gamma

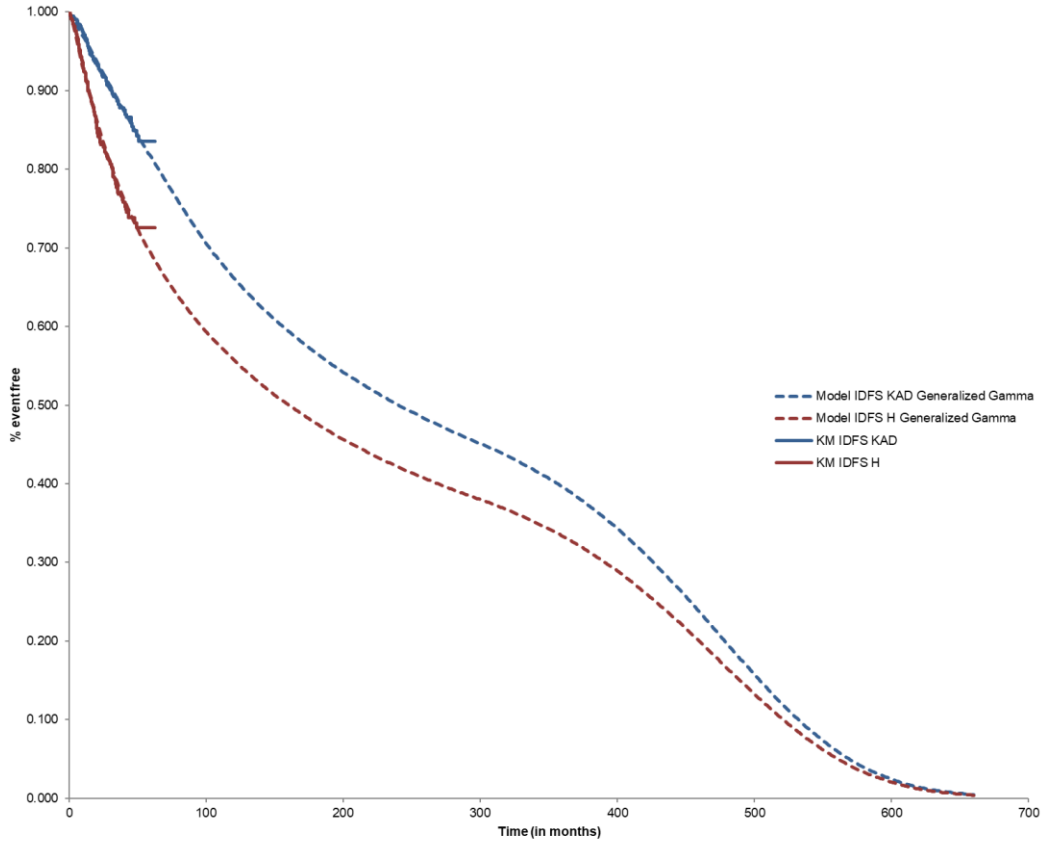


Figure 20. Visual inspection of IDFS curves – No cure model adjustment applied – Log-logistic

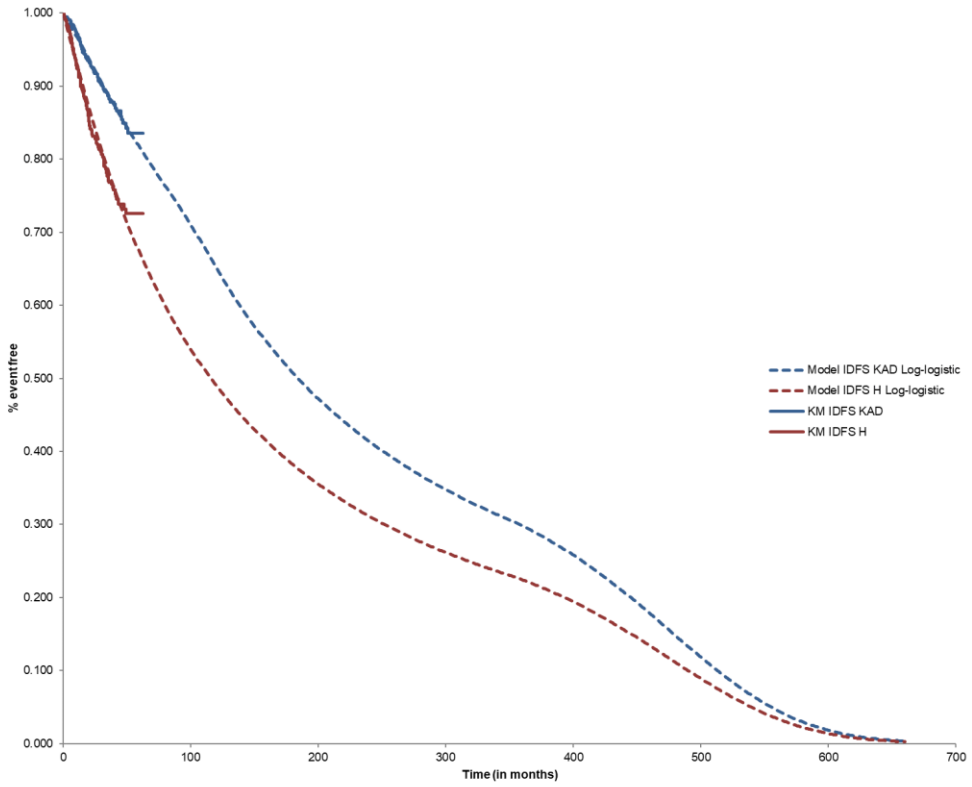
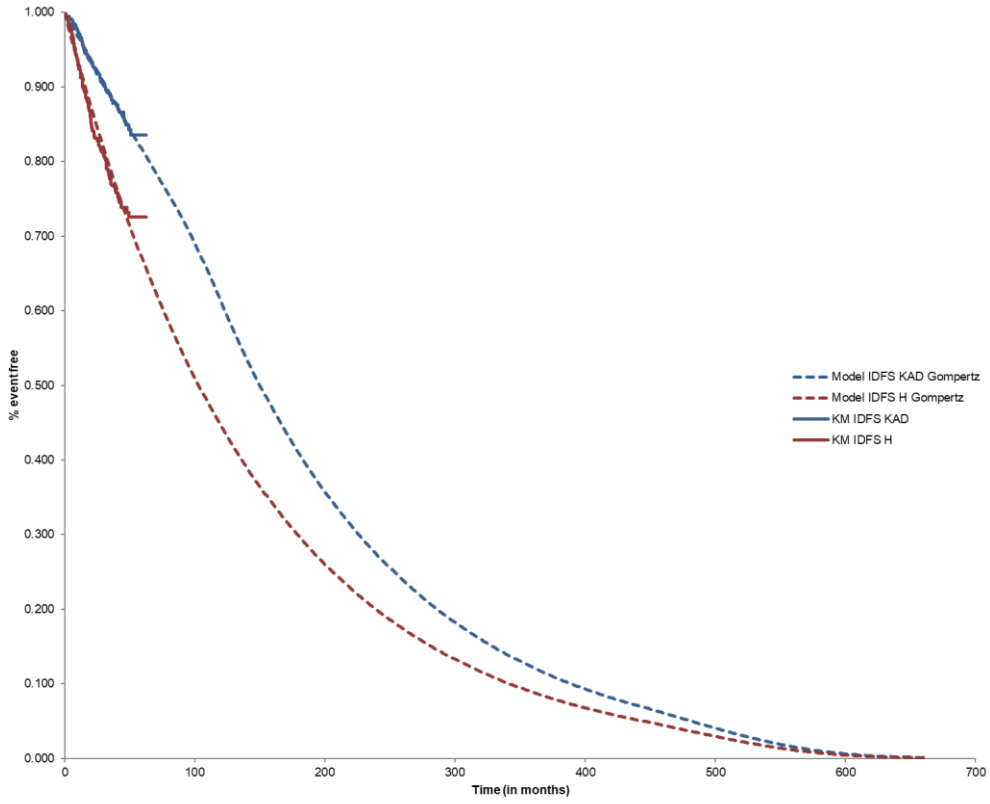


Figure 21. Visual inspection of IDFS curves – No cure model adjustment applied – Gompertz



NICE National Institute for Health and Care Excellence

Professional organisation submission

Trastuzumab emtansine for adjuvant treatment of HER2-positive early breast cancer [ID1516]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	Association of Breast Surgery
3. Job title or position	Consultant Oncoplastic Breast Surgeon

4. Are you (please tick all that apply):	■ an employee or representative of a healthcare professional organisation that represents clinicians? ■ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The Association of Breast Surgery is an independent charitable specialist organisation of healthcare professionals caring for any person with a breast problem. The aim is to promote the highest standards of breast surgery care through research, training and education, guidelines and audit. The organisation is independent of the NHS and funded by its' members
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The main aim of treatment is to cure breast cancer or at least decrease the chances of recurrence by a combination of surgery, chemotherapy, immunotherapy, radiotherapy and endocrine treatment

7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Reduction in tumour size in the breast and / or decrease in the number of positive nodes in the axilla. Ideally a complete pathological response in the breast and axilla is the aim of treatment as that conveys a survival advantage for the patient.

8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes - patients with residual disease after surgery in HER 2positive breast cancer have a worse prognosis than those with a pathological complete response. The ability to offer further anti HER 2 therapy is significant
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Currently Trastuzamab only continues after surgery even when there has been residual disease in the breast/axilla
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are very many guidelines for the treatment of breast cancer : TA 107 - 2006. NG101 (July 2018)

• Is the pathway of care well defined?Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	In England Trastuzamab Emtansine is currently licensed in the metastatic setting when there been disease progression on Trastuzamab. The use of this drug in other settings has only been as part of a clinical trial
• What impact would the technology have on the current pathway of care?	Improve outcomes and hopefully survival for HER 2 positive breast cancer
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes
• How does healthcare resource use differ between the technology and current care?	More chemotherapy chairs in clinics will be required
• In what clinical setting should the technology be used? (For example,	Secondary care in specialist oncology outpatient clinics

primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	You need to ensure there are enough chemotherapy chairs for the additional patients to receive Trastuzamab Emtansine
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
• Do you expect the technology to increase length of life more than current care?	Yes
• Do you expect the technology to increase health-related quality of life more than current care?	Yes

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	HER2 positive patients who have received neoadjuvant chemotherapy and Trastuzamab who have residual disease within the breast/axilla will benefit from this technology. Patients with HER negative disease will not benefit at all
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	

14. Will any rules (informal or formal) be used to start or stop treatment with the technology?Do these include any additional testing?	Cardiac monitoring with 3 monthly echos is standard with Trastuzamab. Deteriorating Left Ventricular Ejection Fraction is a reason to suspend treatment
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	yes
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	Yes

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes

Does the use of the technology address any particular unmet need of the patient population?	Yes - residual HER 2 positive disease after neoadjuvant chemotherapy and Trastuzamab carries a worse prognosis than those with a pathological complete response
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The two commonest Grade 3 side effects of this treatment are low platelet counts and hypertension. Monitoring of blood counts and blood pressure is a well established part of care for patients on chemotherapy and anti HER 2 treatment
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	No - currently this technology is not available in the adjuvant setting only the metastatic one

• If not, how could the results be extrapolated to the UK setting?	The addition of this technology after surgery would be easy to implement
• What, in your view, are the most important outcomes, and were they measured in the trials?	Yes - The KATHERINE study looked at iDisease free survival and is the pivotal study in this area
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Yes
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	I am not aware of any
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator	No

treatment(s) since the publication of NICE technology appraisal guidance [TA569, TA458, TA424]?	
21. How do data on real-world experience compare with the trial data?	The FDA approved the use of this agent only in May 2019 and it is too soon for meaningful results on survival
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	no
22b. Consider whether these issues are different from issues with current care and why.	
Key messages	

23. In up to 5 bullet points, please summarise the key messages of your submission.

- The Association of Breast Surgery (ABS) is committed to excellence in Breast Surgery and MDT working
- ABS fully support the introduction of this drug in the adjuvant setting
- Trastuzamab Emantansine should be available to all eligible patients on the NHS who are fit enough to receive it when there is residual disease after surgery for HER 2 positive breast cancer who have previously received neoadjuvant treatment
- Monitoring of cardiac toxicity and side effects are mandatory
- Continued audit of results and side effects is essential once the use of this novel drug is not as part of a clinical trial

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Trastuzumab emtansine for adjuvant treatment of HER2-positive early breast cancer [ID1516]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Breast Cancer Care and Breast Cancer Now
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Breast Cancer Care and Breast Cancer Now merged on 1 April 2019 to create one charity. From research to care, our new charity has people affected by breast cancer at its heart – providing support for today and hope for the future. United, we'll have the ability to carry out even more world-class research, provide even more life-changing support and campaign even more effectively for better services and care. Prior to merger, funding for the two legacy charities was as follows: Breast Cancer Now's main sources of income are individual giving and corporate partnerships. In particular, we received £2.7 million in 2016/17 and £2.9 million in 2017/18 from Pfizer for our Catalyst programme, which provides grants for research. Further details about our income are set out in our annual report, which is available on our website at http://breastcancernow.org/about-us/what-we-do/annual-report-and-accounts. Our work on access to drugs is independent of any funding we may receive from the pharmaceutical industry and is based on the evidence of the clinical effectiveness of drugs. Breast Cancer Care is funded entirely by voluntary donations, this includes individual and corporate donations, corporate sponsorships, project grants and income generated from events.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the	Breast Cancer Now and Breast Cancer Care utilise their various networks of supporters to gather information about patient experience.

experiences of patients and carers to include in your submission?	
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	A diagnosis of breast cancer will cause considerable anxiety to the patient as well as their family and friends. The initial diagnosis can be shocking, and in the longer-term the fear of breast cancer returning or spreading to other parts of the body (typically the bone, lungs, liver and brain) where it becomes incurable can cause considerable stress for both the patients and their loved ones. Treatment for breast cancer can have a number of side effects which can have a significant impact on everyday activities, ability to work and relationships.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Patients with HER2-positive early breast cancer will normally be offered surgery, and sometimes radiotherapy, together with targeted systemic therapy. This is usually trastuzumab with chemotherapy, which can be given as adjuvant or neoadjuvant treatment, depending on the patient's circumstances. In patients at high risk of recurrence, NICE recommends combining trastuzumab and chemotherapy with pertuzumab as a neoadjuvant treatment. NICE also recommends this combination as an adjuvant treatment in patients with lymph node-positive disease. Targeted therapies for HER2-positive breast cancer tend to be well tolerated by patients when compared to the gruelling side effects with chemotherapy and the menopausal and joint pain experienced by many on hormone therapy.

8. Is there an unmet need for patients with this condition?	Targeted treatments for HER2-positive breast cancer are already available on the NHS. These include trastuzumab and pertuzumab which may be given as neoadjuvant or adjuvant treatment, depending on the patient's circumstances. A third targeted treatment for HER2-positive breast cancer, neratinib, is currently being considered by NICE for patients who have already received trastuzumab. However, new treatment options that improve outcomes are welcomed by patients.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	The main advantage of trastuzumab emtansine is increased invasive disease-free survival, including increased freedom from distant recurrence (when breast cancer spreads to other organs in the body). Women with breast cancer and their carers welcome improvements in these outcomes. The KATHERINE trial demonstrated that following an incomplete response to neoadjuvant therapy, 88.3% of patients treated with adjuvant trastuzumab emtansine were free of invasive disease after 3 years, compared to 77% of patients treated with trastuzumab – a significant increase of 11.3%. Although most patients in the trial had previously received neoadjuvant trastuzumab with chemotherapy, a similar trend was observed in patients who had previously received neoadjuvant trastuzumab and chemotherapy combined with pertuzumab. The KATHERINE trial also demonstrated that after 3 years, 89.7% of patients treated with adjuvant trastuzumab emtansine were free from distant recurrence, compared to 83% of patients treated with trastuzumab – a significant increase of 6.7%.

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Patients experience more side effects with trastuzumab emtansine compared to trastuzumab, which can have a negative impact on their quality of life. In the KATHERINE trial, 25.7% of patients in the trastuzumab emtansine group experienced an adverse effect of grade 3 or above, compared to 15.4% of patients in the trastuzumab group. 18% of patients in the trastuzumab emtansine group in the KATHERINE trial discontinued treatment due to adverse effects, compared to 2.1% in the trastuzumab group. Common side effects that led to patients discontinuing treatment with trastuzumab emtansine included decreased platelet count, peripheral sensory neuropathy, decreased ejection fraction (heart failure) and abnormal blood test results.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	The KATHERINE trial only studied patients with HER2-positive early breast cancer who had residual disease following neoadjuvant therapy with trastuzumab and chemotherapy. On current evidence, it's unknown if adjuvant trastuzumab emtansine would also benefit patients who had a complete response to neoadjuvant therapy. Effective therapy for patients with residual disease after neoadjuvant therapy is particularly welcome as these patients have a poorer prognosis than those who demonstrate a pathological complete response to neoadjuvant therapy. It is estimated that only 40-60% of patients experience a pathological compete response.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	
Other issues	
13. Are there any other issues that you would like the committee to consider?	
Key messages	

14. In up to 5 bullet points, please summarise the key messages of your submission:

- A diagnosis of breast cancer can cause considerable anxiety to patients as well as their family and friends, including fear of recurrence or fear of it spreading to other parts of the body where it becomes incurable
- Trastuzumab emtansine provides significant improvements in 3-year invasive disease-free survival in patients who have residual disease after neoadjuvant chemotherapy, an outcome that is welcomed by women with breast cancer

- There are several significant side effects with trastuzumab emtansine, which can have a negative impact on patient's quality of life and may cause them to discontinue treatment
- Patients who have residual disease following neoadjuvant therapy have a poorer prognosis, and adjuvant trastuzumab emtansine could offer a valuable new treatment option for this group of patients

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Breast cancer (HER2 positive) - trastuzumab emtansine (adjuvant) [ID1516]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Professor Andrew WARDLEY**
2. Name of organisation	**The Christie NHS Foundation Trust**

3. Job title or position	**Medical Director, NIHR Clinical Research Facility at The Christie, Manchester / Consultant in Medical Oncology**
4. Are you (please tick all that apply):	✓ an employee or representative of a healthcare professional organisation that represents clinicians? ✓ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted	☒ yes My views were expressed in the response to the technical engagement

after submission.)	
The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The main outcome is to improve overall survival in the population of patients with the most aggressive form of HER-2 +ve early breast cancer, ie that which is resistant to optimal treatment that is currently available viz chemotherapy with trastuzumab and pertuzumab. Improvement in overall survival is generally considered improvement in “cure” rates
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	The demonstrated improvement in invasive disease free survival (0.50 (0.39–0.64)) and overall survival (0.70 (0.47-1.05) represent some of the best improvements seen in treating breast cancer and are of the same magnitude of benefit as seen with adjuvant trastuzumab in 2005.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes for both. Patients for whom primary medical therapy with chemotherapy with trastuzumab and pertuzumab has not achieved a pathological complete response have a poor outcome and need new more effective treatments. The improvement in 3 year invasive disease free survival with trastuzumab-emtansine compared to trastuzumab represents an important gain. there is clearly still need for further improvement in this as the 3 year invasive disease free survival is only 88% compared up to 97.5% for patients in whom pathological complete response is achieved (Kristine

	trial).
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE ASCO ESMO NCCN
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	there is an increasing recognition internationally in breast cancer opinion leaders that the optimal pathway for HER2 positive breast cancer requires primary medical therapy to enable response directed therapy. Two-thirds of patients in Germany receive primary medical therapy for HER2 positive breast cancer compared to less than half in UK. there is marked variation between larger and smaller breast cancer units and centres in UK
• What impact would the technology have on the current pathway of care?	Increase use of primary medical therapy for HER2 positive breast cancer
11. Will the technology be used (or is it already used) in	Trastuzumab-emtansine will replace adjuvant trastuzumab and trastuzumab and pertuzumab for patients for whom primary medical therapy did not achieve pathological complete response

the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	there is already a shortage in the workforce for all members of the team required to treatment breast cancer there needs to be investment in training. (I realise this is the case across the whole NHS)
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary and tertiary
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	there needs to be recognition of the demands on the service and increased training Saving patients from recurrence will reduce the demand for on-going treatment in these patients who often require many years of complex treatment before they die. A large part of the work could be accommodated by reconfiguration of breast cancer services.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes very much. This is a major clinical improvement.
• Do you expect the technology to increase	Yes as stated this is one of the biggest advances seen for patients with this type of breast cancer. there does need to be consideration of how access to this technology is maximised and delivered equitably

length of life more than current care?	across UK.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes more people will live without cancer recurrence.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant	As above Investment in workforce required Investment in systemic anti-cancer therapy facilities which are already over stretched Ideally reconfiguration of breast cancer services to maximise use of primary medical therapy

treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Timely pathology required as none pathological complete response is sine qua non
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes
17. Do you consider the technology to be innovative in	Yes very much as described above

its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes HR 0.5 for invasive disease free survival is a step change
• Does the use of the technology address any particular unmet need of the patient population?	Yes non pathological complete response is associated with a poor outcome in the population
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Side-effects are well known and there are clearly defined management plans for these. The technology will be delivered in expert centres by oncology specialists
Sources of evidence	

19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes KATHERINE recruited in UK
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Overall survival and invasive disease free survival They were measured
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No. We have used trastuzumab-emtansine in metastatic breast cancer for many years and the side-effects are those described in the trial
20. Are you aware of any relevant evidence that might not be found by a systematic	No

review of the trial evidence?	
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]?	
22. How do data on real-world experience compare with the trial data?	Non available yet
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
23b. Consider whether these issues are different from issues with current care and why.	

Topic-specific questions	
24. [To be added by technical team if required, after receiving the company submission. For example, if the company has deviated from the scope (particularly with respect to comparators) – check whether this is appropriate. Ask specific, targeted questions such as “Is comparator X [excluded from company submission] considered to be established clinical practice in the NHS for treating [condition Y]?”] **if not delete highlighted**	

rows and renumber below	
Key messages	
25. In up to 5 bullet points, please summarise the key messages of your statement. • Improved survival without cancer recurrence in population with poor outcome • Step change in improving chances of cure for these patients • Side-effects are known and manageable • Service reconfiguration maybe required to optimise access to this major advance • Workforce capacity remains an issue in cancer care generally	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

.....

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NICE National Institute for Health and Care Excellence

Patient expert statement

Trastuzumab emtansine for adjuvant treatment of HER2-positive early breast cancer [ID1516]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Tom Beattie**
2. Are you (please tick all that apply):	☐ a patient with the condition? ☐ a carer of a patient with the condition? ☒ a patient organisation employee or volunteer?

	☐ other (please specify):
3. Name of your nominating organisation	Breast Cancer Now
4. Did your nominating organisation submit a submission?	☒ yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

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

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Trastuzumab emtansine for adjuvant treatment of HER2-positive early breast cancer

Produced by Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Contributions of authors

Rob Riemsma acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Isaac Corro Ramos acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Hannah Penton, Nasuh Büyükkaramikli, Steve Ryder and Nigel Armstrong acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Annette Chalker and Stephanie Swift acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Gill Worthy acted as statistician, critiqued the analyses in the company's submission and contributed to the writing of the report. Kate Misso critiqued the search methods in the submission and contributed to the writing of the report. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

AC-T	Doxorubicin + cyclophosphamide followed by docetaxel
AC-TH	Doxorubicin + cyclophosphamide followed by docetaxel + trastuzumab
ADC	Antibody-drug conjugate
AE	Adverse events
AIC	Akaike information criterion
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BCS	Best case scenario
BI	Budget impact
BIC	Bayesian information criterion
CE	Cost effectiveness
CEA	Cost effectiveness analysis
CEAC	Cost effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CNS	Central nervous system
CRD	Centre for Reviews and Dissemination
CS	Company's submission
CSR	Clinical study report
CT	Computerised tomography
CTR	Clinical trial results
DCIS	Ductal carcinoma in situ
DDFS	Distant disease-free survival
DFS	Disease-free survival
DRFI	Distant recurrence-free interval
DSU	Decision Support Unit
eBC	Early breast cancer
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
eMIT	Electronic market information tool
EORTC	European Organisation for Research and Treatment of Cancer
EPAR	European Public Assessment Report
EQ-5D	European Quality of Life-5 Dimensions
ER	Oestrogen receptor
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
EUR	Erasmus University Rotterdam
FAS	Full analysis set
FAD	Final appraisal document
FDA	Food and Drug Administration
FEC	Fluorouracil + epirubicin + cyclophosphamide
FEC-THP	Fluorouracil + epirubicin + cyclophosphamide followed by pertuzumab + trastuzumab + taxane
GHS	Global health status
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUV	Health state utility value
HTA	Health technology assessment
IC	Indirect comparison
ICD	International Statistical Classification of Diseases and Related Health Problems
ICER	Incremental cost effectiveness ratio
IDFS	Invasive disease-free survival

ITC	Indirect treatment comparison
ITT	Intention to treat
IV	Intravenous
KM	Kaplan-Meier
KSR	Kleijnen Systematic Reviews
LVEF	Left ventricular ejection fraction
LYs	Life years
LYG	Life years gained
MAIC	Match-adjusted indirect comparison
mBC	Metastatic breast cancer
MeSH	Medical subject headings
MHRA	Medicines and Healthcare Products Regulatory Agency
MOS SF-36	Medical Outcomes Study Short Form Survey
MTA	Multiple technology appraisal
MTC	Mixed treatment comparison
NA	Not applicable
NCCN	National Comprehensive Cancer Network
NCRI	National Cancer Research Institute
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NMA	Network meta-analysis
NR	Not reported
NYHA	New York Heart Association
OS	Overall survival
PAS	Patient access scheme
pCR	Pathological complete response
PFS	Progression-free survival
PH	Proportional hazards
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PRO	Patient reported outcome
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PTC	Pertuzumab + trastuzumab + chemotherapy
Q3W	Everythree3 weeks
QALY	Quality adjusted life year
QLQ-BR23	Breast cancer-specific quality of life questionnaire
QLQ-C30	Quality of life questionnaire
QoL	Quality of life
RCT	Randomised controlled trial
RECIST	Response evaluation criteria in solid tumours
RID	Residual invasive disease
RR	Relative risk; risk ratio
SABCS	San Antonio Breast Cancer Symposium
SAE	Serious adverse events
SC	Subcutaneous
ScHARR	School of Health and Related Research
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
SoC	Standard of care

STA	Single technology appraisal
STEEP	Standardised definitions for efficacy endpoints
TA	Technology assessment
TCH	Docetaxel + carboplatin + trastuzumab
TC-HP	Docetaxel + carboplatin + trastuzumab + pertuzumab
TEAE	Treatment emergent adverse events
tpCR	Total pathological complete response
TTO	Time trade-off
TTOT	Time-to-off treatment
UK	United Kingdom
UMC	University Medical Centre
USA	United States of America
WHO	World Health Organization
WTP	Willingness-to-pay

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1. SUMMARY

1.1 Critique of the decision problem in the company's submission

The population described in the NICE scope is "Adults with HER2-positive early breast cancer who have residual disease following neoadjuvant therapy containing a taxane (with or without anthracycline) and HER2-targeted therapy". The patient population considered in the company submission is "Adult patients with HER2-positive eBC who have RID, in the breast and/or lymph nodes, after pre-operative systemic treatment that included HER2-targeted therapy". This means that the population in the submission is slightly narrower than that specified in the final scope, which does not specify that a patient's residual disease must be invasive. The narrower population considered in the company submission is in line with the anticipated marketing authorisation for trastuzumab emtansine.

The most recent anticipated marketing authorisation is: trastuzumab emtansine, as a single agent, is indicated for the adjuvant treatment of adult patients with HER2-positive early breast cancer who have residual invasive disease, in the breast and/or lymph nodes, after neoadjuvant taxane-based and HER2 targeted therapy.

The intervention is in line with the NICE scope.

The NICE scope mentions two comparators: trastuzumab and pertuzumab (for people with node-positive disease). The company interpreted this as, pertuzumab is a comparator for node-positive disease only, while trastuzumab is a comparator for the whole population. However, according to technology assessment (TA)-569, pertuzumab, with intravenous trastuzumab and chemotherapy, is recommended for the adjuvant treatment of human epidermal growth factor receptor 2 (HER2)-positive early stage breast cancer in adults with lymph node-positive disease. In addition, the company's proposed use and positioning of adjuvant trastuzumab emtansine (see CS, Chapter B.1.3.5) is as an alternative for trastuzumab in node-negative patients with RID and as an alternative for pertuzumab in node-positive patients with RID (see also Figure 2.1 of this report). This means that there is only one comparator for node-negative patients (trastuzumab), and only one comparator for node-positive patients (pertuzumab). In the company submission, the company has presented two types of analyses, one for the whole population (with trastuzumab as the comparator) and one for node-positive disease only (with pertuzumab as the comparator). The company did not provide a separate analysis for node-negative disease (with trastuzumab as the comparator) in their original submission. Therefore, the ERG requested these data as part of the clarification letter.

1.2 Summary of the key issues in the clinical effectiveness evidence

The clinical effectiveness searches presented in the original company submission lacked sufficient detail for the ERG to assess performance. Following a clarification request regarding missing information reporting hits per line of searches, the company provided sufficient details for the ERG to appraise the searches. Searches were carried out on a range of databases. Supplementary searches of conference proceedings, trials databases and the checking of reference lists were undertaken by the company in order to identify additional studies not retrieved by the main searches. The ERG identified some inconsistencies in the clinical effectiveness searches, however there were not considered to be consequential.

The company identified one randomised controlled trial (RCT): the KATHERINE study, which evaluated the efficacy and safety of adjuvant trastuzumab emtansine (n=743) vs adjuvant trastuzumab (n=743) in patients with HER2-positive eBC who had RID in the breast and/or axilla after receiving neoadjuvant chemotherapy containing a taxane and HER2-targeted therapy.

The primary outcome of the KATHERINE trial was invasive disease-free survival (IDFS), excluding second primary non-breast cancers, defined as the time from randomisation to the first occurrence of one of the following: ipsilateral invasive breast tumour recurrence, ipsilateral local-regional invasive breast cancer recurrence, distant recurrence, contralateral invasive breast cancer or death of any cause. The KATHERINE definition of IDFS excludes second primary non-breast cancer tumours, based on the US Food and Drug Administration's (FDA) recommended definition for a trial intended to support a regulatory filing. Inclusion of second primary non-breast cancer events in the IDFS definition has the disadvantage of including events not related to the cancer or the treatment under study, thereby potentially diluting any treatment effect. As the standardised definitions for efficacy endpoints (STEEP) criteria includes second primary non-breast cancer in the IDFS definition, this broader definition was included as a secondary outcome.

Results in the company submission (CS) are based on the primary efficacy analysis, which took place after 256 IDFS events had occurred. The clinical cut-off date for this analysis was 25 July 2018. One additional IDFS analysis, two additional interim overall survival (OS) analyses and a final OS analysis are planned in the future. The OS data were immature at the clinical cut-off date, with only 26.7% of the events required for the final analysis of OS having occurred (i.e. 98 deaths of the 367 deaths planned at the final OS analysis).

Overall, 212 (28.5%) patients discontinued treatment in the trastuzumab emtansine arm and 135 (18.2%) patients discontinued treatment in the trastuzumab arm. Specifically, 133 (17.9%) patients discontinued treatment due to adverse events (AEs) in the trastuzumab emtansine arm and 15 (2.0%) patients discontinued treatment due to AEs in the trastuzumab arm.

The KATHERINE study met its primary objective; trastuzumab emtansine reduced the risk of an IDFS event by 50% compared to trastuzumab (HR=0.50; 95% CI: 0.39–0.64; p<0.001). The OS analysis did not cross the early reporting boundary (HR=0.70, 95% CI: 0.47 to 1.05; p=0.0848). Three-year OS rates were 95.2% for the trastuzumab emtansine arm compared with 93.6% for trastuzumab).

AEs of any grade were more common in the trastuzumab emtansine arm than in the trastuzumab arm (98.8% vs 93.3%, respectively), as were AEs leading to discontinuation (18.0% vs 2.1%, respectively), although the majority of AEs observed were reversible and could be well managed according to the company. AEs of Grade 3 or higher were more common in the trastuzumab emtansine arm than in the trastuzumab arm (25.7% vs 15.4%, respectively). The most common AEs in either the trastuzumab emtansine arm or trastuzumab arm were fatigue (366 patients [49.5%] vs 243 patients [33.8%], respectively) and nausea (308 patients [41.6%] vs 94 patients [13.1%], respectively). Serious AEs (SAEs) occurred in 94 patients (12.7%) who received trastuzumab emtansine and 58 patients (8.1%) who received trastuzumab.

Results for node-positive patients and node-negative patients separately are reported in Appendix 2. As can been from Tables A2.1 and A2.2 (in Appendix 2), baseline demographic and disease characteristics in the two subgroups are mostly similar to those in the intention to treat (ITT) population. However, the node-negative population seems to include more patients from Western Europe, this applies to both arms of the trial. Most results for node-positive patients are missing, only IDFS was reported in CS (see Table A2.3). IDFS is slightly more favourable for trastuzumab emtansine in the node-negative population. Comparing results in the node-negative population (Table A2.4) with ITT results (Table 4.6), shows more favourable results for trastuzumab emtansine in the node-negative population for the outcomes IDFS (STEEP definition), disease-free survival (DFS) and distant recurrence-free interval (DRFI). However, OS was less favourable for trastuzumab emtansine in the node-negative population.

The company performed a Bucher indirect comparison using the KATHERINE study (trastuzumab emtansine vs trastuzumab) and the APHINITY study (pertuzumab + trastuzumab vs trastuzumab) for node-positive patients. Results for IDFS (HR=0.68 (95% CI: 0.46 to 0.99)), OS (HR=0.78 (95% CI: 0.43 to 1.39)) and DFS (95% CI: 0.71 (0.49 to 1.04)) favour trastuzumab emtansine over pertuzumab, but only IDFS showed a statistically significant difference. These results should be interpreted with caution, as they are based on an indirect comparison using data from two trials that included different populations: KATHERINE included pre-treated patients who had residual invasive disease (RID) and APHINITY included treatment naïve patients.

1.3 Summary of the key issues in the cost effectiveness evidence

Overall, the CS reported cost effectiveness searches were well presented and detailed response to questions regarding limitations and omissions were provided at clarification. The cost effectiveness searches were also used to identify health-related quality of life (HRQoL) studies. A range of databases and additional resources including conference proceedings, specialist and organisational websites were searched. Searches for HRQoL literature were reported as being conducted as part of the cost effectiveness searches. The ERG's concerns regarding the limitations of these searches is reported in Section 5.1.1. The cost effectiveness searches could have been improved by including additional word variants and indexing for the population and study design facets. As a consequence, the cost effectiveness searches may not have performed as well as intended. The ERG was concerned about the language bias of restricting searches to English language only as this is not in line with current best practice.

The cost and healthcare resource identification, measurement and valuation searches contained several incorrect indexing terms and were limited using a geographical filter; however, these issues may not have significantly impaired strategy performance.

The Evidence Review Group (ERG) raised their concerns regarding the choice of trastuzumab as the comparator for the economic analyses in the ITT population. According to the ERG, this comparator is inappropriate because it would imply that standard care for all patients is adjuvant trastuzumab, but this is not true: following TA569, pertuzumab + trastuzumab has been recommended for node-positive patients. TA569, therefore, implies that a whole population analysis (with a common comparator for all patients) is invalid. Subgroup analyses (with the correct comparators) were conducted separately by the company. However, subgroup-specific evidence was limited, which means more uncertainty in the subgroup analyses, and many of the assumptions made in the subgroup analyses were based on the evidence presented for the ITT population. These assumptions might not be valid for the specific subgroups and, more importantly, the subgroup analyses did not necessarily use the appropriate subgroup data from the KATHERINE trial. Additionally, the ERG considered that the methods used to model IDFS in the node-positive population were seriously flawed, which implies that the cost effectiveness analyses for the node-positive population are unreliable and, therefore, inappropriate for decision making. For these reasons, only the cost effectiveness results for the node-negative population were deemed appropriate (yet uncertain) by the ERG for the decision problem at hand and are the main focus of the cost effectiveness sections of the ERG report. For completeness, results for the ITT population and the node-positive subgroup are presented in appendices.

IDFS was one of the main aspects of modelling treatment effectiveness. Unlike the company, the ERG preferred a mixed modelling approach where Kaplan-Meier (KM) curves (up to time point where the last event was observed in each treatment arm) and long-term parametric extrapolations were used. The main reason for this choice was to predict in the model hazard ratios in line to those observed in KATHERINE.

The model fails to replicate the observed recurrence rates in the KATHERINE trial and to reproduce the drop in these rates observed at year 4 in the HERA and BCIRG 006 trials, regardless of whether this has a large impact on the model results or not. The ERG considers that trying to match the modelled long-term IDFS to observed long-term data (e.g. from HERA) would have been easier to implement and probably better approach. A potentially important caveat for this (and other aspects of the model like the duration of the treatment effect) is that the long-term data from HERA and BCIRG 006 were assumed to be a proxy for the KATHERINE ITT population only. Such a proxy for the node-negative subgroup was not available and, therefore, the IDFS adjustments made in the node-negative subgroup were based on ITT data, which might be incorrect, leading to biased results for the node-negative subgroup.

The ERG has concerns regarding the fit of the OS model predictions to the actual OS KM curves from the KATHERINE trial. Since the IDFS model extrapolation is expected to be in line with the IDFS KM curves, this mismatch in the OS curves suggests that the transition probabilities used in the post-IDFS health states might not be in line with the post-IDFS events in KATHERINE. Unfortunately, since OS KM data for the node-negative population were not provided, the ERG cannot investigate further the impact of this in its exploratory analyses.

For the node-positive subpopulation the main concern regarding IDFS modelling was that the populations in KATHERINE and APHINITY, the trials used for the indirect treatment comparison, are not really comparable and the outcomes from this analysis (the hazard ratios [HRs]) are likely to be biased. Furthermore, in the model the HR obtained from the indirect treatment comparison was applied to the IDFS extrapolation in the trastuzumab emtansine arm to derive IDFS data for the pertuzumab arm of the cost effectiveness model. However, the IDFS extrapolation in the trastuzumab emtansine arm of the model is based on the ITT population instead of the node-positive subpopulation. Consequently, the calculation of the IDFS data for the pertuzumab arm in the model is also incorrect. For these reasons, the ERG considers that modelling IDFS in the node-positive population is seriously flawed and the cost effectiveness analyses for the node-positive population inappropriate for decision making.

1.4 Summary of the ERG's preferred assumptions and resulting ICER

The ERG considered that only node-negative subpopulation analyses would be useful for decision making given the provided evidence. Therefore, the ERG analyses are focused on the node-negative subpopulation.

The ERG preferred changes to the company base-case for the node-negative subpopulation are described in Section 7.1.2 and summarised below:

1. IDFS modelled using KM curves from the KATHERINE node-negative population up to the time point where the last event was observed in each treatment arm and an exponential long-term extrapolation.
2. A waning of the trastuzumab emtansine treatment effect from month 36 to month 96 was assumed.
3. Treatment-specific utilities from KATHERINE for the IDFS health state.
4. Lidgren et al. utilities for the recurrence health-states.

The cost effectiveness results of the ERG preferred base-case are presented in Table 1.1. The implementation of the ERG preferred assumptions resulted in trastuzumab emtansine providing 0.95 additional quality adjusted life years (QALYs) at an incremental cost of [redacted]. The incremental cost

effectiveness ratio (ICER) was £9,339. The changes surrounding the IDFS extrapolation and the treatment effect duration had the largest impact. The incremental QALY gains for trastuzumab emtansine all stemmed from the IDFS health state. Incremental costs were highest in the IDFS health state, mostly due to the additional treatment costs of trastuzumab emtansine. However, approximately [redacted]% of these incremental costs were saved in the metastatic breast cancer (mBC) health states, which reduced the overall incremental cost.

Table 1.1: ICER resulting from ERG's preferred assumption (node-negative subpopulation)

Technologies	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER versus baseline (£/QALY)
Trastuzumab	[redacted]	16.76	[redacted]				
Trastuzumab emtansine	[redacted]	17.99	[redacted]	[redacted]	1.23	0.95	£9,339

Source: electronic model, updated from the response to the clarification letter.
Abbreviations: ICER = incremental cost effectiveness ratio; Incr. = incremental; QALYs = quality adjusted life years; LYG = life years gained

1.5 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG also conducted a probabilistic sensitivity analysis (PSA) using their preferred base-case assumptions. This resulted in an ICER of £9,845. This probabilistic ICER was approximately £500 higher than the deterministic ICER, due to slightly higher incremental costs and lower incremental QALYs. [redacted]. Additionally, [redacted]. The cost effectiveness acceptability curve (CEAC) shows that the probability that trastuzumab emtansine is cost effective at thresholds of £20,000 and £30,000 is 95.7% and 100% respectively.

The ERG conducted a series of additional scenario analyses in order to explore important areas of uncertainty in the model. These key uncertainties were related to the survival modelling (in terms of choice of parametric distributions, modelling of cure assumptions and duration of treatment effect), sources of utility data and cost and resource use assumptions. Other sources of uncertainty were deemed less important and were not explored in this section. The results of these analyses indicated that the ICER for the node-negative population was relatively sensitive to some of the assumptions tested by the ERG. In some scenarios, the ICER was increased by approximately 50%. However, all ICERs were below the common threshold of £20,000. The largest ICER (£15,057) was obtained in the scenario where a null treatment effect at 48 months was assumed. Only if some of the changes conducted in these scenarios were applied simultaneously, the ICER can be higher than £20,000 per QALY gained.

2. BACKGROUND

2.1 Introduction

In this report, the ERG provides a review of the evidence submitted by Roche in support of trastuzumab emtansine, trade name KADCYLA®, for patients with HER2-positive early breast cancer who have residual invasive disease in the breast and/or lymph nodes, after pre-operative systemic treatment. In this section, the ERG summarises and critiques the company's description of the underlying health problem and the company's overview of the current service provision. The information for this critique is taken from Document B of the company's submission (CS).[1]

2.2 Critique of company's description of the underlying health problem

The health problem at the focus of this appraisal is HER2-positive early breast cancer (eBC) who have residual invasive disease in the breast and/or lymph nodes. According to the CS, breast cancer is the most common type of cancer and the fourth most common cause of cancer death in the United Kingdom (UK).[2] Fourteen per cent of patients with eBC, in which the disease is localised to the breast or lymph nodes, have HER2-positive breast cancer.[3] In the response to clarification, the company noted the predicted total number of patients with HER2-positive eBC in England to increase from 6,768 in 2019 to 7,176 in 2024.[4] The overexpression of HER2 is associated with the development of a more aggressive form of the disease, which impacts prognosis.[5] The CS identified patients diagnosed with HER2-positive breast cancer are around five years younger than the average breast cancer population and are more likely to still be in work or have dependent children.[6]

The CS noted the impact of early breast cancer on health-related quality of life (HRQoL) among patients and their caregivers to be lower when compared to the general population.[1] UK patients with a progressed version of the disease were noted to experience poorer health utility scores when compared to eBC patients receiving HER2 therapy and chemotherapy.[7] The CS emphasised a higher number of patients with HER2-positive metastatic breast cancer were unable to work and experienced higher levels of activity impairment when compared to eBC.[7, 8] The company highlighted the need for addressing breast cancer while in the early stages in order to maximise the chance of a cure and improve quality of life and reduce economic burden.

ERG comment: The ERG considers the company to have provided an appropriate description of the underlying health problem of this appraisal.

2.3 Critique of company's overview of current service provision

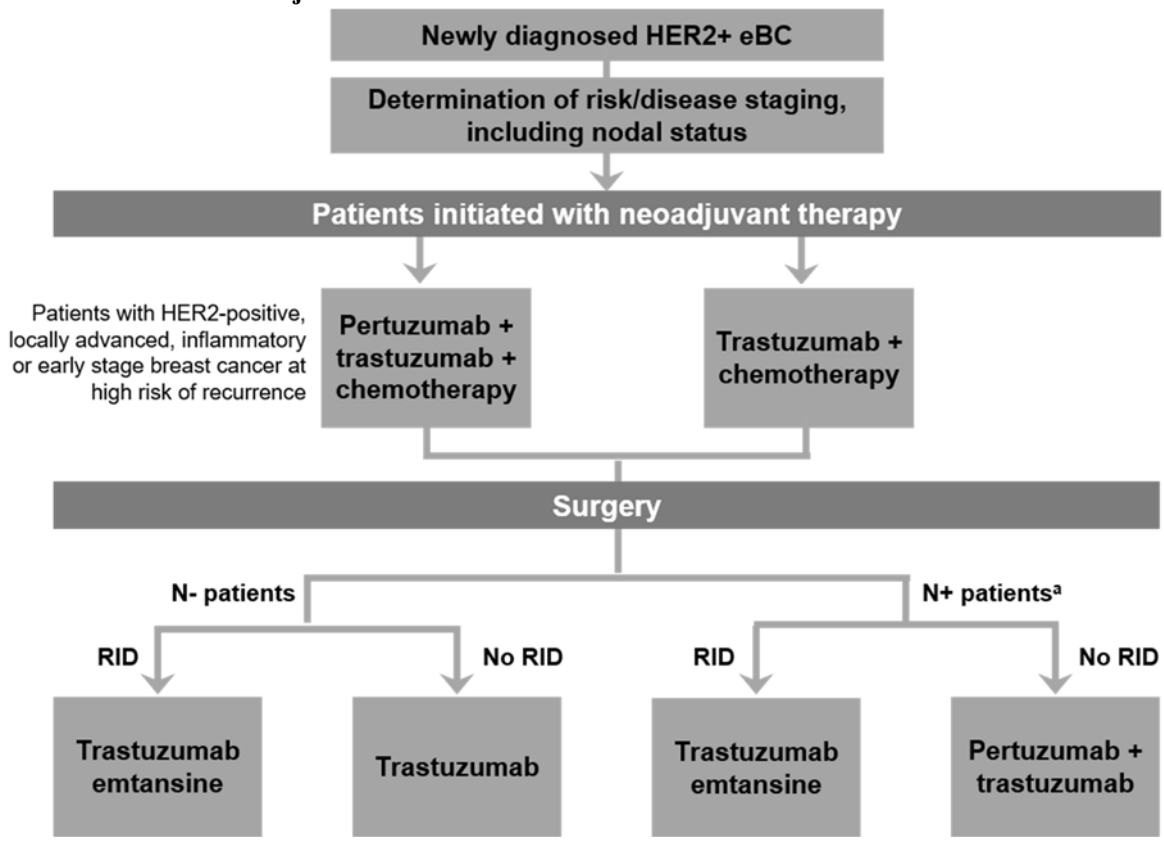
The current standard of care (SoC) for patients with HER2-positive eBC involves HER2-targeted therapy, chemotherapy, surgery, radiotherapy, and hormone therapy, depending on the tumour.[1] The CS noted the initiation of HER2-targeted neoadjuvant therapy as a method to reduce the size of the tumour prior to surgery and reduce the morbidity of surgery.[1] For patients who do not have a pathologically detected invasive tumour, pathological complete response (pCR) is achieved. In the event pCR is not achieved, the patients are determined to have residual invasive disease (RID). However, pCR rates can vary in accordance to the number of cycles of neoadjuvant treatment and types of chemotherapy regimens used.[1] Patients who develop RID after completing neoadjuvant therapy experience a poorer prognosis and higher rates of recurrence.[1]

The CS noted that patients with HER2-positive eBC who received neoadjuvant treatment and developed RID afterwards, represent a group at a greater risk of relapse when compared to patients who achieved pCR.[1, 9] According to the recommendations of NICE guideline NG101, patients with HER2-positive eBC should receive trastuzumab and chemotherapy in a neoadjuvant setting, and patients with HER2-

positive, locally advanced, inflammatory or early stage breast cancer with a high risk of recurrence, should receive pertuzumab in addition.[10, 11] Currently, patients in the UK who received neoadjuvant treatment and have RID at surgery will receive the same adjuvant treatment as those who achieved a pCR.

The proposed position in the treatment pathway is indicated in Figure 2.1. The CS emphasised the recommendation of trastuzumab emtansine for patients with HER2-positive eBC who have RID after a neoadjuvant treatment which included an HER2-targeted therapy was based on the results from the KATHERINE study. [1, 12-14] According to the company, this would provide an opportunity for patients to personalise adjuvant treatment for patients based on the tumour's response to neoadjuvant therapy.[1]

Figure 2.1: Anticipated positioning of trastuzumab emtansine, in patients with HER2-positive eBC initiated with neoadjuvant treatment



Source: CS, Figure 6, page 25.[1]

eBC = early breast cancer; HER2 = human epidermal growth factor receptor 2; N = node; RID = residual invasive disease

Note: a) Node-positive pre-surgery, or evidence of prior node-positivity (i.e. fibrosis) found at surgery.

ERG comment: The ERG had no further comment regarding the company's critique of service provision.

3. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 3.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
Population	Adults with HER2-positive eBC who have residual disease following neoadjuvant therapy containing a taxane (with or without anthracycline) and HER2-targeted therapy.	Adult patients with HER2-positive eBC who have RID, in the breast and/or lymph nodes, after pre-operative systemic treatment that included HER2-targeted therapy.	The patient population considered in this submission is slightly narrower than that specified in the final scope, which does not specify that a patient's residual disease must be invasive. The broader population specified in the final scope may include patients with DCIS, which would not be considered RID in most definitions of pCR. The population considered in this submission is in line with the pivotal clinical trial for trastuzumab emtansine in this indication, the KATHERINE trial, in which patients were required to have RID after neoadjuvant treatment, and with the anticipated marketing authorisation for the adjuvant use of trastuzumab emtansine.	The narrower population considered in the company submission is in line with the anticipated marketing authorisation for trastuzumab emtansine.
Intervention	Trastuzumab emtansine	Trastuzumab emtansine	N/A – in line with the NICE final scope.	The intervention is in line with the NICE scope
Comparator(s)	Standard adjuvant therapies including trastuzumab. For people with node-positive disease, pertuzumab in combination with trastuzumab and chemotherapy.	This submission compares trastuzumab emtansine with trastuzumab in terms of both clinical efficacy and cost effectiveness, as per the final scope.	Comparison against standard adjuvant therapies including trastuzumab: in line with the final scope. Comparison against pertuzumab in combination with trastuzumab and chemotherapy in people with node-positive disease: no statistically robust comparisons were possible for the	The comparators are in line with the NICE scope. However, the ERG does not agree that trastuzumab is a relevant comparator for the total population (see Section 3.3 below)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
		For people with node-positive disease, exploratory results of a naïve clinical efficacy comparison between trastuzumab emtansine and pertuzumab + trastuzumab + chemotherapy, based on a Bucher analysis, are presented in Appendix M. The corresponding economic analysis is presented in Section B.3 and Appendix M as a subgroup analysis.	clinical efficacy of these regimens. Exploratory results based on a Bucher analysis are presented in order to best address the decision problem in this appraisal. However, these analyses are not endorsed by the company because they are likely to lead to biased results and are not methodologically justified. The sizable limitations associated with the analyses mean that the results should be interpreted with caution. In terms of cost effectiveness, this comparison has been presented as a subgroup analysis.	The company refers to the Bucher as a 'naïve clinical efficacy comparison'. However, the term 'naïve comparison' is usually used for a comparison of single arms without a common comparator. In this case, there are two RCTs with a common comparator.
Outcomes	The outcome measures to be considered include: • Overall survival • Disease-free survival • Adverse effects of treatment • Health-related quality of life	The following outcomes have been included within this submission: • Invasive disease-free survival • Distant recurrence-free interval • Overall survival • Disease-free survival • Adverse effects of treatment • Health-related quality of life	Invasive disease-free survival was the primary outcome of the pivotal phase III study for adjuvant trastuzumab emtansine in this indication – the KATHERINE study. Distant recurrence-free interval was a secondary outcome of the KATHERINE study.	The outcomes reported are in line with the NICE scope
Economic analysis	• The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality adjusted life year.	• The cost effectiveness of trastuzumab emtansine vs the relevant comparators has been expressed in terms of incremental cost per quality	N/A – in line with the NICE final scope.	The cost effectiveness analyses were conducted according to the NICE reference case. However, as mentioned above, the ERG does not agree that trastuzumab is a relevant

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
	• The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. • Costs will be considered from an NHS and Personal Social Services perspective. • The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.	adjusted life year (QALY) gained. • A time horizon of 51 years has been chosen for the base-case, which is considered an appropriate duration over which to fully capture meaningful differences in costs and health outcomes between trastuzumab emtansine and the comparators. • All costs have been considered from an NHS and Personal Social Services perspective. • The PAS/commercial access agreements for adjuvant trastuzumab emtansine, trastuzumab and pertuzumab have been taken into account.		comparator for the total population (see Section 3.3 below).
Subgroups to be considered	If evidence allows, the following subgroups will be considered separately: • Prior neoadjuvant therapy including trastuzumab (with no prior pertuzumab therapy). • Prior neoadjuvant therapy including pertuzumab with trastuzumab.	The following subgroups have been considered in the clinical section of this submission: • Prior neoadjuvant therapy including trastuzumab (with no prior pertuzumab therapy). • Prior neoadjuvant therapy including pertuzumab with trastuzumab.	In the KATHERINE trial, the treatment effect of trastuzumab emtansine was consistent for patients who received prior neoadjuvant pertuzumab + trastuzumab + chemotherapy compared to patients who received trastuzumab + chemotherapy. No subgroup analysis was therefore conducted in the economic model based on whether patients received prior pertuzumab +	The ERG considers that trastuzumab is a relevant comparator for node-negative patients only (see Section 3.3 below). Patients with node-negative disease have also been included as a subgroup analysis of the economic model, as requested by the

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
		Patients with node-positive disease have also been included as a subgroup analysis of the economic model in Appendix M.	trastuzumab + chemotherapy or trastuzumab + chemotherapy. In the economic analysis, a subgroup analysis considering node-positive patients specifically was conducted to facilitate a comparison of adjuvant trastuzumab emtansine with pertuzumab + trastuzumab + chemotherapy in these patients.	ERG in the clarification letter.
Special considerations including issues related to equity or equality	None specified.	None identified.	N/A – in line with the NICE final scope.	

Source: CS, Table 1, pages 10-12.[1]

DCIS = ductal carcinoma in situ; eBC = early breast cancer; HER2 = human epidermal growth factor receptor 2; IDFS = invasive disease-free survival; N/A = not applicable; NHS = National Health Service; NICE = National Institute of Health and Care Excellence; PAS = patient access scheme; pCR = pathological complete response; QALY = quality adjusted life year; RID = residual invasive disease.

3.1 Population

The population defined in the scope is: Adults with HER2-positive early breast cancer who have residual disease following neoadjuvant therapy containing a taxane (with or without anthracycline) and HER2-targeted therapy.[15] The population in the CS is limited to 'Adult patients with HER2-positive eBC who have RID, in the breast and/or lymph nodes, after pre-operative systemic treatment that included HER2-targeted therapy'.[1]

According to the company the decision problem addressed in the company submission is slightly narrower than that specified in the final scope, which does not specify that a patient's residual disease must be invasive. The broader population specified in the final scope may include patients with DCIS, which would not be considered RID in most definitions of pCR (CS, Table 1, page 10).[1]

The population considered in the CS is in line with the clinical trial for trastuzumab emtansine in this indication, the KATHERINE trial, in which patients were required to have RID after neoadjuvant treatment, and with the anticipated marketing authorisation for the adjuvant use of trastuzumab emtansine (CS, Table 1, page 10).[1]

In 2013, a European marketing authorisation was granted for trastuzumab emtansine in HER2-positive, unresectable locally advanced or metastatic breast cancer after treatment with trastuzumab and a taxane, separately or in combination. On [redacted], the Committee for Medicinal Products for Human Use (CHMP) adopted an extension for early breast cancer (eBC) to the existing indication. As part of the Factual Error Cha, the company provided the following updated wording: trastuzumab emtansine, "as a single agent, is indicated for the adjuvant treatment of adult patients with HER2-positive early breast cancer who have residual invasive disease, in the breast and/or lymph nodes, after neoadjuvant taxane-based and HER2 targeted therapy".

3.2 Intervention

The intervention (trastuzumab emtansine) is in line with the scope.

Trastuzumab emtansine is administered as an intravenous (IV) infusion at 3.6 mg/kg of body weight every three weeks (21 days) (eBC and mBC). Patients should be treated for 14 cycles (eBC), or until disease progression or unacceptable toxicity (eBC and mBC). Management of symptomatic adverse reactions (including increased AST/ALTs, hyperbilirubinemia, thrombocytopenia, left ventricular dysfunction or peripheral neuropathy) may require temporary interruption, dose reduction, or treatment discontinuation of trastuzumab emtansine, as outlined in the summary of product characteristics (SmPC).[16]

According to the company, it is standard clinical practice to test the HER2 status of tumours at the point of diagnosis. As such, no additional tests are required prior to the administration of trastuzumab emtansine (CS, page 14).[1]

3.3 Comparators

The description of the comparators in the NICE scope is as follows: "Standard adjuvant therapies including trastuzumab. For people with node-positive disease: Pertuzumab in combination with trastuzumab and chemotherapy".[15]

The company interpreted this as, pertuzumab (P) is a comparator for node-positive disease only, while trastuzumab (T) is a comparator for the whole population. However, according to technology assessment (TA)-569, pertuzumab, with intravenous trastuzumab and chemotherapy, is recommended

for the adjuvant treatment of human epidermal growth factor receptor 2 (HER2)-positive early stage breast cancer in adults with lymph node-positive disease. In addition, the company's proposed use and positioning of adjuvant trastuzumab emtansine (see CS, Chapter B.1.3.5[1]) is to replace trastuzumab for node-negative patients with RID and to replace pertuzumab for node-positive patients with RID (see also Figure 2.1 of this report). This means that there is only one comparator for node-negative patients (trastuzumab), and only one comparator for node-positive patients (pertuzumab).

The company seems to confirm this in Appendix M of the company submission, where they state: "Patients with node-positive, HER2-positive eBC who are treated neoadjuvantly with pertuzumab + trastuzumab + chemotherapy can now continue treatment into the adjuvant setting to complete 18 cycles of pertuzumab + trastuzumab, and this continuation of treatment has become the SoC for patients with node-positive, HER2-positive eBC. Pertuzumab + trastuzumab is used in approximately 90–95% of these patients who are treated neoadjuvantly and continue anti-HER2 therapy post-surgery. This market share assumption was confirmed during the budget impact assessment in TA569 (adjuvant pertuzumab)" (CS, Appendix M, page 113).[17]

In the company submission, the company presented two types of analyses, one for the whole population (with T as the comparator) and one for node-positive disease only (with P as the comparator). The company did not provide a separate analysis for node-negative disease (with T as the comparator). Therefore, we asked the company to perform separate analyses for the node-negative population (Clarification letter, Questions A16 and B2).[4]

The company stated that the comparison against pertuzumab in combination with trastuzumab and chemotherapy in people with node-positive disease, based on an indirect comparison using a Bucher analysis, is not endorsed by the company because they are likely to lead to biased results and are not methodologically justified.[1]

ERG comment: While the ERG agrees that all indirect comparisons are potentially biased, a Bucher indirect analysis uses a common comparator which means that the comparison is based on the randomised treatment effect within each trial, however the trials must be clinically and methodologically similar. An indirect comparison can still provide results in the absence of direct head-to-head RCTs. The company's main concern regarding the indirect comparison seems to be the fact that the populations are different in the two trials (treatment naïve versus pre-treated patients); however, the company has not presented evidence that the relative effect of pertuzumab versus trastuzumab and the relative effect of trastuzumab emtansine versus trastuzumab is likely to be different in pre-treated and treatment-naïve patients. Therefore, we asked the company to provide published evidence or to provide expert opinion that there are likely to be differences (Clarification letter, Question A22).[4]

3.4 Outcomes

The NICE final scope lists the following outcome measures:

- Overall survival
- Disease-free survival
- Adverse effects of treatment
- Health-related quality of life.

These were all measured in the KATHERINE trial. In addition, invasive disease-free survival (IDFS) and distant recurrence-free interval were included as outcome measures.

The company used IDFS as the only outcome in the indirect comparison used for the comparison with pertuzumab in node-positive patients and as the main effectiveness outcome in the economic model. This was because it was the primary outcome in the KATHERINE trial.

Both outcomes, DFS and IDFS, are not uniquely defined. For DFS there are different definitions from the US Food and Drug Administration (FDA) and DATECAN[18] (Definition for the Assessment of Time-to-event Endpoints in CANcer trials); for IDFS there are different definitions from DATECAN and STEEP[19] (standardised definitions for efficacy end points in adjuvant breast cancer trials). Therefore, we asked the company to clarify which definitions were used for DFS and IDFS in the KATHERINE and APHINITY trials (Clarification letter, Question A12).[4] The response from the company is described in section 4.2.2 of this report (see Table 4.3).

3.5 Other relevant factors

According to the company, trastuzumab emtansine is innovative because it represents the first opportunity to achieve an as yet unrealised objective of neoadjuvant treatment: to adapt subsequent treatment on the basis of tumour response to neoadjuvant therapy (CS, Section B.2.12).[1]

A PAS is in place between the Department of Health and Roche Products Ltd. for trastuzumab emtansine. Trastuzumab emtansine is offered at a discount of [redacted].

This appraisal does not fulfil the end-of-life criteria as specified by NICE because the life expectancy of patients eligible for trastuzumab emtansine is well beyond 24 months. Therefore, treatment is not indicated for patients with a short life expectancy (normally less than 24 months).

According to the company, no equality issues related to the use of adjuvant trastuzumab emtansine for the treatment of adults with HER2-positive eBC have been identified or are foreseen (CS, Section B.1.4).[1]

4. CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

4.1.1 Searches

Appendix D of the CS details a systematic search of the literature used to identify clinical effectiveness literature undertaken on 30 November 2018, the search was updated (electronic databases and congress proceedings) on 5 June 2019. A summary of the sources searched is provided in Table 4.1. Revised searches were provided at clarification including additional details, the dates and resources recorded below are from the company submission, clarification response and clarification response appendix.[1, 4, 20, 21]

Table 4.1: Data sources for the clinical effectiveness systematic review

Search strategy element	Resource	Host/ source	Reported date range	Date searched
Electronic databases	Medline, Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Medline Daily and Versions	OVID	1946-2018/11/29 1946-2019/06/04	30.11.18 Update searches on 5.6.19
	Embase	OVID	1974-2018/11/29 1974-2019/06/04	30.11.18 Update searches on 5.6.19
	EBM Reviews – Cochrane Database of Systematic Reviews	OVID	2005-2018/11/21 2005-2019/05/31	30.11.18 Update searches on 5.6.19
	EBM Reviews – ACP Journal Club	OVID	1991-2018/10 1991-2019/05	30.11.18 Update searches on 5.6.19
	EBM Reviews – Database of Abstracts of Reviews of Effects	OVID	1st Quarter 2016 *Note DARE ceased 2015/03/31	30.11.18 Update searches on 5.6.19
	EBM Reviews – Cochrane Clinical Answers	OVID	November 2018 May 2019	30.11.18 Update searches on 5.6.19
	EBM Reviews – Cochrane Central Register of Controlled Trials	OVID	October 2018 April 2019	30.11.18 Update searches on 5.6.19
	EBM Reviews – Cochrane Methodology Register	OVID	3rd Quarter 2012 3rd Quarter 2012	30.11.18 Update searches on 5.6.19

Search strategy element	Resource	Host/ source	Reported date range	Date searched
	EBM Reviews – Health Technology Assessment	OVID	4th Quarter 2016 4th Quarter 2016	30.11.18 Update searches on 5.6.19
	EBM Reviews – NHS Economic Evaluation Database	OVID	1st Quarter 2016 *Note NHS EED ceased 2015/03/31	30.11.18 Update searches on 5.6.19
Trials registries	NCI Clinialtrials.gov		Not reported	21.6.19
	WHO ICTRP		Not reported	21.6.19
Conference proceedings	ASCO	Web link provided; no search terms reported	2016-2019	27.12.18 Update search on 17.6.19
	ESMO	Web links provided; no search terms reported	2016-2018	27.12.18
	AACR	Web links provided; no search terms reported	2016-2019	28.12.18 Update searches on 17.6.19
	San Antonio Breast Cancer Symposium (SABCS)	Web links provided; no search terms reported	2016-2018	27.12.18
	EBCC	Web links provided; no search terms reported	2016, 2018	28.12.18
	World Congress on Breast Cancer		Not reported, unclear whether this was searched	Not reported, unclear whether this was searched
	St Gallen International Breast Cancer Conference	Web links provided; no search terms reported	2017, 2019	28.12.18 Update searches on 17.6.19
HTA agencies	NICE	Web link & search terms reported	Not reported.	18.6.19
	SMC	Web link & search terms reported	Not reported.	18.6.19
	AWSMG	Web link & search terms reported	Not reported.	18.6.19
	PBAC	Web link & search terms reported	Not reported.	19.6.19

Search strategy element	Resource	Host/ source	Reported date range	Date searched
	CADTH, including pCODR	Web link & search terms reported	Not reported.	19.6.19
	HAS	Web link & search terms reported	Not reported.	19.6.19

Source: Appendix D of the Company's submission and the Appendix of the clarification response. [20, 21]
Reference lists of included articles, relevant SLRs and meta-analyses were scanned for further potentially relevant references.
Abbreviations: AACR = American Association for Cancer Research; ASCO = American Society of Clinical Oncology; EBCC = European Breast Cancer Conference; ESMO = European Society for Medical Oncology; SABCS = San Antonio Breast Cancer Symposium, SMC = Scottish Medicines Consortium; AWSMG = All Wales Medicines Strategy Group; PBAC = Pharmaceutical Benefits Advisory Committee; CADTH = Canadian Agency for Drugs and Technologies in Health; pCODR = pan-Canadian Oncology Drug Review; HAS = Haute Autorite de Sante.

ERG comments:

- The selection of databases searched was comprehensive, and following clarification, searches were on the whole clearly reported and reproducible. The database name, host and date searched were provided for most searches. An extensive range of resources additional to database searches was included in the SLR to identify further relevant studies and grey literature.
- It is unclear why the EBM Reviews - HTA search update search conducted on 30 November 2018 and updated on 5 June 2019, only included content from 4th Quarter 2016. The HTA database was maintained by the Centre of Reviews and Dissemination until 31 March 2018. The ERG does not have access to OVID EBM Reviews and was unable to check whether this was a reporting error. As no record was made of the results by each separate subset of the EBM Reviews suite of databases, it was not possible to discern how many potentially relevant HTA records were not retrieved.
- The ERG noted that both the Medline and Embase searches contained unwarranted explosion of MeSH and Emtree indexing terms within the Intervention facets. However, these repeated errors were not considered to be consequential, and did not impact on strategy recall.
- Search terms to identify RCTs in Medline and Embase were based on terms suggested by the Cochrane Handbook.[22, 23] The filters contained a combination of subject heading terms (MeSH and Emtree) and free text terms, and the ERG deemed them to be adequate.
- Separate adverse events (AE) searches were not performed. The clinical effectiveness searches incorporated a methodological filter intended to limit the search to RCT studies. Guidance by the Centre for Reviews and Dissemination (CRD)[24] recommends that if searches have been limited by a study design filter, additional searches should be undertaken to ensure that adverse events that are long-term, rare or unanticipated are not missed. The ERG considered that it was possible that some relevant evidence may not have been identified as a consequence of the study design limits used.
- A broad range of additional conference and organisational sources were searched, the web links were provided however search terms used were not reported in full detail.

4.1.2 Inclusion criteria

A brief overview of the systematic review is described in the main body of the CS, with further details provided in Appendix D.

A systematic review was performed to identify studies assessing the efficacy and safety outcomes associated with any licensed or investigational HER2-targeted pharmacological treatments in patients with early breast cancer and residual disease (defined as a non-pathological complete response (pCR)) after neoadjuvant chemotherapy that included HER2-targeted treatment. The eligibility criteria used to select relevant studies are presented in Table 4.2.

Overall, the focus of the systematic review was to identify randomised controlled trials (RCTs) aligned with the company's pivotal study, KATHERINE, in terms of trial design and enrolled patient population i.e. RCTs investigating HER2-targeted agents in the adjuvant setting in patients with HER2-positive eBC and residual disease after prior HER2-targeted therapy in the neoadjuvant setting. However, all RCTs investigating single or dual HER2-targeted agents with or without chemotherapy at any eBC treatment stage (neoadjuvant or adjuvant) were initially considered in the SLR.

Table 4.2: Eligibility criteria used in search strategy for RCT and non-RCT evidence

	Inclusion Criteria	Exclusion Criteria
Population	Patients with HER2-positiive eBC who have residual disease[a] following neoadjuvant treatment which included HER2-targted therapy + chemotherapy. To include patients with any hormone receptor, nodal, or menopausal status.	Patients with: • Non-HER2+ early breast cancer • HER2+ early breast cancer who do not have residual disease following neoadjuvant treatment • Advanced/metastatic breast cancer that has spread beyond the breast or the axillary lymph nodes • In-situ carcinoma only
Interventions	Licensed or investigational pharmacological interventions used in the adjuvant setting, including but not limited to: *HER2-targeted agents (single or dual)* • Pertuzumab; trastuzumab (subcutaneous or intravenous); trastuzumab emtansine; lapatinib; neratinib; afatinib *Chemotherapy (both anthracycline- and non-anthracycline-based chemotherapy) agents, as part of the HER2-targeted regimen:* • Capecitabine; carboplatin; cisplatin; cyclophosphamide; docetaxel; doxorubicin; pegylated doxorubicin; epirubicin; 5-fluorouracil; gemcitabine; methotrexate; paclitaxel / nab-paclitaxel; vinorelbine; vincristine No restriction on dose or regimen (sequential/concurrent use of treatments) or duration of treatment or formulation.	Studies where the investigational agent is solely: • Hormonal therapy • Surgery • Radiotherapy • Vaccine
Outcomes	To include, but not restricted to: *Efficacy:* • Invasive disease-free survival (IDFS) • IDFS including second non-breast cancers • Disease-free survival (DFS) • Distant disease-free survival (DDFS) • Event-free-survival (EFS)	Non-clinical outcomes, including: • Cost effectiveness • Cost/resource use • Epidemiology

	Inclusion Criteria	Exclusion Criteria
	• Progression-free survival (PFS) • Overall survival (OS) • Recurrence-free interval (RFI) • Distant recurrence-free interval (DRFI) • Response rates (complete response, partial response, stable disease) • Recurrence rates *Safety:* • All-grade adverse events (AE) of interest • Serious AE • Cardiac events *HRQoL:* • Measured using generic or disease-specific questionnaires	
Study design	RCTs, Phase II–IV, with no restriction on study design, or number of enrolled patients.	• Non-RCT clinical studies • Phase I dose-ranging studies • Observational studies • Case reports • Reviews • Editorials
Source: CS, Appendix D, Table 10[20] Notes: a) Presence of pathological invasive residual disease in the breast and/or axillary nodes. eBC = early breast cancer; H = trastuzumab; HER2 = human epidermal growth factor receptor-2; HRQoL = health-related quality of life; IDFS = invasive disease-free survival; LAP = lapatinib; NA = not applicable; PRO = patient reported outcome; RCT = randomised controlled trial.		

ERG comments: Studies were screened by a single reviewer and independently checked by a second reviewer, and any discrepancies were resolved by consensus. The ERG considers this to be inappropriate – a minimum of two reviewers should be independently involved in study selection, in line with Cochrane guidelines. Consequently, reviewer error and bias cannot be ruled out, and relevant studies may have been missed. However, the ERG is not aware of any relevant studies that have been missed.

4.1.3 Critique of data extraction

Data extraction was performed by one reviewer and checked by a second reviewer. This was considered appropriate.

Data were extracted as reported. No calculations were performed, e.g. if a percentage and denominator were reported for patients achieving an outcome of interest, the numerator was not calculated. This was considered inappropriate, as this potentially reduced the amount of relevant data that could be included in the economic modelling.

4.1.4 Quality assessment

Study quality was assessed using the eight-criteria checklist provided in Section 2.5 of the NICE single technology appraisal user guide.[25] This included:

1. Was the randomisation method adequate?

2. Was the allocation adequately concealed?
3. Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?
4. Were the care providers, participants and outcome assessors blind to treatment allocation (and if any of these people were not blind to treatment allocation, what might be the likely impact on the risk of bias (for each outcome))?
5. Were there any unexpected imbalances in drop-outs between groups (and if so, were they explained or adjusted for?)
6. Is there any evidence to suggest that the authors measured more outcomes than they reported?
7. Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
8. Consider whether the authors of the study publication declared any conflicts of interest.

ERG comments: Although this checklist does not represent a validated risk of bias assessment tool, many of the domains are similar to the Cochrane risk of bias for randomised controlled trials tool, and as such, this tool was considered appropriate. No information was provided on the number of reviewers involved in the quality assessment, and as such, reviewer error and bias could not be ruled out.

4.1.5 Evidence synthesis

The company identified one trial evaluating trastuzumab emtansine; as no further RCTs studying the efficacy and safety of trastuzumab emtansine as adjuvant treatment of HER2-positive eBC were found, no meta-analysis was conducted (CS, Chapter B.2.8, page 46).[1]

The company did perform a systematic review and feasibility assessment to explore the possibilities of comparing trastuzumab emtansine with pertuzumab + trastuzumab + chemotherapy for people with node-positive disease as per the final scope. This resulted in a Bucher indirect comparison using the KATHERINE study (trastuzumab emtansine vs trastuzumab) and the APHINITY study (pertuzumab + trastuzumab vs trastuzumab).

The feasibility assessment and Bucher indirect comparison will be discussed in sections 4.3 and 4.4 of this report.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

4.2.1 Included studies

The company identified one randomised controlled trial (RCT): the KATHERINE study, which evaluated the efficacy and safety of adjuvant trastuzumab emtansine (n=743) vs adjuvant trastuzumab (n=743) in patients with HER2-positive eBC who had RID in the breast and/or axilla after receiving neoadjuvant chemotherapy containing a taxane and HER2-targeted therapy.[26]

4.2.2 Methodology of the KATHERINE trial

The KATHERINE study is an ongoing, prospective, phase III, open-label, randomised, multicentre study to assess the efficacy and safety of adjuvant trastuzumab emtansine (n=743) compared with adjuvant trastuzumab (n=743) in patients with HER2-positive eBC who had RID in the breast and/or axillary lymph nodes at surgery, following neoadjuvant chemotherapy containing a taxane (with or without anthracycline) and trastuzumab ± a second HER2-targeted agent. Patients had to have completed at least six cycles (16 weeks) of neoadjuvant chemotherapy, containing a minimum of nine weeks of taxane-based therapy and nine weeks of trastuzumab (slightly shorter treatment durations were

permitted for dose-dense regimens).[26] The study included 71 patients from the UK (38/743 (5.1%) were randomised to trastuzumab emtansine and 33/743 (4.4%) were randomised to trastuzumab).

Patients were randomised 1:1 to treatment with either adjuvant trastuzumab emtansine or trastuzumab every three weeks for 14 cycles. Randomisation and treatment occurred within 12 weeks after surgery. Patients were stratified by clinical stage at presentation, hormone receptor status, neoadjuvant HER2-targeted therapy type and pathological nodal status after neoadjuvant therapy.[26]

The primary objective of the KATHERINE study was to compare IDFS (excluding second primary non-breast cancers) between the trastuzumab emtansine and trastuzumab treatment arms.[27] A summary of the methodology in the KATHERINE study is provided in Table 4.3.

Table 4.3: Summary of KATHERINE methodology

Trial name	KATHERINE (NCT01772472, von Minckwitz et al. 2019)[26]
Location	International: 273 sites across 28 countries, of which 14 were in the UK.
Trial design	Prospective, phase III, open-label, randomised, multicentre study.
Eligibility criteria for participants	A summary of key inclusion and exclusion criteria are provided below, with full details presented in Appendix L of the CS.[20] **Key inclusion criteria** • Histologically confirmed HER2-positive invasive breast cancer (stage T1–4/N0–3/M0 except T1a/bN0). o HER2-positivity was confirmed by a central laboratory. • Pathological evidence of RID in the breast and/or axillary lymph nodes following completion of taxane-based neoadjuvant therapy administered with trastuzumab ± additional HER2-targeted agents. o Patients must have completed ≥6 cycles (16 weeks) of neoadjuvant chemotherapy including ≥9 weeks of trastuzumab and ≥9 weeks of taxane-based therapy. • Surgical removal of all clinically evident disease in the breast and axillary lymph nodes. • Eastern Cooperative Oncology Group performance status (ECOG PS) 0–1. • LVEF ≥50% after neoadjuvant treatment and no decrease in LVEF by >15% from pre-neoadjuvant therapy LVEF. **Key exclusion criteria** • Stage IV (metastatic) breast cancer. • Gross residual disease remaining after mastectomy or positive margins after breast-conserving surgery. • Progressive disease during neoadjuvant therapy. • Cardiopulmonary dysfunction (heart failure of NYHA class II or higher or a history of a reduction in LVEF to <40% with previous therapy). • Current Grade ≥2 peripheral neuropathy (according to National Cancer Institute Common Terminology Criteria for Adverse Events, [NCI CTCAE]). • Any known active liver disease (e.g. due to hepatitis B virus [HBV], hepatitis C virus [HCV], autoimmune hepatic disorders or sclerosing cholangitis). • Treatment with anti-cancer investigational drugs within 28 days prior to commencing study treatment. • Exposure to cumulative doses of anthracyclines exceeding:

	○ Doxorubicin: 240 mg/m^2 ○ Epirubicin or liposomal doxorubicin-hydrochloride: 480 mg/m^2 ○ Other anthracyclines: exposure equivalent to doxorubicin >240 mg/m^2
Method of study drug administration	• Trastuzumab emtansine (3.6 mg/kg) and trastuzumab (6 mg/kg) were administered intravenously every 3 weeks for 14 cycles. • A loading dose of trastuzumab (8 mg/kg) was administered if it had been more than 6 weeks since the preceding dose.
Primary outcomes	IDFS (excluding second primary non-breast cancers), defined as the time from randomisation to the first occurrence of one of the following: ipsilateral invasive breast tumour recurrence, ipsilateral local-regional invasive breast cancer recurrence, distant recurrence, contralateral invasive breast cancer or death of any cause.
Secondary and other outcomes	A summary of the secondary outcomes is provided below: • IDFS (STEEP definition): defined as the time from randomisation to the first occurrence of one of the following: second primary non-breast cancer, ipsilateral invasive breast tumour recurrence, ipsilateral local-regional invasive breast cancer recurrence, distant recurrence, contralateral invasive breast cancer or death of any cause. • DFS, including non-invasive breast cancers: defined as the time from randomisation to first occurrence of an IDFS event including second primary non-breast cancer or contralateral or ipsilateral DCIS. • OS: defined as the time from randomisation to death of any cause. • DRFI: defined as the time from randomisation to date of distant breast cancer recurrence. • Incidence of cardiac events: defined as death from cardiac cause or severe chronic heart failure (NYHA Class III or IV). • Overall safety: defined as the incidence of AEs. • Patient reported outcomes (PROs): assessed using the EORTC QLQ-C30 and breast cancer specific (EORTC QLQ-BR23) questionnaires. Full details of domains assessed in the EORTC QLQ-C30 and EORTC QLQ-BR23 are presented in Appendix L.
Pre-planned subgroups	Subgroup analyses of IDFS were performed for randomisation stratification factors (underlined below) as well as other disease or patient related prognostic or predictive factors for the primary endpoint, as outlined below: • Hormone receptor status • Pathological nodal status after neoadjuvant therapy • Clinical stage at presentation • Neoadjuvant HER2-directed therapy type • Age • Race Subgroup analyses are planned based on the same factors for OS but have not been completed at this time.
Duration of study and follow-up	The study began on 3 April 2013, with a primary completion date of 25 July 2018 and an estimated study completion date of 4 April 2023. For the analysis included in this submission, median follow-up duration in the ITT population was 41.4 months (range 0.1–62.7) in the trastuzumab emtansine arm and 40.9 months (range 0.1–62.6) in the trastuzumab arm.

Source: CS, Section B.2.3.2, Table 7.[1]

AE = adverse event; CNS = central nervous system; DCIS = ductal carcinoma in situ; DFS = disease-free survival; DRFI = distant recurrence-free interval; ECOG PS = Eastern Cooperative Oncology Group

performance status; EORTC = European Organization for Research and Treatment of Cancer; FDA = food and drug administration; HBV = hepatitis B virus; HCV = hepatitis C virus; HER2 = human epidermal growth factor receptor 2; HIV = human immunodeficiency virus; HR = hazard ratio; IDFS = invasive disease-free survival; IHC = immunohistochemistry; ISH = in situ hybridisation; ITT = intention-to-treat; LVEF = left ventricular ejection fraction; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NYHA = New York Heart Association; OS = overall survival; QLQ-BR23 = Breast Cancer-Specific Quality of Life Questionnaire; STEEP = standardized definitions for efficacy endpoints; tpCR = total pathological complete response.

The primary outcome of the KATHERINE trial was IDFS (excluding second primary non-breast cancers), defined as the time from randomisation to the first occurrence of one of the following: ipsilateral invasive breast tumour recurrence, ipsilateral local-regional invasive breast cancer recurrence, distant recurrence, contralateral invasive breast cancer or death of any cause. The KATHERINE definition of IDFS excludes second primary non-breast cancer tumours, based on the US FDA's recommended definition for a trial intended to support a regulatory filing. Inclusion of second primary non-breast cancer events in the IDFS definition has the disadvantage of including events not related to the cancer or the treatment under study, thereby potentially diluting any treatment effect. As the STEEP criteria includes second primary non-breast cancer in the IDFS definition, this broader definition was included as a secondary outcome.

In the clarification letter the company was asked to clarify whether the definition for DFS in the KATHERINE study (CS, page 31: "DFS, including non-invasive breast cancers: defined as the time from randomisation to first occurrence of an IDFS event including second primary non-breast cancer or contralateral or ipsilateral DCIS") is in line with the FDA definition: "DFS is defined as the time from randomization until disease recurrence or death from any cause".[1] In addition, the company was asked to provide a table comparing the FDA definition and the Definition for the Assessment of Time-to-event Endpoints in CANcer trials (DATECAN) guidelines IDFS definition with definitions used in KATHERINE and APHINITY trials (see Table 4.4).

Table 4.4: Definitions of DFS and IDFS used in the KATHERINE and APHINITY trials

Trial	Invasive-disease–free survival (IDFS) definition	DFS definition
FDA Definition	Not defined	DFS is defined as the time from randomisation until disease recurrence or death from any cause
CANcer trial (DATECAN)[18]	Defined as including invasive ipsilateral breast tumour recurrence/progression, Local invasive recurrence/Progression, Regional invasive recurrence/progression (M+: regional progression), invasive contralateral breast cancer, Appearance/occurrence of metastasis/distant recurrence, second primary invasive cancer (non-breast cancer), Ipsilateral DCIS, Contralateral DCIS and death from breast cancer, non-breast cancer, related to protocol treatment, any cause and unknown cause.	As stated in the paper[18] DFS was deemed ambiguous and renamed by the experts as invasive DFS (IDFS).
KATHERINE	(STEEP DEFINITION – secondary endpoint)	Defined as the time from randomisation to first occurrence of an IDFS event including

Trial	Invasive-disease–free survival (IDFS) definition	DFS definition
	Defined as the time from randomisation to the first occurrence of one of the following: second primary non-breast cancer, ipsilateral invasive breast tumour recurrence, ipsilateral local-regional invasive breast cancer recurrence, distant recurrence, contralateral invasive breast cancer or death of any cause	second primary non-breast cancer or contralateral or ipsilateral DCIS
APHINITY	(STEEP DEFINITION – secondary endpoint) Defined as time from randomisation until the date of first occurrence of one of: recurrence of ipsilateral invasive breast tumour, recurrence of ipsilateral locoregional invasive disease, a distant disease recurrence, contralateral invasive BC, second primary non-breast cancers or death from any cause	Defined as time between randomisation and the date of the first occurrence of an IDFS event including second primary non-breast cancer event or contralateral or ipsilateral DCIS.
Source: Response to clarification letter, Question A12.[4]		

ERG comment: The KATHERINE trial and the APHINITY trial both used a modified IDFS definition for the primary outcome. This definition of IDFS excluded second primary non-breast cancer tumours, based on the US FDA's recommended definition for a trial intended to support a regulatory filing. Inclusion of second primary non-breast cancer events in the IDFS definition means that events not related to the cancer or the treatment under study are included, thereby potentially diluting any treatment effect. In addition, both trials used IDFS (based on the STEEP criteria) as a secondary outcome.

4.2.3 Baseline characteristics of the KATHERINE trial

Patient demographics and clinical characteristics of the patients enrolled in the KATHERINE study are presented in Table 4.5. According to the company, baseline characteristics were balanced between the two treatment arms,[27] and are consistent with those expected for the UK patient population with eBC.[1] Median age was 49 years, with a majority of participants under 65 years of age. Most patients (72.3%) had hormone receptor-positive disease, approximately 75% presented with operable disease, and just under half of patients were node-positive after neoadjuvant therapy. The majority of patients (76.9%) had received an anthracycline-containing neoadjuvant chemotherapy regimen, and 19.5% of patients had received a second HER2-targeted agent in addition to trastuzumab during neoadjuvant therapy.[26] In the majority of cases, the additional HER2-targeted agent was pertuzumab.[27]

Table 4.5: Baseline demographic and disease characteristics, KATHERINE – ITT population

Characteristics	Trastuzumab (N=743)	Trastuzumab emtansine (N=743)
Age, years		
Median (range)	49 (23–80)	49 (24–79)
Age group, n (%)		
<40	153 (20.6)	143 (19.2)
40–64	522 (70.3)	542 (72.9)
65–74	61 (8.2)	56 (7.5)

Characteristics	Trastuzumab (N=743)	Trastuzumab emtansine (N=743)
≥75	7 (0.9)	2 (0.3)
Region, n (%)		
North America	164 (22.1)	170 (22.9)
Western Europe	403 (54.2)	403 (54.2)
Rest of world	176 (23.7)	170 (22.9)
Race or ethnic group[a], n (%)		
American Indian[b] or Alaska Native	50 (6.7)	36 (4.8)
Asian	64 (8.6)	65 (8.7)
Black or African American	19 (2.6)	21 (2.8)
White	531 (71.5)	551 (74.2)
Multiple/Unknown/Other	79 (10.6)	70 (9.4)
Prior use of anthracycline, n (%)	564 (75.9)	579 (77.9)
Clinical stage at presentation, n (%)		
Inoperable (Stage T4 Nx M0 or Tx N2–3 M0)	190 (25.6)	185 (24.9)
Operable (Stages T1–3 N0–1 M0)	553 (74.4)	558 (75.1)
Hormone receptor status, n (%)		
ER-negative and PR-negative or status unknown	203 (27.3)	209 (28.1)
ER-positive, PR-positive, or both	540 (72.7)	534 (71.9)
Menopausal status at screening, n (%)		
Pre-menopausal	413 (55.6)	399 (53.7)
Post-menopausal	330 (44.4)	344 (46.3)
Neoadjuvant HER2-targeted therapy, n (%)		
Trastuzumab alone	596 (80.2)	600 (80.8)
Trastuzumab + pertuzumab	139 (18.7)	133 (17.9)
Trastuzumab + other HER2-targeted therapy[c]	8 (1.1)	10 (1.3)
Primary tumour stage (at definitive surgery), n (%)		
ypT0, ypT1a, ypT1b, ypT1mic, ypTis	306 (41.2)	331 (44.5)
ypT1[d]/ypT1c	184 (24.8)	175 (23.6)
ypT2	185 (24.9)	174 (23.4)
ypT3	57 (7.7)	51 (6.9)
ypT4, ypT4a, ypT4b, ypT4c	9 (1.2)	7 (0.9)
ypT4d	1 (0.1)	5 (0.7)
ypTX	1 (0.1)	0
Regional lymph node stage (at definitive surgery), n (%)		
ypN0	335 (45.1)	344 (46.3)
ypN1	213 (28.7)	220 (29.6)
ypN2	103 (13.9)	86 (11.6)
ypN3	30 (4.0)	37 (5.0)

Characteristics	Trastuzumab (N=743)	Trastuzumab emtansine (N=743)
ypNX[e]	62 (8.3)	56 (7.5)
Pathological nodal status evaluated after neoadjuvant therapy, n (%)		
Node-positive	346 (46.6)	343 (46.2)
Node-negative/not done	397 (53.4)	400 (53.8)
RID ≤1 cm and negative axillary lymph nodes (ypT1a, ypT1b, ypT1mic and ypN0)	161 (21.7)	170 (22.9)

Source: CS, Section B.2.3.3, Table 8.[1]
ER = oestrogen receptor; HER2 = human epidermal growth factor receptor 2; PR = progesterone receptor; RID = residual invasive disease.
Notes: Please note that staging at initial diagnosis refers to clinical staging, staging at definitive surgery refers to pathologic staging. a) Race or ethnic group was reported by the investigators. b) Includes North, Central and South American Indians. c) Other HER2-targeted agents were neratinib, dacomitinib, afatinib and lapatinib. d) Five patients had ypT1 disease without further sub-specification. e) If extensive axillary evaluation was done prior to neoadjuvant therapy or if sentinel lymph nodes were evaluated before neoadjuvant therapy and were found not to involve tumour or had only micro-metastases, further axillary evaluation was not required and the patient was classified as "not done" with respect to this variable.

4.2.4 Statistical analyses of the KATHERINE trial

The intention-to-treat (ITT) population (n=1,486), included all patients who were randomised to the trastuzumab emtansine (n=743) or trastuzumab (n=743) arms, regardless of whether they received any study treatment. Patients discontinuing trastuzumab emtansine and switching to trastuzumab were included in the ITT population.

The safety population (n=1,460) included all patients who received at least one dose of trastuzumab emtansine (n=740) or trastuzumab (n=720), patients receiving any dose of trastuzumab emtansine were included in the trastuzumab emtansine safety evaluable population, regardless of initial randomisation.

A summary of statistical analyses for the efficacy analyses is presented in Table 4.6.

Table 4.6: Summary of statistical analyses

Trial	KATHERINE
Hypothesis objective	• The primary objective of KATHERINE was to compare IDFS in patients with HER2-positive eBC and RID in the breast and/or axillary lymph nodes, after neoadjuvant chemotherapy and HER2-directed therapy including trastuzumab followed by surgery between the two treatment arms. • The null hypothesis for the primary objective was that the survival distributions of IDFS in the two treatment arms were the same. The alternative hypothesis was that the survival distributions of IDFS in the treatment and the control arm were different: o H0: $S_{\text{trastuzumab emtansine}} = S_{\text{trastuzumab}}$ o H1: $S_{\text{trastuzumab emtansine}} \neq S_{\text{trastuzumab}}$.
Statistical analysis	• A stratified log-rank test was initially planned to compare IDFS between the two treatment arms, with an unstratified log-rank test planned as a sensitivity analysis. However, as the smallest strata per arm contained fewer than five patients, the unstratified log-rank test was used for the primary analysis to compare IDFS

Trial	KATHERINE
	between the two treatment arms as robust stratified analyses could not be conducted. • The Kaplan-Meier approach was used to estimate 3-year IDFS rates and corresponding 95% CIs for each treatment arm. • A Cox proportional hazards model was used to estimate the HR between the two treatment arms (i.e. the magnitude of treatment effect) and its 95% CI. • Data from patients who did not have a documented event were censored at the date the patient was last known to be alive and event-free. • Secondary outcomes were analysed in a similar manner to estimate 3-year event rates for each treatment arm and the HR between arms with 95% CIs. • The final (event-driven) IDFS analysis is planned to be conducted when 384 invasive disease events have occurred. A single pre-specified interim analysis was also planned after approximately 67% of projected invasive disease events (~257) had occurred, with an early reporting boundary of HR<0.732 or p<0.0124 and an interim OS analysis planned if this boundary was crossed. o The overall two-sided type I error was controlled at 0.05 with the use of the Lan-DeMets alpha-spending function with an O'Brien-Fleming boundary. o The results of the interim IDFS analysis crossed the early reporting boundary for benefit of trastuzumab emtansine and are presented in the primary manuscript and in this submission. • The early reporting boundary for the first interim OS analysis (at the time of interim IDFS analysis) was set at p<0.0009 or observed HR<0.5826. • In addition to this first interim OS analysis triggered by the interim IDFS analysis crossing the early reporting boundary, two formal interim OS analyses and one final OS analysis are planned, with the overall two-sided type I error controlled at 0.05 with the use of the Lan-DeMets alpha-spending function with an O'Brien-Fleming boundary: o The second OS interim analysis will be conducted at the time of the final IDFS analysis, after approximately 5 years since enrolment of the first patient. o The third OS interim analysis will be conducted when ~279 deaths have occurred, approximately 2 years after the second OS interim analysis. o A final analysis when ~367 deaths have occurred, at the end of 10 years of follow up from the date of randomisation of the first patient.
Sample size, power calculation	• 384 invasive disease events and 1,484 patients were required for 80% power to detect a HR of 0.75 in IDFS with a two-sided significance level of 5%. o This would correspond to a 6.5% improvement in 3-year IDFS from 70.0% in the trastuzumab arm to 76.5% in the trastuzumab emtansine arm. • A sample size of 1,484 patients and approximately 10 years of follow-up from the date of randomisation of the first patient would provide 56% power to detect a HR of 0.80 in OS with a two-sided significance level of 5%. o This would correspond to a 2.8% improvement in 3-year OS from 85.0% in the trastuzumab arm to 87.8% in the trastuzumab emtansine arm.
Data management, patient withdrawals	• The investigator could discontinue a patient from a study drug or withdraw a patient from the study at any time and patients could voluntarily discontinue a study drug or withdraw from the study at any time, for any reason. • Patient withdrawal was defined within three scenarios: o Discontinuation from study drug: patients were asked to attend a study treatment completion/early termination visit and undergo follow-up assessments. The primary reason for early discontinuation was documented on the appropriate electronic case report form (eCRF), and patients were not

Trial	KATHERINE
	replaced. Patients who discontinued trastuzumab emtansine treatment prior to 14 cycles of study treatment could continue treatment with trastuzumab up to 14 cycles of HER2-directed treatment (unless discontinuation was due to trastuzumab-related toxicity), if considered appropriate by the investigator. o Withdrawal from the entire study: no further data were collected after the date of the patient's withdrawal from the study, but every effort was made to complete and report observations for the patient. The investigator had the responsibility to contact the patient or a legally authorised relative to complete a final evaluation and establish an explanation for the withdrawal. o Partial withdrawal from the study: all provisions regarding withdrawal from the entire study were applicable to partial withdrawal, except that the patient had to consent to be contacted for further information on recurrence as per the primary study outcome and survival status. Medical records were also reviewed for information on recurrence. It was documented in both the medical records and in the eCRF that the patient consented to be contacted for information on survival despite their withdrawal of informed consent. Information on AEs and concomitant medication was also collected during follow-up with these patients where possible. • If patients failed to attend scheduled visits, several attempts were made by the site to contact these patients for follow up information (i.e. at least three attempts within a reasonable amount of time). If contact was unsuccessful the patient's physician was contacted and asked to contact the patient or the patient's family to provide follow-up information. • If contact could not be established after sufficient attempts, the patient was declared "lost to follow-up".
Source: CS, Section B.2.4.1, Table 10.[1] CI = confidence interval; eCRF = electronic case report form; HER2 = human epidermal growth factor receptor 2; HR = hazard ratio; IDFS = invasive disease-free survival; ITT = intention-to-treat; OS = overall survival.	

The primary efficacy analysis took place after 256 IDFS events had occurred, in line with the pre-specified statistical analysis plan, because the early reporting boundary for the interim analysis was crossed. The clinical cut-off date for this analysis was 25 July 2018, at which point the median follow-up duration in the ITT population was 41.4 months (range 0.1–62.7) in the trastuzumab emtansine arm and 40.9 months (range 0.1–62.6) in the trastuzumab arm. The first interim analysis of OS was conducted at the same time, along with other analyses of safety and efficacy. The results from this first cut-off date are presented in the company submission.[1] According to the company, one additional IDFS analysis, two additional interim OS analyses and a final OS analysis are planned in the future.

According to the CS, the "second OS interim analysis will be conducted at the time of the final IDFS analysis, after approximately 5 years since enrolment of the first patient" (CS, Table 10).[1] The first patient was enrolled in April 2013 (CS, page 31); therefore, five years later would be April 2018. However, only the first interim analysis of OS is presented in the CS and the clinical cut-off date for this analysis was 25 July 2018. Therefore, the company was asked to clarify the dates of the analyses in the KATHERINE study. The company clarified that:

- The first interim OS analysis/interim IDFS analysis was on 25 July 2018.
- The second interim OS analysis/final IDFS analysis (per protocol after 384 IDFS events and 206 OS events) will be approximately Q2 2021.
- The third OS interim analysis (per protocol after 279 OS events) will be approximately Q2 2025.
- The final analysis (per protocol after 367 OS events) will be approximately Q1 2029.

However, as these analyses are event-driven, there is a degree of uncertainty surrounding these dates.

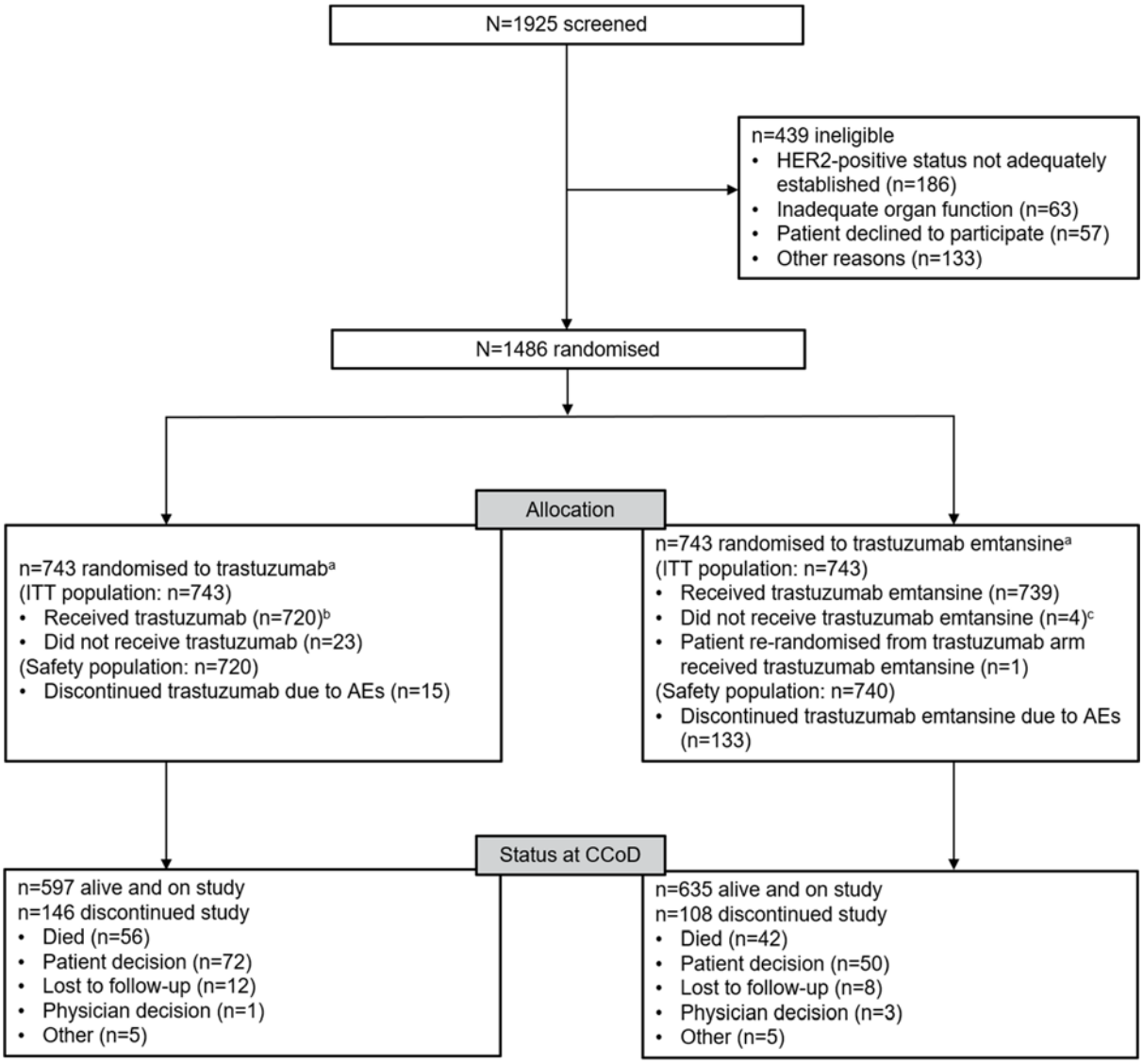
ERG comment: The main issue with the statistical analyses is that the OS data are currently immature, with only 26.7% of the events required for the final analysis of OS having occurred (i.e. 98 deaths of the 367 deaths planned at the final OS analysis).

4.2.5 Results of the KATHERINE trial

A total of 1,925 patients were screened, of whom 1,486 patients were randomised 1:1 to receive trastuzumab emtansine (n=743) or trastuzumab (n=743). Twenty-seven patients were randomised but did not receive their planned study medication (four in the trastuzumab emtansine arm, 23 in the trastuzumab arm).[1]

Overall, 212 (28.5%) patients discontinued treatment in the trastuzumab emtansine arm and 135 (18.2%) patients discontinued treatment in the trastuzumab arm. Specifically, 133 (17.9%) patients discontinued treatment due to AEs in the trastuzumab emtansine arm and 15 (2.0%) patients discontinued treatment due to AEs in the trastuzumab arm. Approximately half (n=71) of patients discontinuing treatment with trastuzumab emtansine went on to receive trastuzumab, of whom 63 completed a total of 14 cycles of HER2-targeted treatment. At follow-up, 635 patients in the trastuzumab emtansine arm were alive and on study, compared with 597 patients in the trastuzumab arm.[1] A CONSORT diagram of patient disposition is presented in Figure 4.1.

Figure 4.1: CONSORT diagram of patient flow during the KATHERINE trial



Source: CS, Appendix D, Figure 3.[20]

AE = adverse event; CCoD = clinical cut-off date; HER2 = human epidermal growth receptor 2; ITT = intention to treat.

Notes: a) One patient was randomised twice in error. The patient was first randomised to the trastuzumab arm but did not receive treatment. The patient was included in the trastuzumab ITT population. The patient was then randomised to the trastuzumab emtansine arm and treated with trastuzumab emtansine. The patient was thus included in the trastuzumab emtansine safety population (n=740) based on treatment actually received. One patient was randomized to trastuzumab but was administered 13 cycles of trastuzumab and one cycle of trastuzumab emtansine in error so was included in the trastuzumab emtansine safety population. One patient was randomised to trastuzumab emtansine but was administered nine cycles of trastuzumab in error and was thus included in the trastuzumab safety population. b) Three of these patients are being followed for disease recurrence and survival. c) Two of these patients are being followed for disease recurrence and survival.

The main results from the KATHERINE study are summarised in Table 4.7. Separate results for node-positive patients and node-negative patients are reported in Appendix 2 of this report.

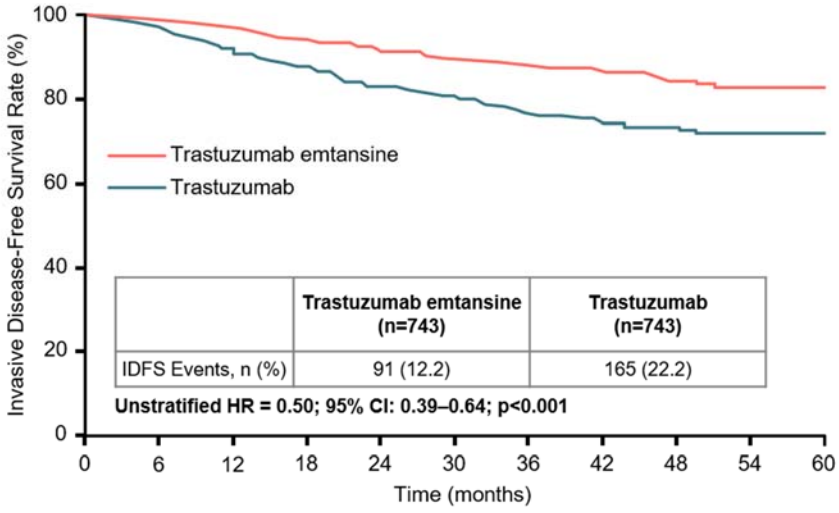
Table 4.7: Summary of results from the KATHERINE trial: ITT population – unstratified analyses[a]

Outcomes	Trastuzumab (N=743)	Trastuzumab emtansine (N=743)
IDFS		
Patients with an event, n (%)	165 (22.2)	91 (12.2)
3-year event-free rate, % (95% CI)	77.0 (73.8 to 80.3)	88.3 (85.8 to 90.7)
HR (95% CI)	0.50 (0.39 to 0.64)	
p-value (log-rank)	<0.001	
OS		
Patients with an event, n (%)	56 (7.5)	42 (5.7)
HR (95% CI)	0.70 (0.47 to 1.05)	
p-value (log-rank)[b]	0.0848	
IDFS (STEEP definition)		
Patients with an event, n (%)	167 (22.5)	95 (12.8)
3-year event-free rate, % (95% CI)	76.9 (73.7 to 80.1)	87.7 (85.2 to 90.2)
HR (95% CI)	0.51 (0.40 to 0.66)	
p-value (log-rank)	<0.0001	
DFS		
Patients with an event, n (%)	167 (22.5)	98 (13.2)
3-year event-free rate, % (95% CI)	76.9 (73.6 to 80.1)	87.4 (84.9 to 89.9)
HR (95% CI)	0.53 (0.41 to 0.68)	
p-value (log-rank)	<0.0001	
DRFI		
Patients with an event, n (%)	121 (16.3)	78 (10.5)
3-year event-free rate, % (95% CI)	83.0 (80.1 to 85.9)	89.7 (87.4 to 92.0)
HR (95% CI)	0.60 (0.45 to 0.79)	
p-value (log-rank)	0.0003	

Source: CS, Section B.2.6, pages 39-43.[1]
CI = confidence interval; DFS = disease-free survival; DRFI = distant recurrence-free interval; HR = hazard ratio; IDFS = invasive disease-free survival; OS = overall survival; STEEP = standardized definitions for efficacy endpoints.
Notes: [a]) No statistical adjustments were made for multiple comparisons. [b]) The boundary for statistical significance in this prespecified interim analysis was p<0.000032 or HR<0.43.

The KATHERINE study met its primary objective; trastuzumab emtansine reduced the risk of an IDFS event by 50% compared to trastuzumab (HR=0.50; 95% CI: 0.39 to 0.64; p<0.001, See Figure 4.2).

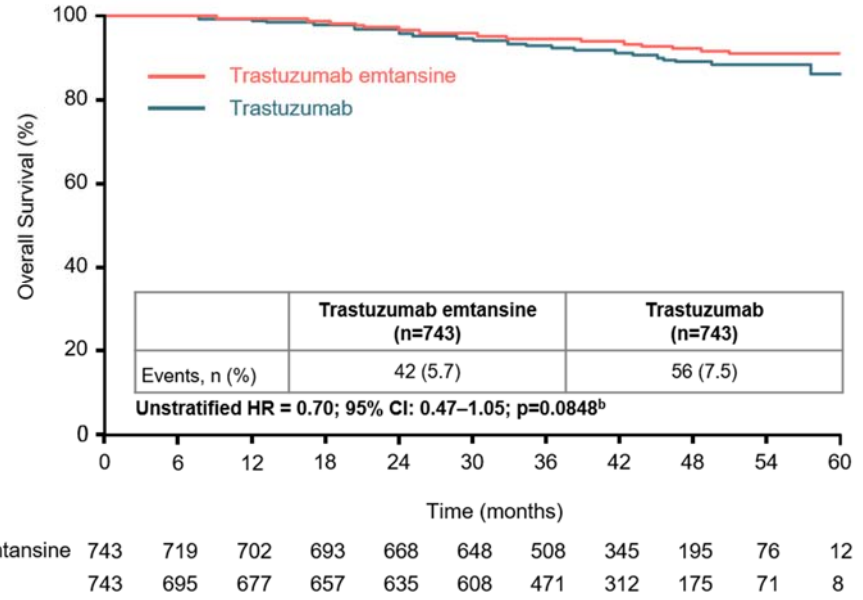
Figure 4.2: ITT primary endpoint analysis of IDFS



Source: CS, Section B.2.6.1, Figure 8.[1]
CI = confidence interval; HR = hazard ratio; IDFS = invasive disease-free survival; ITT = intention-to-treat.

The OS data were immature at the clinical cut-off date, with only 26.7% of the events required for the final analysis of OS having occurred (i.e. 98 deaths of the 367 deaths planned at the final OS analysis). The OS analysis did not cross the early reporting boundary (HR=0.70, 95% CI: 0.47 to 1.05; p=0.0848; See Figure 4.3). Three-year OS rates were 95.2% for the trastuzumab emtansine arm compared with 93.6% for trastuzumab.[1]

Figure 4.3: First interim analysis of OS[a]



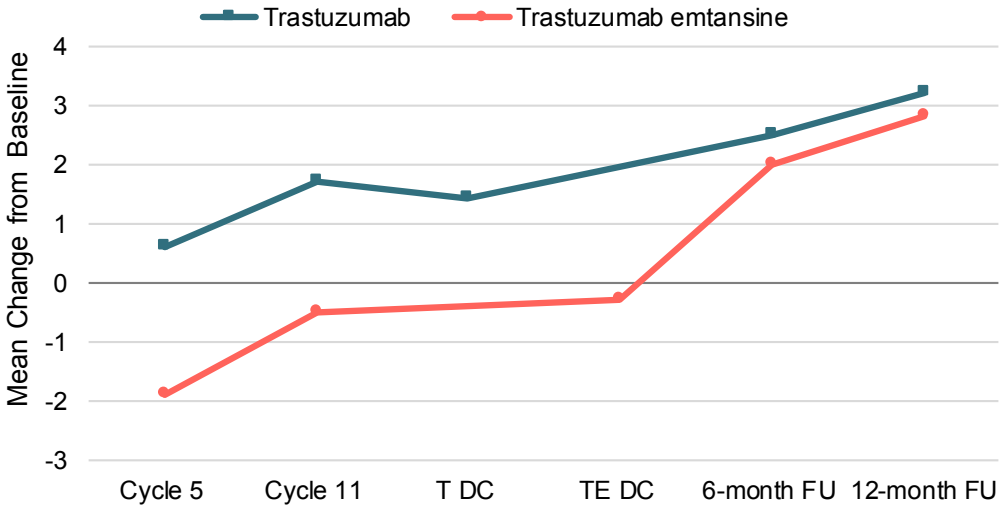
Source: CS, Section B.2.6.2, Figure 10.[1]
CI = confidence interval; HR = hazard ratio; IDFS = invasive disease-free survival; OS = overall survival.

Notes: a) Up to three formal interim OS analyses are planned, in addition to the final OS analysis. Data presented here represent the first interim OS analysis (98 OS events; conducted when ~384 IDFS events had occurred); a second interim OS analysis is planned at the time of final IDFS analysis, with a third when ~279 deaths have occurred, and a final OS analysis at the end of 10 years of follow-up, when ~367 deaths have occurred.
b) Boundary for statistical significance: HR<0.43 or p<0.000032.

Regarding health-related quality of life (HRQoL), mean population change from baseline scores on the EORTC QLQ-C30 and EORTC QLQ-BR23 were small and similar in each treatment arm, indicating no clinically meaningful improvement or deterioration over time and suggesting that baseline functioning and HRQoL levels were maintained over the course of treatment for both treatments.

Mean change over time from baseline in population scores for global health status (GHS) by treatment arm are shown in Figure 4.4.

Figure 4.4: Mean change from baseline over time in EORTC QLQ-C30 GHS



Source: CS, Figure 11, page 44.
DC = discontinuation; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; FU = follow up; GHS = global health status; T = trastuzumab; TE = trastuzumab emtansine.

4.2.6 Adverse events

AEs of any grade were more common in the trastuzumab emtansine arm than in the trastuzumab arm (98.8% vs 93.3%, respectively), as were AEs leading to discontinuation (18.0% vs 2.1%, respectively), although the majority of AEs observed were reversible and could be well managed according to the company.[1] AEs of Grade 3 or higher were more common in the trastuzumab emtansine arm than in the trastuzumab arm (25.7% vs 15.4%, respectively). A summary of all patients experiencing AEs in the KATHERINE study is presented in Table 4.8.

There was one death due to an AE (intracranial haemorrhage), in the trastuzumab emtansine arm.

Table 4.8: Safety summary

Event, n (%)	Trastuzumab (N=720)	Trastuzumab emtansine (N=740)
Any AE	672 (93.3)	731 (98.8)
Grade ≥3 AE	111 (15.4)	190 (25.7)
AE leading to death	0	1 (0.1)[a]

Event, n (%)	Trastuzumab (N=720)	Trastuzumab emtansine (N=740)
SAE	58 (8.1)	94 (12.7)
SAE related to study treatment	8 (1.1)	39 (5.3)
AE leading to discontinuation of trial drug	15 (2.1)	133 (18.0)

Source: CS, Section B.2.10.2, Table 16.[1]
AE = adverse event; SAE = serious adverse event.
Notes: [a]) One patient with a platelet count of 55,000 per cubic millimetre fell at home and died of an intracranial haemorrhage.

The most common AEs in either the trastuzumab emtansine arm or trastuzumab arm were fatigue (366 patients [49.5%] vs 243 patients [33.8%], respectively) and nausea (308 patients [41.6%] vs 94 patients [13.1%], respectively). An overview of all AEs of any grade occurring with an incidence of ≥10% in either treatment arm is presented in Table 4.9.

Table 4.9: All AEs of any grade occurring with incidence ≥10% in either treatment arm

MedDRA Preferred Term, n (%)	Trastuzumab (N=720)	Trastuzumab emtansine (N=740)
Any AE	672 (93.3)	731 (98.8)
Fatigue	243 (33.8)	366 (49.5)
Nausea	94 (13.1)	308 (41.6)
Platelet count decreased	17 (2.4)	211 (28.5)
AST increased	40 (5.6)	210 (28.4)
Headache	122 (16.9)	210 (28.4)
Arthralgia	148 (20.6)	192 (25.9)
Radiation skin injury	199 (27.6)	188 (25.4)
ALT increased	41 (5.7)	171 (23.1)
Epistaxis	25 (3.5)	159 (21.5)
Peripheral sensory neuropathy	50 (6.9)	138 (18.6)
Constipation	59 (8.2)	159 (21.5)
Myalgia	80 (11.1)	138 (18.6)
Vomiting	37 (5.1)	108 (14.6)
Insomnia	86 (11.9)	101 (13.6)
Cough	86 (11.9)	100 (13.5)
Dry mouth	9 (1.3)	100 (13.5)
Influenza-like illness	87 (12.1)	100 (13.5)
Hot flush	146 (20.3)	95 (12.8)
Pain	92 (12.8)	93 (12.6)
Diarrhoea	90 (12.5)	91 (12.3)
Pain in extremity	70 (9.7)	86 (11.6)
Stomatitis	27 (3.8)	80 (10.8)
Pyrexia	29 (4.0)	77 (10.4)
Anaemia	60 (8.3)	74 (10.0)

MedDRA Preferred Term, n (%)	Trastuzumab (N=720)	Trastuzumab emtansine (N=740)
Source: CS, Section B.2.10.2, Table 17.[1] AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; MedDRA = Medical Dictionary for Regulatory Activities.		

The most common AEs of Grade 3 or higher in the trastuzumab emtansine arm were a decreased platelet count and hypertension (42 patients [5.7%] and 15 patients [2.0%], respectively), and hypertension and radiation-related skin injury in the trastuzumab arm (nine patients [1.2%] and seven patients [1.0%], respectively) – see Table 4.10.

Table 4.10: AEs of Grade 3 or higher by treatment arm

Event, n (%)	Trastuzumab (N=720)	Trastuzumab emtansine (N=740)
Any Grade ≥3 AE	111 (15.4)	190 (25.7)
Decreased platelet count	2 (0.3)	42 (5.7)
Decreased neutrophil count	5 (0.7)	9 (1.2)
Radiation-related skin injury	7 (1.0)	10 (1.4)
Hypertension	9 (1.3)	15 (2.0)
Peripheral sensory neuropathy	0	10 (1.4)
Hypokalaemia	1 (0.1)	9 (1.2)
Fatigue	1 (0.1)	8 (1.1)
Anaemia	1 (0.1)	8 (1.1)
Source: CS, Section B.2.10.2, Table 17.[1] AE = adverse event.		

SAEs occurred in 94 patients (12.7%) who received trastuzumab emtansine and 58 patients (8.1%) who received trastuzumab. The total number of SAEs was 114 in the trastuzumab emtansine arm and 70 in the trastuzumab arm. A summary of SAEs occurring in ≥0.5% of patients in either the trastuzumab emtansine or the trastuzumab arm are shown in Table 4.11.

Table 4.11: Serious AEs occurring in ≥0.5% of patients in either treatment arm

MedDRA Preferred Term, n (%)	Trastuzumab (N=720)	Trastuzumab emtansine (N=740)
Mastitis	6 (0.8)	8 (1.1)
Device related infection	0	6 (0.8)
Platelet count decreased	0	10 (1.4)
Hypersensitivity	0	4 (0.5)
Source: CS, Section B.2.10.2, Table 17.[1] AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities.		

Selected AEs for additional analysis were chosen on the basis of prior experience with trastuzumab emtansine. As expected, a higher incidence of these selected AEs (thrombocytopenia, peripheral neuropathy, haemorrhage, hepatotoxicity, infusion-related reactions/hypersensitivity, and pulmonary toxicity) was observed in the trastuzumab emtansine arm than the trastuzumab arm (see CS, pages 60-62 for details).

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

In chapter B.2.9 of the CS,[1] the company described a systematic review and feasibility assessment to explore the possibilities of comparing trastuzumab emtansine with pertuzumab + trastuzumab + chemotherapy for people with node-positive disease as per the final scope.

Through their systematic literature review, the company identified 90 unique trials and 18 ongoing trials that met the criteria for inclusion in the review (see Table 4.2 above for the inclusion criteria). The included trials represent all studies investigating anti-HER2 agents in patients with HER2-positive eBC. Two of the 108 trials were classified as adjuvant trials, where patients had received anti-HER2 neoadjuvant therapy prior to surgery and randomisation (i.e. the same design as the KATHERINE trial). These were NCT03674112 and Peace 2017 which were both small phase II trials, one of which is still ongoing and one (Peace 2017) was only published as an abstract so there was a lack of data about the trial population. Neither trial measured IDFS which was the primary endpoint of KATHARINE and were not suitable for an indirect comparison (See CS, Chapter B.2.9.2, pages 48-52).[1]

ERG comment: The ERG agrees that these studies are not suitable for an indirect comparison.

The company then described why some of the more prominent trials (APHINITY, KRISTINE and BERENICE) cannot be used to inform an ITC of trastuzumab emtansine vs pertuzumab + trastuzumab in the adjuvant setting:

- APHINITY: The APHINITY study includes the intervention of interest for this ITC (pertuzumab + trastuzumab) and also measures the same primary outcome as the KATHERINE study (IDFS) in the treatment setting of interest (adjuvant treatment). However, the two trials include different study populations. KATHERINE participants were pre-treated with neoadjuvant HER2-targeted treatment + chemotherapy whereas patients in the APHINITY trial were treatment-naïve. This means that patient baseline risk was different across the studies.
- KRISTINE: The KRISTINE study is a randomised, open-label phase III trial investigating the safety and efficacy of trastuzumab + pertuzumab + chemotherapy vs trastuzumab emtansine + pertuzumab in the neoadjuvant treatment of HER2-positive eBC. Despite being a neoadjuvant study, data were also collected in the adjuvant setting as part of the follow-up period in this trial.
- BERENICE: BERENICE (NCT02132949) is a non-randomised, phase II, open-label study in patients with normal cardiac function. In the neoadjuvant period, cohort A patients received four cycles of dose-dense doxorubicin + cyclophosphamide, then 12 doses of standard paclitaxel plus four standard trastuzumab + pertuzumab cycles. In cohort B patients received four standard fluorouracil/epirubicin/ cyclophosphamide cycles, then four docetaxel cycles with four standard trastuzumab + pertuzumab cycles. Patients were assigned to the two different cohorts based on investigator choice.

ERG comment: The ERG agrees that the KRISTINE study (pertuzumab in both arms; therefore, no common comparator with the KATHERINE trial) and the BERENICE study (not randomised and no common comparator with the KATHERINE trial) cannot be used to inform a comparison of trastuzumab emtansine vs pertuzumab + trastuzumab in the adjuvant setting. However, the APHINITY study seems suitable for an indirect comparison, albeit with the limitations due to population differences.

The company concludes that a connected network, among trials with the same design as the KATHERINE study, was not feasible (CS, page 54-55).[1] However, the company acknowledges that

some form of comparison between trastuzumab emtansine and pertuzumab + trastuzumab in this setting must be presented and that despite the trial design and population differences, it was deemed most appropriate to use the APHINITY trial data to inform the comparison. The APHINITY study was judged to be most appropriate since it includes a large sample size, the comparator of interest (pertuzumab + trastuzumab), and the same primary outcome as the KATHERINE study (IDFS). Please see Table 4.12 for baseline demographic and disease characteristics of the KATHERINE and APHINITY trials. A Bucher ITC was performed by the company.

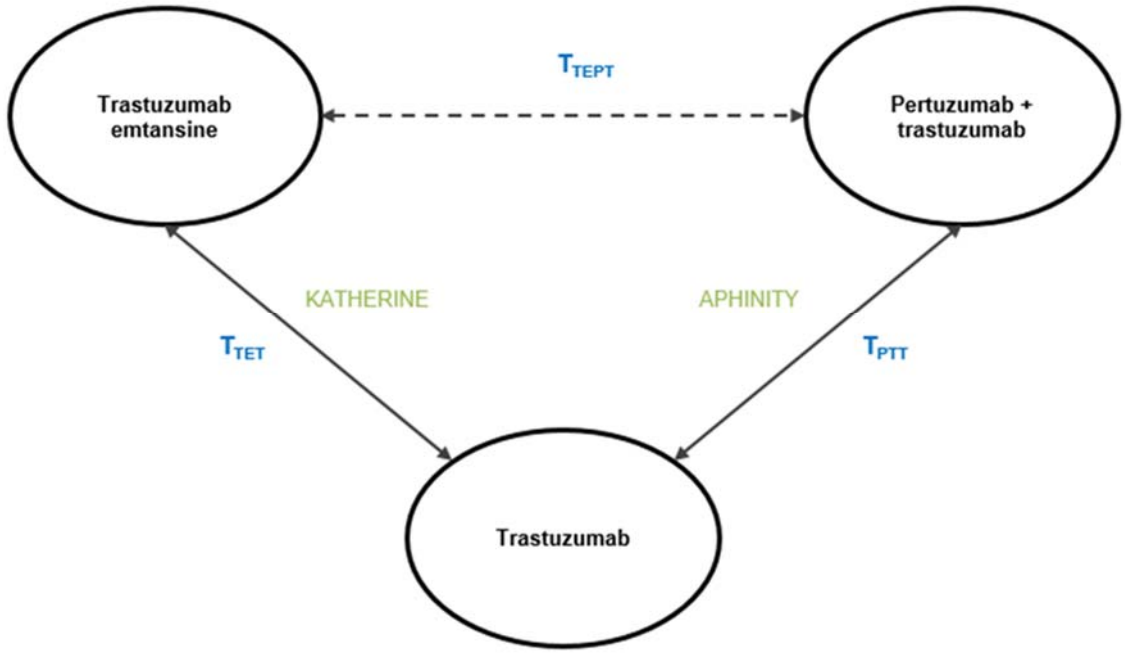
The company states that "These analyses are not endorsed by the company because they are likely to lead to biased results and are not methodologically justified. The exploratory analyses have simply been provided in order to best address the Decision Problem in this appraisal. The sizable limitations associated with the analyses mean that the results should be interpreted with caution" (CS page 55).[1]

ERG comment: The ERG agrees that the populations in the two trials are different. However, the ERG is not convinced that this leads to biased results as it depends whether previous treatment is a treatment effect modifier (i.e. whether the treatment effect is different based on whether or not the participants were pre-treated with neoadjuvant HER2-targeted treatment plus chemotherapy). It is unclear whether the relative effect of pertuzumab versus trastuzumab and the relative effect of trastuzumab emtansine versus trastuzumab is different in pre-treated and treatment-naïve patients. Therefore, we asked the company to provide published evidence; or, in the absence of published evidence, to provide expert opinion that the relative effects will be different (See Response to Clarification, Question A22). The company provided expert statements from three clinicians, all stating that the populations in the two trials are different. However, how these differences will influence the relative effectiveness of trastuzumab emtansine versus pertuzumab is unclear. Therefore, in conclusion, it seems fair to say that the indirect comparison trastuzumab emtansine versus pertuzumab may be biased; however, it is unclear in what direction or to what extend there is a bias. Given the available evidence, the indirect comparison presented by the company seems the best estimate of the relative effectiveness of trastuzumab emtansine versus pertuzumab.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

The company performed a Bucher indirect comparison using the KATHERINE study (trastuzumab emtansine vs trastuzumab) and the APHINITY study (pertuzumab + trastuzumab vs trastuzumab) (see Figure 4.5).

Figure 4.5: Indirect treatment comparison



Source: CS, Appendix M, Figure 8.
TPTT = treatment effect pertuzumab + trastuzumab vs trastuzumab; TTEPT = treatment effect of trastuzumab emtansine vs pertuzumab + trastuzumab; TTET = treatment effect of trastuzumab emtansine vs trastuzumab.

Patient demographics and clinical characteristics of the patients enrolled in the KATHERINE and APHINITY studies are presented in Table 4.12. The main difference between the two trial populations was that patients in the KATHERINE study were pre-treated with neoadjuvant HER2-targeted treatment + chemotherapy whereas patients in the APHINITY trial were treatment-naïve. In addition, patients included in the KATHERINE study were only those who did not achieve a pCR following neoadjuvant treatment, and therefore had RID in the breast and/or axillary lymph nodes. APHINITY also evaluated 18 cycles of adjuvant treatment compared to 14 cycles in KATHERINE.

In terms of age, race, hormone receptor status, and menopausal status at screening the two trial populations were reasonably similar; although, the APHINITY study included more Asian patients (26%) than the KATHERINE study (9%).

Table 4.12: Baseline demographic and disease characteristics, KATHERINE & APHINITY – Node-positive populations

	KATHERINE		APHINITY	
Characteristics	**Trastuzumab (N=346)**	**Trastuzumab emtansine (N=343)**	**Pertuzumab + Trastuzumab + Chemotherapy(N=1503)**	**Placebo + Trastuzumab + Chemotherapy (N=1502)**
Age, years				
Median (range)	49 (27–78)	49 (25–79)	51 (24-86)	51 (19-85)
Age group[f], n (%)				
<40	70 (20.2)	55 (16.0)	222 (14.8)	209 (13.9
40–64	246 (71.1)	258 (75.2)	1097 (72.9)	1122 (74.7)
65–74	28 (8.1)	28 (8.2)	162 (10.8)	152 (10.1)
≥75	2 (0.6)	2 (0.6)	22 (1.5)	19 (1.3)
Region, n (%)				
North America	81 (23.4)	92 (26.8)	NR	NR
Western Europe	168 (48.6)	160 (46.6)	NR	NR
Rest of world	97 (28.0)	91 (26.5)	NR	NR
Race or ethnic group[a], n (%)				
American Indian[b] or Alaska Native	30 (8.7)	19 (5.5)	--	--
Asian	31 (9.0)	33 (9.6)	390 (26.0)	393 (26.2)
Black or African American	14 (4.0)	10 (2.9)	21 (1.4)	24 (1.6)
White	241 (69.7)	248 (72.3)	1045 (69.7)	1041 (69.4)
Multiple/Unknown/Other	30 (8.7)	33 (9.6)	44 (2.9)	43 (2.9)
Prior use of anthracycline, n (%)	253 (73.1)	261 (76.1)	1216 (80.9)*	1219 (81.2)*
Clinical stage at presentation, n (%)				
Inoperable (Stage T4 Nx M0 or Tx N2–3 M0)	NR	NR	NR	NR
Operable (Stages T1–3 N0–1 M0)	NR	NR	NR	NR

	KATHERINE		APHINITY	
Characteristics	**Trastuzumab (N=346)**	**Trastuzumab emtansine (N=343)**	**Pertuzumab + Trastuzumab + Chemotherapy(N=1503)**	**Placebo + Trastuzumab + Chemotherapy (N=1502)**
Hormone receptor status, n (%)				
ER-negative and PR-negative or status unknown	104 (30.1)	102 (29.7)	556 (37.0)	537 (35.8)
ER-positive, PR-positive, or both	242 (69.9)	241 (70.3)	947 (63.0)	965 (64.2)
Menopausal status at screening, n (%)				
Pre-menopausal	186 (53.8)	187 (54.5)	760 (50.6)	759 (50.7)
Post-menopausal	160 (46.2)	156 (45.5)	740 (49.3)	736 (49.2)
Neoadjuvant HER2-targeted therapy, n (%)				
Trastuzumab alone	278 (80.3)	277 (80.8)	NR	NR
Trastuzumab + pertuzumab	68 (19.7)	66 (19.2)	NR	NR
Trastuzumab + other HER2-targeted therapy[c]			NR	NR
Primary tumour stage (at definitive surgery), n (%)				
ypT0, ypT1a, ypT1b, ypT1mic, ypTis	125 (36.1)	131 (38.2)	NR	NR
ypT1[d]/ypT1c	68 (19.7)	65 (19.0)	NR	NR
ypT2	100 (28.9)	101 (29.4)	NR	NR
ypT3	43 (12.4)	36 (10.5)	NR	NR
ypT4, ypT4a, ypT4b, ypT4c	8 (2.3)	6 (1.7)	NR	NR
ypT4d	1 (0.3)	4 (1.2)	NR	NR
ypTX	1 (0.3)	0	NR	NR
Regional lymph node stage (at definitive surgery), n (%)				
ypN0	--	--	NR	NR
ypN1	213 (61.6)	220 (64.1)	NR	NR
ypN2	103 (29.8)	86 (25.1)	NR	NR

	KATHERINE		APHINITY	
Characteristics	**Trastuzumab (N=346)**	**Trastuzumab emtansine (N=343)**	**Pertuzumab + Trastuzumab + Chemotherapy(N=1503)**	**Placebo + Trastuzumab + Chemotherapy (N=1502)**
ypN3	30 (8.7)	37 (10.8)	NR	NR
ypNX[e]	--	--	NR	NR
Pathological nodal status evaluated after neoadjuvant therapy, n (%)				
Node-positive	NR	NR	NR	NR
Node-negative/not done	NR	NR	NR	NR
RID ≤1 cm and negative axillary lymph nodes (ypT1a, ypT1b, ypT1mic and ypN0)	NR	NR	NR	NR

Source: Response to Clarification, Question A15.[4]

ER = oestrogen receptor; HER2 = human epidermal growth factor receptor 2; PR = progesterone receptor; RID = residual invasive disease.

Notes: Please note that staging at initial diagnosis refers to clinical staging, staging at definitive surgery refers to pathologic staging. a) Race or ethnic group was reported by the investigators. b) Includes North, Central and South American Indians. c) Other HER2-targeted agents were neratinib, dacomitinib, afatinib and lapatinib. d) Five patients had ypT1 disease without further sub-specification. e) If extensive axillary evaluation was done prior to neoadjuvant therapy or if sentinel lymph nodes were evaluated before neoadjuvant therapy and were found not to involve tumour or had only micro-metastases, further axillary evaluation was not required and the patient was classified as "not done" with respect to this variable. f) In Aphinity, the age groups are: <35, 35-39, 40-49, 50-64, 65-74 and ≥75. *) Adjuvant chemotherapy regimen (randomised).

The company compared trastuzumab emtansine with pertuzumab + trastuzumab using a Bucher analysis. The analysis used the log HR from the KATHERINE and APHINITY trials; the calculation of the treatment effect and corresponding standard error (SE) are shown below:

Equation 1. Derivation of log hazard ratio using Bucher method: $T_{TEPT} = T_{TET} - T_{PTT}$

Equation 2. Derivation of standard error of log hazard ratio: $SE(T_{TEPT}) = \sqrt{(SE(T_{TET})^2 + (SE(T_{PTT})^2)}$

The company conducted analyses using HRs from different subgroups in the APHINITY and KATHERINE trials:

- Scenario A – Uses the HR from the node-positive subgroup of the APHINITY population and the HR from the node-positive subgroup of the KATHERINE population.
- Scenario B – Uses the HR from the node-positive subgroup of the APHINITY population and the HR from the ITT population of the KATHERINE trial.
- Scenario C – Uses the ITT populations from both trials.

As the comparison of trastuzumab emtansine versus pertuzumab + trastuzumab is only relevant for node-positive disease, the ERG considers scenario A only to be relevant for this appraisal. The company provided indirect comparison results for one outcome: IDFS. In the clarification response the company provided results for the following outcomes: OS, DFS, and decrease in platelet count.[4] There was a high degree of variability in the result of the Bucher analysis for decrease in platelet count, resulting in an uninformative odds ratio (OR=113.05 (95% CI: 5.52 to 2316.24)). This was principally due to there being zero events in the trastuzumab arm of the KATHERINE study. As reported in section 4.2.2 of this report, the definition of IDFS excluded second primary non-breast cancer tumours. Inclusion of second primary non-breast cancer events in the IDFS definition means that events not related to the cancer or the treatment under study are included. Results for IDFS, OS and DFS are presented in Table 4.13.

Table 4.13: Hazard ratios from Bucher analysis

Outcome	APHINITY (TP vs T)	KATHERINE (TE vs T)	ITC (TE vs TP)
	HR (95% CI)	HR (95% CI)	HR (95% CI)
IDFS	0.77 (0.62–0.96)	0.52 (0.38–0.71)	0.68 (0.46–0.99)
OS	0.85 (0.61-1.18)	0.66 (0.41-1.06)	0.78 (0.43-1.39)
DFS	0.77 (0.62-0.95)	0.55 (0.40-0.75)	0.71 (0.49-1.04)

Source: CS, Appendix M, Table 37 and Response to Clarification, Question A21A.[1, 4, 20]
CI = confidence interval; HR = hazard ratio; ITC = indirect treatment comparison; ITT = intention to treat; T = trastuzumab; TE = trastuzumab emtansine; TP = trastuzumab plus pertuzumab.

ERG comments: As pointed out by the company, these results should be interpreted with caution, as they are based on an indirect comparison using data from two trials that included different populations: KATHERINE included pre-treated patients who had residual invasive disease (RID) and APHINITY included treatment naïve patients. In conclusion, it seems fair to say that the indirect comparison trastuzumab emtansine versus pertuzumab may be biased; however, it is unclear in what direction or to what extend there is a bias. Given the available evidence, the indirect comparison presented by the company seems the best estimate of the relative effectiveness of trastuzumab emtansine versus pertuzumab.

4.5 Additional work on clinical effectiveness undertaken by the ERG

No further additional work was undertaken by the ERG.

4.6 Conclusions of the clinical effectiveness section

The NICE scope mentions two comparators: trastuzumab and pertuzumab (for people with node-positive disease). The company interpreted this as, pertuzumab is a comparator for node-positive disease only, while trastuzumab is a comparator for the whole population. However, according to technology assessment (TA)-569, pertuzumab, with intravenous trastuzumab and chemotherapy, is recommended for the adjuvant treatment of human epidermal growth factor receptor 2 (HER2)-positive early stage breast cancer in adults with lymph node-positive disease. In addition, the company's proposed use and positioning of adjuvant trastuzumab emtansine (see CS, Chapter B.1.3.5) is as an alternative for trastuzumab in node-negative patients with RID and as an alternative for pertuzumab in node-positive patients with RID (see also Figure 2.1 of this report). This means that there is only one comparator for node-negative patients (trastuzumab), and only one comparator for node-positive patients (pertuzumab). In the company submission, the company presented two types of analyses, one for the whole population (with trastuzumab as the comparator) and one for node-positive disease only (with pertuzumab as the comparator). The company did not provide a separate analysis for node-negative disease (with trastuzumab as the comparator) in their original submission. Therefore, the ERG requested these data as part of the clarification letter.

In this ERG report, baseline characteristics and results for the two subgroups, patients with node-positive disease and patients with node-negative disease, are presented in Appendix 2.

The company identified one randomised controlled trial (RCT): the KATHERINE study, which evaluated the efficacy and safety of adjuvant trastuzumab emtansine (n=743) vs adjuvant trastuzumab (n=743) in patients with HER2-positive eBC who had RID in the breast and/or axilla after receiving neoadjuvant chemotherapy containing a taxane and HER2-targeted therapy.

The primary outcome of the KATHERINE trial was IDFS (excluding second primary non-breast cancers), defined as the time from randomisation to the first occurrence of one of the following: ipsilateral invasive breast tumour recurrence, ipsilateral local-regional invasive breast cancer recurrence, distant recurrence, contralateral invasive breast cancer or death of any cause. The KATHERINE definition of IDFS excludes second primary non-breast cancer tumours, based on the US FDA's recommended definition for a trial intended to support a regulatory filing. Inclusion of second primary non-breast cancer events in the IDFS definition has the disadvantage of including events not related to the cancer or the treatment under study, thereby potentially diluting any treatment effect. As the STEEP criteria includes second primary non-breast cancer in the IDFS definition, this broader definition was included as a secondary outcome.

Results in the CS are based on the primary efficacy analysis, which took place after 256 IDFS events had occurred. The clinical cut-off date for this analysis was 25 July 2018. One additional IDFS analysis, two additional interim OS analyses and a final OS analysis are planned in the future. The OS data were immature at the clinical cut-off date, with only 26.7% of the events required for the final analysis of OS having occurred (i.e. 98 deaths of the 367 deaths planned at the final OS analysis).

Overall, 212 (28.5%) patients discontinued treatment in the trastuzumab emtansine arm and 135 (18.2%) patients discontinued treatment in the trastuzumab arm. Specifically, 133 (17.9%) patients discontinued treatment due to AEs in the trastuzumab emtansine arm and 15 (2.0%) patients discontinued treatment due to AEs in the trastuzumab arm.

The KATHERINE study met its primary objective; trastuzumab emtansine reduced the risk of an IDFS event by 50% compared to trastuzumab (HR=0.50; 95% CI: 0.39–0.64; p<0.001). The OS analysis did not cross the early reporting boundary (HR=0.70, 95% CI: 0.47 to 1.05; p=0.0848). Three-year OS rates were 95.2% for the trastuzumab emtansine arm compared with 93.6% for trastuzumab).

AEs of any grade were more common in the trastuzumab emtansine arm than in the trastuzumab arm (98.8% vs 93.3%, respectively), as were AEs leading to discontinuation (18.0% vs 2.1%, respectively), although the majority of AEs observed were reversible and could be well managed according to the company. AEs of Grade 3 or higher were more common in the trastuzumab emtansine arm than in the trastuzumab arm (25.7% vs 15.4%, respectively). The most common AEs in either the trastuzumab emtansine arm or trastuzumab arm were fatigue (366 patients [49.5%] vs 243 patients [33.8%], respectively) and nausea (308 patients [41.6%] vs 94 patients [13.1%], respectively). SAEs occurred in 94 patients (12.7%) who received trastuzumab emtansine and 58 patients (8.1%) who received trastuzumab.

Results for node-positive patients and node-negative patients separately are reported in Appendix 2. As can been from Tables A2.1 and A2.2 (in Appendix 2), baseline demographic and disease characteristics in the two subgroups are mostly similar to those in the ITT population. However, the node-negative population seems to include more patients from Western Europe, this applies to both arms of the trial. Most results for node-positive patients are missing, only IDFS was reported in CS (see Table A2.3). IDFS is slightly more favourable for trastuzumab emtansine in the node-negative population. Comparing results in the node-negative population (Table A2.4) with ITT results (Table 4.7), shows more favourable results for trastuzumab emtansine in the node-negative population for the outcomes IDFS (STEEP definition), DFS and DRFI. However, OS was less favourable for trastuzumab emtansine in the node-negative population.

The company performed a Bucher indirect comparison using the KATHERINE study (trastuzumab emtansine vs trastuzumab) and the APHINITY study (pertuzumab + trastuzumab vs trastuzumab) for the comparison of trastuzumab emtansine vs pertuzumab + trastuzumab in node-positive patients. Results for IDFS (HR=0.68 (95% CI: 0.46 to 0.99)), OS (HR=0.78 (95% CI: 0.43 to 1.39)) and DFS (95% CI: 0.71 (0.49 to 1.04)) favour trastuzumab emtansine over pertuzumab, but only IDFS showed a statistically significant difference. These results should be interpreted with caution, as they are based on an indirect comparison using data from two trials that included different populations: KATHERINE included pre-treated patients who had residual invasive disease (RID) and APHINITY included treatment naïve patients.

5. COST EFFECTIVENESS

5.1 ERG comment on company's review of cost effectiveness evidence

This section pertains mainly to the review of cost effectiveness analysis studies. However, the search section (5.1.1) also contains summaries and critiques of other searches related to cost effectiveness presented in the company submission. Therefore, the following section includes searches for the cost effectiveness analysis review, measurement and evaluation of health effects as well as for cost and healthcare resource identification, measurement and valuation.

5.1.1 Searches performed for cost effectiveness section

The following paragraphs contain summaries and critiques of all searches related to cost effectiveness, HRQoL and cost and healthcare resource identification presented in the company submission and clarification responses.[1, 4, 20, 21]

Appendix G of the CS details systematic searches of the literature used to identify cost effectiveness studies. The same searches were used to identify HRQoL studies. Appendix I of the CS details systematic searches of the literature used to identify cost and healthcare resource identification, measurement and valuation studies.[20] Additional cost and healthcare resource identification, measurement and valuation searches were provided within the clarification response and associated appendix.[4, 21]

Database searches for cost effectiveness and HRQoL were undertaken on 20 November 2014 and updated twice, once on 20 November 2017 and again on 4 February 2019. The searches for cost and healthcare resource identification, measurement and valuation took place on 26 October 2017 and 12 June 2019. A summary of the sources searched is provided in Table 5.1 and Table 5.2 below.

Table 5.1: Data sources for the cost effectiveness and HRQoL systematic reviews

Search strategy element	Resource	Host/ source	Reported date range	Date searched
Electronic databases	PubMed (including Medline & In-Process & Other Non-Indexed Citations)	PubMed	Not reported Update 1: 2014/11/20-2017/11/20 Update 2: 2017/11/20-2019/02/4	20.11.14 Update searches on 20.11.17 & 4.2.19
	Embase	Embase.com	Not reported Update 1: 2014/11/20-2017/11/20 Update 2: 2017/11/20-2019/02/4	20.11.14 Update searches on 20.11.17 & 4.2.19
Conference proceedings	SMDM (Society for Medical Decision Making)	No search terms or web links were reported.	Not fully reported; approx 3 years from first search.	Not reported. Updates in 2017 & 2019

Search strategy element	Resource	Host/ source	Reported date range	Date searched
	HTAi (Health Technology Assessment international)	No search terms or web links were reported.	Not fully reported; approx 3 years from first search.	Not reported Updates in 2017 & 2019
	ISPOR (International Society for Pharmacoeconomics and Outcomes Research)	No search terms or web links were reported.	Not fully reported; approx 3 years from first search.	Not reported Updates in 2017 & 2019
HTA websites	Cost effectiveness analysis (CEA) registry	No search terms or web links were reported.	Not reported	Not reported Updates in 2017 & 2019
	Research Papers in Economics website (RePEc)	No search terms or web links were reported.	Not reported	Not reported Updates in 2017 & 2019
	National Institute for Health and Care Excellence (NICE)	No search terms or web links were reported.	Not reported	Not reported Updates in 2017 & 2019
	Australian Pharmaceutical Benefit Advisory Committee (PBAC)	No search terms or web links were reported.	Not reported	Not reported Updates in 2017 & 2019
	Canadian Agency for Drugs and Technologies in Health (CADTH)	No search terms or web links were reported.	Not reported	Not reported Updates in 2017 & 2019
	Institut national d'excellence en santé et en services sociaux (INESSS)	No search terms or web links were reported.	Not reported	Not reported Updates in 2017 & 2019
	Pan-Canadian Oncology Drug Review (pCODR)	No search terms or web links were reported.	Not reported	Not reported Updates in 2017 & 2019
	HTA Database of the International Network of Agencies for Health Technology Assessment (INAHTA)	No search terms or web links were reported.	Not reported	Not reported Updates in 2017 & 2019
	National Institute for Health Research (NIHR) Health Technology Assessment	No search terms or web links were reported.	Not reported	Not reported Updates in 2017 & 2019

Source: Appendices G and H of the CS and Appendices of the company's clarification response.[20, 21]

ERG comments:

The ERG considers the database searches and methodology reported in the CS and clarification responses to support the systematic review of cost effectiveness data, HRQoL and resource use on the whole to be transparent and reproducible. Unfortunately, the strategies omitted information reporting hits per line of searches, which made the ERG's assessment of search performance difficult. The strategy used to identify cost effectiveness and HRQoL studies could have been improved with the inclusion of a comprehensive cost effectiveness filter, containing appropriate MeSH and Emtree indexing.

There were several issues in the way the searches were conducted and reported, as follows:

- Searches were conducted over a good range of resources, and the majority of searches were clearly reported and reproducible.
- The PubMed and Embase cost effectiveness/HRQOL strategies were not reported fully in the company submission, and additional searches were provided in the clarification response appendices.
- The original search date for the conferences proceedings was not reported.
- Both the PubMed and Embase searches were structured the same, therefore some of the structural issues impaired performance of both database searches.
- There was limited word variants in the Breast cancer facet (line 2 of the PubMed and Embase searches). Sensitivity of the search would have been improved by including US spelling of tumor and truncation of neoplasms, to pick up neoplasms, neoplasia and neoplastic.
- The PubMed and Embase strategies contained a facet to limit the population to adjuvant or neoadjuvant therapy. Line 6 contained repetition and redundancy: neoadjuvant was searched alone, therefore neoadjuvant therapy was redundant. Inclusion of the term adjuvant meant that adjuvant radiotherapy, adjuvant therapy and adjuvant chemotherapy were redundant terms. The ERG felt this facet would have been much more sensitive and therefore effective if the named treatment and comparators had been included using the OR operator, to pick up records referring to neoadjuvant or adjuvant treatments by drug name as well.
- The PubMed strategy used a study design search facet to include terms for health technology assessments, cost studies and HRQoL. The strategy failed to include any MeSH subject indexing for costs, economics or pharmacoeconomics. All terms for costs and economics were restricted to title and abstract only. When the ERG queried these omissions during clarification, the company responded that better, validated cost filters have become available since their original search was conducted in 2014. They also responded that they felt inclusion of the MeSH term "Technology Assessment, Biomedical" would mitigate this omission, when combined with title and abstract terms for cost and economic evaluation. The ERG tested this explanation by comparing performance of the company's PubMed facet with the Centre for Reviews and Dissemination Economic Evaluation filter, which was publicly available in 2014.[28] The ERG found that the company's facet failed to pick up 707266 records in Medline (Ovid), when compared the CRD economic evaluation filter. Consequently, the ERG believes the company's cost effectiveness and HRQoL search could have been improved by inclusion of a well-designed and recognised economics filter, and did not accept the company explanation that inclusion of the MeSH term "Technology Assessment, Biomedical" mitigated against omission of indexing terms for cost and economics. Therefore, the ERG did not consider the cost search adequately robust. Unfortunately, the ERG was unable to undertake independent cost effectiveness searches and review the results within the STA timeline, as this would be outside of the ERG remit.

- The Embase cost effectiveness/HRQoL strategy incorporated similar limitations as the PubMed strategy in terms missing indexing for cost and economics terms. As described above, cost and economics terms were restricted to title and abstract only. One Emtree term for "Economic Evaluation" was incorporated. As before "Biomedical technology assessment" was included as an Emtree term. Nonetheless the ERG does not feel this compensates for the omission of an appropriately designed Emtree cost effectiveness filter which combines both free-text with relevant economics and costs Emtree indexing.
- The Embase strategy would have benefitted from inclusion of the Emtree indexing for "Short Form 36"; explosion of this term would also have picked up indexing for "Short Form 12", "Short Form 20" and "Short Form 8". Free-text terms for these instruments were restricted to title and abstract only. When the ERG queried these omissions during clarification, the company responded that they felt the title and abstract free-text combined with quality of life terms (also in title and abstract), would have compensated for this omission. The company reported testing inclusion of the missed indexing, and said that this had "no substantial impact on the final numbers... captured". The test searches were not provided to the ERG as part of the clarification response. The ERG remains concerned that lack of available and appropriate indexing for the SF instruments may have impaired performance of the company's search and does not consider the company's explanation adequate.
- A broad range of additional conference proceedings and organisational website sources were searched to inform the cost effectiveness and HRQoL systematic reviews. No information was reported regarding URLs for these sources, search terms used, or date of search. Date parameters remain unclear and were reported as the last three years, however without a date for the original search, it is not clear which three years were searched.
- The NHS Economic Evaluation Database (NHS EED) was not searched for the cost effectiveness systematic review and would have been a useful and appropriate resource to include.
- The ERG was concerned that limiting the MEDLINE and Embase cost effectiveness/HRQoL searches to English language may have introduced potential language bias. Current best practice states that "If searches are restricted by publication status or by language of publication, there is a possibility of publication bias, or language bias".[29] The English language limit was queried during the clarification process. The company responded that they considered the impact of this language restriction to be minimal as "...economic models would have been published in peer-reviewed journals which are typically in English". The ERG remains concerned that the blanket English language restrictions applied to Embase and MEDLINE searches were too restrictive and not in line with current best practice.[29-32]

Table 5.2: Data sources for the cost and healthcare resource identification, measurement and valuation

Search strategy element	Resource	Host/source	Date range	Date searched
Electronic databases	Medline, Medline Daily, In-Process and Epub Ahead of Print	OVID	2012-present*	26.10.17 Update searches on 12.6.19
	Embase	OVID	2012-2019/06/11	26.10.17 Update searches on 12.6.19

Search strategy element	Resource	Host/source	Date range	Date searched
	NHS EED, via the Cochrane Library	Wiley	2012 - Issue 2, April 2015	26.10.17 No update as NHS EED had ceased.
Conference proceedings	ASCO	Search terms & web links reported	2016-2019	9.11.17 Update search on 24.6.19
	ESMO	Search terms & web links reported	2016-2019	9.11.17
	San Antonio Breast Cancer Symposium (SABCS)	Search terms & web links reported	2015-2018	9.11.17 Update search on 24.6.19
	ISPOR Annual International Meeting	Search terms & web links reported	2016-2019	9.11.17 Update search on 24.6.19
	ISPOR Annual European meeting	Search terms & web links reported	2016-2018	9.11.17 Update search on 24.6.19
HTA agency	NICE	NICE website	2007-2017	9.11.17 Update search on 26.6.19
*date parameters not reported. The bibliographies of all relevant SLRs, meta-analyses, HTA submissions and economic evaluations identified through the electronic database searches were also manually searched to identify any additional studies of relevance. Reference lists of included articles, relevant SLRs and meta-analyses were scanned for further potentially relevant references.				
Sources: Company's clarification response and associated Appendix.[4, 21] ASCO = American Society of Clinical Oncology; ESMO = European Society for Medical Oncology; HTA Database = Health Technology Assessment Database; ISPOR= International Society for Pharmacoeconomics and Outcomes Research; NHS EED = NHS Economic Evaluation Database; NICE = National Institute for Health and Care Excellence; SABCS = San Antonio Breast Cancer Symposium.				

ERG comments:

The ERG considers the database searches and methodology reported in the CS and clarification responses to support the systematic review of cost and healthcare resource identification, measurement and valuation on the whole to be transparent and reproducible.

There were several issues in the way the searches were conducted and reported, as follows:

- Searches were conducted over a good range of resources, and the majority of searches were clearly reported and reproducible. Search terms for economics studies were based on recognised filters developed by the Scottish Intercollegiate Guidelines Network (SIGN), which is an adaptation of the original CRD NHS EED costs filter discussed in the section above.[28] The strategies also employed a geographical filter, developed in-house by NICE.
- The company submission appendices presented searches run on 26 October 2017. Following clarification, the ERG was provided with a set of new searches conducted on 12 June 2019.

- The Medline and Embase strategies were structured to retrieve references reporting breast cancer, together with terms for either adjuvant, early or metastasis. The ERG noted that the Medline strategy contained indexing terms which were not MeSH, for example "exp metastasis/". Whilst Ovid Medline appears to conduct a certain degree of automated mapping between MeSH and Emtree, it is unclear how well this works and the approach is not transparent. Given the potential limitations of including Emtree in a Medline search, the ERG considered it preferable to search each database separately, and to ensure inclusion of MeSH or Emtree in Medline or Embase searches respectively.
- The ERG found that the Embase searches included MeSH indexing in both the breast cancer (exp Breast Neoplasms/) and the metastasis facets (exp neoplasm metasis/ and exp neoplasm recurrence/local). As above, automated mapping may not have adequately compensated for the incorrect indexing being applied to the search. It is always preferable to search Medline with MeSH indexing and Embase with Emtree.
- The Embase search also incorporated a Medline limit to remove animal studies (line 48). Usual practice recommends adopting an adapted approach when searching Embase, to allow for the fact Embase does not index all records with animal/human check tags, in the same way Medline does. The ERG was unable to undertake independent searches to test an Embase-appropriate animal limit and review the results within the STA timeline, as this would be outside of the ERG remit.
- The ERG noted that both the Medline and Embase searches contained unwarranted explosion of MeSH and Emtree indexing terms within the population facet. However these repeated errors were not considered to be consequential, and did not impact on strategy recall.
- A broad range of additional conference proceedings were searched to inform the cost effectiveness and HRQoL systematic reviews. Reporting of conference searches appeared complete and reproducible.

5.1.2 Inclusion/exclusion criteria used in the study selection

Cost effectiveness SLR

Inclusion/exclusion criteria applied to the studies identified in the cost effectiveness searches were provided in Table 18, Appendix G.[20] These were based on the PICOS framework, to identify the population, interventions, comparators, outcomes, and study designs of interest. The population of interest was described by the company as patients with early stage (i.e. stage I or stage II) breast cancer being treated with adjuvant or neoadjuvant therapies. The study type of interest was health economic evaluations reporting at least one economic outcome of interest, such as cost per QALY, cost per life year or any other health economic endpoint. The inclusion criteria stated that studies must include an adjuvant or neoadjuvant therapy. No further restrictions were applied to the interventions or comparators assessed in the studies identified by the search. In the original SLR (up to November 2014), no language or publication date restrictions were applied. In the updated searches, relevant date restrictions were applied to avoid overlap and language was limited to English.

HRQoL SLR

The company stated that the aim of the HRQoL SLR was to *"identify all published studies evaluating HRQoL using instruments that can be used to estimate patient utility (i.e. by mapping disease specific instruments to generic instruments such as the EQ-5D or by using generic instruments, such as the SF-36 or the EQ-5D directly)".* [20]Again, inclusion/exclusion criteria (shown in Table 22 of the appendices) were based on the PICOS framework. The company stated that studies of interest included interventional and observational studies and no restrictions were applied to the type of intervention or to the comparator evaluated, as long as an adjuvant or neoadjuvant therapy was evaluated. The outcome

of interest in this search was QoL data which could be mapped to the EQ-5D. As the searches for the cost effectiveness and HRQoL SLRs were conducted together, the same restrictions were applied to language and publication dates in the updated searches.

Cost and resource use SLR

The inclusion/exclusion criteria applied to the cost and resource use SLR are detailed in Table 27 of the appendices.[20] Criteria were again based on PICOS as well as the geographical setting and language of the study. The SLR was conducted in 2017, for an economic model for pertuzumab. Studies which collected direct cost or resource use data within the last five years relevant to the National Health Service (NHS) and Personal Social Services (PSS) and the company model in patients with breast cancer receiving treatment at the adjuvant stage (i.e. after initial surgery) or later in the disease pathway (i.e. for metastatic disease) were included. Accepted study designs included randomised controlled trials, budget impact models, cost of illness studies and comparative economic evaluations. Case studies and systematic reviews were excluded once systematic reviews had been hand searched for relevant primary studies. The geographical setting was restricted to the UK. Multi country studies were only included where data were presented separately for UK. Non-English language publications were excluded.

ERG comment: The ERG identified several areas of concern regarding the inclusion and exclusion criteria adopted in the SLRs. Firstly, the language limitation of only English language publications applied in the cost and resource use SLR and in the updates of the cost effectiveness and HRQoL SLRs and may have introduced language bias. Current best practice states that "*Whenever possible review authors should attempt to identify and assess for eligibility all possibly relevant reports of trials irrespective of language of publication".*[33] The exclusion of non-UK settings in the cost/resource use SLR is very restrictive and could have excluded useful evidence. The SLR could have identified costs and resource use evidence for this population from other countries and converted costs to UK costs using standard and accepted techniques.

There were also several issues with the inclusion/exclusion criteria adopted for the HRQoL SLR which have led to concerns that relevant studies may have been missed. Firstly, the inclusion of interventions in the inclusion criteria may have missed quality of life studies that did not focus on any intervention, but focussed instead on the stages of breast cancer, which would be relevant for many of the health states requiring utility values in the model. In fact, a HRQoL study by Lidgren et al.,[34] which was excluded in the SLR due to it not including an adjuvant or neoadjuvant intervention, was later utilised by the company in the model to provide mBC utility values in scenario analyses. This was also critiqued by the ERGs in TA424 and TA569, who noted that the inclusion criteria for interventions may have been a particular issue for HRQoL studies of metastatic breast cancer patients.[17, 35]

Additionally, from the description of the HRQoL SLR in the company submission, it is unclear whether studies were included for all stages of breast cancer or only early breast cancer. For example, the company introduce the SLR in the main submission document by stating "*An SLR was conducted to identify HRQoL evidence in patients treated in the adjuvant setting for HER2-positive eBC*". In the appendices, when describing selection criteria for studies, the company submission states "*The selection criteria were pre-specified and related to the disease of interest, outcome measures and publication type. Inclusion and exclusion for the initial and updated cost effectiveness searches are reported in Table 18. The population of interest consisted of patients with early stage (i.e. stage I or stage II) breast cancer being treated with adjuvant or neoadjuvant therapies*".[20] However, in Table 18 no criteria regarding stage of breast cancer is mentioned. Yet in the description of the results of the SLR updates the company make statements such as "*The first time-restricted SLR update identified an additional*

486 total cost effectiveness and QoL studies for neoadjuvant and adjuvant therapies in eBC". If only early breast cancer studies were included, this would explain why the company had to search outside of their SLR to find utility values for metastatic states. This would indicate that the HRQoL SLR was not entirely fit for purpose. Metastatic values were required for the model and should have been searched for systematically.

5.1.3 Identified studies

Cost effectiveness and HRQoL SLRs

The cost effectiveness and QoL searches for neoadjuvant and adjuvant therapies were performed together. In the original electronic search, 1,346 citations were identified, of which 1,014 remained after duplicates were removed. No additional studies were identified through hand searching. After title and abstract screening, 171 papers were assessed at full text, of which 54 cost effectiveness studies (53 for adjuvant therapies and one for neoadjuvant therapies) and 17 HRQoL studies (all adjuvant) were included.

In the first update (20 November 2017) the electronic searches identified an additional 486 cost effectiveness and QoL studies for adjuvant and neoadjuvant therapies in eBC, of which 383 remained after duplicates were removed. Seventy-eight were assessed at full text, of which 12 cost effectiveness and four HRQoL studies in the adjuvant treatment of breast cancer and two cost effectiveness studies in neoadjuvant treatment were included. The hand search also identified TA424 which assessed pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer.[35]

In the second update (4 February 2019) an additional 155 cost effectiveness and QoL studies for adjuvant and neoadjuvant therapies in eBC were identified in the electronic searches. The removal of duplicates left 123 abstracts to be screened, of which 33 were assessed at full text. Seven relevant cost effectiveness and four HRQoL studies in the adjuvant treatment of breast cancer and three cost effectiveness studies in neoadjuvant treatment were included. The hand search also identified TA569, which assessed pertuzumab for adjuvant treatment of HER2-positive early stage breast cancer.[17]

The overview of the identified neoadjuvant and adjuvant cost effectiveness studies were given in Table 20 and Table 19 of Appendix G of the company submission, respectively.[20] The company stated the cost effectiveness of adjuvant/neoadjuvant trastuzumab emtansine treatment in the UK setting was not analysed in any of the identified studies.

The company also stated that none of the 25 HRQoL studies identified reported utility values that could be considered for direct use in the cost effectiveness analysis. Given this, and the availability of EQ-5D data from the KATHERINE trial to directly inform model utilities for eBC health states, none of the HRQoL studies identified by the SLR were considered further in the submission.[20] In the submission the company utilised additional sources of HRQoL evidence from the literature which were not identified or included in their HRQoL SLR. This included utility values from Lloyd et al., Lidgren et al., Hedden et al. and Paracha et al.[34, 36-38] The details of these publications are described further in Section 5.2.8 of this report.

Cost and Resource use SLR

The electronic database searches returned 756 records to be reviewed at title and abstract level. Seventy-one studies were reviewed at full text, of which five met the inclusion criteria. No additional studies were identified through congress or hand searching or searches of the NICE website. Summaries of the included studies are provided in Table 29 of the company submission appendices.

ERG comment: The company did not use any of the 25 studies included in the HRQoL SLR, stating that none provided utility values that could be considered for direct use in the model. No justification was provided as to why the results of each of these 25 studies were not appropriate for use in the model. Instead, the company used utility values for mBC states from other literature sources. No information was provided on how these alternative sources were identified or selected.

Similar to the identified HRQoL studies, among the five identified studies on cost and resource use SLR, none provided inputs for direct use in the model. The company used resource use/cost estimates mainly from previous technology appraisals in breast cancer. No information was provided on how these alternative sources were identified or selected.

5.1.4 Interpretation of the review

The HRQoL SLR was not fit for purpose, as by focusing on early breast cancer and studies linked with interventions the company failed to identify relevant utility values for states beyond IDFS on- and off-treatment, which were the exact two states for which they had their own data. Therefore, the company had to search beyond their review for relevant health state utility values, making no use of any studies identified and included in the SLR. It was unclear how these additional studies were searched for and selected. This has been previously criticised by other ERGs, as the company have previously submitted reviews using the same techniques in TA424 and TA569.[17, 35]

In the cost and resource use SLR, the language restrictions and restriction to only include UK cost and resource use data could have resulted in relevant studies being missed.

5.2 Summary and critique of company's submitted economic evaluation by the ERG

A summary of the economic evaluation conducted by the company is presented in Table 5.3.

Table 5.3: Data Summary of the company submission economic evaluation

	Approach	Source/Justification in the company submission	Signpost (location in ERG report)
Model	The company developed a seven-health-state Markov model in Excel. The health states included in the model are IDFS – on treatment, IDFS – off treatment, non-metastatic recurrence, remission, first line treatment for mBC, subsequent treatment lines for mBC and death.	Same model structure was used in TA569, which is the technology appraisal of pertuzumab for the adjuvant treatment of HER2-positive early stage breast cancer. The committee and the ERG in that appraisal considered that the overall design and structure of the model as plausible.[17]	Section 5.2.2.
States and events	Patients start at the IDFS-on treatment state. After a maximum of 14 cycles, patients discontinue their treatment and transition to the IDFS-off treatment state. Patients in the IDFS are at risk of non-distant and distant recurrence. When patients in the IDFS state experience a distant recurrence, they are assumed to be in the first line metastatic breast cancer (mBC) state. When patients in the IDFS state experience non-distant recurrence, they will be in the non-metastatic recurrence state, which is a tunnel state that takes 12 months. All non-metastatic recurrence patients are assumed to be transitioning into the remission state. In the remission state, patients are at risk of distant recurrence, and when they experience a distant recurrence, they are assumed to transition to the first line mBC state. In the first line mBC state, patients can receive different mix of treatments, depending on the time of the recurrence from the IDFS state (early vs late). Once in the first line mBC health state, patients are at risk of disease progression and transitioning to the metastatic – progressed health	Consistent with the assumptions in TA569.[17]	Section 5.2.2.

	Approach	Source/Justification in the company submission	Signpost (location in ERG report)
	state (second+ line mBC). In this progressed mBC state patients are administered subsequent lines of treatment for their progressed mBC. Death is an absorbing state. Patients can transition to death from any health state in the model.		
Comparators	The analysis evaluated the cost effectiveness of trastuzumab emtansine (intervention arm) vs. trastuzumab (comparator arm) in the adjuvant treatment of patients with HER2-positive early breast cancer treatment. For people with node-positive disease, pertuzumab in combination with trastuzumab and chemotherapy can be also considered as a comparator. However, the exploratory results of a comparison between trastuzumab emtansine and pertuzumab + trastuzumab + chemotherapy, was not presented in the main company submission but was presented in the Appendices.	The company considered that the comparison against trastuzumab was in line with the final scope. Also, the company considered that the comparison against pertuzumab in combination with trastuzumab and chemotherapy in people with node-positive disease was presented in Appendix M, as no statistically robust comparisons were possible for the clinical efficacy of these regimens.	Section 5.2.4.
Natural history	Breast cancers are distinguished by the tumour-node-metastasis (TNM) staging system and molecular biomarkers, which can be used to drive prognosis and treatment-related decisions. Such molecular biomarkers include HR+, HER2+, oestrogen (ER+), or progesterone (PR+). The dominant driver to the development of breast cancer tumours is the overexpression of the HER2 oncogene which can influence the metabolic functions of the tumour cells, enable cell survival, induce cell proliferation, and increase invasiveness. Typically, HER2+ patients with residual invasive disease in the breast and/or lymph nodes, after surgery would start adjuvant therapy and they would be invasive disease free until the disease recurrence		Section 2.1

	Approach	Source/Justification in the company submission	Signpost (location in ERG report)
Treatment effectiveness	Treatment effectiveness parameters (i.e. transition probabilities) were derived from the KATHERINE trial wherever possible.[27] Otherwise, external sources (including UK life tables, other trials in breast cancer such as EMILIA, CLEOPATRA, M77001, or other published studies, expert advice or modelling assumptions) were used.	Observed IDFS Kaplan Meier curves were extrapolated and the long-term extrapolation were justified by using external data sources and clinical expert opinion	Section 5.2.6
Adverse events	Only the following adverse event (AE) was taken into account: decreased platelet count. The effects of AEs are captured by applying a one-off cost in the first cycle and no extra utility decrement was applied.	The Grade 3 and above treatment related AEs were included if the incidence threshold ≥ 2%. The company considered that the utility impact of the treatments would be captured by the EQ-5D measurements in the KATHERINE trial.	Section 5.2.7
Health related QoL	HRQoL data for the IDFS state was taken from the KATHERINE data and valued using the UK EQ-5D-3L tariff [39]. Same utilities were assumed for both trastuzumab and trastuzumab emtansine arms. Different utilities are applied for IDFS on-treatment and IDFS off-treatment states. The company assumed that utility in the non-metastatic recurrence and remission states were equal to utility in the IDFS on-treatment and IDFS off-treatment values, respectively. For the metastatic breast cancer states (first and second+ line mBC state), utility values were sourced from Lloyd et al.[36]	The choice of the KATHERINE trial as the source of the utility input for the IDFS states were in line with the choice for the effectiveness and safety model inputs. The other assumptions and the utility sources were justified by the previous appraisals (TA569, TA424 and TA509).[17, 35, 40]	Section 5.2.8
Resource utilisation and costs	The economic analysis was performed from the NHS and PSS perspective. The following state-specific costs were included: • drug acquisition and administration costs in the IDFS state • subsequent treatment costs	Unit costs were obtained from the PSSRU 2018, NHS reference costs.[41, 42] Drug costs were taken from the BNF and eMIT. Frequency of resource use was mostly based on estimates from the NICE pertuzumab appraisal (TA569), the NICE clinical guideline for advanced breast cancer (CG81) and the expert	Section 5.2.9

	Approach	Source/Justification in the company submission	Signpost (location in ERG report)
	• treatment-related AE costs • Resource use costs in different health states (professional and social services, health care professionals and hospital resource use such as test/monitoring costs)	opinion.[10, 17] The AE costs were taken from the NHS reference costs and previous technology appraisals TA458 and TA509.[40, 43]	
Discount rates	Cost and health outcomes discounted at 3.5%	As per NICE reference case	Section 5.2.5
Sensitivity analysis	Probabilistic, deterministic one-way sensitivity analysis and scenario analyses conducted	As per NICE reference case	Section 6.2

Source: Company submission.[1]
Abbreviations: AE = adverse event; BNF = British National Formulary; DLBCL = diffuse large B cell lymphoma; eMIT = electronic Market Information Tool; EQ-5D-3L = EuroQol, 5 dimensions, 3 levels; HRQoL = health-related quality of life; IDFS = Invasive disease-free survival; KM = Kaplan-Meier; mBC = metastatic breast cancer; NICE = The National Institute of Health and Care Excellence; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; OS = overall survival; PFS = progression-free survival; PSS = personal social services; PSSRU = Personal Social Services Research Unit; QoL= Quality of life; TA= technology appraisal; TNM = tumour-node-metastasis; TTOT = time to off treatment.

5.2.1 NICE reference case checklist (TABLE ONLY)

Table 5.4: NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers.	Direct health effects for patients included.
Perspective on costs	NHS and PSS.	NHS and PSS perspective taken.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis.	Cost-utility analysis with fully incremental analysis undertaken.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared.	The model time horizon of 52 years is appropriate for a lifetime horizon as the average age of patients at the start of treatment was 49 years.
Synthesis of evidence on health effects	Based on systematic review.	Systematic review conducted to identify evidence on health effects for the IDFS state. However, the health effects in the subsequent states were not obtained from systematic review.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Health effects expressed in QALYs. For the utilities in the IDFS state, HRQoL measured using the EQ-5D-3L. For the utilities in the subsequent states, HRQoL measured using vignettes.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers.	For the IDFS state, HRQoL reported by the patients in the trial. For the utilities in the subsequent states, HRQoL measured using vignettes.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population.	UK EQ-5D-3L value set was used.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit.	No equity issues have been identified.

Element of health technology assessment	Reference case	ERG comment on company's submission
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS.	Unit costs were sourced from NHS Reference Costs 2017–18, PSSRU 2018, and the BNF and eMIT.
Discounting	The same annual rate for both costs and health effects (currently 3.5%).	Costs and health effects are discounted at 3.5%.

Abbreviations: BNF = British National Formulary; eMIT = electronic Market Information Tool; EQ-5D-3/5L = EuroQol, 5 dimensions, 3/5 levels; HRQoL = health-related quality of life; IDFS = Invasive disease-free survival; NHS = National Health Service; PSS = personal social services; PSSRU = Personal Social Services Research Unit; QALYs = quality adjusted life years.

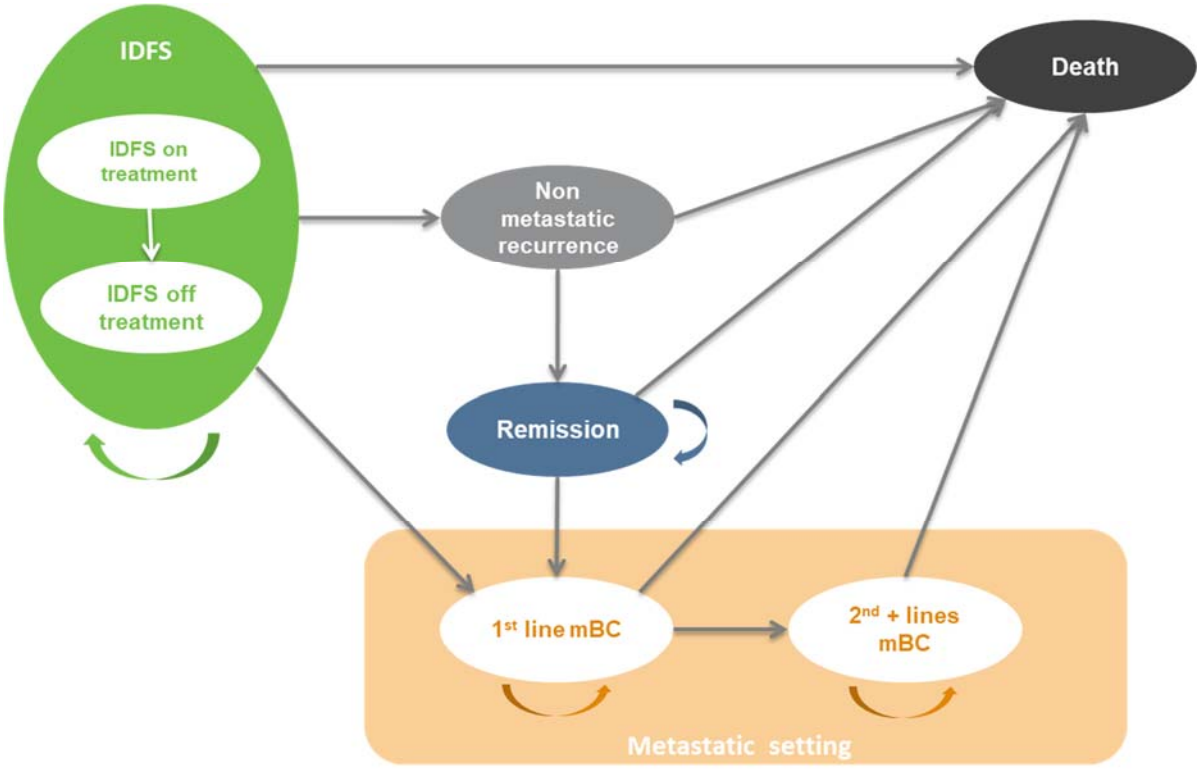
5.2.2 Model structure

The company developed a seven-health-state Markov model in Excel. The health states included in the model are IDFS – on treatment, IDFS – off treatment, non-metastatic recurrence, remission, first line treatment for mBC, subsequent treatment lines for mBC and death. A schematic representation of the model transitions is shown in Figure 5.1.

Patients enter the simulation in the IDFS health state and remain there until recurrence (non-metastatic or metastatic) or death. While in IDFS, patients are assumed to receive a maximum of 14 cycles of trastuzumab emtansine in the intervention arm and a maximum of 14 cycles of trastuzumab in the comparator arm (health state IDFS – on-treatment). After patients discontinue their eBC assigned regimen they are assumed to transition to the IDFS – off-treatment health state. Patients transition to the non-metastatic recurrence health state after experiencing a non-distant recurrence. Patients entering this health state are assumed to receive 12 months of additional adjuvant therapy. Thus, the non-metastatic recurrence health state acts as a one year "tunnel" health state. Afterwards, all alive patients are assumed to move to the remission health state. If patients in remission experience another recurrence, then this is assumed to be metastatic and, therefore, patients transition to the first line treatment for mBC health state. The first line treatment for mBC health state can also be reached from IDFS, when patients experience a distant recurrence. Patients in the first line mBC health state who experience disease progression are assumed to transition to the subsequent treatment lines for mBC health state. From any health state in the model patients can transition to the death health state.

The model uses a cycle length of one month (30.4 days) and half-cycle correction. Costs and utilities are applied to each health state of the model (except death) to calculate per-cycle costs and quality adjusted life-years (QALYs) which are subsequently discounted at a rate of 3.5% per annum, as is recommended in the NICE Reference Case.[44]

Figure 5.1: Model structure



Source: Figure 15 in CS.[1]
Abbreviations: CS = company submission; IDFS = invasive disease-free survival; mBC = metastatic breast cancer

ERG comment: Overall, the ERG considers the model structure appropriate. As explained in Section 5.2.6.4 below, timing of recurrence was incorporated into the model. Depending on whether it occurs before or after 18 months, recurrence is classified as "early" or "late". Different cost and effect parameters are used to model "early" and "late" recurrence. Thus, in practice, the model consists of nine health states instead of seven. The modelling approach used by the company was in line with previous NICE technology appraisals in this disease area (TA107, TA424 and TA569).[17, 35, 45] A comparison of the model structures is provided in Table 5.5.

Table 5.5: Comparison of model structures used in this and previous (related) NICE appraisals

	Previous appraisals			Current appraisal	
	TA107 – Trastuzumab for the adjuvant treatment of early-stage HER2-positive breast cancer[45]	**TA424 – Pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer[35]**	**TA569 – Pertuzumab for adjuvant treatment of HER2-positive early stage breast cancer[17]**	**Chosen values**	**Justification (company)**
Time horizon	45 years (lifetime)	50 years (lifetime)	52 years (lifetime)	52 years (lifetime)	In accordance with NICE Reference Case[44]
Treatment waning effect	Effect maintained for ten years. Two-thirds of this benefit is seen until year 45	No waning. Treatment effect set equal after seven years	Effect maintained for four years before waning to null at seven years	Effect maintained for seven years before waning to null at ten years	Section 5.2.6.1 in this report
Source of utilities	Published literature	Published literature	eBC health states - EQ-5D data from the APHINITY trial mBC health states - Lloyd, 2006[36]	eBC health states - EQ-5D data from the KATHERINE trial mBC health states - Lloyd, 2006[36]	In accordance with NICE Reference Case[44]
Source of costs	MEDTAP study, ABACUS study, HERA database, and MIMS	NHS reference costs, BNF, published literature, and expert opinion	Published literature and expert opinion	Published literature and expert opinion	In accordance with NICE Reference case[44]

Source: Table 21 in CS. [1]
Abbreviations: BNF: British National Formulary; eBC: early breast cancer; EQ-5D: EuroQol 5-Dimension; HER2: human epidermal growth factor receptor 2; mBC: metastatic breast cancer; MIMS: Monthly Index of Medical Specialities; NHS: National Health Service; NICE: National Institute for Health and Care Excellence.

5.2.3 Population

The health economic evidence and the cost effectiveness economic analyses presented in the CS focused on the ITT population of the KATHERINE trial, which is aligned with the anticipated label. This population is slightly narrower than the final scope of this appraisal, as described in Section 3.1 of this report. In the CS, it was stated that expert opinion was sought to confirm that the ITT trial population observed in KATHERINE was representative of patients with RID who could expect to receive adjuvant trastuzumab emtansine in the UK. As a result, the company assumed that the responses and outcomes seen in this study were reflective of UK clinical practice. The company also presented evidence for two of the subgroups included in the NICE final scope: node-negative and node-positive patients.[15] The baseline characteristics of the patients used in the economic model are provided in **Error! Reference source not found.** below. These values are based on the average baseline values sourced from the pooled data from the pivotal KATHERINE trial.

Table 5.6: Baseline characteristics of the patients used in the model

Patient characteristics*	ITT population	Node-negative subpopulation	Node-positive subpopulation
Average age of cohorts (years)	49.10	48.85	NA – assumed equal to ITT in the model
Body weight (kg)	70.91	70.05	
Height (cm)	163.10	163.36	
BSA (m^2)**	1.77	1.76	

Source: Economic model attached to the CS and Table 22 of the response to the clarification letter – Part II.[1, 4]
* Demographic parameters pooled across treatment arms.
** Calculated from average body weight and height using Dubois formula
BSA = body surface area, cm = centimetre; ITT = intention to treat; kg = kilogram; NA = Not available.

ERG comment: As explained in the next section of this report, comparators are different for node-positive (pertuzumab + trastuzumab + chemotherapy) and node-negative (trastuzumab monotherapy) subpopulations. For this reason, the cost effectiveness analyses for the ITT population are invalid. Only subgroup analyses should have been conducted separately. However, subgroup-specific evidence was limited and many of the assumptions made in the subgroup cost effectiveness analyses were based on the evidence presented for the ITT population. Thus, the subgroup analyses did not necessarily use the appropriate subgroup data from the KATHERINE trial. As explained in Section 5.2.6.3, the ERG considers that only the cost effectiveness results for the node-negative population are appropriate for the decision problem at hand. Therefore, only the cost effectiveness results for the node-negative subgroup were discussed in Sections 6 and 7 of this report. Results for the ITT population and the node-positive subgroup are presented in Appendix 3 and 4 of this report, respectively.

5.2.4 Interventions and comparators

The comparator for the ITT and node-negative subgroup in the model is trastuzumab. For the node-positive population subgroup, the comparator used is pertuzumab + trastuzumab. For the ITT and node-negative model analyses, dosing schedules for the intervention and comparator follow the schedules used in the KATHERINE trial.

Intervention

Trastuzumab emtansine is administered as an intravenous (IV) infusion on day 1 of a three-week cycle at a dose of 3.6 mg/kg.

Comparator (ITT and node-negative subgroup)

Trastuzumab is administered on day 1 of a three-week cycle at a maintenance dose of 6 mg/kg. Branded trastuzumab (Herceptin®) IV was the comparator in the KATHERINE trial. However, subcutaneous (SC) branded trastuzumab and trastuzumab biosimilars have also been included in the economic analysis.

Comparator (node-positive subgroup)

Pertuzumab is administered as an IV injection, according to an initial loading dose of 840 mg, followed thereafter by a maintenance dose of 420 mg administered over a period of 30 to 60 minutes on day 1 of a three-week cycle. Typically, pertuzumab + trastuzumab is given in combination with six cycles of chemotherapy. Expert advice elicited by the company has shown that patients would expect to receive generic chemotherapy as part of their neoadjuvant therapy regimen and would therefore not also receive it in the adjuvant setting. Given that this analysis is only concerned with neoadjuvantly treated patients, the company assumed that all chemotherapy would be given prior to surgery and omitted chemotherapy from this analysis of the adjuvant setting. The company further justify this choice, noting that chemotherapy drugs are inexpensive and would not likely have impacted the cost effectiveness results presented below. Further, they argue that this approach could be seen as conservative, given that the inclusion of these drugs would have only increased the cost of the comparator arm, thereby reducing the ICER.

ERG comment: As explained in Section 3.3, the chosen comparators are inappropriate for the ITT population (i.e. regardless of node status). This is because what is implied by the whole population analysis is that standard care for all patients is adjuvant trastuzumab, but this is not true: following TA569, pertuzumab + trastuzumab has been recommended for node-positive patients.[17] TA569, therefore, implies that a whole population analysis (with a common comparator for all patients) is invalid. However, it is expected that if the analysis had been conducted correctly, i.e. trastuzumab as comparator for only the node-negative subgroup, with all the model input parameters derived from KATHERINE node-negative data, the ICER would decrease, since the effectiveness of the intervention was greater in this subgroup (see Section 4.6 and Appendix 2). For completeness, results for the ITT population are presented in Appendix 3 of this report, even though these results are invalid. As explained in Section 5.2.6.3, the ERG considers that the cost effectiveness results for the node-positive population are also not valid for the decision problem at hand. In any case, these results are presented in Appendix 4 of this report. Therefore, only the cost effectiveness results for the node-negative subgroup are relevant for the current submission and these are the main focus in Sections 6 and 7 of this report.

5.2.5 Perspective, time horizon and discounting

The economic analyses took the perspective of the NHS and Personal Social Services (PSS). The model had a time horizon of 51 years, which given the base-case starting age of 49 years was long enough to be considered a lifetime horizon. Costs and QALYs were discounted at 3.5% per annum according to the NICE methods guidance.

5.2.6 Treatment effectiveness and extrapolation

Treatment effectiveness parameters were derived from the KATHERINE trial wherever possible.[27] Otherwise, external sources (including published literature, expert advice or modelling assumptions) were used. The company submission focused on the KATHERINE ITT population, for which the comparator used was trastuzumab monotherapy. In Appendix M of the CS, the company also presented cost effectiveness analyses for the KATHERINE node-positive subpopulation, for which the

appropriate comparator is pertuzumab in combination with trastuzumab.[20] As requested by the ERG in the clarification letter (question B2),[4] the company also conducted subgroup analyses for the node-negative subpopulation, for which trastuzumab monotherapy is the appropriate comparator. As mentioned above, the cost effectiveness analyses for the ITT population are invalid. However, the methodology used by the company in this population is still relevant because, in many cases, only evidence for the ITT population was presented, and this evidence was assumed to be valid for the specific subgroups. For this reason, the treatment effectiveness parameters discussed in this section of the ERG report include the ITT, node-negative and node-positive populations. To avoid having an extremely lengthy section, only the most relevant information is presented here. Further details are shown in the appendices to this report.

5.2.6.1 Invasive disease-free survival (IDFS) – ITT population

General approach

The probability of remaining in the IDFS health state was derived from the patient-level data observed in the ITT population of the KATHERINE trial. For this trial population, the median follow-up period was 41.43 months in the trastuzumab emtansine arm and 40.94 months in the trastuzumab arm. At the time of the primary analysis (data cut-off 25 July 2018),[27] 91 (12.2%) and 165 (22.2%) IDFS events had occurred in the trastuzumab emtansine and trastuzumab arms, respectively. Therefore, parametric survival curves were used by the company to extrapolate these data beyond the trial follow-up period. The process of selecting parametric survival curves was guided by the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14.[46]

However, the company indicated that the IDFS extrapolations based on the KATHERINE ITT trial data alone would not produce valid long-term outcomes. Therefore, the selected parametric survival curves were adjusted by the company to produce a more clinically plausible extrapolation. These adjustments were informed by external empirical evidence. Since trastuzumab emtansine is not yet licensed in the adjuvant eBC setting, the long-term empirical evidence only exists for the trastuzumab arm. In particular, the HERA and BCIRG 006 trials were used to inform the adjustments of the extrapolations.[47, 48] The HERA study was a randomised, open-label, multicentre, phase III trial investigating the efficacy of trastuzumab over one and two years after standard neoadjuvant chemotherapy, adjuvant chemotherapy, or both, in patients with HER2-positive eBC. The primary outcome in HERA was DFS (as opposed to IDFS in KATHERINE). The BCIRG 006 study was also a randomised phase III trial where patients with node-positive or high-risk node-negative eBC were enrolled. The treatments compared were doxorubicin + cyclophosphamide followed by docetaxel (AC-T), AC-T + trastuzumab and a non-anthracycline-containing arm, docetaxel + carboplatin + trastuzumab.

Finally, the company decided to model IDFS by breaking down the time horizon of the model into three discrete time periods:

- Time period 1 – Zero to three years: KATHERINE data.
- Time period 2 – From year three to year ten: IDFS curves adjusted based on long-term external data on trastuzumab (comparator arm).
- Time period 3 – From year 10 until the end of the time horizon: 95% “cured” (background mortality only).

For each time period, different data and assumptions were used to generate the IDFS curves. The methodology used is explained in the following subsections.

Time period 1 (zero to three years) – KATHERINE trial data

Parametric survival curves were fitted to the Kaplan-Meier (KM) data from the KATHERINE ITT trial data. First, the proportional hazards assumption was tested by the company. Goodness of fit was then assessed for all standard parametric models (exponential, Weibull, log-logistic, log-normal, generalised gamma and Gompertz) following the recommendations of TSD 14 and was based on the following criteria: Akaike information criterion (AIC), visual inspection and absolute deviation with respect to observed data.[46] Based on the company assessment, a log-logistic distribution was chosen to model IDFS in the base-case. Other distributions were explored in scenario analysis. Additional details are provided below.

Assessment of the proportional hazards assumption

The ERG refers to Appendix 3 of this report for a complete assessment of the proportional hazards (PH) assumption for IDFS. The company tested the PH assumption graphically by using the log-cumulative hazard plot shown in Figure A3.1 and a plot of the Schoenfeld residuals as shown in Figure A3.2. Based on these plots, the company considered it difficult to conclusively prove whether the PH assumption is appropriate or not, but, based on the available evidence, preferred to assume that it does not hold. As a consequence, a "stratified" approach was taken and the parametric survival curves were fitted separately to each treatment arm. The company further showed in Table 22 of the CS (not shown in this report) that the modelled IDFS was relatively insensitive to whether or not proportional hazards were assumed and that this is expected to have a minor on the cost effectiveness results.[1]

ERG comment: Based on the presented evidence, the ERG agrees with the company that assuming non-proportional hazards for IDFS is more plausible and, thus, fitting parametric survival curves separately to each treatment arm is more appropriate. The company indicated that this approach is conservative and likely to result in less-favourable cost effectiveness results compared to those obtained should the PH assumption had been used. The ERG does not agree with this statement. The "stratified" approach is not conservative: based on the presented evidence it is the most appropriate choice. The fact that it will result in less-favourable results can be due to the PH assumption being too optimistic for trastuzumab emtansine but yet, based on the presented evidence, it is a less plausible assumption. However, given the expected minor impact on the model results, scenarios using PH extrapolations are not considered informative by the ERG and were not included in Section 7 of this report.

Selection of parametric models

The ERG refers to Appendix 3 of this report for a detailed description of the methods used for selecting parametric models to extrapolate IDFS beyond the duration of the KATHERINE trial. Goodness of fit of the parametric survival curves was first assessed using the AIC. The AIC values for each parametric model considered by the company, for both trastuzumab emtansine and trastuzumab IDFS are shown in Table A3.1. Based on the AIC values, the exponential distribution should be chosen to model IDFS in the trastuzumab emtansine arm and the log-normal distribution should be chosen for the trastuzumab arm. However, the company noted that small differences in AIC values would imply negligible differences in terms of fit. Furthermore, following the recommendations of NICE DSU TSD 14,[46] the same type of parametric model was used for both treatment arms. The company judged that, when the fit across the two arms jointly was considered, the best fitting extrapolation was produced by either the exponential or the log-logistic distributions.

The company also performed visual inspection of the parametric survival curves against the KM data. This assessment was based on the plot of each parametric distribution and the KM curves as in Figure A3.3. Based on this figure, the company indicated that all distributions seemed to fit the KM data well,

especially in the trastuzumab emtansine arm, and that in the trastuzumab arm, all extrapolations overestimated IDFS. The company concluded that the log-logistic and the generalised gamma appeared to provide the best fitting across both treatment arms.

Finally, the company conducted an assessment of the absolute fit of the parametric survival curves to the KM data by comparing the percentage of patients who did not experience an IDFS event at 12, 24, 36 and 48 months as shown in Table A3.2. Based on this table, the company concluded that, overall, all parametric survival curves across both treatment arms provided a good absolute fit to the KM data since incremental differences between the parametric extrapolations and the KM data were always below 2% in absolute value. Because of this, the company considered that it can be reasonably assumed the differences in the absolute fit of the parametric extrapolations to be negligible.

Based on the results of all the assessments described above, the company chose the log-logistic distribution as the best candidate distribution to model IDFS in both treatment arms in years zero to three (time period 1). Therefore, this distribution was also used as basis for the adjusted curves from year three onwards. The choice of different probability distributions to extrapolate IDFS was explored by the company in scenario analysis.

ERG comment: There are some points in which the ERG does not completely agree with the choices made by the company. These are summarised below:

- The company mentioned that in the trastuzumab arm, all extrapolations overestimated IDFS. While this may be the case between 10 and 40 months approximately, at the tail of the KM curve, the opposite seems to occur, since most of the extrapolations, including the log-logistic, fall below the KM curve for the trastuzumab arm. This is supported by the figures provided by the company in Table A5.2 for 48 months. Based on these, it could be concluded that all extrapolations considered for the trastuzumab arm, underestimate IDFS at 48 months. Since these extrapolations are used for the entire model time horizon, this might be an indication that IDFS is underestimated for the trastuzumab arm from year 4 to year 52, which it is expected to have a larger impact on the results than the overestimation that might occur between years 0 and 3.
- The company considered that all extrapolations (across both treatment arms) provided a good absolute fit to the KM data since incremental differences between the extrapolations and the KM data were always below 2%. For this reason, the company argued that it can be assumed that the differences in the absolute fit of the extrapolations are negligible. Even though deviations at year 4 can be considered minor, the shape of the tails of the parametric extrapolations can vary significantly between different survival functions, which may have a non-negligible impact on the model results.
- Based on the results of all the assessments described above, the company chose the log-logistic distribution as the best candidate distribution to extrapolate IDFS in both treatment arms in years zero to three (time period 1). Since up to year 3 KATHERINE data provided complete IDFS observations, the ERG prefers using KM data directly to model IDFS between at least year 0 and 3 and use parametric extrapolations as basis for the adjusted curves from year three onwards. Using KM curves directly, overcomes the potential issue of IDFS overestimation observed between months 10 and 40 approximately for the trastuzumab arm when using parametric functions.
- Furthermore, the ERG considers that, since KM curves should be used up to the time point where the last event was observed in each treatment arm (51 months for trastuzumab emtansine

and 49 for trastuzumab), the selection of the parametric models to extrapolate IDFS after this time should be based on the best fit at the tails.

In summary, based on the above points for the ITT population, the ERG prefers using KM curves up to 51 months for trastuzumab emtansine and 49 for trastuzumab and a generalised gamma for long-term extrapolations because the generalised gamma seems to fit well the KM data both visually and in terms of AIC, and also gives the lowest absolute difference with respect to KM data in the trastuzumab arm (see Table A5.2).

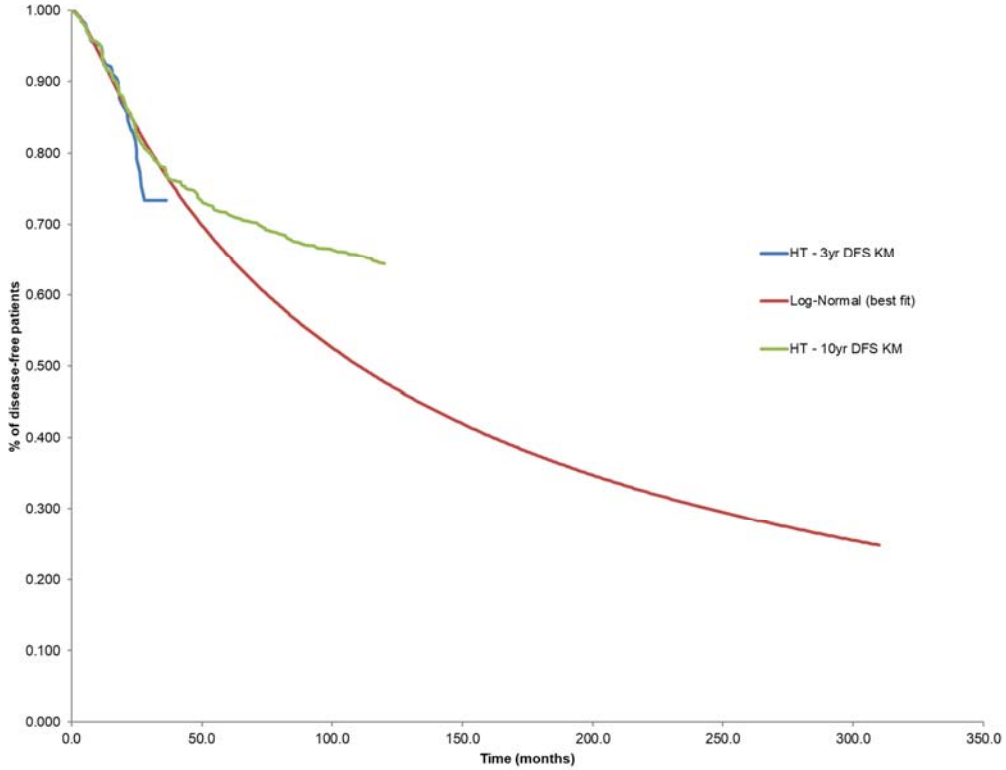
Time period 2 (three to 10 years) – long-term external data (trastuzumab arm)

The company referred to the findings of two long-term clinical trials of trastuzumab therapy (BCIRG 006 and HERA)[47, 48] showing that the risk of recurrence for eBC patients in the first three years is not representative of the long-term risk of recurrence. Thus, according to the company, patients in the IDFS health state are exposed to a far greater risk of recurrence in the first three to five years. Afterwards, this risk is expected to decrease over time.

Figure 5.2 shows the log-normal DFS extrapolation based on the three-year data cut of the node-positive (after one year of trastuzumab therapy) HERA trial population alongside the KM curves obtained at year 3 and at year 10.[47] These curves show that the extrapolation based on the three-year data-cut (red line) largely underestimated the DFS observed at year 10 (green line) after approximately four years. The node-positive population from HERA and BCRIG 006 was chosen since, according to the company, the ITT populations in both trials have a far better prognosis than those patients included in KATHERINE. The company believed that node-positive populations in these trials represent a higher risk population and that they are a more appropriate proxy to the ITT KATHERINE population.

Since at the time of the submission, the KATHERINE trial had a follow-up period of approximately four years, the company considered that, based on the findings from BCIRG 006 and HERA, the observed data correspond to a time period with a greater risk of recurrence. As a consequence, the extrapolations based on the KATHERINE data would overestimate the long-term rate of recurrence. Thus, the company expects that long-term KATHERINE data would show a similar behaviour to that seen in HERA (and depicted in Figure 5.2). For that reason, the company considered that an adjustment of the underlying IDFS risk (i.e. the IDFS log-logistic curve) after year 3 was required.

Figure 5.2: Comparison of three year HERA data extrapolation (log-normal) and 10 year HERA data cut (node-positive population – one year of trastuzumab therapy cohort)



Source: Figure 19 in CS.[1]
Abbreviations: DFS: disease-free survival; HT: trastuzumab + chemotherapy; KM: Kaplan-Meier; yr: year.

ERG comment: Evidence from HERA and BCIRG 006 suggests that an adjustment to IDFS data is needed to properly model IDFS in the long-term. The ERG identified uncertainty associated with the following aspects:

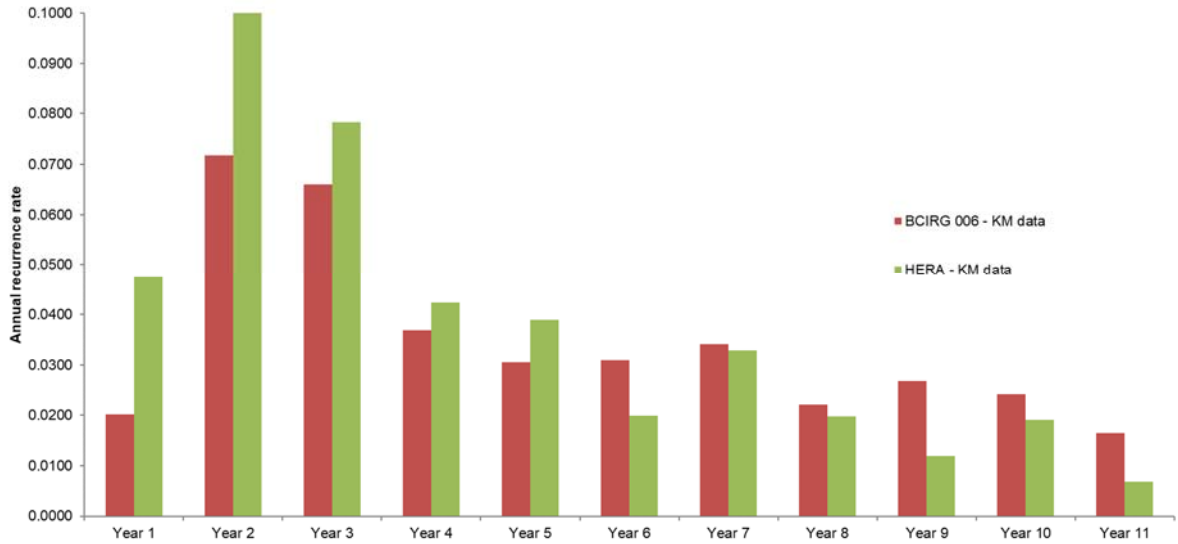
- The company assumed that the node-positive populations in BCIRG 006 and HERA (higher risk populations) are a more appropriate proxy to patients with RID following neoadjuvant therapy (KATHERINE ITT population). The ERG asked the company to provide evidence to justify this statement (see clarification question B5).[4] The rationale for this question was to include for example a comparison of baseline characteristics. In their response, the company stressed that it was more appropriate to compare two higher risk populations rather than a high risk population (RID patients in KATHERINE) and a lower risk population (ITT population in HERA).[4] While this is clear, it remains uncertain whether the two populations are really comparable and, therefore, whether the magnitude of the adjustment is also comparable with the one observed in HERA. This should be confirmed with long-term KATHERINE data when available.
- IDFS curves were adjusted based on long-term external data on trastuzumab (comparator arm). However, as explained in the next sub-section, the same adjustment is applied to the trastuzumab emtansine arm. This implies that the same long-term behaviour is assumed for trastuzumab emtansine but there is no evidence to support this assumption.
- The primary endpoint in HERA is DFS and not IDFS. Based on the company's response to the clarification question B9,[4] the ERG agrees with the company that this is expected to have a minor impact the cost effectiveness results.

- The choice of the "cut-off" point of three years for adjusting the extrapolation is also uncertain. It seems clear that, based on the three-year data-cut extrapolation (red curve in Figure 5.2), DFS in HERA was vastly underestimated at year 10 (green curve in Figure 5.2). However, the extrapolation seems to fit the long-term KM curve well up to year 4 and not to year 3 only. This supports the ERG preferred assumption of using KM curves for modelling IDFS up to the time point where the last event was observed in each treatment arm (51 months for trastuzumab emtansine and 49 for trastuzumab).

Adjustment of the extrapolation based on external data

As mentioned above, the node-positive populations in the trastuzumab arms of the BCIRG 006 and HERA trials,[47, 48] were used by the company to adjust the IDFS extrapolations (log-logistic in the base-case) obtained from KATHERINE ITT data after year 3. Figure 5.3 shows the annual recurrence rate (DFS endpoint) over 11 years from HERA and BCIRG 006. Based on this figure, the company interpreted that up to 36 months, the recurrence rate was high in both trials, decreased sharply after 36 months and stabilised at approximately 120 months.

Figure 5.3: Annual recurrence rate (DFS endpoint for trastuzumab) from the HERA and BCIRG 006 clinical trials (node-positive population)*



Source: Figure 20 in CS.[1]
Abbreviations: KM: Kaplan-Meier.
* Node-positive in HERA was used as a proxy for KATHERINE ITT.

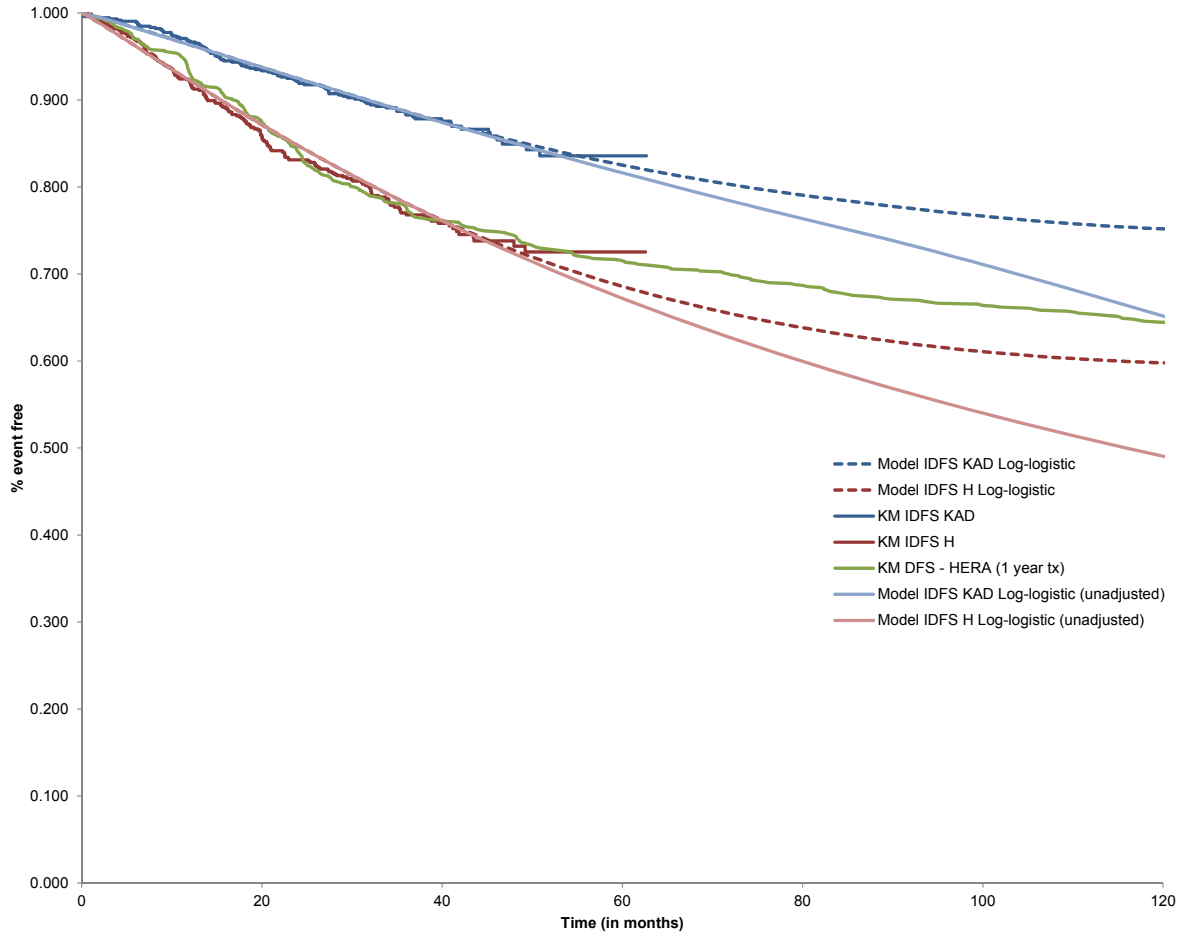
The approach taken by the company was to implement in the model a trend similar to the one observed in Figure 5.3. This was operationalised by including patients being "cured", where "cured" means that patients are assumed to be no longer at risk of recurrence and, therefore, only subject to background mortality. In particular, the company assumed that the proportion of patients being "cured" linearly increased with time from 0% at 36 months to 95% at 120 months. The company selected 36 months as the starting point of the "cure" based on their interpretation of Figure 5.3 (the figure shows a clear change in the hazard rate from this time point) and because 36 months was also the preferred choice of the Appraisal Committee in TA569.[17]

The company also referred to the case study report by Takeuchi et al. 2009,[49] where the incidence of late recurrence in 1,114 Japanese patients with surgically treated breast carcinoma was examined. The study reports that 12 patients (1.07%) experienced a disease recurrence after 10 years. Using 95% as

the "maximum cure rate" at 120 months, the company's model predicted that 1.42% of patients in the trastuzumab arm experienced a disease recurrence after 10 years, which is in line with the recurrence rate reported by Takeuchi et al. study.[49] Furthermore, the same cure rate was TA569.[17]

Finally, according to the company, the resulting adjusted IDFS curves shown in Figure 5.4 were broadly reflective of the long-term trend in recurrence rate observed in the HERA trial.

Figure 5.4: Unadjusted KATHERINE IDFS extrapolation (log-logistic - 0% cure proportion) vs. adjusted KATHERINE IDFS extrapolation (log-logistic - 95% cure proportion, 36 –120 months) vs. HERA 10-year KM curve

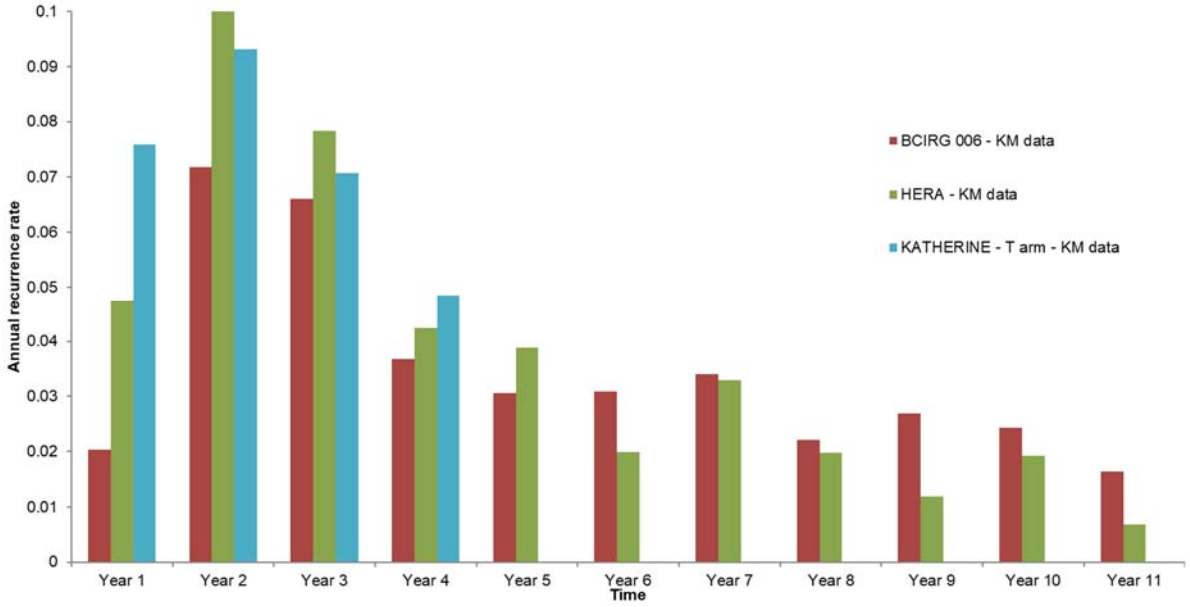


Source: Electronic model attached to the CS.[1]
Abbreviations: DFS: disease-free survival; H: trastuzumab; IDFS: invasive disease-free survival; KAD: trastuzumab emtansine; KM: Kaplan-Meier; tx: treatment.

ERG comment: In general, the ERG agrees with the company's interpretation of Figure 5.3, where the annual recurrence rate drops after 36. However, as pointed out in the clarification question B4,[4] this drop should have been observed in the KATHERINE trial. Figure 5.5 presents the annual recurrence rates from HERA and BCIRG 006 as in Figure 5.3 but also includes the rates observed in the trastuzumab arm of the KATHERINE trial. Figure 5.5 confirms that the drop in recurrence rate is also present in the KATHERINE data although it seems to be smaller than the one observed in HERA and BCIRG 006. Nevertheless, as the company mentioned in their response to the clarification question B4,[4] due to the censoring in the KATHERINE KM data, there is uncertainty associated with the

recurrence rates, especially from year 4 and onwards (median follow-up in the trastuzumab arm was approximately 41 months and only two events were observed during year 5).

Figure 5.5: Annual recurrence rate from the HERA, BCIRG 006 (node-positive population – DFS endpoint for trastuzumab) and the KATHERINE (ITT population – IDFS endpoint for trastuzumab) clinical trials



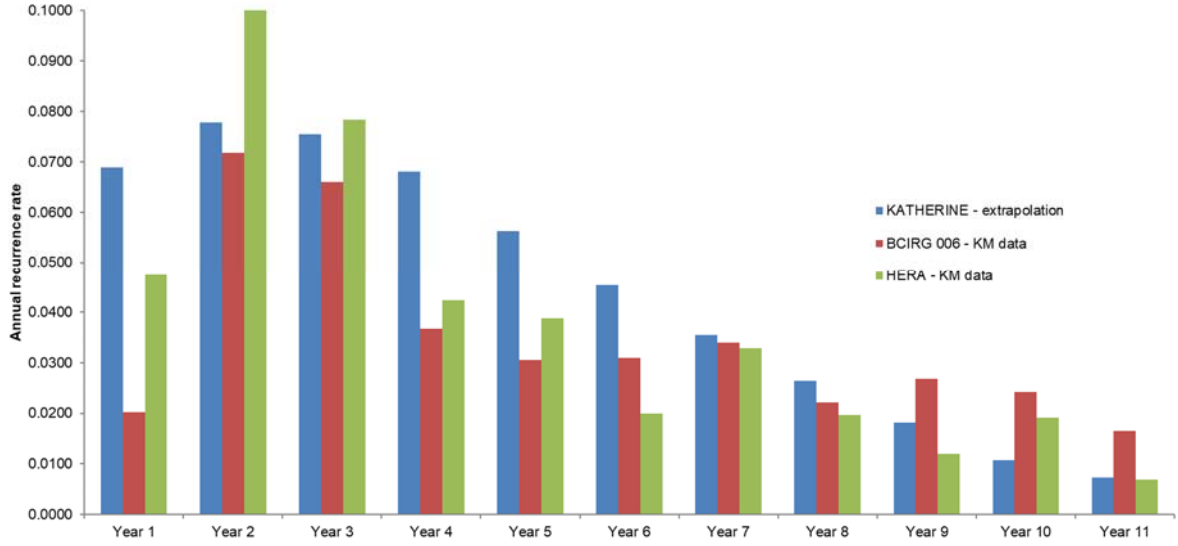
Source: Figure 2 in CL response.[4]
Abbreviations: KM=Kaplan Meier; T = trastuzumab;
Note: Year 5 data for KATHERINE has been omitted due to the low number of events observed (n=2)

Subsequently, in order to implement in the model a trend in recurrence rates similar to the one observed in HERA and BCIRG 006, the company included a "cure" rate depending on three parameters (the initial time from where the "cure" rate starts to apply [36 months], the maximum proportion of patients being cured [95%] and the time point where the cure rate stops increasing [120 months]) and one structural assumption (the proportion of patients being "cured" increased linearly). The company stressed that the same data sources, rationale, and adjustments were also used, and subsequently accepted, in TA569.[17] While this might be the case, the ERG would like to point out that this does not necessarily imply that the same approach is valid here.

To further justify their assumptions, the company referred to the recurrence rate after 10 years in Takeuchi et al. 2009.[49] While it is true that the company's model predicts a similar rate, it is unclear to the ERG whether this could have been predicted by choosing a different "cure" rate over different time periods.

In an attempt to validate the long-term extrapolations obtained with the model, the company presented in Figure 5.6 the recurrence rate in the trastuzumab arm of the model, and the observed recurrence rate of both trastuzumab arms in the BCIRG 006 and HERA studies. The company considered that the difference in recurrence rates observed in the first four years was driven by the results from the respective trials, that from year 4 to year 10 the recurrence rates observed in BCIRG 006 and HERA were broadly similar to the modelled recurrence rate and that this confirms that the adjustments made were reasonable and appropriately reflect the long-term risk of eBC patients.

Figure 5.6: Annual recurrence rate observed in the trastuzumab arms of the BCIRG 006* and HERA* trials compared to modelled recurrence rate in trastuzumab arm of KATHERINE**



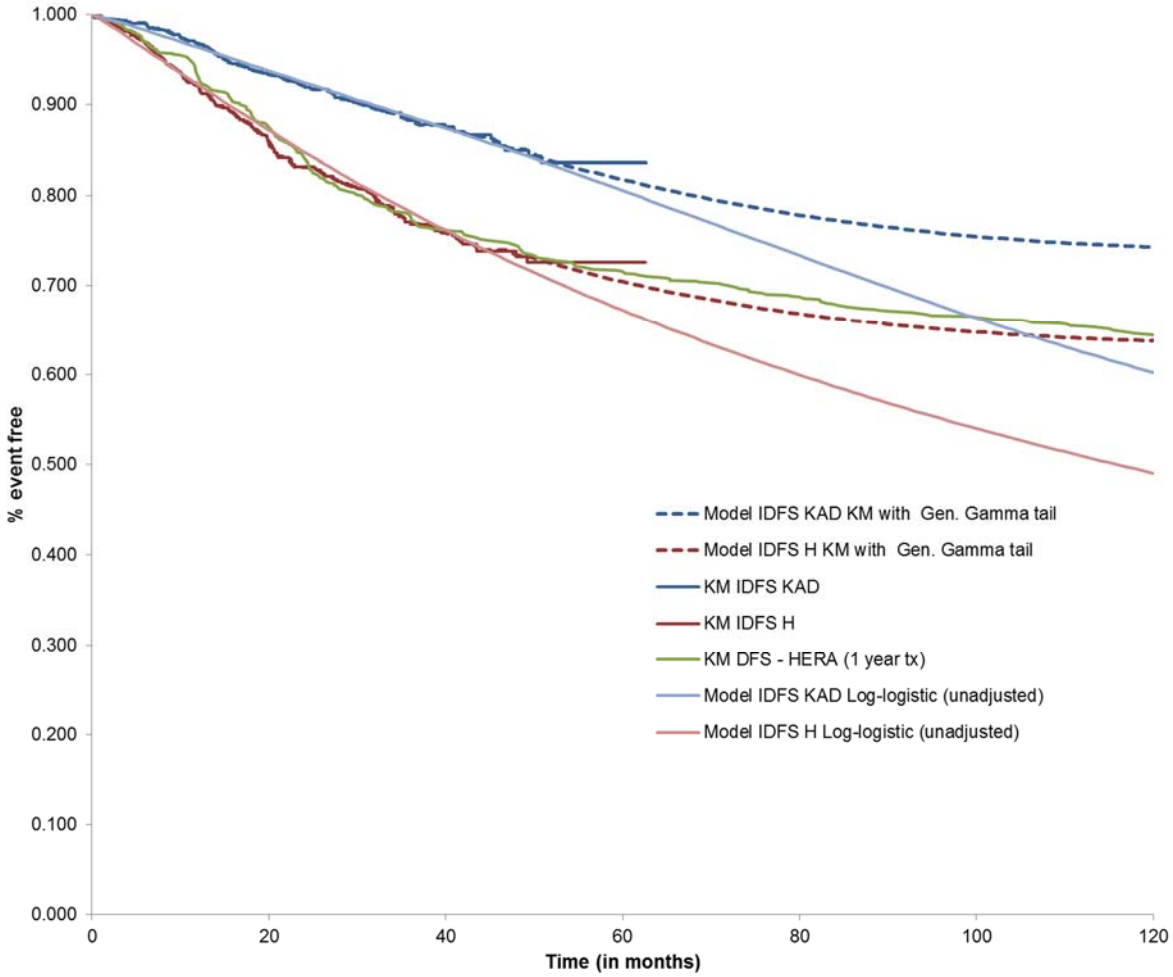
Source: Figure 23 in CS.[1]
Abbreviations: KM: Kaplan Meier.
* node-positive population; **, ITT population.

As mentioned in the clarification question B7,[4] the ERG does not consider the company's interpretation of Figure 5.6 evident. For example, in both HERA and BCIRG 006 the drop at year 4 is much larger than the drop observed in the model. The company agreed with this but noted that the overestimation of the recurrence rates persisted only between year 4 and year 6. From year 7 onwards, the extrapolated recurrence rate is more in line with those KATHERINE and BCIRG 006. Also, an overestimation of the comparator arm recurrence rate in three years of a 52-year analysis (6%) is unlikely to have a large impact on the cost effectiveness results. While this might be the case, the ERG considers that it is important to note that the recurrence rates for the trastuzumab arm predicted by the model do not seem to be in line with those observed in the KATHERINE trial, as shown in Figure 5.5. This is especially clear at year 2 and year 4. Thus, for the trastuzumab arm, the model fails to replicate the observed recurrence rates in the KATHERINE trial and to reproduce the drop observed at year 4 in the HERA and BCIRG 006 trials. The same might happen with the trastuzumab emtansine arm but, with the current information, the ERG is not able to verify this statement. Whether this has a large impact on the model results or not is a different matter.

While the efforts of the company were mostly focused on replicating the trend observed in the long-term recurrence rates, the ERG considers that the evidence provided in Figure 5.4 might have been overlooked by the company. If the node-positive population in the HERA trial is assumed to be a more appropriate proxy for the trastuzumab arm in KATHERINE, the modelled IDFS (red-dashed curve in Figure 5.4) should be closer to the observed DFS in HERA (green line in Figure 5.4). However, as can be seen in Figure 5.4, the modelled IDFS curve is clearly below the KM curve from HERA from approximately month 40 and beyond, which may imply an underestimation of IDFS for the trastuzumab arm for almost the entire time horizon. As shown in Figure 5.7, with the ERG's preferred choice for IDFS (KM KATHERINE data up to 51 months for trastuzumab emtansine, 49 months for trastuzumab, with generalised gamma tail), the extrapolated IDFS curve for the trastuzumab arm is closer to the HERA KM curve (although it is still below). Trend in recurrence rates is an outcome of the model and might be difficult to replicate, especially when simple approaches, like a linear decline in the rate, are

assumed. Matching two survival curves in this case is easier as can be tackled by selecting different parametric distributions (i.e. model inputs).

Figure 5.7: Unadjusted KATHERINE IDFS extrapolation (KM data up to month 51 for TE and 49 for T with generalised gamma tail - 0% cure proportion) vs. adjusted KATHERINE IDFS extrapolation (KM data up to month 51 for TE and 49 for T with generalised gamma tail - 95% cure proportion, 36 –120 months) vs. HERA 10-year KM curve



Source: Electronic model attached to the CS.[1]
Abbreviations: DFS: disease-free survival; Gen: generalized; H: trastuzumab; IDFS: invasive disease-free survival; KAD: trastuzumab emtansine; KM: Kaplan-Meier; tx: treatment

In summary, the company adjusted the long-term IDFS extrapolations following the rationale in TA569.[17] As mentioned above, while this might be the case, the ERG considers that this does not necessarily imply that the same approach is valid here. However, since there is no alternative evidence to support a better-informed choice of "cure" parameters, the ERG decided to accept the company's approach and explored the impact of changing the cure parameters on the results with scenario analyses.

Duration of the trastuzumab emtansine treatment effect

The company assumed for the base-case analysis that the treatment effect of trastuzumab emtansine was maintained for 84 months before gradually decreasing to no treatment effect at 120 months. The assumption of maintenance of treatment effect beyond the KATHERINE follow-up time was based on the duration of the treatment effect observed in the HERA and BCIRG 006 trials,[47, 48] since the company expects a similar pattern to be observed in the long-term KATHERINE data. The hazard ratios (HRs)

between year 7 and year 10 observed in the HERA and BCIRG 006 trials were 0.803 and 0.801, respectively. This HRs can be used to support the presence of a treatment effect between seven and 10 years after treatment.

In TA424 (appraisal of pertuzumab in the neoadjuvant treatment of HER2-positive eBC) a treatment effect duration of seven years was assumed. In the current submission, the company assumed an incremental treatment effect duration of seven years, before decreasing linearly to no treatment effect at ten years. The addition of the waning effect period was justified by the company by indicating that patients received a total of 14 cycles of trastuzumab emtansine in the adjuvant setting, as opposed to only four to six cycles in the neoadjuvant setting.

The company also noted that when the IDFS KM curves from KATHERINE were capped at median follow-up (approximately 41 months), i.e. before the large part of the censoring occurs, the difference between the two curves seemed to be maximum and interpreted this as an increasing treatment effect.

Finally, the company mentioned that the base-case assumptions regarding treatment effect were aligned to the company's base-case of TA569.[17] The ERG for that appraisal preferred to assume that the treatment effect was maintained for 48 months (4 years) before ceasing completely at 84 months (seven years). Even though this was accepted by the appraisal committee, the company of the current appraisal considers these assumptions to be overly conservative and unreflective of clinical practice (in line with the company of TA569 and the clinical expert in attendance at the TA569 meetings). The company expects that the OS interim analysis (2nd analysis of IDFS) from the APHINITY trial (Q4 of 2019),[1] will prove the ERG's assumptions in TA569 to be conservative.

ERG comment: Given the evidence presented by the company and the results in HERA and BCIRG 006 trials,[47, 48] the ERG considers it plausible a treatment effect duration beyond the KATHERINE follow-up time. In their base-case, the company assumed that the treatment effect of trastuzumab emtansine was maintained for 84 months before gradually decreasing to no effect at 120 months. In the clarification question B11,[4] the ERG asked the company for further clarification on these assumptions. In their response,[4] the company indicated that:

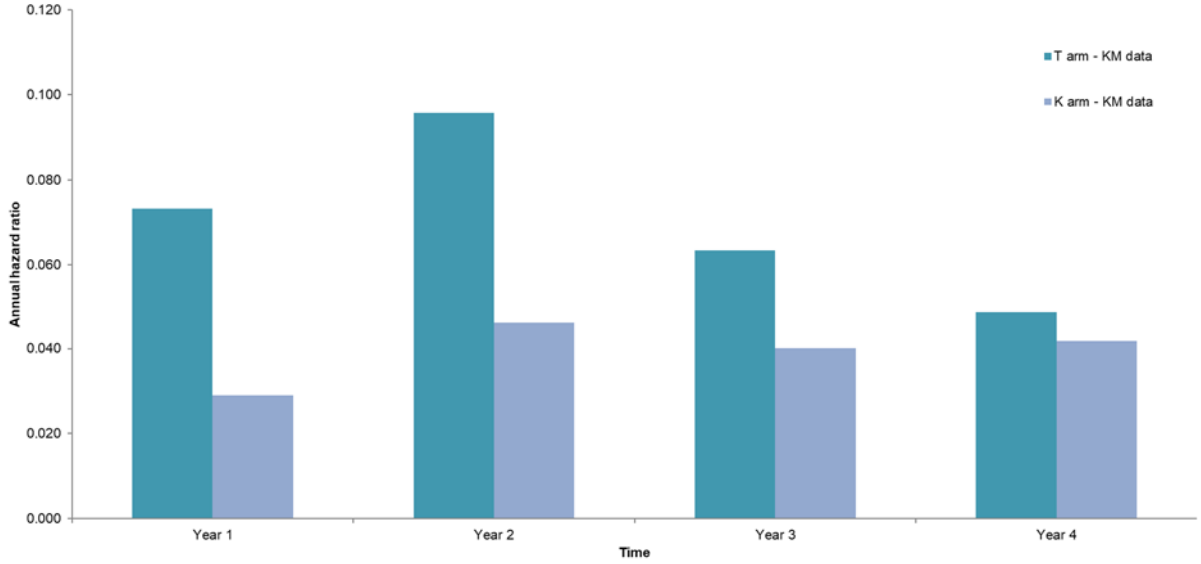
- "Maintained" treatment effect means that the extrapolation of the KM curve for trastuzumab emtansine remains unadjusted until the time point where it is assumed that the effect starts waning (84 months in the base-case).
- The company clarified that including "cure" adjusts the extrapolations for both arms from 36 months in the base-case. However, the "cure" adjustment is applied (equivalently) to both treatment arms and it is independent of the treatment effect duration (which is applied to trastuzumab emtansine only).
- "Gradually decreased" is operationalised as follows: the hazard (recurrence) rates in the trastuzumab emtansine arm increase linearly (at month 84) until they are equivalent to those in the trastuzumab arm at month 120 (at that point hazard ratio = 1).
- No additional rationale was provided as to why 84 months and 120 months were chosen as the beginning and end of the waning of the treatment effect.

In response to the clarification question B13,[4] the company provided the following plots shown below:

- Figure 5.8: IDFS hazard rates over time for both arms based on the IDFS KM curves in KATHERINE (ITT population)
- Figure 5.9: IDFS hazard ratio over time based on the IDFS KM curves in KATHERINE (ITT population).

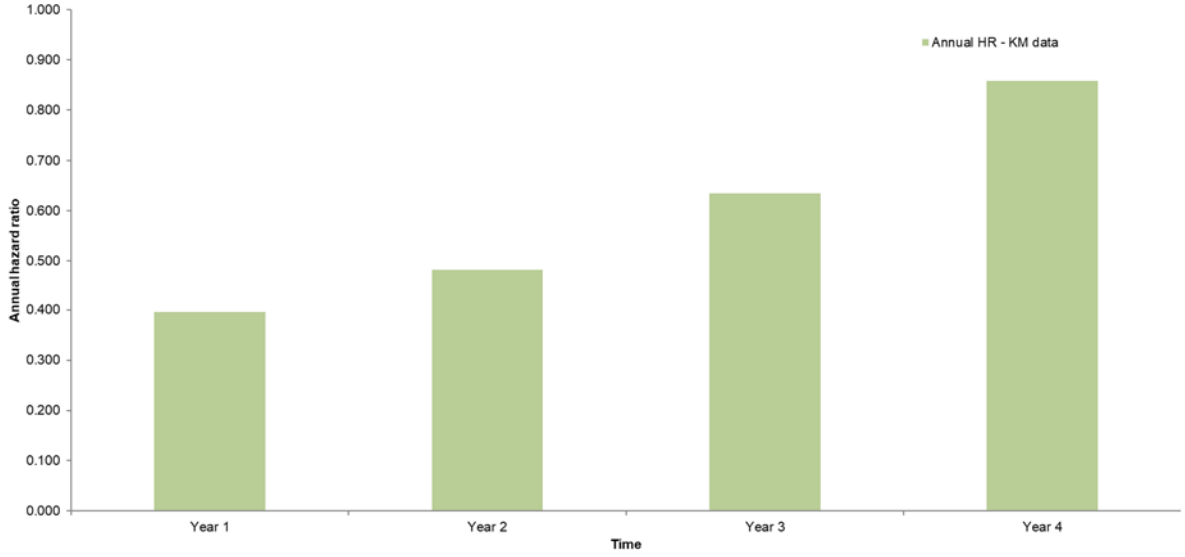
- Figure 5.10: IDFS hazard rates over time for both arms based on extrapolated curves.
- Figure 5.11: IDFS hazard ratio over time based on extrapolated curves.

Figure 5.8: Annual recurrence rate over time in KATHERINE KM data (ITT population)



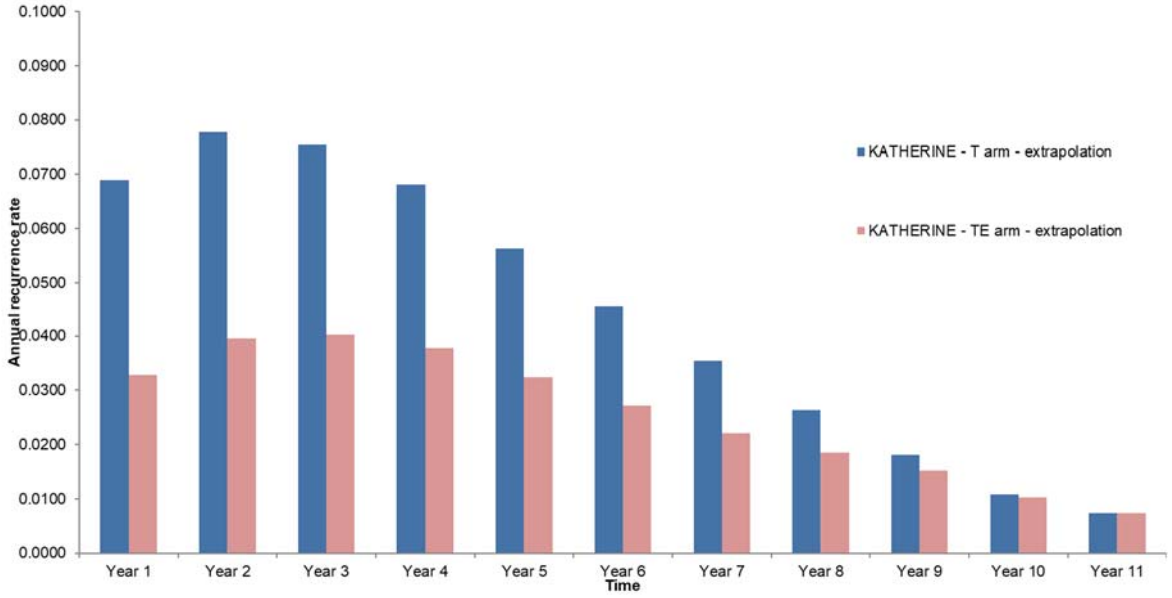
Source: Figure 5 in clarification letter response.[4]
Abbreviations: ITT: intention to treat; KM: Kaplan-Meier; K: trastuzumab emtansine; T: trastuzumab.

Figure 5.9: Annual hazard ratio over time in KATHERINE KM data (ITT population)



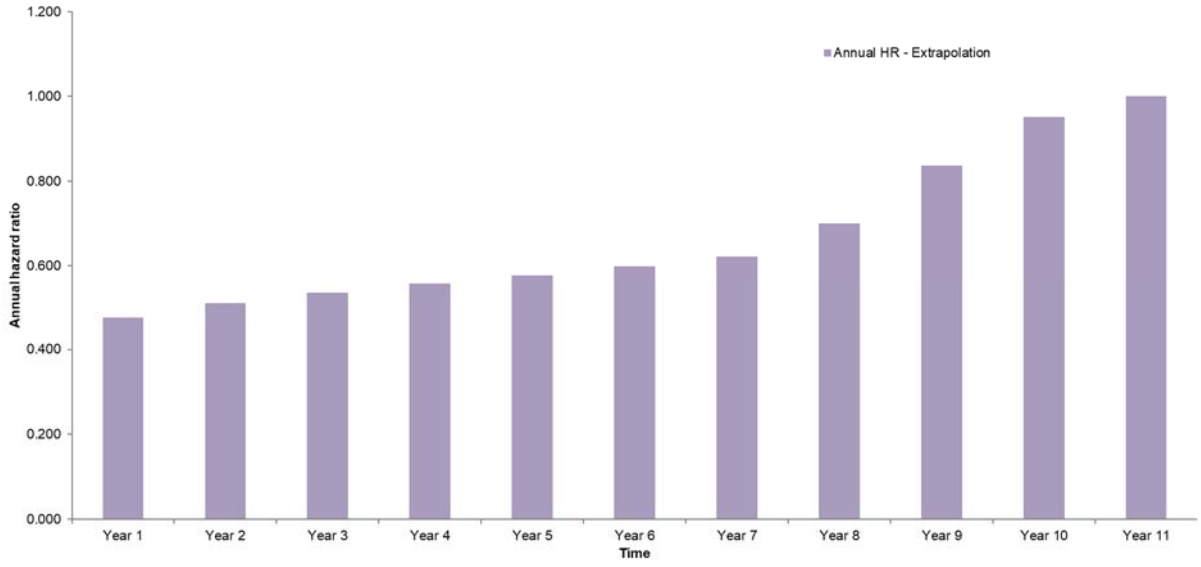
Source: Figure 6 in clarification letter response.[4]
Abbreviations: HR: hazard ratio; KM: Kaplan-Meier; K: trastuzumab emtansine; T: trastuzumab.

Figure 5.10: Annual recurrence rate over time in IDFS extrapolations of KATHERINE data (ITT population)



Source: Figure 7 in clarification letter response.[4]
Abbreviations: TE: trastuzumab emtansine; T: trastuzumab.

Figure 5.11: Annual hazard ratio over time in IDFS extrapolations of KATHERINE data (ITT population)



Source: Figure 8 in clarification letter response.[4]
Abbreviations: HR = Hazard ratio.

From these figures, the ERG concluded that:

- Recurrence rates predicted by the model do not seem to be in line with those observed in the KATHERINE ITT data. For the trastuzumab arm see Figure 5.6 and 5.8. For the trastuzumab emtansine arm see Figure 5.6 and 5.10.

- Figure 5.8: there is practically no drop in the recurrence rates for the trastuzumab emtansine arm. This might indicate that the adjustment should be different for the trastuzumab emtansine and trastuzumab arms.
- Figure 5.9 shows that the HR observed in the KATHERINE ITT data at year 4 is approximately 0.85, whereas Figure 5.11 shows that the HR predicted by the model at year 4 is approximately 0.6.

The ERG agrees with the company though that the plots presented above should be interpreted with caution due to censoring. Table 5.7 shows the patients at risk and IDFS events over time in the KM ITT data. Median follow-up in both arms was approximately 41 months. There is substantial censoring at year 4 and limited event numbers, which would result in results in uncertainty in the observed hazard rates in this time period. The company acknowledged the uncertainty around this modelling aspect conducted a number of scenario analyses. The results of these analyses are shown in Section 6.2.3 of this report.

Table 5.7: Patients at risk and event numbers in the KATHERINE ITT trial data*

Time	Trastuzumab arm			Trastuzumab emtansine arm		
	Patients at risk at start of year (%)	Patients at risk at end of year (%)	Number of IDFS events	Patients at risk at start of year (%)	Patients at risk at end of year (%)	Number of IDFS events
Year 1 (0-11 months)	743 (100.00%)	635 (85.46%)	53	743 (100.00%)	685 (92.19%)	21
Year 2 (12-23 months)	635 (85.46%)	555 (74.70%)	63	682 (91.79%)	640 (86.14%)	32
Year 3 (24-35 months)	555 (74.70%)	350 (47.11%)	33	633 (85.20%)	443 (59.62%)	24
Year 4 (36-47 months)	350 (47.11%)	110 (16.02%)	14	409 (55.05%)	170 (22.88%)	12
Year 5 (48-59 months)a	110 (16.02%)	0 (0.00%)	2	170 (22.88%)	0 (0.00%)	2

Source: Table 8 in clarification letter response.[4]
*Discrepancies exist in the "patients at risk…" categories due to the non-uniform time intervals in KM data.
a Year 5 has been omitted from
and **Error! Reference source not found.** due to low event numbers
Abbreviations: IDFS: invasive disease-free survival;

Despite the uncertainty associated with the observed hazard rates, these are still the best source of available evidence to inform this aspect of the model. At year 4, the modelled HR was less than 0.6, as opposed to almost 0.85 seen in the trial. This is a considerable difference in favour of trastuzumab emtansine and may indicate that the waning of the treatment effect should end (HR = 1) before month 120. This deviation between observed and modelled HR already occurs at year 3, even though the difference is smaller. The starting point of the treatment effect waning (the point where the trastuzumab emtansine extrapolation starts to be adjusted) is difficult to assess because there is simply no evidence to inform this parameter. For this reason, the ERG took the following approach for its preferred base-case. As mentioned above, based on the HRs observed in KATHERINE, the ERG considers it plausible that the waning of the treatment ends before month 120. The exact end point was determined by looking at the predicted annual HR assuming a generalised gamma extrapolation (this was the preferred choice

for the ERG). It was observed that after eight years the model predicted a HR above 1, implying thus a better treatment effect for trastuzumab during years 8 to 10. The ERG considered this implausible and set the end point of the treatment effect exactly at eight years (96 months). That way, the treatment effect for trastuzumab and trastuzumab emtansine during years 8 to 10 were equal (HR = 1). As expected, choosing a starting point for the treatment effect waning was more difficult. Based on the HRs observed in KATHERINE (Figure 5.9), it seems plausible to expect HRs increasing with time. However, with the ERG preferred choice for modelling IDFS this did not happen. By using KM data up to the month where the last event was observed, the exact HRs observed in KATHERINE (up to year 4 in the model) were replicated in the model. However, from year 5 onwards, the HRs were based on the IDFS extrapolation and, with the generalised gamma, the HR dropped at year 5 and started to increase again after that. To minimise the impact of this drop, the ERG chose the 36 months as the starting point for the treatment effect waning. The ERG acknowledges the uncertainty around the choice of these parameters and assessed the impact on the results with scenario analyses.

Time period 3 (10 years and beyond) – (background mortality)

Based on the HERA trial, where the hazard rate observed at year 11 was similar to the hazard rate of the general population in the UK for a 65 years old patient, [47] the company assumed in the model that 95% of the patients are only exposed to background mortality after 10 years. In particular, the model assumes that in the trastuzumab arm 5% of patients are at risk of recurrence. For these patients, the risk of recurrence was derived from the KATHERINE ITT data. The remaining 95% of patients are assumed to be subjected to the background mortality rate of the UK general population (adjusted for age) only. For the trastuzumab emtansine arm, since no treatment effect is assumed beyond 10 years, the hazard rate of recurrence from the trastuzumab arm was also applied to the trastuzumab emtansine arm.

ERG comment: Empirical data pertaining to this time period does not exist in this indication. This makes it difficult to validate the IDFS curves beyond the 10-year time point. In response to the clarification question B10,[4] the company conducted several scenario analyses to quantify the impact on the model results of changing the start and end point of the "cure" in the model. The results of these analyses are shown in Appendix 3 and indicated that the impact on the ICER was minor. This is because "cure" is applied equivalently across both arms of the model.

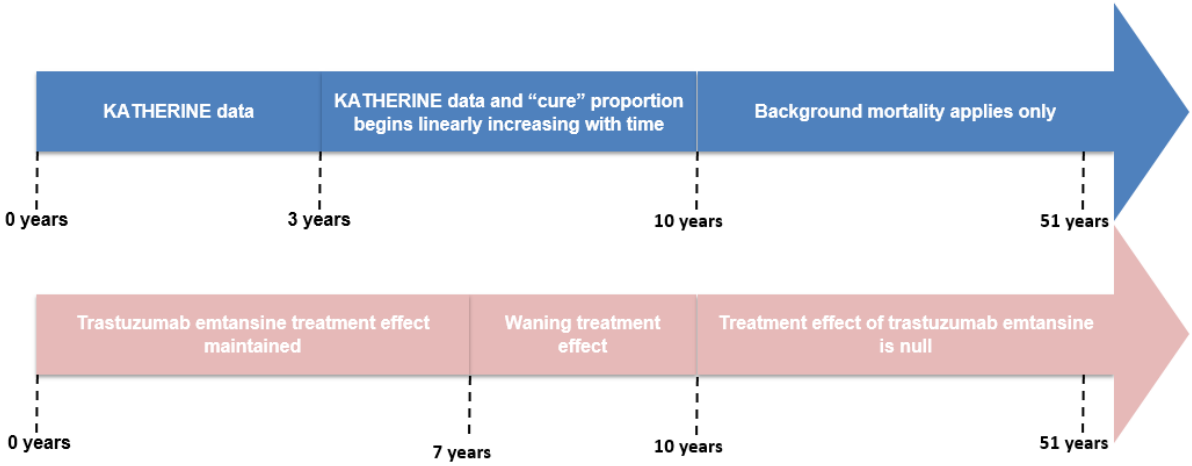
Modelling of death from IDFS

Patients in the IDFS health state are at risk of recurrence (metastatic and non-metastatic) and death. The risk of death without recurrence was estimated from the KATHERINE ITT population data, where five deaths were observed prior to the occurrence of any events (two in the trastuzumab emtansine arm and three in the trastuzumab arm). The company considered this number too low to accurately and robustly extrapolate this probability (5/1,486 = 0.34%) over a long time period. Therefore, the probability of dying without recurrence events was assumed to be constant for the entire the time horizon. Nevertheless, after rescaling this to weekly probability (0.0001), the company observed that this was lower than the weekly mortality for the UK general population from cycle one of the model. Therefore, the company assumed that the probability of dying in the IDFS health state (prior to the occurrence of any events) was the same as the probability of dying for the age-adjusted UK general population.

Summary IDFS modelling

Figure 5.12 summarises the main assumptions made by the company regarding the modelling of IDFS. The resulting IDFS curves used in the company base-case (ITT KATHERINE data, log-logistic extrapolation) are shown in Figure 5.13.

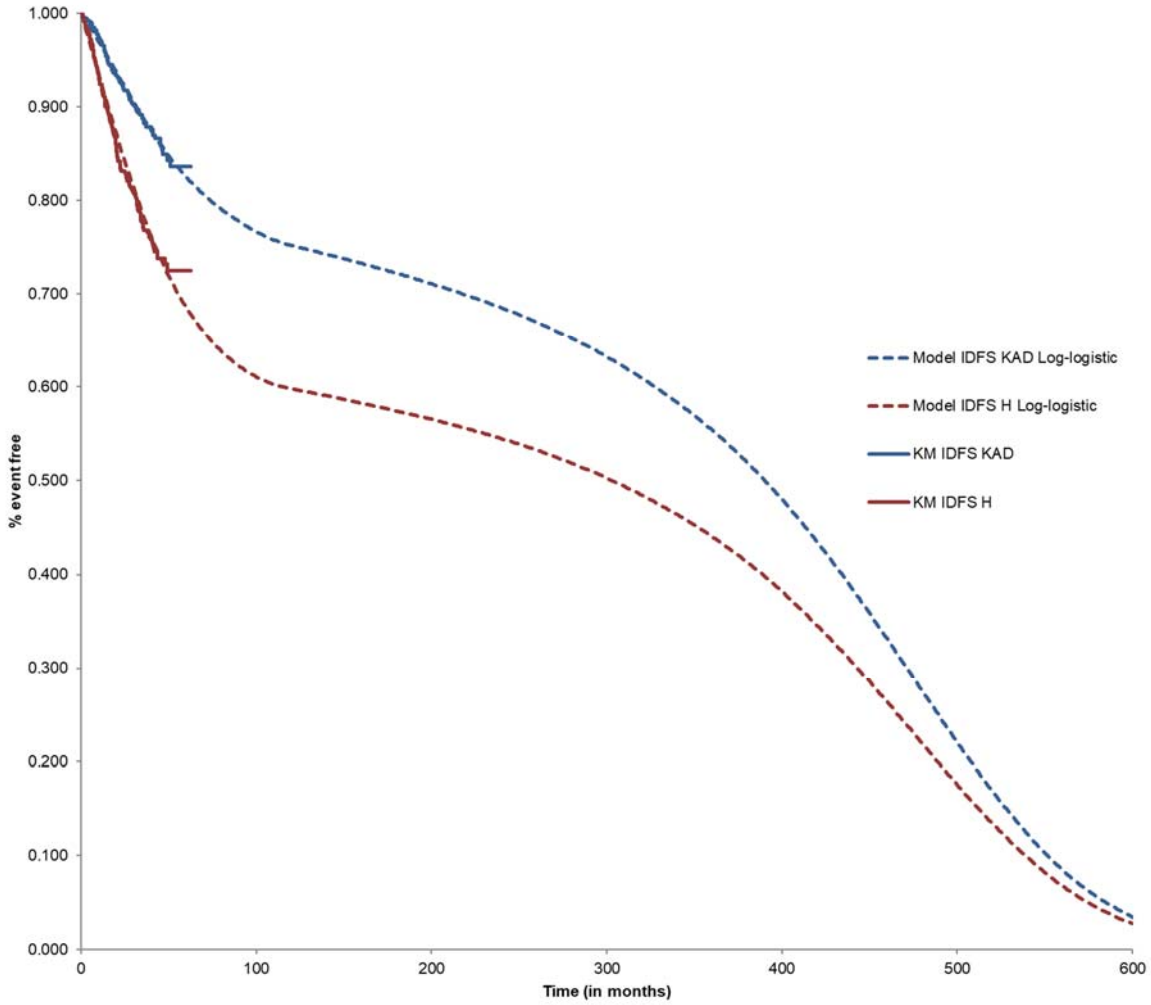
Figure 5.12: Summary of the construction of IDFS curves and timing of treatment effect



Source: Figure 25 in CS.[1]

Time period 1 (0–3 years): KATHERINE data used to estimate recurrence rates. **Time period 2 (3–10 years)**: extrapolated recurrence rate adjusted to reflect the trend observed in long-term trastuzumab studies. **Time period 3 (10–51 years)**: 95% of patients are "cured" and no longer at risk of recurrence (only background mortality). Also based on long-term trastuzumab studies.

Figure 5.13: Company base-case IDFS extrapolation (ITT KATHERINE data, log-logistic extrapolation)



Source: Figure 26 in CS.[1]
Abbreviations: H, trastuzumab; IDFS: invasive disease-free survival; KAD: trastuzumab emtansine; KM: Kaplan-Meier.

5.2.6.2 Invasive disease-free survival (IDFS) – node-negative subpopulation

General approach

The probability of remaining in the IDFS health state was derived from patient-level data in the KATHERINE node-negative population. At the time of the primary analysis of IDFS (data cut-off 25 July 2018), 29 (7.25%) and 62 (15.62%) IDFS events had occurred in the node-negative population of the trastuzumab emtansine and trastuzumab arms, respectively. To model IDFS over a lifetime time horizon, the same approach as for the ITT population was taken by the company. The ERG, therefore, refers to Section 5.2.6.1 of this report for further details. Details on the methodology used to extrapolate IDFS in each time period are provided below.

Time period 1 (zero to three years) – KATHERINE trial data

Assessment of the proportional hazards assumption

The assessment of the proportional hazards (PH) assumption was based on the log-cumulative hazard plots (Figure A3.1). Based on this, the company concluded that it is difficult to prove that it is appropriate to apply the PH assumption to this data but preferred to assume that PH do not exist between the two treatment arms. IDFS results were also in this case rather insensitive to whether or not proportional hazards is assumed. Landmark IDFS figures from extrapolations that have assumed proportional and non-proportional hazards shown in Table 16 of the response to clarification question B2 (not shown here) seems to confirm this.[4]

ERG comment: The ERG agrees with the company's approach and considers that stratified modelling for IDFS is more appropriate.

Selection of parametric models

Goodness of fit of the parametric survival curves was assessed in the same way it was done for the ITT population. Thus, the company used AIC values, visual inspection of the parametric survival curves against the KM data and absolute fit of the parametric survival curves to the KM data in the first four years. For a complete assessment the ERG refers to Appendix 5 of this report.

The AIC values are shown in Table A5.1. Based on the AIC values, the company judged that, when the fit across the two arms jointly was considered, the best fitting extrapolation was produced by the exponential distribution. Visual goodness of fit of each parametric distribution and the KM curves was assessed with Figure A5.2. Based on this figure, the company indicated that none of the extrapolations fit the data particularly well in the trastuzumab arm, since nearly all the extrapolations overestimated IDFS when compared to the KM data. The absolute fit of the parametric survival curves to the KM data was assessed by comparing the percentage of patients who did not experience an IDFS event at 12, 24, 36 and 48 months as shown in Table A5.2. Based on this table, the company concluded that, overall, all parametric survival curves across both treatment arms provided a good absolute fit to the KM data since incremental differences between the parametric extrapolations and the KM data were always below 2.5% in absolute value. Because of this, the company considered that it can be reasonably assumed the differences in the absolute fit of the parametric extrapolations to be negligible.

Based on the results of all the assessments described above, the company chose the exponential distribution as the best candidate distribution to model IDFS in both treatment arms in years zero to three (time period 1).

ERG comment: The same points discussed by the ERG in Section 5.2.6.1 for the ITT population are also valid here. Thus, the ERG also prefers using KM data directly to model IDFS up to the time when the last event was observed (46 months for trastuzumab emtansine and 49 months for trastuzumab) and use parametric extrapolations as basis for the adjusted curves from these points onwards. The selection of the parametric models to extrapolate IDFS afterwards was also based on the best fit at the tails. The generalised gamma was also chosen in this case (see Table A3.2). It should be noted though that data for the node-negative subpopulation is limited compared to the ITT data which makes the selection of an appropriate survival distribution more uncertain.

Time period 2 (three to 10 years) – long-term external data (trastuzumab arm)

The approach taken by the company was the same as the one used for the ITT population. The ERG refers to Section 5.2.6.1 of this report for further details.

ERG comment: The company assumed that the node-positive populations in BCIRG 006 and HERA were a more appropriate proxy to the KATHERINE ITT population. However, it uncertain to what extent that node-positive populations in BCIRG 006 and HERA are an appropriate proxy to the KATHERINE node-negative population. Since the node-negative population can be considered to be, in terms of disease prognosis, better in comparison to the node-positive population, and, thus, better than the ITT population (which is mixed), it could be speculated that IDFS for node-negative patients would have been high in comparison to IDFS in the ITT population. For this reason, the adjustments made to the IDFS extrapolations in the ITT population are very likely to be invalid for the node-negative population. For example, the long-term HERA data (green line from Figure 5.7) used as proxy for the trastuzumab arm in the KATHERINE ITT population are not valid for the trastuzumab arm in the KATHERINE node-negative population. For the KATHERINE node-negative population we would need another proxy, probably from a different subgroup in HERA, which unfortunately is not available. Thus, all the adjustments made to the KATHERINE node-negative data are based on a proxy from HERA that was meant for the KATHERINE ITT population, which means that it is likely to be a wrong proxy for the KATHERINE node-negative data. Furthermore, recurrence rates for the node-negative population were not reported by the company. Therefore, the ERG is unable to assess whether these rates are properly captured by the node-negative model or not. Something similar can be said about the duration of the treatment effect as hazard ratios were only reported in detail for the ITT population. Thus, the ERG is also unable to assess whether the treatment effect duration assumed for the ITT population is valid for node-negative patients. However, based on the model extrapolations when selecting a generalised gamma distribution for IDFS in the node-negative population, the ERG observed that by using KM data up to month 46 for trastuzumab emtansine and 49 months for trastuzumab, the exact HRs observed in the KATHERINE node-negative subpopulation (up to year 4) were replicated in the model. This KM data showed that the HR was above 1 already at year 3 but dropped to less than 0.5 at year 4. This behaviour is different to the one observed in the ITT population where the HRs increased with time but it could be due to the limited data on the node-negative subgroup. However, from year 5 onwards, the HRs were based on the IDFS extrapolation with the generalised gamma, and the HR immediately above 1 at year 5. The ERG considered that this may lack face validity and for that reason decided to change the IDFS extrapolation and use an exponential as the company did. This illustrates the difficulty, and the associated uncertainty, to choose an appropriate IDFS parametric curve for the node-negative subpopulation.

In conclusion, as mentioned in Section 5.2.4, only results for the node-negative subgroup are relevant for this report. However, due to the issues described above, the uncertainty around these results is expected to be larger than the uncertainty in the ITT population.

Time period 3 (10 years and beyond) – (background mortality)

The approach taken by the company was the same as the one used for the ITT population. The ERG refers to Section 5.2.6.1 of this report for further details.

ERG comment: The same points discussed by the ERG in Section 5.2.6.1 are also valid here.

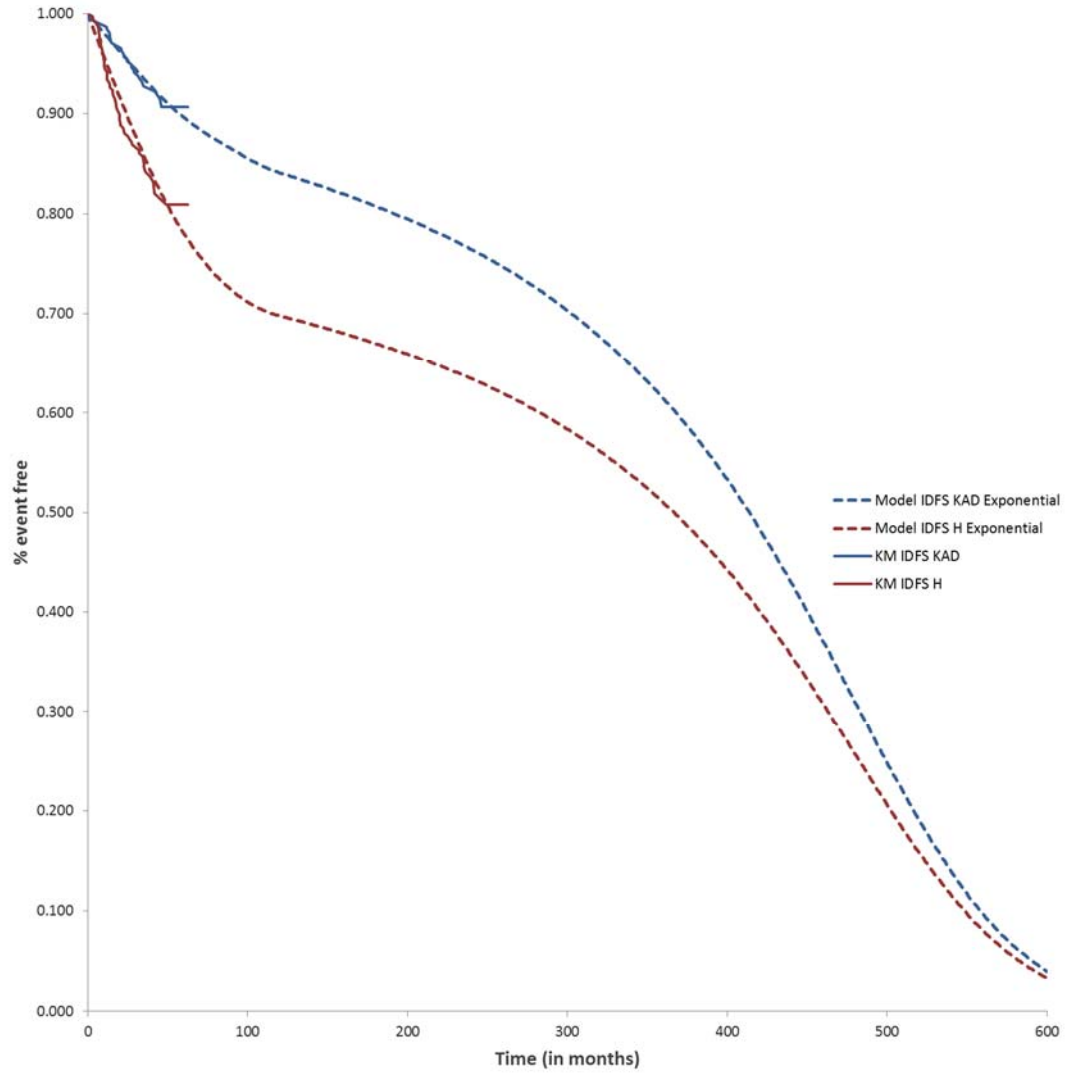
Modelling of death from IDFS

Given the low number of deaths observed in the node-negative population (4/797 = 0.5%), the company assumed that the probability of dying in the IDFS health state (prior to the occurrence of any events) was the same as the probability of dying for the age-adjusted UK general population.

Summary IDFS modelling

In general, the approach to model IDFS in the node-negative population was the same as the approach in the ITT population. The only difference was to use node-negative specific data from KATHERINE which resulted in selecting an exponential distribution to guide the long-term extrapolation. The resulting IDFS curves used by the company (node-negative KATHERINE data, exponential extrapolation) are shown in Figure 5.14.

Figure 5.14: Company IDFS extrapolation (node-negative KATHERINE data, exponential extrapolation)



Source: electronic model submitted with the response to the clarification letter – Part II.[4]
Abbreviations: H, trastuzumab; IDFS: invasive disease-free survival; KAD: trastuzumab emtansine; KM: Kaplan Meier.

5.2.6.3 Invasive disease-free survival (IDFS) – node-positive subpopulation

In the absence of direct comparative evidence between trastuzumab emtansine and pertuzumab, the company relied on an indirect treatment comparison (ITC) between KATHERINE data (trastuzumab emtansine vs trastuzumab) and APHINITY data (pertuzumab + trastuzumab vs. trastuzumab) given that in both trials the common comparator was trastuzumab monotherapy. The company's preferred approach to derive a comparison of trastuzumab emtansine vs. pertuzumab was through the use of the Bucher method. An overview of the Bucher approach is given in Sections 4.3 and 4.4 of this report.

The output of the Bucher method is a hazard ratio (HR) between trastuzumab emtansine and pertuzumab + trastuzumab. This HR was applied to the IDFS extrapolation in the trastuzumab emtansine arm to derive IDFS data for the pertuzumab arm of the cost effectiveness model. The company acknowledged uncertainty associated with this analysis, and for this reason three variations of the Bucher analysis were presented. These variations were called scenario A, B and C. The differences between the three approaches are summarised below and the resulting HRs are presented in Table 5.8.

- Scenario A – The HR was obtained from the node-positive APHINITY population and the node-positive KATHERINE population.
- Scenario B – The HR was obtained from the node-positive APHINITY population and the ITT KATHERINE population.
- Scenario C – The HR was obtained from the ITT populations in both trials.

Table 5.8: Hazard ratios from Bucher analysis

Scenario	APHINITY			KATHERINE			ITC	
	Population	HR (95% CI)	Log HR (±SE)	Population	HR (95% CI)	Log HR (±SE)	Log HR (±SE)	HR (95% CI)
A	N+	0.77 (0.62–0.96)	-0.26 (0.11)	N+	0.52 (0.38–0.71)	-0.65 (0.16)	-0.39 (0.19)	0.675 (0.461–0.989)
B	N+	0.77 (0.62–0.96)	-0.26 (0.11)	ITT	0.50 (0.39–0.64)	-0.69 (0.13)	-0.43 (0.17)	0.649 (0.467–0.904)
C	ITT	0.81 (0.67–1.00)	-0.21 (0.10)	ITT	0.50 (0.39–0.64)	-0.69 (0.13)	-0.48 (0.16)	0.617 (0.449–0.849)

Source: Table 37 in Appendix M of the CS.[20]
Abbreviations: 95% CI: 95% confidence interval; CS: company submission; HR: hazard ratio; ITC: indirect treatment comparison; ITT: intention to treat; N+: node-positive.

ERG comment: In the absence of direct comparative evidence between trastuzumab emtansine and pertuzumab, the company performed an indirect treatment comparison between KATHERINE data (trastuzumab emtansine vs trastuzumab) and APHINITY data (pertuzumab + trastuzumab vs. trastuzumab) given that in both trials the common comparator was trastuzumab monotherapy. However, as explained in Section 4.4 of this report, the populations in the two trials are not really comparable and the outcomes from this analysis (the HRs) are likely to be biased.

The company preferred the Bucher fixed-effect method over other ITC methods due to its relative simplicity and lack of data. A complete critique of the Bucher approach was presented in Section 4.4. The company argued that more complex methods (random-effects or individual patient level data methods such as meta-regression) would not resolve the differences in the population characteristics/effect modifiers (and therefore the bias) and would introduce additional uncertainty. Therefore, the company concluded that "*the methodological flaws resulting from the lack of clinical comparability of both the covariates and the study populations are likely to lead to uninterpretable and biased results which are not informative or useful for the purposes of decision-making*" (p. 19 from the Part II of the response to the clarification document).[4] The ERG considers that the conclusion of the company on the more advanced ITC methods would also hold for the simple Bucher-based ITC method. Furthermore, the ERG considers that the company could have attempted to demonstrate the lack of

clinical comparability between these trials, for instance by comparing the outcomes of the trastuzumab arms of both trials (the difference in these outcomes could be partially attributed to the differences in the observed trial/population characteristics). Less biased estimates could have been obtained, if the company had used data from alternative sources (i.e. not only from company conducted RCTs, but also from alternative registries) to provide relative clinical and cost effectiveness of trastuzumab emtansine versus pertuzumab + trastuzumab).

The company indicated that the HR in scenario A is the most appropriate (amongst A, B and C – but all of them are derived from different populations, so it could be said instead that it is the least inappropriate) since it is derived from node-positive populations in both trials. The ERG agrees with the company but considers that B and C can only be misleading and, therefore, should not be used.

Finally, it should be noted that, as mentioned above, in the model the HR was applied to the IDFS extrapolation in the trastuzumab emtansine arm to derive IDFS data for the pertuzumab arm of the cost effectiveness model. However, the IDFS extrapolation in the trastuzumab emtansine arm of the model is based on the ITT population instead of the node-positive subpopulation. Thus, even though the HR in scenario A was derived from the node-positive population in KATHERINE (and APHINITY), in the model it is applied to the KATHERINE ITT population, which is incorrect. As a consequence, the calculation of the IDFS data for the pertuzumab arm in the model is also incorrect. As separate data for the node-positive population are not available in the model, the ERG was not able to correct this error.

In summary, modelling IDFS in the node-positive population is seriously flawed. For this reason, the ERG considers the cost effectiveness analyses for the node-positive population unreliable and, therefore, inappropriate for decision making.

5.2.6.4 Recurrence – ITT population

General approach

As shown in Figure 5.1, patients in the IDFS health state can experience a metastatic or a non-metastatic recurrence. The transition probabilities from the IDFS health state to the recurrence health states were estimated from the recurrence events observed in each treatment arm of the KATHERINE ITT population. A breakdown of these events can be observed in Table 5.9. Death events were modelled separately and were not included as recurrence events. In the base-case analysis, the company applied treatment-specific probabilities (as opposed to probabilities pooled across both arms). Using the pooled probabilities was explored by the company in scenario analysis. Once in recurrence, patients can experience progression (from non-metastatic to metastatic, or from first line metastatic to second line metastatic) or death. Details are provided in the remaining of this section.

Table 5.9: Types of IDFS events observed in the KATHERINE ITT population

	Trastuzumab emtansine (n=743)	Trastuzumab (n=743)	Both arms (n=1,486)
IDFS event, n	91	165	256
Deaths without prior event, n (%)	2 (2.20%)	3 (1.82%)	5 (1.95%)
IDFS event excluding deaths, n	89	162	251
Metastatic recurrence, n (%)	78 (87.64%)	118 (72.84%)	196 (78.09%)
Non-metastatic recurrence, n (%)	11 (12.36%)	44 (27.16%)	55 (21.91%)

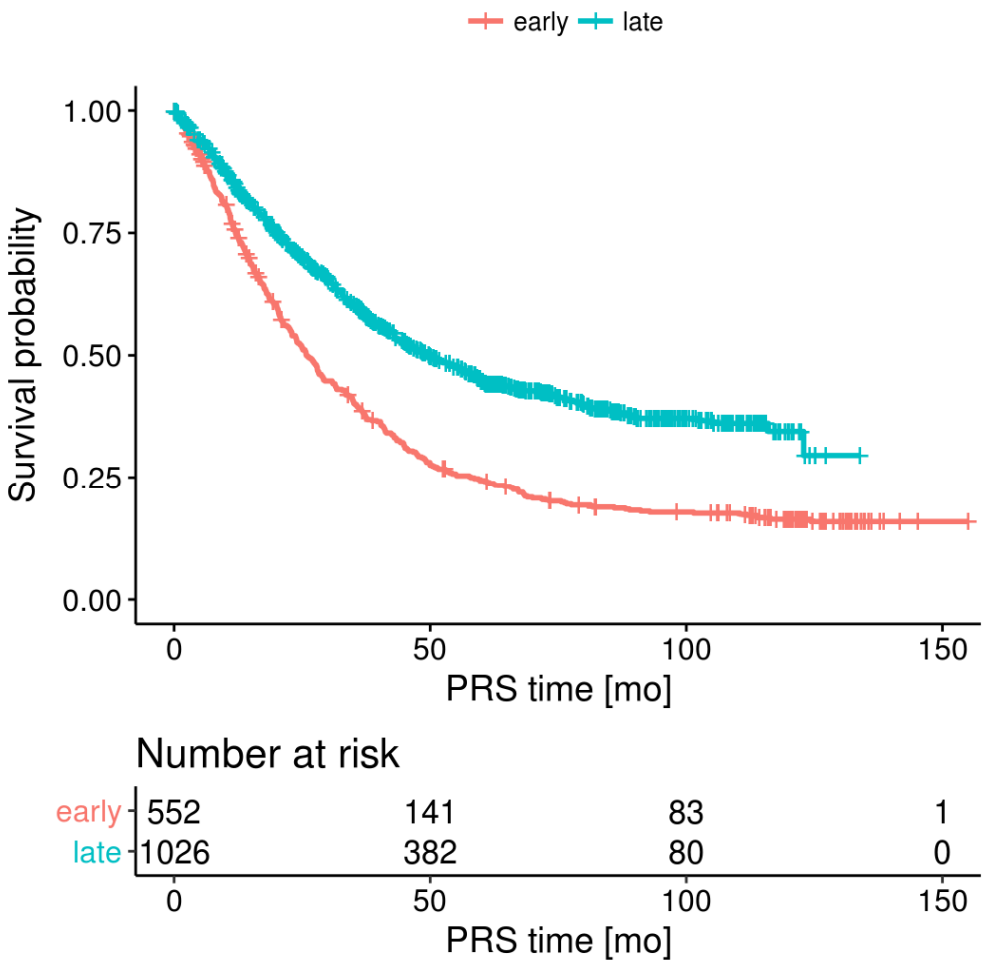
Source: Table 25 in CS.[1]
Abbreviations: IDFS: invasive disease-free survival, n: number of events.

Timing of recurrence

Based on the feedback provided by clinical experts consulted by the company, timing of recurrence was incorporated into the economic model since it is expected to have an impact on treatment outcomes and costs. According to these experts, patients who experience an "early" recurrence are more likely to have a more aggressive disease, which does not respond well to treatment, and to be on later lines of therapy for a relatively short time. Conversely, patients experiencing a "late" recurrence are more likely to have a less aggressive disease, which responds better to treatment, and to be on later lines of therapy for longer time, and, therefore, have higher total treatment costs.

The next step was to define what was considered an "early" and a "late" recurrence. This was assessed with the help of the HERA trial.[47] As shown in Figure 5.15, patients in the HERA trial who experienced a disease recurrence within 18 months of adjuvant treatment initiation had a better post-progression survival compared to patients who experienced a disease recurrence after 18 months of adjuvant treatment initiation. Based on this evidence, the company assumed 18 months as the time point to define "early" and "late" recurrence in the model. A breakdown of the recurrence events observed in each treatment arm of the KATHERINE ITT population, stratified by the timing of recurrence ("early" or "late"), can be seen in Table 5.10.

Figure 5.15: PRS of patients with disease recurrence in HERA ("early" vs "late" recurrence)



Source: Figure 27 in CS.[1]
Abbreviations: mo: months; PRS: post-recurrence survival.

Table 5.10: Proportion of "early" and "late" recurrences which are metastatic and non-metastatic by treatment arm in the KATHERINE ITT population

	Trastuzumab emtansine (n=743)	Trastuzumab (n=743)	Both arms (n=1,486)
Recurrence events excluding deaths, n	89	162	251
"Early" recurrence (before 18 months)			
Metastatic recurrence, n (%)	36 (85.71%)	60 (72.29%)	96 (76.80%)
Non-metastatic recurrence, n (%)	6 (14.29%)	23 (27.71%)	29 (23.20%)
"Late" recurrence (after 18 months)			
Metastatic recurrence, n (%)	42 (89.36%)	58 (73.42%)	100 (79.37%)
Non-metastatic recurrence, n (%)	5 (10.64%)	21 (26.58%)	26 (20.63%)

Source: Table 26 in CS.[1]
Abbreviations: IDFS: invasive disease-free survival.

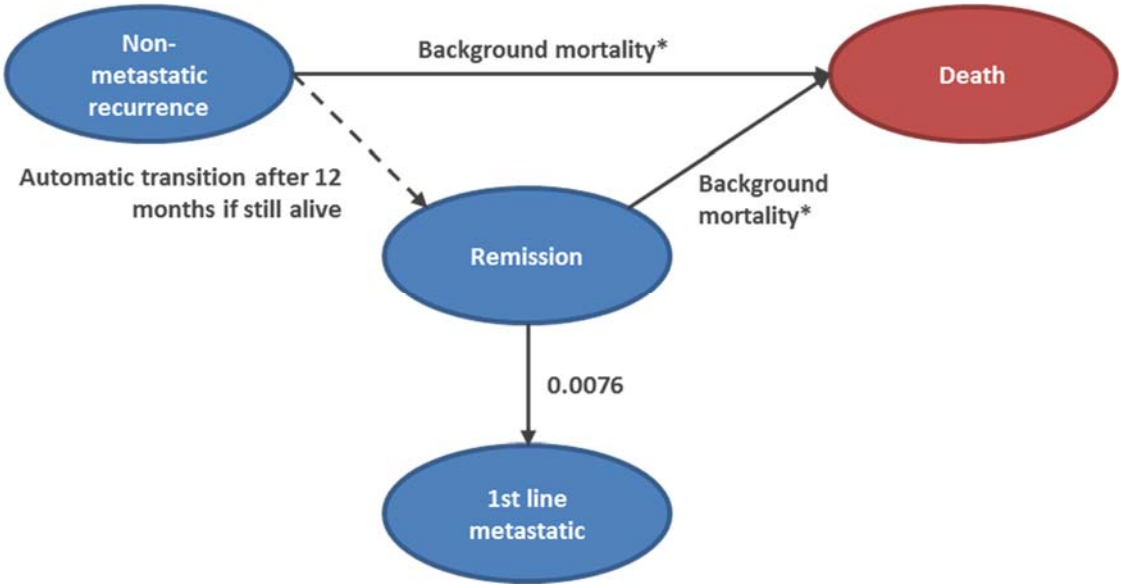
Additionally, the company indicated that breast cancer patients in the UK may be eligible for different treatments depending on the timing of disease progression. As an example, the company indicated that patients who experience an "early" metastatic recurrence (within 18 months of beginning adjuvant initiation) can be treated with trastuzumab emtansine. The ERG refers to Section 5.2.9.1 of this report for complete treatment sequences.

ERG comment: Data from the HERA trial confirmed that there is a difference in prognosis for patients who experienced a recurrence before and after 18 months from adjuvant initiation. The use of an 18-month "cut-off" point was judged reasonable by the ERG and Appraisal Committee during TA569 and was also adopted by the company here. The ERG for the current appraisal considers more appropriate to derive that "cut-off" point from KATHERINE data should these be available. However, given the small impact of this parameter on the model results, the selection made by the company seems reasonable too.

Non-metastatic recurrence

The non-metastatic recurrence pathway consists of two model health states: "Non-metastatic recurrence" and "Remission" (see Figure 5.1). The transition probabilities used in the model for the non-metastatic recurrence pathway are shown in Figure 5.16. The derivation of the transition probabilities are described separately below.

Figure 5.16: Monthly transition probabilities in the non-metastatic recurrence pathway



Source: Figure 29 in CS.[1]
Footnotes: *This risk of death without recurrence observed in KATHERINE was lower than the risk based on background mortality in the age-adjusted UK population.

Non-metastatic recurrence

The transition probabilities from IDFS to non-metastatic recurrence are estimated from the percentage of events observed in KATHERINE (see Table 5.10). Therefore, the model distinguishes between "early" and "late" non-metastatic recurrence. In the model it is further assumed that all patients experiencing non-metastatic recurrence would undergo one year of additional adjuvant therapy. Afterwards, all patients move to "remission". The "non-metastatic recurrence" health state is thus a "tunnel" state. The risk of dying with non-metastatic recurrence and in remission observed in KATHERINE was lower than the background mortality in the age-adjusted UK population. Therefore, only background mortality was applied in the model for the transition probabilities from non-metastatic recurrence to death and from remission to death.

ERG comment: The company acknowledged that the assumption that all patients transition to remission following non-metastatic recurrence may not be realistic and that some patients may experience a metastasis during these 12 months treatment period. However, clinical experts consulted by the company suggested that this would occur in very few patients. The same assumption was used in the NICE appraisal of adjuvant pertuzumab and was judged to be appropriate by the ERG and appraisal committee. The ERG for the current appraisal considers this assumption reasonable too.

Patients in the non-metastatic recurrence health state are also at risk of death. In their response to the clarification question B18,[4] the company indicated that the number of breast cancer-related deaths in KATHERINE was 91 (from a total of 1,460 patients, so 91/1,460 = 6.23%). Even though there is no information available on the proportion of deaths that were observed in the non-metastatic and metastatic health states, the company expects that the vast majority of these would have occurred because of a metastatic event. Therefore, the company assumed that in the non-metastatic health state, the risk of death would be equal to background mortality. The same approach was taken in TA569.[17] Furthermore, the cost effectiveness results are not expected to be sensitive to this assumption because the same approach was applied across both treatment arms.

Remission

Patients in remission can either die or experience another recurrence. The risk of death in the remission health state was assumed to be the same as in the IDFS and non-metastatic recurrence health states, thus, equal to background mortality in the age-adjusted UK population. The model also assumes that any recurrence experienced in remission will be metastatic (transition from remission to first line mBC). This transition probability was assumed to be constant over time and was sourced from Hamilton et al. 2015, a study including a cohort of 12,836 patients with eBC and reporting a mean time to progression of 7.6 years (91.2 months).[50] This value was converted into a monthly transition probability of 0.00760 by assuming an exponential distribution.

ERG comment: In their response to the clarification question B16,[4] the company explained that data to inform transition probabilities and utilities for patients in remission were not collected in KATHERINE. Fifty-five non-metastatic recurrences occurred across both treatment arms in KATHERINE (see Table 5.9) but the proportion of those 55 who would have transitioned to metastatic recurrence in the follow-up period (approximately 62 months) was unknown (yet thought to be minimal). For this reason, the transition probability from remission to first line metastatic recurrence and the utilities for patients in remission could not be estimated from the current KATHERINE data cut.

A constant monthly transition probability from Hamilton et al. was used by the company to inform the transition from remission to first line mBC.[50] In response to the clarification question B17,[4] the company justified their choice by referring to TA569 in which the committee accepted the use of this probability since it was believed to be the best available evidence. The company also believes this to be true here despite the differences between the populations in KATHERINE and the one in the study by Hamilton pointed out by the company.[17] The population in Hamilton et al. was heterogeneous, and included stage I/II female patients with BC (HER2-positive, negative or unknown status), ranging between 20 to 79 years of age, diagnosed between 1989 and 2005. Furthermore, all patients were treated with adjuvant chest-wall radiation and were from one institution in Canada. This concern was raised by the ERG in the appraisal of pertuzumab in the neoadjuvant setting but, as mentioned above, the source for the transition probability was accepted. The company, acknowledging the uncertainty surrounding this parameter, performed a number of sensitivity/scenario analyses to test the impact of changing this value on the model results, which in turn it was minor (see e.g. Table 9 in the clarification letter response).[4]

In summary, the company assumed that patients in remission were not actively experiencing a recurrence and, therefore, were assumed to be as in IDFS without receiving treatment. This assumption was in line with the approach taken in TA569.[17] However, since in the economic model it is assumed that patients can only experience a non-metastatic recurrence once and, given that patients in remission have already experienced a non-metastatic recurrence, it is further assumed that the risk of experiencing metastatic recurrence is higher than the risk from IDFS. The ERG agrees with this approach.

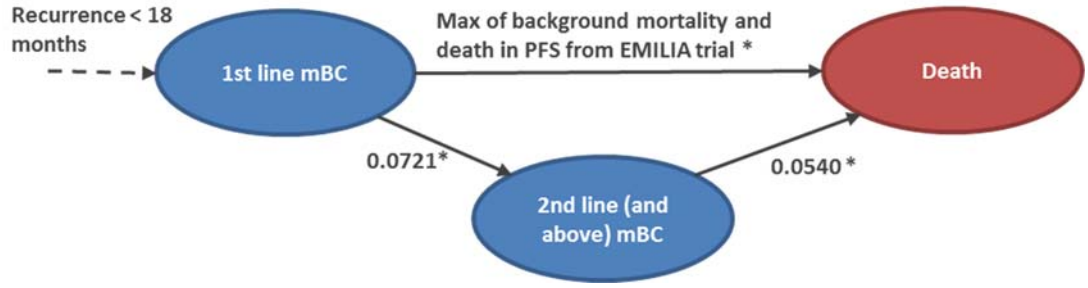
Metastatic recurrence

Two health states are considered in the metastatic recurrence pathway: first line mBC treatment and second (and subsequent) mBC treatment lines. In both health states, different transition probabilities are applied depending on whether recurrence was classified as “early” or “late”. The derivation of the transition probabilities used in the metastatic recurrence pathway are described below.

Early metastatic recurrence

Transition probabilities for patients experiencing "early" metastatic recurrence were derived from the subgroup of patients who had a metastatic recurrence within 18 months of adjuvant treatment initiation in the EMILIA study.[51] The transition probabilities shown in Figure 5.17 were obtained from the progression-free survival (PFS) and post-progression survival (PPS) estimated in the EMILIA "early" recurrence subgroup. The company pooled the outcomes from both treatment arms (i.e. analysed as a single treatment group) in order to increase the number of events with the purpose of generating more robust survival estimates.

Figure 5.17: Summary of monthly transition probability sources in the metastatic setting following "early" recurrence



Source: Figure 28 in CS.[1]
*All data derived from the EMILIA study based on "early" recurrence subpopulation.
Abbreviations: mBC: metastatic breast cancer; PFS: progression-free survival.

ERG comment: Transition probabilities for patients in the "early" metastatic recurrence setting were sourced from the EMILIA study.[51] In response to the clarification question B15,[4] the company explained that patient-level data from a subpopulation (approximately 12% of patients) of patients who had received prior systemic treatment for eBC but had relapsed within six months of completing treatment (18-months from treatment initiation) were available from the EMILIA study (trastuzumab emtansine vs. lapatinib + capecitabine [LC] for mBC). These data were used to derive survival estimates in the early recurrence setting of the model. The company considered pooled PFS estimates across the two treatment arms of the EMILIA early recurrence subpopulation. The main reason for pooling was that this would result in more robust transition probabilities. Furthermore, the company stated that deriving treatment-specific transition probabilities from the EMILIA subpopulation was inappropriate. This was because there were 34 PFS events and 27 PFS events in the LC and trastuzumab emtansine arms, respectively. These numbers are deemed low by the company and, consequently, treatment-specific transition probabilities based on them are likely to be associated with large of uncertainty. The same argument is used for OS, where 14 and 11 OS events were observed in the LC and the trastuzumab emtansine arms, respectively. The ERG does not agree with this interpretation. The fact that there is more (or less) uncertainty should not be a reason for deciding to pool these data. In case there is more uncertainty, this should be captured in the PSA. Pooling would be appropriate if the efficacy of trastuzumab emtansine and LC in this setting were assumed to be equal but this is not supported by any evidence submitted by the company.

A second potential issue is that transition probabilities for patients in the "early" metastatic recurrence setting were assumed to be equal for both treatment arms in the model. However, the first line mBC treatments differed for patients in the trastuzumab emtansine arm and the trastuzumab arm of the model. In particular, patients in the trastuzumab emtansine arm experiencing "early" metastatic recurrence may be eligible for pertuzumab + trastuzumab + chemotherapy (PTC), trastuzumab IV + chemotherapy, trastuzumab SC + docetaxel and chemotherapy. Patients in the trastuzumab arm experiencing "early"

metastatic recurrence may be eligible for trastuzumab emtansine, trastuzumab IV + chemotherapy, trastuzumab SC + docetaxel and chemotherapy. In summary, patients in the trastuzumab emtansine arm may receive PTC instead of trastuzumab emtansine. This difference was accounted for only in the cost part of the model. This approach implicitly assumes that, for patients experiencing an "early" metastatic recurrence, PTC and trastuzumab emtansine have the same efficacy, but the company did not provide any evidence to support this assumption. If that assumption was correct and PTC and trastuzumab emtansine have the same efficacy for patients experiencing an "early" metastatic recurrence, then it would be irrational to give patients the more expensive treatment. On the contrary, if the assumption was incorrect and PTC and trastuzumab emtansine do not have the same efficacy for patients experiencing an "early" metastatic recurrence, then different transition probabilities should have been used for the trastuzumab emtansine and the trastuzumab monotherapy arms of the model. The latter would also imply that, in terms of cost effectiveness, the difference between the two treatment arms (both effects and costs) is not only due to the differences between trastuzumab emtansine and trastuzumab in the adjuvant setting but also due to the differences between PTC and trastuzumab emtansine after "early" metastatic recurrence.

Late metastatic recurrence

The company mentioned in the CS that the risk of progression in the mBC setting has evolved substantially over the past five years and that, on average, patients remain in progression-free (first line mBC in the model) for longer than ever before. Therefore, the company assumed that mBC patients now would experience different progression rates (from first line to second line or death) than those observed in the KATHERINE trial.

Transition probabilities from the first line mBC health state (to second line and to death) are dependent on the first line treatment received. According to the company, in the UK, three different first line treatment regimens are available to patients in the metastatic setting: PTC, trastuzumab in combination with chemotherapy (TC), and chemotherapy alone (C). Transition probabilities for PTC and TC were derived from the CLEOPATRA trial,[52] and for C were derived from the M77001 trial.[53] In the model, the transition probability from first line mBC to second line mBC was calculated as a weighted average of the probabilities from the three different first line treatments. The "weights" are based on usage data from a market research conducted by the company.[54] A summary is presented in Table 5.11. Transition to death (from first line mBC) was modelled by the company using the number of deaths (without progression events) observed in CLEOPATRA and M77001, provided that this probability was not lower than general population mortality.

Table 5.11: Monthly probability from first line to second line in "late" recurrence

Transition	Treatment regimen	Treatment usage	Data source	Monthly probability	Data source
First line mBC to 2+ line mBC	PTC	75%	Market research[54]	0.0317	CLEOPATRA[52]
	TC	16%		0.0470	
	C	9%		0.0694	M77001[53]
	Probability in the model (weighted average)			**0.0373**	

Source: Table 27 in CS.[1]
Abbreviations: C: chemotherapy alone; mBC: metastatic breast cancer; PTC: Pertuzumab + trastuzumab + chemotherapy; TC: trastuzumab + chemotherapy.

From the second (and subsequent) lines of mBC health state, the only possible transition is to the death health state. This transition probability also depends on the second line treatment received. According

to the company, besides PTC, TC and C, trastuzumab emtansine is also available for these patients in the UK. As with the first line probabilities, transitions for PTC and TC were derived from the CLEOPATRA trial,[52] and for C were derived from the M77001 trial.[53] For trastuzumab emtansine, the company assumed the same survival probabilities as for TC. In the model, the transition probability second line mBC to death was calculated as a weighted average of the probabilities from the four different second line treatments. The "weights" are based on usage data from a market research conducted by the company.[54] A summary is presented in presented in Table 5.12.

Table 5.12: Summary of monthly risk of death in progressed metastatic (second line mBC) disease

Transition	Treatment regimen	Treatment usage	Data source	Monthly probability	Data source
2+ line mBC to death	PTC	10%	Market research[54]	0.0273	CLEOPATRA[52]
	TC	7%		0.0315	
	C	5%		0.0598	M77001[53]
	TE	78%		0.0315	Modelling assumption
	Probability in the model (weighted average)			**0.0325**	

Source: Table 28 in CS.[1]
Abbreviations: C: chemotherapy alone; mBC: metastatic breast cancer; PTC: Pertuzumab + trastuzumab + chemotherapy; TC: trastuzumab + chemotherapy; TE: trastuzumab emtansine.

ERG comment: The company noted that metastatic progression (transition probability from first line to second) would be expected to be time-dependent. Implementing time-dependent transition probabilities in a Markov model is usually complex since it would require tracking patients (when they enter or how long they stay in a health state). To avoid using time-dependent transition probabilities (which would require a more complex modelling approach), the company extrapolated the KM data from the CLEOPATRA and M77001 trials using an exponential distribution, which implicitly assumes constant hazards over time and, therefore, transition probabilities independent of time. The ERG agrees with the company that, with the current modelling approach (Markov model), assuming an exponential distribution is probably the most pragmatic way to overcome the limitation of the "memoryless" property of the Markov models. However, it should be noted that the exponential distribution might not fit the KM data well and, therefore, the estimated transition probabilities might be inaccurate.

For trastuzumab emtansine, the company assumed the same survival probabilities as for TC. If that assumption was correct then it would be irrational to give patients the more expensive treatment. However, a minor impact on the incremental results is be expected impact because the same second line regimens in the same proportions are applied to both treatment arms of the model.

5.2.6.5 Recurrence – node-negative subpopulation

The same methodology and assumptions used to model recurrence in the ITT population were also used here. A breakdown of the recurrence events for the KATHERINE node-negative population can be observed in Table 5.13. The company applied treatment-specific probabilities (as opposed to probabilities pooled across both arms).

Table 5.13: Types of IDFS events observed in the KATHERINE node-negative population

	Trastuzumab emtansine (n=400)	Trastuzumab (n=397)
IDFS event, n	29	62
Deaths without prior event, n (%)	2 (0.5%)	2 (0.5%)
Recurrence events excluding deaths, n	27	60
"Early" recurrence (before 18 months)		
Metastatic recurrence, n (%)	9 (81.82%)	24 (68.33%)
Non-metastatic recurrence, n (%)	2 (22.22%)	9 (31.67%)
"Late" recurrence (after 18 months)		
Metastatic recurrence, n (%)	12 (75.00%)	17 (62.96%)
Non-metastatic recurrence, n (%)	4 (25.00%)	10 (37.04%)

Source: Table 20 of the response to the clarification letter – Part II.[4]
Abbreviations: IDFS: invasive disease-free survival, n: number of events.

ERG comment: The same points discussed by the ERG in Section 5.2.6.2 are also valid here.

5.2.6.6 Recurrence – node-positive subpopulation

In the base-case analysis for the ITT population, the proportion of IDFS events were derived from KATHERINE data (see Table 5.9 and 5.10). However, there are no available IDFS data for the pertuzumab arm. The company assumed for the pertuzumab arm the average of the proportions observed in the trastuzumab emtansine arm and the trastuzumab arm of the KATHERINE ITT population. A breakdown of the recurrence events for both arms in the node-positive population can be observed in Table 5.10.

ERG comment: The same points discussed by the ERG in Section 5.2.6.2 are also valid here. Furthermore, the ERG considers that for the trastuzumab emtansine arm, the proportion of IDFS events should have been derived from the node-positive population and not from the ITT. Assuming the average of the proportions observed in the trastuzumab emtansine arm and the trastuzumab arm of the KATHERINE trial seems speculative and should be tested in case this has impact on the model results. In any case, as previously mentioned, the average should be calculated from node-positive data instead of ITT.

5.2.6.7 Summary of the transition probabilities used in the model

A summary of the transition probabilities used in the economic model is shown in Table 5.14.

Table 5.14: Summary of transition probabilities used in the economic model

Start	Destination	Base-case value	Source	Section in ERG report
IDFS	Non-metastatic recurrence	ITT & Node-negative: Adjusted Log-logistic	KATHERINE[27] APHINITY[55]	5.2.6.1 5.2.6.2

Start	Destination	Base-case value	Source	Section in ERG report
	Metastatic recurrence	Node-positive: HR from ITC		5.2.6.3
	Death	Maximum of BGM or IDFS death rate	UK life tables[56], KATHERINE[27]	5.2.6.1 5.2.6.2 5.2.6.3
Non-metastatic recurrence	Remission	1.00	Assumption	5.2.6.4 5.2.6.5 5.2.5.6
	Death	Max of BGM or IDFS death rate	UK life tables, KATHERINE[27]	
Remission	First line mBC	0.0076	Hamilton et al. [50]	
	Death	Max of BGM or IDFS death rate	UK life tables, KATHERINE[27]	
First line mBC – Early recurrence	2nd + line mBC	0.0721	EMILIA (pooled treatment arms)[51]	
	Death	Max of BGM or PFS in relevant trial	UK life tables, or EMILIA (pooled treatment arms) [56 51]	
First line mBC	2nd + line mBC	0.0373	Weighted average of post-progression survival in various trials	
	Death	Max of BGM or PFS in relevant trial	UK life tables, CLEOPATRA, [52] or M77001[53]	
Second+ line mBC – Early recurrence	Death	0.0540	EMILIA (pooled treatment arms) [51]	
Second+ line mBC	Death	0.0325	Weighted average of risk of death in various trials	

Source: Table 30 in CS.[1]
Abbreviations: BGM: background mortality; IDFS: invasive disease-free survival; mBC: metastatic breast cancer; N/A: not applicable; NMR: non-metastatic recurrence; PFS: progression-free survival; REM: remission.

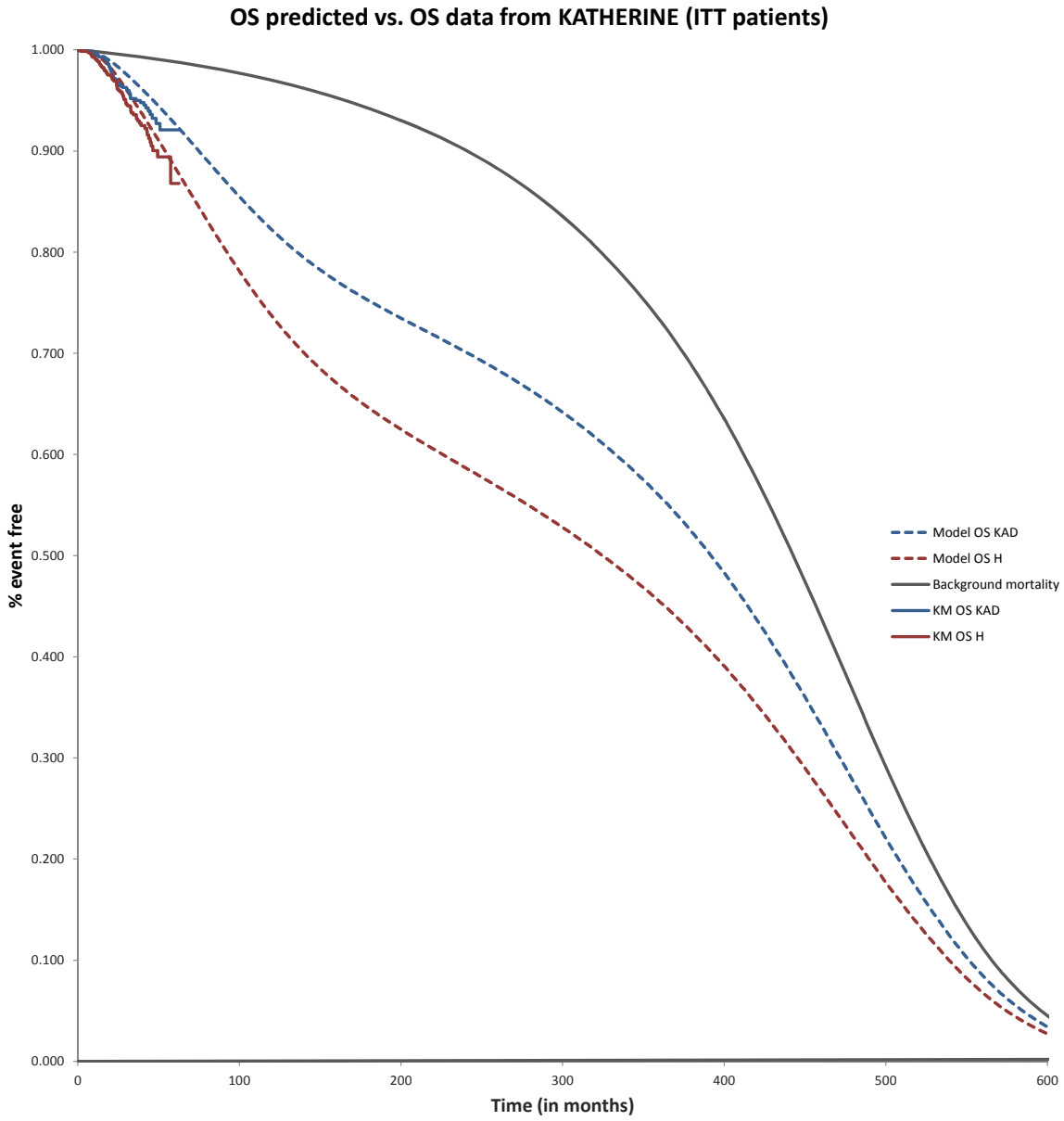
5.2.6.8 Overall survival

Overall survival (OS) data from the KATHERINE trial was not explicitly included in the model. The company mentioned that, while it was possible to conduct survival analysis on the KATHERINE OS data, the company judged the data to be immature (98 deaths observed across both treatment arms in the ITT population of KATHERINE, i.e. approximately 93% of patients were alive at the end of follow-up) to robustly extrapolate OS parametrically over the model time horizon. For this reason, the company took a different approach and the risk of death was modelled for each individual health state separately as explained in the previous sub-sections. For the node-negative and node-positive subpopulations the approach taken by the company was the same as the one used for the ITT population.

ERG comment: The ERG agrees with the company that OS data from KATHERINE are immature and that fitting survival curves to those data could result in poor OS extrapolations. The company included OS results in the model but for the ITT population only. In this case, OS is an outcome of the model

(calculated as the complement of the predicted cumulative number of deaths over time) instead of an input. As can be seen in Figure 5.18, the OS curves predicted by the model do not seem to fit the OS KM ITT data very well: the predictions for both arms overestimate the OS data from the KATHERINE ITT population, especially the trastuzumab emtansine arm. This can be an indication of an underlying issue related to OS which might be due to the combination of the several assumptions made regarding the transition probabilities in the post-recurrence health states. At this stage, the ERG was not able to identify the source of this potential issue.

Figure 5.18: Company base-case OS predicted vs. OS data from KATHERINE ITT patients



Source: electronic model submitted in the CS.[1]
Abbreviations: H, trastuzumab; ITT: intention to treat; KAD: trastuzumab emtansine; KM: Kaplan-Meier; OS: overall survival.

5.2.6.9 Time on treatment

Time-to-off-treatment (TTOT) data observed in the KATHERINE trial were used to model treatment duration. Patients in both arms of KATHERINE were expected to receive treatment for a maximum of

14 cycles. However, it was allowed to discontinue treatment due to unacceptable toxicity or disease progression. In total, 81.0% of patients in the trastuzumab arm and 71.4% in the trastuzumab emtansine arm in the Safety Evaluable population completed the 14 cycles of treatment without discontinuation. Patients who discontinued from trastuzumab emtansine were allowed to complete the 14 cycles of therapy by switching to the trastuzumab arm, when this was deemed appropriate based on toxicity considerations. Thus, a total of 593 patients (80.1%) receiving initially trastuzumab emtansine completed 14 cycles of any treatment (trastuzumab emtansine only or trastuzumab emtansine and trastuzumab after switching). Furthermore, from the 71 patients who switched to trastuzumab from trastuzumab emtansine, a total of 63 patients (88.7%) completed the 14 cycles of trastuzumab emtansine and trastuzumab. The company indicated that treatment duration is not expected to be dependent on nodal status. Therefore, TTOT data used in the ITT analysis was used for the node-negative and the node-positive subpopulations. The company noted that across all treatment cycles there are only minor differences between the ITT and the node-negative data, as can be seen in Table 5.15. Treatment duration data for pertuzumab were sourced from the TTOT data in the APHINITY trial.

Table 5.15: Summary of treatment discontinuation in KATHERINE (ITT vs. node-negative populations)

		ITT		Node-negative	
		Trastuzumab (n=740)	**Trastuzumab emtansine (n=740)**	**Trastuzumab (n=389)**	**Trastuzumab emtansine (n=400)**
Total treatment duration (median)		10 months	10 months	10 months	10 months
Number of cycles (median)		14	14	14	14
Number (%) of patients completing at least a total of X cycles of TE	*1 cycle*	720 (100.0%)	740 (100.0%)	389 (100.0%)	400 (100.0%)
	4 cycles	683 (94.9%)	677 (91.5%)	374 (96.1%)	365 (91.3%)
	7 cycles	664 (92.2%)	637 (86.1%)	367 (94.3%)	345 (86.3%)
	11 cycles	618 (85.8%)	579 (78.2%)	345 (88.7%)	311 (77.8%)
	14 cycles	583 (81.0%)	528 (71.4%)	323 (83.0%)	288 (72.0%)
Number (%) of patients completing at least a total of X cycles of either TE or T*	*1 cycle*	N/A	740 (100.0%)	N/A	400 (100.0%)
	4 cycles	N/A	698 (94.3%)	N/A	374 (93.5%)
	7 cycles	N/A	673 (90.9%)	N/A	362 (90.5%)
	11 cycles	N/A	639 (86.4%)	N/A	343 (85.8%)
	14 cycles	N/A	593 (80.1%)	N/A	322 (80.5%)

Source: Table 31 in CS[1] and Table 21 of the response to the clarification letter – Part II.[4]
Abbreviations: IDFS = invasive disease-free survival; n = number of events; N/A = not applicable; T = trastuzumab monotherapy; TE = trastuzumab emtansine

* This includes patients who discontinued trastuzumab emtansine therapy and completed the remaining 14 cycles of therapy with trastuzumab

The company included two options for modelling treatment duration. In the base-case, the treatment duration as observed in KATHERINE was used. Thus, treatment duration is calculated using the proportion of patients receiving trastuzumab emtansine or trastuzumab at each treatment cycle in the trial. In the model, TTOT data in the trastuzumab emtansine arm include patients who remained on trastuzumab emtansine therapy and patients who switched to trastuzumab therapy, but only trastuzumab emtansine costs are used for all treatment cycles (costs were not adjusted for patients switching treatments). Trastuzumab emtansine is [redacted], taking this approach therefore gives a conservative view of the cost effectiveness of trastuzumab emtansine compared to trastuzumab in this population. The proportions of patients receiving trastuzumab emtansine or trastuzumab at each treatment cycle are shown in Table 5.16.

Table 5.16: Percentage of patients on treatment in both arms at each of the 14 cycles

Cycle number	Trastuzumab arm (trastuzumab only)	Trastuzumab emtansine arm (Any study treatment)
1	99.9%	100.0%
2	97.9%	97.8%
3	96.3%	95.9%
4	94.7%	94.3%
5	93.9%	92.7%
6	93.1%	91.9%
7	92.1%	90.9%
8	90.6%	90.0%
9	89.7%	88.8%
10	88.5%	87.7%
11	85.8%	86.4%
12	83.9%	84.7%
13	82.5%	82.4%
14	81.0%	80.1%
Source: Table 32 in CS.[1]		

As a second option, treatment duration can be modelled as per the KATHERINE protocol or the summary of product characteristics (SmPC) label, where the proportion of patients on treatment is determined by the proportion of patients in the IDFS health state of the model until a maximum of 14 cycles. With this option, it is assumed that treatment discontinuation is only possible due to progression (treatment switching – discontinuations due to toxicity – is not considered). This assumption is clinically implausible and was included by the company as part of the scenario analyses.

Dose reductions

Dose reductions for patients receiving trastuzumab emtansine were permitted during the KATHERINE trial but were not included in the model. The rationale for this was that since 85.7% of patients in the trastuzumab emtansine arm did not require any dose modification, the company decided that it was not necessary to complicate the model to account for 14.3% of patients who had a dose reduction.[27] The company considered that this assumption is likely to have a minor impact the cost effectiveness results

and that, in any case, the approach considered is conservative (dose reductions would reduce the costs in the intervention arm of the model).

ERG comment: In the clarification question B8,[4] the ERG asked the company to clarify how treatment discontinuation (in both arms) was operationalised in the model. In particular, whether the estimation of the survival curves to extrapolate IDFS in the trastuzumab emtansine arm accounts for treatment switching (i.e. patients were allowed to switch to trastuzumab after discontinuation from trastuzumab emtansine). The company explained that during the KATHERINE study, 71 patients switched from trastuzumab emtansine to trastuzumab monotherapy, which was less than 10% of the patients in the intervention arm. This percentage was deemed small by the company and, therefore, it was decided not to perform any crossover adjustments that, according to the company, would introduce additional uncertainty into the analysis. The company also considered that the approach of not adjusting the IDFS curves for treatment switching is conservative for the cost effectiveness of trastuzumab emtansine for the following reasons:

- The proportion of patients who switched from trastuzumab emtansine to trastuzumab monotherapy is small. Therefore, it should not have a large effect on the efficacy profiles observed in KATHERINE.
- Based on the ITT principle, switching would lead to an underestimation of the trastuzumab emtansine treatment effect: patients who switched to trastuzumab monotherapy received less trastuzumab emtansine but they were analysed as if they were in the trastuzumab emtansine arm.
- TTOT data in the trastuzumab emtansine arm included patients who remained on trastuzumab emtansine and patients who switched to trastuzumab monotherapy. However, trastuzumab emtansine costs were used for all patients in all treatment cycles of the intervention arm.

The combination of the three items mentioned above would result in in an analysis that potentially underestimates the efficacy and overestimates the costs in the trastuzumab emtansine arm of the model. *"The lack of crossover adjustment is therefore an incredibly conservative analysis with respect to the cost effectiveness of trastuzumab emtansine"*.[4]

The ERG agrees that there are minor differences between the ITT and the node-negative populations regarding TTOT. Possibly this is true for the node-positive too. However, if data specific for the node-negative and node-positive populations were available, these should have been used in the subgroup analyses.

5.2.7 Adverse events

In their base-case analysis (ITT population), the company mentioned that the adverse events in the IDFS state were included in the economic model if:

- the AE is Grade 3 and above
- the AE occurred in at least 2% of the study population from the KATHERINE trial.

Based on these criteria, the only AE that was included in the model was platelet count decrease. The frequency of the included adverse events can be seen in Table 5.17 below

Table 5.17: Incidence of TRAEs included in the model (CTCAE ≥ Grade 3, serious)

AE	Incidence)	
	TE (n=740)	**T (n=720)**
Platelet count decreased	42 (5.68%)	0 (0.00%)
Source: Based on Table 51 from the CS[1] Abbreviations: AE = adverse event; TE = trastuzumab emtansine; T = trastuzumab;		

These included adverse events had an impact on the costs, only. It was considered that the utility decrements due to the AEs would have been incorporated already in the measured HRQoL estimates from the KATHERINE trial, hence additional utility decrements were not included. This will be discussed in Section 5.2.8 of the ERG report.

The adverse event costs related to IDFS state for pertuzumab + trastuzumab treatment and to the post-IDFS states were sourced from literature, without any AE incidence data. These will be discussed in Section 5.2.9.4 of the ERG report.

For the node-negative subgroup analysis, the company assumed the same adverse event incidences as in their ITT population analysis for both trastuzumab monotherapy and trastuzumab emtansine treatments. For the node-positive subgroup analysis, same ITT-population based adverse event incidences were used for the trastuzumab emtansine arm, whereas for the pertuzumab arm, adverse event costs related to the IDFS and post-IDFS states were sourced from the literature, without any AE incidence data. This will be discussed further in Section 5.2.9 of the ERG report.

ERG comment: It was not clear to the ERG, why hypertension was not included as an adverse event in the economic model, as the incidence of hypertension in the trastuzumab emtansine arm of the KATHERINE trial was 2%, as can be seen in Table 4.8 of the ERG report. In their response to the clarification letter, the company stated that in the economic model, not all adverse events but those considered to be "treatment-related" were included. Additionally, in their response to the clarification letter, they provided the incidence of selected "treatment related" adverse events and the costs associated with the management of those adverse events as can be seen in Table 5.18 below. The impact of including these adverse events, with an assumption of a utility decrement of -0.5 per each adverse event, was explored in one of the company scenario analysis provided in the response to the clarification letter.

Table 5.18: Incidence of TRAEs included in the model (CTCAE ≥ Grade 3, serious)

AE	Incidence)		Treatment	Event cost	Source
	TE (n=740)	T (n=720)			
Hypertension	5 (0.68%)	2 (0.28%)	Hypertension – Total HRG	£659.95	NHS Ref. 2017/18 – EB04Z
Platelet count decreased	46 (5.68%)	0 (0.00%)	Platelet disorder drugs – Band 1 – Total HRG activity	£1,712.99[a]	NHS Ref. 2016/17 – XD43Z
Haemorrhage	1 (0.14%)	0 (0.00%)	Haemorrhagic Cerebrovascular disorders[b] – Total HRG activity	£2,985.08	NHS Ref. 2017/18 – AA23C-G
Increased AST/ALTs	4 (0.54%)	1 (0.14%)	Liver failure disorders[b] – Total HRG activity	£2,412.54	NHS Ref. 2017/18 – GC01C-F
Peripheral neuropathy[c]	12 (1.62%)	0 (0.00%)	Muscular, Balance, Cranial or Peripheral Nerve Disorders, Epilepsy or Head Injury[b] – Total HRG activity	£1,292.75	NHS Ref. 2017/18 – AA26C-H

Source: Based on Table 18 from the response to the clarification letter[4]
Abbreviations: AE = adverse event; TE = trastuzumab emtansine; T = trastuzumab; NHS= National Health Service; HRG = Healthcare resource group; Ref. = Reference; ALT = alanine aminotransferase; AST = aspartate aminotransferase
Footnotes: a. Equal to £1,641.93 in 2016 before being inflated to reflect the 2019 price year. b, A weighted average of the costs for all casemix companion codes were used to generate the event cost. i.e. the cost for a CC code was weighted by the "Activity" value reported in the schedule. c. Includes events classed as "peripheral neuropathy", "peripheral motor neuropathy", and "peripheral sensory neuropathy"

It was not clear to the ERG how the company decided an adverse event to be "treatment-related" in the KATHERINE trial. Furthermore, it was not clear why the company selected these five adverse events specifically from all of the other observed adverse events. Upon request from the ERG, the company conducted additional scenario analyses in its response to the clarification letter.[4] These analyses revealed that the inclusion of additional AEs other than decreased platelet counts did not have a significant effect on the incremental results. Therefore, this is not investigated further in the exploratory analyses conducted by the ERG.

In the absence of evidence, the ERG cannot comment on the plausibility of the company assumption of identical adverse incidences for node-negative and node-positive subgroups. However, the ERG expects that the impact of this assumption on the incremental results to be negligible.

5.2.8 Health-related quality of life

5.2.8.1 Identification and selection of utility values – ITT population

Patients in the KATHERINE trial completed the EORTC QLQ-C30, EORTC QLQ-BR23 and EQ-5D-3L at screening, during treatment (cycle 5 and 11) and every six months for one year after the study completion visit. [57, 58] Given NICE's preference for the EQ-5D-3L, only data from this measure was included in the company submission from the KATHERINE trial.

An SLR was also conducted to identify sources of health state utility values for patients treated in the adjuvant setting for HER2-positive eBC. The methods used in this SLR are summarised in section 5.1 of this ERG report. The company's SLR identified 25 studies reporting HRQoL data. However, the company state that none of these sources reported utility values that could directly inform the model and that given the availability of the EQ-5D data from the KATHERINE trial for eBC states, none of the 25 identified studies were considered further in the submission.

HRQoL data for the IDFS state was measured in the KATHERINE ITT population using the EQ-5D-3L and valued using the UK EQ-5D-3L tariff [39]. All potential KATHERINE utility values are shown in Table 5.19. The company assume that patients receiving the different treatments have equal utility, as no significant difference was found between the EQ-5D results of the two arms. Therefore, EQ-5D data from each treatment arm was pooled in the base-case. Patients in the IDFS state can be either on- or off-treatment. The company note that treatment-related AEs can impact HRQoL, meaning that utility values obtained can be expected to vary depending on whether patients are receiving treatment or not. Therefore, different utilities are applied for IDFS on-treatment and IDFS off-treatment states.

HRQoL was not measured in patients who had progressed in the KATHERINE trial. Therefore, this data was only able to provide utility estimates for the disease free on- and off-treatment model states. In order to identify utility values for the remaining model states, the company utilised assumptions and published sources of utility values in the literature.

The company assumed that utility in the non-metastatic recurrence and remission states were equal to utility in the IDFS on-treatment and IDFS off-treatment values respectively. These assumptions were justified as being similar to assumed equivalencies in the pertuzumab appraisals (TA569 and TA424).[17, 35]

Table 5.19: Utility values considered by the company for their base-case and scenario analyses

Health state	Utility (SE) [95% CI]	Source
eBC		
KATHERINE		
IDFS – On treatment, pooled	0.775 (0.009)	KATHERINE data [1]
IDFS – Off treatment, pooled	0.788 (0.010)	
IDFS – On treatment, per treatment arm	TE = 0.774 (0.009) Trast. = 0.776 (0.010)	
IDFS – Off treatment, per treatment arm	TE = 0.784 (0.010) Trast. = 0.791 (0.010)	
Non metastatic recurrence	= IDFS on treatment	Assumption
Remission	= IDFS off treatment	Assumption
Lidgren et al.		
IDFS – On chemotherapy	0.696 [0.63-0.75]	Lidgren et al. [34]
IDFS – On treatment/off chemotherapy	0.696 [0.63-0.75]	
IDFS – Off treatment	0.779 [0.75-0.81]	
Non metastatic recurrence	0.779 [0.75-0.81]	
Remission	0.779 [0.75-0.81]	
Hedden et al.		

IDFS – On chemotherapy	0.97 (0.026)	Hedden et al. [37]
IDFS – On treatment/off chemotherapy	0.97 (0.026)	
IDFS – Off treatment	0.99 (0.010)	
Non metastatic recurrence	0.75 (0.194)	
Remission	0.99 (0.010)	
mBC		
Lloyd et al.		
First line mBC	0.765 (0.004)	Lloyd et al. [36]
Second+ line mBC	0.508 (0.004)	
Lidgren et al.		
First line mBC	0.685 [0.620-0.735]	Lidgren et al. [34]
Second+ line mBC	0.685 [0.620-0.735]	
Hedden et al.		
First line mBC	0.65 [0.50-0.80]	Hedden et al. [37]
Second+ line mBC	0.29 [0.16-0.41]	
Paracha et al.		
First line mBC	0.806 [0.645-0.967]	Paracha et al. [38]
Second+ line mBC	0.536 [0.423-0.643]	
Source: Table 40 Company Submission[1] Abbreviations: CI: confidence interval; eBC: early breast cancer; IDFS: invasive disease-free survival; mBC: metastatic breast cancer; SE: standard error; TE: trastuzumab emtansine; Trast: trastuzumab.		

The company identified several potential literature sources for the mBC utility values, including values from Lloyd et al, Lidgren et al, Hedden et al, Paracha et al.[34, 36-38] All utility values considered by the company are displayed in Table 5.19. The Lloyd study asked 100 members of the UK general population to value vignettes reflecting breast cancer health states, which had been developed for that study using expert opinion. These health states were valued by general population participants using a standard gamble exercise.[36] The Lidgren et al. 2007 study measured and valued the health of 361 consecutive breast cancer patients visiting an outpatient clinic in Sweden using the EQ-5D-3L and the corresponding UK EQ-5D-3L value set. [34] The Hedden study is a cost effectiveness analysis of the real-world effectiveness of adjuvant trastuzumab in HER-2/neu positive breast cancer in Canada.[37] Utility values used in this study were sourced from a previous systematic review of health state utilities in cancer.[59] The ERG could not access this article and therefore could not identify the original source of these utility values or assess their relation to the population of interest in this appraisal. The company described the Paracha study as having analysed data from a large dataset of 906 patients and 11,451 observations from the MARIANNE trial to estimate utility values.[38] However, the Paracha paper cited is a systematic review of utility values in locally advanced and metastatic breast cancer by treatment line.[38] The utility values cited in Table 39 of the company submission could not be located in the Paracha paper and neither could any reference to a MARIANNE trial. Therefore, the ERG was unable to verify the source of these values.

The company chose to use values from Lloyd et al. as the utility source for first and second+ line mBC states.[36] This choice was justified with the statement that this was a well-established source of utilities,

which had been previously used in appraisals in this disease area (TA569, TA424 and TA509).[17, 35, 40] Table 5.20 summarises the utility values utilised in the company base-case.

Table 5.20: Health state utility values for company base-case

Health state	Base-case Value (SE)	Source
IDFS on-treatment	0.775 (0.009)	KATHERINE trial EQ-5D-3L ITT data, pooled
IDFS off-treatment	0.788 (0.010)	
Non-metastatic recurrence	0.775 (0.009)	Assumed equal to IDFS on-treatment
Remission	0.788 (0.010)	Assumed equal to IDFS off-treatment
First line mBC	0.773 (0.004)	Lloyd et al [36]
Second+ line mBC	0.520 (0.004)	Lloyd et al [36]

Source: Table 34 in CS. [1]
Abbreviations: IDFS = invasive disease-free survival; mBC = metastatic breast cancer; SE = Standard error.

ERG comment: Concerns have already been raised and discussed in Section 5.1 regarding the quality of the HRQoL SLR conducted to identify sources of utility values required for the model. The main concerns were as follows. Firstly, the inclusion criteria that studies must include an adjuvant or neoadjuvant therapy meant that relevant HRQoL studies may have been missed if they did not focus on any intervention, but focussed instead on the stages of breast cancer, which would be relevant for many of the health states requiring utility values in the model. In fact, Lidgren et al. was excluded from the SLR for exactly this reason, but then later utilised in the model.[34] Secondly, in the reporting of the SLR it was unclear whether only studies providing values for eBC were included. If this is the case, the SLR was unfit for purpose as metastatic values were required for the model. It is a concern that none of the studies used in the company base-case and scenario analyses as sources of mBC utility values were identified in the HRQoL SLR and no further information was provided regarding how these were searched for or selected for inclusion in the model. These concerns were also raised by the ERG in appraisal TA424, an appraisal conducted by the same company in which a very similar SLR was delivered and the same mBC utility sources were identified outside of the SLR. [35]

The HRQoL SLR concludes by stating that despite 25 studies being included, none of them reported utility values that could be considered for direct use in the model and given the availability of the KATHERINE data for the IDFS states, none of the 25 studies identified in the SLR were considered further. The basis for excluding all of these studies from use in the model is unclear and no justification as to why any values were not appropriate is provided. While the ERG agree with the use of the KATHERINE trial data in the base-case for IDFS states, as this is likely to best represent the target population in clinical practice, it would have been much better if the company had fully and systematically searched the literature for the remaining health states.

The ERG also has concerns regarding the utility values chosen for the non-IDFS states. At the clarification phase, the ERG requested evidence from the company that utility in local recurrence and remission states can be considered equal to utility in the IDFS on treatment and IDFS off treatment states. [60]The company responded that they were not aware of any published evidence on this topic and that this assumption had been made due to a lack of robust evidence. [4] The ERG does not consider this to be sufficient evidence for the assumption of equal utility. However, the ERG were encouraged by the fact that the utility values obtained from Lidgren et al 2007 for the first year after recurrence (0.779)

and the second+ years after primary breast cancer or recurrence (0.779) were very similar to the assumed utility values for remission (0.788) and recurrence (0.775) based on the KATHERINE trial.[34] Therefore, despite the fact that the ERG would have preferred further evidence, the company assumption was retained in the base-case.

No information was provided by the company about how utility values for mBC states were searched for or identified. Several of these identified sources for mBC utility values also contained eBC values, including Lidgren, [34] which was excluded from the HRQoL SLR due to a lack of intervention, which raises additional concerns regarding the quality of the original HRQoL SLR. The company chose to use values from Lloyd et al as the utility source for first and second+ line mBC states.[36] This choice was only justified by its previous use in similar technology appraisals. [17 35, 40] No further comparisons or justifications were made as to why this source was chosen over the other cited potential sources. The ERG feel that the methods used to measure and value HRQoL in the Lloyd study do not reflect the NICE reference case as closely as other sources cited. The Lloyd study measured and valued HRQoL using expert elicitation generated vignettes valued using SG by members of the UK general population. [36] While the ERG could not trace the utility values obtained from Hedden et al or Paracha et al, which is a problem in itself, the ERG feel that the methods used in Lidgren et al better reflect the NICE reference case. In Lidgren, HRQoL was measured in patients themselves, using the EQ-5D-3L.[34] Despite being measured in Swedish patients, the UK value set was used to value HRQoL. Therefore the ERG feel this source much better reflects the NICE reference case and is a preferable base-case source of utility values for the mBC states.

5.2.8.2 Adverse event disutilities – ITT population

In the KATHERINE trial, 98.9% of patients in the trastuzumab emtansine arm and 93.3% of patients in the trastuzumab arm experienced at least one AE during the treatment period. [1] More than 95% of these were grade 1 and 2 in each arm. The most frequently reported AEs in the trastuzumab emtansine arm vs the trastuzumab arm were fatigue (33.8% vs 49.5%), nausea (13.1% vs 41.6%), radiation skin injury (27.6% vs 25.4%), arthralgia (20.6% vs 25.9%), headache (16.9% vs 28.4%), aspartate aminotransferase increased (5.6% vs 28.4%) and hot flush (20.3% vs 12.8%).

Given that IDFS utility values for patients on- and off-treatment were estimated from the KATHERINE trial data, the company assumed that any disutility associated with treatment-related AEs experienced during the trial was already captured in the EQ-5D data. Therefore additional disutilities related to AEs were not included in the model. The company acknowledged that this may underestimate the disutility associated with the AEs, *"particularly in the trastuzumab emtansine arm"* [1]. However they justify their choice by stating that the difference in the incidence of treatment-related Grade ≥3 AEs between the treatment arms was negligible and ultimately, the omission of AE disutility does not significantly impact the overall cost effectiveness results.

ERG comment: The ERG has some concerns about the company's assumption that the impact of AEs will have been captured in the EQ-5D data collection. Firstly, the EQ-5D was only collected twice during the treatment period, in cycles 5 and 11. Therefore for AEs to have been captured in the EQ-5D data collection, we would have to assume that all AEs that occurred during the treatment period were being experienced on those two occasions. Any AEs that resulted in discontinuation before these time points would not be reflected. The assumption that AEs are captured in HRQoL data requires that HRQoL be assessed regularly on presentation of AEs, otherwise it is likely that the impact is missed. Therefore it is likely that the impact of AEs is underestimated. This concern was also raised by the ERG in TA569. [17]

Additionally, if the company are to assume that the impact of AEs was captured in the EQ-5D data collected, then it is inappropriate to assume that the HRQoL of patients is equal across treatment arms. This assumption will mask any differences in the impact of AEs captured by the data, which effectively assumes that the incremental impact of AEs between the two treatments is zero. The company justifies this assumed equivalence in utility across the treatment arms by stating that "*no significant difference was found in the EQ-5D results of the two treatment arms in the KATHERINE study*".[1] However the company immediately go on to state that "*this was because the schedule of EQ-5D administration was designed to capture differences in QoL across the various stages of disease, not between treatment arms*".[1] Therefore, if the HRQoL data collection was not designed to find differences across arms, we cannot be surprised that a significant difference was not found. This approach was also criticised in TA569. [17] A lack of significance in this infrequent data collection schedule is not necessarily sufficient evidence to assume no difference in the impact of AEs on HRQoL across treatment arms. If the assumption is that the impact of AEs should be captured in the EQ-5D responses of patients in different treatment groups, the EQ-5D scores, by design, should not be pooled.

Interestingly, Figure 11 in the company submission shows the mean change from baseline in EORTC QLQ-C30 global health status for each treatment arm over time. This graph shows that in the trastuzumab emtansine arm, the mean global health status score remained below the mean baseline score until after treatment discontinuation, while for the trastuzumab arm the mean score never dropped below the mean baseline score. This would suggest that the AE impact of trastuzumab emtansine may be larger than that for trastuzumab. However, the company also state that there were no major differences (≥5%) in change from baseline between treatment arms in the five EQ-5D domains. This difference in scoring patterns could suggest that the EQ-5D data collection failed to pick up elements of the impact of the treatments on HRQoL. This may be another argument for including additional disutilities.

Overall, given the evidence provided in the original CS, the ERG would prefer to include additional AE disutilities for Grade 3+ AE included in the model base-case. In this case the ERG would agree that the utility values of each treatment group could be pooled. The ERG requested that the company include such AE disutilities in the model at the clarification phase.[60] In the clarification response the company stated that disutilities were not readily available for the included AEs and they therefore assumed that they were all associated with a disutility of 0.5.[4] This 0.5 value was combined with an assumed AE duration of the full treatment period (10.64 months). These values were selected as extreme values to demonstrate the limited impact on cost effectiveness results. Given that actual estimates of the disutility associated with the AEs included the model were not available and given the very limited impact of the inclusion of even extreme disutility values at the full treatment duration, the ERG decided that the best option for the ERG base-case was not to include additional disutilities. Instead the ERG chose to utilise the treatment-specific utility values for the IDFS, local recurrence and remission states, acknowledging that these values are likely to underestimate the impact of AEs on HRQoL, but also acknowledging that this makes little difference to the ICER in this case.

5.2.8.3 Measurement and valuation of health effects in the node-negative subpopulation

The company did not provide IDFS utility estimates from the KATHERINE trial separated according to nodal status, arguing that HRQoL is not expected to be dependent on nodal status. Therefore, the HRQoL approach taken by the company for the node-positive sub population was the same as the one used for the ITT population. The ERG refers to the previous summaries and critiques within Section 5.2.8 of this report for further details.

ERG comment: The same points discussed by the ERG earlier in Section 5.2.8 are also valid here. The company did not provide utility estimates from the KATHERINE trial separated according to nodal status. The HRQoL of patients could be dependent on nodal status due to different prognosis, treatments and AE received. However, the ERG could not identify any evidence regarding the impact of nodal status on utility. Therefore, the same ERG base-case assumptions for the ITT population were also adopted for the node-negative population.

5.2.8.4 Measurement and valuation of health effects in the node-positive subpopulation

The company did not provide IDFS utility estimates from the KATHERINE trial separated according to nodal status. The company argued that HRQoL is not expected to be dependent on nodal status. Therefore, the HRQoL approach taken by the company for the node-positive sub population was the same as the one used for the ITT population. The ERG refers to the previous summaries and critiques within Section 5.2.8 of this report for further details. Furthermore, for the IDFS, local recurrence and remission states, the company assumed the same utilities for the PTC arm as in the company base-case, based on the pooled treatment arms from the KATHERINE trial.

ERG comment: The same points discussed by the ERG earlier in Section 5.2.8 are also valid here. The company did not provide utility estimates from the KATHERINE trial separated according to nodal status. The HRQoL of patients could be dependent on nodal status due to different prognosis, treatments and AE received. However, the ERG could not identify any evidence regarding the impact of nodal status on utility

Due to a lack of direct evidence comparing the IDFS utility of patients receiving trastuzumab emtansine and pertuzumab + trastuzumab, the company assumes that IDFS utility in the pertuzumab arm is equivalent to the pooled utility values for IDFS on and off treatment from the KATHERINE trial. However, there is no evidence that the utility of patients receiving PTC is equivalent to the utility of patients receiving trastuzumab emtansine. In TA569 the APHINITY trial provided data on the utility of IDFS patients on treatment/off chemotherapy receiving PTC and trastuzumab + chemotherapy. [17] This showed that patients receiving PTC had slightly better HRQoL than those receiving trastuzumab + chemotherapy (0.787 versus 0.784). The KATHERINE trial showed that patients receiving trastuzumab had slightly better HRQoL than those receiving trastuzumab emtansine (0.776 versus 0.774). The ERG feels that differences in population mean that it is inappropriate to simply adopt the utility values for PCT and trastuzumab emtansine in the subgroup analyses. However, given that the existing evidence suggests that patients receiving PCT have a slightly better HRQoL than patients receiving trastuzumab, who have a slightly better HRQoL than those receiving trastuzumab emtansine, the ERG feel that using the IDFS utility values from the KATHERINE trial separated according to treatment group may be appropriate as this would reflect, although possibly slightly underestimate, the HRQoL benefit of PCT over trastuzumab emtansine. The ERG has found no evidence to support further changes in the ERG ITT base-case assumptions for the node-positive subgroup. Therefore, the ERG feels that the ERG ITT base-case assumptions are also the best reflection of the available evidence for this subgroup analysis.

5.2.9 Resources and costs

As explained in Section 5.1 of the ERG report, an SLR was conducted to identify studies on resource use and costs in breast cancer, however the identified studies were not used in the economic model. The economic analysis was performed from the NHS and PSS perspective.

The following costs were included in the economic model: drug acquisition and administration costs, treatment-related AE management costs, resource use and supportive care costs.

5.2.9.1 Drug acquisition costs

IDFS state

In the base-case, the drug acquisition and administration costs in the IDFS state for both trastuzumab monotherapy and trastuzumab emtansine, were applied in the model, according to the TTOT data observed in the KATHERINE trial, at a maximum of 14 three-weekly cycles. In a scenario analysis, the company assumed that all patients receive their assigned treatments during the maximum period of 14 cycles, as long as they are invasive disease free (hence no discontinuation due to toxicity and other reasons than progression).

In the base-case, no vial sharing and no dose reduction was assumed.

Trastuzumab emtansine drug acquisition costs

Trastuzumab emtansine is available as 100 mg and 160 mg vials with list prices of £1,641.01 and £2,625.62, respectively. The recommended dose of trastuzumab emtansine is 3.6 mg/kg, administered as an IV infusion (no loading doses are required). In the economic model, the weight of the patient was assumed to be constant and it was assumed that one small and one large vial of trastuzumab emtansine were administered in each cycle on day 1 of a three-week cycle (q3w) for a maximum of up to 14 cycles. Trastuzumab emtansine, in the adjuvant and metastatic settings, is subject to a confidential PAS and is offered at a discount of [redacted]. Trastuzumab emtansine drug acquisition costs were assumed to be identical for node-positive and node-negative subpopulations.

Trastuzumab monotherapy drug acquisition costs

There are three different forms of trastuzumab included in this economic analysis:

- Trastuzumab branded IV (Herceptin)
- Trastuzumab branded SC (Herceptin) administered as an SC injection
- Trastuzumab biosimilar IV

The list price of branded trastuzumab IV is £407.40 for a 150 mg vial. The recommended initial loading dose of trastuzumab is 8 mg/kg, followed every three weeks thereafter by a maintenance dose of 6 mg/kg body weight. Hence, in the model, four and three vials of trastuzumab IV was administered in the initial loading and the following maintenance cycles.

Trastuzumab SC is available as a 600 mg vial for a list price of £1,222.20. The SC form of trastuzumab is given as a fixed dose of 600 mg, without any loading dose.

Herceptin (trastuzumab) is also subject to a confidential CAA. A discount of [redacted], respectively.

Trastuzumab biosimilars are available in the UK, and they are administered intravenously at a dosing and treatment schedule identical to that of branded trastuzumab (Herceptin IV). The list price of all available trastuzumab biosimilars is the same and equal to £366.66 (Table 41 from CS[1]), however these products underwent a national tendering process in Q3 of 2018, during which the companies were able to offer confidential discounts to the NHS. Since the actual amount of the confidential discount was unknown, in this CS, it was assumed that the biosimilar trastuzumab IV costs 30% of the list price of branded trastuzumab (Herceptin) IV. This assumption is in line with the TA569 for pertuzumab in the adjuvant treatment of HER2-positive early breast cancer.[17]

In the economic model, it is assumed that 95% of the trastuzumab monotherapy is in the branded SC (Herceptin) form and the remaining 5% is in the biosimilar IV form, in line with the discussions in the

TA569 appraisal and the findings of the market research conducted by the company. [17] An overview of the drug acquisition costs, dosage and cost per cycle in the IDFS state is given in Table 5.21 below.

Table 5.21: Drug acquisition costs and costs per cycle in the IDFS state (for the ITT population analysis, company base-case)

Drug	Vial / pack size (mg)	Vial / pack price	Cost source	Dosing	Dosing source	Cycle length (days)	Cost per cycle
Trastuzumab emtansine	100 mg	[redacted]	Planned list price and the offered PAS	3.6 mg/kg on day 1 of each cycle for a maximum of 14 cycles	The KATHERINE study	21 days	[redacted]
	160 mg	[redacted]					
Trastuzumab IV-branded	150 mg	[redacted]	Planned list price and the offered PAS	8 mg/ kg initial loading dose followed by 6 mg/kg on day 1 of each cycle for a maximum of 14 cycles	Medicines Complete [61]	21 days	Initial dosing [redacted] Maintenance [redacted]
Trastuzumab IV-biosimilar	150 mg	£122.22	Assumed in TA569.	8 mg/ kg initial loading dose followed by 6 mg/kg on day 1 of each cycle for a maximum of 14 cycles	Medicines Complete [61]	21 days	Initial dosing £488.88 Maintenance £366.66
Trastuzumab SC-branded	600 mg	[redacted]	Assumed in TA569.	600 mg on day 1 of each cycle for a maximum of 14 cycles	Medicines Complete [61]	21 days	[redacted]

Source: Table 41 and Table 42 from the CS.[1]
Abbreviations: IV= intravenous; PAS = patient access scheme; SC = subcutaneous;

In the subgroup analysis of the company for node-negative population, it was assumed that the trastuzumab monotherapy costs would be identical to the costs used in the ITT population analysis.

Drug acquisition costs associated with the pertuzumab + trastuzumab + chemotherapy in the IDFS state

Pertuzumab is available as a 420 mg vial at a list price of £2,395. The recommended initial loading dose of pertuzumab is 840 mg administered as an IV infusion, followed q3w thereafter by a maintenance dose of 420 mg administered over a period of 30 to 60 minutes. Pertuzumab, in the adjuvant and metastatic settings, is subject to a confidential commercial access agreement (CAA) between the company and NHS England. Pertuzumab (list price) is offered at a [redacted]

No loading doses were accounted for in this analysis. The company stated that pertuzumab + trastuzumab is the standard of care for the neoadjuvant treatment of patients with HER2-positive breast cancer in England, with approximately 85% market share. According to the company, patients would typically receive the loading dose in the neoadjuvant setting and would only have to be re-loaded in the adjuvant setting if a sizable amount of time had lapsed between the final administration in the neoadjuvant setting and the first administration in the adjuvant setting. The clinical experts that the company communicated, mentioned that physicians would generally attempt to minimise the time between surgery and starting adjuvant therapy – thereby reducing the chance of a patient having to be re-loaded. In the model, the pertuzumab + trastuzumab related drug acquisition costs are applied during the TTOT data observed in the APHINITY trial.

In England, pertuzumab is not commissioned in combination with trastuzumab subcutaneous (SC); thus, only used in combination with trastuzumab intravenous (IV). The company assumed that only biosimilar IV formulations would be prescribed in the pertuzumab + trastuzumab therapy in the adjuvant setting.

The company state that pertuzumab + trastuzumab is typically given in combination with 6 cycles of chemotherapy. However, in their submitted evidence, according to the clinical expert advice, they also argued that, patients would have their generic chemotherapy already received as part of their neoadjuvant therapy regimen and therefore, patients would not receive another chemotherapy in the adjuvant setting. In the company submission, it was assumed that all patients would be neoadjuvantly treated, and therefore all patients have already received chemotherapy prior to surgery. Therefore, chemotherapy was omitted in the adjuvant regimens.

ERG comments: In the economic model, the ERG noticed that the company did not use the loading dose of 8 mg/kg for the trastuzumab IV treatment, but instead, the maintenance dose of 6 mg/kg was used for the initial cycle. This error was corrected by the ERG in the cost effectiveness analyses conducted in Section 7.

Another point of concern for the ERG was the patient weight. In the company submission model, the patient weight was always considered to be fixed in the economic model company. The impact of the average patient weight on incremental results was not investigated neither in the PSA, nor as a scenario analysis. However, the impact of patient weight on incremental costs is substantial for the trastuzumab emtansine arm. For instance, when a patient's weight is 73 kg instead of 70.91 kg used in the base-case, then that patient would necessitate an additional small vial, which would increase the incremental costs. Therefore, the uncertainty in the patient weight will be incorporated into the PSA and scenario analyses in the cost effectiveness analyses conducted by the ERG in Section 7.

Finally, the ERG is doubtful on the market share assumptions used in the company submission (95% trastuzumab SC and 5% trastuzumab IV). In the CS, it was stated that the proportion of patients who receive trastuzumab IV and SC was drawn from research on market shares conducted by the company. However, from the communicated market share details by the company upon ERG's request, these values could not be verified by the ERG. Instead, in the market research details, the ERG has found that in a sample of 229 patients, 106 were using trastuzumab in the SC formulation (Question 30a for the Breast Cancer Tracker Wave 2 2019).[54] Therefore, the ERG will use a split of 46% (106/229) and 54% (123/229) for the market share percentages of SC trastuzumab and biosimilar IV trastuzumab formulations in one of the scenarios conducted in the cost effectiveness analyses in Section 7.

For the node-negative/node-positive populations, without any evidence, the ERG could not judge the plausibility of the company assumption (identical drug acquisition costs in different subgroups). Also,

the ERG could not verify all clinical expert-based assumptions taken by the company for pertuzumab therapy for node-positive population (e.g. no chemotherapy in the adjuvant setting), due to the lack of time. However, the ERG considers that the impact of these assumptions would not be significant and, especially for the node-positive population, would be of secondary importance, considering the uncertainty on the relative effectiveness of trastuzumab emtansine versus pertuzumab + trastuzumab.

Non-metastatic state

In the non-metastatic recurrence state, for all analyses (ITT, node-negative and node-positive) it is assumed that patients receive trastuzumab (18 cycles) and docetaxel (six cycles), where cycle length was three weeks. The dosage of trastuzumab in this state is the same as the dosage in the IDFS state. Similarly, in the non-metastatic state, it is also assumed that 95% of the trastuzumab is in the branded SC (Herceptin) form and the remaining 5% is in the biosimilar IV form. Docetaxel was administered six cycles in total, with a dosage of 1.77 mg/ m^2, based on BSA. It is available in 20 mg and 160 mg vials, and in the base-case, one large and one small vial of docetaxel is needed in the base-case. An overview of the drug acquisition costs, dosage and cost per cycle in the non-metastatic recurrence state is given in Table 5.22 below.

Table 5.22: Drug acquisition costs and costs per cycle in the non-metastatic recurrence state

Drug	Vial / pack size (mg)	Vial / pack price	Cost source	Dosing	Dosing source	Cycle length (days)	Cost per cycle
Docetaxel IV	20 mg	£11.61	eMIT-June 2018	1.77 mg/m^2 on day 1 of each cycle for 6 cycles	Not reported	21 days	£37.20
	160 mg	£28.48					
Trastuzumab IV-biosimilar	150 mg	£122.22	Assumed in TA569.	8 mg/ kg initial loading dose followed by 6 mg/kg on day 1 of each cycle for 18 cycles	Medicines Complete [61]	21 days	Initial dosing £488.88 Maintenance £366.66
Trastuzumab SC-branded	600 mg	[redacted]	Assumed in TA569.	8 mg/ kg initial loading dose followed by 6 mg/kg on day 1 of each cycle for 18 cycles	Medicines Complete [61]	21 days	[redacted]

Source: Table 43 and Table 44 from the CS.[1]
Abbreviations: eMIT = electronic market information tool; IV= intravenous; SC = subcutaneous.

In the model, the average monthly cost for the drug acquisition in the non-metastatic recurrence state was calculated by taking the weighted average of the monthly drug acquisition costs of biosimilar trastuzumab IV+ docetaxel and trastuzumab SC + docetaxel regimens. For a given regimen, the average monthly drug acquisition cost was calculated by dividing the accumulated drug acquisition costs for all treatments in that regimen, during their treatment durations, by the maximum treatment duration among

all the treatments in that regimen. The calculation of the average monthly drug acquisition cost in non-metastatic recurrence is demonstrated below.

$$0.95 * \frac{(£37.20 * 6 + [redacted] * 18)}{\frac{18 * 21 * 12}{365.25}} + 0.05 * \frac{(£37.20 * 6 + [redacted] + [redacted] * 17)}{\frac{18 * 21 * 12}{365.25}}$$

Early recurrence first line mBC state

In the early recurrence first line mBC state, it is assumed that trastuzumab and trastuzumab emtansine arm patients receive different treatments. The market shares used in the base-case of the economic model pertaining to the trastuzumab and trastuzumab emtansine arms are given below in Table 5.23.

Table 5.23: Market share and total number of cycle information for the drugs used in the early recurrence, first line mBC state.

Treatment regimen	% market share for the trastuzumab emtansine arm	% market share for the trastuzumab arm	Source for market share	Total number of cycles	Source for # of cycles
Pertuzumab + trastuzumab biosimilar IV + docetaxel	75%	0%	Market research and assumptions	37.39, for pertuzumab and trastuzumab 6 for docetaxel	TA 509
Trastuzumab biosimilar IV + docetaxel	4%	4%		23.65, for trastuzumab 6 for docetaxel	TA509
Trastuzumab branded SC + docetaxel	13%	13%		23.65, for trastuzumab 6 for docetaxel	TA509
Trastuzumab emtansine	0%	75%		19.3 for trastuzumab emtansine	TA458
Docetaxel IV	8%	8%		6 for docetaxel	Assumption

Source: Table 43 and Table 44 from the CS.[1]
Abbreviations: IV= intravenous; SC = subcutaneous.

Except for the number of the cycles, the dosage of trastuzumab (IV and SC), trastuzumab emtansine and docetaxel were assumed to be same as the dosage used in the previous IDFS and non-metastatic recurrence states (Table 5.21 and Table 5.22 above). Pertuzumab is administered at a fixed dose, using 840 mg (two 420 mg vials) in the loading cycle and one 420 mg vial in the maintenance cycles. The vial price of pertuzumab is [redacted], when taking the PAS discount into account. An overview of the drug acquisition costs, dosage and cost per cycle in the early recurrence first line mBC state is given in Table 5.24 below.

Table 5.24: Drug acquisition costs and costs per cycle in the early recurrence first line mBC state

Drug	Vial / pack size (mg)	Vial / pack price	Cost source	Dosing	Dosing source	Cycle length (days)	Cost per cycle
Trastuzumab emtansine	100 mg	[redacted]	Planned list price and the offered PAS	3.6 mg/kg on day 1 of each cycle for 19.33 cycles	TA458	21 days	[redacted]
	160 mg	[redacted]					
Trastuzumab IV-biosimilar	150 mg	£122.22	Assumed in TA569.	8 mg/ kg initial loading dose followed by 6 mg/kg on day 1 of each cycle for 37.39 cycles in pertuzumab + trastuzumab + docetaxel regimen and for 23.65 cycles in the trastuzumab + docetaxel regimen	Medicines Complete [61]	21 days	Initial dosing £488.88 Maintenance £366.66
Trastuzumab SC-branded	600 mg	[redacted]	Assumed in TA569.	600 mg on day 1 of each cycle for 23.65 cycles in the trastuzumab+docetaxel regimen	Medicines Complete [61]	21 days	[redacted]
Pertuzumab IV-branded	420 mg	[redacted]	Assumed in TA569.	840 mg initial loading dose followed by 420 mg maintenance on day 1 of each cycle for 37.39 cycles in pertuzumab+trastuzumab+docetaxel regimen	Not reported	21 days	Initial dosing [redacted] Maintenance [redacted]
Docetaxel IV	20 mg	£11.61	eMIT-June 2018	1.77 mg/m^2 on day 1 of each cycle for 6 cycles (in all regimens)	Not reported	21 days	£37.20
	160 mg	£28.48					

Source: Table 43 and Table 44 from the CS.[1]
Abbreviations: IV= intravenous; SC = subcutaneous;

In the model, the average monthly cost for the drug acquisition in the early recurrence first line mBC state was calculated separately for the trastuzumab emtansine and the trastuzumab monotherapy arms.

For each arm, the weighted average of the monthly drug acquisition costs of the included treatment regimens was taken according to the arm-specific market share assumptions. The average monthly drug acquisition cost for a given treatment regimen was calculated in the same way as explained in the non-metastatic recurrence state.

Late recurrence, first line mBC state

In the late recurrence first line mBC state, it is assumed that patients from both arms receive similar treatments. The market shares used in the base-case of the economic model pertaining to the late recurrence first line mBC state are given below in Table 5.25.

Table 5.25: Market share and total number of cycle information for the drugs used in late recurrence, first line mBC state.

Treatment regimen	% market share for both arms	Source for market share	Total number of cycles	Source for # of cycles
Pertuzumab+ trastuzumab biosimilar IV + docetaxel	75%	Market research and assumptions	37.39, for pertuzumab and trastuzumab 6 for docetaxel	TA 509
Trastuzumab biosimilar IV + docetaxel	4%		23.65, for trastuzumab 6 for docetaxel	TA509
Trastuzumab branded SC + docetaxel	13%		23.65, for trastuzumab 6 for docetaxel	TA 509
Docetaxel	8%		6 for docetaxel	Assumption
Source: Table 43 and Table 44 from the CS.[1] Abbreviations: IV= intravenous; SC = subcutaneous.				

An overview of the drug acquisition costs, dosage and cost per cycle in the late recurrence first line mBC state is given in Table 5.26 below.

Table 5.26: Drug acquisition costs and costs per cycle in late recurrence, first line mBC state.

Drug	Vial / pack size (mg)	Vial / pack price	Cost source	Dosing	Dosing source	Cycle length (days)	Cost per cycle
Trastuzumab IV-biosimilar	150 mg	£122.22	Assumed in TA569.	8 mg/ kg initial loading dose followed by 6 mg/kg on day 1 of each cycle for 37.39 cycles in pertuzumab +trastuzumab+docetaxel regimen and for 23.65 cycles in the trastuzumab+docetaxel regimen	Medicines Complete [61]	21 days	Initial dosing £488.88 Maintenance £366.66
Pertuzumab IV-branded	420 mg	[redacted]	Assumed in TA569.	840 mg initial loading dose followed by 420 mg maintenance on day 1 of each cycle for 37.39 cycles in pertuzumab+trastuzumab+docetaxel regimen	Not reported	21 days	Initial dosing [redacted] Maintenance [redacted]
Trastuzumab SC-branded	600 mg	[redacted]	Assumed in TA569.	600 mg on day 1 of each cycle for 23.65 cycles in the trastuzumab+docetaxel regimen	Medicines Complete [61]	21 days	[redacted]
Docetaxel IV	20 mg	£11.61	eMIT-June 2018	1.77 mg/m^2 on day 1 of each cycle for 6 cycles (in all regimens)	Not reported	21 days	£37.20
	160 mg	£28.48					

Source: Table 43 and Table 44 from the CS.[1]
Abbreviations: eMIT = electronic market information tool; IV= intravenous; SC = subcutaneous.

In the model, the average monthly cost for the drug acquisition in the late recurrence first line mBC state was calculated by taking the weighted average of the monthly drug acquisition costs of the included treatment regimens according to the market share assumptions. The average monthly drug acquisition cost for a given treatment regimen was calculated in the same way as explained in the non-metastatic recurrence state.

Early/late recurrence, second and later lines mBC state

In the early and late recurrence second and later lines mBC state, it is assumed that patients from both arms receive similar treatments. The market shares used in the base-case of the economic model pertaining to the second and later lines are given below in Table 5.27.

Table 5.27: Market share and total number of cycle information for the drugs used in early/late recurrence, second and later lines mBC state.

Treatment regimen	% market share for both arms	Source for market share	Total number of cycles	Source for # of cycles
Pertuzumab+ trastuzumab biosimilar IV + docetaxel	10%	Market research and assumptions	9.36, for pertuzumab and trastuzumab 6 for docetaxel	TA 509
Trastuzumab biosimilar IV + docetaxel	4%		9.36, for trastuzumab 6 for docetaxel	TA509
Trastuzumab branded SC + docetaxel	3%		9.36, for trastuzumab 6 for docetaxel	TA509
Trastuzumab emtansine	78%		19.33 for trastuzumab emtansine	TA458
Docetaxel	4%		6 for docetaxel	Assumption
Lapatinib	1%		12.29	TA458
Source: Table 43 and Table 44 from the CS.[1] Abbreviations: eMIT = electronic market information tool; IV= intravenous; SC = subcutaneous;				

The dosage of pertuzumab, trastuzumab (IV and SC), trastuzumab emtansine, docetaxel are same as the dosage used in the previous IDFS and non-metastatic recurrence states (Table 5.26 and Table 5.24 above).

Lapatinib is taken orally once a day at a fixed dose of 1250 mg (five pills each 250 mg) during 12.29 cycles (each cycle three weeks). Lapatinib is available in packages, including 84 pills at a price of £965.16. An overview of the drug acquisition costs, dosage and cost per cycle in the early/late recurrence second and later line mBC state is given in Table 5.28 below.

In the model, the average monthly cost for the drug acquisition in the early/late recurrence second and later lines mBC state was calculated by taking the weighted average of the monthly drug acquisition costs of the included treatment regimens according to the market share assumptions. The average monthly drug acquisition cost for a given treatment regimen was calculated in the same way as in the previous states.

Table 5.28: Drug acquisition costs and costs per cycle in early/late recurrence, second and later lines mBC state.

Drug	Vial / pack size (mg)	Vial / pack price	Cost source	Dosing	Dosing source	Cycle length (days)	Cost per cycle
Trastuzumab emtansine	100 mg	[redacted]	Planned list price and the offered PAS	3.6 mg/kg on day 1 of each cycle for 19.33 cycles	TA458	21 days	[redacted]
	160 mg	[redacted]					
Trastuzumab IV-biosimilar	150 mg	£122.22	Assumed in TA569.	8 mg/ kg initial loading dose followed by 6 mg/kg on day 1 of each cycle for 9.36 cycles in all regimens	Medicines Complete [61]	21 days	Initial dosing £488.88 Maintenance £366.66
Pertuzumab IV-branded	420 mg	[redacted]	Assumed in TA569.	840 mg initial loading dose followed by 420 mg maintenance on day 1 of each cycle for 9.36 cycles in pertuzumab+trastuzumab+docetaxel regimen	Not reported	21 days	Initial dosing [redacted] Maintenance [redacted]
Trastuzumab SC-branded	600 mg	[redacted]	Assumed in TA569.	600 mg on day 1 of each cycle for 9.36 cycles in all regimens	Medicines Complete [61]	21 days	[redacted]
Lapatinib	21000 mg	£965.16	eMIT-June 2018	1,250 mg per day. 12.29 cycles, each cycle 21 days	TA458	21 days	£1,206.45
Docetaxel IV	20 mg	£11.61	eMIT-June 2018	1.77 mg/m^2 on day 1 of each cycle for 6 cycles (in all regimens)	Not reported	21 days	£37.20
	160 mg	£28.48					

Source: Table 43 and Table 44 from the CS.[1]
Abbreviations: eMIT = electronic market information tool; IV= intravenous; SC = subcutaneous;

The company assumed that in the node-positive population, the market share and the post-IDFS drug acquisition costs would be the same as those used for the trastuzumab monotherapy arm in the ITT analysis.

ERG comments: The ERG found the drug acquisition cost calculations in the post-IDFS states to be generally plausible. There was a reporting error detected, in the company submission, the price for the 160 mg docetaxel IV was reported as £28.48, however in the economic model, £25.59 was used.

The market share assumptions for the post-IDFS states in the company submission could not be verified by the ERG. Generally, same market shares were assumed for both arms in the post-IDFS states. Only in the early recurrence, first line mBC state, arm-specific market shares were assumed, which incurred more drug acquisition costs in the trastuzumab monotherapy arm. Since the ERG could not verify these market shares, the arm-specific market share assumption in the early-recurrence first line mBC state will be challenged in a scenario analysis conducted in Section 7.

Additionally, in the model, for chemotherapy regimen, only docetaxel treatment was considered. Also, the costs related with capecitabine (which is generally co-administered with lapatinib) were not included in the mBC states. Due to the negligible impact on the costs, the ERG did not change the calculation of chemotherapy related drug acquisition costs.

For the node-negative/node-positive populations, without any evidence, the ERG could not judge the plausibility of the company assumption (identical drug acquisition costs in different subgroups). However, the ERG considers that the impact of these assumptions would not be significant and, especially for the node-positive population, would be of secondary importance, considering the uncertainty on the relative effectiveness of trastuzumab emtansine versus pertuzumab + trastuzumab.

5.2.9.2 Drug administration costs

The administration costs associated with each technology have been sourced using the National Tariff for Chemotherapy Regimens list 2017–2018, the NHS reference costs schedule 2017/18, and the Personal Social Services Research Unit (PSSRU) costs 2017 document.[41, 42]

Trastuzumab emtansine and trastuzumab monotherapy

The assumptions in the company submission are in line with the assumptions taken in the TA569 appraisal.[17]. For the administration of the initial dose of trastuzumab emtansine IV and trastuzumab biosimilar IV, unit cost of the code SB14Z in the NHS reference costs schedule 2017/18 (Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance [chemotherapy delivery: day case]) was used, whereas for the administration cost for subsequent (maintenance) cycles, unit cost corresponding to the SB13Z code of the reference schedule (Deliver more Complex Parenteral Chemotherapy at First Attendance [chemotherapy delivery: day case]) was considered. This is designed to reflect the difference in delivery time, since both trastuzumab emtansine and trastuzumab IV initial doses should comprise of a 90-minute IV infusion, whereas the subsequent doses can be given as 30-minute infusions.[16, 62] The costs quoted above are applied to all treatments that are administered via IV infusion.

For the subcutaneous administration cost of trastuzumab, it is assumed that unit cost would be from the cost in SB12Z (Deliver Simple Parenteral Chemotherapy at First Attendance [chemotherapy delivery: day case]) according to the National Tariff of chemotherapy regimens.[42]

Additionally, costs related to the pharmacist's time for the prescription and preparation of treatments were also accounted for. It has been assumed that each administration will require 12 minutes of a pharmacist's time.[63] This cost is applied to every administration, regardless of treatment or treatment arm. Note that when a medication is administered orally, the pharmacy cost is the only administration cost applied.

The administration costs in the IDFS states were applied per cycle, based on the actual time on treatment data, whereas the administration costs in the post-IDFS state costs were calculated based on similar assumptions (i.e. calculating average administration costs per cycle based on number of cycles in each state similar to the calculation of the drug acquisition costs in post-IDFS states).

A full breakdown of administration costs applied in the model is given in Table 5.29 below. The administration costs were assumed to be the same for all investigated populations (ITT, node-negative and node-positive)

Table 5.29: Drug administration tariffs and costs per cycle

Drug	First cycle			Subsequent cycles		
	NHS reference code	Cost per admin.	Source	NHS reference code	Cost per admin.	Source
IV delivery	SB14Za	£374.52	NHS ref. costs 2017/18	SB13Zb	£309.22	NHS ref. costs 2017/18
H SC delivery	SB12Zc	£247.74	NHS ref. costs 2017/18	SB12Zc	£247.74	NHS ref. costs 2017/18
Pharmacy cost	N/A	£9.27d	PSSRU 2018	N/A	£9.27d	PSSRU 2018

Source: Table 45 from the CS.[1]

Footnotes: a: Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance – day case. b: Deliver more Complex Parenteral Chemotherapy at First Attendance – day case. c: Deliver Simple Parenteral Chemotherapy at First Attendance - day case. d: Average hourly cost of "Hospital-based health care staff (band 6) – 12 minutes of time.

Abbreviations: admin: administration; IV: intravenous; N/A: not applicable; NHS: National Health Service; PSSRU: Personal and Social Services Research Unit; ref.: reference; SC: subcutaneous.

Pertuzumab + trastuzumab administration costs

The company mentioned that costs and resource use are not expected to be dependent on nodal status. Unlike the intervention and comparator arms in the base-case analysis, the pertuzumab + trastuzumab arm requires two intravenous administrations. To account for this difference, for the administration cost calculations, the company used for all administrations in the pertuzumab + trastuzumab arm the SB14Z code from the NHS reference costs schedule 2017/18.[42] Please see Table 5.30 for the administration unit costs used in this subgroup analysis. Additional pharmacist time for the administration was costed similar to the trastuzumab emtansine and trastuzumab monotherapy arms.

Table 5.30: Drug administration costs

Drug	First cycle			Subsequent cycles		
	NHS reference code	**Cost per admin.**	**Source**	**NHS reference code**	**Cost per admin.**	**Source**
IV delivery	SB14Z[a]	£374.52	NHS ref. costs 2017/18	SB13Z[b]	£309.22	NHS ref. costs 2017/18
H SC delivery	SB12Z[c]	£247.74	NHS ref. costs 2017/18	SB12Z[c]	£247.74	NHS ref. costs 2017/18
Pharmacy cost	N/A	£9.27[d]	PSSRU 2018	N/A	£9.27[d]	PSSRU 2018

Source: Table 43 in Appendix M of the CS. [20]

Footnotes: aDeliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance – day case. bDeliver More Complex Parenteral Chemotherapy at First Attendance – day case. cDeliver Simple Parenteral Chemotherapy at First Attendance - day case. dAverage hourly cost of "Hospital-based health care staff (band 6) – 12 minutes of time.

Abbreviations: admin: administration; IV: intravenous; N/A: not applicable; NHS: National Health Service; PSSRU: Personal and Social Services Research Unit; ref.: reference; SC: subcutaneous.

ERG comment: The ERG considers the administration cost calculations in the CS to be plausible. There is no evidence on the company assumption of identical administration costs, but the ERG does not consider that this is a major issue.

5.2.9.2 Health state unit costs and resource use

Health state costs have been applied cyclically and irrespective of treatment arm throughout the duration of the model time horizon. The cost and resource use required in each health state is outlined below.

IDFS state resource use costs

Resource use and supportive care regimens are expected to differ depending on how long a patient has remained in the IDFS health state. Specific supportive care costs have been derived and applied in the following time periods:

- Year 1
- Years 2–5
- Years ≥5

The company stated that the resource use assumed here is in line with the "IDFS" health state resource use of the adjuvant pertuzumab appraisal (TA569).[17] The unit costs are mostly from the NHS reference costs from 2017/2018 and PSSRU costs from 2018.[41, 42] The unit costs and the resource use in the IDFS states are given below (Table 5.31):

Table 5.31: health state – resource use and supportive care costs

Resource	Unit cost	Source	% of patients	Frequency per year		
				Year 1	Years 2–5	Years ≥5
Oncologist visit	£130.00	NHS ref. 2017/18 – 800[42]	100%	2	0	0
GP visit	£37.00	PSSRU 2018 – page 162[41]	100%	0	1	1
Mammogram	£11.34	TA767 – NHS BSP (inflated)	100%	1	1	0
ECHO scan	£70.36	NHS ref. 2017/18 – RD51A[42]	70%	4	0	0
MUGA scan	£249.00	NHS ref. 2017/18 – RN22Z[42]	30%			
Total base-case cost per (four-week) cycle:				£63.93	£7.11	£3.08

Source: Table 46 from the CS.[1]
Abbreviations: BSP: breast screening programme; ECHO: echocardiogram; GP: general practitioner; MUGA: multigated acquisition; NHS: National Health Service; PSSRU: Personal and Social Services Research Unit.

Non-metastatic recurrence state resource use costs

The resource use in this state was assumed to be the same as the resource use in the first year in the IDFS. In addition, it was assumed that 75% of patients would receive a computerised tomography (CT) scan to facilitate the monitoring of the recurrence, based on clinical expert opinion from a previous appraisal (TA 569). The overview of costs is given in Table 5.32.

Table 5.32: Non-metastatic recurrence health state – resource use and supportive care costs

Resource	Unit cost	Source	% of patients	Frequency per year		
				Year 1	Years 2–5	Years ≥5
Oncologist visit	£130.00	NHS ref. 2017/18 – 800	100%	2	0	0
GP visit	£37.00	PSSRU 2018 – page 162	100%	0	1	1
Mammogram	£11.34	TA767 – NHS BSP (inflated)	100%	1	1	0
ECHO scan	£70.36	NHS ref. 2017/18 – RD51A	70%	4	0	0
MUGA scan	£249.00	NHS ref. 2017/18 – RN22Z	30%			
CT scan	£90.47	NHS ref. - 2017/18 – RD20A	75%	2	£11.31	CT scan
Total base-case cost per (four-week) cycle:				£63.93	£7.11	£3.08

Source: Table 47 from the CS.[1]
Abbreviations: BSP: breast screening programme; CT: computerised tomography; ECHO: echocardiogram; GP: general practitioner; MUGA: multigated acquisition; NHS: National Health Service; PSSRU: Personal and Social Services Research Unit.

Remission state resource use costs

In this submission model, it was assumed that the patients in remission would incur the same health state costs as those patients who are in year 2–5 of IDFS which was presented in Table 5.31.

Metastatic health states (first line mBC and second + line mBC)

In the metastatic health states, response to treatment is assessed using outpatient visits, CT scans, cardiac monitoring, and health care practitioner time. It is assumed that resource use would not vary between early and late recurrence patients. The full breakdown of the costs in the first and second line mBC states are given in Table 5.33 and Table 5.34, respectively.

Table 5.33: First line mBC state – resource use and supportive care costs

Items	Frequency (yearly)	Unit cost per contact	Proportion of patients	Cost sources	Resource use sources
Cycle costs					
GP visit	12	£37.40	100%	PSSRU 2018 – page 127	Assumption
ECHO Scan	2	£107.84	70%	NHS ref. 2017/18 – RD51A	CG81
MUGA Scan	2	£283.61	30%	NHS ref. 2017/18 – RN22Z	CG81
Clinical nurse specialist	12	£77.98	100%	NHS ref. 2017/18 – N09AF	CG81

Items	Frequency (yearly)	Unit cost per contact	Proportion of patients	Cost sources	Resource use sources
District Nurse (home visit)	22	£38.45	100%	NHS ref. 2017/18 - N02AF	CG81
CT Scan	One off cost	£90.47	75%	NHS ref. 2017/18 – RD20A	Ad. board (03/2013); CG81
Social worker	One off cost	£84.00	100%	PSSRU 2018 – 11.1 – page 139	CG81
Total base-case cost per (monthly) cycle = £231.70 Source: Table 48 from the CS.[1] Abbreviations: CT: computerised tomography; ECHO: echocardiogram; GP: general practitioner; MUGA: multigated acquisition; NHS: National Health Service; PSSRU: Personal and Social Services Research Unit.					

Table 5.34: Second + line mBC state – resource use and supportive care costs

Items	Frequency (yearly)	Unit cost per contact	Proportion of patients	Cost sources	Resource use sources
GP visit	12	£37.40	100%	PSSRU 2018 – page 127	Assumption
Clinical nurse specialist	12	£77.98	100%	NHS ref. 2017/18 – N09AF	CG81
District Nurse (home visit)	24	£38.45	100%	NHS ref. 2017/18 – N02AF	CG81
Average monthly supportive care cost = £192.28					
Source: Table 49 from the CS.[1] Abbreviations: GP: general practitioner; NHS: National Health Service; PSSRU: Personal and Social Services Research Unit.					

All health state costs, were assumed to be independent of the nodal treatment status.

ERG comment: The ERG could not verify all of the assumptions on the resource use frequencies, however confirms that these estimates were identical to the assumptions used in the TA569 appraisal, which were considered by the previous committee to be plausible.[17]

Since the node-positive population can be considered to be, in terms of disease prognosis, worse in comparison to the node-negative population, it could be speculated that the resource use frequency values for the node-positive patients could have been more in comparison to the resource use frequency values of the node-negative population. However, since this would hold true in both arms, the ERG considers that it would be unlikely that the incremental results would have changed by assuming identical resource use frequencies in all node specific subgroups.

5.2.9.4 Adverse event costs

Adverse events in the IDFS state

As discussed in Section 5.2.7, only "decreased platelet count" was considered be relevant to be included in the economic model. Table 5.35 below provides the frequency and the unit costs for adverse events in the IDFS state. These costs were applied to patients in the first cycle.

Table 5.35: List of adverse events and costs included in the economic model

Adverse events	Frequency		Treatment	Event cost	Source
	Trastuzumab emtansine (n=740)	Trastuzumab (n=720)			
Platelet count decreased	42 (5.68%)	0 (0.00%)	Platelet disorder drugs – Band 1 – Total HRG activity	£1,712.99a	NHS Ref. 2016/17 – XD43Z

Source: Table 51 from the CS.[1]
Footnotes: [a]Equal to £1,641.93 in 2016 before being inflated to reflect the 2019 price year.
Abbreviations: HRG: Healthcare resource group; NHS: National Health Service.

Adverse events due to the subsequent therapies

As described in Section 5.2.9.1, following progression patients will receive subsequent therapies. The cost of managing treatment-related AEs on these subsequent therapies were incorporated in a similar approach to how the subsequent drug acquisition and administration costs were accrued in the model. The treatment-specific weekly adverse event management costs were sourced from previous appraisals as shown in Table 5.36 below. A separate cost of death was not applied to the model.

Table 5.36: Adverse event management costs for subsequent therapies (per patient, per week)

Regimen	Original cost	Original price year	Inflated cost	Reference
Trastuzumab[a] + docetaxel	£13.51	2015	£14.85	T arm in PTC in mBC appraisal – TA509[40]
Pertuzumab + trastuzumab[a] + docetaxel	£15.09	2015	£16.59	PTC arm in PH in mBC appraisal – TA509[40]
Chemotherapy	£1.28	2017	£1.34	Capecitabine arm in trastuzumab emtansine in mBC appraisal – TA458[43]
Trastuzumab emtansine	£2.12	2017	£2.21	Trastuzumab emtansine arm in trastuzumab emtansine in mBC appraisal – TA458[43]
Lapatinib + capecitabine	£7.21	2017	£7.52	Lap + cap arm in trastuzumab emtansine in mBC appraisal – TA458[43]

Source: Table 52 from the CS.[1]
Footnotes: aApplies to all types of trastuzumab in the analysis – branded IV, branded SC, and biosimilar.
Abbreviations: cap: capecitabine; lap: lapatinib; mBC: metastatic breast cancer; PTC: pertuzumab + trastuzumab + chemotherapy; T: trastuzumab.

Pertuzumab AE management in IDFS

Adverse event (AE) management costs in the pertuzumab arm were sourced from the cost effectiveness model in the TA569.[17] Only Grade 3 (or above) AEs with an incidence of at least 2% as observed in APHINITY were included in the cost effectiveness analysis. AEs were costed using the NHS reference cost schedule 2016/17 and subsequently inflated to reflect the current price year (2019). AE management costs are summarised in Table 5.37. Finally, the company pointed out that AE management costs from the cost effectiveness model used in TA569 was based on a pertuzumab regimen with a length of 6 cycles. In the model for the current submission, it was assumed that pertuzumab was administered 13 cycles. However, the company argued that the impact of the adverse events on the overall cost effectiveness results was expected to be minor.

Table 5.37: AE management costs (per patient)

Treatment arm	AE management cost per patient
Trastuzumab emtansine	£106.48
Pertuzumab + trastuzumab	£17.18
Source: Table 42 in Appendix M of the CS. [20]	

ERG comment: The ERG already expressed its concerns on the selection of the AES in Section 5.2.7. The ERG considers that the post-IDFS state, treatment-specific AE management costs could have been obtained by the treatment specific AE incidences and unit costs instead of using the AE costs in the previous appraisals, however, in the ERG's opinion, these costs are highly unlikely to have a notable effect on the final cost effectiveness results. The ERG could not check the AE costs of pertuzumab however, considers that this issue would be of secondary importance, especially in consideration of the uncertainty of relative effectiveness of pertuzumab + trastuzumab versus trastuzumab emtansine in the node-positive population.

6. COST EFFECTIVENESS RESULTS

For node-positive patients, trastuzumab monotherapy does not reflect clinical practice any longer. Since the ITT population has both node-positive and node-negative patients, and the standard of care for node-positive patients is pertuzumab + trastuzumab, using trastuzumab monotherapy as comparator for the ITT population is incorrect. As a consequence, all results presented for the ITT population are incorrect. Given all the limitations and flaws regarding the node-positive analyses described throughout Chapter 5, the cost effectiveness analyses for the node-positive population are unreliable and, therefore, inappropriate for decision making. Thus, the ERG considers that only the cost effectiveness results are relevant for decision making and these are the ones shown in this section of the report. For completeness, results based on the ITT population and the node-positive subgroup are shown in Appendix 3 and 4, respectively.

The cost effectiveness evidence and economic analyses regarding the node-negative subpopulation were received by the ERG on November 12th, 2019, in the second batch of responses to the clarification questions (question B2).[4] Given the proximity of the final deadline to submit the ERG report, it was unfeasible for the ERG to critique the cost effectiveness evidence for the node-negative population in the same detailed way as it was done for the ITT population (the latter was received with the original submission). Likewise, while major errors are not expected, the ERG was not able to properly validate the most recent version of the electronic model.

6.1 Company's cost effectiveness results (node-negative population)

The company's base-case cost effectiveness results for the node-negative population are displayed in Table 6.1. Trastuzumab emtansine is found to be both more costly and more effective than trastuzumab, with incremental costs and QALYs of [redacted] and 1.32, respectively. The ICER in this case was £2,634.

Table 6.1: Company base-case cost effectiveness results for the node-negative population (discounted)

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Trastuzumab	[redacted]	16.74	[redacted]	[redacted]	1.61	1.32	£2,634
Trastuzumab emtansine	[redacted]	18.35	[redacted]				

Source: electronic model, updated from the response to the clarification letter.[4]
Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year

ERG comment: As mentioned in Section 5.2.4, it is expected that if the analysis had been conducted correctly, i.e. trastuzumab as comparator for only the node-negative subgroup, with all the model input parameters derived from KATHERINE node-negative data, the ICER would be lower than the ICER for the ITT population, because the efficacy profile of the intervention was more favourable in the node-negative population compared to the ITT (HR=0.42 vs 0.50). However, this did not happen since the ICER for the ITT population was £1,293 (see Appendix 3). The company indicated that this could be due to the *de novo* extrapolation parameters that have been calculated for the node-negative population. This might be the case but it might also be for other reasons, for example, that not all parameters were derived from node-negative data. This might have introduced some biased which seems to work in the opposite direction than the one expected. The ERG agrees with the company though that, regardless of

this uncertainty, the ICER in the node-negative subgroup is considerably below the common threshold of £20,000.

6.2 Company's sensitivity analyses (node-negative population)

6.2.1 Probabilistic sensitivity analysis (node-negative population)

The parameters and the probability distributions used in the probabilistic sensitivity analysis (PSA) are shown in Table 24 of the clarification letter response (question B31).[4] These are the same included in the ITT analyses. The results of the company PSA (obtained from 1,000 Monte Carlo simulations) are shown in Table 6.2. The probabilistic ICER was £3,219, thus, slightly larger than the deterministic ICER. The resulting cost effectiveness plane and CEAC are displayed in Figure 6.1 and 6.2. The cost effectiveness plane shows that [redacted].

The CEAC shows that the probability that trastuzumab emtansine is cost effective at thresholds of £20,000 and £30,000 was 93% and 96%, respectively.

Table 6.2: Company base-case probabilistic cost effectiveness results for the node-negative population (discounted)*

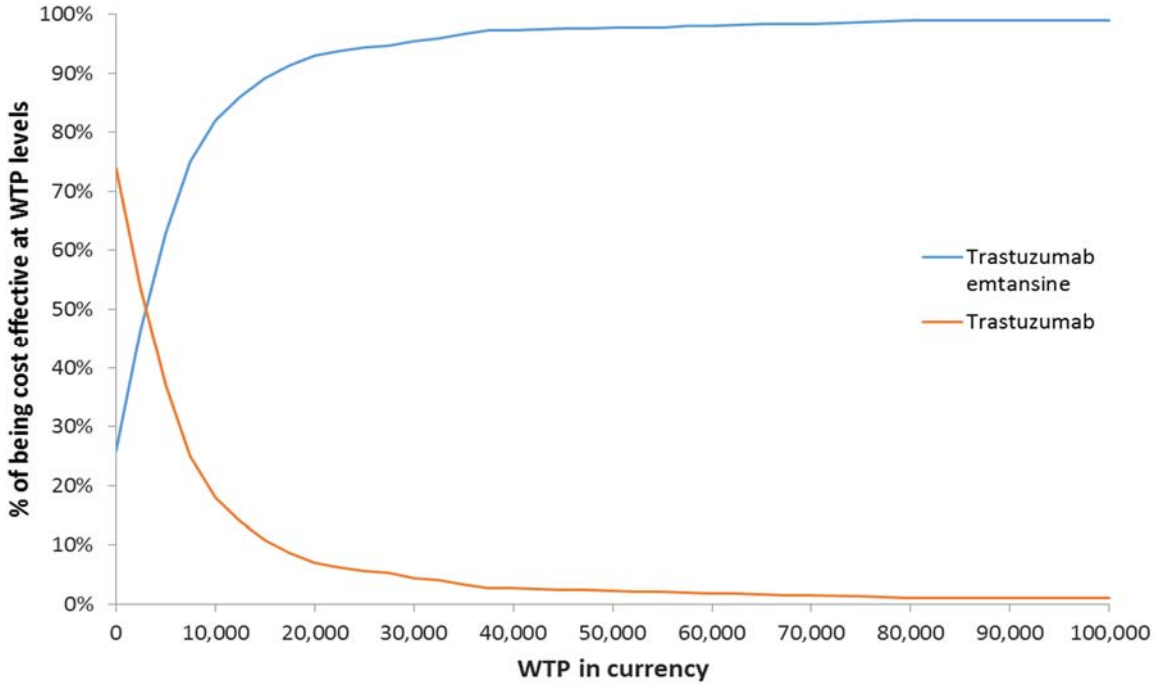
Technologies	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER versus baseline (£/QALY)
Trastuzumab	[redacted]	NR	[redacted]				
Trastuzumab emtansine	[redacted]	NR	[redacted]	[redacted]	NR	1.28	£3,219

Source: electronic model, updated from the response to the clarification letter.[4]
* The ERG repeated the PSA with the company settings.
Abbreviations: ICER = incremental cost effectiveness ratio; Incr. = incremental; LYGs = life years gained; NR = not reported, QALYs = quality adjusted life years.

Figure 6.1: Scatterplot from the PSA (node-negative population)

Source: electronic model, updated from the response to the clarification letter.[4]
Abbreviations: inc. = incremental; PSA = probabilistic sensitivity analysis; QALY= quality adjusted life year.

Figure 6.2: Cost effectiveness acceptability curve (node-negative population)



Source: based on electronic model, updated from the response to the clarification letter.[4]
Abbreviations: QALY= quality adjusted life year

ERG comment: The ERG identified a selection of model parameters which had not been included in the PSA conducted by the company in the original submission (for the ITT population). These included patient demographics such as weight and height, treatment market shares and AE costs. The ERG also identified parameters, which had been included in the PSA, but with inappropriate or inconsistent probability distributions assumed. These included:

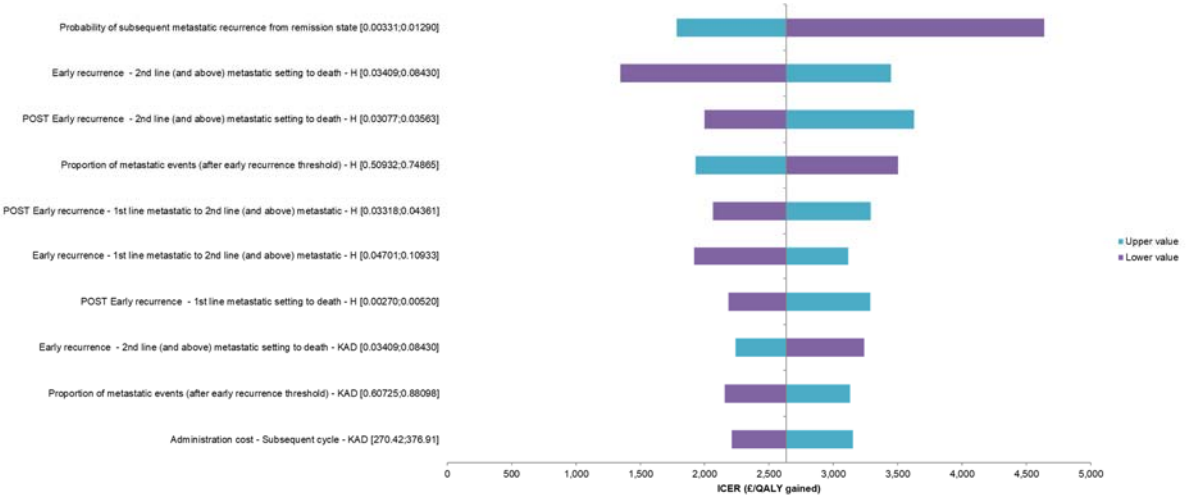
- Transition probabilities modelled using a multivariate normal distribution instead of a Dirichlet distribution.
- Utilities modelled using a Beta distribution instead of a Gamma distribution.
- Inconsistent use of a Gamma distribution for modelling some cost parameters and a log-normal for other parameters.

In Table 21 of the clarification response, the company indicated that they had included patient weight and height in the updated PSA using a normal distribution, updated the utility distributions to Beta distributions, incorporated treatment shares using a Dirichlet distribution, included AE costs using a log normal and amended all cost distributions to log normal. Regarding the transition probabilities, the company responded that the sum of all probabilities leaving a specific health state would not be above one with current data inputs.[4] The company created a worksheet named "Transition probabilities" in which they calculated, based on the 1,000 simulations, the maximum probability of cumulative transitions per node (= sum of the maximum values generated in 1,000 simulations for each transition probability pertaining to the respective node). This showed that the sum was never above one with current data inputs. The ERG was satisfied with the company's updated PSA. These changes, even though were based on the ITT model, were also applied to the node-negative analysis. Therefore, the results shown above are based on the updated PSA.

6.2.2 Deterministic sensitivity analysis (node-negative population)

The company conducted deterministic sensitivity analyses by varying one-by-one the base-case values of a series of cost and utility parameters by ±25% of the base-case value. The tornado diagram displayed in Figure 6.3 shows that, overall, the transition probabilities in the metastatic setting were found to have the largest impact on the ICER.

Figure 6.3: Tornado diagram – company's preferred assumptions (node-negative population)



Source: Figure 9 of the response to the clarification letter – Part II.[4]
Abbreviations: H = trastuzumab; IDFS = invasive disease-free survival; KAD = trastuzumab emtansine.

ERG comment: The ERG found the choice to vary those parameters included in the deterministic sensitivity analysis by ±25% of the base-case value to be arbitrary and felt that this may not produce values that are equally plausible across all parameters. It would be better practice to use the 95% confidence intervals as upper and lower bounds within the deterministic sensitivity analysis.

Furthermore, no patient demographic variables, such as weight and height, or clinical variables, such as transition probabilities, were included in the original deterministic sensitivity analysis conducted by

the company (for the ITT population). The ERG requested to include these parameters at the clarification stage and some of these were included in the model accompanying the clarification response. The company addressed this partially as no patient demographics were included in the one-way sensitivity analysis and no justification was provided for this choice. These changes, even though were based on the ITT model, were also applied to the node-negative analysis. Therefore, the results shown above are based on the updated deterministic sensitivity analysis.

6.2.3 Scenario analyses (node-negative population)

As mentioned at the beginning of this chapter, the cost effectiveness analyses regarding the node-negative subpopulation were received by the ERG on 12 November 2019, in the second batch of responses to the clarification questions (question B2).[4] The company referred to the updated economic model for a full breakdown of the scenario analyses results in the node-negative population but a summary of these analyses was not presented by the company. Given the proximity of the final deadline to submit the ERG report, it was unfeasible for the ERG to re-run all the scenario analyses for the node-negative population (approximately 80 scenarios were run by the company for the ITT population). However, it is expected that the conclusions drawn for the ITT population are also valid for the node-negative population. The ITT scenario analyses indicated that the model results were robust for the majority of the assumptions tested by the company. Only extreme and implausible scenarios resulted in a relative large increase in the ICER. For example, when a 10year time horizon was assumed, the ICER increased by approximately £10,000 compared to the ITT base-case ICER. When a 0% cure rate was assumed, the ICER increased by approximately £4,000 compared to the ITT base-case ICER. In all cases the ICERs were below the common threshold of £20,000. The ERG refers to Appendix 3 of this report for further details.

ERG comment: The ERG feel that the impact of some key assumptions were not sufficiently tested. While the company did conduct a scenario regarding the duration of treatment effect, only the impact of assuming that the treatment effect was maintained indefinitely over time, rather than the treatment effect being maintained to seven years and waning to 10 years, was tested. Therefore, the only scenario considered for the duration of treatment effect was more favourable to trastuzumab emtansine. The ERG felt that alternative scenarios, including more conservative approaches than the base-case, should have been tested, as treatment effect duration is a key driver in the model. Additionally, no scenarios were conducted for the assumptions around the mortality rate of "cured" patients or the transition probabilities (other than remission to first line mBC in the clarification response) or mortality rates assumed throughout the model. Given the importance of transition probability and mortality parameters in the one-way sensitivity analysis, the ERG felt that these variables should have been tested in scenarios, particularly as many of these assumptions were sourced from the literature and previous appraisals of different treatments and not linked to trial evidence.

6.3 Model validation and face validity check

In the CS, it was stated that a formal quality assessment and validation of model outcomes was conducted by an independent assessor prior to submission. According to the CS, this validation included a technical cell by cell verification of formulae, functions and coding was performed as part of this process, a number of 'pressure tests' using extreme values. However, the detailed explanation of the validation efforts were not presented.

For the health state resource use costs, the company compared the per cycle health state resource use costs used in previous appraisals in the same/similar indication (TA424 and TA569 for other treatments

from the same company). Per cycle costs used in these appraisals were in close proximity to the resource use costs used in this submission (Table 6.3).

Table 6.3: Comparison of health state costs in the neoadjuvant and adjuvant appraisals

TA424 – pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer[35]		**TA569 – pertuzumab for the adjuvant treatment of HER2-positive breast cancer[17]**		**ID1516 - Trastuzumab emtansine for adjuvant treatment of HER2-positive early breast cancer**	
Health state	**Cycle cost**	**Health state**	**Cycle cost**	**Health state**	**Cycle cost**
EFS	Year 1–2 = £67.85 Year 3–5 = £15.11 ≥5 years = £3.83	IDFS	Year 1-2 (on treatment) = £63.93 Year 3–5 = £7.11 ≥5 years = £3.08	IDFS	Year 1-2 =£76.57 Year 3-5 = £4.12 ≥5 years = £3.12
Locoregional recurrence	£73.97	Non-metastatic recurrence	£76.80	Non-metastatic recurrence	£87.88
Remission	£67.85	Remission	£7.11	Remission	£4.15
mBC – non-progressed	£232.00	First line mBC	£214.78	First line mBC	£231.70
mBC – progressed	£185.00	Second+ line mBC	£180.85	Second+ line mBC	£192.28
Source: Table 50 from the CS.[1] Abbreviations: EFS: event-free survival; HER2: human epidermal growth factor receptor 2; IDFS: invasive disease-free survival; mBC: metastatic breast cancer.					

Additionally, the company provided a comparison table for the IDFS estimates from the cost effectiveness model to the observed data from the KATHERINE, APHINITY, HERA and BCIRG 006 trials in Table 31 of Appendix J.[20] The long-term model IDFS outcomes for the trastuzumab arm of the model were lower than the IDFS observations from the HERA and BCIRG 006 trials' EFS KM curves. The company argued that this difference can be due to the difference of baseline patient characteristics as well as the difference in EFS and IDFS endpoint definitions.

ERG comment: The ERG considers that it was not very useful to compare the per cycle health state costs from this submission to the per cycle health state costs from previous appraisals (as in Table 6.3 above), since the resource use frequency assumptions of this appraisal were already based on those previous appraisals. Additionally, the ERG, in the clarification letter question B29,[4] asked for the actual sources to validate resource use frequencies reported in the company submission. However, the company, just reiterated that the sources were taken from TA569, and since both appraisals were on the same indication and same type therapy (anti-HER2 therapy for adjuvant therapy in early BC), there was no clear rationale to deviate from the accepted values.

Upon the request from the ERG, the company provided the following additional details of their validation efforts:

- Details on the clinical expert validation details conducted for TA569
- Technical validation of the economic model by an external vendor

For the clinical expert validation, the breakdown of the expert validation efforts was provided by the company, as can be seen in Table 6.4 below.

Table 6.4: Comparison of health state costs in the neoadjuvant and adjuvant appraisals

Study	Expert background	Forum and justification
Model structure	Consultant in Medical Oncology, The Christie NHS Foundation Trust, Manchester	Feedback on the modelling structure was sought as part of a HTA advisory board that took place as part of TA569. Given that TA569 also evaluated an anti-HER2 therapy in the adjuvant treatment of HER2+ eBC, it was deemed reasonable to use the same structure here.
	Consultant Medical Oncologist, Northern Centre for Cancer Care, Newcastle	
	The Christie NHS Foundation Trust, Manchester	
	London School of Hygiene and Tropical Medicine, London	
	London School of Hygiene and Tropical Medicine, London	
	Institute for Health Services Research University of Exeter Medical School, Exeter	
	Senior Research Fellow, Centre for Health Economics, York	
Subsequent treatments and market shares	61 medical or clinical oncologists practicing in breast cancer across the UK.	This information was collected as part of market research conducted by the company (readout = August, 2019). A summary of this research has been submitted as an appendix to this response.
Health state costs and resource use	Not applicable	Resource use frequencies in this analysis are identical to those in the TA569 (pertuzumab in adjuvant treatment of HER2+ breast cancer) which were in turn based upon those used in TA424 (appraisal of neoadjuvant pertuzumab in HER2+ breast cancer). The resource usage in these appraisals is not expected to have changed over time. Additionally, this appraisal focuses on the same disease area (early HER2+ breast cancer) and the same type of therapy (anti-HER2). Consequently, there appears to be no clear rationale to deviate from the accepted values used in TA569.
Modelling of IDFS, recurrence,	Consultant in Medical Oncology, The Christie NHS Foundation Trust, Manchester	Feedback on these aspects were discussed as part of the HTA advisory board that took place for TA569. The

Study	Expert background	Forum and justification
and Treatment effect duration	Consultant Medical Oncologist, Northern Centre for Cancer Care, Newcastle	approach and the assumptions taken in that analysis were judged appropriate for decision-making by the appraisal Committee. Given the similarity in disease area (HER2+ eBC), therapy class (anti-HER2), and data availability there appeared to be no clear rationale to deviate from the methodology accepted as part of the TA569.
	The Christie NHS Foundation Trust, Manchester	
	London School of Hygiene and Tropical Medicine, London	
	London School of Hygiene and Tropical Medicine, London	
	Institute for Health Services Research University of Exeter Medical School, Exeter	
	Senior Research Fellow, Centre for Health Economics, York	

Source: Table 2 from the response to the CL part I.[4]
Abbreviations: eBC: early breast cancer; HER2: human epidermal growth factor receptor 2; HTA: health technology assessment; IDFS: invasive disease-free survival; mBC: metastatic breast cancer; NHS: National Health Service.

The ERG could not verify the assumptions on the subsequent treatments and market shares from the provided details of the market research conducted by the company.

Furthermore, the ERG is doubtful, to what extent the validation efforts from TA569 would be applicable for the validation of the evidence used in this submission. Since the model structure used in both appraisals were similar, even though the ERG would have preferred de novo validation efforts for the model structure, the expert validation from TA569 could be still applicable.

On the other hand, the ERG disagrees with the company on the usefulness of the validation efforts on IDFS, recurrence and treatment effect duration modelling conducted in TA569. The ERG considers that these aspects are closely related with the observed treatment effect from the KATHERINE trial, and the validation efforts based on the observed treatment effect from the APHINITY trial for the pertuzumab adjuvant therapy would not be valuable for the modelling of the treatment effect of trastuzumab emtansine adjuvant therapy, observed from the KATHERINE trial.

The ERG checked the technical model validation documentation appended to the response to the clarification letter. The documentation summarised the required changes on the previous version of the economic model to improve the functionality, clarity, accuracy and consistency aspects. Even though the ERG considered the requested changes to be useful, the documentation did not include any reproducible black-box tests or the definition of white-box or replication based tests for verifying the economic model calculations as outlined in TECH-VER publication.[64] Therefore, from the details provided by the company, the ERG considers that the verification and other validation efforts conducted by the company were non-systematic and insufficient.

7. EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

7.1 Exploratory and sensitivity analyses undertaken by the ERG

As discussed in previous sections, the ERG considers that only node-negative subpopulation analysis would be useful for decision making given the provided evidence. Therefore, in this section, only results related to the node-negative subpopulation were presented.

7.1.1 Explanation of the company adjustments after the request for clarification

During the process of responding to the clarification questions, the company discovered and corrected an error in the cost effectiveness model. As explained in Section 5.2.6.2 of this report, the base-case analysis should consider both non-metastatic and metastatic "early" recurrences. However, an incorrect formula was used and, as a consequence, all "early" recurrences were considered as metastatic. Nevertheless, since the cost effectiveness analyses for the node-negative population were conducted with the model submitted with the response of the clarification letter, all results shown in Section 6 already included this correction.

7.1.2 Explanation of the ERG adjustments

The changes made by the ERG (to the model received with the response to the clarification letter) were subdivided into the following three categories (according to Kaltenthaler et al. 2016)[65]:

- Fixing errors (correcting the model where the company's electronic model was unequivocally wrong).
- Fixing violations (correcting the model where the ERG considered that the NICE reference case, scope or best practice has not been adhered to).
- Matters of judgement (amending the model where the ERG considered that reasonable alternative assumptions are preferred).

After these changes were implemented in the company's model, additional scenario analyses were explored by the ERG in order to assess the impact of alternative assumptions on the cost effectiveness results.

7.1.2.1 Fixing errors

The ERG corrected the errors identified in the model, as explained in the critique of Section 5.2.9. However, the correction of these errors did not impact the incremental results in the base-case.

7.1.2.2 Fixing violations

A large number of input parameters were not included in the original PSA. However, the company changed this after clarification. Therefore, the most recent version of the model accounts for this. Note that this has no impact on the base-case.

7.1.2.3 Matters of judgement

1. IDFS modelled using KM curves from the KATHERINE node-negative population up to the time point where the last event was observed in each treatment arm and an exponential long-term extrapolation (see Section 5.2.6.2 for details).
2. Duration of trastuzumab emtansine treatment effect: from month 36 to month 96 (see Sections 5.2.6.1 and 5.2.6.2 for details).
3. Treatment-specific utilities from KATHERINE (see Section 5.2.8 for details).
4. Lidgren et al. utilities for recurrence health-states (see Section 5.2.8 for details).

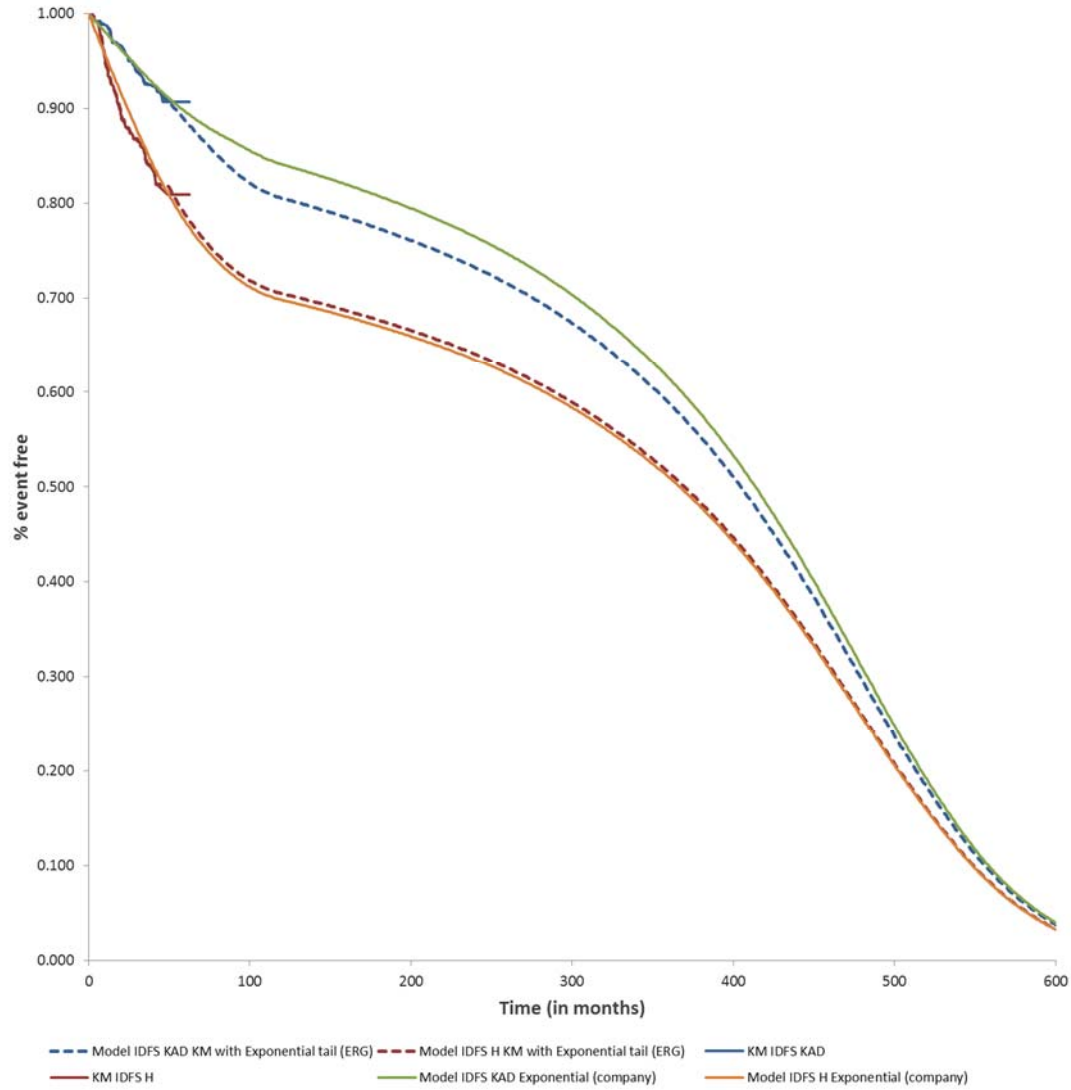
The overview of the changes and the bookmarks for the justification of the ERG changes are presented in Table 7.1.

Table 7.1: Company and ERG base-case preferred assumptions (node-negative population)

Base-case preferred assumptions	Company	ERG	Justification for change
Survival model IDFS	Exponential extrapolations	KM data up to last event and after that exponential extrapolation	Section 5.2.6.2
Treatment effect duration	84 to 120 months	36 to 96 months	Sections 5.2.6.1 and 5.2.6.2
IDFS utilities	KATHERINE pooled	KATHERINE treatment-specific	Section 5.2.8
Utilities in metastatic health states	Lloyd et al.	Lidgren et al.	Section 5.2.8
Abbreviations: IDFS = invasive disease-free survival, KM = Kaplan-Meier,			

The main difference between the company's and ERG's base-case was in the method used to model IDFS. A comparison of the IDFS extrapolations obtained by the company and the ERG can be seen in Figure 7.1. As expected, the largest difference was observed in the trastuzumab emtansine arm, where the survival probability in the company's base-case was higher than the survival probability in the ERG base-case.

Figure 7.1: Company base-case vs. ERG base-case IDFS extrapolation



Source: Electronic model attached to the CS.
Abbreviations: ERG = Evidence Review Group; H = trastuzumab; IDFS = invasive disease-free survival; ITT = intention to treat; KAD = trastuzumab emtansine; KM = Kaplan-Meier.

7.1.3 Additional scenarios conducted by the ERG

The ERG conducted a series of additional scenario analyses in order to explore important areas of uncertainty in the model. These key uncertainties were related to the survival modelling (in terms of choice of parametric distributions, modelling of cure assumptions and duration of treatment effect), sources of utility data and cost and resource use assumptions. Other sources of uncertainty were deemed less important and were not explored in this section. A list of scenario analyses conducted by the ERG is provided below.

7.1.3.1 Scenario set 1: alternative IDFS parametric distributions

The plausibility of long-term IDFS extrapolations was based on HERA data. However, these data was assumed to be a proxy for the ITT population in KATHERINE. No alternative HERA subgroup data were provided with which to assess the plausibility of long-term extrapolations of IDFS in the node-negative population. Therefore, the ERG had to rely on the assessment of fit to the node-negative KM data only, noting that this resulted in considerable uncertainty surrounding the choice of parametric

distributions for this subgroup. For their base-case, the ERG selected the exponential curve. As explained in Section 5.2.6.2, initially the ERG's preferred choice was the generalised gamma but the ERG considered that this choice resulted in implausible hazard ratios over time. Therefore, the ERG reconsidered this choice and, as the company did, selected the exponential distribution as this provided the best fit to the KM data for the trastuzumab emtansine arm (but not for the trastuzumab arm). Alternative parametric distributions were tested in this series of scenarios.

7.1.3.2 Scenario set 2: changing the time point "switch" from KM to parametric extrapolation in IDFS

In the ERG base-case IDFS extrapolations began at the time where the last event was observed in each treatment arm in the node-negative population. The last events in node-negative patients occurred in month 46 in the trastuzumab emtansine arm and month 49 in the trastuzumab arm. After these points the model utilises the selected extrapolation. Scenarios of 24 and 36 months were also tested.

7.1.3.3 Scenario set 3: changing start time of treatment effect waning

The company base-case assumed that treatment effect waning began at 84 months. However, the ERG considered this choice resulted in implausible treatment effect HRs over time. Therefore, in order to model more plausible HRs (i.e. increasing over time) the ERG assumed that treatment effect waning began at 36 months in the base-case. Scenarios between 12 and 108 months were also tested by the ERG.

7.1.3.4 Scenario set 4: changing time point where treatment effect is null

In the company base-case, it was assumed that the treatment effect waned to null at 120 months. Note this choice was based on ITT data and assumed to be the same for the node-negative subgroup. When a log-logistic distribution is assumed to model IDFS (company base-case ITT population), this resulted in treatment effect HRs slowly increasing until reaching 1 at 120 months. When KM data are used to model IDFS in the beginning (company base-case), the model reproduced the HRs observed in KATHERINE but these HRs were higher than those obtained by the company. As a consequence, the extrapolated HRs became larger than 1 before month 120 (at 96 months with a generalised gamma, the ERG's preferred choice for the ITT population), implying a treatment effect benefit for trastuzumab compared to trastuzumab emtansine. The ERG considered this implausible and for that reason selected 96 months as the time where the treatment effect waned to null. In scenario analyses a range from 48 to 144 months was tested.

7.1.3.5 Scenario set 5: maintaining treatment effect

Both the company and ERG base-cases assumed treatment effect waning. However, the company did conduct a scenario where treatment effect was maintained indefinitely without waning. This scenario was also tested by the ERG.

7.1.3.6 Scenario set 6: changing HRQoL modelling assumptions

The company base-case utilised utility estimates from the KATHERINE trial for eBC health states and values from Lloyd et al [36] for mBC health states. The KATHERINE utility values were insignificantly different across treatment arms and, therefore, the company chose to pool the values across arms. The company assumed that the disutility related to AEs experienced in the trial were captured within the EQ-5D trial data collection and, therefore, no additional disutilities were applied. The ERG felt that utility values from Lidgren et al.[34] better reflected the NICE reference case than those from Lloyd et al.[36] and, therefore, these values were used for mBC health states. The ERG felt that if no additional AE

disutilities were to be utilised, and the company was relying on the impact of AEs having been captured in the EQ-5D data collection, it was inappropriate to also pool the utility values across arms, masking any (even small) differences in utility due to differential incidence of AEs. Therefore, KATHERINE utilities per treatment arm were used for eBC health states and Lidgren et al. utility values for mBC health states in the ERG base-case. The impact of these changes were provided, as well as the impact of assuming pooled KATHERINE estimates with additional AE disutility of 0.5 at the full treatment duration for included AEs.

7.1.3.7 Scenario set 7: changing dosing modelling assumptions

The company and ERG base-cases assumed actual dosing observed in the trial (rather than planned dosing) with no vial sharing (rather than 100% vial sharing). The impact of these assumptions was tested in scenario analyses. An additional scenario was tested examining the impact of a small increase in cohort weight of 2.5 kg. This was tested because the required doses at the assumed cohort weight of 70.05 kg do not leave much remainder in optimal combinations of current vial sizes. Therefore, a small increase in weight could have a large impact on results if no vial sharing is assumed. This scenario had to be conducted using the planned dosing assumption, since actual dosing values were incorporated into the model as hardcoded values, not dependent on weight and, therefore, treatment costs did not change according to weight when actual dosing was applied. The ERG did not have the data to override this issue and, therefore, planned dosing had to be assumed.

7.1.3.8 Scenario set 8: changing market share modelling assumptions

In the company base-case, it was assumed a 95% market share for trastuzumab in the SC formulation. In the detailed market research slides provided by the company, the ERG observed that in the mentioned sample, 106 out of 229 patients received trastuzumab SC. Therefore, the ERG conducted a scenario surrounding the market share of trastuzumab SC using the 106/229 market share and assuming that the remaining patients received trastuzumab biosimilar. The ERG also conducted a scenario on the market share of early 1st line mBC treatments. The company assumed that the market shares in the trastuzumab emtansine and trastuzumab monotherapy arms were different in the early 1st line mBC health state. In this scenario, the ERG assumed that both arms have the same market shares (i.e. market share of trastuzumab monotherapy was assumed to be the same as the trastuzumab emtansine). An addition scenario testing both market share assumptions together was also explored.

7.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

This section of the report focuses on the ERG analyses undertaken in the node-negative subgroup, due to issues with the ITT and node-positive analyses previously discussed.

7.2.1 Results of the ERG preferred base-case scenario (node-negative subpopulation)

The results of the ERG preferred base-case for the node-negative subgroup are provided in Table 7.2. The implementation of the ERG's preferred assumptions resulted in an ICER of £9,339. Trastuzumab emtansine was estimated to provide 0.95 additional QALYs in node-negative patients at an incremental cost of [redacted]. The incremental QALY gains for trastuzumab emtansine all stemmed from the IDFS state, as shown in Table 7.3. As shown in Table 7.4, incremental costs were highest in the IDFS health state, mostly due to the additional treatment costs of trastuzumab emtansine. However, approximately [redacted]% of these incremental costs were saved in the mBC health states, which reduced the overall incremental cost.

Table 7.2: ERG base-case deterministic results for the node-negative subgroup (discounted)

Technologies	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER versus baseline (£/QALY)
Trastuzumab	[redacted]	16.76	[redacted]				
Trastuzumab emtansine	[redacted]	17.99	[redacted]	[redacted]	1.23	0.95	£9,339

Source: electronic model, updated from the response to the clarification letter.[4]
Abbreviations: ICER = incremental cost effectiveness ratio; Incr. = incremental; QALYs = quality adjusted life years; LYG = life years gained

Table 7.3: ERG base-case disaggregated discounted QALYs (node-negative subgroup)

QALYs gained	Trastuzumab Emtansine	Trastuzumab	Incremental
IDFS	[redacted]	[redacted]	[redacted]
Non-metastatic recurrence	[redacted]	[redacted]	[redacted]
Remission	[redacted]	[redacted]	[redacted]
1st line metastatic	[redacted]	[redacted]	[redacted]
2nd line+ metastatic	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]

Source: electronic model, updated from the response to the clarification letter.[4]
Abbreviations: ICER = incremental cost effectiveness ratio; IDFS = invasive disease-free survival; QALYs = quality adjusted life years

Table 7.4: ERG base-case disaggregated costs (node-negative subgroup)

Costs per health state	Trastuzumab Emtansine	Trastuzumab	Incremental
IDFS state			
Trastuzumab emtansine	[redacted]	[redacted]	[redacted]
Trastuzumab	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]
Diagnostic test	[redacted]	[redacted]	[redacted]
Drug administration	[redacted]	[redacted]	[redacted]
AE management	[redacted]	[redacted]	[redacted]
Supportive care	[redacted]	[redacted]	[redacted]
Total IDFS cost	[redacted]	[redacted]	[redacted]
Non-metastatic recurrence state			
Supportive care	[redacted]	[redacted]	[redacted]
Remission state			
Supportive care	[redacted]	[redacted]	[redacted]
1st line mBC state			
Supportive care	[redacted]	[redacted]	[redacted]
2nd line+ mBC state			
Supportive care	[redacted]	[redacted]	[redacted]

Total cost	[redacted]	[redacted]	[redacted]

Source: Based on electronic model, updated from the response to the clarification letter.[4]
Abbreviations: IDFS = invasive disease-free survival; mBC = metastatic breast cancer

The ERG also conducted a PSA using their preferred base-case assumptions. This resulted in an ICER of £9,845 (Table 7.5). This probabilistic ICER was approximately £500 higher than the deterministic ICER, due to slightly higher incremental costs and lower incremental QALYs. [redacted], as shown in Figure 7.2. Additionally, [redacted]. The CEAC (Figure 7.3) shows that the probability that trastuzumab emtansine is cost-effective at thresholds of £20,000 and £30,000 is 95.7% and 100% respectively.

Table 7.5: ERG base-case probabilistic results for the node-negative subgroup (discounted)

Technologies	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER versus baseline (£/QALY)
Trastuzumab	[redacted]	16.84	[redacted]				
Trastuzumab emtansine	[redacted]	18.03	[redacted]	[redacted]	1.19	0.92	£9,845

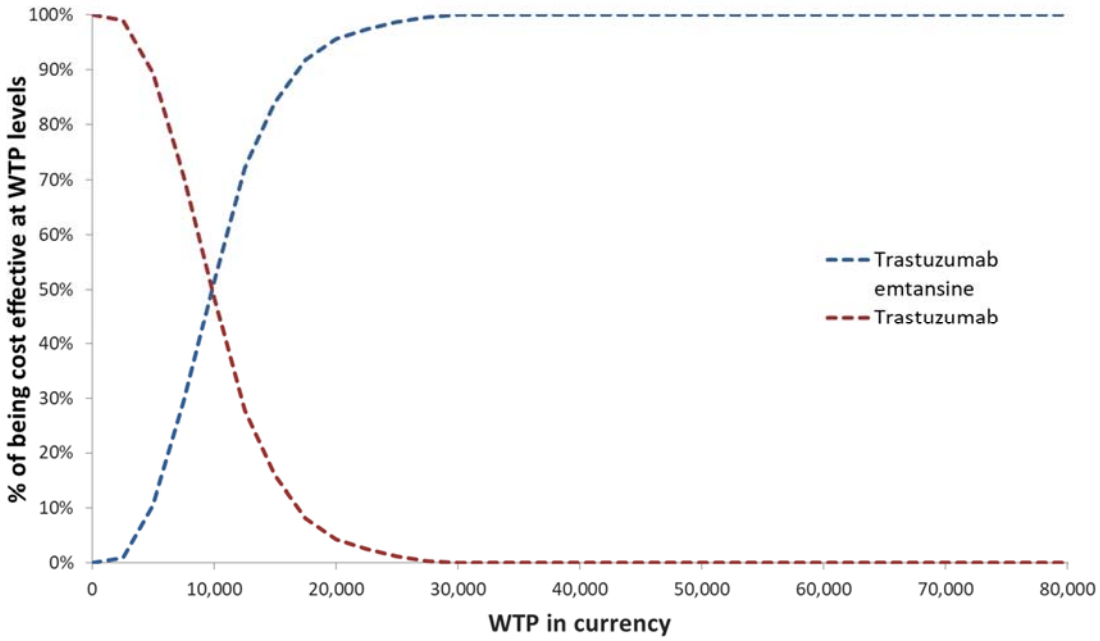
Source: Based on electronic model, updated from the response to the clarification letter.[4]
Abbreviations: ICER = incremental cost effectiveness ratio; Incr. = incremental; QALYs = quality adjusted life years; LYG = life years gained

Figure 7.2: ERG preferred cost effectiveness plane (node-negative subgroup)

[redacted]

Based on electronic model, updated from the response to the clarification letter.[4]
H = trastuzumab; Inc. = incremental; KAD = trastuzumab emtansine; QALY = quality adjusted life year

Figure 7.3: ERG preferred cost effectiveness acceptability curve (node-negative subgroup)



Based on electronic model, updated from the response to the clarification letter.[4]
ERG = Evidence Review Group; WTP = willingness-to-pay

7.2.2 Results of the ERG additional exploratory scenario analyses (node-negative subgroup)

7.2.2.1 Additional scenario 1: alternative IDFS parametric distributions

For their base-case, the ERG selected KM curves from the KATHERINE node-negative population up to the time point where the last event was observed in each treatment arm and an exponential long-term extrapolation for IDFS. In these scenarios, alternative extrapolations were considered by the ERG, while keeping the KM part of the IDFS curve unchanged. Results are provided in Table 7.6. The generalised gamma and log-normal distributions resulted in the highest and lowest ICERs at £12,975 and £8,596, respectively. The log-logistic and Weibull provided very similar ICERs to the ERG base-case, providing some confidence in the choice of the exponential distribution.

Table 7.6: ERG IDFS scenario analyses (node-negative subgroup)

IDFS distribution	Trastuzumab emtansine		Trastuzumab		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
Exponential (ERG BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.95	£9,339
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.94	£9,499
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.98	£8,596
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.83	£12,975
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.95	£9,304
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.92	£10,138
Source: Based on electronic model, updated from the response to the clarification letter.[4]							

IDFS distribution	Trastuzumab emtansine		Trastuzumab		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
Abbreviations: BC = base-case; ERG = evidence review group; ICER = incremental cost effectiveness ratio; IDFS = invasive disease-free survival; Incr. = incremental; KM = Kaplan Meier; QALYs = quality adjusted life years							

7.2.2.2 Additional scenario 2: changing the time point "switch" from KM to parametric extrapolation in IDFS

The choice of the time point at which the model switches from estimating IDFS based on the KM data to the extrapolated data also has an impact on the model results. As can be seen in Table 7.7, the earlier the "switch", the lower the ICER. This is probably due to the HRs predicted by the model in each scenario. Using longer parametric extrapolations and less KM data, resulted in lower HRs compared to the HRs observed in KATHERINE, which favours trastuzumab emtansine.

Table 7.7: ERG time point switch from KM to extrapolation scenario analyses (node-negative subgroup)

KM-extrapolation time point (months) scenario	Trastuzumab emtansine		Trastuzumab		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.18	£4,868
36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.02	£7,633
Last event (TE=46, T=49) (ERG BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.95	£9,339
Source: Based on electronic model, updated from the response to the clarification letter.[4] Abbreviations: BC = base-case; ERG = evidence review group; ICER = incremental cost effectiveness ratio; IDFS = invasive disease-free survival; Incr. = incremental; KM = Kaplan Meier; QALYs = quality adjusted life years; T = trastuzumab; TE = trastuzumab emtansine							

7.2.2.3 Additional scenario 3: changing start time of treatment effect waning

The assumption of when in the model the treatment effect begins to wane also has a notable impact on the model results. The company assumed that waning began at 84 months. However, the ERG felt that, based on KATHERINE data, the HRs increased much earlier. The ERG assumption increased the ICER by approximately £4,000 (Table 7.8). However, even assuming that waning begins at year 1 would not increase the ICER sufficiently to change a decision based on a £20,000 threshold.

Table 7.8: ERG start time of treatment effect waning scenario analyses (node-negative subgroup)

Start time of treatment effect waning, months (years) scenario	Trastuzumab emtansine		Trastuzumab		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
12 (1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.83	£12,591
36 (3) (ERG BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.95	£9,339
60 (5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.05	£6,993
84 (7)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.15	£5,202
108 (11)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.23	£3,966

Source: Based on electronic model, updated from the response to the clarification letter.[4]
Abbreviations: BC = base-case; ERG = evidence review group; ICER = incremental cost effectiveness ratio; IDFS = invasive disease-free survival; Incr. = incremental; KM = Kaplan Meier; QALYs = quality adjusted life years;

7.2.2.4 Additional scenario 4: changing time point where treatment effect is null

In their base-case the ERG assumed that the treatment effect became null at 96 months. This resulted in an increase of approximately £1,800 in the ICER compared to the company assumption of 120 months (Table 7.9). A null treatment effect at 48 months was still not sufficient to change a decision based on a threshold of £20,000.

Table 7.9: ERG Time point treatment effect null scenario analyses (node-negative subgroup)

Time point treatment effect null, months (years) scenario	Trastuzumab emtansine		Trastuzumab		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
48 (4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.76	£15,057
72 (6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.84	£12,331
96 (8) (ERG BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.95	£9,339
120 (10)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.03	£7,526
144 (12)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.08	£6,494

Source: Based on electronic model, updated from the response to the clarification letter.[4]
Abbreviations: BC = base-case; ERG = evidence review group; ICER = incremental cost effectiveness ratio; IDFS = invasive disease-free survival; Incr. = incremental; KM = Kaplan Meier; QALYs = quality adjusted life years;

7.2.2.5 Additional scenario 5: maintaining treatment effect

The ERG base-case assumes that the treatment effect wanes between 36 and 96 months. Assuming a maintained, not waning treatment effect, reduced the ICER by approximately £7,000 (Table 7.10).

Table 7.10: ERG treatment effect maintained scenario analysis (node-negative subgroup)

Scenario	Trastuzumab emtansine		Trastuzumab		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
Treatment effect maintained	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.32	£2,206
Treatment effect wanes (from 36 to 96 months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.95	£9,339

Source: Based on electronic model, updated from the response to the clarification letter.[4]
Abbreviations: BC = base-case; ERG = evidence review group; ICER = incremental cost effectiveness ratio; IDFS = invasive disease-free survival; Incr. = incremental; KM = Kaplan Meier; QALYs = quality adjusted life years;

7.2.2.6 Additional scenario 6: changing HRQoL modelling assumptions

None of the scenarios tested around the choice of utility values utilised in the eBC and mBC health states, or the inclusion of AE disutilities, had a substantial effect on the ICER (Table 7.11).

Table 7.11: ERG HRQoL scenario analyses (node-negative subgroup)

HRQoL scenario	Trastuzumab emtansine		Trastuzumab		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
eBC Utilities							
KATHERINE per arm (ERG BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.95	£9,339
KATHERINE pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.98	£9,016
mBC Utilities							
Lidgren	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.95	£9,339
Lloyd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.96	£9,197
AE disutilities							
AE disutilities excl. (KATHERINE per arm) (ERG BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.95	£9,339
AE disutilities inc. (KATHERINE pooled)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.01	£8,763
AE disutilities inc. (KATHERINE per arm)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.98	£9,069

Source: Based on electronic model, updated from the response to the clarification letter.[4]
Abbreviations: AE = adverse events; BC = base-case; ERG = evidence review group; ICER = incremental cost effectiveness ratio; Incr. = incremental; KM = Kaplan Meier; QALYs = quality adjusted life years;

7.2.2.7 Additional scenario 7: changing Dosing assumptions

Scenarios comparing planned versus actual dosing observed in the trial and vial sharing versus no vial sharing had a limited impact on the ICER (Table 7.12). However, assuming planned dose without vial sharing with the addition of a small cohort weight gain of 2.5 kg increased the ICER to £13,355, as the

required doses at the assumed cohort weight of 70.05 kg do not leave much remainder in optimal combinations of current vial sizes.

Table 7.12: ERG dosing scenario analyses (node-negative subgroup)

Dosing scenarios	Trastuzumab emtansine		Trastuzumab		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
Planned dose, no vial sharing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.95	£9,339
Planned dose, no vial sharing, 2.5 kg average baseline weight	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.95	£13,355
Actual dose, no vial sharing (ERG BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.95	£9,339
Planned dose, 100% vial sharing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.95	£8,609
Actual dose, 100% vial sharing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.95	£8,376

Source: Based on electronic model, updated from the response to the clarification letter.[4]
Abbreviations: BC = base-case; ERG = evidence review group; ICER = incremental cost effectiveness ratio; Incr. = incremental; KM = Kaplan Meier; QALYs = quality adjusted life years;

7.2.2.8 Additional scenario 8: changing market share assumptions

Assuming SC trastuzumab market shares from the market research sample increased the ICER to approximately £13,000. Assuming the same market shares for first line early mBC in both arms increased the ICER by approximately £1,000 (Table 7.13).

Table 7.13: ERG market share scenario analyses (node-negative subgroup)

Scenario market shares	Trastuzumab emtansine		Trastuzumab		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
SC T 95% Arm specific 1st line early mBC (ERG BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.95	£9,339
SC T from market research sample Arm specific 1st line early mBC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.95	£13,007
SC T 95% Equal 1st line early mBC in both arms	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.95	£10,266
SC T from market research sample Equal 1st line early mBC in both arms	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.95	£13,934

Source: Based on electronic model, updated from the response to the clarification letter.[4]
Abbreviations: BC = base-case; ERG = evidence review group; ICER = incremental cost effectiveness ratio; Incr. = incremental; KM = Kaplan Meier; mBC = metastatic breast cancer; QALYs = quality adjusted life years; SC = subcutaneous; T = trastuzumab

7.3 ERG's preferred assumptions (node-negative subpopulation)

The ERG preferred changes to the updated company base-case were described in Section 7.1.2 of this report. The cost effectiveness results of the ERG preferred base-case are presented in Table 7.14 in five steps. In each step, the cumulative impact on the model results is shown. The changes that had the largest impact on the ICER were the changes made on the IDFS extrapolation distribution (increased the ICER around £2,000) and the changes around the assumption of the treatment waning (increased the ICER around £4,000).

Table 7.14: ERG's preferred model assumptions (node-negative population)

Preferred assumption	Section in ERG report	Trastuzumab emtansine		Trastuzumab		Inc. Costs (£)	Inc. QALYs	Cumulative ICER (£/QALY)
		Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs			
Company base-case	6.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.32	£2,634
ERG change 1: Alternative IDFS distribution (KM up to last event + exponential tail)	7.1.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.25	£4,204
ERG changes 1 + 2: Treatment effect duration (36 to 96 months)	7.1.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.00	£8,883
ERG changes (1-2) + 3: IDFS treatment-specific utilities from KATHERINE	7.1.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.96	£9,197
ERG changes (1-3) + 4: mBC utilities from Lidgren at al. (ERG preferred base-case)	7.1.2 & 7.2.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.95	£9,339

Abbreviations: ERG = Evidence Review Group; IDFS= invasive disease-free survival; ICER = incremental cost effectiveness ratio; Inc. = incremental; QALY = quality adjusted life year; KM = Kaplan Meier;

7.4 Conclusions of the cost effectiveness section

The company developed a Markov model to evaluate the cost effectiveness of trastuzumab emtansine (intervention arm) vs. trastuzumab (comparator arm) in the adjuvant treatment of patients with HER2-positive early breast cancer treatment. For people with node-positive disease, pertuzumab in combination with trastuzumab and chemotherapy is considered the appropriate comparator.

Patients enter the simulation in the IDFS health state and remain there until recurrence (non-metastatic or metastatic) or death. Patients transition to the non-metastatic recurrence health state after experiencing a non-distant recurrence. Patients entering this health state are assumed to receive 12 months of additional adjuvant therapy. Afterwards, all alive patients are assumed to move to the remission health state. If patients in remission experience another recurrence, then this is assumed to be metastatic. The first line treatment for mBC health state can also be reached from IDFS, when patients experience a distant recurrence. Patients in the first line mBC health state who experience disease progression are assumed to transition to the subsequent treatment lines for mBC health state. From any health state in the model patients can transition to the death health state. Health states costs and utilities are used to calculate total costs and total QALYs over a lifetime time horizon.

Model input parameters were derived from the KATHERINE trial wherever possible.[27] Otherwise, external sources were used. The main focus of the company submission was the ITT population of the KATHERINE trial, which is aligned with the anticipated label, but the company also presented evidence for the subgroups of node-negative and node-positive patients. The comparator for the ITT population and the node-negative subgroup is trastuzumab. For the node-positive population subgroup, the comparator is pertuzumab + trastuzumab.

Modelling treatment effectiveness involved two main aspects of the disease: IDFS and recurrence. For the ITT population and the node-negative subgroup, IDFS was modelled based on patient-level data observed in the ITT and node-negative populations of the KATHERINE trial, respectively. Parametric survival curves were subsequently used by the company to extrapolate these data beyond the trial follow-up period following the recommendations of TSD 14.[46] Based on the company assessment, a log-logistic distribution was chosen to model IDFS in the base-case for the ITT population. For the node-negative population, the company chose an exponential distribution.

Based on long-term empirical evidence for the trastuzumab arm, HERA and BCIRG 006 trials,[47, 48] the selected parametric survival curves were adjusted (from year 3 to year 10) to produce a more clinically plausible extrapolations, as extrapolations based on the KATHERINE data alone would not produce valid long-term outcomes. The approach taken by the company was to reproduce in the model recurrence rates and survival curves similar to those observed in HERA and BCIRG 006. This was operationalised by including patients being "cured" (i.e. only subject to background mortality). In particular, it was assumed that the proportion of "cured" patients linearly increased from 0% at 36 months to 95% at 120 months. From year 10 until the end of the time horizon, the 95% "cured" was assumed.

Furthermore, the company assumed that the treatment effect of trastuzumab emtansine was maintained for 84 months before gradually decreasing to no treatment effect at 120 months. This assumption was based on the duration of the treatment effect observed in the HERA and BCIRG 006 trials,[47, 48] since the company expects a similar behaviour to be observed in long-term KATHERINE data. This was also in line with the company's base-case of TA569.[17]

For the node-positive subgroup there was no direct comparative evidence between trastuzumab emtansine and pertuzumab, the correct comparator for this subpopulation. Therefore, IDFS was modelled through an indirect treatment comparison between KATHERINE data (trastuzumab emtansine vs trastuzumab) and APHINITY data (pertuzumab + trastuzumab vs. trastuzumab). The company's preferred approach was Bucher method. The output of the Bucher method was a hazard ratio between trastuzumab emtansine and pertuzumab + trastuzumab, which was applied to the IDFS extrapolation in the trastuzumab emtansine arm to derive IDFS data for the pertuzumab arm of the cost effectiveness model. In the base-case analysis, the HR was obtained from the node-positive APHINITY population and the node-positive KATHERINE population.

The second main aspect of modelling treatment effectiveness was recurrence. The same approach was assumed regardless node status. Recurrence was subdivided into metastatic or a non-metastatic recurrence. Transition probabilities from the IDFS health state to the recurrence health states were estimated from the recurrence events observed in KATHERINE. Furthermore, timing of recurrence was incorporated into the economic model since this is expected to have an impact on treatment outcomes and costs (patients experiencing an "early" recurrence are more likely to have a worse disease prognosis). In line with the HERA trial, 18 months was assumed as the time point to define "early" and "late" recurrence in the model. Once in recurrence, patients can experience progression or death. Transition probabilities for the recurrence pathway were derived from external sources. Metastatic recurrence can be reached from non-metastatic recurrence only through remission. Patients in remission can either die or experience another recurrence. The risk of death in the remission health state was assumed to be equal to background mortality. The model also assumes that any recurrence experienced in remission will be metastatic. This transition probability was assumed to be constant over time and was sourced from Hamilton et al. 2015.[50] Two health states are considered in the metastatic recurrence pathway: first line mBC treatment and second (and subsequent) mBC treatment lines. In both health states, different transition probabilities are applied depending on whether recurrence was classified as "early" or "late". Transition probabilities for "early" metastatic recurrence were derived from the EMILIA study.[51] Transition probabilities for patients experiencing "late" metastatic recurrence are dependent on the first line treatment received and were derived from the CLEOPATRA and the M77001 trials.[52, 53] An overall transition probability was calculated as a weighted average of the probabilities from the different first line treatments. The "weights" were based on usage data from a market research conducted by the company.[54]

IDFS adverse events were included in the model when they were Grade 3 and above or they occurred in at least 2% of the study population from the KATHERINE trial, regardless of node status. Based on these criteria, the only adverse event included in the model was platelet count decrease. Adverse event costs for pertuzumab and post-IDFS adverse events were sourced from the literature.

HRQoL data for the IDFS health state were measured in the KATHERINE ITT population using the EQ-5D-3L and valued using the UK EQ-5D-3L tariff.[39] EQ-5D data from each treatment arm were pooled by the company in the base-case. The company further assumed that utility in the non-metastatic recurrence and remission states were equal to utility in the IDFS on-treatment and IDFS off-treatment values respectively. The company identified several potential literature sources for the mBC utility values and chose to use Lloyd et al. as the utility source for the first and second line mBC health states. Given that IDFS utility values for patients on- and off-treatment were estimated from the KATHERINE data, the company assumed that any disutility associated with treatment-related AEs experienced during the trial was already captured in the EQ-5D data and additional disutilities were not included in the model. The company did not provide IDFS utility estimates from the KATHERINE trial separated according to nodal status, arguing that HRQoL is not expected to be dependent on nodal status.

An SLR was conducted to identify studies on resource use and costs in breast cancer. However, the identified studies were not used in the economic model, and the company used mostly the findings from previous technology appraisals. The following cost categories were included in the model: drug acquisition and administration costs, TRAE management costs, resource use and supportive care costs. It was assumed that the unit costs and resource use frequency would not differ among different node specific subgroups. The drug acquisition costs used in the economic model for the IDFS health state were based on the TTOT data and the actual dose given during the KATHERINE trial. It was assumed that 95% of the patients used trastuzumab in the subcutaneous form. The drug acquisition and administration costs in the post-IDFS health states were based on assumptions from market share percentages and unit costs from PSSRU and NHR reference costs.[41, 42] TRAE costs due to trastuzumab emtansine and trastuzumab in the IDFS health state were based on the KATHERINE trial. TRAE costs for pertuzumab in the IDFS health state and all TRAE costs post-IDFS were based on previous NICE appraisals. All healthcare resource frequency assumptions were based on TA569, with updated unit prices from PSSRU/NHS reference costs.[42, 66]

The company's base-case cost effectiveness results for the node-negative population indicated that trastuzumab emtansine was both more costly and more effective than trastuzumab, with an ICER equal to £2,634. The ICER obtained from the PSA was £3,219, slightly larger than the deterministic ICER. The cost effectiveness plane showed that [redacted]. The CEAC shows that the probability that trastuzumab emtansine is cost effective at thresholds of £20,000 and £30,000 was 93% and 96%, respectively.

The company also conducted deterministic sensitivity analyses and the results suggested that, overall, the transition probabilities in the metastatic setting were found to have the largest impact on the ICER. The cost effectiveness analyses for the node-negative subpopulation were received by the ERG on November 12th, 2019, in the second batch of responses to the clarification questions (question B2).[4] The company referred to the updated economic model for a full breakdown of the scenario analyses results in the node-negative population but a summary of these analyses was not presented by the company. Given the proximity of the final deadline to submit the ERG report, it was unfeasible for the ERG to re-run all the scenario analyses for the node-negative population (approximately 80 scenarios were run by the company for the ITT population). However, it is expected that the conclusions drawn for the ITT population (in Appendix 3 of this report) are also valid for the node-negative population. The ITT scenario analyses indicated that the model results were robust for the majority of the assumptions tested by the company. Only extreme and possibly implausible scenarios resulted in a relative large increase in the ICER. For example, when a 10-year time horizon was assumed, the ICER increased by approximately £10,000 compared to the ITT base-case ICER. When a 0% cure rate was assumed, the ICER increased by approximately £4,000 compared to the ITT base-case ICER. In all cases the ICERs were below the common threshold of £20,000.

The ERG raised their concerns regarding choice of trastuzumab as the comparator for the economic analyses in the ITT population. According to the ERG, this comparator is inappropriate because that would imply that standard care for all patients is adjuvant trastuzumab, but this is not true: following TA569, pertuzumab + trastuzumab has been recommended for node-positive patients.[17] TA569, therefore, implies that a whole population analysis (with a common comparator for all patients) is invalid. Subgroup analyses (with the correct comparators) were conducted separately by the company. However, subgroup-specific evidence was limited, which means more uncertainty in the subgroup

analyses, and many of the assumptions made in the subgroup analyses were based on the evidence presented for the ITT population. These assumptions might not be valid for the specific subgroups and, more importantly, the subgroup analyses did not necessarily use the appropriate subgroup data from the KATHERINE trial. Additionally, the ERG considered that the methods used to model IDFS in the node-positive population were seriously flawed, which implies that the cost effectiveness analyses for the node-positive population are unreliable and, therefore, inappropriate for decision making. For these reasons, only the cost effectiveness results for the node-negative population were deemed appropriate (yet uncertain) by the ERG for the decision problem at hand and were the main focus of the cost effectiveness sections of the ERG report. For completeness, results for the ITT population and the node-positive subgroup were presented in appendices.

IDFS was one of the main aspects of modelling treatment effectiveness. Unlike the company, the ERG preferred a mixed modelling approach where KM curves (up to time point where the last event was observed in each treatment arm) and long-term parametric extrapolations were used. The main reason for this choice was to predict in the model HRs in line to those observed in KATHERINE.

Long-term IDFS extrapolations were further adjusted following the rationale in TA569.[17] The ERG considers that this does not necessarily imply that the same approach would be valid here. However, since there is no alternative evidence to support a better informed choice of "cure" parameters, the ERG decided to accept the company's approach and explored the impact of changing the cure parameters on the results with scenario analyses. It should be noted though that the model fails to replicate the observed recurrence rates in the KATHERINE trial and to reproduce the drop in these rates observed at year 4 in the HERA and BCIRG 006 trials, regardless of whether this has a large impact on the model results or not. Reproducing recurrence rates in the model can be difficult, especially when simple approaches, like a linear decline in rates, are assumed. While the efforts of the company seemed to be focused on replicating long-term recurrence rates, the ERG considers that trying to match the modelled long-term IDFS to observed long-term data (e.g. from HERA) would have been easier to implement and probably better approach. A potentially important caveat for this (and other aspects of the model like the duration of the treatment effect) is that the long-term data from HERA and BCIRG 006 were assumed to be a proxy for the KATHERINE ITT population only. Such a proxy for the node-negative subgroup was not available and, therefore, the IDFS adjustments made in the node-negative subgroup were based on ITT data, which might be incorrect, leading to biased results for the node-negative subgroup. For example, since the node-negative population can be considered to be, in terms of disease prognosis, better in comparison to the node-positive population, and, thus, better than the ITT population (which is mixed), it could be speculated that IDFS for node-negative patients would have been high in comparison to IDFS in the ITT population. Recurrence rates for the node-negative population were not reported by the company. Therefore, the ERG is unable to assess whether these rates are properly captured by the node-negative model or not. Something similar can be said about the duration of the treatment effect as hazard ratios were only reported in detail for the ITT population.

For the node-positive subpopulation the main concern regarding IDFS modelling was that the populations in KATHERINE and APHINITY, the trials used for the indirect treatment comparison, are not really comparable and the outcomes from this analysis (the HRs) are likely to be biased. The company preferred the Bucher fixed-effect method over other ITC methods due to its relative simplicity and lack of data. The company argued that more complex methods would not resolve the differences in the population characteristics/effect modifiers (and, therefore, the bias) and would introduce additional uncertainty. The ERG considered that less biased estimates could have been obtained, if the company had used data from alternative sources. Furthermore, in the model the HR obtained from the indirect treatment comparison was applied to the IDFS extrapolation in the trastuzumab emtansine arm to derive

IDFS data for the pertuzumab arm of the cost effectiveness model. However, the IDFS extrapolation in the trastuzumab emtansine arm of the model is based on the ITT population instead of the node-positive subpopulation. Thus, even though the HR was derived from the node-positive population in KATHERINE (and APHINITY), in the model it is applied to the KATHERINE ITT population, which is incorrect. Consequently, the calculation of the IDFS data for the pertuzumab arm in the model is also incorrect. As separate data for the node-positive population are not available in the model, the ERG was not able to correct this error. For these reasons, the ERG considers that modelling IDFS in the node-positive population is seriously flawed and the cost effectiveness analyses for the node-positive population inappropriate for decision making.

Another potential issue (yet thought to be minor compared to IDFS) relates to the transition probabilities for patients in the "early" metastatic recurrence setting. These transitions were assumed to be equal for both treatment arms in the model. However, the first line mBC treatments differed for the trastuzumab emtansine and the trastuzumab arms of the model. In summary, patients in the trastuzumab emtansine arm of the model may receive first line mBC pertuzumab instead of first line trastuzumab emtansine (the latter was allowed as first line mBC therapy for patients in the trastuzumab arm of the model). This difference was accounted for only in the cost part of the model. However, this approach implicitly assumes that, for patients experiencing an "early" metastatic recurrence, pertuzumab and trastuzumab emtansine have the same efficacy. If that assumption was correct, then it would be irrational to give patients the more expensive treatment. On the contrary, if the assumption was incorrect, then different transition probabilities should have been used for the model arms. The latter would also imply that, in terms of cost effectiveness, the difference between the two treatment arms (both in effects and costs) is not only due to the differences between trastuzumab emtansine and trastuzumab in the adjuvant setting but also due to the differences between pertuzumab and trastuzumab emtansine after "early" metastatic recurrence. Similarly, in the metastatic setting the company assumed for trastuzumab emtansine the same survival probabilities as for trastuzumab + chemotherapy. If that assumption was correct then it would be irrational to give patients the more expensive treatment. However, a minor impact on the incremental results is be expected because the same second line regimens in the same proportions are applied to both treatment arms of the model.

OS data was not included in the model to inform input parameters. The ERG agrees with the company that OS data from KATHERINE are immature and that fitting survival curves to those data could result in poor OS extrapolations. The company included though OS results in the model but for the ITT population only. In this case, OS is an outcome of the model (calculated as the complement of the predicted cumulative number of deaths over time) instead of an input. The ERG has concerns regarding the fit of the OS model predictions to the actual OS KM curves from the KATHERINE trial, which can be seen in Figure 5.18. Since the IDFS model extrapolation is expected to be in line with the IDFS KM curves, this mismatch in the OS curves suggests that the transition probabilities used in the post-IDFS health states might not be in line with the post-IDFS events in KATHERINE. The same issue is expected to be observed in the node-negative and the node-positive subgroups. Unfortunately, since the OS KM data for the node-negative population were not provided, the ERG cannot investigate further the impact of this in its exploratory analyses.

Several uncertainties regarding adverse events remained even after the company's response to the clarification letter. However, the impact of these on the model results is expected to be minor and, therefore, the ERG did not investigate this further in their exploratory analyses.

No information was provided by the company about how utility values for mBC states were searched for or identified. The company chose to use values from Lloyd et al. as the utility source for first and second+ line mBC states, [36] but this was only justified by its previous use in similar technology appraisals. [17, 35, 40] The ERG feel that the methods used to measure and value HRQoL in the Lloyd study do not reflect the NICE reference case as closely as the methods used in Lidgren et al. do. Therefore, the ERG preferred the latter as base-case source of utility values for the mBC states. During KATHERINE, the EQ-5D was only collected twice during the treatment period, in cycles 5 and 11. Therefore, for AEs to have been captured in the EQ-5D data collection, we would have to assume that all AEs that occurred during the treatment period were being experienced on those two occasions. Additionally, if the company are to assume that the impact of AEs was captured in the EQ-5D data collected, then it is inappropriate to assume that the HRQoL of patients is equal across treatment arms. The HRQoL of patients could be dependent on nodal status due to different prognosis, treatments and AE received. However, the ERG could not identify any evidence regarding the impact of nodal status on utility.

Regarding cost/resource use assumptions in the economic analysis, the company did not consider the uncertainty on the patient weight, even though just a small increase (e.g. 2 kg) in weight would have necessitated an additional small trastuzumab emtansine vial. The ERG could not verify the market share assumptions by the company on the trastuzumab monotherapy (95% trastuzumab SC and 5% trastuzumab biosimilar IV). The assumption that patients who have progressed from IDFS with trastuzumab monotherapy and with trastuzumab emtansine would receive different therapies as their 1st line metastatic breast cancer treatment was also not possible to verify. Finally, for the node-negative and node-positive subpopulations, without any evidence, the ERG could not judge the plausibility of the company assumption of identical drug acquisition costs in different subgroups.

As discussed throughout this report, the ERG considers that only node-negative subpopulation analyses would be useful for decision making given the provided evidence. Therefore, the ERG additional analyses were focused on the node-negative subpopulation. During the process of responding to the clarification questions, the company discovered and corrected an error in the cost effectiveness model regarding the implementation of the proportions of non-metastatic and metastatic "early" recurrences. Nevertheless, since the cost effectiveness analyses for the node-negative population were conducted with the model submitted with the response of the clarification letter, all results shown in Section 6 already included this correction. Additionally, for the node-negative population, the ERG modelled IDFS using KM curves from the KATHERINE node-negative population up to the time point where the last event was observed in each treatment arm and an exponential long-term extrapolation. The ERG also assumed a waning of the trastuzumab emtansine treatment effect from month 36 to month 96. These assumptions led to more realistic IDFS estimates and more plausible HRs. Finally, the ERG used treatment-specific utilities from KATHERINE for the IDFS health state and Lidgren et al. utilities for the recurrence health-states. These changes increased the ICER value for node-negative subpopulation from £2,634 (company) to £9,339 (ERG) per QALY gained. The changes surrounding the IDFS extrapolation and the treatment effect duration had the largest impact. In particular, trastuzumab emtansine was estimated to provide 0.95 additional QALYs in this subgroup at an incremental cost of [redacted]. The incremental QALY gains for trastuzumab emtansine all stemmed from the IDFS health state. Incremental costs were highest in the IDFS health state, mostly due to the additional treatment

costs of trastuzumab emtansine. However, approximately [redacted]% of these incremental costs were saved in the mBC health states, which reduced the overall incremental cost.

The ERG also conducted a PSA using their preferred base-case assumptions. This resulted in an ICER of £9,845. This probabilistic ICER was approximately £500 higher than the deterministic ICER, due to slightly higher incremental costs and lower incremental QALYs. [redacted]. The CEAC shows that the probability that trastuzumab emtansine is cost-effective at thresholds of £20,000 and £30,000 is 95.7% and 100% respectively.

The ERG conducted a series of additional scenario analyses in order to explore important areas of uncertainty in the model. These key uncertainties were related to the survival modelling (in terms of choice of parametric distributions, modelling of cure assumptions and duration of treatment effect), sources of utility data and cost and resource use assumptions. Other sources of uncertainty were deemed less important and were not explored in this section. The results of these analyses indicated that the ICER for the node-negative population was relatively sensitive to some of the assumptions tested by the ERG. In some scenarios, the ICER was increased by approximately around 50%. However, all ICERs were below the common threshold of £20,000. The largest ICER (£15,057) was obtained in the scenario where a null treatment effect at 48 months was assumed. Only if some of the changes conducted in these scenarios were applied simultaneously, the ICER can be higher than £20,000 per QALY gained.

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Appendix 1: Supplementary Information – ERG searches

Comparison of company cost strategy vs. CRD NHS EED filter[28]

Medline (Ovid): 1946-2019/11/19
Searched 21.11.19

1 exp Technology Assessment, Biomedical/ (10860)
2 (health technology assessment or health technology assessments or health technologies assessment).ti,ab. (4491)
3 1 or 2 (13634)
4 (economic and (evaluation or evaluations)).ti,ab. (22897)
5 pharmacoeconomic*.ti,ab. (3645)
6 (cost effectiveness or cost effectiveness or cost-effective or cost effective or cost-benefit or cost benefit or cost-benefits or cost benefits or cost-utility or cost tility or cost-utilities or cost utilities or cost-minimisation or cost minimisation or cost-minimization or cost minimization).ti,ab. (137157)
7 or/3-6 [Company Cost facet] (165207)
8 economics/ (27103)
9 exp "costs and cost analysis"/ (230263)
10 economics, dental/ (1908)
11 exp "economics, hospital"/ (24040)
12 economics, medical/ (9040)
13 economics, nursing/ (3995)
14 economics, pharmaceutical/ (2897)
15 (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (753417)
16 (expenditure$ not energy).ti,ab. (28538)
17 (value adj1 money).ti,ab. (33)
18 budget$.ti,ab. (28137)
19 or/8-18 (902320)
20 ((energy or oxygen) adj cost).ti,ab. (3986)
21 (metabolic adj cost).ti,ab. (1361)
22 ((energy or oxygen) adj expenditure).ti,ab. (24223)
23 or/20-22 (28609)
24 19 not 23 (895734)
25 letter.pt. (1052586)
26 editorial.pt. (509744)
27 historical article.pt. (355291)
28 or/25-27 (1898564)
29 24 not 28 [CRD economic evaluation strategy, 2014] (860462)
30 7 not 29 (12011) [records found by company search, not CRD filter]
31 7 and 29 (153196) [records found by both searches]
32 29 not 7 (707266) [records missed by company search, picked up by CRD filter]

CRD cost effectiveness filter:

Centre for Reviews and Dissemination. Search strategies: NHS EED MEDLINE using OvidSP (economics filter) [Internet]. York: Centre for Reviews and Dissemination; 2014 [accessed 2.6.14]. Available from:
http://www.crd.york.ac.uk/crdweb/searchstrategies.asp#nhseedmedline

Appendix 2: Subgroup data for node-positive and node-negative patients

Patient demographics and clinical characteristics of the node-positive and node-negative patients enrolled in the KATHERINE study are presented in Tables A2.1 and A2.2, respectively.

As can been from Tables A2.1 and A2.2, baseline demographic and disease characteristics in the two subgroups are mostly similar to those in the ITT population. However, the Node-negative population seems to include more patients from Western Europe, this applies to both arms of the trial. In addition, there are differences in primary tumour stage (at definitive surgery) between the two subgroups.

Table A2.1: Baseline demographic and disease characteristics, KATHERINE – Node-positive population

Characteristics	Trastuzumab (N=346)	Trastuzumab emtansine (N=343)
Age, years		
Median (range)	49 (27–78)	49 (25–79)
Age group, n (%)		
<40	70 (20.2)	55 (16.0)
40–64	246 (71.1)	258 (75.2)
65–74	28 (8.1)	28 (8.2)
≥75	2 (0.6)	2 (0.6)
Region, n (%)		
North America	81 (23.4)	92 (26.8)
Western Europe	168 (48.6)	160 (46.6)
Rest of world	97 (28.0)	91 (26.5)
Race or ethnic group[a], n (%)		
American Indian[b] or Alaska Native	30 (8.7)	19 (5.5)
Asian	31 (9.0)	33 (9.6)
Black or African American	14 (4.0)	10 (2.9)
White	241 (69.7)	248 (72.3)
Multiple/Unknown/Other	30 (8.7)	33 (9.6)
Prior use of anthracycline, n (%)	253 (73.1)	261 (76.1)
Clinical stage at presentation, n (%)		
Inoperable (Stage T4 Nx M0 or Tx N2–3 M0)	NR	NR
Operable (Stages T1–3 N0–1 M0)	NR	NR
Hormone receptor status, n (%)		
ER-negative and PR-negative or status unknown	104 (30.1)	102 (29.7)
ER-positive, PR-positive, or both	242 (69.9)	241 (70.3)
Menopausal status at screening, n (%)		
Pre-menopausal	186 (53.8)	187 (54.5)
Post-menopausal	160 (46.2)	156 (45.5)
Neoadjuvant HER2-targeted therapy, n (%)		
Trastuzumab alone	278 (80.3)	277 (80.8)

Characteristics	Trastuzumab (N=346)	Trastuzumab emtansine (N=343)
Trastuzumab + pertuzumab	68 (19.7)	66 (19.2)
Trastuzumab + other HER2-targeted therapy[c]		
Primary tumour stage (at definitive surgery), n (%)		
ypT0, ypT1a, ypT1b, ypT1mic, ypTis	125 (36.1)	131 (38.2)
ypT1[d]/ypT1c	68 (19.7)	65 (19.0)
ypT2	100 (28.9)	101 (29.4)
ypT3	43 (12.4)	36 (10.5)
ypT4, ypT4a, ypT4b, ypT4c	8 (2.3)	6 (1.7)
ypT4d	1 (0.3)	4 (1.2)
ypTX	1 (0.3)	0
Regional lymph node stage (at definitive surgery), n (%)		
ypN0	--	--
ypN1	213 (61.6)	220 (64.1)
ypN2	103 (29.8)	86 (25.1)
ypN3	30 (8.7)	37 (10.8)
ypNX[e]	--	--
Pathological nodal status evaluated after neoadjuvant therapy, n (%)		
Node-positive	NR	NR
Node-negative/not done	NR	NR
RID ≤1 cm and negative axillary lymph nodes (ypT1a, ypT1b, ypT1mic and ypN0)	NR	NR

Source: Response to Clarification, Question A15.[4]

ER = oestrogen receptor; HER2 = human epidermal growth factor receptor 2; PR = progesterone receptor; RID = residual invasive disease.

Notes: Please note that staging at initial diagnosis refers to clinical staging, staging at definitive surgery refers to pathologic staging. a) Race or ethnic group was reported by the investigators. b) Includes North, Central and South American Indians. c) Other HER2-targeted agents were neratinib, dacomitinib, afatinib and lapatinib. d) Five patients had ypT1 disease without further sub-specification. e) If extensive axillary evaluation was done prior to neoadjuvant therapy or if sentinel lymph nodes were evaluated before neoadjuvant therapy and were found not to involve tumour or had only micro-metastases, further axillary evaluation was not required and the patient was classified as "not done" with respect to this variable.

Table A2.2: Baseline demographic and disease characteristics, KATHERINE – Node-negative population

Characteristics	Trastuzumab (N=397)	Trastuzumab emtansine (N=400)
Age, years		
Median (range)	48 (23–80)	49 (24–73)
Age group, n (%)		

Characteristics	Trastuzumab (N=397)	Trastuzumab emtansine (N=400)
<40	83 (20.9)	88 (22.0)
40–64	276 (69.5)	284 (71.0)
65–74	33 (8.3)	28 (7.0)
≥75	5 (1.3)	0
Region, n (%)		
North America	83 (20.9)	78 (19.5)
Western Europe	235 (59.2)	243 (60.8)
Rest of world	79 (19.9)	79 (19.8)
Race or ethnic group[a], n (%)		
American Indian[b] or Alaska Native	20 (5.0)	17 (4.3)
Asian	33 (8.3)	32 (8.0)
Black or African American	5 (1.3)	11 (2.8)
White	290 (73.0)	303 (75.8)
Multiple/Unknown/Other	49 (12.4)	37 (9.3)
Prior use of anthracycline, n (%)	311 (78.3)	318 (79.5)
Clinical stage at presentation, n (%)		
Inoperable (Stage T4 Nx M0 or Tx N2–3 M0)	NR	NR
Operable (Stages T1–3 N0–1 M0)	NR	NR
Hormone receptor status, n (%)		
ER-negative and PR-negative or status unknown	106 (26.7)	111 (27.8)
ER-positive, PR-positive, or both	291 (73.3)	289 (72.3)
Menopausal status at screening, n (%)		
Pre-menopausal	227 (57.2)	212 (53.0)
Post-menopausal	170 (42.8)	188 (47.0)
Neoadjuvant HER2-targeted therapy, n (%)		
Trastuzumab alone	322 (81.1)	324 (81.0)
Trastuzumab + pertuzumab	75 (18.9)	76 (19.0)
Trastuzumab + other HER2-targeted therapy[c]		
Primary tumour stage (at definitive surgery), n (%)		
ypT0, ypT1a, ypT1b, ypT1mic, ypTis	181 (45.6)	200 (50.0)
ypT1[d]/ypT1c	116 (29.2)	110 (27.5)
ypT2	85 (21.4)	73 (18.3)
ypT3	14 (3.5)	15 (3.8)
ypT4, ypT4a, ypT4b, ypT4c	1 (0.3)	1 (0.3)
ypT4d	0	1 (0.3)
ypTX	--	--
Regional lymph node stage (at definitive surgery), n (%)		
ypN0	335 (84.4)	344 (86.0)

Characteristics	Trastuzumab (N=397)	Trastuzumab emtansine (N=400)
ypN1	--	--
ypN2	--	--
ypN3	--	--
ypNX[e]	62 (15.6)	56 (14.0)
Pathological nodal status evaluated after neoadjuvant therapy, n (%)		
Node-positive	NR	NR
Node-negative/not done	NR	NR
RID ≤1 cm and negative axillary lymph nodes (ypT1a, ypT1b, ypT1mic and ypN0)	NR	NR

Source: Response to Clarification, Question A16.[4]
ER = oestrogen receptor; HER2 = human epidermal growth factor receptor 2; PR = progesterone receptor; RID = residual invasive disease.
Notes: Please note that staging at initial diagnosis refers to clinical staging, staging at definitive surgery refers to pathologic staging. a) Race or ethnic group was reported by the investigators. b) Includes North, Central and South American Indians. c) Other HER2-targeted agents were neratinib, dacomitinib, afatinib and lapatinib. d) Five patients had ypT1 disease without further sub-specification. e) If extensive axillary evaluation was done prior to neoadjuvant therapy or if sentinel lymph nodes were evaluated before neoadjuvant therapy and were found not to involve tumour or had only micro-metastases, further axillary evaluation was not required and the patient was classified as "not done" with respect to this variable.

The main results from the KATHERINE study for the node-positive and node-negative populations are summarised in Tables A.2.3 and A2.4, respectively.

Most results for node-positive patients are missing, only IDFS was reported in CS (see Table A2.3). IDFS is slightly more favourable for trastuzumab emtansine in the node-negative population. Comparing results in the node-negative population (Table A2.4) with ITT results (Table 4.6), also shows more favourable for trastuzumab emtansine in the node-negative population for the outcomes IDFS (STEEP definition), DFS and DRFI; however, OS was less favourable for trastuzumab emtansine in the node-negative population.

Table A2.3: Summary of results from the KATHERINE trial: Node-positive – unstratified analyses[a]

Secondary endpoint	Trastuzumab (N=346)	Trastuzumab emtansine (N=343)
OS		
Patients with an event, n (%)	NR	NR
HR (95% CI)	NR	
p-value (log-rank)	NR	
IDFS		
Patients with an event, n (%)	NR	NR
3-year event-free rate, % (95% CI)	67.7 (NR)	83.0 (NR)
HR (95% CI)	0.52 (0.38–0.71)	
p-value (log-rank)	NR	
IDFS (STEEP definition)		
Patients with an event, n (%)	NR	NR
3-year event-free rate, % (95% CI)	NR	NR
HR (95% CI)	NR	
p-value (log-rank)	NR	
DFS		
Patients with an event, n (%)	NR	NR
3-year event-free rate, % (95% CI)	NR	NR
HR (95% CI)	NR	
p-value (log-rank)	NR	
DRFI		
Patients with an event, n (%)	NR	NR
3-year event-free rate, % (95% CI)	NR	NR
HR (95% CI)	NR	
p-value (log-rank)	NR	

Source: CS, Section B.2.7, Figure 12.[1]

CI = confidence interval; DFS = disease-free survival; DRFI = distant recurrence-free interval; HR = hazard ratio; IDFS = invasive disease-free survival; OS = overall survival; STEEP = standardized definitions for efficacy endpoints.

Notes: [a]) No statistical adjustments were made for multiple comparisons.

Table A2.4: Summary of results from the KATHERINE trial: Node-negative/not done – unstratified analyses[a]

Secondary endpoint	Trastuzumab (N=397)	Trastuzumab emtansine (N=400)
OS		
Patients with an event, n (%)	16 (4.0)	13 (3.3)
HR (95% CI)	0.79 (0.38–1.63)	
p-value (log-rank)	0.5171	
IDFS		
Patients with an event, n (%)	62 (15.6)	29 (7.3)
3-year event-free rate, % (95% CI)	84.6 (80.8-88.32)	92.8 (90.1-95.5)
HR (95% CI)	0.44 (0.28–0.68)	
p-value (log-rank)	0.0002	
IDFS (STEEP definition)		
Patients with an event, n (%)	NR	NR
3-year event-free rate, % (95% CI)	NR	NR
HR (95% CI)	NR	
p-value (log-rank)	NR	
DFS		
Patients with an event, n (%)	64 (16.1)	32 (8.0)
3-year event-free rate, % (95% CI)	84.3 (80.5–88.1)	92.0 (89.2–94.8)
HR (95% CI)	0.47 (0.31–0.72)	
p-value (log-rank)	0.0004	
DRFI		
Patients with an event, n (%)	43 (10.8)	21 (5.3)
3-year event-free rate, % (95% CI)	89.5 (86.3–92.7)	94.5 (92.1–96.8)
HR (95% CI)	0.47 (0.28–0.79)	
p-value (log-rank)	0.0035	

Source: Response to Clarification, Question A16.[4]

CI = confidence interval; DFS = disease-free survival; DRFI = distant recurrence-free interval; HR = hazard ratio; IDFS = invasive disease-free survival; OS = overall survival; STEEP = standardized definitions for efficacy endpoints.

Notes: [a]) No statistical adjustments were made for multiple comparisons.

Appendix 3: Company cost effectiveness analyses results for the ITT population

Assessment of the proportional hazards assumption for IDFS (ITT population)

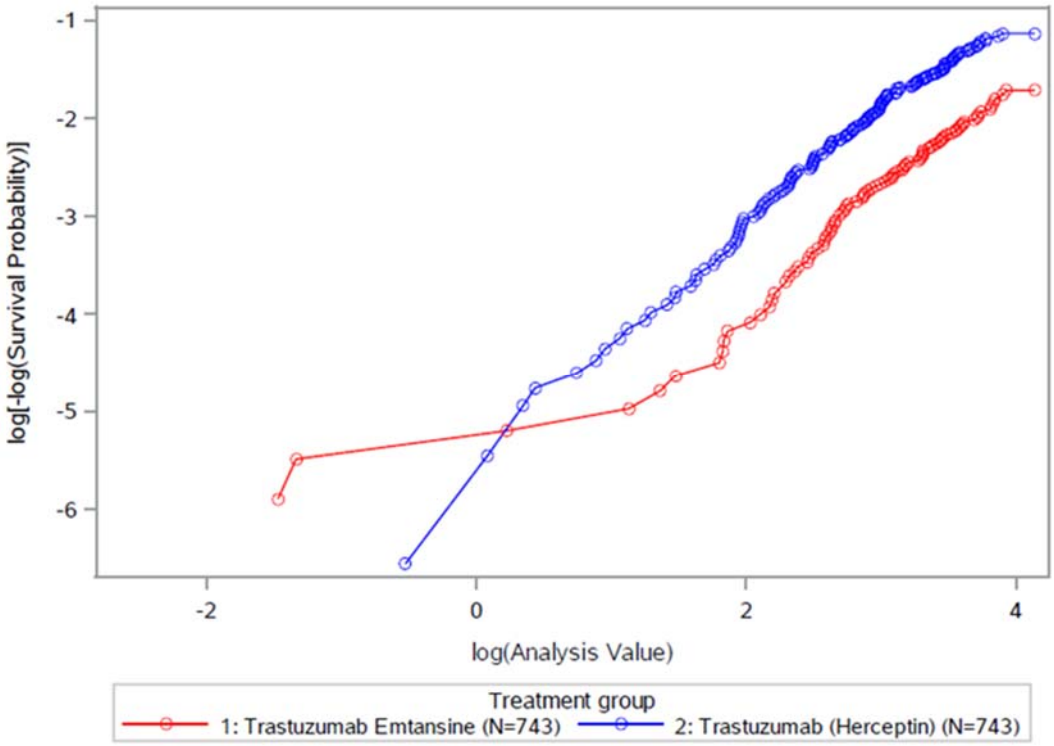
The company tested the proportional hazards (PH) assumption graphically by using the log-cumulative hazard plot shown in Figure A3.1. The PH assumption can be assumed when the two curves are (approximately) parallel. The company considered that, since the two curves in Figure A3.1 cross, the PH assumption may not hold. However, the company noted that the intersection occurred early in time, when a minimal number of events had occurred. After the crossing point, the two curves seem to remain parallel. Therefore, the company considered this test inconclusive and performed and additional one.

The PH assumption can also be graphically tested by using a plot of Schoenfeld residuals as shown in Figure A3.2. The PH assumption can be assumed when the line in the middle of the plot is (approximately) horizontal (this would indicate that the residuals are independent of time). The company considered that the line on the graph had a negative slope and, therefore, it was not horizontal, which was interpreted as a signal that the PH assumption may not hold.

The company further showed in Table 22 of the CS (not shown in this report) that the modelled IDFS was relatively insensitive to whether or not proportional hazards were assumed and that this is expected to have a minor on the cost effectiveness results.[1]

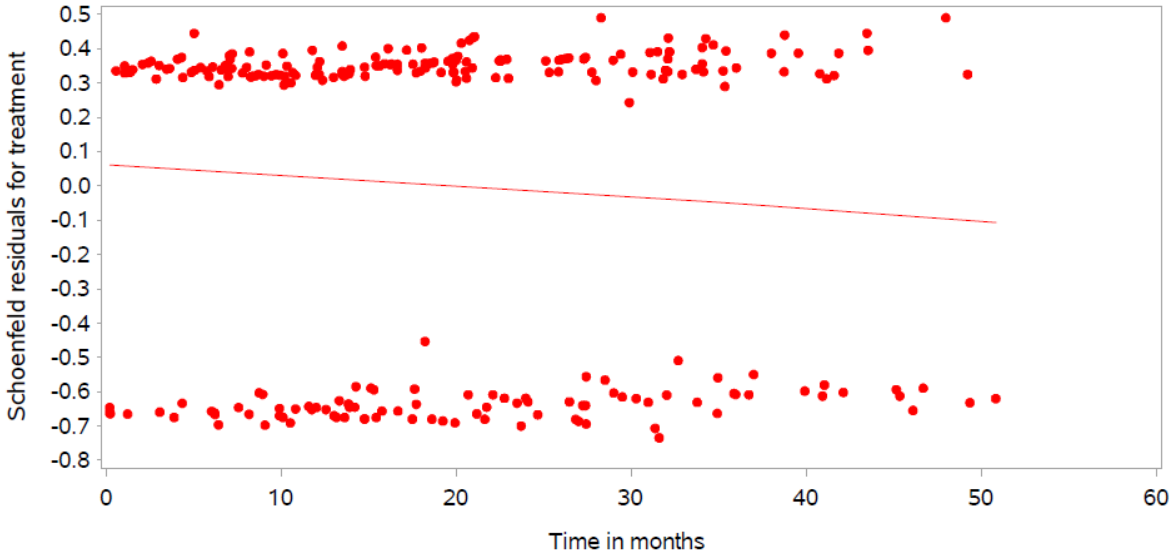
In summary, the company considered it difficult to conclusively prove whether the PH assumption is appropriate or not, but, based on the available evidence, preferred to assume that it does not hold. As a consequence, a "stratified" approach was taken and parametric survival curves were fitted separately to each treatment arm.

Figure A3.1: IDFS log-cumulative hazard plot (ITT population)



Source: Figure 16 in CS.[1]
Abbreviations: CS: company submission; IDFS: invasive disease-free survival; ITT: intention to treat.

Figure A3.2: Plot of the Schoenfeld residuals (ITT population)



Source: Figure 17 in CS.[1]
Abbreviations: CS: company submission; ITT: intention to treat.

Selection of parametric models for IDFS (ITT population)

Goodness of fit of the parametric survival curves was first assessed using the AIC. BIC values were also presented by the company for completeness but were not used in the selection of the parametric survival curves since the company claimed to follow a frequentist, as opposed to Bayesian, approach to statistics. The AIC and BIC values for each parametric model considered by the company, for both trastuzumab emtansine and trastuzumab IDFS are shown in Table A3.1. Based on the AIC values, the exponential distribution should be chosen to model IDFS in the trastuzumab emtansine arm and the log-normal distribution should be chosen for the trastuzumab arm. However, the company noted that small differences in AIC values would imply negligible differences in terms of fit and, therefore, other parametric models can also be considered as potential candidates to model IDFS. Furthermore, following the recommendations of NICE DSU TSD 14,[46] the same type of parametric model was used for both treatment arms. The company judged that, when the fit across the two arms jointly was considered, the best fitting extrapolation was produced by either the exponential or the log-logistic distributions. Nevertheless, the company pointed out that both the AIC and BIC are relative measures of goodness of fit to the observed data but cannot measure the appropriateness of the extrapolation beyond the KM curves. Since in the KATHERINE trial the degree of immaturity and censoring is high, the AIC and BIC values presented by the company, and, therefore, the selection of the parametric models based on them, should be interpreted with caution.

Table A3.1: AIC and BIC for the regression models fit to the KATHERINE IDFS data (ITT population)

	AIC		BIC	
Regression model	**TE arm**	**T arm**	**TE arm**	**T arm**
Exponential	718.91 (1)	1105.56 (4)	723.52 (1)	1110.17 (2)
Weibull	720.52 (3)	1107.55 (5)	729.74 (3)	1116.77 (5)
Log-normal	725.23 (6)	1098.36 (1)	734.45 (5)	1107.58 (1)
Generalised gamma	722.49 (5)	1099.83 (2)	736.33 (6)	1113.67 (4)
Log-logistic	720.35 (2)	1104.06 (3)	729.57 (2)	1113.28 (3)

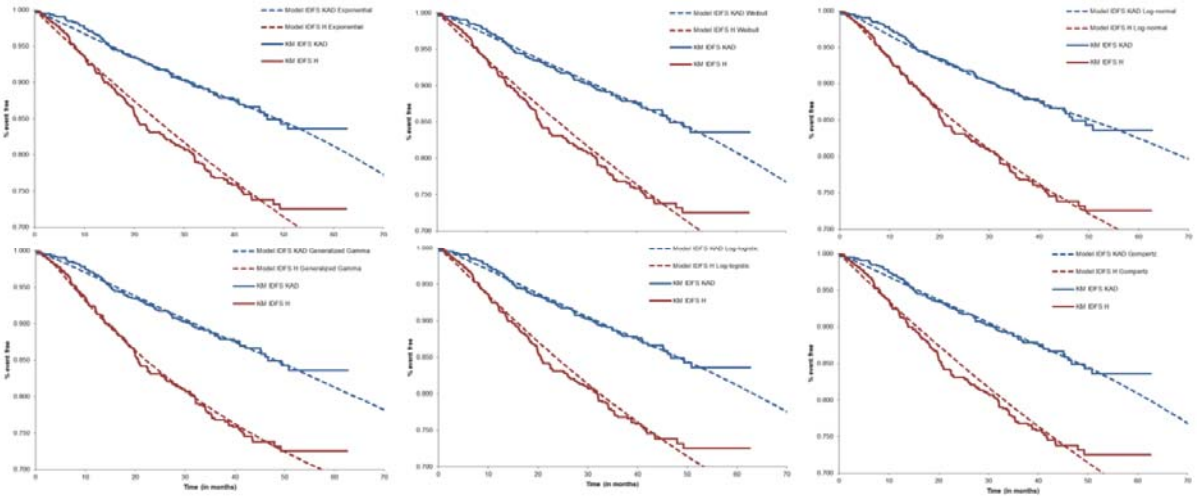
	AIC		BIC	
Regression model	**TE arm**	**T arm**	**TE arm**	**T arm**
Gompertz	720.82 (4)	1107.56 (6)	730.04 (4)	1116.78 (6)

Based on Table 23 of the CS.[1]

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; CS = company submission; IDFS = invasive disease-free survival; ITT = intention to treat; T = trastuzumab; TE = trastuzumab emtansine

To further help with the selection of parametric models to extrapolate IDFS, the company performed visual inspection of the parametric survival curves against the KM data. This assessment was based on the plot of each parametric distribution and the KM curves as in Figure A5.3. Based on this figure, the company indicated that all distributions seemed to fit the KM data well, especially in the trastuzumab emtansine arm, and that in the trastuzumab arm, all extrapolations overestimated IDFS. Finally, the company concluded that the log-logistic and the generalised gamma appeared to provide the best fitting across both treatment arms, even though it was emphasised that this conclusion was subjective since all distributions seem to fit the data reasonably well.

Figure A3.3: KM curves and parametric extrapolations of IDFS for both treatment arms (ITT population)



Source: Figure 18 in CS.[1]

Abbreviations: IDFS: invasive disease-free survival; H: trastuzumab; KAD: trastuzumab emtansine; ITT: intention to treat; KM: Kaplan-Meier.

Finally, the company conducted an assessment of the absolute fit of the parametric survival curves to the KM data by comparing the percentage of patients who did not experience an IDFS event at 12, 24, 36 and 48 months as shown in Table A3.2. Based on this table, the company concluded that, overall, all parametric survival curves across both treatment arms provided a good absolute fit to the KM data since incremental differences between the parametric extrapolations and the KM data were always below 2% in absolute value. Because of this, the company considered that it can be reasonably assumed the differences in the absolute fit of the parametric extrapolations to be negligible.

Table A3.2: Observed and predicted percentage of patients without IDFS events at 12, 24, 36 and 48 months (ITT population)

Time	Survival function	TE arm	T arm	TE vs. T	Difference vs. KM	
					TE arm	T arm
12 months	KM data	96.64%	92.11%	4.53%	0.00%	0.00%
	Exponential	95.90%	91.93%	3.97%	-0.74%	-0.18%
	Weibull	96.20%	92.00%	4.20%	-0.44%	-0.11%
	Log-normal	95.74%	91.51%	4.23%	-0.90%	-0.60%
	Gen. gamma	96.19%	91.26%	4.93%	-0.45%	-0.85%
	Log-logistic	96.18%	91.88%	4.30%	-0.46%	-0.23%
	Gompertz	96.04%	91.93%	4.11%	-0.60%	-0.18%
24 months	KM data	92.05%	83.11%	8.94%	0.00%	0.00%
	Exponential	92.13%	84.80%	7.32%	0.08%	1.69%
	Weibull	92.37%	84.85%	7.52%	0.32%	1.74%
	Log-normal	91.79%	83.92%	7.87%	-0.26%	0.81%
	Gen. gamma	92.34%	83.65%	8.68%	0.29%	0.54%
	Log-logistic	92.29%	84.46%	7.83%	0.24%	1.35%
	Gompertz	92.28%	84.80%	7.48%	0.23%	1.69%
36 months	KM data	88.26%	76.79%	11.47%	0.00%	0.00%
	Exponential	88.50%	78.23%	10.27%	0.24%	1.44%
	Weibull	88.57%	78.23%	10.34%	0.31%	1.44%
	Log-normal	88.40%	77.79%	10.62%	0.14%	1.00%
	Gen. gamma	88.55%	77.75%	10.80%	0.29%	0.96%
	Log-logistic	88.50%	77.88%	10.62%	0.24%	1.09%
	Gompertz	88.57%	78.23%	10.34%	0.31%	1.44%
48 months	KM data	84.27%	73.19%	11.08%	0.00%	0.00%
	Exponential	85.01%	72.16%	12.86%	0.74%	-1.03%
	Weibull	84.85%	72.12%	12.73%	0.58%	-1.07%
	Log-normal	85.45%	72.70%	12.75%	1.18%	-0.49%
	Gen. gamma	84.87%	72.99%	11.88%	0.60%	-0.20%
	Log-logistic	84.89%	72.09%	12.80%	0.62%	-1.10%
	Gompertz	84.90%	72.16%	12.74%	0.63%	-1.03%

Based on Table 24 of the CS[1]

Abbreviations: CS = company submission; IDFS = invasive disease-free survival; ITT = intention to treat; KM = Kaplan-Meier; T = trastuzumab; TE = trastuzumab emtansine

Based on the results of all the assessments described above, the company chose the log-logistic distribution as the best candidate distribution to model IDFS in both treatment arms in years zero to three. Therefore, this distribution was also used as basis for the adjusted curves from year three onwards. The choice of different probability distributions to extrapolate IDFS was explored by the company in scenario analysis.

Base-case results (ITT population)

The results presented in this appendix were submitted with the original company submission.[1] A new version of the model, including updated results, was received by the ERG on 12 November 2019, in the second batch of responses to the clarification questions.[4] The changes made by the company after clarification (see Section 7.1.1 of this report) had a minimal impact on the model results (the updated ICER for the ITT population was £1,247). However, given the proximity of the final deadline to submit the ERG report, it was unfeasible for the ERG to update all the cost effectiveness analyses results for the ITT population.

The company's base-case cost effectiveness results for the ITT population are displayed in Table A3.3. Trastuzumab emtansine is found to be both more costly and more effective than trastuzumab, with incremental costs and QALYs of [redacted] and 1.60, respectively. However, the relatively small incremental cost compared to the relatively large QALY gain leads to a low ICER of £1,293.

Table A3.3: Company base-case cost effectiveness results for the ITT population (discounted)

Technologies	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER versus baseline (£/QALY)
Trastuzumab	[redacted]	15.02	[redacted]				
Trastuzumab emtansine	[redacted]	16.99	[redacted]	[redacted]	1.97	1.60	£1,293

Source: Table 55 of the CS. [1]
Abbreviations: CS = company submission; ICER = incremental cost effectiveness ratio; Incr. = incremental; LYGs = life years gained; QALYs = quality adjusted life years.

The disaggregated discounted QALYs by health state are given in Table A3.4. The disaggregated discounted costs by health state and category are given in Table A3.5. The majority of the difference in QALYs between treatment arms is found in the IDFS state, where trastuzumab emtansine provides an additional 2.170 QALYs compared to trastuzumab. In all remaining states trastuzumab as a comparator provides small QALY gains, due to the fact that patients in the trastuzumab emtansine arm spending less time in these states compared to patients treated with the comparator.

Table A3.4: Summary of QALYs disaggregated by health state (ITT population)

Health state	QALYs intervention (TE)	QALY comparator (T)	Increment
IDFS	[redacted]	[redacted]	[redacted]
Non-metastatic recurrence	[redacted]	[redacted]	[redacted]
Remission	[redacted]	[redacted]	[redacted]
Metastatic disease	[redacted]	[redacted]	[redacted]
Metastatic progression	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

Source: Company submission ITT model [1]
Abbreviations: IDFS = invasive disease-free survival; QALY = quality adjusted life year; T = trastuzumab; TE = trastuzumab emtansine

The largest differences in costs across treatment arms are seen in the IDFS state. This is due to large differences in the cost of the drugs, and smaller differences in AE management and supportive care costs, which collectively result in an incremental cost of [redacted] for trastuzumab emtansine compared to trastuzumab. Despite the large increase in treatment costs which comes with trastuzumab emtansine, this treatment results in lower costs in all other heath states, with particularly large savings in the mBC states. These savings almost cancel out the increase in treatment costs in the IDFS state, resulting in an overall total incremental cost of only [redacted] for trastuzumab emtansine compared to trastuzumab.

Table A3.5: Summary of disaggregated costs by health state and cost category (ITT population)

Cost category	Costs intervention (TE)	Costs comparator (T)	Increment
Trastuzumab emtansine	[redacted]	[redacted]	[redacted]
Trastuzumab	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]
Diagnostic test	[redacted]	[redacted]	[redacted]
Drug administration	[redacted]	[redacted]	[redacted]
AE management	[redacted]	[redacted]	[redacted]
Supportive care	[redacted]	[redacted]	[redacted]
Productivity loss	[redacted]	[redacted]	[redacted]
Travel	[redacted]	[redacted]	[redacted]
Informal care	[redacted]	[redacted]	[redacted]
IDFS Total Cost	[redacted]	[redacted]	[redacted]
Supportive care	[redacted]	[redacted]	[redacted]
Productivity loss	[redacted]	[redacted]	[redacted]
Travel	[redacted]	[redacted]	[redacted]
Informal care	[redacted]	[redacted]	[redacted]
Total non-metastatic recurrence cost	[redacted]	[redacted]	[redacted]
Supportive care	[redacted]	[redacted]	[redacted]
Total remission cost	[redacted]	[redacted]	[redacted]
Supportive care	[redacted]	[redacted]	[redacted]
Total 1st line mBC cost	[redacted]	[redacted]	[redacted]
Supportive care	[redacted]	[redacted]	[redacted]
Total 2nd line mBC cost	[redacted]	[redacted]	[redacted]
Total Cost	[redacted]	[redacted]	[redacted]

Source: Company submission ITT model [1]
Abbreviations: AE = adverse event; IDFS = invasive disease-free survival; mBC = metastatic breast cancer; QALY = quality adjusted life year; T = trastuzumab; TE = trastuzumab emtansine

Probabilistic sensitivity analysis results (ITT population)

The company investigated parametric uncertainty by conducting a probabilistic sensitivity analysis (PSA) with 1,000 Monte Carlo simulation runs. The distributions assigned to each parameter are displayed in Table 53 of the company submission. [1] The results of the company PSA are shown in Table A3.6. The probabilistic ICER is slightly lower than the deterministic ICER, at £1,127 rather than

£1,293. This is mostly due to the lower incremental cost in the PSA ([redacted] vs [redacted]). The resulting cost effectiveness plane and cost effectiveness acceptability curve (CEAC) are displayed in Figures A3.4 and A3.5. The cost effectiveness plane shows that [redacted]. This results in a low probabilistic ICER of £1,127. [redacted]. The CEAC shows that the probability that trastuzumab emtansine is cost-effective at thresholds of £20,000 and £30,000 is 99.3% and 99.8% respectively.

Table A3.6: Company base-case probabilistic cost effectiveness results for the ITT population (discounted)

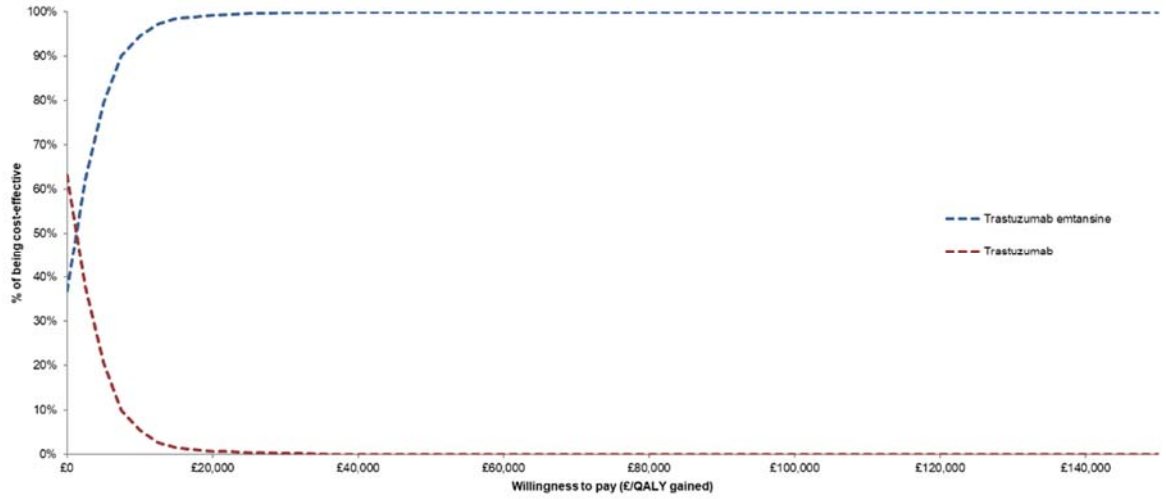
Technologies	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER versus baseline (£/QALY)
Trastuzumab	[redacted]	15.00	[redacted]				
Trastuzumab emtansine	[redacted]	16.95	[redacted]	[redacted]	1.96	1.59	£1,127

Source: Table 56 of the CS [1] and company submission ITT model [1]
Abbreviations: CS = company submission; ICER = incremental cost effectiveness ratio; Incr. = incremental; LYGs = life years gained; QALYs = quality adjusted life years.

Figure A3.4: Scatterplot from the probabilistic sensitivity analysis (ITT population)

Source: Figure 31 of the CS.
Abbreviations: CS = company submission; inc. = incremental; PSA = probabilistic sensitivity analysis; QALY= quality adjusted life year.

Figure A3.5: Cost effectiveness acceptability curve (ITT population)



Based on Figure 32 of the CS.
CS = company submission; QALY= quality adjusted life year

ERG comment: The ERG identified a selection of model parameters which had not been included in the PSA conducted by the company in the original submission. These included patient demographics such as weight and height, treatment market shares and AE costs. The ERG requested that these be included in the model in the clarification letter.

The ERG also identified parameters which had been included in the PSA, but with inappropriate or inconsistent distributions attached. For example, transition probabilities were modelled using a multivariate normal distribution. However, the ERG felt that a Dirichlet distribution should be used, to avoid values above 1 and below 0. This was requested in the clarification letter. Similarly, the ERG requested that the included utilities be modelled using a Beta distribution instead of a Gamma to avoid the possibility of inconsistent values. The ERG also felt that it was inconsistent to use a Gamma distribution for modelling some cost parameters and a log-normal for other parameters. In the clarification letter they requested that the company justify the choice of the most appropriate distribution and consider modelling costs in a consistent way.

In Table 21 of the clarification response the company indicated that they had included patient weight and height in the updated PSA using a normal distribution, updated the utility distributions to Beta distributions, incorporated treatment shares using a Dirichlet distribution, included AE costs using a log normal and amended all cost distributions to log normal.[4]

Regarding the ERG request to model transition probabilities using a Dirichlet distribution to avoid the potential for values above 1 or below 0, the company responded that the sum of all probabilities leaving a specific health state would not be above one with current data inputs.[4] The company created a worksheet named "Transition probabilities" in which they calculated, based on the 1,000 simulations, the maximum probability of cumulative transitions per node (= sum of the maximum values generated in 1,000 simulations for each transition probability pertaining to the respective node). This showed that the sum was never above one with current data inputs. The ERG was satisfied with the company's updated PSA. Updated PSA results were provided in Part I of the clarification response. [4]These are displayed below in Table A3.7. The updated probabilistic ICER was higher than the updated deterministic ICER. This is due to higher incremental costs and lower incremental QALYs in the probabilistic analysis.

Table A3.7: Updated company base-case probabilistic cost effectiveness results compared to updated deterministic results (ITT population)

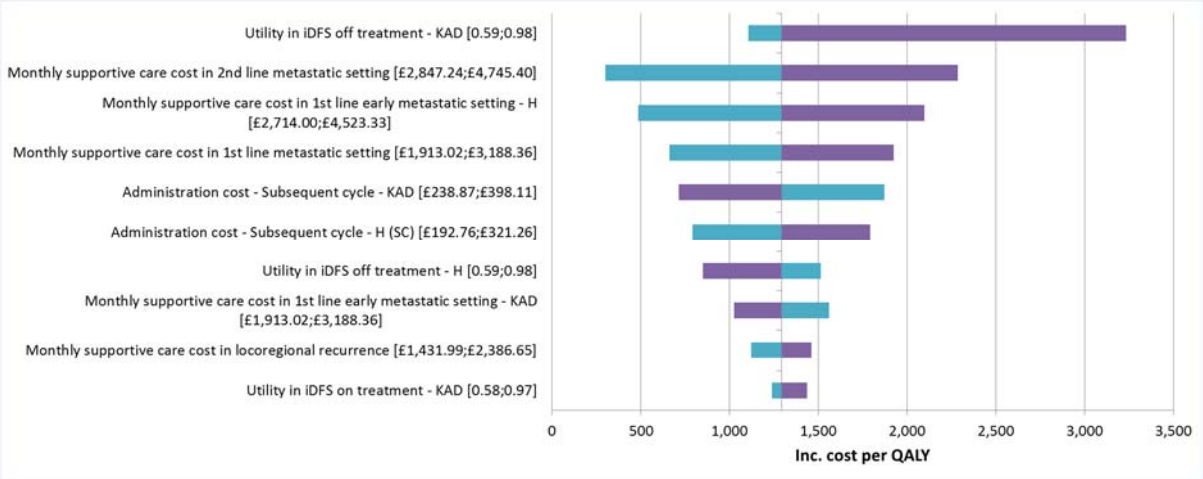
	Costs		QALYs		ICERs (£/QALY)	
	Deterministic	PSA	Deterministic	PSA	Deterministic	PSA
Trastuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£1,247	£1,436
Trastuzumab emtansine	[redacted]	[redacted]	[redacted]	[redacted]		

Source: Table 23 Clarification response Part I.[4]
Abbreviations: ICER = incremental cost effectiveness ratio; PSA = probabilistic sensitivity analysis; QALYs = quality adjusted life years.

Deterministic sensitivity analysis results (ITT population)

The company conducted deterministic sensitivity analyses by varying one-by-one the base-case values of a series of cost and utility parameters by ±25% of the base-case value. The tornado diagram displayed in Figure A3.6 shows that the utility value for IDFS off treatment for trastuzumab emtansine was found to have the largest impact on the ICER, followed by monthly supportive care costs in the second line metastatic setting (all patients), first line early metastatic setting (trastuzumab patients) and first line metastatic setting (all patients).

Figure A3.6: Tornado diagram – company's preferred assumptions (ITT population)



Source: Figure 33 of the CS.
Abbreviations: H = trastuzumab; IDFS = invasive disease-free survival; KAD = trastuzumab emtansine.

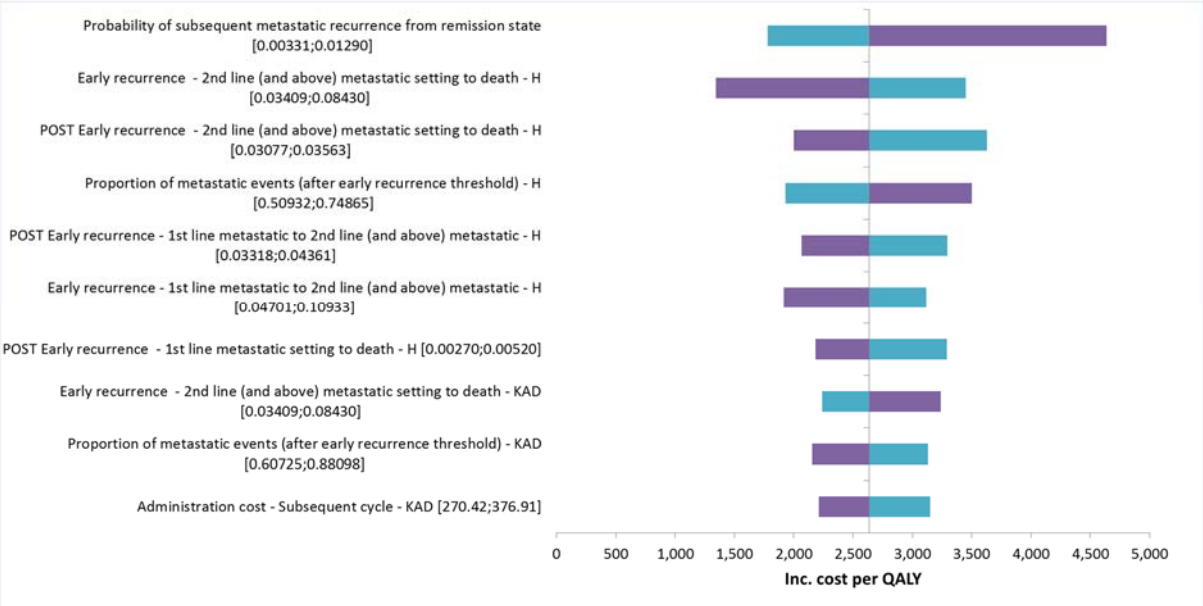
ERG comment: No patient demographic variables, such as weight and height, or clinical variables, such as transition probabilities, were included in the original deterministic sensitivity analysis conducted by the company. The ERG requested that these be included at the clarification stage and some of these were included in the model accompanying the clarification response. The company still did not include patient demographics in the one-way sensitivity analysis and no justification was provided for this choice.

The results of the updated deterministic sensitivity analysis, displayed in Figure A3.7 show that the newly included clinical variables have a larger impact on results than the cost and utility parameters, which had previously had the largest impact on results. The parameter with the largest impact on results in the updated deterministic sensitivity analysis was the probability of subsequent metastatic recurrence from the remission state, followed by the probability of transitioning from second+ mBC to death for

trastuzumab patients in who experienced early and post-early recurrence and the proportion of mBC events after the early recurrence threshold for trastuzumab patients.

The ERG found the choice to vary those parameters included in the deterministic sensitivity analysis by ±25% of the base-case value to be arbitrary and felt that this may not produce values that are equally plausible across all parameters. It would be better practice to use the 95% confidence intervals as upper and lower bounds within the deterministic sensitivity analysis.

Figure A3.7: Updated tornado plot provided with clarification response (ITT population)



Source: Model submitted alongside Phase II of the clarification response – model dated 11-11-19
Abbreviations: H = trastuzumab; KAD = trastuzumab emtansine; mBC = metastatic breast cancer

Scenario analysis results (ITT population)

The company conducted a series of scenario analyses to test the impact of various assumptions made in the model. The results of these scenario analyses are displayed in Table A3.8. The scenarios which had the largest impact on the ICER were shortening the model time horizon to 10 years (£13,625), extrapolating the IDFS curve using a generalised gamma distribution (£5,314) and removing the cure assumption (setting the maximum cure proportion to 0%) (£5,744). The remaining scenarios had a limited impact on the ICER and none of the scenarios resulted in an ICER above the NICE threshold.

The clarification response provided by the company also included some additional scenario analyses, displayed in Table A3.9. Some of these were conducted on the original company submission model, which had a base-case ICER of £1,293, while some were conducted on the updated clarification response model, which had a base-case of £1,247. Scenarios have been split according to whether they were conducted on the original or updated model; however, the relative impact should be similar across models as the change in results is not substantial. The additional scenarios tested all had a fairly small impact on the ICER, with the largest resulting ICER being £3,481 for the scenario which initiated the cure model from month 0. The company stating that there was no clinical rationale for this and that this scenario was provided as a demonstration of the limited clinical impact only.

ERG comment: The company conducted a range of important scenario analyses. However, the ERG feel that the impact of some key assumptions were not sufficiently tested. While the company did conduct a scenario regarding the duration of treatment effect, they only tested the impact of assuming

that the treatment effect was maintained indefinitely over time, rather than the treatment effect being maintained to seven years and waning to 10 years. Therefore, the only scenario tested for the duration of treatment effect was more favourable to the company. The ERG feels that an alternative scenario, which was more conservative than the base-case should also have been tested, as this is a key assumption in the model. Additionally, no scenarios were conducted for the assumptions around the mortality rate of "cured" patients or the transition probabilities (other than remission to first line mBC in the clarification response) or mortality rates assumed throughout the model. Given the importance of transition probability and mortality parameters in the one-way sensitivity analysis, the ERG feel that these variables should have been tested in scenarios, particularly as many of these assumptions were sourced from the literature and previous appraisals of different treatments and not linked to trial evidence.

Table A3.8: Scenario analyses conducted by the company in the company submission (ITT population)

Scenario	Alternative value	Base-case value	Alternative source for input	Incremental QALYs	Incremental costs (£)	ICER (£)
Base-case				1.60	[redacted]	£1,293
1. Model time horizon						
Time horizon (years)	10	51	Assumption	0.42	[redacted]	£13,625
	20			0.99	[redacted]	£2,967
	30			1.38	[redacted]	£1,653
	40			1.56	[redacted]	£1,342
	50			1.60	[redacted]	£1,293
	60			1.60	[redacted]	£1,292
2. Utilities						
eBC utility sources	IDFS-on Tx and NmBC recurrence = 0.775 IDFS-off Tx and remission = 0.788	IDFS-on Tx and NmBC recurrence = 0.775 IDFS-off Tx and remission = 0.788	KATHERINE trial, pooled treatment arms + assumption	1.60	[redacted]	£1,293
	IDFS-on Tx TE = 0.774 Trast. = 0.776 IDFS-off Tx TE = 0.784 Trast. = 0.791		KATHERINE trial, per treatment arm + assumption	1.57	[redacted]	£1,318
	IDFS-on Tx = 0.970 IDFS-off Tx and remission = 0.990 NmBC Recurrence = 0.750		Hedden et al.	1.62	[redacted]	£1,273
	IDFS-on Tx = 0.696		Lidgren et al.	1.60	[redacted]	£1,296

Scenario	Alternative value	Base-case value	Alternative source for input	Incremental QALYs	Incremental costs (£)	ICER (£)
	other eBC = 0.779					
mBC utility sources	1st line = 0.650 2nd line = 0.290	Lloyd values 1st line = 0.773 2nd line = 0.520	Hedden et al.	1.67	[redacted]	£1,238
	0.685		Lidgren et al.	1.58	[redacted]	£1,312
	1st line = 0.773 2nd line = 0.520		Lloyd et al.	1.60	[redacted]	£1,293
	1st line = 0.806 2nd line = 0.536		Paracha et al.	1.59	[redacted]	£1,304
3. Survival modelling						
Distribution IDFS - TE	Exponential	Log-logistic	Assumption	1.69	[redacted]	£379
	Weibull			1.63	[redacted]	£1,009
	Log-normal			1.65	[redacted]	£918
	Generalized Gamma			1.30	[redacted]	£5,314
	Log-logistic			1.60	[redacted]	£1,293
	Gompertz			1.60	[redacted]	£1,158
4. Treatment effect						
Duration of treatment effect	Effect is maintained over time	Effect is limited in time (effect to 7 years, wane to 10 years)		1.66	[redacted]	£601
	Effect is limited in time (effect to 7 years, wane to 10 years)			1.60	[redacted]	£1,293
Incremental treatment effect begins to decrease (months)	48	84	Assumption	1.36	[redacted]	£3,889
	60			1.48	[redacted]	£2,555
	72			1.55	[redacted]	£1,755
	84			1.60	[redacted]	£1,293

Scenario	Alternative value	Base-case value	Alternative source for input	Incremental QALYs	Incremental costs (£)	ICER (£)
	96			1.62	[redacted]	£1,054
	108			1.64	[redacted]	£944
	120			1.64	[redacted]	£893
Maximum cure proportion	0%	95%	Assumption	1.23	[redacted]	£5,744
	20%			1.30	[redacted]	£4,726
	40%			1.37	[redacted]	£3,751
	60%			1.45	[redacted]	£2,819
	80%			1.53	[redacted]	£1,931
	100%			1.62	[redacted]	£1,086
Time at which cure proportion begins to increase	36	36	Assumption	1.60	[redacted]	£1,293
	48			1.63	[redacted]	£928
	60			1.65	[redacted]	£664
	72			1.66	[redacted]	£489
	84			1.67	[redacted]	£411
	96			1.65	[redacted]	£461
	108			1.63	[redacted]	£627
	120			1.60	[redacted]	£861
5. Recurrence						
Definition of early recurrence (months)	6	18	Assumption	1.47	[redacted]	£910
	12			1.54	[redacted]	£1,132
	18			1.60	[redacted]	£1,293
	24			1.66	[redacted]	£1,405
	Average			1.77	[redacted]	£668

Scenario	Alternative value	Base-case value	Alternative source for input	Incremental QALYs	Incremental costs (£)	ICER (£)
Proportion of recurrences which are metastatic	Individual arm data	Individual arm data		1.60	[redacted]	£1,293
6. Costs and resource use						
Treatment duration	Observed treatment duration	Observed treatment duration	Observed treatment duration	1.60	[redacted]	£1,293
	Until disease recurrence (per label)		Until disease recurrence (per label)	1.60	[redacted]	£2,734
Dosing and vial sharing	Planned dose without vial sharing	Actual dose without vial sharing	Planned dose without vial sharing	1.60	[redacted]	£1,297
	Planned dose with vial sharing		Planned dose with vial sharing	1.60	[redacted]	£1,104
	Actual dose without vial sharing		Actual dose without vial sharing	1.60	[redacted]	£1,293
	Actual dose with vial sharing		Actual dose with vial sharing	1.60	[redacted]	£729
Herceptin SC market share	70%	95%	Assumption	1.60	[redacted]	£2,407
	75%			1.60	[redacted]	£2,184
	80%			1.60	[redacted]	£1,961
	85%			1.60	[redacted]	£1,738
	90%			1.60	[redacted]	£1,516
	95%			1.60	[redacted]	£1,293
	100%			1.60	[redacted]	£1,070

Source: Tables 58 and 59 Company submission and ITT electronic model submitted with company submission
Abbreviations: eBC = early breast cancer; ICER = incremental cost effectiveness ratio; IDFS = invasive disease-free survival; mBC = metastatic breast cancer; NmBC = non-metastatic breast cancer; QALYs = quality adjusted life years; SC =; TE = trastuzumab emtansine.

Table A3.9: Scenario analyses conducted by the company in the clarification response (ITT population)

Scenario	Alternative value	Base-case value	Alternative source for input	Incremental QALYs	Incremental costs (£)	ICER (£)
Original company base-case						
Base-case				1.60	[redacted]	£1,293
1. Cure model						
Cure model begins (months)	0	36	Assumption	1.26	[redacted]	£3,481
	36			1.60	[redacted]	£1,293
Maximum cure rate reached, months (years)	96 (8)	120 (10)	Assumption	1.57	[redacted]	£1,758
	108 (9)			1.59	[redacted]	£1,452
	120 (10)			1.60	[redacted]	£1,293
	132 (11)			1.60	[redacted]	£1,252
	144 (12)			1.60	[redacted]	£1,287
2. Baseline Characteristics						
Baseline Characteristics	ITT	ITT	Assumption	1.60	[redacted]	£1,293
	UK-specific			1.65	[redacted]	£210
Updated company base-case provided with clarification response						
Base-case				1.44	[redacted]	£1,247
3. Utilities						
Remission utility value	Remission = IDFS off treatment	Remission = IDFS off treatment	Assumption	1.44	[redacted]	£1,247
	Remission = 90% of IDFS off treatment			1.48	[redacted]	£1,215
4. Transition probabilities						
Remission to 1st line mBC	0.0068	0.0076	Hamilton et al. [50]	1.74	[redacted]	£1,459
	0.0076			1.44	[redacted]	£1,247
	0.0084			1.80	[redacted]	£1,070

Scenario	Alternative value	Base-case value	Alternative source for input	Incremental QALYs	Incremental costs (£)	ICER (£)
5. Adverse event costs and disutilities						
AE costs and disutilities	Company base-case		ERG request	1.44	[redacted]	£1,247
	ERG requested AE costs and disutilities			1.40	[redacted]	£1,309
Source: Clarification Response Part I [4] Abbreviations: AE = Adverse event; ICER = incremental cost effectiveness ratio; IDFS = invasive disease-free survival; ITT = intention to treat; mBC = metastatic breast cancer; NA = not available; QALY = quality adjusted life years;						

Appendix 4: Company cost effectiveness analyses for the node-positive subpopulation

The results presented in this appendix were submitted with the original company submission (in Appendix M).[20] A new version of the model, including updated results for the node-positive population, was received by the ERG on 12 November 2019, in the second batch of responses to the clarification questions (question B2).[4] The changes made by the company after clarification (see Section 7.1.1 of this report) had a minimal impact on the model results. However, the company did not submit an updated version of the results presented in Appendix M of the original submission. Given the proximity of the final deadline to submit the ERG report, it was unfeasible for the ERG to update all the cost effectiveness analyses results for the node-positive population.

The ERG would like to emphasise that, given all the limitations and flaws regarding the cost effectiveness analyses for the node-positive population discussed throughout Section 5 of this report, the ERG considers the cost effectiveness results for the node-positive population unreliable and, therefore, inappropriate for decision making. Results for the node-positive population are presented in this appendix for completeness only. The ERG did not conduct any additional exploratory analyses for this subgroup of patients, as none of these limitations and flaws would be overcome with new analyses.

Company's base-case results (node-positive subpopulation)

The company's base-case cost effectiveness results for the node-positive population (HR scenario A) are displayed in Table A4.1. Trastuzumab emtansine is found to be both more costly and more effective than pertuzumab + trastuzumab, with incremental costs and QALYs of [redacted] and [redacted], respectively. The ICER in this case was £354. As mentioned in Section 5.2.6.3, two additional variations on the Bucher analysis were performed, leading to two different hazard ratios. The cost effectiveness results when using the hazard ratios from scenarios B and C (see e.g. Table 5.8) were presented by the company in Table 46 and 47 in Appendix M of the CS.[20] The ERG considered these scenarios misleading and, therefore, their results are not presented here (in both cases trastuzumab emtansine dominated pertuzumab).

Table A4.1: Company base-case (HR scenario A) cost effectiveness results for the node-positive population (discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Pertuzumab + trastuzumab	[redacted]	15.92	[redacted]	[redacted]	1.07	0.87	£354
Trastuzumab emtansine	[redacted]	16.99	[redacted]				

Source: Table 45 in Appendix M to the CS.[20]
Abbreviations: CS: company submission; HR: hazard ratio; ICER: incremental cost effectiveness ratio; LYG: life years gained; QALY: quality adjusted life year.

Probabilistic sensitivity analysis (node-positive subpopulation)

The parameters and the probability distributions used in the PSA for the node-positive population are shown in Table 44 of Appendix M to the CS.[20] Note, however, that in response to the clarification question B31,[4] the company decided to include more parameters in the PSA, as requested by the ERG. Results for the node-positive population based on the model after clarification were not provided by the company. The ERG was not able to get these results from the model either. Therefore, the results presented here, which are those in the original submission, underestimate the actual parameter uncertainty in the model.

The results of the company PSA (obtained from 1,000 Monte Carlo simulations) are shown in Table A4.2. The probabilistic ICER was £260, thus, slightly lower than the deterministic ICER. The resulting cost effectiveness plane and CEAC are displayed in Figures A4.1 and A4.2. The cost effectiveness plane shows that [redacted]. The CEAC shows that the probability that trastuzumab emtansine is cost effective at thresholds of £20,000 and £30,000 was 100% in both cases.

Table A4.2: Company base-case (HR scenario A) probabilistic cost effectiveness results for the node-positive population (discounted)

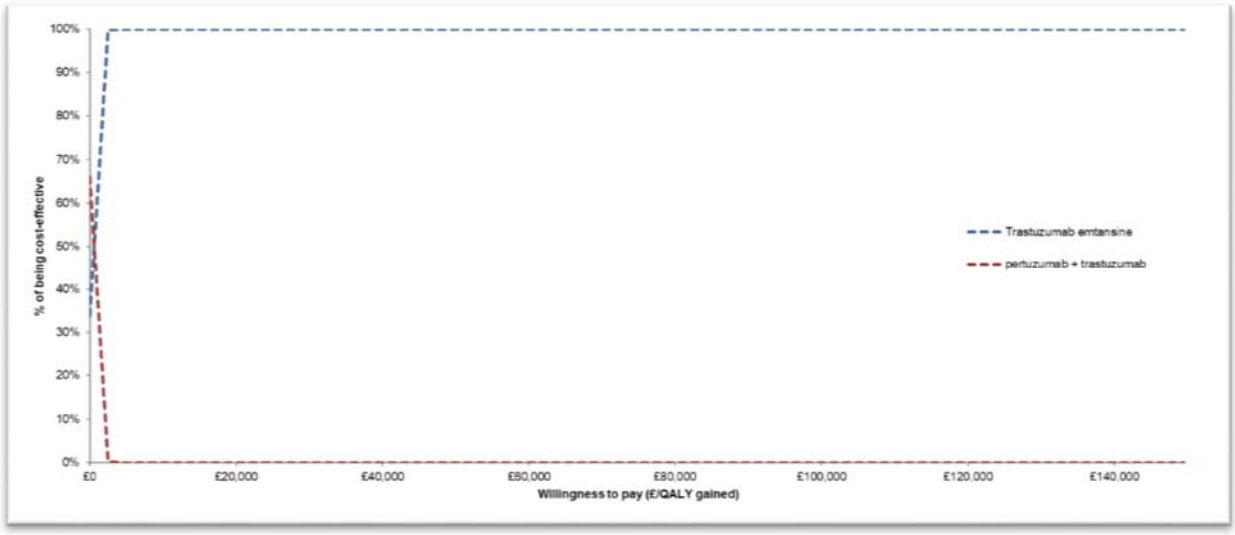
Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Pertuzumab + trastuzumab	[redacted]	NR	[redacted]	[redacted]	NR	0.83	£260
Trastuzumab emtansine	[redacted]	NR	[redacted]				

Source: Table 48 in Appendix M to the CS.[20]
Abbreviations: CS: company submission; HR: hazard ratio; ICER: incremental cost effectiveness ratio; LYG: life years gained; QALY: quality adjusted life year.

Figure A4.1: Scatterplot from the probabilistic sensitivity analysis (node-positive population)

Source: Figure 10 in Appendix M to the CS.[20]
Abbreviations: CS = company submission; inc. = incremental; PSA = probabilistic sensitivity analysis; QALY= quality adjusted life year.

Figure A4.2: Cost effectiveness acceptability curve (node-positive population)

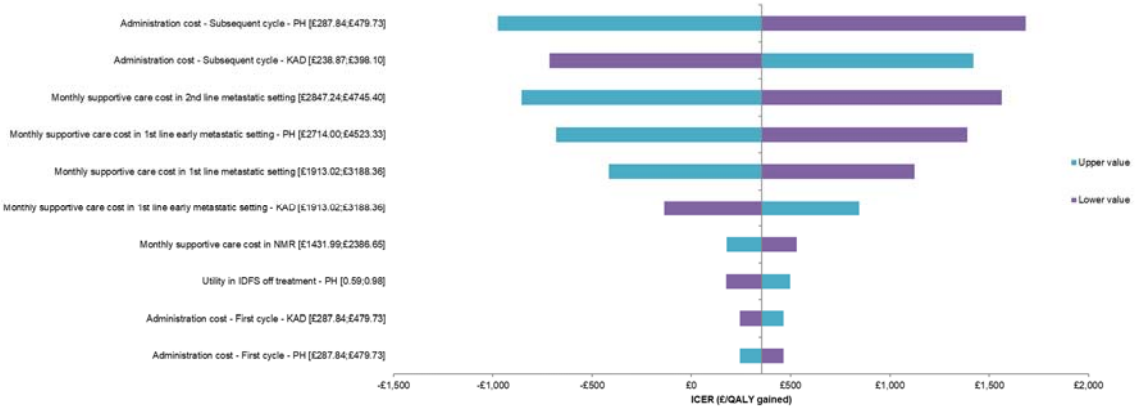


Based on Figure 11 in Appendix M to the CS.[20]
Abbreviations: CS = company submission; QALY= quality adjusted life year

Deterministic sensitivity analysis (node-positive population)

The approach taken by the company was the same as the one used for the ITT and the node-negative populations. The ERG refers to Appendix 3 of this report for further details. The tornado diagram displayed in Figure A4.3 shows that, overall, administration and supportive care costs were found to have the largest impact on the ICER.

Figure A4.3: Tornado diagram – company's preferred assumptions (node-positive population)



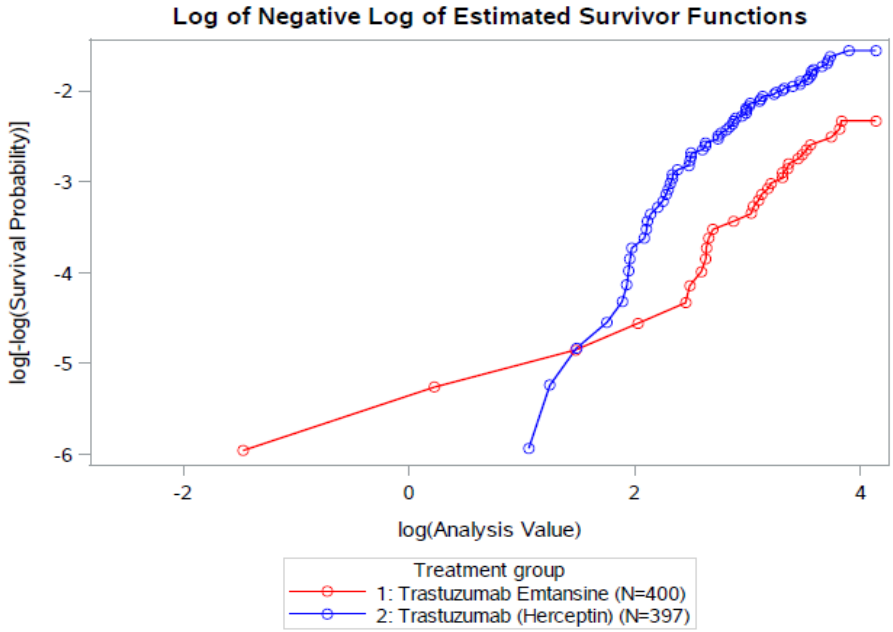
Source: Figure 12 in Appendix M to the CS.[20]
Abbreviations: KAD: trastuzumab emtansine; ICER: incremental cost effectiveness ratio; IDFS: invasive disease-free survival; mBC: metastatic breast cancer; NMR: non-metastatic recurrence; PH: pertuzumab + trastuzumab; QALY: quality adjusted life year.

Scenario analyses (node-positive population)

The scenarios conducted by the company in the node-positive population were similar to those conducted for the ITT population in Appendix 3 of this report. The results of these scenario analyses were reported in Table 50 and 51 of Appendix M of the CS,[20] but are not shown in this report. The conclusions drawn from these analyses are the same as those based on Tables A3.8 and A3.9 for the ITT population.

Appendix 5: Survival analyses for the node-negative subpopulation (additional information)

Figure A5.1: Log of negative log of estimated survivor functions – IDFS endpoint from the KATHERINE study (node-negative subpopulation)



Source: Figure 3 of the response to the clarification letter – Part II.[4]

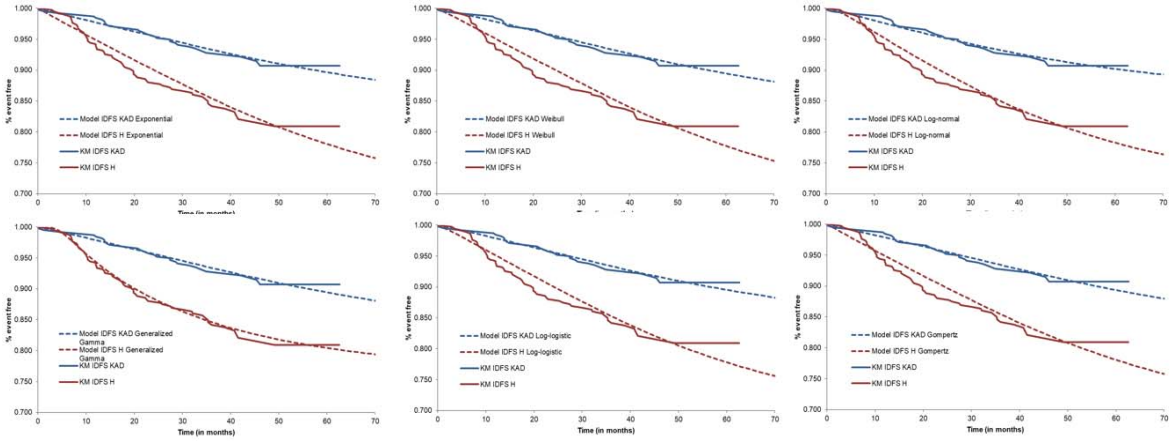
Table A5.1: AIC and BIC for the regression models fit to the KATHERINE IDFS data (node-negative population)

	AIC		BIC	
Regression model	**TE arm**	**T arm**	**TE arm**	**T arm**
Exponential	261.53 (1)	460.47 (3)	265.52 (1)	464.45 (3)
Weibull	263.42 (2)	462.34 (5)	271.41 (2)	470.30 (5)
Log-logistic	263.43 (3)	460.89 (4)	271.41 (3)	468.86 (4)
Log-Normal	265.40 (5)	455.32 (2)	273.39 (5)	463.29 (2)
Generalised gamma	265.42 (6)	447.95 (1)	277.39 (6)	459.90 (1)
Gompertz	263.45 (4)	462.47 (6)	271.43 (4)	470.44 (6)

Based on Table 17 of the response to the clarification letter – Part II.[4]

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; IDFS = invasive disease-free survival; T = trastuzumab; TE = trastuzumab emtansine

Figure A5.2: KM curves and parametric extrapolations of IDFS for both treatment arms (node-negative population)



Source: Figure 4 of the response to the clarification letter – Part II.[4]
Abbreviations: IDFS: invasive disease-free survival; H: trastuzumab; KAD: trastuzumab emtansine; KM: Kaplan-Meier.

Table A5.2: Observed and predicted percentage of patients without IDFS events at 12, 24, 36 and 48 months (node-negative population)

Time	Survival function	TE arm	T arm	TE vs. T	Difference vs. KM	
					TE arm	T arm
12 months	KM data	98.70%	94.19%	4.50%	0.00%	0.00%
	Exponential	97.63%	94.69%	2.94%	-1.07%	0.50%
	Weibull	97.80%	94.96%	2.84%	-0.90%	0.77%
	Log-normal	97.52%	94.99%	2.53%	-1.18%	0.80%
	Gen. gamma	97.80%	94.04%	3.76%	-0.90%	-0.15%
	Log-logistic	97.80%	94.91%	2.88%	-0.90%	0.72%
	Gompertz	97.77%	94.69%	3.08%	-0.93%	0.50%
24 months	KM data	95.75%	88.02%	7.73%	0.00%	0.00%
	Exponential	95.41%	89.86%	5.55%	-0.34%	1.84%
	Weibull	95.55%	90.07%	5.48%	-0.20%	2.05%
	Log-normal	95.21%	89.61%	5.60%	-0.54%	1.59%
	Gen. gamma	95.57%	88.22%	7.34%	-0.18%	0.20%
	Log-logistic	95.53%	89.87%	5.67%	-0.22%	1.85%
	Gompertz	95.58%	89.86%	5.72%	-0.17%	1.84%
36 months	KM data	92.80%	84.57%	8.22%	0.00%	0.00%
	Exponential	93.25%	85.28%	7.97%	0.45%	0.71%
	Weibull	93.30%	85.33%	7.96%	0.50%	0.76%
	Log-normal	93.18%	84.90%	8.28%	0.38%	0.33%
	Gen. gamma	93.30%	84.51%	8.79%	0.50%	-0.06%
	Log-logistic	93.28%	85.09%	8.18%	0.48%	0.52%
	Gompertz	93.33%	85.28%	8.05%	0.53%	0.71%

Time	Survival function	TE arm	T arm	TE vs. T	Difference vs. KM	
					TE arm	T arm
48 months	KM data	90.68%	82.06%	8.62%	0.00%	0.00%
	Exponential	91.27%	81.25%	10.03%	0.59%	-0.81%
	Weibull	91.20%	81.11%	10.09%	0.52%	-0.95%
	Log-normal	91.50%	81.08%	10.41%	0.82%	-0.98%
	Gen. gamma	91.19%	82.04%	9.16%	0.51%	-0.02%
	Log-logistic	91.22%	80.98%	10.24%	0.54%	-1.08%
	Gompertz	91.19%	81.25%	9.94%	0.51%	-0.81%

Based on Table 18 of the response to the clarification letter – Part II.[4]

Abbreviations: IDFS = invasive disease-free survival; KM = Kaplan-Meier; T = trastuzumab; TE = trastuzumab emtansine

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

ERG report – factual accuracy check

Trastuzumab emtansine for adjuvant treatment of HER2-positive early breast cancer [ID1516]

You are asked to check the ERG report to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies, you must inform NICE by **5pm on Friday 6 December 2019** using the below 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 committee papers.

The factual accuracy check form should act as a method of detailing any inaccuracies found and how and why they should be corrected.

#	Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
1	**Page 13 - Section 1.1** - "The most recent anticipated marketing authorisation is: trastuzumab emtansine is indicated for the adjuvant treatment of adult patients with HER2-positive early breast cancer who have residual invasive disease, in the breast and/or lymph nodes, after neoadjuvant taxane- and trastuzumab or pertuzumab and trastuzumab-based therapy."	"The most recent marketing authorisation is: Kadcyla, as a single agent, is indicated for the adjuvant treatment of adult patients with HER2-positive early breast cancer who have residual invasive disease, in the breast and/or lymph nodes, after neoadjuvant taxane-based and HER2 targeted therapy"	Updated indication wording as per the CHMP opinion received on 14th November. Please note, this change has already been communicated to NICE via email	This has been updated.
2	**Page 15 - Section 1.2** - "KATHERINE included pre-treated patients who had residual invasive disease (RID) and APHINITY included treatment naïve patients."	"KATHERINE included only pre-treated patients who had residual invasive disease (RID) and APHINITY included only treatment naive patients."	It should be made clear that the KATHERINE and APHINITY cohorts consisted of **only** pre-treated patients with RID and **only** treatment-naive patients, respectively. How the sentence is currently written leaves it ambiguous as to whether or not other types of patients were also included.	Not a factual error.
3	**Page 19 – Section 2.3 – Figure 2.1**	Please see an updated figure submitted as an appendix to this response.	While the Figure 2.1 is not considered factually inaccurate, we realize that the current depiction may have led to some confusion. Consequently, the Company has provided a revised	Thank you for the clarification. Not a factual error.

			schematic (Figure 1) as part of this response. Specifically, the revised figure emphasizes that upon diagnosis of residual invasive disease following surgery, patients should receive trastuzumab emtansine regardless of nodal status, given that trastuzumab emtansine demonstrated similar efficacy in both patient subgroups (N+ and N-). The Company hopes that this updated schematic will also help to explain the rationale behind presenting the hazard ratio derived from the Bucher analysis using the APHINITY node-positive and the KATHERINE ITT data. The reason for choosing the ITT patient population (from KATHERINE) and the Node-positive patients (from APHINITY) for the Bucher ITC was that residual invasive disease patients (from KATHERINE) are considered to be more severe compared to neoadjuvant treatment-naive patients (from APHINITY). In order to match the patient populations as much as possible from a severity perspective, it was important to choose the Node-positive patients (from APHINITY) which are, in	

			general, considered more severe compared to the ITT population in APHINITY. A comparison of Node-positive patients from APHINITY versus Node-positive patients in KATHERINE results in a comparison of patient populations that differ in severity levels.	
4	**Page 21 - Section 3 - Table 3.1** - "The company refers to the Bucher as a 'naïve clinical efficacy comparison'. However, the term 'naïve comparison' is usually used for a comparison of single arms without a common comparator. In this case, there are two RCTs with a common comparator."	The company refers to the Bucher as a 'naïve clinical efficacy comparison' due to a lack of adjustment for the difference in population characteristics. However, the term 'naïve comparison' is usually used for a comparison of single arms without a common comparator. In this case, there are two RCTs with a common comparator."	The Company used the term "naive" referring to the overall comparison, not to the methodology used for the comparison (i.e. Bucher method) . "Naïve" refers to the fact that the comparison has been conducted despite the considerable differences in the KATHERINE population (RID at surgery following neoadjuvant treatment) and the APHINITY population (adjuvant initiated - treatment naive before surgery). Further, it is also an acknowledgement of the inability to replicate a RID population in the APHINITY cohort and subsequently calculate a corresponding Hazard ratio to be used for the (Bucher) ITC with the KATHERINE study.	Not a factual error.

			The Company agrees that this is perhaps an atypical usage of the term naive in this context.	
5	**Page 24 - Section 3.1** - "As part of the response to clarification,4 the company provided the following updated wording: “Kadcyla, as a single agent, is indicated for the adjuvant treatment of adult patients with HER2-positive early breast cancer who have residual invasive disease, in the breast and/or lymph nodes, after neoadjuvant taxane- and trastuzumab or pertuzumab and trastuzumab -based therapy”.	Remove this statement	The label wording has changed (see Comment 1). The wording in the clarification letter is no longer relevant to the appraisal	This has been updated.
6	**Page 25 - Section 3.3** - "The company’s main concern regarding the indirect comparison seems to be the fact that the populations are different in the two trials (treatment naïve versus pre-treated patients);"	“The Companies concerns regarding the indirect treatment comparison can be summarised in the following key points: - Patient population in APHINITY consist of broad risk groups, including low-risk patients as well as high-risk patients usually indicated for neoadjuvant therapy. - In KATHERINE, randomization happened only after the neoadjuvant therapy and surgery and only adjuvant part of the therapy was administered within the study. Therefore, efficacy results represent effect of 14 cycles of treatment instead of 18 cycles used in APHINITY.	Current statement does not comprehensively cover the reasons the Company thinks the ITC is biased or inappropriate.	Not a factual error.

		- Patients in KATHERINE study were pre-treated by neoadjuvant therapy that was administered outside of clinical study based on real clinical practice. The neoadjuvant therapy eradicated tumour cells sensitive to standard chemotherapy and trastuzumab-based agents (including dual-blockade) while those invasive cells that remained in breast and/or lymph nodes likely developed escape mechanisms to neo-adjuvant treatment that can be overcome by the change of the therapy (Bedard PL, et al. Nature 2013; 105:355–364). The main rationale for KATHERINE study was to investigate if the change of adjuvant treatment can improve efficacy in treatment pre-selected patients with unique treatment biology. However, this is not possible to achieve in situation where the tumour has been removed by the surgery, like in APHINITY trial. - Patients recruited in KATHERINE are only those who didn't achieve a pCR following neoadjuvant treatment and remained with residual invasive disease in breast and/or lymph nodes. Such "residual invasive or non-pCR subgroup"		

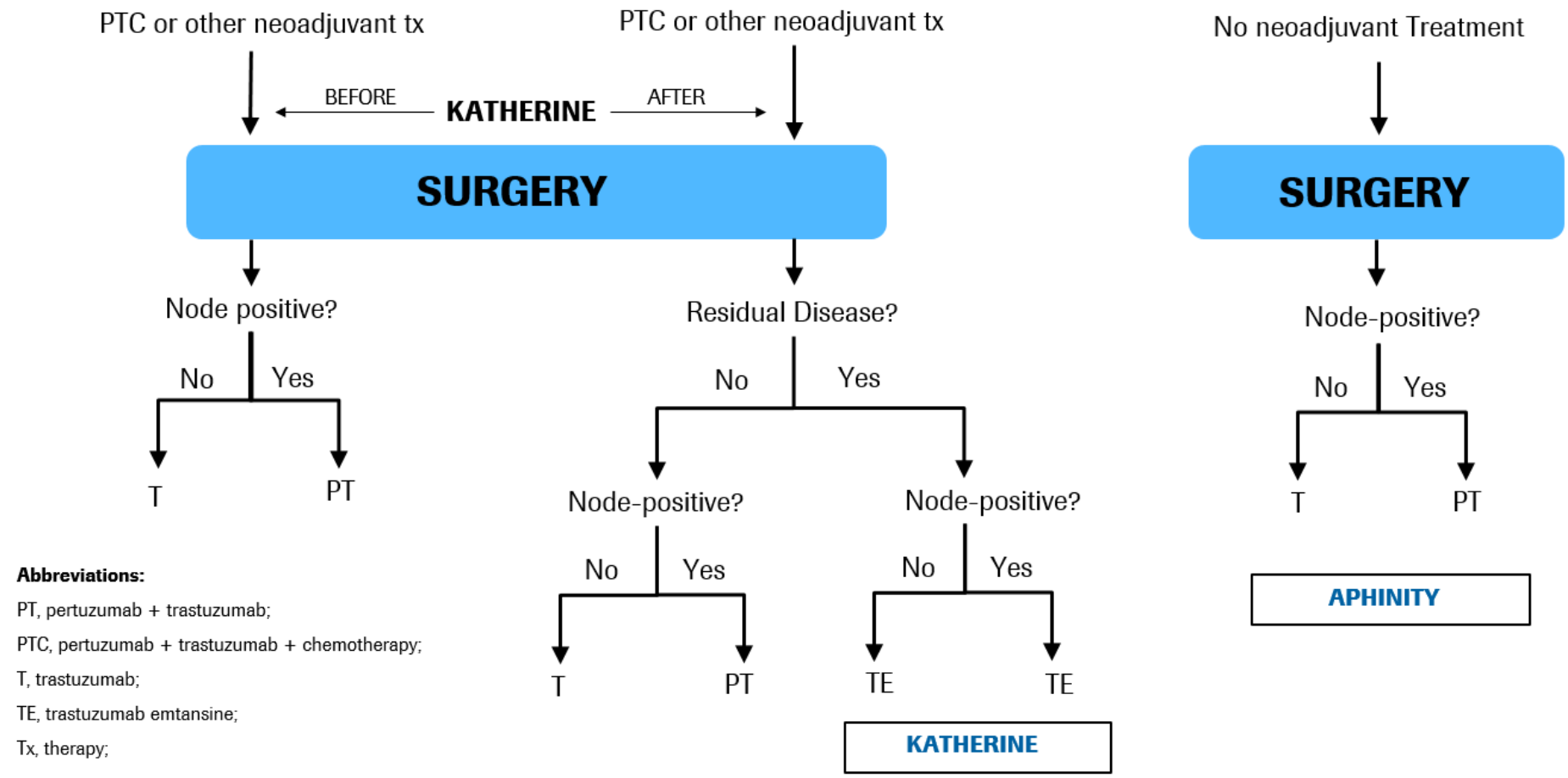
		is not reproducible in APHINITY‘s population.”		
7	**Page 25 - Section 3.3** - "Therefore, we asked the company to provide published evidence or to provide expert opinion that there are likely to be differences (Clarification letter, Question A22)"	Add in a summary of the responses to this question	It is misrepresentative and misleading to state that the Company was asked for evidence/expert opinion and then not go on to talk about said expert opinion. Upon reading, it appears as though the Company ignored the ERG's request, which is unreflective.	Not a factual error.
8	**Page 65 - Section 5.1.4** - "Similarly, the cost and resource use SLR was also not fit for purpose, as the SLR was conducted in 2017, with the aim of identifying recent studies (published in the last five years) presenting novel cost and resource use data relevant to an economic model of pertuzumab as adjuvant treatment for HER2-positive early breast cancer, including the management of recurrence and/or metastatic disease in the longer-term. The SLR did not cover the period after 2017, and many other studies relevant for an economic model of trastuzumab emtansine might have been missed"	Remove this statement	This is false. Unfortunately, due to a copying error, the write up of the June 2019 update was not included in the original submission. However, the update had been conducted and was subsequently provided during the response to clarification questions.	This has been updated. The statement in Issue 8 has been replaced by the following text: “In the cost and resource use SLR, the language restrictions and restriction to only include UK cost and resource use data could have resulted in relevant studies being missed”.
9	**Page 78 - Section 5.2.6** - "The company considered that all extrapolations (across both treatment arms) provided a good absolute fit to the KM data since incremental differences between the extrapolations and the KM data were	Remove this statement	The statement made by the Company refers exclusively to the "absolute fit" of the extrapolation exclusively to the KM data. It was not the Company's intention for this statement to hold for the tails.	Not a factual error. It is clear that the company refers to the “absolute fit” to the KM data but the implications of this on the tails

	always below 2%. For this reason, the company argued that it can be assumed that the differences in the absolute fit of the extrapolations are negligible. Even though deviations at year 4 can be considered minor, the shape of the tails of the parametric extrapolations can vary significantly between different survival functions, which may have a non-negligible impact on the model results."			of the extrapolations were not discussed and they are relevant.
10	**Page 84 - Section 5.2.6** - "If the node-positive population in the HERA trial is assumed to be a good proxy for the trastuzumab arm in KATHERINE, the modelled IDFS (red-dashed curve in Figure 5.4) should be closer to the observed DFS in HERA (green line in Figure 5.4)."	"If the node-positive population in the HERA trial is assumed to be a more appropriate proxy for the trastuzumab arm in the ITT population of KATHERINE , the modelled IDFS (red-dashed curve in Figure 5.4) should be closer to the observed DFS in HERA (green line in Figure 5.4)."	The Company argued that the node-positive population in HERA is a more appropriate proxy to the ITT population of KATHERINE - not a "good" proxy.	This has been updated.
11	**Page 96 - Section 5.2.6** - "The output of the Bucher method is a hazard ratio (HR) between trastuzumab emtansine and pertuzumab."	"The output of the Bucher method is a hazard ratio (HR) between trastuzumab emtansine and pertuzumab + trastuzumab."	The comparator in the node-positive analysis is pertuzumab + trastuzumab.	This has been updated.
12	**Page 97 - Section 5.2.6** - "Less biased estimates could have been obtained, if the company had used data from alternative sources (i.e. not only from company conducted RCTs, but also from alternative registries) to provide relative clinical and cost effectiveness of trastuzumab emtansine versus pertuzumab + trastuzumab)."	Remove this statement	The APHINITY regimen has only recently become available in routine practice. The Company is aware of no such registry that holds the data required to conduct the analysis suggested by the ERG. This statement should only be allowed to stand if the ERG is able to point to a specific registry that could have been used.	Not a factual error. The ERG thanks the company for this comment. However, the ERG considers that the burden of the proof was on the company for identifying relevant studies for the relative effectiveness. The systematic review of the company was designed for identifying the randomised evidence and non-RCT

			Otherwise, it is purely hypothetical and potentially misleading given that a suitable registry does not exist.	designs, but observational studies were excluded. If the company had included observational studies and non-RCT designs in its review, potentially relevant studies and the registries that could have been useful would have been identified.
13	**Page 100 - Section 5.2.6.4** - "In their response to the clarification question B18,4 the company indicated that the number of breast cancer-related deaths in KATHERINE was 91 (from a total of 1,480 patients, so 91/1,480 = 6.12%)."	"In their response to the clarification question B18,4 the company indicated that the number of breast cancer-related deaths in KATHERINE was 91 (from a total of 1,460 patients, so 91/1,460 = 6.23%)."	There is an error in the Company's response to clarification question B18. The safety evaluable population in both arms sums to 1460 - as per Table 46 of the KATHERINE CSR.	This has been updated.
14	**Page 121/122 - Section 5.2.9.1** - "Also, the ERG could not verify all clinical expert-based assumptions taken by the company for pertuzumab therapy for node-positive population (e.g. no chemotherapy in the adjuvant setting), due to the late submission of the additional evidence."	Remove this statement	The "late submission of the additional evidence" pertained to questions on the indirect treatment comparison and the efficacy in the node-negative subgroup of KATHERINE - not costs and resource use in the economic analysis. Consequently, the submission of late evidence had no impact on the ERG's ability to verify the clinical-expert based cost assumptions.	This has been updated. The ERG thanks the company for this comment and acknowledges that the cost assumptions were provided in time. The sentence was amended as follows: "Also, the ERG could not verify all clinical expert-based assumptions taken by the company for pertuzumab therapy for node-positive population (e.g. no chemotherapy in the adjuvant setting), due to the lack of time."

15	**Page 136 - Section 6.1 - Table 6.1** - "* The results submitted by the company in Table 23 of the response to the clarification letter – Part II (ICER = £2,364) did not match those in the electronic model".	Remove this statement	First, the ICER figure quoted in the Company's response to the clarification letter was £2,634 (as per Table 23) and not £2,364 as quoted in Table 6.1 of the ERG report. Additionally, there was no discrepancy between the submitted economic model and the clarification letter results. We assume the discrepancy the ERG are quoting here (£2,634 versus £2,755) was because the ERG have not updated the IDFS extrapolations when switching from the ITT analysis (Log-logistic) to the node-negative analysis (Exponential) in the model.	This has been updated.
16	**Page 137 - Section 6.2 - Table 6.2** - "* The results submitted by the company in Table 26 of the response to the clarification letter – Part II (ICER = £2,364) did not match those in the electronic model."	Remove this statement		This has been updated.
17	**Page 141 - Section 6.3** - "In contradiction to their claim, additional tables from TA569 were not provided in the appendix of their response to the clarification letter."	Remove this statement	Incorrect and misleading. The response to clarification question B.29 in the "*ID1516_CQs_Apps_11-11-2019_CIC*" document contains the additional tables referred to by the Company.	This has been updated. The ERG confirms that additional tables were overlooked. Therefore, this statement is removed. However, the provision of these tables were not that informative since these were more or less identical to the tables in the company submission.

Figure 1. Identifying adjuvant trastuzumab emtansine eligible patients in clinical practice



Abbreviations:

PT, pertuzumab + trastuzumab;

PTC, pertuzumab + trastuzumab + chemotherapy;

T, trastuzumab;

TE, trastuzumab emtansine;

Tx, therapy;

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft technical report

Trastuzumab emtansine for adjuvant treatment of HER2-positive early breast cancer [ID1516]

This document is the draft technical report for this appraisal. It has been prepared by the technical team with input from the lead team and chair of the appraisal committee.

The technical report and stakeholder's responses to it are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting.

The technical report includes:

- topic background based on the company's submission
- a commentary on the evidence received and written statements
- technical judgements on the evidence by the technical team
- reflections on NICE's structured decision-making framework.

This report is based on:

- the evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

The technical report should be read with the full supporting documents for this appraisal.

Issue date: January 2020

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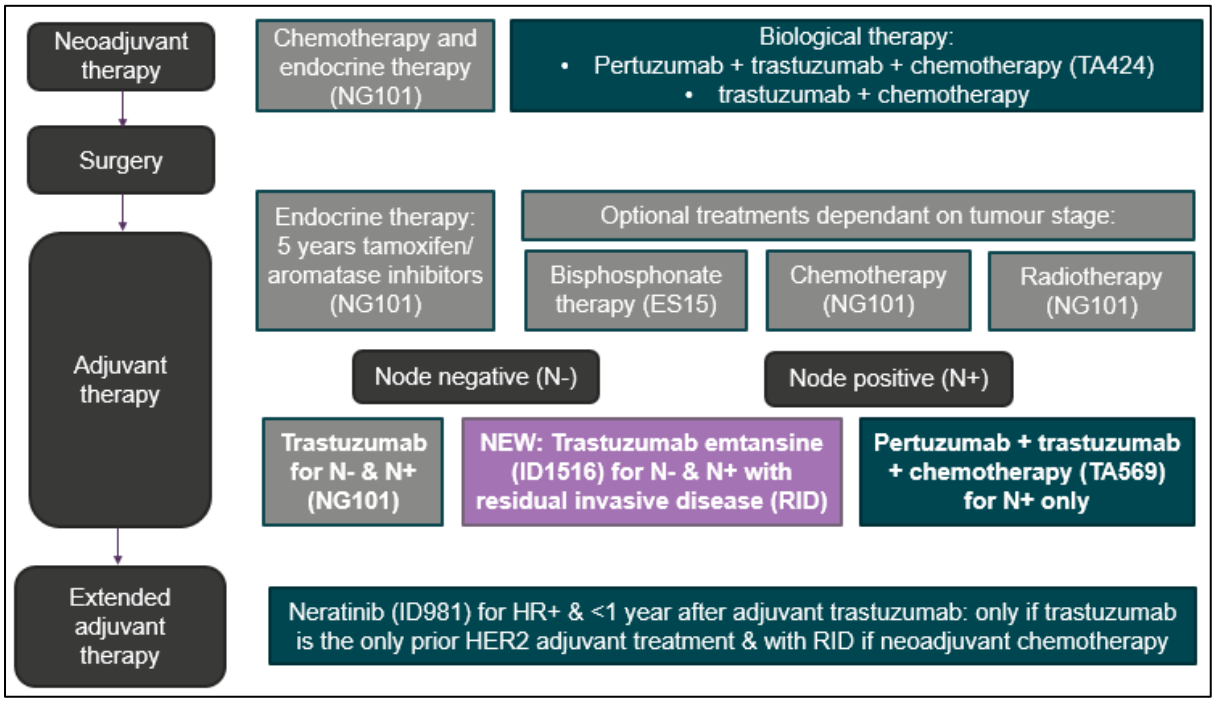
1. Topic background

1.1 Disease background: HER2-positive early breast cancer

- Breast cancer is the most common cancer in the UK among women.
- Is described as 'early' if it is restricted to the breast, or the breast and nearby lymph nodes, and has not spread to other parts of the body
- Human epidermal growth factor receptor 2 (HER2) is a receptor for a growth factor which occurs naturally in the body. Breast cancer cells with higher than normal level of HER2 receptors are HER2-positive.
- In 2016 in England, around 45,960 people were diagnosed with breast cancer. Approximately 15-25% of people will have HER2-positive tumours.
- People with detectable invasive tumour (without pathological complete response; PCR) after neoadjuvant therapy have residual invasive disease (RID).
- The company estimated that 3,113 people are treated neoadjuvantly in England:
  - 809 (26%) have node-negative disease and 227 (28%) have RID
  - 2,304 (74%) have node-positive disease and 783 (34%) have RID

1.2 Treatment pathway: HER2-positive early breast cancer



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1.3 KATHERINE: baseline characteristics

	ITT		Node negative		Node positive	
	T (n=743)	TE (n= 743)	T (n=397)	TE (n= 400)	T (n=346)	TE (n= 343)
Median age (range)	49 (23–80)	49 (24–79)	48 (23–80)	49 (24–73)	49 (27–78)	49 (25–79)
Female, n (%)	740 (99.6%)	741 (99.7%)	394 (99.2%)	399 (99.8%)	346 (100.0%)	342 (99.7%)
Mean weight (SD)	71.19 (15.67)	70.64 (14.64)	70.36 (15.05)	69.74 (14.38)	72.16 (16.32)	71.70 (14.89)
HR-positive	540 (72.7%)	534 (71.9%)	296 (74.6%)	293 (73.3%)	244 (70.5%)	241 (70.3%)
Tumour stage T4 At diagnosis At surgery	88 (11.8%) 10 (1.3%)	102 (13.7%) 12 (1.6%)	32 (8%) 1 (0.3%)	41 (10.3) 2 (0.5%)	56 (16.2%) 9 (2.6%)	61 (17.8%) 10 (2.9%)
Neoadjuvant T	596 (80.2%)	600 (80.8%)	319 (80.4%)	323 (80.8%)	277 (80.1%)	277 (80.8%)
Neoadjuvant pertuzumab plus trastuzumab	139 (18.7%)	133 (17.9%)	72 (18.1%)	69 (17.3%)	67 (19.4%)	64 (18.7%)
Prior Anthracycline	564 (75.9%)	579 (77.9%)	311 (78.3%)	318 (79.5%)	253 (73.1%)	261 (76.1%)
North America	164 (22.1%)	170 (22.9%)	83 (20.9%)	78 (19.5%)	81 (23.4%)	92 (26.8%)
Western Europe	403 (54.2%)	403 (54.2%)	235 (59.2%)	243 (60.8%)	168 (48.6%)	160 (46.6%)
Rest of the world	176 (23.7%)	170 (22.9%)	79 (19.9%)	79 (19.8%)	97 (28.0%)	91 (26.5%)
ECOG 0, n (%)	613 (82.5%)	597 (80.3%)	330 (83.1%)	328 (82.0%)	283 (81.8%)	269 (78.4%)

Key: P + T, pertuzumab +trastuzumab; T, trastuzumab; TE, trastuzumab emtansine.

1.4 KATHERINE: key results

	ITT		Node negative		Node positive	
	T (n=743)	TE (n= 743)	T (n=397)	TE (n= 400)	T (n=346)	TE (n= 343)
IDFS, % (n)	22.2 (165)	12.2 (91)	15.6 (62)	7.3 (29)	NR	NR
- HR (95%CI)	**0.50 (0.39 to 0.64)**		**0.44 (0.28 to 0.68)**		**0.52 (0.38 to 0.71)**	
DFS, % (n)	22.5 (167)	13.2 (98)	16.1 (64)	8 (32)	NR	NR
- HR (95%CI)	**0.53 (0.41 to 0.68)**		**0.47 (0.31 to 0.72)**		**NR**	
OS, % (n)	7.5 (56)	5.7 (42)	4.0 (16)	3.3 (13)	NR	NR
- HR (95%CI)	0.70 (0.47 to 1.05)		0.79 (0.38 to 1.63)		NR	

Key: DFS, disease-free survival; IDFS, invasive disease-free survival; OS, overall survival; T, trastuzumab; TE, trastuzumab emtansine.

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1.5 **Indirect comparison in the node positive population: baseline**

	KATHERINE node-positive		APHINITY node-positive	
	T (n=346)	TE (n= 343)	P+T (n=1,503)	T+PBO (n= 1,503)
Median age (range)	49 (27–78)	49 (25–79)	51 (21-86)	51 (19-85)
Female, n (%)	346(100.0%)	342 (99.7%)	1501 (99.9%)	1496 (99.6%)
Mean weight (SD)	72.16 (16.32)	71.70 (14.89)	67.3 (15.0)	68.1 (15.3)
HR-positive	244 (70.5%)	241 (70.3%)	947 (63.0%)	965 (64.2%)
American Indian[b] or Alaska Native	30 (8.7%)	19 (5.5)	--	--
Asian	31 (9.0%)	33 (9.6)	390 (26.0%)	393 (26.2%)
Black or African American	14 (4.0%)	10 (2.9)	21 (1.4%)	24 (1.6%)
White	241 (69.7%)	248 (72.3)	1045 (69.7%)	1041 (69.4%)
Multiple/Unknown/Other	30 (8.7%)	33 (9.6)	44 (2.9%)	43 (2.9%)

Key: P + T, pertuzumab + trastuzumab; PBO, placebo; T, trastuzumab; TE, trastuzumab emtansine.

1.6 **Indirect comparison results in the node positive population: results from analyses using the node positive populations from KATHERINE and APHINITY as used in the company's base case**

Outcome	APHINITY (P+T vs T)	KATHERINE (TE vs T)	ITC (TE vs P+T)
	HR (95% CI)	HR (95% CI)	HR (95% CI)
IDFS	0.77 (0.62–0.96)	0.52 (0.38–0.71)	0.68 (0.46–0.99)
DFS	0.77 (0.62-0.95)	0.55 (0.40-0.75)	0.71 (0.49-1.04)
OS	0.85 (0.61-1.18)	0.66 (0.41-1.06)	0.78 (0.43-1.39)

Key: DFS, disease-free survival; IDFS, invasive disease-free survival; OS, overall survival; ITC, indirect treatment comparison, P + T, pertuzumab +trastuzumab; T, trastuzumab; TE, trastuzumab emtansine.

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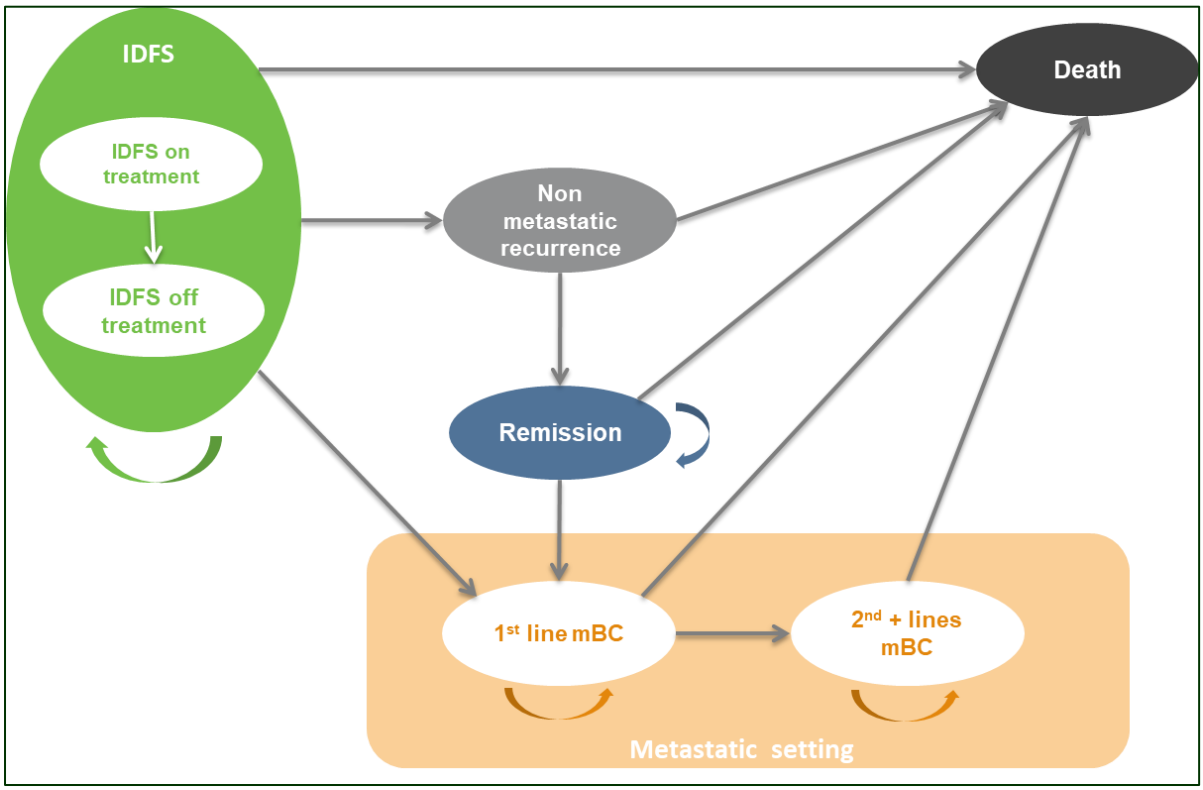
1.7 Model structure



Key: IDFS, invasive disease-free survival; mBC, metastatic breast cancer (see CS Table 54 for more details).

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1.8 Key model assumptions

Area	Assumption
Time horizon	51 years
Clinical inputs	Treatment duration as observed in KATHERINE
	Incremental treatment effect duration (See Issue 5)
	"Cure" proportion assumptions (See Issue 4)
	Fast or early relapse vs late relapse: Patients who experience a recurrence in under 18 months from commencing adjuvant therapy are classed as "Fast relapsers".
	Probability from remission to first-line mBC: Monthly probability of subsequent metastatic recurrence has been derived from Hamilton et al.
	Late relapse probabilities: Slow relapsers are assumed to receive the three most commonly used therapies in the UK: Pertuzumab + trastuzumab + taxane, Trastuzumab + taxane, Chemotherapy.
HRQoL	Pooled utilities across treatment arms
	Utilities for the "non-metastatic recurrence" and "remission" health states have been assumed equal to "IDFS – on chemotherapy" and "IDFS – off treatment", respectively
	AE disutilities are not applied in the model
Costs and resource use	Post-recurrence treatments: Usage of various treatment regimens in the mBC health states has been estimated using market research commissioned by the company.
	Remission health state costs are assumed equal to IDFS (off-treatment): clinically plausible and in line with the methodology used in TA424 and TA569
	Trastuzumab biosimilar vs branded trastuzumab IV use in subsequent therapies: It has been assumed that all IV trastuzumab used in the supportive care setting is biosimilar
	Trastuzumab emtansine usage in first-line mBC – early relapser patients: Supportive care in the first-line mBC – early relapser health state has therefore been stratified according to treatment received in the adjuvant setting. It has been assumed that in the trastuzumab emtansine arm, patients would expect to receive pertuzumab + trastuzumab + chemotherapy instead of trastuzumab emtansine.
	Pertuzumab + trastuzumab + chemotherapy usage in ≥ 2L mBC: Pertuzumab + trastuzumab + chemotherapy is only reimbursed in patients who have not had prior anti-HER2 therapy for their metastatic disease. The market research in 1L mBC showed that a small proportion of generic chemotherapy was being used, therefore there is some usage of pertuzumab + trastuzumab + chemotherapy in the second-line setting. The duration of treatment in this setting has been assumed equal to that of the trastuzumab arm in the trastuzumab emtansine in second-line mBC cost-effectiveness model (TA458).
	Chemotherapy as a subsequent treatment: costed as docetaxel

Key: IDFS, invasive disease-free survival; mBC, metastatic breast cancer.
Notes: see CS Table 54 for more details.

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1.9 **ERG base-case disaggregated discounted QALYs for node-negative population**

QALYs gained	TE	T	Incremental
IDFS	[redacted]	[redacted]	[redacted]
Non-metastatic recurrence	[redacted]	[redacted]	[redacted]
Remission	[redacted]	[redacted]	[redacted]
1st line metastatic	[redacted]	[redacted]	[redacted]
2nd line+ metastatic	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]

Key: T, trastuzumab; TE, trastuzumab emtansine.

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2. Summary of the draft technical report

In summary, the technical team considered the following:

Issue 1 The company used the evidence from the intention to treat (ITT) population of KATHERINE trial in its submission for a comparison of trastuzumab emtansine with trastuzumab. Evidence from the node positive population in the KATHERINE trial was used for a comparison with pertuzumab plus trastuzumab (pertuzumab plus trastuzumab). The ERG considers results from the KATHERINE node negative population to be relevant for a comparison with trastuzumab as node positive patients would usually be given pertuzumab plus trastuzumab.

It is presently unclear whether, and in what circumstances trastuzumab emtansine would be preferred to pertuzumab plus trastuzumab in node positive disease, or whether there is a group of people with node positive disease who would receive trastuzumab as their only HER2 directed therapy and who might benefit from trastuzumab emtansine. If only node-negative disease is likely to be treated with trastuzumab emtansine, then estimates of clinical and cost effectiveness should take into account the fact that these people are at lower risk of disease recurrence than people with node-positive disease.

Issue 2 The company conducted an indirect comparison using evidence from KATHERINE (pre-treated patients) and APHINITY (treatment naïve patients) trials to compare trastuzumab emtansine with pertuzumab plus trastuzumab in the node positive population. The company considered the results of the comparison to be biased and associated with a high degree of uncertainty. The ERG agreed with the company that the results are biased and concluded that they are not suitable for decision making.

The technical team agrees with the ERG and company that the indirect comparisons have potential biases that cannot be addressed but that doesn't necessarily mean that a conclusion on the clinical and

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cost-effectiveness of trastuzumab emtansine in the node-positive population cannot be made.

Issues 3 to 6 focus on the node negative population, but also relate to the ITT, and node positive populations (issue 7 and 8)

Issue 3 Based on long term data from the HERA trial, the company argued the risk of recurrence in the first 3 years in the trastuzumab arm of KATHERINE is not representative of the long-term risk. Therefore, the IDFS extrapolations based on KATHERINE data would overestimate the long-term rate of recurrence. The company decided to model IDFS by breaking down the time horizon of the model into 3 discrete time periods. The ERG agreed with the company's approach, however the ERG used KM curves up to the time point where the last event was observed in each treatment arm (for the node negative population, KM data are available up to 46 months and 49 months for trastuzumab emtansine and trastuzumab respectively) instead of exponential curves extrapolating data in the company's approach for the first period time period.

The technical team agrees with the ERG and prefers to use KM data from the KATHERINE trial for the first period time period. However, it is concerned with the use of a mix of ITT and node negative KATHERINE data to inform the modelling of the node negative population. This concern extends to the use of node-positive evidence from HERA to inform the long-term modelling in the node-negative population, given that the node negative population is at lower risk of recurrence than people with node positive disease.

Issue 4 The company assumed that the trastuzumab emtansine treatment effect was maintained for 7 years, before gradually decreasing to no treatment effect at 10 years. The ERG noted that the treatment effect assumed for the ITT population was applied to the model for the node-negative population and it cannot assess whether this assumption is valid. It agrees with the company that the evidence suggests a treatment effect duration beyond the KATHERINE follow-up time. Based on the available data, the ERG assumed that treatment effect waning starts at year 3 and stops at year 8.

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The technical team agrees with the ERG's approach but would like to know if it is appropriate to assume that treatment effect based on the ITT population can be applied to the node negative population. In addition, it would like to see a scenario analysis assuming that treatment effect waning starts at year 4 and stops at year 7 based on assumptions in TA569.

Issue 5 No significant difference was found in the EQ-5D-3L data between both arms of the KATHERINE trial. The company therefore pooled utilities from the ITT population in both arms for IDFS. Utility values from Lloyd et al. were used for first and subsequent line metastatic recurrences. The ERG considered utilities per arm to be more appropriate as this does not assume that the impact of adverse effects between the two treatments is zero. It also considered Lidgren et al. utilities for first and subsequent lines of metastatic recurrence to be more appropriate as the Lloyd et al. study does not reflect the NICE reference case.

The technical team agrees with the ERG, that the utilities from the KATHERINE trial calculated per treatment for IDFS, and Lidgren et al. 2007 utilities for metastatic states are more appropriate.

Issue 6 The company:

- assumed trastuzumab and trastuzumab emtansine patients receive different treatments in the early recurrence, first line metastatic state,
- assumed that most (95%) people, who are treated with trastuzumab as the only HER2-directed adjuvant therapy, would be given subcutaneous trastuzumab, and 5% would be given intravenous trastuzumab biosimilar,
- assumed all people treated with pertuzumab plus trastuzumab are given intravenous trastuzumab biosimilar,
- based models' patient's characteristic on KATHERINE data (demographic parameters were pooled across treatment arms), and
- vial sharing was not assumed in the model.

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The ERG explored these assumptions and noted that the mean weight of 70.05 kg in the node-negative KATHERINE population happened to be well aligned with the trastuzumab emtansine vial sizes. However, an increment of 2.5 kg to the mean weight would result in a large increase of incremental cost-effectiveness ratio (ICER) estimates as more vials would be needed, but not "fully" used.

The technical team would like clinical opinion on the drug and cost modelling assumptions above so these can be correctly incorporated in the model.

Issue 7 The company's submission focused on the ITT population for a comparison of trastuzumab emtansine with trastuzumab. The ERG's report focused on the node negative population for a comparison of trastuzumab emtansine with trastuzumab (Issue 1). The ERG raised the same issues (issues 3-6) for all populations.

Similarly to the node-negative population, the technical team accepted the ERG's changes to modelling in the ITT population.

Issue 8 The company submitted results for the node positive population because of the limitation of the indirect treatment comparison of trastuzumab emtansine with pertuzumab plus trastuzumab (Issue 2). It applied the IDFS hazard ratio of trastuzumab emtansine versus pertuzumab plus trastuzumab of 0.68 from the indirect comparison using the node positive data to the ITT KATHERINE IDFS data in the model. The ERG explained that the estimated IDFS data are not based on the node positive population and are therefore incorrect. IDFS data for the node positive population are not available in the company's model.

The technical team agrees with the ERG that the current version of the model is not appropriate for decision making for the comparison of trastuzumab emtansine with pertuzumab plus trastuzumab, however it is aware that the available evidence is very limited. It would like to see the model updated using the node positive IDFS data from KATHERINE and the technical team's preferred assumptions (Issues 2-6). In addition, a scenario analysis using indirect comparison results with ITT KATHERINE and APHINITY data is requested.

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1.10 The technical team recognised that the following uncertainties would remain in the analyses and could not be resolved:

- The ERG identified a number of issues with the company's systematic reviews. Studies relevant to the model were missed and studies not identified in the reviews informed the model.
- No adjustment was done in KATHERINE for treatment switching, although 71 patients (<10%) who discontinued trastuzumab emtansine switched to trastuzumab. The model assumed that only trastuzumab emtansine was used in the intervention arm.
- In KATHERINE, 14.3% of patients receiving trastuzumab emtansine had their dose reduced. However, the model did not include dose reductions.
- The model did not include chemotherapy as a part of adjuvant pertuzumab plus trastuzumab, because it was assumed that generic chemotherapy would have already been received in the neoadjuvant setting.
- Some data from the ITT population in KATHERINE were used in the model for the node negative population and this makes the cost-effectiveness results comparing trastuzumab emtansine with trastuzumab uncertain.

1.11 The cost-effectiveness results include commercial arrangements for trastuzumab emtansine, pertuzumab plus trastuzumab (Herceptin). Both the ERG's and company's results also included an assumed discount for trastuzumab biosimilars of 70%.

1.12 Taking these aspects into account, the assumptions summarised in Table 1a, result in an incremental cost-effectiveness ratio (ICER) of £9,339 per QALY gained for a comparison of trastuzumab emtansine with trastuzumab using the node negative population from KATHERINE trial (Table 1a). However, some data from the ITT population in KATHERINE were used in the model for the node negative population and this makes the cost-effectiveness results comparing trastuzumab emtansine with trastuzumab uncertain. Using the ITT population, and applying the same assumptions as for the node negative population (Table 1a) result in an incremental cost-effectiveness ratio (ICER) of £7,648 per QALY gained for a comparison of trastuzumab emtansine with trastuzumab (Table 1b). These estimates do not include the commercial arrangements for the trastuzumab biosimilars because these are confidential and cannot be reported

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here. Estimates that included these commercial arrangements would be higher than those reported above.

No ICER is presented by the ERG and technical team for a comparison of trastuzumab emtansine with pertuzumab plus trastuzumab because the analyses are not suitable for decision making. The technical team is asking the company to update their analyses for the comparison with pertuzumab plus trastuzumab.

1.13 No equality issues were identified.

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3. Key issues for consideration

Issue 1 – Treatment pathway

Background/description of issue	The disease background and the treatment pathway for HER2-positive early breast cancer are summarised in section 1.1 and 1.2 respectively. KATHERINE, an open-label, randomised, multicentre trial that assessed the efficacy and safety of adjuvant trastuzumab emtansine (n=743) compared with adjuvant intravenous trastuzumab (n=743) in patients with HER2-positive early breast cancer (EBC) who had residual invasive disease (RID) in the breast and/or axillary lymph nodes at surgery, following neoadjuvant chemotherapy and trastuzumab is the key trial in this appraisal. The trial was designed to detect a HR of 0.75 in IDFS (a 6.5% improvement in 3-year IDFS from 70% in the trastuzumab arm to 76.5% in the trastuzumab emtansine arm) in the ITT population. The scope defined the comparators as: • Standard adjuvant therapies including trastuzumab, as this is an option for patients with node negative and node positive disease For people with node-positive disease there is also the option of • Pertuzumab in combination with trastuzumab and chemotherapy (pertuzumab plus trastuzumab; TA569) **The company** used the evidence from the intention to treat (ITT) population of KATHERINE trial in its submission for a comparison with trastuzumab. Evidence from the node positive population in the KATHERINE trial was used for a comparison with pertuzumab plus trastuzumab. **The ERG** asked the company to provide results for a subgroup of people with node negative disease in KATHERINE. It considers results from the KATHERINE node negative population to be relevant for a comparison with trastuzumab. The ERG agrees with the company that pertuzumab plus trastuzumab is the relevant comparator for the node positive population and that the evidence from the node positive population in KATHERINE trial should be used for this comparison. **The technical team** is unsure whether any node positive patients currently receive trastuzumab monotherapy in this place in the pathway, given the pertuzumab plus trastuzumab recommendation for this group. While the results from the ITT population provided the most robust estimate of the relative effectiveness of trastuzumab emtansine and trastuzumab, it is unclear how relevant these results are to the population with node

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	positive disease. People with node positive disease have the option of pertuzumab plus trastuzumab, and it is unclear whether trastuzumab alone remains an important option in this group. If only people with node negative disease would receive trastuzumab emtansine, then any estimation of the clinical and cost-effectiveness of trastuzumab emtansine relative to trastuzumab should take into account the fact that these people are at lower risk of disease recurrence than people with node-positive disease.
Why this issue is important	It is important to make appropriate estimates of effectiveness for the relevant populations versus the correct comparators.
Technical team preliminary judgement and rationale	It is presently unclear whether, and in what circumstances trastuzumab emtansine would be preferred to pertuzumab plus trastuzumab in node positive disease, or whether there is a group of people with node positive disease who would receive trastuzumab as their only HER2 directed therapy and who might benefit from trastuzumab emtansine. If only node-negative disease is likely to be treated with trastuzumab emtansine, then estimates of clinical and cost effectiveness should take into account the risk of recurrence specific to this group.
Questions for engagement	1 a. Is there any reason to prefer trastuzumab emtansine over pertuzumab plus trastuzumab in node positive disease? 1 b. In clinical practice, do patients with node positive disease only receive pertuzumab plus trastuzumab or are there some people with node positive disease who would receive trastuzumab monotherapy?

Issue 2 – Indirect comparison: trastuzumab emtansine versus pertuzumab plus trastuzumab

Background/description of issue	No study compared trastuzumab emtansine with pertuzumab plus trastuzumab. **The company** conducted an indirect comparison using evidence from KATHERINE and APHINITY trials. KATHERINE (n=1,486) compared trastuzumab emtansine with trastuzumab in people with HER2-positive EBC who had residual invasive disease following neoadjuvant chemotherapy. Approximately 80% of people received trastuzumab monotherapy and approximately 18% of people had pertuzumab plus trastuzumab as their neoadjuvant therapy. APHINITY (n=4,804) compared pertuzumab plus trastuzumab with trastuzumab + placebo in people who were not previously treated for EBC.

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Section 1.6 summarises the baseline characteristics of the node positive populations of KATHERINE and APHINITY trials. The results from the comparison are presented in section 1.7 and Table B, C and D.

Table A Indirect treatment comparison in the node positive population: results

Outcome	APHINITY (P+T vs T) node positive	KATHERINE (TE vs T) node positive	ITC (TE vs P+T)
	HR (95% CI)	HR (95% CI)	HR (95% CI)
IDFS	0.77 (0.62–0.96)	0.52 (0.38–0.71)	**0.68 (0.46–0.99)**
DFS	0.77 (0.62-0.95)	0.55 (0.40-0.75)	0.71 (0.49-1.04)
OS	0.85 (0.61-1.18)	0.66 (0.41-1.06)	0.78 (0.43-1.39)

Key: DFS, disease-free survival; IDFS, invasive disease-free survival; OS, overall survival; P+T, pertuzumab + trastuzumab; T, trastuzumab; TE, trastuzumab emtansine.
Source: Response to clarification Qs A21 and Table 37 in Appendix M of the CS and Table 5.8 ERG report.

Table B Indirect treatment comparison in the node positive population for APHINITY and the ITT population from KATHERINE: results

Outcome	APHINITY (P+T vs T) node positive	KATHERINE (TE vs T) ITT	ITC (TE vs P+T)
	HR (95% CI)	HR (95% CI)	HR (95% CI)
IDFS	0.77 (0.62–0.96)	0.50 (0.39–0.64)	**0.649 (0.467–0.904)**
DFS	0.77 (0.62-0.95)	0.53 (0.41-0.68)	**0.69 (0.49-0.96)**
OS	0.85 (0.61-1.18)	0.70 (0.47-1.05)	0.82 (0.49-1.39)

Key: DFS, disease-free survival; IDFS, invasive disease-free survival; OS, overall survival; P+T, pertuzumab + trastuzumab; T, trastuzumab; TE, trastuzumab emtansine.
Source: Response to clarification Qs A21 and Table 37 in Appendix M of the CS and Table 5.8 ERG report.

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Table C Indirect treatment comparison in ITT population: results

Outcome	APHINITY (P+T vs T) ITT	KATHERINE (TE vs T) ITT	ITC (TE vs P+T)
	HR (95% CI)	HR (95% CI)	HR (95% CI)
IDFS	0.81 (0.67–1.00)	0.50 (0.39–0.64)	**0.617 (0.449–0.849)**
DFS	0.82 (0.68-0.99)	0.53 (0.41-0.68)	**0.65 (0.47-0.89)**
OS	0.91 (0.67-1.23)	0.70 (0.47-1.05)	0.77 (0.46-1.27)

Key: DFS, disease-free survival; IDFS, invasive disease-free survival; OS, overall survival; P+T, pertuzumab + trastuzumab; T, trastuzumab; TE, trastuzumab emtansine.
Source: Response to clarification Qs A21 and Table 37 in Appendix M of the CS and Table 5.8 ERG report.

Results from analyses using the node positive populations from KATHERINE and APHINITY were used in the company's base case (Table B). The company also provided analyses with the combination of ITT (from KATHERINE) and node-positive population (from APHINITY) and ITT from both trials as scenario analyses (Table C and D). The company considered the indirect analyses made using the Bucher method to be a naïve comparison referring to the fact that the comparison has been conducted despite the considerable differences in the KATHERINE and APHINITY trials' populations. No attempts were made to adjust for the differences. This means that any results from the analyses are likely to be associated with a high degree of uncertainty.

The ERG agreed with the company that because KATHERINE included pre-treated patients who had residual invasive disease and APHINTY included treatment naïve patients, all the ITC results are potentially biased. It concluded that it is unclear in what direction or to what extent there is a bias. The ERG also agreed with the company and considered the comparison using node-positive populations from both trials to be the most appropriate. The IDFS results, comparing the node positive populations, showed a statistically significant difference suggesting an improved IDFS with trastuzumab emtansine over pertuzumab plus trastuzumab (Table B).

The ERG asked the company to conduct a comparison using individual participant data meta-regression during clarification. The company explained that it is not possible to do this in a robust way as the lack of clinical

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	comparability of the trials' covariates and the populations is likely to lead to uninterpretable and biased results which are not informative or useful. The ERG considers that the company could have attempted to demonstrate the clinical comparability of these trials, for instance by comparing the outcomes of trastuzumab arms of both trials (the difference in these outcomes could be partially attributed to the differences in the observed trial/population characteristics) and noted that non-randomised evidence was not explored by the company. The ERG concluded, that although the indirect comparison was conducted correctly, because the populations in the two trials used are not comparable, the results of the comparison are not suitable for decision making.
Why this issue is important	To estimate the cost-effectiveness of trastuzumab emtansine compared with pertuzumab plus trastuzumab, it is important to have a reliable estimate of its clinical effectiveness.
Technical team preliminary judgement and rationale	The technical team agrees with the ERG and company that the indirect comparisons are affected by unknown variables that cannot be adjusted for. But that doesn't necessarily mean that the results of the cost-effectiveness analyses based on those results are meaningless, or that no decision can be made. With proper exploration of the uncertainty around the relative treatment effects, it may be possible to reassure the committee that trastuzumab emtansine is likely to be a cost-effective option in the node-positive population.
Questions for engagement	2 a. Are the results of the indirect treatment comparison of trastuzumab emtansine versus pertuzumab plus trastuzumab, using the node-positive populations from APHINITY and KATHERINE trials, clinically plausible? 2 b. Are there any other data that could be used to for the comparison of trastuzumab emtansine versus pertuzumab plus trastuzumab? 2 c. How should the uncertainty about the relative treatment effects of trastuzumab emtansine and pertuzumab plus trastuzumab be explored. Would a cost comparison be useful?

Issue 3 – IDFS extrapolation

Background/description of issue	This issue applies equally to the modelling of the ITT and node-positive populations (discussed in issue 7 and 8) but here the focus is on the node negative population. Section 1.8 summarises the model structure and section 1.9 summarises the key assumptions.

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	The company explained that the same model structure was used in TA569, the technology appraisal of pertuzumab for the adjuvant treatment of HER2-positive early stage breast cancer. The company's submission focused on the ITT population and results for the node negative population were submitted in response to clarification questions. At the time of the primary analysis (data cut-off 25 July 2018), 91 (12.2%) and 165 (22.2%) IDFS events had occurred in the ITT population of trastuzumab emtansine and trastuzumab arms, respectively. After clarification, the company extrapolated IDFS using patient data in the KATHERINE node-negative population. At the time of the primary analysis (data cut-off 25 July 2018), 29 (7.25%) and 62 (15.62%) IDFS events had occurred in the node-negative population of trastuzumab emtansine and trastuzumab arms, respectively. To produce valid long-term outcomes, parametric survival curves were adjusted using data from HERA and BCIRG 006 trials to produce a more clinically plausible extrapolation. The HERA study (n=5.099) was a randomised, open-label, multicentre, trial investigating the efficacy of trastuzumab over 1 and 2 years after standard neoadjuvant chemotherapy, adjuvant chemotherapy, or both, in patients with HER2-positive EBC; the primary outcome was DFS (as opposed to IDFS in KATHERINE). It has approximately 11 years follow-up data. The BCIRG 006 study (n=3,222) was a randomised trial where patients with node-positive or high-risk node-negative EBC were enrolled; primary outcome was DFS at 5 years. The treatments compared were anthracycline chemotherapy (doxorubicin + cyclophosphamide followed by docetaxel) with or without trastuzumab, and chemotherapy without anthracyclines (docetaxel + carboplatin) with trastuzumab; it has approximately 10 years follow-up data. It was assumed that the node-positive populations in BCIRG 006 and HERA were a proxy for the KATHERINE ITT population. Node positive populations were chosen because the ITT populations from the 2 studies have a far better prognosis than patients included in KATHERINE. The company believed that the node-positive populations in these trials represent a higher risk population and that they are a more appropriate proxy to the ITT population in KATHERINE. An analysis using the ITT population in KATHERINE was the company's preferred base case and results for the node-negative population were provided during clarification. The long-term modelling adjustments used for the ITT KATHERINE population, based on the node-positive evidence from HERA, were incorporated into modelling in the node-negative population. **The company** explained that based on HERA data (ERG report figure 5.2; Company submission figure 19), the risk of recurrence for EBC patients in the first 3 years is not representative of the long-term. Therefore, the

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	extrapolations based on KATHERINE data would overestimate the long-term rate of recurrence. It decided to model IDFS by breaking down the time horizon of the model into 3 discrete time periods. 1. **Time period 1: 0 to 3 years, KATHERINE data.** The company used a stratified approach as it did not consider that the proportional hazards assumption was conclusively met and chose an exponential distribution to model IDFS in both treatment arms. 2. **Time period 2: 3 to 10 years, IDFS curves adjusted based on long-term external data on trastuzumab (comparator arm).** The recurrence rate was high in HERA and BCIRG 006, decreased sharply after 36 months, and stabilised at approximately 120 months (ERG report figure 5.5; Figure 2 in clarification response). Patients are assumed to be "cured", meaning that patients are no longer at risk of recurrence and are only subject to background mortality. The proportion of patients being "cured" linearly increased with time from 0% at 36 months to 95% at 120 months. The company noted that the same approach was used in TA569. Exponential curves for trastuzumab emtansine and trastuzumab were adjusted using trastuzumab data from HERA and BCIRG 006. The long-term modelling adjustments used for ITT KATHERINE population, based on node-positive evidence from HERA, were incorporated into the modelling in the node-negation population. Figure 1 shows the adjusted and unadjusted company's curves in the in the KATHERINE ITT population.

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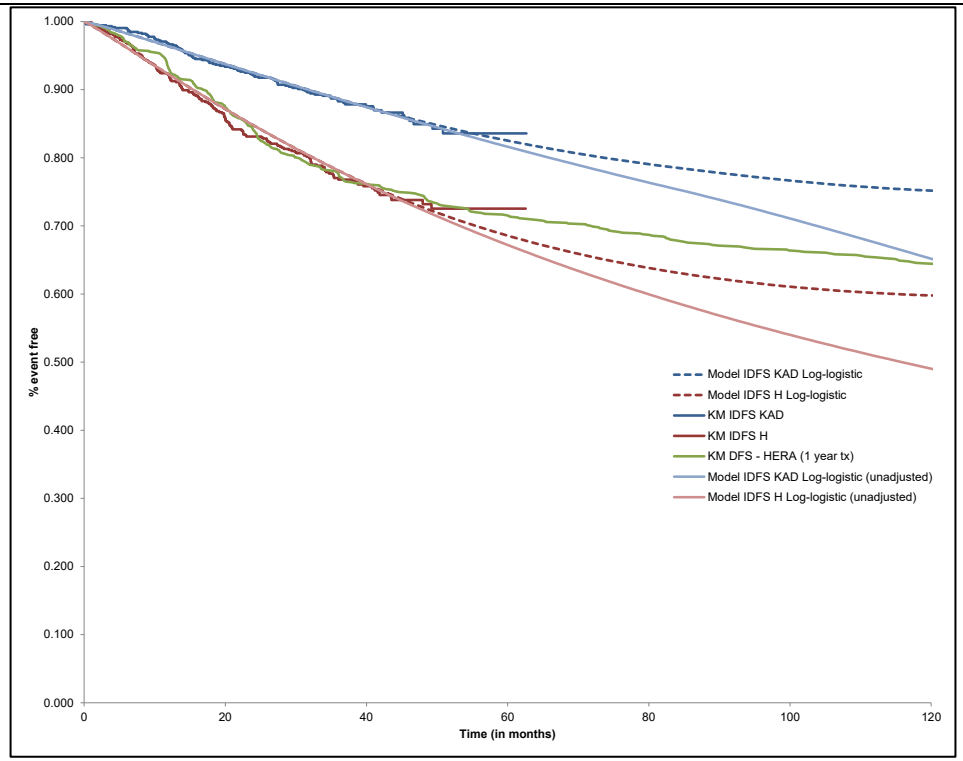

Figure 1 Unadjusted and adjusted company's IDFS extrapolation using ITT KATHERINE data and 10-year KM curve from the node-positive HERA population

Key: H, trastuzumab; KAD, trastuzumab emtansine. **Notes**: The company assumed that node-positive HERA KM data was a proxy for the KATHERINE ITT population. Blue line = KM TE; red line = KM pertuzumab plus trastuzumab; blue dashed line = adjusted approach TE; red dashed line = adjusted approach T; green line + KM HERA; light blue line = unadjusted approach TE; light pink line = unadjusted approach T. **Source**: ERG report figure 5.4.

Figure 2 shows the adjusted and unadjusted company's curves in the in the KATHERINE node negative population.

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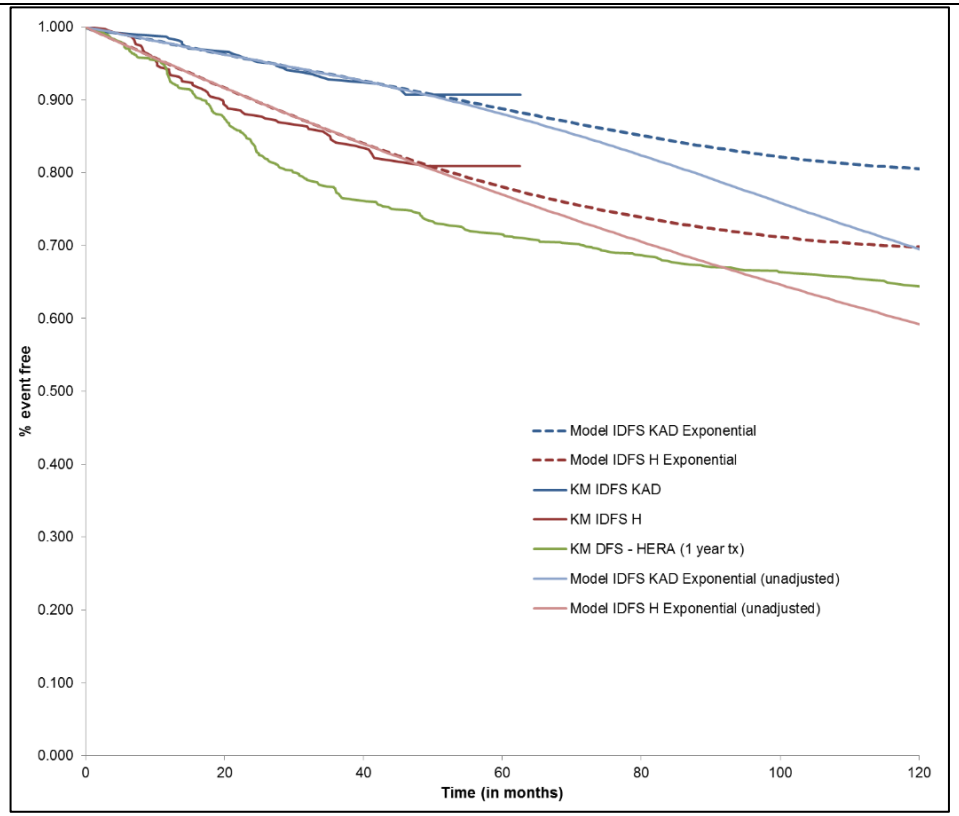

Figure 2 Unadjusted and adjusted company's IDFS extrapolation using node-negative KATHERINE data and 10-year KM curve from the node-positive HERA population

Key: H, trastuzumab; KAD, trastuzumab emtansine. **Notes**: The company assumed that node-positive HERA KM data was a proxy for the KATHERINE ITT population. Thus, using HERA KM data for a comparison with KATHERINE node negative can be misleading (see ERG critique below). Blue line = KM TE; red line = KM pertuzumab plus trastuzumab; blue dashed line = adjusted approach TE; red dashed line = adjusted approach T; green line + KM HERA; light blue line = unadjusted approach TE; light pink line = unadjusted approach T. **Source**: model

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	3. **Time period 3 –10 years until the end of the time horizon: 95% "cured" (background mortality only).** Based on the HERA trial, where the hazard rate observed at year 11 was similar to the hazard rate of the general population in the UK for a 65 years old patient, the company assumed that 95% of the patients are only exposed to background mortality after 10 years. **The ERG** agrees that stratified models are appropriate. However, it chose a different approach to modelling of IDFS: 1. **Time period 1: 0 to 46 months and 49 months for trastuzumab emtansine and trastuzumab respectively, KM KATHERINE data.** KM data are available for trastuzumab emtansine and trastuzumab for 46 months and 49 months respectively in the node negative KATHERINE population and can be used directly to model IDFS. Using KM curves directly, overcomes the potential issue of IDFS overestimation observed between months 10 and 40 for trastuzumab when using exponential curves in the company's approach. The ERG explored the effect of moving the time point when KM are switched to extrapolated data. The earlier the "switch", the lower the ICER (Table 7.7 in ERG report). It used KM data for time period 1 up to the time point where the last event was observed in each treatment arm in its preferred base-case. 2. **Time period 2: IDFS curves adjusted based on long-term external data on trastuzumab (comparator arm).** The ERG noted that data for the node-negative population were limited (for example recurrence rates for the node-negative population were not reported) compared to ITT data and that it made the selection of an appropriate distribution more uncertain. It considered the best fit for node negative data and chose generalised gamma after the use of KM data. However, when the generalised gamma was fitted, it showed HRs that lacked clinical validity and therefore the ERG used an exponential curve, as did the company. It noted that this further highlights the difficulty in choosing the correct extrapolation curve in this population. It critiqued the use of node-positive populations in HERA and BCIRG 006. This assumption seemed plausible when used with the ITT KATHERINE data (although it remains uncertain whether the two populations are really comparable). It is more uncertain to what extent the node-positive populations in BCIRG 006 and HERA are an appropriate proxy to the KATHERINE node-negative population. The company based the "cure" parameter on TA569. The ERG considers that this does not necessarily imply that the same approach is valid here. However, since there is no alternative evidence, the ERG decided to accept the company's approach. In response to the clarification questions the company conducted several

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scenario analyses changing the start and end point of the “cure” in the model. The results of these analyses indicated that the impact on the ICER was minor. This is because “cure” is applied equivalently across both arms of the model.

3. **Time period 3 –10 years until the end of the time horizon: 95% “cured” (background mortality only)**

Empirical data pertaining to this time period does not exist in this indication. This makes it difficult to validate the IDFS curves beyond the 10-year time point. The ERG accepted the company’s approach. Figure 3 compares the 2 approaches overall.

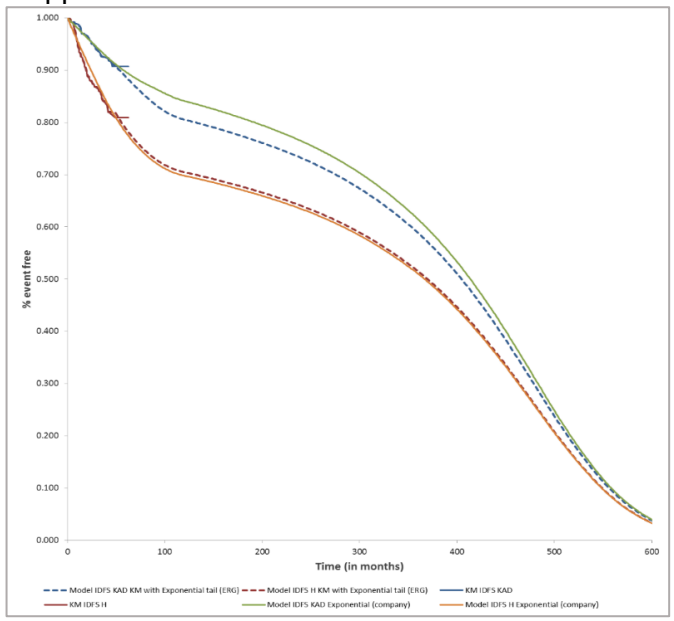

Figure 3. Company’s and ERG's approach to modelling IDFS modelling (node negative KATHERINE data)
Key: Blue line = KM TE; red line = KM pertuzumab plus trastuzumab; blue dashed line = ERG’s approach TE; red dashed line = ERG’s approach T; green line = company’s approach TE; orange line = company’s approach T. **Source:** ERG report figure 5.14.

Treatment effect is discussed separately in Issue 4.

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	The technical team agrees with the ERG and prefers to use KM data from the KATHERINE node negative population for time period 1, up to the time point where the last event was observed in each treatment arm. However, it is concerned with the use of a mix of ITT and node-negative KATHERINE data to inform the modelling of the node negative population. This concern extends to the use of the node-positive evidence from HERA to inform the long-term modelling in the node-negative population. The technical team notes that modelling in the ITT population (Issue 7) only used ITT KATHERINE data.
Why this issue is important	To estimate the cost-effectiveness of trastuzumab emtansine, it is important to have a reliable estimate of long-term clinical effectiveness. The choice of IDFS modelling has a large effect on cost-effectiveness results (Table 1).
Technical team preliminary judgement and rationale	The technical team prefers the ERG's approach to IDFS modelling for time period 1 as it uses KM data directly to model IDFS for trastuzumab emtansine and trastuzumab instead of using exponential curves which overcomes the potential issue of IDFS overestimation.
Questions for engagement	3 a. Which approach to IDFS modelling, the ERG's or the company's, is more clinically plausible? 3 b. Is it appropriate to use evidence from the intention to treat population in KATHERINE trial and the node-positive population in HERA trial to adjust modelling in the node negative population?

Issue 4 – Treatment waning effect of trastuzumab emtansine

Background/description of issue	This issue applies equally to the modelling of the ITT and node-positive populations (discussed in issue 7 and 8) but here the focus is on the node negative population. The type and duration of the treatment effect was only reported in detail for the ITT population. Therefore, this section is related to the ITT population, but the conclusions from the ITT population were applied to the company's and ERG's preferred base-case for the node-negative population. **Comparison of treatment effects in NICE appraisals:** TA107 - trastuzumab for the adjuvant treatment of early-stage HER2-positive breast cancer • Effect maintained for ten years. Two-thirds of this benefit is seen until year 45. TA424 - pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer

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- No waning. Treatment effect set equal after seven years.

TA569 - pertuzumab for adjuvant treatment of HER2-positive early stage breast cancer

- Effect maintained for four years before waning to null at seven years.

TA612 - neratinib for treating early hormone receptor-positive, HER2-positive breast cancer after adjuvant trastuzumab

- Tapering of treatment effect for 6.4 years.

The company assumed that the trastuzumab emtansine treatment effect was maintained for 7 years, before gradually decreasing to no treatment effect at 10 years (figure 4). The assumption of treatment effect beyond the KATHERINE follow-up time was based on HERA and BCIRG 006 trials. The HRs between year 7 and year 10 observed in the HERA and BCIRG 006 trials were 0.803 and 0.801, respectively. This difference in HRs was used to support the presence of a treatment effect between 7 and 10 years after treatment. Compared to TA424, the addition of the waning effect period was justified because patients received 14 cycles of trastuzumab emtansine in the adjuvant setting, as opposed to 4-6 cycles in the neoadjuvant setting. This treatment effect is in line with company's base-case in TA569 (although this was not accepted by committee in TA569).

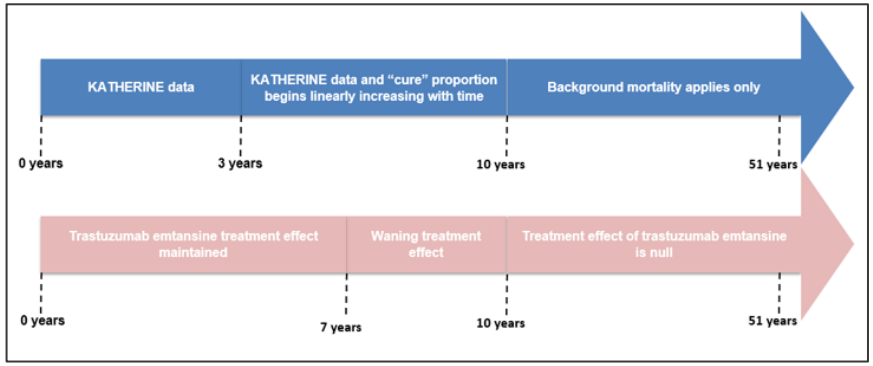

Figure 4 Construction of IDFS curves and timing of treatment effect

Key: Figure 5.12 ERG report, figure 5 clarification questions appendix.
Note: Time period 1 (0–3 years): KATHERINE data used to estimate recurrence rates. Time period 2 (3–10 years): extrapolated recurrence rate adjusted to reflect the trend observed in long-term trastuzumab studies. Time period 3 (10–51

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	years): 95% of patients are “cured” and no longer at risk of recurrence (only background mortality). Also based on long-term trastuzumab studies. **The ERG** is unable to assess whether the treatment effect assumed for the ITT population is valid for the node-negative population. The ERG noted that the committee for TA569 preferred the ERG’s approach of maintaining treatment effect for 4 years before waning to null at 7 years. The ERG agrees with the company that the evidence suggests a treatment effect duration beyond the KATHERINE follow-up time. It estimated the treatment effect as follows: • **Endpoint point for treatment waning:** Despite the uncertainty associated with the observed hazard rates, these are still the best source of available evidence to inform this aspect of the model. At year 4, the modelled HR was less than 0.6, as opposed to almost 0.85 seen in the trial. This is a considerable difference in favour of trastuzumab emtansine and may indicate that the waning of the treatment effect should end (HR = 1) before year 10. The exact end point was determined by looking at the predicted annual HR assuming a generalised gamma extrapolation (this was the preferred choice for the ERG for the ITT population). It was observed that after 8 years the model predicted a HR above 1, implying thus a better treatment effect for trastuzumab during years 8 to 10. The ERG considered this implausible and set the end point of the treatment effect exactly at 8 years (96 months). • **Starting point for treatment waning:** The starting point of the treatment effect waning (the point where trastuzumab emtansine extrapolation starts to be adjusted) is difficult to assess because there is no evidence to inform this parameter. Based on the HRs observed in KATHERINE, it seems plausible to expect HRs increasing with time. However, with the ERG preferred choice for modelling IDFS this did not happen. By using KM data up to the month where the last event was observed, the exact HRs observed in KATHERINE (up to year 4 in the model) were replicated in the model. However, from year 5 onwards, the HRs were based on the IDFS extrapolation and, with the generalised gamma, the HR dropped at year 5 and started to increase again after that. To minimise the impact of this drop, the ERG chose the 36 months as the starting point for the treatment effect waning. The ERG acknowledges the uncertainty around the choice of these parameters and assessed the impact on the results with scenario analyses (Table 7.8 and 7.9 in ERG report). Decreasing the treatment effect duration increases the ICERs. **The technical team** prefers the ERG’s approach because it utilised the data collected in KATHERINE trial, albeit recognising the uncertainty with it, to the company’s but would like to know if it is appropriate to assume that the type and duration of treatment effect for the ITT population is the same as in the node negative population.

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Why this issue is important	To estimate the cost-effectiveness of trastuzumab emtansine, it is important to have a reliable estimate of a treatment effect duration. The assumptions around the treatment effect have a large effect on the cost-effectiveness results (Table 1a).
Technical team preliminary judgement and rationale	The technical team prefers the ERG's approach of starting the waning of trastuzumab emtansine treatment effect at year 3 with the effect stopping at year 8, with the overall treatment effect lasting 8 years, to the company's approach of starting the waning of trastuzumab emtansine treatment effect at year 7 with the effect stopping at year 10, with the overall treatment effect lasting 10 years. Although the technical team is aware that both approaches are uncertain. In addition, because of the recent appraisal of pertuzumab plus trastuzumab, the technical team would like to see a scenario analysis assuming treatment effect maintained for 4 years before waning to null at 7 years.
Questions for engagement	4 a. What approach to treatment effect duration, the ERG's, the company's, or a different one, is the most clinically plausible? 4 b. Would you expect that the duration of treatment effect in the ITT and node-negative populations is the same?

Issue 5 – Utilities

Background/description of issue	This issue applies equally to the modelling of the ITT and node-positive populations (discussed in issue 7 and 8) but here the focus is on the node negative population. **The company** used utility values obtained from the HRQoL data that was collected in the KATHERINE trial, using the EQ-5D-3L for the IDFS state in the model. HRQoL is not expected to be dependent on nodal status, so ITT data were used for the node negative population. No significant difference was found between the EQ-5D results of the two arms, EQ-5D data from each treatment arm was pooled in the base-case, assuming that patients receiving the different treatments have equal utility. Different utilities are applied for IDFS on-treatment and IDFS off-treatment states. HRQoL was not measured in patients who had progressed in the KATHERINE trial. Utility values from Lloyd et al. were used for first and subsequent line metastatic recurrences in the company base case, the reasoning being that this source has been used in previous appraisals. The utilities used in the company model are summarised in table E.

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Table D Utility values considered by the company and the ERG

Heath state	Company Utility (SE) [95%CI]	ERG Utility (SE) [95%CI]
IDFS – On treatment	KATHERINE, pooled: TE&T = 0.775 (0.009)	KATHERINE, per treatment: TE = 0.774 (0.009) T = 0.776 (0.010)
IDFS – Off treatment	KATHERINE, pooled: TE&T = 0.788 (0.010)	KATHERINE, per treatment: TE = 0.784 (0.010) T= 0.791 (0.010)
Non metastatic occurrence	= IDFS on treatment	= IDFS on treatment
Remission	= IDFS off treatment	= IDFS off treatment
Metastatic recurrence 1st line	Lloyd et al: 0.765 (0.004)	Lidgren et al: 0.685 [0.620-0.735]
Metastatic recurrence 2nd line	Lloyd et al: 0.508 (0.004)	Lidgren et al: 0.685 [0.620-0.735]

Key: T, trastuzumab; TE, trastuzumab emtansine.
Source: modified Table 40 company submission, ERG report table 5.19.

The ERG had concerns about the utilities used by the company and used different values in their base case (table E). For the IDFS on and off treatment health states the ERG disagreed with the pooling of the values as the company assumed that the impact of adverse events (AEs) was captured in the EQ-5D data collected. This assumption will mask any differences in the impact of AEs captured by the data, when pooled, which effectively assumes that the incremental impact of AEs between the two treatments is zero. This means that it is inappropriate to assume that the HRQoL of patients is equal across treatment arms. The ERG therefore uses KATHERINE utilities calculated per treatment for IDFS its preferred base-case. The ERG also did not agree with using the Lloyd et al study as the methods that measure and value HRQoL in the Lloyd et al study do not reflect

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	the NICE reference case. In comparison, in Lidgren et al study, HRQoL was measured in patients themselves, using the EQ-5D-3L. The ERG therefore used Lidgren utilities, for first and subsequent lines of metastatic recurrence, in its preferred base-case. **The technical team** agrees with the ERG, that the utilities from the KATHERINE trial calculated per treatment for IDFS, and Lidgren et al. 2007 utilities for metastatic states are more appropriate. It notes that Lidgren et al. 2007 utilities were accepted by committee for TA612.
Why this issue is important	It is important to establish the correct utilities for the calculation of the cost-effectiveness results.
Technical team preliminary judgement and rationale	The technical team applied utilities used by the ERG in their base case.
Questions for engagement	5 a. Is it appropriate to use the per treatment calculated utility from KATHERINE trial for the IDFS state to take account of the difference in AEs? 5 b. Are the utilities from Lidgren et al. 2007 more clinically plausible than the Lloyd utilities for the 2 metastatic states in the model?

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Issue 6 – Drug costs and modelling assumptions

Background/description of issue

Market share and drugs used in the early recurrence

The company assumed that trastuzumab and trastuzumab emtansine patients receive different treatments in the early recurrence, first line metastatic state (Table F). Only in the early recurrence, first line metastatic breast cancer state, arm-specific market shares were assumed.

Table E Market share and drugs used in the early recurrence, first line metastatic state

Treatment regimen	% market share TE	% market share for T
Pertuzumab + trastuzumab biosimilar IV + docetaxel	**75%**	0%
Trastuzumab biosimilar IV + docetaxel	4%	4%
Trastuzumab branded SC + docetaxel	13%	13%
Trastuzumab emtansine	0%	**75%**
Docetaxel IV	8%	8%

Key: T, trastuzumab; TE, trastuzumab emtansine.
Source: modified ERG report table 5.23.

The ERG noted that using arm specific market shares incurred more drug acquisition costs in the trastuzumab arm. The ERG could not verify these market shares, therefore it assumed equal market shares in a scenario analysis. Assuming equal market share increased the ERG's preferred ICER to £10,266 (see ERG report Table 7.13).

The technical team would like to know, if the arm specific market shares assumed by the company for early recurrence, first line metastatic state are plausible or if equal (or different values of) market shares should be used in the model.

Dosing modelling assumptions

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The company based models patient's characteristics on the KATHERINE data. Demographic parameters were pooled across treatment arms (Table G). Vial sharing was not assumed and the dose for the node-negative model was based on the average weight in the node-negative KATHERINE population of 70.05 kg.

Table F Baseline characteristics of the patients used in the model

Patient characteristics	ITT population	Node negative population	Node positive population Note: ITT values are used in model for this population
Mean age (years)	49.10	48.85	49.35
Mean body weight (kg)	70.91	70.05	71.93
Mean height (cm)	163.10	163.36	162.78
BSA (m^2)	1.77	1.76	1.77

Key: BSA, body surface area; cm, centimetre; ITT, intention to treat; kg, kilogram.
Note: BSA calculated by Dubois formula. Values for node positive population calculated using data submitted as part of clarification questions by the company (A15).
Source: modified ERG report table 5.6.

The ERG tested a scenario examining the impact of a small increase in cohort weight of 2.5 kg. This was tested because the required doses at the KATHERINE cohort weight of 70.05 kg do not leave much remainder in optimal combinations of current vial sizes. Therefore, a small increase in weight could have a large impact on results if no vial sharing is assumed. Assuming planned dose without vial sharing with the addition of a small cohort weight gain of 2.5 kg increased the ERG's preferred ICER to £13,355 (see ERG report Table 7.12).

The technical team prefers using KATHERINE data for the model, however it notes that increasing the mean weight reported in the trial by 2.5 kg increased the ICER significantly. It further notes that vial sharing was not assumed in the model and if vial sharing was assumed the ERG's preferred ICER would decrease to £8,853 (see ERG report Table 7.12). The technical team would like to know the clinical opinion about the drug and cost modelling assumptions above so these can be correctly incorporated in the model.

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	Trastuzumab **The company** assumed that most (95%) people, who are treated with trastuzumab as the only HER2-directed adjuvant therapy, would be given subcutaneous trastuzumab, and 5% would be given intravenous trastuzumab biosimilar. The company noted that the same assumption was used in TA569. It was assumed that all people treated with pertuzumab plus trastuzumab are given intravenous trastuzumab biosimilar. A range of market shares assumptions were explored in scenario analyses for the ITT and node positive populations. **The ERG** explored changing the assumption around percentage of people having subcutaneous and intravenous trastuzumab. Based on the company's market research sample, only 105 out of 229 people (~46%) had subcutaneous trastuzumab. Assuming subcutaneous and intravenous biosimilar trastuzumab use, based on this research, increased the ERG's preferred ICER to £13,007 (Table 7.13 ERG report). Combining the company's market research shares for subcutaneous trastuzumab and assuming same market shares in the early recurrence (above) increases the ERG's preferred ICER to £13,934 (Table 7.13 ERG report). **The technical team** would like to know, what are the proportions of people who would be given subcutaneous and intravenous trastuzumab biosimilar when given trastuzumab monotherapy, and if only intravenous trastuzumab biosimilar is used in combination with P in the adjuvant setting.
Why this issue is important	The cost inputs and assumptions in the model need to be fit for purpose.
Technical team preliminary judgement and rationale	The technical team, along with the ERG did not include changes in cost assumptions described above in its preferred base case. However, as it has concerns about these assumptions, for completeness Table 1 also includes cost-effectiveness results of the relevant scenarios. The technical teams preferred ICER will be updated following the technical engagement accordingly.
Questions for engagement	6 a. Are the arm specific market shares for trastuzumab and trastuzumab emtansine assumed by the company for early recurrence, first line metastatic state plausible? Or should equal, (or different market share values) be used in the model? 6 b. Approximately what are the proportions of people who would be given either subcutaneous or intravenous trastuzumab biosimilar when given trastuzumab monotherapy in the adjuvant setting? 6 c. Is only intravenous trastuzumab biosimilar used in combination with pertuzumab when given in combination in the adjuvant setting? 6 d. What assumption about patient weight and vial sharing should be adopted in the model?

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Issue 7 – Modelling the intention to treat population

Background/description of issue	Section 1.8 summarises the model structure. **The company's** submission focused on the ITT population for a comparison of trastuzumab emtansine with trastuzumab. **The ERG's** report focused on the node negative population for a comparison of trastuzumab emtansine with trastuzumab (ERG report section 5) and the node negative population was discussed in issue 3-6. Regarding the ITT population, the ERG raised same issues. For example, for IDFS modelling it preferred to use KM date for time period 1 and generalised gamma for period 2, while the company's used stratified log-logistic extrapolation for time period 1 and 2 (ERG report Section 5.2.6.1). Issue 3 discusses IDFS extrapolation in the node-negative population. The ERG did not present ERG's preferred base case for the ITT population. **The technical team** accepted the ERG's changes to modelling in the ITT population as described in Issue 3-6 for the node-negative population.
Why this issue is important	The inputs in the model for the ITT population needs to be fit for purpose.
Technical team preliminary judgement and rationale	Similarly to the node-negative population, the technical team applied the same changes as were used in the node-negative population (summarised in Table 1a and 1b) to the model in the ITT population.
Questions for engagement	7. Is the model for the intention to treat population, with the technical team changes applied, suitable for decision making?

Issue 8 – Modelling the node positive population

Background/description of issue	Section 1.8 summarises the model structure. **The company's** submission focused on the ITT population and results for the node positive population were included in an appendix because of the limitation of the indirect treatment comparison of trastuzumab emtansine with pertuzumab plus trastuzumab (Issue 2). A high degree of uncertainty is associated with the analyses. However, given the absence of head-to-head data comparing trastuzumab emtansine and

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	pertuzumab plus trastuzumab, these analyses were considered the most appropriate for addressing the decision problem in the node positive population. **The ERG** agrees with the company that the indirect comparison of trastuzumab emtansine with pertuzumab plus trastuzumab is very uncertain and concluded that the results are not suitable for decision making (Issue 2). The ERG explained that the company used ITT data to model IDFS in the node positive population and considered the result incorrect: • **IDFS extrapolation:** The HR for IDFS of 0.68 (0.46–0.99) calculated form the indirect comparison using data from the node-positive populations from KATHERINE and APHINITY (Issue 2) is used in the model. However, this HR is applied to the ITT KATHERINE data, instead of to the node-positive data in the model. The ERG considers the modelling of IDFS in the node-positive population to be seriously flawed and not appropriate for decision making. Data for the node positive population are not available in the model. The ERG therefore did not present an alternative preferred base-case for the node positive population. However, the same issues that were discussed for the node negative population are also applicable to the model for the node positive population (Issues 3-6). The ERG raised further issues with the model: • **Utilities:** For IDFS, local recurrence and remission states, the company assumed the same utilities for trastuzumab emtansine and pertuzumab plus trastuzumab (pooled analyses of KATHERINE ITT data; Table E in Issue 5). The utility value for IDFS from KATHERINE ITT pooled analyses is 0.775, assumed to be the utility for trastuzumab emtansine and pertuzumab plus trastuzumab. However, data from AFINITY reported a utility of 0.787 for pertuzumab plus trastuzumab and 0.784 for trastuzumab suggesting that pertuzumab plus trastuzumab may be associated with a slightly better utility than trastuzumab. Data from KATHERINE reported utility of 0.774 for trastuzumab emtansine and 0.776 for trastuzumab suggesting that trastuzumab may be associated with a slightly better utility than trastuzumab emtansine. Using the IDFS utility values from the KATHERINE trial separated according to treatment group may be more appropriate as this would reflect, although possibly slightly underestimate, the HRQoL benefit of pertuzumab plus trastuzumab over trastuzumab emtansine. The ERG also included treatment specific utilities in its preferred base-case for the node-negative population (see issue 5)

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	• **Recurrence:** Recurrence rates for trastuzumab emtansine were derived from the ITT population. For pertuzumab plus trastuzumab it was assumed that it is same as the average rate across trastuzumab emtansine and trastuzumab arms in the ITT population. • **Adverse events (AEs):** The incidence of AEs for trastuzumab emtansine is based on the KATHERINE ITT-population (same as for node-negative population). For pertuzumab, adverse event costs related to the IDFS and post-IDFS states were sourced from the literature, without any AE incidence data. The AEs management cost of £17.18 for P is taken from 6 cycles in TA569 model, while the current model assumes 13 cycles. The management cost for trastuzumab emtansine is £106.48. However, the ERG considers the expected impact of the management cost on cost-effectiveness results is small. The ERG considers the cost effectiveness results for the node-positive population unreliable and, inappropriate for decision making and did not provide an alternative preferred base-case for the node positive population. **The technical team** agrees with the ERG and company that the node positive results have serious limitations. It would like to see the model updated using the node positive IDFS KATHERINE data as the basis for extrapolation, and with the technical team's preferred assumptions for the node negative population incorporated (Issues 3-6). Given the uncertainties with the node positive specific analyses, it would also like to see a scenario analysis using indirect comparison results with ITT KATHERINE data.
Why this issue is important	The inputs in the model for the node positive population needs to be fit for purpose.
Technical team preliminary judgement and rationale	It agrees with the ERG that the current version of the model is not appropriate for decision making for the comparison of trastuzumab emtansine with pertuzumab plus trastuzumab in the node-positive population, however it is aware that the available evidence is very limited. It would like the company to provide an updated model that includes: • node-positive IDFS KATHERINE data with an option to toggle between ERG and company's approach to modelling (Issue 3); • recurrence rates based on the node-positive population;

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	• indirect comparison results using node positive KATHERINE and APHINITY data (Table B) applied to the trastuzumab emtansine IDFS curve from KATHERINE for the node-positive population; • treatment effect with an option to toggle between the assumption used by company, in TA569 and the ERG's approach (Issue 4); • IDFS utilities from the KATHERINE trial calculated per treatment and Lidgren et al. 2007 utilities for metastatic states (Issue 5); and • explore drug costs and modelling assumptions as discussed in Issue 6. Given the uncertainties summarised in above and in Issue 2 (indirect comparison), the technical team would like to see an exploratory analysis with indirect comparison results using ITT KATHERINE and APHINITY data utilising: • node-positive IDFS KATHERINE with an option to toggle between ERG and company's approach to modelling (Issue 3); • indirect comparison results using ITT KATHERINE and APHINITY data (Table D) applied to the trastuzumab emtansine IDFS curve from KATHERINE for the node-positive population; • ITT data consistently for all outcomes used in the model; • treatment effect with an option to toggle between the assumption used by company, in TA569 and the ERG's approach (Issue 4); • IDFS utilities from the KATHERINE trial calculated per treatment and Lidgren et al. 2007 utilities for metastatic states (Issue 5); and • explore drug costs and modelling assumptions as discussed in Issue 6.
Questions for engagement	8 a. If the company uses the correct IDFS data, would the model for the node positive population be suitable for decision making? 8 b. Given the uncertainties with the node positive specific analyses, do you think that in this instance, evidence from the ITT population, could be used to support the decision about a comparison of trastuzumab emtansine versus pertuzumab?

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Issue 9 – Outstanding issues

Background/description of issue	This technical report lists all key issue (issue 1 to issue 8) and clinical opinion would be valued on these issues. Further outstanding issues are listed in Table 2: Outstanding uncertainties in the evidence base and issues that were resolved are listed in Table 3: Other issues for information below.
Why this issue is important	To understand the uncertainty of the cost-effectiveness estimates presented in this report all key sources of uncertainty needs to be identified.
Technical team preliminary judgement and rationale	**The technical team** would welcome any additional comments relevant to this appraisal.
Questions for engagement	9. Are there any issues which are not covered above which are relevant to the appraisal?

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4. Issues for information

Tables 1 to 3 are provided to stakeholders for information only and not included in the technical report comments table provided.

Table 1a: Node negative population: trastuzumab emtansine versus trastuzumab

Alteration	Rationale	ICER	Change from base case
Company base case	**–**	**£2,634**	**-**
1. IDFS for time period 1: using KM curves up to the time point where the last event was observed in each treatment arm and an exponential long-term extrapolation instead of exponential curves extrapolating data in the company's approach.	Issue 3	£4,204	+£1,570
2. Treatment effect: treatment effect starts waning at 3 years instead of at 7 years in the company's approach.	Issue 4	£5,675	+£3,041
3. Treatment effect: treatment effect became null at 8 years instead of at 10 years in the company's approach.	Issue 4	£3,309	+£675
Change 2 & 3 combined: decreasing of treatment effect from 3 to 8 years instead of company's approach of duration from 7 to 10.	Issue 4	£7,400	+£4,766
4. IDFS utilities: using treatment specific utilities instead of pooled utilities in the company's approach.	Issue 5	£2,705	+£71
5. Utilities for metastatic heath states: Lidgren et al. utilities instead of Lloyd utilities in the company's approach.	Issue 5	£2,679	+£45
Change 4 & 5 combined: treatment specific & Lidgren et al. utilities	Issue 5	£2,751	+£117
6. Assuming same market in the early recurrence, first line metastatic state, instead of using assuming a different market shares in the company's base case.	Issue 6	£3,288	+£654
7. Assuming subcutaneous trastuzumab market shares from the market research sample, instead of 95% market share used in the company's base case.	Issue 6	£5,449	+£2,815

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Alteration	Rationale	ICER	Change from base case
8. Assuming a small cohort weight gain of 2.5 kg (with planned dose without vial sharing) instead of basing weight on KATHERINE data (with actual dose without vial sharing) in the company's base case.	Issue 6	£5,448	+£2,814
Cumulative impact of assumptions 1-5 (ERG's preferred base case)	–	**£9,339**	+£6.705
Cumulative impact of assumptions 1-6	–	**£10,266**	+£7,632
Cumulative impact of assumptions 1-7	–	**£13,934**	+11,300
Cumulative impact of assumptions 1-8	–	**£18,312**	+£15,678

Table 1b: Intention to treat (ITT) population: trastuzumab emtansine versus trastuzumab

Alteration	Rationale	ICER	Change from base case
Company's base case	–	**£1,247**	–
Cumulative impact of applying assumptions 1-5 described in Table 1a to modelling in ITT population	See Table 1a	**£7,648**	+£6,401

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Table 1c: Node positive population: trastuzumab emtansine versus pertuzumab plus trastuzumab

Alteration	Rationale	ICER	Change from base case
Company base case	–	**£354**	
The ERG did not present an alternative preferred base-case for node positive population.			
Technical team's preferred ICER	The technical team would like to see the results for node positive population updated. In addition, it would like to see a scenario analysis that utilises ITT data for a comparison with pertuzumab plus trastuzumab (Issue 8).		

Table 2: Outstanding uncertainties in the evidence base

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
Systematic reviews	The ERG identified a number of issues with cost-effectiveness and cost and resource searches. Cost-effectiveness searches were also used to identify health-related quality of life (HRQoL) studies (see ERG section 5 for more details). Systematic review was conducted to identify evidence on health effects for the IDFS state. However, the health effects in the subsequent states were not obtained from systematic review.	Unknown. Studies relevant to the model were missed and studies not identified in the reviews informed the model.
Treatment switching	Patients who discontinued from trastuzumab emtansine were allowed to complete the 14 cycles of therapy by switching to the trastuzumab arm, when this was deemed appropriate based on toxicity considerations. From the 71 patients who switched to trastuzumab from trastuzumab emtansine, a total of 63 patients (88.7%) completed the 14 cycles of trastuzumab emtansine and trastuzumab.	Minor, but unknown.

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Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
	The company explained that, 71 patients, is less than 10% of the patients in the intervention arm. This percentage was deemed small and, therefore, it was decided not to perform any crossover adjustments that, according to the company, would introduce additional uncertainty into the analysis. Therefore, trastuzumab trastuzumab emtansine treatment duration data included patients who remained on trastuzumab emtansine and patients who switched to trastuzumab. However, only trastuzumab emtansine costs were used for all patients in all treatment cycles of the intervention arm. The company considered this approach to be conservative.	
Dose reductions	Dose reductions for patients receiving trastuzumab emtansine were permitted in KATHERINE trial. Because 85.7% of patients in the trastuzumab emtansine arm did not require any dose modification, the company decided that it was not necessary to complicate the model to account for 14.3% of patients who had a dose reduction and did not include dose reduction on the model.	Minor, the approach is considered to be conservative.
Adjuvant chemotherapy	Typically, pertuzumab plus trastuzumab is given in combination with 6 cycles of chemotherapy. Company's clinical experts considered that generic chemotherapy would have already been received in neoadjuvant setting and the company therefore assumed that no chemotherapy as given in the model as part of adjuvant pertuzumab plus trastuzumab treatment. The company also noted that chemotherapy drugs are inexpensive and the impact on the cost effectiveness results would be small and if they were included, they would increase the cost of pertuzumab plus trastuzumab and thereby reduce the cost-effectiveness results.	Likely a minor decrease in cost-effectiveness estimates.
ITT population	Some data from the ITT population in KATHERINE were used in the model for the node negative population. Some data from the ITT population in KATHERINE were used in the model for the node positive population (Issue 8).	Unknown

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Table 3: Other issues for information

Issue	Comments
Equality considerations	No equalities issues were identified by the company, consultees and their nominated clinical experts and patient experts.
Innovation	The company considers the drug to be innovative, with all relevant benefits associated with the drug are adequately captured in the model.
Trastuzumab vial sizes	The model includes only the 150 mg vial size, the 420 mg biosimilar vial size is not included. However, the cost per mg is the same in both 150 mg and 420 mg vials. The model would take the minimum cost of all small and large vial combinations, so the impact on cost-effectiveness results is likely to be minimal.
IDFS utilities from KATHERINE and model populations	The company did not expect that HRQoL is dependent on nodal status. Therefore values form ITT population were used for the node-negative and node-positive analyses. The ERG could not identify any evidence regarding the impact of nodal status on utility. Therefore, the same ERG base-case assumptions for the ITT population were also adopted for the node-negative population.
Time on treatment data and model populations	The company indicated that treatment duration is not expected to be dependent on nodal status. Therefore, ITT data were used for the node-negative and the node-positive subpopulations. The company noted that across all treatment cycles there are only minor differences between the data. ERG table 5.15 summarises treatment discontinuation in the ITT and the node-negative population.
Adverse events included in the model	Only decreased platelet counts were included in the model. It was not clear to the ERG how the company decided an adverse event to be "treatment-related" in the KATHERINE trial. For example, the incidence of hypertension in the trastuzumab emtansine arm of the KATHERINE trial was 2%, however it was not included as an adverse event in the economic model. Upon request from the ERG, the company conducted additional scenario analyses in its response to the clarification letter. These analyses revealed that the inclusion of additional AEs other than decreased platelet counts did not have a significant effect on the incremental results. Therefore, this is not investigated further in the exploratory analyses conducted by the ERG.

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Issue	Comments
Adverse events and model populations	For the node-negative subgroup analysis, the company assumed the same adverse event incidences as in their ITT population analysis for trastuzumab emtansine and trastuzumab. For the node-positive subgroup analysis, ITT-population based adverse event incidences were used for trastuzumab emtansine.
Adverse effects disutilities	The ERG has some concerns about the company's assumption that the impact of AEs will have been captured in the EQ-5D data collection. Firstly, the EQ-5D was only collected twice during the treatment period, in cycles 5 and 11. Therefore for AEs to have been captured in the EQ-5D data collection, we would have to assume that all AEs that occurred during the treatment period were being experienced on those two occasions. Any AEs that resulted in discontinuation before these time points would not be reflected. The assumption that AEs are captured in HRQoL data requires that HRQoL be assessed regularly on presentation of AEs, otherwise it is likely that the impact is missed. Therefore it is likely that the impact of AEs is underestimated. This concern was also raised by the ERG in TA569.
Deterministic analyses	The company conducted deterministic sensitivity analyses by varying one-by-one the base-case values of a series of cost and utility parameters by ±25% of the base-case value. The ERG found the choice to vary those parameters included in the deterministic sensitivity analysis by ±25% of the base-case value to be arbitrary and felt that this may not produce values that are equally plausible across all parameters. It would be better practice to use the 95% confidence intervals as upper and lower bounds within the deterministic sensitivity analysis.
Model errors	• An incorrect formula was used and, as a consequence, all "early" recurrences were considered as metastatic. This was corrected during clarification by company and the model include both non-metastatic and metastatic "early" recurrences. • Maintenance dose of 6 mg/kg was used instead of a loading dose of 8 mg/kg for the initial trastuzumab intravenous cycle. ERG corrected this and a loading dose of 8 mg/kg is included in the model. • There was a reporting error in the company submission, the price for the 160 mg docetaxel IV was reported as £28.48, however in the economic model, the price of £25.59 was used.

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List of abbreviations

AEs, adverse events

DCIS, ductal carcinoma in situ

DDFS, Distant disease-free survival

DFS, disease-free survival

DFS-DCIS, disease-free survival including ductal carcinoma in situ

EQ-5D-3L, European Quality of Life-5-dimension-3 levels questionnaire

ERG, evidence review group

IDFS, invasive disease-free survival

ICERs, incremental cost-effectiveness ratio

PFS, progression free survival

OS, overall survival

PDRS, post distant recurrence survival

QALY, quality adjusted life years

TTD, time-to-treatment discontinuation

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Glossary

Quality-adjusted life year (QALY): An index of survival that is adjusted to account for the patient's quality of life during this time. QALYs incorporate changes in both quantity (longevity/mortality) and quality (morbidity, psychological, functional, social, and other factors) of life. Used to measure benefits in cost–utility analysis.

Surrogacy, progression-free survival or disease free survival as a surrogate outcome for overall survival: It may not be possible to obtain a precise estimate of the difference in median overall survival between 2 treatments based on data from a trial where participants have only been followed up for a relatively short time (in particular where <50% of patients have died). Progression-free survival (PFS) or disease-free survival (DFS) is a surrogate outcome for overall survival (OS) if a gain in PFS/DFS comparing 1 treatment with another can be assumed to translate to an equivalent gain in OS. Partial surrogacy would imply that the gain in OS is a certain percentage of the gain in PFS/DFS.

Systematic review: Research that summarises the evidence on a clearly formulated question according to a predefined protocol. Systematic and explicit methods to identify, select and appraise relevant studies, and to extract, collate and report their findings are used. Statistical methods for meta-analysis may or may not be appropriate for application to the quantitative results from the different studies.

Utility: A measure of the strength of a person's preference for a specific health state in relation to alternative health states. The utility scale assigns numerical values on a scale from 0 (death) to 1 (optimal or 'perfect' health). Health states can be considered worse than death and thus have a negative value.

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Technical engagement response form

Trastuzumab emtansine for adjuvant treatment of HER2-positive early breast cancer [ID1516]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments: **20 February 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a second version of

your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Roche Products Ltd.**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

NICE National Institute for Health and Care Excellence

Overview

The Company response is split into two components. First, the Company has responded to the specific issues highlighted by NICE in their technical report. Secondly, the Company has conducted the model updates requested by the ERG and NICE and provided revised base case results produced by this model (please note, ICERs quoted in the "Questions for Engagement" subsection have been derived using the revised Company base case). The overall objective of this response was to attempt to ensure that all relevant information was available for decision-making at the Committee meeting on March 24th.

Questions for engagement

Issue 1: Treatment pathway	
1 a. Is there any reason to prefer trastuzumab emtansine over pertuzumab plus trastuzumab in node positive disease?	Yes. Whilst trastuzumab emtansine and pertuzumab/trastuzumab are both currently licensed in node positive disease, their relative efficacy cannot be easily compared as the data upon which their respective indications are based were generated in different patient populations. The KATHERINE trial[i], the basis for adjuvant licence for trastuzumab emtansine, enrolled only patients with residual invasive disease (RID) following neoadjuvant treatment, and benefit was seen regardless of nodal status. The adjuvant pertuzumab plus trastuzumab licence is based on the APHINITY[ii] study in which no patients were treated neoadjuvantly and therefore there was no selection of a subgroup of patients based on response to neoadjuvant treatment. However, subgroups analyses showed that it was node positive patients in the APHNITY study who were deriving benefit. Thus, trastuzumab emtansine has clinical trial evidence of efficacy in the poor prognosis RID population (regardless of nodal status) whereas pertuzumab plus trastuzumab does not. We understand from the clinical community that due to the different mechanism of action of trastuzumab emtansine, it is preferable to switch to this treatment in the event of the suboptimal outcome of RID after neoadjuvant therapy including pertuzumab and trastuzumab and that this preference is driven by the RID not the nodal status of the patient.
1 b. In clinical practice, do patients with node positive disease only receive pertuzumab plus trastuzumab or are there some people with node positive disease who would receive trastuzumab monotherapy?	Currently in clinical practice, the company understands that the majority of patients with node positive disease receive pertuzumab and trastuzumab. This is because Pertuzumab and trastuzumab for node-positive patients has been deemed more effective than using trastuzumab monotherapy alone. Node positive patients typically represent a higher risk group and therefore benefit from dual anti-HER2 targeted therapy. However, very few patients may not be able to tolerate this regime and could be offered monotherapy.

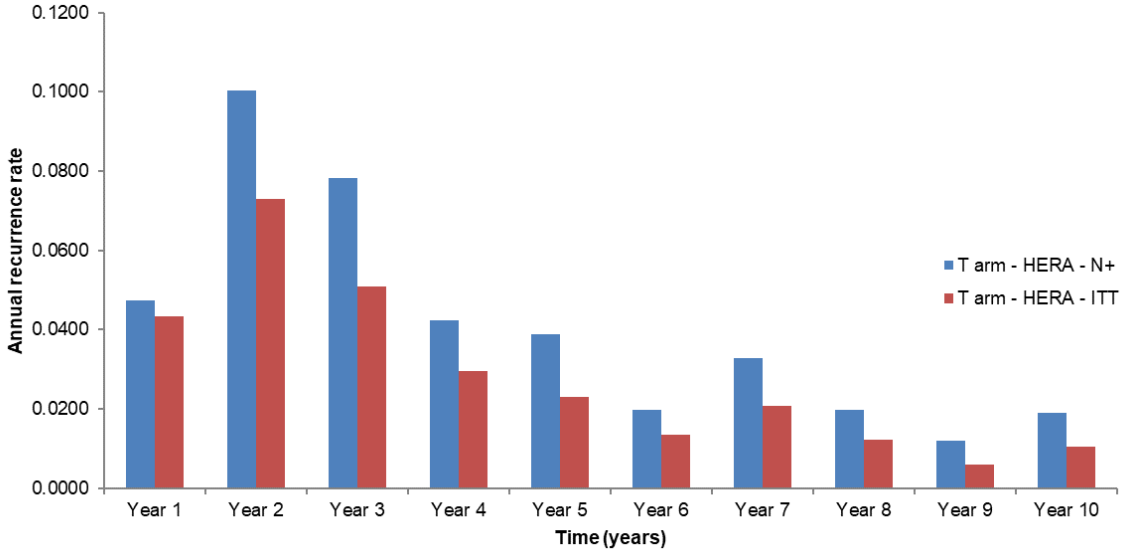
Issue 2: Indirect comparison: trastuzumab emtansine versus pertuzumab plus trastuzumab	
2 a. Are the results of the indirect treatment comparison of trastuzumab emtansine versus pertuzumab plus trastuzumab, using the node-positive populations from APHINITY and KATHERINE trials, clinically plausible?	Clinical experts on the Technical Engagement teleconference stated that they would expect trastuzumab emtansine to be more efficacious than pertuzumab + trastuzumab in the RID following neoadjuvant therapy population. The results of the indirect treatment comparison are broadly aligned with this testimony as all hazard ratios produced were below 1.0. The clinical experts went on to say that although plausible, the HRs produced by the Bucher analysis[iii] are likely to give a conservative reflection of the comparative efficacy of trastuzumab emtansine in a RID population (i.e. we could expect the "true" hazard ratio to be lower than the Bucher outputs) due to the study population differences in the APHINITY and KATHERINE trials.[i,ii] Despite the expert testimony, the Company is cognisant of the uncertainty around the outputs of the ITC. For this reason, extensive scenario analyses have been undertaken. Results of these analyses are discussed fully in the response to Issue 8a. In brief, even when adopting the most conservative output of the ITC, the ICER is only £4,955 / QALY gained in the node-positive population. Based on the expert testimony, which in the absence of head-to-head data and a network meta-analysis is likely the best available validation, the ITC outputs can be broadly considered clinically plausible. Importantly, trastuzumab emtansine in this indication is cost-effective, irrespective of which ITC output is used.
2 b. Are there any other data that could be used to for the comparison of trastuzumab emtansine versus pertuzumab plus trastuzumab?	As part of the original evidence submission, the Company conducted a comprehensive systematic review of the available literature in this area. The full results of this review are discussed in Document B. In brief, no suitable sources were captured. Other key sources, not captured by the SLR, were also discussed and found to be inappropriate for use in an indirect treatment comparison. In their report, the ERG were unable to cite any alternative sources not previously discussed by the Company. Similarly, during the Technical Engagement teleconference, neither clinical expert was able to suggest any suitable sources upon which to base an ITC.

	In conclusion, it can be reasonably assumed that the ITC provided by the Company uses the most appropriate sources available for the derivation of comparative effectiveness between trastuzumab emtansine and pertuzumab + trastuzumab.
2 c. How should the uncertainty about the relative treatment effects of trastuzumab emtansine and pertuzumab plus trastuzumab be explored. Would a cost comparison be useful?	The issue of a cost comparison was resolved on the Technical Engagement teleconference. The Clinical Experts stated that the population differences in APHINITY and KATHERINE mean that all of the hazard ratios produced by the Bucher analysis are likely to be conservative reflections of the comparative efficacy of trastuzumab emtansine (compared to pertuzumab + trastuzumab) in RID patients.[iii] In light of this, they noted that a cost-comparison (assuming equivalent efficacy between trastuzumab emtansine and pertuzumab + trastuzumab) would be inappropriate. This was subsequently agreed by the ERG and NICE Technical Team. To capture the uncertainty around the relative treatment effect of trastuzumab emtansine versus pertuzumab + trastuzumab, the Company has provided scenario analyses using a range of outputs from the Bucher analysis – see Table 19.
Issue 3: IDFS extrapolation	
3 a. Which approach to IDFS modelling, the ERG's or the company's, is more clinically plausible?	The preferred extrapolations proposed by the Company in the original submission overestimate IDFS in the trastuzumab arm during the KATHERINE observation period. Consequently, the ERG proposed using the observed KM data in both arms until the time point where the last event occurs. Following this, the best fitting function should be used to extrapolate IDFS for the remainder of the time horizon. The approach suggested by the ERG appears to resolve the underestimation of IDFS in the short term. The ERG's preferred approach has therefore been adopted by the Company in their revised base case – see below.
3 b. Is it appropriate to use evidence from the intention to treat population in KATHERINE trial and the node-positive population in HERA trial to adjust modelling in the node negative population?	Patients with residual invasive disease following neoadjuvant therapy (KATHERINE ITT) are at a higher risk of disease recurrence. Similarly, patients in which disease has spread to the lymph nodes (node-positive in HERA[iv]) are also at a higher risk of disease recurrence. Both RID following neoadjuvant therapy and node-positivity are well-documented risk factors. It was therefore believed to be more appropriate to compare data in two higher risk populations (RID in KATHERINE and node-positive in HERA) in the Company original submission rather than a high risk population (RID in KATHERINE) and a lower risk population (ITT in HERA).

If separating out the ITT population and submitting results for the node-negative subgroup and the node-positive subgroup (as we have done here), it is possible to argue that using evidence from the node-positive population of HERA to adjust modelling in the node-negative population of KATHERINE is inappropriate. The node-negative population in KATHERINE can be deemed to be lower risk (than the KATHERINE ITT population) it is therefore perhaps more appropriate to use a lower risk proxy from HERA, such as the ITT population. Though this equivalence is undoubtedly flawed, it is likely the most appropriate given the absence of a like-for-like comparison across the two trials.

Figure 1 presents the recurrence patterns seen in the node-positive population and the ITT population of HERA. Broadly speaking, the patterns seen in the two populations are similar (i.e. very few recurrences while on treatment in year one, high risk of recurrence in years two and three, before a notable decrease in year 4).

Figure 1. Recurrence patterns in ITT and node-positive populations of HERA[iv] trial



	This evidence does not seem to suggest that the adjustments made to the IDFS extrapolation should be altered depending on nodal status. Nevertheless, the Company has presented cost-effectiveness estimates for a range of cure model assumptions (see Table 19). As the assumptions around the cure model are applied equivalently across both arms of the model, the impact on the overall cost-effectiveness is negligible.
Issue 4: Treatment waning effect of trastuzumab emtansine	
4 a. What approach to treatment effect duration, the ERG's, the company's, or a different one, is the most clinically plausible?	The Company is concerned that the treatment effect assumptions preferred by the ERG are uncertain and are likely to lead to an underestimation of the trastuzumab emtansine treatment effect. Much of the rationale for the selection of the ERG's preferred assumptions centres on the annualized hazard ratios derived from the KATHERINE trial. Though this may be the best available evidence, it is important to reiterate the flaws in this data. The principle issue with the use of annualised hazard ratios is the uncertainty arising from limited patients at risk (due to censoring) and event numbers. Median follow-up in both arms of the KATHERINE trial was approximately 41 months. As can be seen in Table 1 there is substantial censoring at year 4 and limited event numbers, which would result in uncertainty in the observed hazard rates in this period.

Table 1. Patients at risk and event numbers in the KATHERINE trial* - ITT

Time	Trastuzumab arm			Trastuzumab emtansine arm		
	Patients at risk at start of year (%)	Patients at risk at end of year (%)	Number of IDFS events	Patients at risk at start of year (%)	Patients at risk at end of year (%)	Number of IDFS events
Year 1 (0-11 months)	743 (100.00%)	635 (85.46%)	53	743 (100.00%)	685 (92.19%)	21
Year 2 (12-23 months)	635 (85.46%)	555 (74.70%)	63	682 (91.79%)	640 (86.14%)	32
Year 3 (24-35 months)	555 (74.70%)	350 (47.11%)	33	633 (85.20%)	443 (59.62%)	24

Year 4 (36-47 months)	350 (47.11%)	110 (16.02%)	14	409 (55.05%)	170 (22.88%)	12
Year 5 (48-59 months)[a]	110 (16.02%)	0 (0.00%)	2	170 (22.88%)	0 (0.00%)	2

*Discrepancies exist in the "patients at risk…" categories due to the non-uniform time intervals in KM data.

In TA569[v] (pertuzumab + trastuzumab + chemotherapy in adjuvant HER2-positive early breast cancer), available evidence did not definitively point to a treatment effect duration. Consequently, much like the ERG for this appraisal, the ERG for TA569 chose to focus on the shape of the KM curves and the annualised hazard ratios as those were believed to be the best available evidence at the time. While this may be true, it is important to acknowledge that the use of this evidence led to an underestimation of the pertuzumab treatment effect (full effect to four years before waning and ceasing completely at seven years), according to the most recent analysis of APHINITY data.

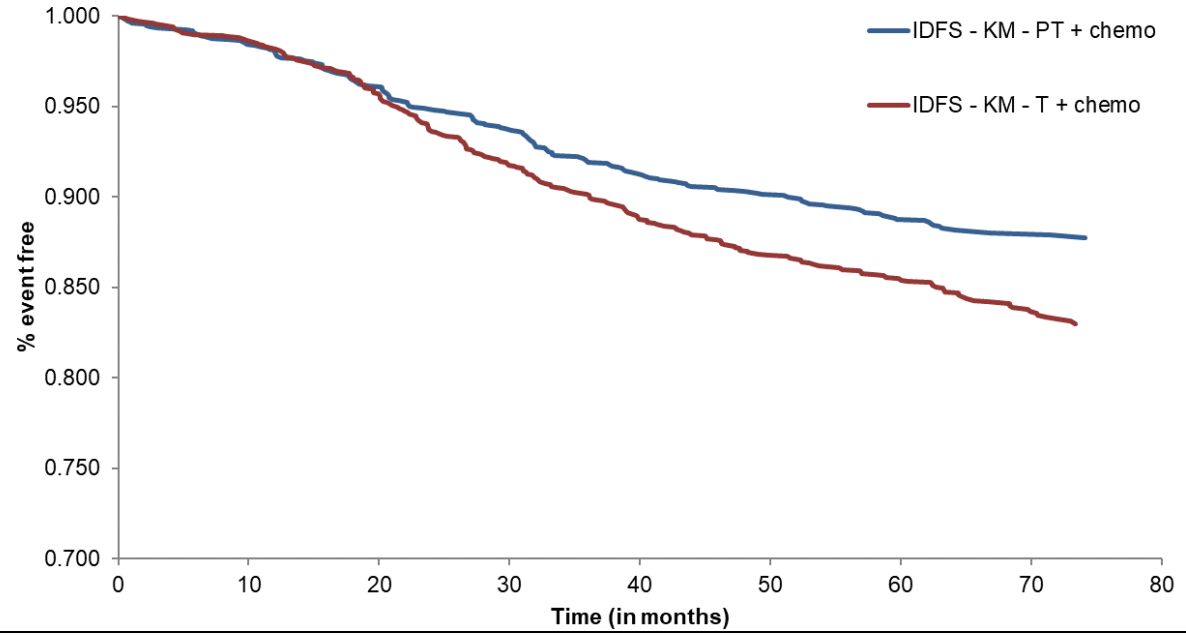
The TA569 appraisal was based on the results of the primary analysis (IDFS) of the APHINITY trial. In December of 2019, the interim OS analysis (updated IDFS) of APHINITY read out. The median duration of follow-up is now 73.5 months (~6 years) in the node-positive population (compared to 45.4 months at primary [IDFS] analysis). The cumulative hazard ratios across the entirety of the observation period are presented below in Table 2.

Table 2. Cumulative hazard ratios from interim OS analysis (median follow-up = 73.5 months) in node-positive population

Time period	Cumulative hazard ratio
Year 0–1	1.024
Year 0–2	0.793
Year 0–3	0.797
Year 0–4	0.731
Year 0-5	0.757
Year 0-6	0.722
Year 0-7	0.715

The values in Table 2 clearly show that the cumulative hazard ratio is below one and decreasing year upon year. This evidence seems directly contradictory to the TA569 Committee's assumption that the treatment benefit would begin to lessen after four years. Admittedly, median follow-up in the lymph node-positive population is at 73.5 months and significant censoring occurs after year 6. This means year 0-6 and year 0-7 ratios can therefore be associated with a larger degree of uncertainty. Nevertheless, if the Kaplan-Meier IDFS curves are capped at median follow-up, before the bulk of the censoring occurs, we can see that the greatest separation in the curves occurs at 73.5 months (Figure 2). This, once again, points to the fact that the treatment effect is still increasing at median follow-up and that to assume that the treatment effect has begun to wane from month 48, as the TA569 Committee did, is overly conservative and clinically implausible.

Figure 2. APHINITY Kaplan-Meier IDFS curves – capped at ~73.5 months (median follow-up) (lymph node-positive population)



Abbreviations: HC, trastuzumab + chemotherapy; IDFS, invasive disease-free survival; KM, Kaplan-Meier; PHC, pertuzumab + trastuzumab + chemotherapy.

This evidence is believed to be relevant to this appraisal as pertuzumab and trastuzumab emtansine are both anti-HER2 therapies being used in the adjuvant breast cancer setting. However, the Company understands that to use this evidence may not be an ideal analogue due to the differences in study population and design between KATHERINE and APHINITY. The objective of presenting this evidence is simply to illustrate that though annualised hazard ratios and curve shape may be the best available evidence – they can lead to an underestimation of treatment effect at later timepoints.

Even when assuming the treatment effect in both populations ceases at the end of the KATHERINE follow-up period (~48 months) – which is an implausibly conservative scenario - the ICER reaches ~£15,000 / QALY gained (see Table 19). Although the Company does not agree with the ERG's view here, for pragmatic purposes, in the revised Company base case (see below) the ERG's preferred treatment effect duration has been assumed. In summary, regardless of the treatment effect assumptions utilised in the model, trastuzumab emtansine in this indication can be considered a cost-effective use of NHS resources.

Table 3. Scenario analyses on treatment effect duration

Area	#	Value	Node-negative		Node-positive	
			ICER (/QALY gained)	Δ from base case	ICER (/QALY gained)	Δ from base case
	0	Revised base case	£8,829	£0	£4,955	£0
Treatment effect duration	1	Stops at 4 years	£14,654	+£5,825	£13,071	+£8,116
	2	Begins waning at 4 years ceases at 7 years	£9,115	+£286	£4,454	-£501
	3	Begins waning at 5 years ceases at 8 years	£6,534	-£2,295	£1,889	-£3,066
	4	Begins waning at 6 years ceases at 9 years	£4,942	-£3,887	£389	-£4,566
	5	Begins waning at 7 years ceases at 10 years	£3,988	-£4,841	TE dominant	N/A

Abbreviations: TE, trastuzumab emtansine.

4 b. Would you expect that the duration of treatment effect in the ITT and node-negative populations is the same?	Nodal status was one of several stratification factors in the pivotal KATHERINE trial. As can be seen from the forest plot presented in Figure 12 (page 45) of Document B, IDFS results were consistent across node-positive (HR = 0.52 [95% CI; 0.38-0.71]) and node-negative/unknown (HR = 0.44 [95% CI; 0.28-0.68]) patients. However, the results seen in the KATHERINE trial cannot speak to the duration of the treatment effect beyond this observation period. In fact, there is no evidence evaluating the trastuzumab emtansine treatment effect duration across node-positive and node-negative populations in the mid to long-term. In the absence of such clinical data, the Company would suggest the most appropriate course of action would be to defer to clinical experts on this issue. In attempt to capture the uncertainty in this area, the Company has presented cost-effective estimates for a range of treatment effect assumptions in both the node-positive and node-negative subgroups. Results of these additional analyses show that even when assuming the treatment effect in both populations ceases at the end of the KATHERINE follow-up period (~48 months) – which is an implausibly conservative scenario - the ICER reaches ~£15,000 / QALY gained in both subgroups (see Table 3). In summary, regardless of the treatment effect assumptions utilised in the model, trastuzumab emtansine in this indication can be considered a cost-effective use of NHS resources.
Issue 5: Utilities	
5 a. Is it appropriate to use the per treatment calculated utility from KATHERINE trial for the IDFS state to take account of the difference in AEs?	In their report, the ERG argued that given the decision to omit AE disutilities from the economic analysis, it is most appropriate to use treatment-specific utilities in the IDFS health states. The use of values that had been pooled across treatment arms would have led to the masking of any HRQoL impacts from treatment-related AEs collected as part of the KATHERINE EQ-5D data. The Company agrees with the ERG's proposed approach to apply treatment-specific utilities for the IDFS health states in the model. This is reflected in the revised base case provided by the Company – see below.
5 b. Are the utilities from Lidgren et al. 2007 more clinically plausible than the Lloyd utilities for the 2 metastatic states in the model?	The ERG felt that the methods used by Lidgren *et al.*[vi] to derive utilities in the metastatic health states better reflected those outlined in the NICE reference case[ix] (HRQoL reported by patients themselves using EQ-5D-3L) than Lloyd *et al.*[vii]

	The Company agrees with the ERG's proposed approach of using the utilities from Lidgren *et al.* for the metastatic health states in the model. This is reflected in the revised base case provided by the Company – see below.
Issue 6: Drug costs and modelling assumptions	
6 a. Are the arm specific market shares for trastuzumab and trastuzumab emtansine assumed by the company for early recurrence, first line metastatic state plausible? Or should equal, (or different market share values) be used in the model?	Expert opinion elicited by the Company signalled that physicians would not re-challenge patients with trastuzumab emtansine in the 1st-line mBC (early relapser) setting after a patient has received trastuzumab emtansine therapy in the adjuvant setting. Supportive care in the 1L mBC – early relapser health state was therefore stratified according to treatment received in the adjuvant setting. In the Company base case, it has been assumed that in the trastuzumab emtansine arm, patients would receive pertuzumab + trastuzumab + chemotherapy whereas patients who receive either trastuzumab monotherapy or pertuzumab + trastuzumab in the adjuvant setting would receive trastuzumab emtansine. The Clinical experts present on the Technical Engagement teleconference agreed that the approach taken by the Company is appropriate.
6 b. Approximately what are the proportions of people who would be given either subcutaneous or intravenous trastuzumab biosimilar when given trastuzumab monotherapy in the adjuvant setting?	In TA569 (pertuzumab + trastuzumab + chemotherapy in the adjuvant treatment of HER2-positve early breast cancer), 95% of the trastuzumab monotherapy market was assumed to be Herceptin SC (March 2019). The original assumption (market share of subcutaneous trastuzumab = 95%) used in TA569 was also utilised in the base case analysis of the Company's submission in this appraisal.[v] Market research commissioned by the Company (and provided during the response to clarification questions) contained the following sentence; "in a sample of 229 patients, 106 were using trastuzumab in the SC formulation".[viii] Consequently, in their report, the ERG assumed that the split between SC and IV usage in trastuzumab monotherapy is (106/229) 46% and (123/229) 54%, respectively. It appears there may have been a misinterpretation and it is therefore critical to note here that this sample does not refer to trastuzumab monotherapy exclusively. In fact, some of the trastuzumab usage in those 229 patients has been used in combination with pertuzumab. As clarified on the teleconference by the Company, the figures suggested by the

	ERG are therefore inappropriate for use in this context (trastuzumab monotherapy). The original split used by the company (95% SC vs. 5% IV) was confirmed by Professor Clark during the teleconference when he stated that "virtually all" trastuzumab monotherapy usage is administered subcutaneously.
6 c. Is only intravenous trastuzumab biosimilar used in combination with pertuzumab when given in combination in the adjuvant setting?	In England and Wales, using pertuzumab in combination with trastuzumab subcutaneous (SC) is not commissioned by the NHS. In the Company submission, it was therefore assumed that all trastuzumab used in combination with pertuzumab would be given intravenously. The price differential between intravenous (IV) trastuzumab biosimilar and IV originator (Herceptin) trastuzumab is such that there is no plausible reason as to why a physician would prescribe the more expensive originator product. As a result, there is no usage of branded trastuzumab (Herceptin) IV in the Company's economic analysis. This assumption was also used in TA569 and was incorporated into decision-making. In summary, Professor Peter Clark (Cancer Drugs Fund – Clinical Lead) confirmed that only trastuzumab biosimilar is used in combination with pertuzumab in the adjuvant setting during the Technical Engagement teleconference. Therefore, the Company was correct to make this assumption in its base case.
6 d. What assumption about patient weight and vial sharing should be adopted in the model?	The patient weights collected at baseline during the KATHERINE trial should be used for the purposes of cost-effectiveness analysis. Similarly, the actual dose and Time to Off Treatment (TTOT) data used in the model should also come from the KATHERINE trial. In their report, the ERG refers to ICERs that have been generated using "planned dose" data. It is far more appropriate to use the "actual dose" data. Planned dose data does not account for missed doses, dose moderations etc., this is a clinically implausible data set, unreflective of real world practice, and consequently inappropriate for the purposes of decision-making. The Company agrees with the NICE Technical team that the patient weight and time-on-treatment parameters in the model should be taken from the pivotal trial data. This approach would also be consistent with previous NICE appraisals assessing agents for the treatment of HER2-positive breast cancer. Deviation from this approach here would be inappropriate in the absence of a clear rationale.

The base case analysis submitted by the Company assumes no vial sharing. Attendees on the Technical Engagement teleconference heard from clinical experts that this might not be wholly reflective of UK clinical practice. Experts stated that the increase in usage of trastuzumab emtansine in the adjuvant setting (in addition to the metastatic setting) would likely increase the opportunities for vial sharing in various centres. Based on this testimony, the Company base case results represent a conservative reflection of cost-effectiveness (i.e. in the model, centres are paying for drugs which they are not using whereas in clinical practice, the amount of product being paid for but not being administered is likely to be significantly less). Scenario analyses evaluating the impact of patient weight and vial sharing on the ICERs have been presented for the node-negative population and the node-positive population in Table 19 (scenarios 6-14). The results have also been re-produced below in Table 4 for convenience.

Table 4. Cost-effectiveness results of vial sharing scenario analyses

Area	#	Value	Node-negative		Node-positive	
			ICER (/QALY gained)	Δ from base case	ICER (/QALY gained)	Δ from base case
	0	Revised base case	£8,829	*£0*	£4,955	*£0*
Patient weight	6	Planned dose - 70 kg	£8,829	£0	£4,955	£0
	7	Planned dose - 72.5 kg	£12,822	+£3,993	£12,532	+£7,577
	8	Planned dose - 75 kg	£12,810	+£3,981	£12,519	+£7,564
Vial sharing	9	Actual dose – 0% vial sharing	£8,829	£0	£4,955	£0
	10	Actual dose – 50% vial sharing	£8,350	-£479	£4,008	-£947
	11	Actual dose – 100% vial sharing	£7,871	-£958	£3,061	-£1,894
	12	Planned dose – 0% vial sharing	£8,829	£0	£4,955	£0
	13	Planned dose – 50% vial sharing	£8,467	-£362	£5,055	£100
	14	Planned dose – 100% vial sharing	£8,104	-£725	£5,155	£200

At first glance, results presented in Table 4 may seem counter intuitive, several clarifying points are provided below:

- Planned dose is used for the scenario analyses around patient weight. Varying the patient weight has no impact on the ICER when the actual dose data from the trials is used.

	• Pertuzumab is given at a fixed dose of 421.75mg (actual dose from APHINITY) using a vial containing 420mg. Therefore, there is minimal wastage in the administration of pertuzumab, regardless of whether or not vial sharing is assumed. • As there is negligible difference between the actual dose and planned dose of pertuzumab and trastuzumab emtansine (+1.75mg and +8,5mg, respectively), there is a limited impact on IDFS drug costs, regardless of whether actual or planned dose is used. • It is important to caveat these results by stating that any vial sharing assumptions are applied across drug use in all health states of the model. For example, it is possible for any expected cost savings in the IDFS health state to be offset by supportive care costs in the metastatic health states. In summary, assumptions on patient weight and vial sharing are not main drivers of cost-effectiveness. Even when adopting the most conservative assumptions (increase in patient weight, planned dosage, and no vial sharing), the ICER is still only £12,822 / QALY gained and £12,532 / QALY gained in the node-negative and node-positive analyses, respectively.
Issue 7: Modelling the intention to treat population	
7. Is the model for the intention to treat population, with the technical team changes applied, suitable for decision making?	A model evaluating the ITT population of KATHERINE formed the basis of the Company's original evidence submission. If looked at in isolation, an argument could be made that the ITT analysis is not robust enough to base a reimbursement decision on. Nevertheless, given the uncertainty associated with the comparison to pertuzumab + trastuzumab, the ITT analysis could still prove useful in the decision-making process. For example, cost-effectiveness results of the ITT analysis (see Table 5) confirm the conclusions drawn from the results of the node-positive and node-negative analyses. This may help to provide reassurance to the Committee that, despite the uncertainty of the ITC, trastuzumab emtansine in the adjuvant setting is still an extremely cost-effective use of NHS resources. **Table 5. Revised cost-effectiveness results for ITT, node-negative, and node-positive analyses**

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
ITT population							

Trastuzumab	[redacted]	15.06	[redacted]	[redacted]	1.36	[redacted]	£5,985
Trastuzumab emtansine	[redacted]	16.42	[redacted]				
Pertuzumab + trastuzumab	[redacted]	15.77	[redacted]	[redacted]	0.65	[redacted]	£8,203
Trastuzumab emtansine	[redacted]	16.42	[redacted]				
Node-negative							
Trastuzumab	[redacted]	16.76	[redacted]	[redacted]	1.23	[redacted]	£8,829
Trastuzumab emtansine	[redacted]	17.99	[redacted]				
Node-positive							
Pertuzumab + trastuzumab	[redacted]	13.97	[redacted]	[redacted]	0.67	[redacted]	£4,955
Trastuzumab emtansine	[redacted]	14.64	[redacted]				

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

Issue 8: Modelling the node positive population

8 a. If the company uses the correct IDFS data, would the model for the node positive population be suitable for decision making?

The changes requested by the ERG and the NICE Technical team in the node-positive analysis have now been actioned by the Company (see above). Further, the Company has provided a series of scenario analyses in attempt to capture the uncertainty in this subgroup analysis.

Table 6. Cost-effectiveness results of ITC scenario analyses

Area	#	Value	Node-positive	
			ICER (/QALY gained)	Δ from base case
	0	Revised base case	£4,955	£0
Bucher outputs	12	Scenario A - N+ KATHERINE / N+ APHINITY (4yr)	£1,094	-£3,861
	13	Scenario B – ITT KATHERINE / N+ APHINITY (4yr)	TE dominant	N/A
	14	Scenario C – ITT KATHERINE / ITT APHINITY (4yr)	TE dominant	N/A

	<table><tr><td></td><td>15</td><td>Scenario A – N+ KATHERINE / N+ APHINITY (6yr)</td><td>£4,955</td><td>£0</td></tr><tr><td></td><td>16</td><td>Scenario B – ITT KATHERINE / N+ APHINITY (6yr)</td><td>£2,468</td><td>-£2,487</td></tr><tr><td></td><td>17</td><td>Scenario C – ITT KATHERINE / ITT APHINITY (6yr)</td><td>£69</td><td>-£4,886</td></tr></table> As agreed during the Technical Engagement teleconference, the approach taken by the Company to derive the ITC outputs is likely the most appropriate given the data limitations. The results of these scenario analyses show that regardless of the ITC output used, the ICER does not rise above £4,955 / QALY gained. Further, as highlighted by the clinical experts on the Technical Engagement teleconference, the population differences in APHINITY and KATHERINE mean that all of the hazard ratios used in these scenarios are also likely to be conservative reflections of the comparative efficacy of trastuzumab emtansine in RID patients. The results presented in Table 6, and the testimony from clinical experts, means that the "true" value of cost-effectiveness in the node-positive population is likely to be lower than the revised base case ICER (£4,955 / QALY gained) submitted by the Company. In light of this, deciding to reimburse trastuzumab emtansine in this population is a low-risk decision for the Appraisal Committee and consequently the node-positive analysis is certainly robust enough for decision-making.
8 b. Given the uncertainties with the node positive specific analyses, do you think that in this instance, evidence from the ITT population, could be used to support the decision about a comparison of trastuzumab emtansine versus pertuzumab?	As mentioned in response to Issue 8a, the Company believes that the changes implemented in the economic analysis now makes the node-positive subgroup analysis robust enough for decision-making. However, sizable uncertainty around the ITC persists. Given this uncertainty, the Company would encourage the Committee to consider the cost-effectiveness results generated across the ITT, node-negative, and node-positive analyses. The ICERs in each of these analyses illustrate that trastuzumab emtansine in the adjuvant setting can be regarded as a cost-effective use of NHS resources, regardless of the ITC outputs used and across all relevant subgroups.
Issue 9: Outstanding issues	
9. Are there any issues which are not covered above which are relevant to the appraisal?	None

Model updates

As part of the response to the NICE Technical report, the Company has altered its cost-effectiveness model. The majority of updates centre on ensuring that when a certain subgroup is selected, the data pertaining to that subgroup from the KATHERINE trial is used in the analysis (i.e. if the node-negative subgroup is selected, then node-negative IDFS, recurrence rates, utilities and time to off-treatment data are used). This was a principle request of both the ERG and NICE. For clarity, the following updates have now been integrated into the model:

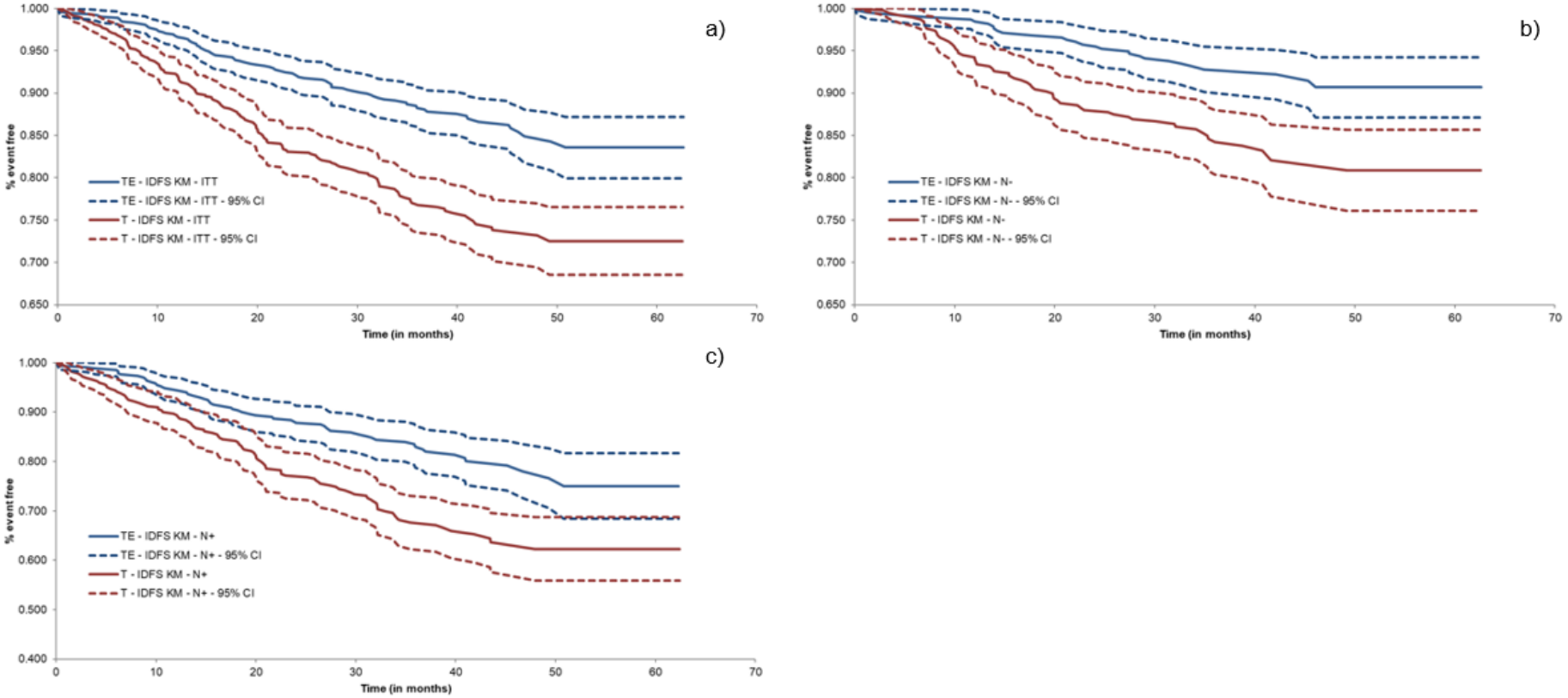
i. ***IDFS KM data – ("KM IDFS" sheet)***
ii. ***IDFS extrapolations based on the KM data – ("SAS outputs" sheet)***
iii. ***Rates of metastatic and non-metastatic recurrences – ("IDFS Events" sheet)***
iv. ***IDFS health state utilities ("Utilities" sheet)***
v. ***TTOT data ("TTOT tables")***
vi. ***Baseline characteristics (age, weight, height) – ("Demo data" sheet)***
vii. ***Updated APHINITY data cut (relevant to node-positive analysis only) – ("Bucher outputs" sheet)***

The following subsections briefly outline each of the updates and present revised cost-effectiveness results generated by the amended model.

i) IDFS KM data

As mentioned above, the model now contains IDFS KM data for the ITT, node-negative, and node-positive populations. Figure 3 presents the KM curves below. Please see the Company cost-effectiveness model for the exact data points.

Figure 3. IDFS KM data from KATHERINE trial in the a) ITT, b) node-negative and c) node-positive populations



Abbreviations: IDFS, Invasive disease-free survival; ITT, Intention to treat; KM, Kaplan-Meier; N-, Node-negative; N+, Node-positive; T, trastuzumab; TE, trastuzumab.
* Y-axes have been adjusted to magnify curves.

ii) IDFS extrapolations based on KM data

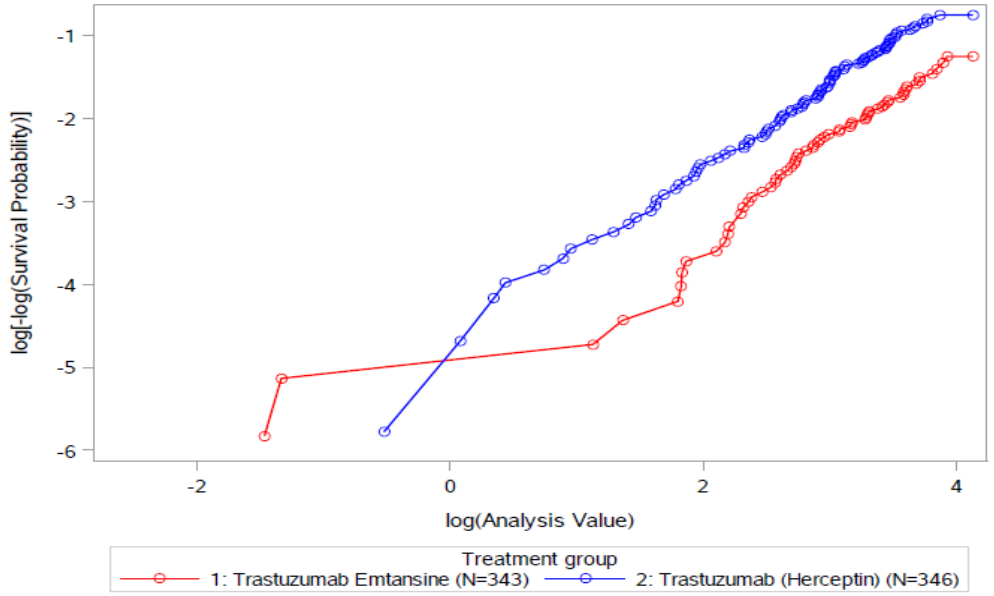
Survival analyses have now been run on each of the KM curves presented in Figure 3. The IDFS extrapolations in the ITT and node-negative subgroups have been presented in Document B and the response to clarification questions, respectively. Only the node-positive extrapolation selection process is presented here.

Assessment of Proportional Hazards Assumption

The PH assumption can be tested graphically, using log-cumulative hazard plots. As shown in Figure 4, the two curves cross, which signals that the PH assumption may not hold. However, this crossing takes place at a time when minimal events have occurred, and the curve is therefore associated with a lot of uncertainty at this timepoint.

A similar situation was observed in the ITT population (Figure 16 of Document B). In Document B, the Company decided not to assume the proportional hazards assumption holds and this was agreed reasonable by the ERG. The same approach has been taken here.

Figure 4. Log of negative log of estimated survivor functions – IDFS endpoint from the KATHERINE study – node-positive population



Statistical fit

Akaike information criterion (AIC) and Bayesian information criterion (BIC) values for the extrapolation of node-positive IDFS data are presented below.

Table 7. IDFS extrapolation – AIC and BIC values (relative ranking of goodness of fit shown in brackets) – node-positive population

	AIC		BIC	
	Trastuzumab emtansine arm	Trastuzumab arm*	Trastuzumab emtansine arm	Trastuzumab arm
Exponential	438.44 (1)	619.47 (1)	442.28 (1)	623.32 (1)
Weibull	439.94 (3)	621.45 (5)	447.62 (3)	629.15 (4)
Log-normal	443.19 (6)	619.83 (2)	450.86 (5)	627.52 (2)
Gamma	441.88 (5)	621.39 (4)	453.39 (6)	632.93 (6)
Log-logistic	439.74 (2)	619.86 (3)	447.42 (2)	627.55 (3)
Gompertz	440.30 (4)	621.47 (6)	447.97 (4)	629.16 (5)

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion.

Based on the values in Table 7 the Exponential appears to be the best statistical fit to the KM data.

Extrapolation approach

The Company has decided to adopt the ERG's preferred approach for the extrapolation of IDFS in the node-positive analysis (i.e. use of KM data until the point of the last observed event, then the best fitting function thereafter).

Invasive disease-free survival in the node-positive subgroup analysis has been extrapolated by using KM data until 50.83 months (trastuzumab emtansine arm) and 47.97 months (trastuzumab arm) then the Exponential function thereafter. The choice of extrapolation function post-KM data has been evaluated in scenario analysis.

iii) Rates of metastatic and non-metastatic recurrence

In their report, the ERG cited that there was potential uncertainty surrounding the model results in the node-negative subgroup analysis because the rates of metastatic and non-metastatic recurrence observed in the ITT population of KATHERINE were used, rather than those of the node-negative population. This has been rectified – Table 8 below presents the metastatic and non-metastatic recurrence rates used in the updated model for each of the subgroups.

Table 8. Proportion of recurrences which are non-metastatic by treatment arm in the "early" and "late" relapser population

	ITT		Node-negative		Node-positive	
	Trastuzumab emtansine (n=743)	Trastuzumab (n=743)	Trastuzumab emtansine (n=400)	Trastuzumab (n=397)	Trastuzumab emtansine (n=343)	Trastuzumab* (n=346)
IDFS event, n	91	165	29	62	62	103
Deaths without prior event, n (%)	2 (2.20%)	3 (1.82%)	2 (6.90%)	2 (3.23%)	0 (0.0%)	1 (0.97%)
IDFS event excluding deaths, n	89	162	27	60	62	102
"Early" relapser – pre-18 months[a]						
Metastatic recurrence, n (%)	36 (85.71%)	60 (72.29%)	9 (81.82%)	24 (72.73%)	30 (96.77%)	41 (78.85%)
Non-metastatic recurrence, n (%)	6 (14.29%)	23 (27.71%)	2 (18.18%)	9 (27.27%)	1 (3.23%)	11 (21.15%)
"Late" relapser – post-18 months[a]						
Metastatic recurrence, n (%)	42 (89.36%)	58 (73.42%)	12 (75.00%)	17 (62.96%)	27 (87.10%)	36 (72.00%)
Non-metastatic recurrence, n (%)	5 (10.64%)	21 (26.58%)	4 (25.00%)	10 (37.04%)	4 (12.90%)	14 (28.00%)

* Given that trastuzumab is not a relevant comparator in the node-positive population, these figures have been presented for completeness.
Footnotes: [a]Deaths are not counted as IDFS events in these figures. Death is accounted for separately in the model.
Abbreviations: IDFS: invasive disease-free survival.

Much like the base case, the rates presented in Table 8 were applied by treatment arm. Rates seen in the node-positive and node-negative subgroups are broadly similar to those seen in the ITT. For example, the proportion of metastatic recurrences is always superior to non-metastatic recurrences regardless of treatment, there is a higher proportion of metastatic recurrences in the early relapser period, and trastuzumab emtansine has a higher proportion of metastatic recurrences regardless of nodal status. There are however, some anomalies in these figures, for example, patients on trastuzumab emtansine arm in the early relapser node-positive population would expect their IDFS event to be metastatic in nature 97% of the time. This is likely an artefact of the data due to low event numbers.

A note on the rates of metastatic and non-metastatic recurrences applied in the pertuzumab + trastuzumab arm of the model
In the node-positive population, the relevant comparator is pertuzumab + trastuzumab. Pertuzumab + trastuzumab was not included in the KATHERINE trial, it is therefore not possible to derive the rates of metastatic and non-metastatic recurrence from this data source. In the base case analysis, the rates observed in both arms of the KATHERINE trial were pooled and applied to the pertuzumab + trastuzumab arm in the model.

The updated model now includes the option to use the rates of metastatic and non-metastatic recurrences seen in the node-positive population of the pertuzumab + trastuzumab arm of APHINITY. At the time of writing, there have been two data cuts of the APHINITY trial (primary analysis at ~4 years and interim OS analysis at ~6 years). The rates derived from each of these data cuts, along with the KATHERINE pooled values are presented below in Table 9.

Table 9. Proportion of recurrences which are non-metastatic by treatment arm in the "early" and "late" relapser population in the node-positive patients of pertuzumab + trastuzumab arms

	KATHERINE - Pooled	APHINITY – 4-year	APHINITY – 6-year
	Pertuzumab + trastuzumab (n=689)	Pertuzumab + trastuzumab (n=1503)	Pertuzumab + trastuzumab (n=1503)
IDFS event, n	165	139	173
Deaths without prior event, n (%)	1 (0.61%)	20 (14.39%)	26 (15.03%)
IDFS event excluding deaths, n	164	119	147
"Early" relapser – pre-18 months[a]			
Metastatic recurrence, n (%)	63 (77.78%)	31 (75.61%)	31 (75.61%)
Non-metastatic recurrence, n (%)	18 (22.22%)	10 (24.39%)	10 (24.39%)
"Late" relapser – post-18 months[a]			
Metastatic recurrence, n (%)	71 (85.54%)	67 (85.90%)	93 (87.74%)
Non-metastatic recurrence, n (%)	12 (14.46%)	11 (14.10%)	13 (12.26%)

Footnotes: [a]Deaths are not counted as IDFS events in these figures. Death is accounted for separately in the model.
Abbreviations: IDFS: invasive disease-free survival.

The choice of rates used in the pertuzumab + trastuzumab arm negligibly affects cost-effectiveness. Scenario analyses on the choice of the source used for the rates are presented in scenarios 18-20 of Table 19.

iv) IDFS health state utilities

In the Company submission and response to clarification questions, all subgroup analyses used health state utilities derived from the ITT population in KATHERINE. It could be argued that for the node-negative and node-positive analyses, it is perhaps more appropriate to use health state utilities collected in these populations.
IDFS state utilities for the ITT, node-negative, and node-positive populations are presented below in Table 10.

Table 10. IDFS health state utilities from KATHERINE

State	ITT (Utility (SE))			Node-negative (Utility (SE))			Node-positive (Utility (SE))			Source
	TE arm	T arm	Pooled	TE arm	T arm	Pooled	TE arm	T arm*	Pooled	
IDFS – On treatment	0.774 (0.009)	0.776 (0.010)	0.775 (0.009)	0.778 (0.013)	0.783 (0.012)	0.781 (0.012)	0.769 (0.013)	0.767 (0.017)	0.768 (0.015)	EQ-5D data from KATHERINE
IDFS – Off treatment	0.784 (0.010)	0.791 (0.009)	0.788 (0.010)	0.798 (0.012)	0.802 (0.011)	0.800 (0.012)	0.769 (0.015)	0.777 (0.015)	0.773 (0.015)	
Non metastatic recurrence	0.774 (0.009)	0.776 (0.010)	0.775 (0.009)	0.778 (0.013)	0.783 (0.012)	0.781 (0.012)	0.769 (0.013)	0.767 (0.017)	0.768 (0.015)	Assumption
Remission	0.784 (0.010)	0.791 (0.009)	0.788 (0.010)	0.798 (0.012)	0.802 (0.011)	0.800 (0.012)	0.769 (0.015)	0.777 (0.015)	0.773 (0.015)	

* Given that trastuzumab is not a relevant comparator in the node-positive population, these figures have been presented for completeness.
Abbreviations: IDFS, Invasive disease-free survival; ITT, Intention to treat; SE, Standard error; T, trastuzumab; TE, trastuzumab emtansine.

As anticipated there are minimal differences in the utility values, thereby signalling that health-related quality of life (HRQoL) is not expected to vary according to nodal status alone. Upon further inspection, some of these utilities lack face validity. For example, in the trastuzumab emtansine arm of the node-positive population there is no difference in the utility values across the IDFS health states. It seems illogical to assume that being in IDFS and receiving no treatment (i.e. no treatment-related adverse events) is associated with the same level of health-related quality of life as a non-metastatic recurrence. Discrepancies in these figures are likely due to the limited number of observations in the EQ-5D data.

Due to the issues with face-validity and the fact that HRQoL does not appear to vary according to nodal status, the Company argues that it is still most appropriate to use the ITT values in all subgroup analyses for the purposes of decision-making. Scenario analyses using the subgroup-specific values are presented below. Please note, in the KATHERINE trial no EQ-5D data was collected after recurrence. Therefore, subgroup data for the utilities in metastatic health states are not available. Finally, as in the base case analysis, pertuzumab + trastuzumab utilities in the node-positive analysis are equal to the pooled values in the ITT population of KATHERINE.

Safety

Subgroup-specific safety analyses have now been run. As anticipated, no new safety signals were identified. The criteria set out in Document B meant that none of the AEs in either the node-negative or the node-positive subgroups qualified for inclusion in the economic model (i.e. all had an incidence of <2%). Consequently, no subgroup-specific safety data has been integrated into the model.

v) Time to-off Treatment (TToT)

In the response to clarification questions, the Company postulated that the time at which a patient remained on treatment would not be expected to vary according to nodal status. Nevertheless, the ERG argued that this point remained uncertain. The TToT data for each of the relevant subgroups in KATHERINE is presented below and has now been integrated into the economic model.

Table 11. Time to off-treatment data across relevant subgroups in the KATHERINE trial

Cycle number	ITT		Node-negative		Node-positive	
	TE arm	T arm	TE arm	T arm	TE arm	T arm*
Cycle 1	100.0%	99.9%	100.0%	100.0%	100.0%	99.7%
Cycle 2	97.8%	97.9%	97.5%	98.5%	98.2%	97.3%
Cycle 3	95.9%	96.3%	95.5%	96.9%	96.5%	95.5%
Cycle 4	94.3%	94.7%	93.5%	96.1%	95.3%	93.1%
Cycle 5	92.7%	93.9%	92.0%	95.9%	93.5%	91.5%
Cycle 6	91.9%	93.1%	91.3%	95.1%	92.6%	90.6%
Cycle 7	90.9%	92.1%	90.5%	94.3%	91.5%	89.4%
Cycle 8	90.0%	90.6%	89.8%	93.1%	90.3%	87.6%
Cycle 9	88.8%	89.7%	88.3%	92.8%	89.4%	86.1%
Cycle 10	87.7%	88.5%	87.3%	91.3%	88.2%	85.2%
Cycle 11	86.4%	85.8%	85.8%	88.7%	87.1%	82.5%
Cycle 12	84.7%	83.9%	83.5%	86.6%	86.2%	80.7%
Cycle 13	82.4%	82.5%	82.3%	84.3%	82.6%	80.4%
Cycle 14	80.1%	81.0%	80.5%	83.0%	79.7%	78.5%

* Given that trastuzumab is not a relevant comparator in the node-positive population, these figures have been presented for completeness. Pertuzumab + trastuzumab TToT data has been taken from the APHINITY trial – as outlined in the Company's original submission.

Abbreviations: ITT, Intention to treat; T, trastuzumab; TE, trastuzumab emtansine.

It is evident that there is no material difference between the times spent on treatment across the three subgroups. Therefore, the impact of using subgroup specific TTOT data in the model is negligible.

vi) Baseline characteristics

The model now incorporates subgroup specific baseline characteristics. Please see Table 12.

Table 12. Baseline characteristics across relevant subgroups in the KATHERINE trial

Baseline characteristic	ITT		Node-negative		Node-positive	
	Mean	Std. Err	Mean	Std. Err	Mean	Std. Err
Age (years)	49.10	10.65	48.85	10.80	49.35	10.5
Weight (kg)	70.91	15.15	70.05	14.71	71.93	15.61
Height (cm)	163.10	7.17	163.36	7.17	162.79	7.17

Abbreviations: cm, Centimetre; ITT, Intention to treat; kg, Kilograms; Std. Err.; Standard error.

vii) Updated APHINITY data cut

In the node-positive subgroup analysis of this submission, pertuzumab + trastuzumab is the relevant comparator. The indirect treatment comparison used to derive comparative effectiveness of trastuzumab emtansine compared to pertuzumab + trastuzumab relies on the hazard ratios from the APHINITY trial. At the time of the original evidence submission, only the hazard ratios from the primary analysis of the APHINITY trial were available. However, in December 2019, the interim OS analysis from the APHINITY trial became available. As communicated on the Technical Engagement teleconference, the Company modified the ITC to include the updated hazard ratios. Outputs of the revised Bucher analysis are presented alongside the original figures in Table 13 and Table 14 below.

Table 13. Hazard ratios from Bucher analysis – 4-year APHINITY data cut

Scenario	APHINITY			KATHERINE			ITC	
	Population	HR (95% CI)	Log HR (±SE)	Population	HR (95% CI)	Log HR (±SE)	Log HR (±SE)	HR (95% CI)
A	Node-positive	0.77 (0.62–0.96)	-0.26 (0.11)	Node-positive	0.52 (0.38–0.71)	-0.65 (0.16)	-0.39 (0.19)	0.675 (0.461–0.989)
B	Node-positive	0.77 (0.62–0.96)	-0.26 (0.11)	ITT	0.50 (0.39–0.64)	-0.69 (0.13)	-0.43 (0.17)	0.649 (0.467–0.904)
C	ITT	0.81 (0.67–1.00)	-0.21 (0.10)	ITT	0.50 (0.39–0.64)	-0.69 (0.13)	-0.48 (0.16)	0.617 (0.449–0.849)

Abbreviations: 95% CI, 95% confidence interval; HR, Hazard ratio; ITC, Indirect treatment comparison; ITT, Intention to treat; SE, Standard error.

Table 14. Hazard ratios from Bucher analysis – 6-year APHINITY data cut

Scenario	APHINITY			KATHERINE			ITC	
	Population	HR (95% CI)	Log HR (±SE)	Population	HR (95% CI)	Log HR (±SE)	Log HR (±SE)	HR (95% CI)
A	Node-positive	0.72 (0.59-0.87)	-0.33 (0.10)	Node-positive	0.52 (0.38–0.71)	-0.65 (0.16)	-0.33 (0.19)	0.722 (0.50-1.04)
B	Node-positive	0.72 (0.59-0.87)	-0.33 (0.10)	ITT	0.50 (0.39–0.64)	-0.69 (0.13)	-0.36 (0.16)	0.694 (0.51-0.95)
C	ITT	0.76 (0.64-0.91)	-0.27 (0.09)	ITT	0.50 (0.39–0.64)	-0.69 (0.13)	-0.42 (0.16)	0.658 (0.49-0.89)

Abbreviations: 95% CI, 95% confidence interval; HR, Hazard ratio; ITC, Indirect treatment comparison; ITT, Intention to treat; SE, Standard error.

Both sets of outputs are available for use in the revised cost-effectiveness model. However, the values derived using the six-year APHINITY data are the most robust and should therefore be used for the purposes of decision-making.

Revised base case analysis

Given the updates to the model highlighted in the previous section, and the preferred assumptions highlighted by the NICE Technical Team, the Company has developed a revised base case to aid with decision-making. The tables below summarise the list of changes in the revised analyses (node-negative and node-positive subgroup) along with the accompanying cost-effectiveness results.

Node-negative analysis (trastuzumab emtansine vs. trastuzumab)

A list of the changes made in the node-negative economic analysis are detailed below in Table 15 along with the corresponding cost-effectiveness estimates (see Table 17).

Table 15. Changes to the Company base case - node-negative analysis

Issue	Change	Justification
IDFS extrapolation approach	KM data until last event then Exponential distribution thereafter in both treatment arms	ERG preferred approach. Use of KM data avoids over/underestimation of IDFS during observation period. Exponential distribution is best fitting function across both arms.
Treatment effect duration	Full treatment effect to three years (36 months) before ceasing completely at eight years (96 months)	ERG preferred assumptions
Recurrence rates	Treatment arm-specific recurrence rates derived from the node-negative population of KATHERINE	Change was requested by ERG and NICE team. Most appropriate to apply the rates derived from the node-negative population in the node-negative economic analysis. These figures were provided to the ERG by the Company in response to clarification questions.
Time to off-treatment data	Time to off-treatment data collected in the node-negative population of KATHERINE	Change was requested by ERG and NICE team. Most appropriate to apply the TToT data collected in the node-negative population in the node-negative economic analysis
Baseline characteristics (age, weight, height)	Baseline characteristics in the node-negative population of KATHERINE. Values are pooled across treatment arms	Most appropriate to use baseline characteristics of node-negative population in the node-negative economic analysis. These figures were provided to the ERG by the Company in response to clarification questions.
IDFS health state utilities	Treatment arm specific health state utilities derived from EQ-5D responses in the ITT population of KATHERINE	ERG preferred assumption. This approach more likely to account for HRQoL impact of AEs.
Metastatic breast cancer health state utilities	Utility values taken from Lidgren *et al.*[vi]	ERG preferred assumption. Lidgren *et al.* publication more closely aligns to the NICE reference case[ix]

Abbreviations: AEs, Adverse events; HR, Hazard ratio; IDFS, Invasive disease-free survival; KM, Kaplan-Meier; TE, trastuzumab emtansine.

The preferred assumptions used in the Company's revised base case now very closely aligns to the ERG's. The small difference in the Company and ERG ICER in the node-negative analysis is driven solely by the use of TTOT data observed in the node-negative population of KATHERINE, instead of the ITT data.

Table 16. Revised base case cost-effectiveness results compared to ERG – node-negative analysis

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
ERG preferred analysis							
Trastuzumab	[redacted]	16.76	[redacted]	[redacted]	1.23	[redacted]	£9,339
Trastuzumab emtansine	[redacted]	17.99	[redacted]				
Company revised base case							
Trastuzumab	[redacted]	16.76	[redacted]	[redacted]	1.23	[redacted]	£8,829
Trastuzumab emtansine	[redacted]	17.99	[redacted]				

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

Node-positive analysis (trastuzumab emtansine vs. pertuzumab + trastuzumab)

A list of the changes made in the node-positive economic analysis are detailed below in Table 17 along with the corresponding cost-effectiveness estimates (see Table 17).The majority of changes made here echo those made in the node-negative analysis.

Table 17. Changes to the revised base case - node-positive analysis

Issue	Change	Justification
IDFS extrapolation	KM data until last event then Exponential distribution thereafter in trastuzumab emtansine	Use of KM data avoids over/underestimation of IDFS during observation period. Exponential distribution is best fitting function.
APHINITY HRs used in Bucher analysis	Hazard ratio taken from the 6-year data cut of the APHINITY trial.	Most appropriate to use the longer term, more robust efficacy data from APHINITY.
Bucher analysis output	Scenario A – HR in node-positive population of APHINTY and HR in node-positive population of KATHERINE	Most conservative HR. Comparison to pertuzumab + trastuzumab only relevant in node-positive populations
Treatment effect duration	Full treatment effect to three years (36 months) before ceasing completely at eight years (96 months)	ERG preferred assumptions
Recurrence rates	TE arm: Treatment arm-specific recurrence rates derived from the node-positive population of KATHERINE. P + T arm: Rates in the node-positive population of the P + T arm of APHINITY (6-year data cut) have been used.	Change was requested by ERG and NICE team. Most appropriate to apply treatment-specific rates derived from node-positive populations.
Time to off-treatment data	TE arm: Time to off-treatment data collected in the node-positive population of KATHERINE P + T arm: Time to off-treatment data collected in the node-positive population of APHINITY (as per Company base case)	Change was requested by ERG and NICE team. Most appropriate to apply treatment-specific Time to off-treatment data collected in node-positive populations.
Baseline characteristics (age, weight, height)	Baseline characteristics in the node positive population of KATHERINE. Values are pooled across treatment arms	Most appropriate to use baseline characteristics of node-positive population in the node-positive economic analysis.
IDFS health state utilities	Treatment arm specific health state utilities derived from EQ-5D responses in the ITT population of KATHERINE	ERG preferred assumption. This approach more likely to account for HRQoL impact of AEs.
Metastatic breast cancer health state utilities	Utility values taken from Lidgren *et al.*	ERG preferred assumption. Lidgren *et al.* publication more closely aligns to the NICE reference case[ix]

Abbreviations: AEs, Adverse events; HR, Hazard ratio; IDFS, Invasive disease-free survival; KM, Kaplan-Meier; P + T, pertuzumab + trastuzumab; TE, trastuzumab emtansine.

Table 18. Revised base case cost-effectiveness results – node-positive analysis

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Pertuzumab + trastuzumab	[redacted]	13.97	[redacted]	[redacted]	0.67	[redacted]	£4,955
Trastuzumab emtansine	[redacted]	14.64	[redacted]				

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

Scenario analyses

As part of this response, the Company has undertaken a significant number of scenario analyses in an attempt to quantify any remaining uncertainty and to illustrate that the reimbursement of trastuzumab emtansine in this setting represents a low-risk decision for the Appraisal Committee. Scenario analyses centre on the following list of issues highlighted by the NICE Technical Team and the ERG as possible areas of remaining uncertainty:

- Treatment effect duration
- Patient weight
- Vial sharing
- Bucher analysis outputs
- Recurrence rates in pertuzumab + trastuzumab arm
- Subgroup specific IDFS utilities
- Assumptions on the parameterisation of the cure model
- Choice of IDFS extrapolation function post-KM period in node-positive analysis

Results of these scenario analyses are presented in Table 19 below. Please note, all results presented in Table 19 incorporate the assumptions in the Company's revised base case unless stated otherwise.

Table 19. Scenario analyses

Area	#	Value	Node-negative		Node-positive	
			ICER (/QALY gained)	Δ from base case	ICER (/QALY gained)	Δ from base case
	0	Revised base case	£8,829	*£0*	£4,955	*£0*
Treatment effect duration	1	Stops at 4 years	£14,654	*+£5,825*	£13,071	*+£8,116*
	2	Begins waning at 4 years, ceases at 7 years	£9,115	*+£286*	£4,454	*-£501*
	3	Begins waning at 5 years ceases at 8 years	£6,534	*-£2,295*	£1,889	*-£3,066*
	4	Begins waning at 6 years ceases at 9 years	£4,942	*-£3,887*	£389	*-£4,566*
	5	Begins waning at 7 years ceases at 10 years	£3,988	*-£4,841*	TE dominant	*N/A*
Patient weight	6	Planned dose - 70 kg	£8,829	£0	£4,955	£0
	7	Planned dose - 72.5 kg	£12,822	+£3,993	£12,532	+£7,577
	8	Planned dose - 75 kg	£12,810	+£3,981	£12,519	+£7,564
Vial sharing	9	Actual dose – 0% vial sharing	£8,829	£0	£4,955	£0
	10	Actual dose – 50% vial sharing	£8,350	-£479	£4,008	-£947
	11	Actual dose – 100% vial sharing	£7,871	-£958	£3,061	-£1,894
	12	Planned dose – 0% vial sharing	£8,829	£0	£4,955	£0
	13	Planned dose – 50% vial sharing	£8,467	-£362	£5,055	£100
	14	Planned dose – 100% vial sharing	£8,104	-£725	£5,155	£200
Bucher outputs	15	Scenario A - N+ KATHERINE / N+ APHINITY (4yr)	N/A	*N/A*	£1,094	*-£3,861*
	16	Scenario B – ITT KATHERINE / N+ APHINITY (4yr)	N/A	*N/A*	TE dominant	*N/A*
	17	Scenario C – ITT KATHERINE / ITT APHINITY (4yr)	N/A	*N/A*	TE dominant	*N/A*
	18	Scenario A – N+ KATHERINE / N+ APHINITY (6yr)	N/A	*N/A*	£4,955	*£0*
	19	Scenario B – ITT KATHERINE / N+ APHINITY (6yr)	N/A	*N/A*	£2,468	*-£2,487*
	20	Scenario C – ITT KATHERINE / ITT APHINITY (6yr)	N/A	*N/A*	£69	*-£4,886*
Recurrence in P + T arms	21	KATHERINE - pooled	N/A	*N/A*	£5,646	*+£691*
	22	APHINITY (4yr) - P + T arm	N/A	*N/A*	£5,627	*+£672*
	23	APHINITY (6yr) - P + T arm	N/A	*N/A*	£4,955	*£0*
IDFS utilities	24	Subgroup specific	£8,700	*-£129*	£4,958	*+£3*
	25	ITT	£8,829	*£0*	£4,955	*£0*

Cure model	26	Start at 36 months, 95% at 120 months	£8,829	*£0*	£4,955	*£0*
	27	Start at 48 months, 95% at 120 months	£8,688	*-£141*	£5,060	*+£105*
	28	Start at 60 months, 95% at 120 months	£8,537	*-£292*	£5,569	*+£614*
	29	Start at 36 months, 85% at 120 months	£10,147	*+£1,318*	£8,732	*+£3,777*
	31	Start at 36 months, 90% at 120 months	£9,481	*+£652*	£6,784	*+£1,829*
	32	Start at 36 months, 100% at 120 months	£8,191	*-£638*	£3,233	*-£1,722*
	33	Start at 36 months, 95% at 96 months	£8,589	*-£240*	£3,679	*-£1,276*
	34	Start at 36 months, 95% at 108 months	£8,636	*-£193*	£4,215	*-£740*
Choice of extrap. function post-KM in TE arm of N+ analysis	35	Exponential	N/A	*N/A*	£4,955	*£0*
	36	Weibull	N/A	*N/A*	£4,822	*-£133*
	37	Log-Normal	N/A	*N/A*	£2,732	*-£2,223*
	38	Gamma	N/A	*N/A*	£2,589	*-£2,366*
	39	Log-Logistic	N/A	*N/A*	£2,902	*-£2,053*
	40	Gompertz	N/A	*N/A*	£3,360	*-£1,595*

Abbreviations: extrap. extrapolation; ICER, Incremental cost-effectiveness ratio; IDFS, Invasive disease-free survival; ITT, Intention to treat; N-, Node-negative; N+, Node-positive; P + T, pertuzumab + trastuzumab; TE, trastuzumab emtansine.

Conclusion on revised cost-effectiveness estimates

In the node-negative analysis, the ICER is £8,829 / QALY gained. It is important to bear in mind that this figure incorporates conservative assumptions regarding treatment effect duration (see Issue 4), treatment switching, and vial sharing. In this subgroup analysis, the uncertainty is now minimal and the assumptions have been agreed by all parties. Consequently, trastuzumab emtansine in the node-negative subgroup can be considered an extremely cost-effective use of NHS resources.

With respect to the node-positive subgroup analysis, the updates conducted mean that the model can now be considered robust enough for decision-making. To mitigate for the uncertainty in this subgroup, the Company has adopted conservative assumptions in key aspects of the analysis (IDFS extrapolation, treatment effect duration, ITC output). Despite this conservative approach, the base case ICER in the node-positive analysis is still only £4,955 / QALY gained.

In summary, the revised base case and scenario analyses above help to prove that trastuzumab emtansine can be considered a cost-effective use of NHS resources across all subgroups (ITT, node-negative, and node-positive). This conclusion stands regardless of the assumptions used for the indirect treatment comparison, treatment effect duration, or extrapolation approach. Given this, the Company believes that, despite

the uncertainty, a positive recommendation of trastuzumab emtansine in this indication represents a low-risk decision for the Appraisal Committee.

[i] von Minckwitz G, Huang C-S, Mano MS, et al. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. New England Journal of Medicine 2019;380:617-628.

[ii] von Minckwitz G, Procter M, de Azambuja E, et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. New England Journal of Medicine 2017;377:122-131.

[iii] Bucher HC, Guyatt GH, Griffith LE, et al. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. Journal of Clinical Epidemiology 1997;50:683-691.

[iv] Cameron D, Piccart-Gebhart MJ, Gelber RD, et al. 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. The Lancet 2017;389:1195-1205.

[v] NICE. TA569: Pertuzumab for adjuvant treatment of HER2-positive early stage breast cancer. 2019. Available at: https://www.nice.org.uk/guidance/ta569.

[vi] Lidgren M, Wilking N, Jonsson B, et al. Health related quality of life in different states of breast cancer. Qual Life Res 2007;16:1073-81.

[vii] Lloyd A, Nafees B, Narewska J, et al. Health state utilities for metastatic breast cancer. British journal of cancer 2006;95:683-690.

[viii] Roche Market Research. Available on request.

[ix] NICE. Guide to the methods of technology appraisal 2013. Process and methods [PMG9]. Available at: https://www.nice.org.uk/process/pmg9/chapter/the-reference-case.

As requested, a column has been added to denote exactly where the changes listed in Table 15 and Table 17 of the original response are implemented in the economic model. Additionally, a separate table has been added for the ITT population. The revised tables are presented below in Table 1 (node-negative), Table 2 (node-positive), and Table 3 (ITT).

Table 1. Changes to the Company base case - node-negative analysis

Issue	Change	Location in economic model	Justification
IDFS extrapolation approach	KM data until last event then Exponential distribution thereafter in both treatment arms	**Location:** "Model inputs" sheet – Cell I104 & I106 **Input:** "KM + Exponential tail" in both cells	ERG preferred approach. Use of KM data avoids over/underestimation of IDFS during observation period. Exponential distribution is best fitting function across both arms.
Treatment effect duration	Full treatment effect to three years (36 months) before ceasing completely at eight years (96 months)	**Location:** "Model inputs" sheet – Cell I150 **Input:** "ERG"	ERG preferred assumptions
Recurrence rates	Treatment arm-specific recurrence rates derived from the node-negative population of KATHERINE	**Location:** "Model inputs" sheet – Cell I130 **Input:** "Node-negative"	Change was requested by ERG and NICE team. Most appropriate to apply the rates derived from the node-negative population in the node-negative economic analysis. These figures were provided to the ERG by the Company in response to clarification questions.
Time to off-treatment data	Time to off-treatment data collected in the node-negative population of KATHERINE	**Location:** "TTOT tables" sheet **Input:** TTOT data used is dependent on population that's selected in cell I40 of "Model Inputs" sheet	Change was requested by ERG and NICE team. Most appropriate to apply the TToT data collected in the node-negative population in the node-negative economic analysis
Baseline characteristics (age, weight, height)	Baseline characteristics in the node-negative population of KATHERINE. Values are pooled across treatment arms	**Location:** "Model inputs" sheet – Cell I25 to K30 **Input:** Baseline characteristics are dependent on population that's selected cell I40 of "Model Inputs" sheet.	Most appropriate to use baseline characteristics of node-negative population in the node-negative economic analysis. These figures were provided to the ERG by the Company in response to clarification questions.
IDFS health state utilities	Treatment arm specific health state utilities derived from EQ-5D responses in the ITT population of KATHERINE	**Location:** "Model inputs" sheet – Cell G55 **Input:** "ITT"	ERG preferred assumption. This approach more likely to account for HRQoL impact of AEs.
Metastatic breast cancer health state utilities	Utility values taken from Lidgren *et al.*	**Location:** "Model inputs" sheet – Cell G66 **Input:** "Lidgren et al."	ERG preferred assumption. Lidgren *et al.* publication more closely aligns to the NICE reference case

Abbreviations: AEs, Adverse events; HR, Hazard ratio; IDFS, Invasive disease-free survival; KM, Kaplan-Meier; TE, trastuzumab emtansine.

Table 2. Changes to the revised base case - node-positive analysis

Issue	Change	Location and input in economic model	Justification
IDFS extrapolation	KM data until last event then Exponential distribution thereafter in trastuzumab emtansine	**Location:** "Model inputs" sheet – Cell I104 & I106 **Input:** "KM + Exponential tail" in both cells	Use of KM data avoids over/underestimation of IDFS during observation period. Exponential distribution is best fitting function.
APHINITY HRs used in Bucher analysis	Hazard ratio taken from the 6-year data cut of the APHINITY trial.	**Location:** "Model inputs" sheet – Cell I192 **Input:** "6 year"	Most appropriate to use the longer term, more robust efficacy data from APHINITY.
Bucher analysis output	Scenario A – HR in node-positive population of APHINTY and HR in node-positive population of KATHERINE	**Location:** "Model inputs" sheet – Cell I193 **Input:** "Scenario A – APHINITY N+ / KATHERINE N+"	Most conservative HR. Comparison to pertuzumab + trastuzumab only relevant in node-positive populations
Treatment effect duration	Full treatment effect to three years (36 months) before ceasing completely at eight years (96 months)	**Location:** "Model inputs" sheet – Cell I150 **Input:** "ERG"	ERG preferred assumptions
Recurrence rates	TE arm: Treatment arm-specific recurrence rates derived from the node-positive population of KATHERINE. P + T arm: Rates in the node-positive population of the P + T arm of APHINITY (6-year data cut) have been used.	**TE arm** **Location:** "Model inputs" sheet – Cell I130 **Input:** "Node-positive" **P + T arm** **Location:** "Model Inputs" sheet – Cell I131 **Input:** "Yes – 6yr data cut"	Change was requested by ERG and NICE team. Most appropriate to apply treatment-specific rates derived from node-positive populations.
Time to off-treatment data	TE arm: Time to off-treatment data collected in the node-positive population of KATHERINE P + T arm: Time to off-treatment data collected in the node-positive population of APHINITY (as per Company base case)	**Location:** "TTOT tables" sheet **Input:** TTOT data used is dependent on population that's selected in cell I40 of "Model Inputs" sheet	Change was requested by ERG and NICE team. Most appropriate to apply treatment-specific Time to off-treatment data collected in node-positive populations.
Baseline characteristics (age, weight, height)	Baseline characteristics in the node positive population of KATHERINE. Values are pooled across treatment arms	**Location:** "Model inputs" sheet – Cell I25 to K30 **Input:** Baseline characteristics are dependent on population that's selected cell I40 of "Model Inputs" sheet.	Most appropriate to use baseline characteristics of node-positive population in the node-positive economic analysis.
IDFS health state utilities	Treatment arm specific health state utilities derived from EQ-5D responses in the ITT population of KATHERINE	**Location:** "Model inputs" sheet – Cell G55 **Input:** "ITT"	ERG preferred assumption. This approach more likely to account for HRQoL impact of AEs.
Metastatic breast cancer health state utilities	Utility values taken from Lidgren *et al.*	**Location:** "Model inputs" sheet – Cell G66 **Input:** "Lidgren et al."	ERG preferred assumption. Lidgren *et al.* publication more closely aligns to the NICE reference case

Abbreviations: AEs, Adverse events; HR, Hazard ratio; IDFS, Invasive disease-free survival; KM, Kaplan-Meier; P + T, pertuzumab + trastuzumab; TE, trastuzumab emtansine.

Table 3. Changes to the revised base case - ITT analysis

Issue	Change	Location and input in economic model	Justification
IDFS extrapolation	KM data until last event then Exponential distribution thereafter in trastuzumab emtansine	**Location:** "Model inputs" sheet – Cell I104 & I106 **Input:** "KM + Exponential tail" in both cells	Use of KM data avoids over/underestimation of IDFS during observation period. Exponential distribution is best fitting function.
APHINITY HRs used in Bucher analysis	Hazard ratio taken from the 6-year data cut of the APHINITY trial.	**Location:** "Model inputs" sheet – Cell I192 **Input:** "6 year"	Most appropriate to use the longer term, more robust efficacy data from APHINITY.
Bucher analysis output	Scenario A – HR in node-positive population of APHINTY and HR in node-positive population of KATHERINE	**Location:** "Model inputs" sheet – Cell I193 **Input:** "Scenario A – APHINITY N+ / KATHERINE N+"	Most conservative HR.
Treatment effect duration	Full treatment effect to three years (36 months) before ceasing completely at eight years (96 months)	**Location:** "Model inputs" sheet – Cell I150 **Input:** "ERG"	ERG preferred assumptions
Recurrence rates	TE arm: Treatment arm-specific recurrence rates derived from the node-positive population of KATHERINE. P + T arm: Rates in the node-positive population of the P + T arm of APHINITY (6-year data cut) have been used.	**TE arm & T arm** **Location:** "Model inputs" sheet – Cell I130 **Input:** "ITT" **P + T arm** **Location:** "Model Inputs" sheet – Cell I131 **Input:** "Yes – 6yr data cut"	Change was requested by ERG and NICE team. Most appropriate to apply treatment-specific rates derived from population of interest
Time to off-treatment data	TE arm: Time to off-treatment data collected in the node-positive population of KATHERINE P + T arm: Time to off-treatment data collected in the node-positive population of APHINITY (as per Company base case)	**Location:** "TTOT tables" sheet **Input:** TTOT data used is dependent on population that's selected in cell I40 of "Model Inputs" sheet	Change was requested by ERG and NICE team. Most appropriate to apply treatment-specific Time to off-treatment data collected in population of interest.
Baseline characteristics (age, weight, height)	Baseline characteristics in the node positive population of KATHERINE. Values are pooled across treatment arms	**Location:** "Model inputs" sheet – Cell I25 to K30 **Input:** Baseline characteristics are dependent on population that's selected cell I40 of "Model Inputs" sheet.	Most appropriate to use baseline characteristics of ITT population in the ITT analysis.
IDFS health state utilities	Treatment arm specific health state utilities derived from EQ-5D responses in the ITT population of KATHERINE	**Location:** "Model inputs" sheet – Cell G55 **Input:** "ITT"	ERG preferred assumption. This approach more likely to account for HRQoL impact of AEs.
Metastatic breast cancer health state utilities	Utility values taken from Lidgren *et al.*	**Location:** "Model inputs" sheet – Cell G66 **Input:** "Lidgren et al."	ERG preferred assumption. Lidgren *et al.* publication more closely aligns to the NICE reference case

Abbreviations: AEs, Adverse events; HR, Hazard ratio; IDFS, Invasive disease-free survival; KM, Kaplan-Meier; P + T, pertuzumab + trastuzumab; TE, trastuzumab emtansine.

A note on the ITT results presented in Table 5 of the original response

Upon reflection, the ITT results presented in Table 5 of the original response perhaps require further explanation. The ICER of £3,943 / QALY gained refers to the comparison of trastuzumab to pertuzumab + trastuzumab in the ITT population. Instead, a revised table has been included below in which the ICERs for the comparisons of trastuzumab to trastuzumab emtansine and pertuzumab + trastuzumab to trastuzumab emtansine in the ITT population are presented. This is perhaps more relevant for the purposes of decision-making than the original table.

Table 4. Revised cost-effectiveness results for ITT, node-negative, and node-positive analyses

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
ITT population							
Trastuzumab	[redacted]	15.06	[redacted]	[redacted]	1.36	[redacted]	£5,985
Trastuzumab emtansine	[redacted]	16.42	[redacted]				
Pertuzumab + trastuzumab	[redacted]	15.77	[redacted]	[redacted]	0.65	[redacted]	£8,203
Trastuzumab emtansine	[redacted]	16.42	[redacted]				
Node-negative							
Trastuzumab	[redacted]	16.76	[redacted]	[redacted]	1.23	[redacted]	£8,829
Trastuzumab emtansine	[redacted]	17.99	[redacted]				
Node-positive							
Pertuzumab + trastuzumab	[redacted]	13.97	[redacted]	[redacted]	0.67	[redacted]	£4,955
Trastuzumab emtansine	[redacted]	14.64	[redacted]				

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

NICE National Institute for Health and Care Excellence

Technical engagement response form

Trastuzumab emtansine for adjuvant treatment of HER2-positive early breast cancer [ID1516]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments: **20 February 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a second version of

your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Breast Cancer Now**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	

Questions for engagement

Issue 1: Treatment pathway	
1 a. Is there any reason to prefer trastuzumab emtansine over pertuzumab plus trastuzumab in node positive disease?	All breast cancer treatments can cause side effects and both trastuzumab emtansine and pertuzumab plus trastuzumab can cause significant adverse effects. A choice of effective treatment options can provide greater potential control over quality of life and is highly valued by many patients. Some node positive patients may feel the side effect profile of trastuzumab emtansine can enable them to have a better quality of life compared to that of pertuzumab plus trastuzumab. It may be helpful to seek clinical expert opinion on whether there are likely to be scenarios in which a patient might prefer the potential side effects of trastuzumab emtansine over pertuzumab plus trastuzumab.
1 b. In clinical practice, do patients with node positive disease only receive pertuzumab plus trastuzumab or are there some people with node positive disease who would receive trastuzumab monotherapy?	
Issue 2: Indirect comparison: trastuzumab emtansine versus pertuzumab plus trastuzumab	
2 a. Are the results of the indirect treatment comparison of trastuzumab emtansine versus pertuzumab plus trastuzumab, using the node-positive populations from APHINITY and KATHERINE trials, clinically plausible?	
2 b. Are there any other data that could be used to for the comparison of trastuzumab emtansine versus pertuzumab plus trastuzumab?	

2 c. How should the uncertainty about the relative treatment effects of trastuzumab emtansine and pertuzumab plus trastuzumab be explored. Would a cost comparison be useful?	
Issue 3: IDFS extrapolation	
3 a. Which approach to IDFS modelling, the ERG's or the company's, is more clinically plausible?	
3 b. Is it appropriate to use evidence from the intention to treat population in KATHERINE trial and the node-positive population in HERA trial to adjust modelling in the node negative population?	
Issue 4: Treatment waning effect of trastuzumab emtansine	
4 a. What approach to treatment effect duration, the ERG's, the company's, or a different one, is the most clinically plausible?	
4 b. Would you expect that the duration of treatment effect in the ITT and node-negative populations is the same?	
Issue 5: Utilities	
5 a. Is it appropriate to use the per treatment calculated utility from KATHERINE trial for the IDFS state to take account of the difference in AEs?	
5 b. Are the utilities from Lidgren et al. 2007 more clinically plausible than the Lloyd utilities for the 2 metastatic states in the model?	
Issue 6: Drug costs and modelling assumptions	

6 a. Are the arm specific market shares for trastuzumab and trastuzumab emtansine assumed by the company for early recurrence, first line metastatic state plausible? Or should equal, (or different market share values) be used in the model?	
6 b. Approximately what are the proportions of people who would be given either subcutaneous or intravenous trastuzumab biosimilar when given trastuzumab monotherapy in the adjuvant setting?	
6 c. Is only intravenous trastuzumab biosimilar used in combination with pertuzumab when given in combination in the adjuvant setting?	
6 d. What assumption about patient weight and vial sharing should be adopted in the model?	
Issue 7: Modelling the intention to treat population	
7. Is the model for the intention to treat population, with the technical team changes applied, suitable for decision making?	
Issue 8: Modelling the node positive population	
8 a. If the company uses the correct IDFS data, would the model for the node positive population be suitable for decision making?	
8 b. Given the uncertainties with the node positive specific analyses, do you think that in this instance, evidence from the ITT population, could be used to support the decision about a comparison of trastuzumab emtansine versus pertuzumab?	

Issue 9: Outstanding issues	
9. Are there any issues which are not covered above which are relevant to the appraisal?	

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Trastuzumab emtansine for adjuvant treatment of HER2-positive early breast cancer

ADDENDUM

Critique of new evidence submitted by the company

Produced by Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Date completed 04/03/2020

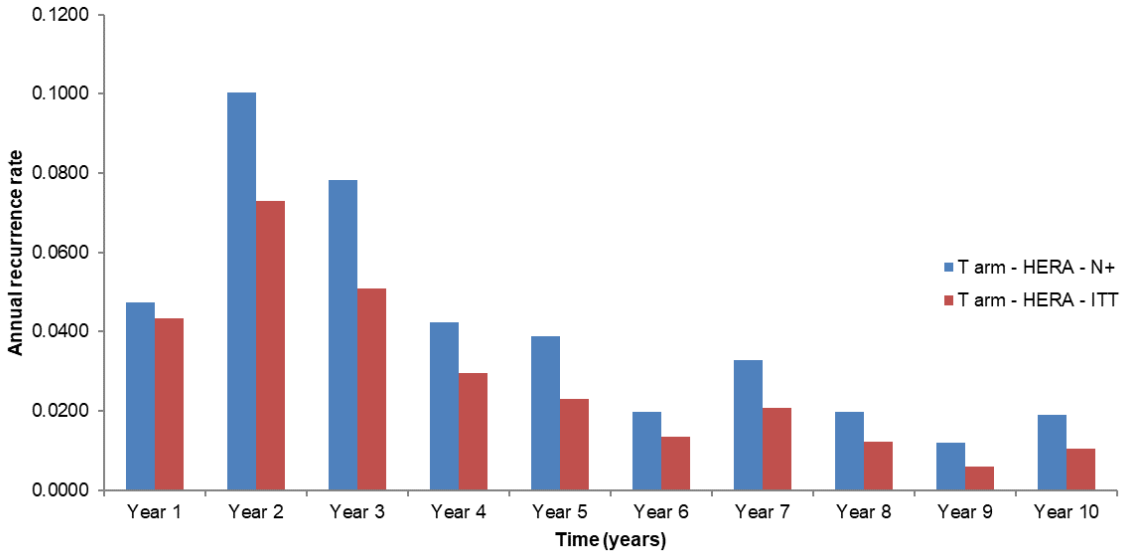
1. Critique of the cost effectiveness evidence submitted by the company in response to the NICE technical report

1.1 Invasive disease-free survival (IDFS) extrapolation

In their revised base-case, the company adopted the ERG's preferred approach for extrapolating IDFS data using the observed KM data from KATHERINE in both treatment arms until the time point where the last event occurs, and then selecting the best fitting parametric survival function to model long-term IDFS.

One potential issue identified by the ERG was that the adjustments made by the company to the KATHERINE node-negative IDFS extrapolations were based on those observed in the node-positive HERA data, which was assumed to be a proxy for the KATHERINE ITT population only. Such a proxy for the node-negative subgroup was not available by the time the ERG report was finished and, therefore, the IDFS adjustments made in the node-negative subgroup might be incorrect, leading to biased results for the node-negative subgroup. The company agreed with this potential issue and suggested that since the node-negative population in KATHERINE can be deemed to be lower risk (than the KATHERINE ITT population) it would be more appropriate to use a lower risk proxy from HERA, such as the ITT population. The company pointed out that, although this equivalence is flawed, it is likely to be the most appropriate given the absence of a direct comparison across the two trials. The company presented in Figure 1.1 the recurrence rates observed in the node-positive population and ITT population of the HERA trial (proxies for KATHERINE ITT and KATHERINE node-negative populations, respectively). The company considered the patterns observed in these two populations to be similar (very few recurrences while on treatment in year one, high risk of recurrence in years two and three, before a notable decrease in year 4). Based on this, the company suggested that the adjustments made to the IDFS extrapolation should not be depending on nodal status. In any case, the company conducted a large number of scenario analyses to test the impact of cure model assumptions on the ICER (see Table 1.9). The company finally, noted that since the cure assumptions are applied equivalently to both treatment arms, the overall impact on the ICER is negligible.

Figure 1.1: Recurrence patterns in ITT and node-positive populations of HERA trial



Source: Figure 1 in company response to NICE technical report.

ERG comment: The ERG agrees with the company that the ITT population from the HERA trial is likely to be a more appropriate proxy for the node-negative subpopulation in KATHERINE. For this purpose, it would have been useful to see a figure like Figure 5.2 in the original ERG report but comparing KATHERINE node-negative with ITT HERA data.

The ERG also agrees with the company that the patterns observed in Figure 1.1 in the two populations are similar. However, the rates are lower for the HERA ITT population, as expected. As discussed in its original report, the ERG considers it important to note that the recurrence rates for the trastuzumab arm predicted by the model were not in line with those observed in the KATHERINE trial. Thus, for the trastuzumab arm, the model fails to replicate the observed recurrence rates in the KATHERINE trial and to reproduce the drop observed at year 4 in the HERA and BCIRG 006 trials. The same might happen with the trastuzumab emtansine arm but, with the current information, the ERG is not able to verify this statement. Whether this has a large impact on the model results or not is a different matter.

The ERG does not agree with the interpretation of the company that the adjustment should not be based on nodal status. Since the model does not seem to replicate recurrence rates, the adjustment should be based on a figure like Figure 5.2 in the original ERG report. This is likely to be different depending on the nodal status (see e.g. the rates in Figure 1.1 are different). Probably what would happen in the model is that in absolute terms IDFS might be wrongly adjusted (it is not possible to know how much because an equivalent to Figure 5.2 is not available) but incrementally, since the same adjustment is applied to both arms, it would not make a difference in the ICER, as the company mentioned. However, as pointed out in the original ERG report, it is also uncertain whether the same adjustment should be applied to both arms equally. In any case, with the current evidence and modelling assumptions, the company's approach of testing the impact of this adjustment on the ICER by conducting scenario analyses, seems appropriate.

1.2 Duration of the trastuzumab emtansine treatment effect

The company is concerned that the ERG preferred assumptions for the treatment effect duration are uncertain and, in the company's opinion, are likely to lead to an underestimation of the trastuzumab emtansine treatment effect.

The rationale for the selection of the ERG's preferred assumptions focused on the annualized hazard ratios observed in the KATHERINE trial. The company considered that, even though this may be the best available evidence, it is important to emphasize the flaws in this data. The main issue is the uncertainty arising from limited patients at risk (due to censoring) and the event numbers. The median follow-up in both arms of the KATHERINE trial was approximately 41 months. As shown in Table 1.1, censoring becomes large at year 4 and the limited event numbers would result in uncertainty in the observed hazard ratios in this and subsequent time periods.

Table 1.1: Patients at risk and event numbers in the KATHERINE trial* - ITT population

Time	Trastuzumab arm			Trastuzumab emtansine arm		
	Patients at risk at start of year (%)	Patients at risk at end of year (%)	Number of IDFS events	Patients at risk at start of year (%)	Patients at risk at end of year (%)	Number of IDFS events
Year 1 (0-11 months)	743 (100.00%)	635 (85.46%)	53	743 (100.00%)	685 (92.19%)	21

Year 2 (12-23 months)	635 (85.46%)	555 (74.70%)	63	682 (91.79%)	640 (86.14%)	32
Year 3 (24-35 months)	555 (74.70%)	350 (47.11%)	33	633 (85.20%)	443 (59.62%)	24
Year 4 (36-47 months)	350 (47.11%)	110 (16.02%)	14	409 (55.05%)	170 (22.88%)	12
Year 5 (48-59 months)	110 (16.02%)	0 (0.00%)	2	170 (22.88%)	0 (0.00%)	2
Source: Table 1 in company response to technical report. Abbreviations: IDFS = invasive disease-free survival *Discrepancies exist in the "patients at risk…" categories due to the non-uniform time intervals in KM data.						

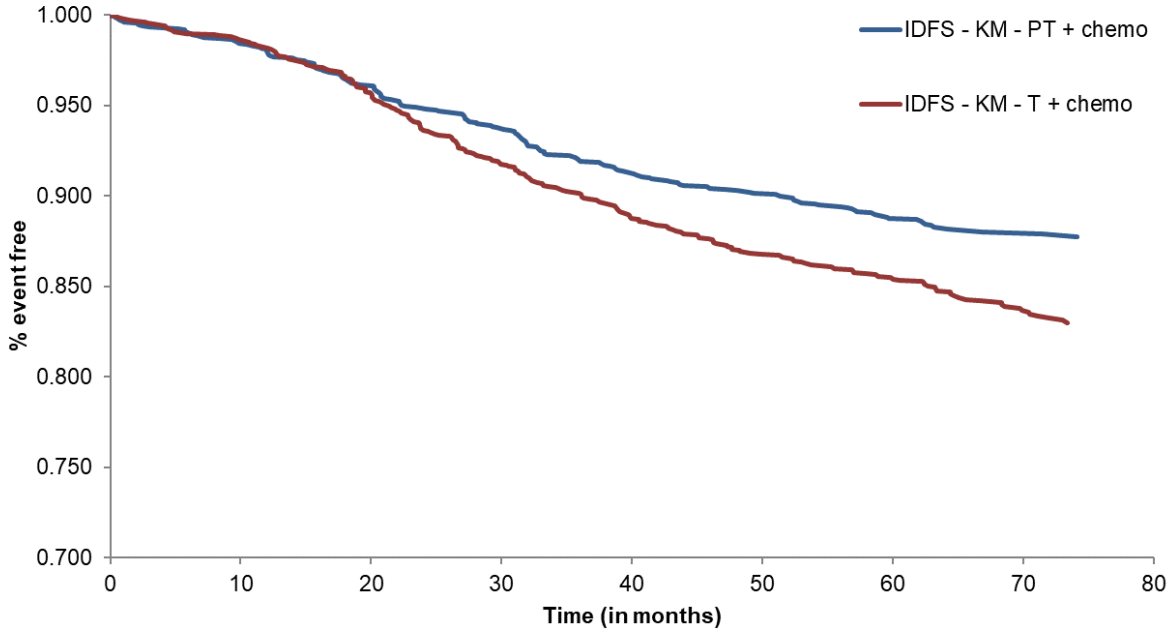
The company also referred to TA569 (pertuzumab + trastuzumab + chemotherapy in adjuvant HER2-positive early breast cancer), where the available evidence was not enough to definitively estimate a treatment effect duration. Consequently, in line with the approach of the ERG for this appraisal, the ERG for TA569 chose to focus on the shape of the KM curves and the annualised hazard ratios as those were believed to be the best available evidence at the time. While the company acknowledges that this may be true, it also considers it important to acknowledge that the use of this evidence led to an underestimation of the pertuzumab treatment effect (full effect to four years before waning and ceasing completely at seven years), according to the most recent analysis of APHINITY data. TA569 was based on the results of the primary analysis (IDFS) of the APHINITY trial. In December of 2019, the interim OS analysis (updated IDFS) of APHINITY was produced. The median duration of follow-up is now 73.5 months (~6 years) in the node-positive population (compared to 45.4 months at primary [IDFS] analysis). The cumulative hazard ratios across the entirety of the observation period are presented below in Table 1.2.

Table 1.2: Cumulative hazard ratios from interim OS analysis (median follow-up = 73.5 months) in node-positive population

Time period	Cumulative hazard ratio
Year 0–1	1.024
Year 0–2	0.793
Year 0–3	0.797
Year 0–4	0.731
Year 0-5	0.757
Year 0-6	0.722
Year 0-7	0.715
Source: Table 1 in company response to technical report. Abbreviations: OS = overall survival.	

The company also presented in Figure 1.2 the Kaplan-Meier IDFS curves from APHINITY capped at median follow-up (before most of the censoring occurs). It was pointed out that that the greatest separation in the curves occurs at 73.5 months, which may suggest that the treatment effect is still increasing at median follow-up.

Figure 1.2: APHINITY Kaplan-Meier IDFS curves – capped at ~73.5 months (median follow-up) (lymph node-positive population)



Source: Figure 2 in response to technical report.
Abbreviations: IDFS = invasive disease-free survival; KM = Kaplan-Meier; PT + chemo = pertuzumab + trastuzumab + chemotherapy; T + chemo = trastuzumab + chemotherapy.

The company considers this evidence to be relevant to this appraisal as pertuzumab and trastuzumab emtansine are both anti-HER2 therapies being used in the adjuvant breast cancer setting. However, the company understands that to use this may not be an ideal analogue due to the differences in study population and design between KATHERINE and APHINITY.

In any case, the company conducted a large number of scenario analyses to test the impact of treatment effect duration assumptions on the ICER (see Table 1.9).

ERG comment: The ERG acknowledges the uncertainty and limitations associated with the duration of the treatment effect assumptions. However, as mentioned in its original report, the ERG still considers that KATHERINE data is the best available source to inform this aspect of the model.

As mentioned by the company there is no evidence evaluating the trastuzumab emtansine treatment effect duration across node-positive and node-negative populations in the mid to long-term. In the absence of such data, the company would suggest deferring to clinical experts on this issue. The ERG agrees with this approach.

The ERG also agrees with the company that the most recent data from APHINITY prove that the assumptions of the ERG for TA569 led to an underestimation of the pertuzumab treatment effect. However, it should be noted that this does not necessarily imply that the same will occur with trastuzumab emtansine. Even if it does, it is not possible to determine whether the duration of the treatment effect will be similar to the one observed for pertuzumab. If the company seeks to obtain a reliable estimate of the trastuzumab emtansine treatment effect duration, the ERG would suggest for this using new KATHERINE data when these become available and then updating the model. In the absence of such data, the ERG still considers that it is preferable to base assumptions on the current

available data even if this would result in a conservative approach. With the current evidence and modelling assumptions, the company's approach of testing the impact of treatment effect duration on the ICER by conducting scenario analyses, seems appropriate.

1.3 Health-related quality of life

The company has agreed with the ERG's proposed approach to 1) apply KATHERINE treatment-specific utilities for the IDFS health states in the model and 2) using the utilities from Lidgren et al. 2007 for the metastatic health states in the model.

1.4 Resource use and costs

In the company base-case, it was assumed that in the trastuzumab emtansine arm, patients would receive pertuzumab + trastuzumab + chemotherapy, whereas patients who receive either trastuzumab monotherapy or pertuzumab + trastuzumab in the adjuvant setting would receive trastuzumab emtansine. This assumption was confirmed by clinical experts.

In TA569 (pertuzumab + trastuzumab + chemotherapy in the adjuvant treatment of HER2-positve early breast cancer), 95% of the trastuzumab monotherapy market was assumed to be Herceptin SC (March 2019). This assumption was also utilised in the company's base-case analysis for this appraisal.

Market research commissioned by the company mentioned that "*in a sample of 229 patients, 106 were using trastuzumab in the SC formulation*" (Roche Market Research. Available on request). Consequently, in their report, the ERG assumed that the split between SC and IV usage in trastuzumab monotherapy was (106/229) 46% and (123/229) 54%, respectively. This may have been a misinterpretation and the company noted that this sample does not refer to trastuzumab monotherapy exclusively: some of the trastuzumab usage in those 229 patients was used in combination with pertuzumab. Therefore, the figures suggested by the ERG were inappropriate for use in this context (trastuzumab monotherapy). The original split used by the company (95% SC vs. 5% IV) was confirmed by Professor Clark during the teleconference when he stated that "virtually all" trastuzumab monotherapy usage is administered subcutaneously.

In England and Wales, using pertuzumab in combination with trastuzumab subcutaneous (SC) is not commissioned by the NHS. The company, therefore, assumed that all trastuzumab used in combination with pertuzumab would be given intravenously. The price differential between intravenous (IV) trastuzumab biosimilar and IV originator (Herceptin) trastuzumab is such that prescribing the more expensive originator product would be irrational. Consequently, there is no usage of branded trastuzumab (Herceptin) IV in the company's model.

The company considers that patient weights collected at baseline during the KATHERINE trial should be used for the purposes of cost effectiveness analysis. Likewise, the actual dose and Time to Off Treatment (TTOT) data used in the model should also come from the KATHERINE trial. In their report, the ERG refers to ICERs that have been generated using "planned dose" data. In this respect, the company indicated that it is more appropriate to use the "actual dose" data as planned dose data does not account for missed doses, dose moderations etc., this is a clinically implausible data set, unreflective of real-world practice, and consequently inappropriate for the purposes of decision-making.

The company's base-case analysis assumed no vial sharing. Attendees on the Technical Engagement teleconference heard from clinical experts that this might not be completely reflective of UK clinical practice. Experts stated that the increase in usage of trastuzumab emtansine in the adjuvant setting (in addition to the metastatic setting) would likely increase the opportunities for vial sharing in various

centres. Based on this, the company considers that its base-case results may represent a conservative reflection of cost-effectiveness. Scenario analyses evaluating the impact of patient weight and vial sharing on the ICERs were conducted for the node-negative population and the node-positive population. The results are shown in Table 1.9.

ERG comments: The ERG agrees with the company's modelling approaches to the issues regarding the market shares in the early recurrence, first line metastatic state as well as the market share assumptions related to trastuzumab SC vs. trastuzumab IV or use of biosimilar trastuzumab in combination with pertuzumab in the adjuvant setting. Therefore, in the ERG base-case these assumptions were not changed. However, even though the clinical experts are generally agreeing with the assumptions made by the company, the ERG considers that there can still be some level uncertainty in these estimates and, therefore, considers that the scenario analyses can be useful.

The ERG considered that the "no vial sharing" assumption should be the base case, since vial sharing cannot be guaranteed and cannot be plausible for all clinical settings (e.g. a care setting with infrequent breast cancer patients).

The ERG has concerns on the company's responses on patient weight and vial sharing assumptions. It should be emphasized that in both the ERG and company base-case, "actual dose" data was used, and these data were not dependent on patient weight. Therefore, to reflect the sensitivity of the cost-effectiveness on patient weight, the ERG used planned dose in scenario analyses.

Even though planned dose data do not account for missed doses, dose moderations, wastage due to mistakes in administration etc., the ERG still considers that planned dose can be informative for decision making as well, especially to reflect the sensitivity of costs to different patient weight/BSA assumptions. Based on the ERG's experience, there are many other STAs, where the drug acquisition costs were calculated based on planned dose (e.g. Ribociclib, TA496), sometimes using a mean dose intensity adjustment. Therefore, the ERG considers the scenarios with planned dose and with different patient weights to be informative and valuable. As shown in Table 1.9, the ICER is sensitive to patient weight, since the current formulation is just enough for an average patient weight and if a patient weight is 2.5 kg more (72.5), the ICER increases around 50% in the node negative population and around 200% in the node positive population. Even though the results are still within the acceptable ICER limits, they show that the costs are quite sensitive to patient weight assumption.

1.5 Revised cost effectiveness analyses

Based on the new evidence presented by the company discussed in the previous section, the company defined revised base-cases for the node-negative, node-positive populations and ITT populations. The company revised base-case analyses are summarised in Tables 1.3, 1.4 and 1.5. Details on the specific model updates are described in Appendix 1. Overall, the company preferred assumptions are now very closely aligned to the ERG's. As will be seen in the next section, the only difference in the company and ERG ICER for the node-negative population is determined by using node-negative-specific TTOT data from KATHERINE, instead of ITT data. Most of the changes made for the node-positive population are in line with those made in the node-negative analysis. For completeness, a base-case analysis for the ITT population was also conducted.

Table 1.3: Changes to the company base-case (node-negative population)

Base-case preferred assumptions	Change	Justification	Location in economic model
IDFS extrapolation approach	KM data until last event then Exponential distribution thereafter in both treatment arms	ERG preferred approach. Use of KM data avoids over/underestimation of IDFS during observation period. Exponential distribution is best fitting function across both arms.	Location: "Model inputs" sheet – Cell I104 & I106 Input: "KM + Exponential tail" in both cells
Treatment effect duration	Full treatment effect to three years (36 months) before ceasing completely at eight years (96 months)	ERG preferred assumptions	Location: "Model inputs" sheet – Cell I150 Input: "ERG"
Recurrence rates	Treatment arm-specific recurrence rates derived from the node-negative population of KATHERINE	Change was requested by ERG and NICE team. Most appropriate to apply the rates derived from the node-negative population in the node-negative economic analysis. These figures were provided to the ERG by the company in response to clarification questions.	Location: "Model inputs" sheet – Cell I130 Input: "Node-negative"
Time to off-treatment data	Time to off-treatment data collected in the node-negative population of KATHERINE	Change was requested by ERG and NICE team. Most appropriate to apply the TTOT data collected in the node-negative population in the node-negative economic analysis	Location: "TTOT tables" sheet Input: TTOT data used is dependent on population that's selected in cell I40 of "Model Inputs" sheet
Baseline characteristics (age, weight, height)	Baseline characteristics in the node-negative population of KATHERINE. Values are pooled	Most appropriate to use baseline characteristics of node-negative population in the node-negative economic analysis. These figures were	Location: "Model inputs" sheet – Cell I25 to K30 Input: Baseline characteristics are dependent on population that's selected cell I40 of "Model Inputs" sheet.

Base-case preferred assumptions	Change	Justification	Location in economic model
	across treatment arms	provided to the ERG by the company in response to clarification questions.	
IDFS health state utilities	Treatment arm specific health state utilities derived from EQ-5D responses in the ITT population of KATHERINE	ERG preferred assumption. This approach more likely to account for HRQoL impact of AEs.	Location: "Model inputs" sheet – Cell G55 Input: "ITT"
Metastatic breast cancer health state utilities	Utility values taken from Lidgren et al. 2007	ERG preferred assumption. Lidgren et al. 2007 publication more closely aligns to the NICE reference case	Location: "Model inputs" sheet – Cell G66 Input: "Lidgren et al."

Source: Table 1 in company response to NICE Technical Report.
Abbreviations: AEs = Adverse events; HR = Hazard ratio; HRQoL = Health related quality of life; IDFS = Invasive disease-free survival; ITT = Intention to treat; KM = Kaplan-Meier; TTOT = Time to off treatment.

Table 1.4: Changes to the company base-case (node-positive population)

Base-case preferred assumptions	Change	Justification	Location in economic model
IDFS extrapolation	KM data until last event then Exponential distribution thereafter in trastuzumab emtansine	Use of KM data avoids over/underestimation of IDFS during observation period. Exponential distribution is best fitting function.	Location: "Model inputs" sheet – Cell I104 & I106 Input: "KM + Exponential tail" in both cells
APHINITY HRs used in Bucher analysis	Hazard ratio taken from the 6-year data cut of the APHINITY trial.	Most appropriate to use the longer term, more robust efficacy data from APHINITY	Location: "Model inputs" sheet – Cell I192 Input: "6 year"
Bucher analysis output	Scenario A – HR in node-positive population of APHINTY and HR in node-positive population of KATHERINE	Most conservative HR. Comparison to pertuzumab + trastuzumab only relevant in node-positive populations	Location: "Model inputs" sheet – Cell I193 Input: "Scenario A – APHINITY N+ / KATHERINE N+"
Treatment effect duration	Full treatment effect to three years (36 months) before ceasing completely	ERG preferred assumptions	Location: "Model inputs" sheet – Cell I150 Input: "ERG"

Base-case preferred assumptions	Change	Justification	Location in economic model
	at eight years (96 months)		
Recurrence rates	TE arm: Treatment arm-specific recurrence rates derived from the node-positive population of KATHERINE. P+T arm: Rates in the node-positive population of the P+T arm of APHINITY (6-year data cut) have been used.	Change was requested by ERG and NICE team. Most appropriate to apply treatment-specific rates derived from node-positive populations.	TE arm Location: "Model inputs" sheet – Cell I130 Input: "Node-positive" P+T arm Location: "Model Inputs" sheet – Cell I131 Input: "Yes – 6yr data cut"
Time to off-treatment data	TE arm: Time to off-treatment data collected in the node-positive population of KATHERINE P + T arm: Time to off-treatment data collected in the node-positive population of APHINITY (as per Company base case)	Change was requested by ERG and NICE team. Most appropriate to apply treatment-specific Time to off-treatment data collected in node-positive populations.	Location: "TTOT tables" sheet Input: TTOT data used is dependent on population that's selected in cell I40 of "Model Inputs" sheet
Baseline characteristics (age, weight, height)	Baseline characteristics in the node positive population of KATHERINE. Values are pooled across treatment arms	Most appropriate to use baseline characteristics of node-positive population in the node-positive economic analysis.	Location: "Model inputs" sheet – Cell I25 to K30 Input: Baseline characteristics are dependent on population that's selected cell I40 of "Model Inputs" sheet.
IDFS health state utilities	Treatment arm specific health state utilities derived from EQ-5D responses in the ITT population of KATHERINE	ERG preferred assumption. This approach more likely to account for HRQoL impact of AEs.	Location: "Model inputs" sheet – Cell G55 Input: "ITT"
Metastatic breast cancer health state utilities	Utility values taken from Lidgren et al. 2007	ERG preferred assumption. Lidgren et al. 2007 publication more closely aligns to the NICE reference case	Location: "Model inputs" sheet – Cell G66 Input: "Lidgren et al."

Base-case preferred assumptions	Change	Justification	Location in economic model
Source: Table 2 in company response to NICE Technical Report. Abbreviations: AEs = Adverse events; HR = Hazard ratio; HRQoL = Health related quality of life; IDFS = Invasive disease-free survival; ITT = Intention to treat; KM = Kaplan-Meier; P+T = pertuzumab + trastuzumab; TE = trastuzumab emtansine; TTOT = Time to off treatment.			

Table 1.5: Changes to the company base-case (ITT population)

Base-case preferred assumptions	Change	Justification	Location in economic model
IDFS extrapolation	KM data until last event then Exponential distribution thereafter in trastuzumab emtansine	Use of KM data avoids over/underestimation of IDFS during observation period. Exponential distribution is best fitting function.	Location: "Model inputs" sheet – Cell I104 & I106 Input: "KM + Exponential tail" in both cells
APHINITY HRs used in Bucher analysis	Hazard ratio taken from the 6-year data cut of the APHINITY trial.	Most appropriate to use the longer term, more robust efficacy data from APHINITY	Location: "Model inputs" sheet – Cell I192 Input: "6 year"
Bucher analysis output	Scenario A – HR in node-positive population of APHINTY and HR in node-positive population of KATHERINE	Most conservative HR.	Location: "Model inputs" sheet – Cell I193 Input: "Scenario A – APHINITY N+ / KATHERINE N+"
Treatment effect duration	Full treatment effect to three years (36 months) before ceasing completely at eight years (96 months)	ERG preferred assumptions	Location: "Model inputs" sheet – Cell I150 Input: "ERG"
Recurrence rates	TE arm: Treatment arm-specific recurrence rates derived from the node-positive population of KATHERINE. P + T arm: Rates in the node-positive population of the P + T arm of APHINITY (6-year data cut) have been used.	Change was requested by ERG and NICE team. Most appropriate to apply treatment-specific rates derived from population of interest	TE arm & T arm Location: "Model inputs" sheet – Cell I130 Input: "ITT" P + T arm Location: "Model Inputs" sheet – Cell I131 Input: "Yes – 6yr data cut"

Base-case preferred assumptions	Change	Justification	Location in economic model
Time to off-treatment data	TE arm: Time to off-treatment data collected in the node-positive population of KATHERINE P + T arm: Time to off-treatment data collected in the node-positive population of APHINITY (as per Company base case)	Change was requested by ERG and NICE team. Most appropriate to apply treatment-specific Time to off-treatment data collected in population of interest	Location: "TTOT tables" sheet Input: TTOT data used is dependent on population that's selected in cell I40 of "Model Inputs" sheet
Baseline characteristics (age, weight, height)	Baseline characteristics in the node positive population of KATHERINE. Values are pooled across treatment arms	Most appropriate to use baseline characteristics of ITT population in the ITT analysis.	Location: "Model inputs" sheet – Cell I25 to K30 Input: Baseline characteristics are dependent on population that's selected cell I40 of "Model Inputs" sheet.
IDFS health state utilities	Treatment arm specific health state utilities derived from EQ-5D responses in the ITT population of KATHERINE	ERG preferred assumption. This approach more likely to account for HRQoL impact of AEs.	Location: "Model inputs" sheet – Cell G55 Input: "ITT"
Metastatic breast cancer health state utilities	Utility values taken from Lidgren et al. 2007	ERG preferred assumption. Lidgren et al. 2007 publication more closely aligns to the NICE reference case	Location: "Model inputs" sheet – Cell G66 Input: "Lidgren et al."

Source: Table 3 in company response to NICE Technical Report.
Abbreviations: AEs = Adverse events; HR = Hazard ratio; HRQoL = Health related quality of life; IDFS = Invasive disease-free survival; ITT = Intention to treat; KM = Kaplan-Meier; P+T = pertuzumab + trastuzumab; TE = trastuzumab emtansine; TTOT = Time to off treatment.

1.5.1 Revised base-case cost effectiveness results

The company's updated base-case cost effectiveness results for the ITT, node-negative and node-positive populations are displayed in Tables 1.6, 1.7 and 1.8, respectively.

Table 1.6: Company base-case cost effectiveness results for the ITT population (discounted)

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Trastuzumab	[redacted]	15.06	[redacted]	[redacted]	1.36	[redacted]	£5,985
Trastuzumab emtansine	[redacted]	16.42	[redacted]				
Pertuzumab + Trastuzumab	[redacted]	15.77	[redacted]	[redacted]	0.65	[redacted]	£8,203
Trastuzumab emtansine	[redacted]	16.42	[redacted]				

Source: Table 5 in company response to NICE Technical Report.
Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year; ITT = intention to treat.

Table 1.7: Company base-case cost effectiveness results for the node-negative population (discounted)

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Trastuzumab	[redacted]	16.76	[redacted]	[redacted]	1.23	[redacted]	£8,829
Trastuzumab emtansine	[redacted]	17.99	[redacted]				

Source: Table 5 in company response to NICE Technical Report.
Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year.

Table 1.8: Company base-case cost effectiveness results for the node-positive population (discounted)

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Pertuzumab + Trastuzumab	[redacted]	13.97	[redacted]	[redacted]	0.67	[redacted]	£4,955
Trastuzumab emtansine	[redacted]	14.64	[redacted]				

Source: Table 5 in company response to NICE Technical Report.
Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year.

ERG comment: The results for the ITT population are reported as pairwise comparisons between trastuzumab emtansine vs. trastuzumab (monotherapy) or pertuzumab + trastuzumab. These results are difficult to interpret since the comparator depends on nodal status. Therefore, there is no single comparator for the ITT population. The company was aware of this and indicated in the response to the NICE Technical Report that "*given the uncertainty associated with the comparison to pertuzumab + trastuzumab, the ITT analysis could still prove useful in the decision-making process*".

1.5.2 Probabilistic sensitivity analysis

The company did not conduct any additional probabilistic sensitivity analyses.

1.5.3 Deterministic sensitivity analysis

The company did not conduct any additional deterministic sensitivity analyses.

1.5.4 Scenario analyses

The company conducted 40 additional scenario analyses in both the node-negative and node-positive populations (where applicable) in order to quantify the remaining uncertainties and to illustrate the impact of those uncertainties on the ICER. These areas of uncertainty included assumptions regarding treatment effect duration, patient weight, vial sharing, Bucher analysis outputs, recurrence rates in pertuzumab + trastuzumab arm, subgroup specific IDFS utilities, parameterisation of the cure model and choice of IDFS extrapolation function post-KM period in node-positive analysis. The results of these scenario analyses are presented in Table 1.9.

Table 1.9: Company additional scenario analyses

Assumption	Node-negative		Node-positive	
	ICER (£/QALY)	**Difference vs. base-case**	**ICER (£/QALY)**	**Difference vs. base-case**
Company revised base-case	£8,829		£4,955	
Treatment effect duration				
Stops at 4 years	£14,654	+£5,825	£13,071	+£8,116
Begins waning at 4 years, ceases at 7 years	£9,115	+£286	£4,454	-£501
Begins waning at 5 years ceases at 8 years	£6,534	-£2,295	£1,889	-£3,066
Begins waning at 6 years ceases at 9 years	£4,942	-£3,887	£389	-£4,566
Begins waning at 7 years ceases at 10 years	£3,988	-£4,841	TE dominant	N/A
Patient weight				
Planned dose - 70 kg	£8,829	£0	£4,955	£0
Planned dose - 72.5 kg	£12,822	+£3,993	£12,532	+£7,577
Planned dose - 75 kg	£12,810	+£3,981	£12,519	+£7,564
Vial sharing				
Actual dose – 0% vial sharing	£8,829	£0	£4,955	£0
Actual dose – 50% vial sharing	£8,350	-£479	£4,008	-£947
Actual dose – 100% vial sharing	£7,871	-£958	£3,061	-£1,894
Planned dose – 0% vial sharing	£8,829	£0	£4,955	£0
Planned dose – 50% vial sharing	£8,467	-£362	£5,055	£100
Planned dose – 100% vial sharing	£8,104	-£725	£5,155	£200
Bucher analysis outputs				
Scenario A - N+ KATHERINE / N+ APHINITY (4yr)	N/A	N/A	£1,094	-£3,861
Scenario B – ITT KATHERINE / N+ APHINITY (4yr)	N/A	N/A	TE dominant	N/A

Assumption	Node-negative		Node-positive	
	ICER (£/QALY)	**Difference vs. base-case**	**ICER (£/QALY)**	**Difference vs. base-case**
Scenario C – ITT KATHERINE / ITT APHINITY (4yr)	N/A	N/A	TE dominant	N/A
Scenario A – N+ KATHERINE / N+ APHINITY (6yr)	N/A	N/A	£4,955	£0
Scenario B – ITT KATHERINE / N+ APHINITY (6yr)	N/A	N/A	£2,468	-£2,487
Scenario C – ITT KATHERINE / ITT APHINITY (6yr)	N/A	N/A	£69	-£4,886
Recurrence rates in P+T arm				
KATHERINE - pooled	N/A	N/A	£5,646	+£691
APHINITY (4yr) - P+T arm	N/A	N/A	£5,627	+£672
APHINITY (6yr) - P+T arm	N/A	N/A	£4,955	£0
IDFS utilities				
Subgroup specific	£8,700	-£129	£4,958	+£3
ITT	£8,829	£0	£4,955	£0
Cure assumptions				
Start at 36 months, 95% at 120 months	£8,829	£0	£4,955	£0
Start at 48 months, 95% at 120 months	£8,688	-£141	£5,060	+£105
Start at 60 months, 95% at 120 months	£8,537	-£292	£5,569	+£614
Start at 36 months, 85% at 120 months	£10,147	+£1,318	£8,732	+£3,777
Start at 36 months, 90% at 120 months	£9,481	+£652	£6,784	+£1,829
Start at 36 months, 100% at 120 months	£8,191	-£638	£3,233	-£1,722
Start at 36 months, 95% at 96 months	£8,589	-£240	£3,679	-£1,276
Start at 36 months, 95% at 108 months	£8,636	-£193	£4,215	-£740

Assumption	Node-negative		Node-positive	
	ICER (£/QALY)	**Difference vs. base-case**	**ICER (£/QALY)**	**Difference vs. base-case**
IDFS extrapolation function post-KM period in node-positive analysis				
Exponential	N/A	N/A	£4,955	£0
Weibull	N/A	N/A	£4,822	-£133
Log-Normal	N/A	N/A	£2,732	-£2,223
Gamma	N/A	N/A	£2,589	-£2,366
Log-Logistic	N/A	N/A	£2,902	-£2,053
Gompertz	N/A	N/A	£3,360	-£1,595

Source: Table 19 in company response to NICE Technical Report.
Abbreviations: ICER = Incremental cost-effectiveness ratio; IDFS = Invasive disease-free survival; ITT = Intention to treat; KM = Kaplan-Meier; N/A = not applicable; P+T = pertuzumab + trastuzumab; QALY = quality adjusted life year; TE = trastuzumab emtansine

ERG comment: The revised base-case and scenario analyses conducted by the company resulted in ICERs below the commonly used threshold of £20,000 per QALY. Based on these, trastuzumab emtansine is likely to be considered cost effective compared to trastuzumab (node-negative subgroup) and to pertuzumab + trastuzumab (node-positive subgroup). However, additional probabilistic sensitivity analyses (PSA) were not presented by the company.

1.6 Exploratory and sensitivity analyses undertaken by the ERG

The ERG agrees with the company revised base-case for the node-negative and node-positive subpopulations. For the ITT analysis, although not as relevant as those for the node-negative and node-positive subgroups, as mentioned in the ERG report, the ERG preferred to model IDFS using a generalised gamma extrapolation.

Given the large number of scenario analyses presented by the company in Section 1.5.4 of this addendum (and those presented by the company and the ERG in the original ERG report), no additional scenario analyses were conducted by the ERG.

In order to illustrate the potential decision uncertainty, the ERG conducted a PSA for the node-negative and node-positive subgroups.

1.7 PSA results for the node-negative subpopulation

The ERG conducted a PSA on the company's revised base-case for the node-negative subpopulation, as submitted in the company's response to the technical engagement report. This resulted in a probabilistic ICER of £8,721 (Table 1.10), approximately £100 lower than the deterministic ICER. [redacted] as shown in Figure 1.3. [redacted]. The CEAC (Figure 1.4) shows that the probability that trastuzumab emtansine is cost-effective at thresholds of £20,000 and £30,000 is 97.6% and 99.8% respectively.

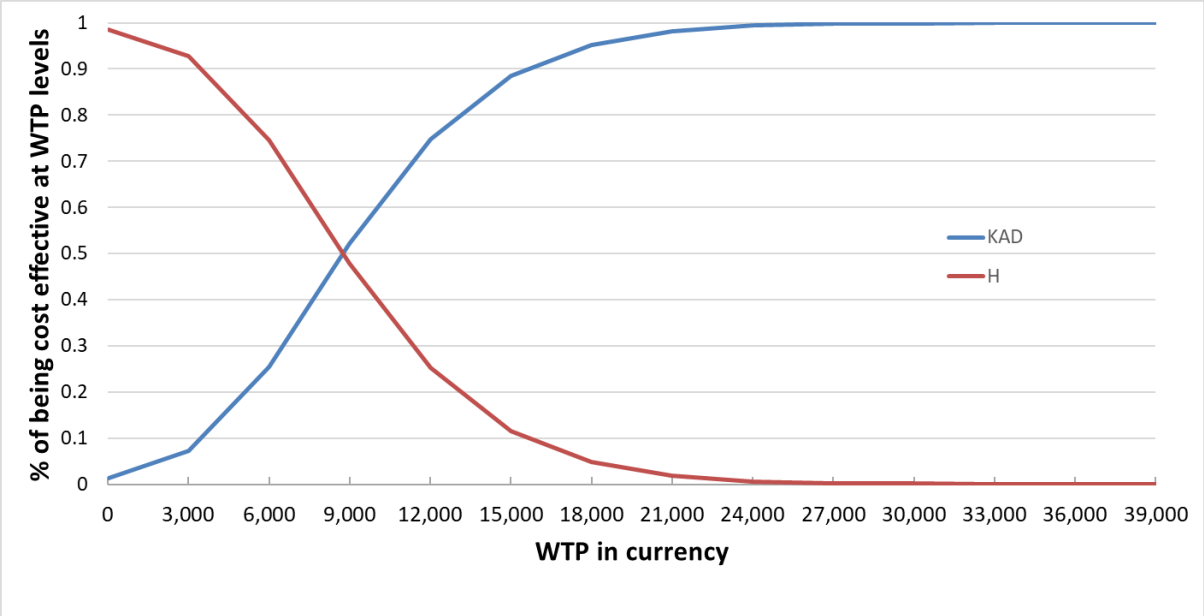
Table 1.10: Revised company base-case probabilistic results for the node-negative subgroup (discounted)

Technologies	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER versus baseline (£/QALY)
Trastuzumab	[redacted]	18.02	[redacted]				
Trastuzumab emtansine	[redacted]	16.83	[redacted]	[redacted]	1.197	[redacted]	£8,721
Source: Based on electronic model, updated from the company response to technical engagement. Abbreviations: ICER = incremental cost effectiveness ratio; Incr. = incremental; QALYs = quality adjusted life years; LYG = life years gained							

Figure 1.3: Revised company base-case cost effectiveness plane (node-negative subgroup)

Source: Based on electronic model, updated from the company response to technical engagement.
Abbreviations: H = trastuzumab; Inc. = incremental; KAD = trastuzumab emtansine; QALY = quality adjusted life year

Figure 1.4: Revised company base-case cost effectiveness acceptability curve (node-negative subgroup)



Source: Based on electronic model, updated from the company response to technical engagement.
Abbreviations: H = trastuzumab; KAD = trastuzumab emtansine; WTP = willingness-to-pay.

1.8 PSA results for the node-positive subpopulation

The ERG also conducted a PSA on the company's revised base-case for the node-positive subpopulation, as submitted in the company's response to the technical engagement report. This

resulted in a probabilistic ICER of £4,413 (Table 1.11), approximately £500 lower than the deterministic ICER. [redacted] as shown in Figure 1.5. The CEAC (Figure 1.6) shows that the probability that trastuzumab emtansine is cost-effective at thresholds of £20,000 and £30,000 is 64.8% and 71.3% respectively.

Table 1.11: Revised company base-case probabilistic results for the node-negative subgroup (discounted)

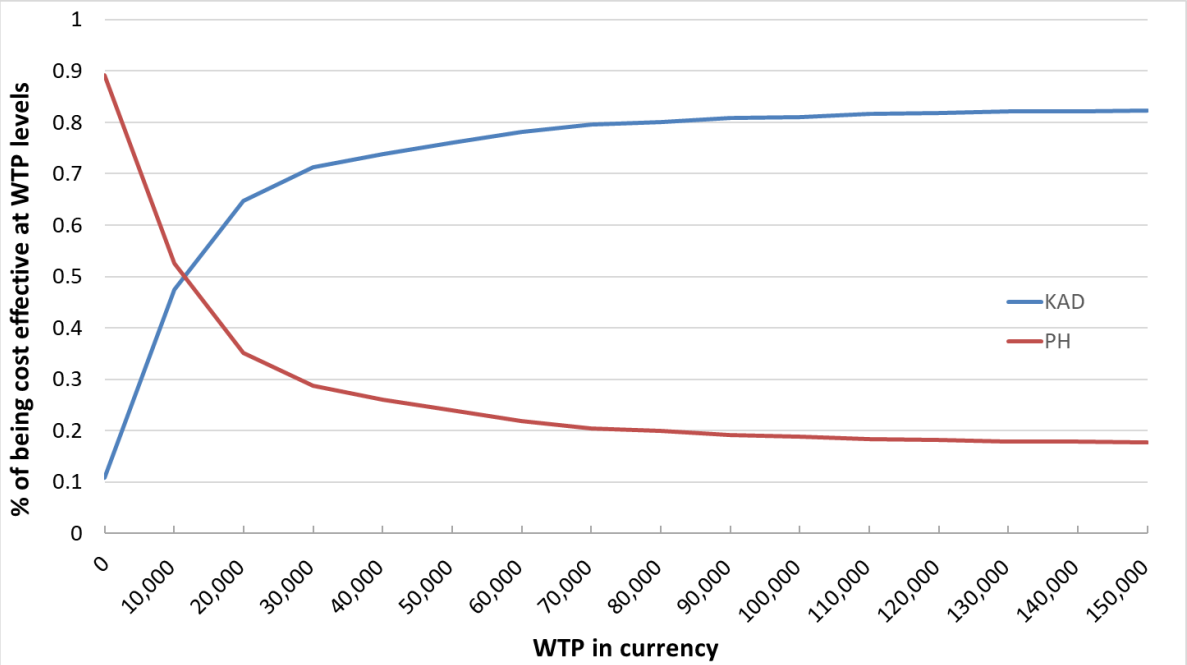
Technologies	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER versus baseline (£/QALY)
Trastuzumab	[redacted]	14.65	[redacted]				
Trastuzumab emtansine	[redacted]	14.01	[redacted]	[redacted]	0.643	[redacted]	£4,413
Source: Based on electronic model, updated from the company response to technical engagement. Abbreviations: ICER = incremental cost effectiveness ratio; Incr. = incremental; QALYs = quality adjusted life years; LYG = life years gained							

Figure 1.5: Revised company base-case cost effectiveness plane (node-negative subgroup)

[redacted]

Source: Based on electronic model, updated from the company response to technical engagement.
Abbreviations: Inc. = incremental; KAD = trastuzumab emtansine; PH = pertuzumab + trastuzumab; QALY = quality adjusted life year

Figure 1.6: Revised company base-case cost effectiveness acceptability curve (node-negative subgroup)



Source: Based on electronic model, updated from the company response to technical engagement.
Abbreviations: KAD = trastuzumab emtansine; PH = pertuzumab + trastuzumab; WTP = willingness-to-pay.

1.9 ERG base-case for the ITT population

As discussed in the original ERG report and in Section 1.6 of this addendum, the ERG prefers to model IDFS using a generalised gamma extrapolation in the ITT population. Therefore, the ERG base-case is the same as the company revised base-case for the ITT population (shown in Table 1.5) with the exception that IDFS is extrapolated using the generalised gamma rather than the company's preferred exponential model. The deterministic results of the ERG preferred base-case for the ITT population are displayed in Table 1.12.

Table 1.12: ERG base-case cost effectiveness results for the ITT population (discounted)

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Trastuzumab	[redacted]	15.69	[redacted]	[redacted]	1.29	[redacted]	£7,213
Trastuzumab emtansine	[redacted]	16.98	[redacted]				
Pertuzumab + Trastuzumab	[redacted]	16.28	[redacted]	[redacted]	0.71	[redacted]	£6,388
Trastuzumab emtansine	[redacted]	16.98	[redacted]				

Source: electronic model submitted with company response to NICE Technical Report.
Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year; ITT = intention to treat.

1.10 Conclusions of the cost effectiveness section

Despite the remaining areas of uncertainty and disagreement between the company and the ERG discussed in this addendum, all deterministic ICERs for the company's revised base-cases (for the ITT, node-negative and node-positive populations) and scenario analyses, and the ERG's preferred base-case for the ITT population are well within the range considered acceptable by NICE, with none of these ICERs exceeding £20,000 (none of the additional scenario analyses conducted by the company and shown in Table 1.9 resulted in ICERs over £15,000). Probabilistic ICERs for the node-positive and node-negative subgroups were in line with the deterministic ICERs. The probability that trastuzumab emtansine is considered cost effective at a threshold of £20,000 was 64.8% in the node-positive subgroup and 97.6% in the node-negative subgroup. Therefore, despite the remaining areas of uncertainty to be discussed by the Committee, with the current evidence the ERG considers that trastuzumab emtansine is likely to be deemed as a cost-effective alternative to trastuzumab for node-negative patients and to pertuzumab + trastuzumab for node-positive patients.

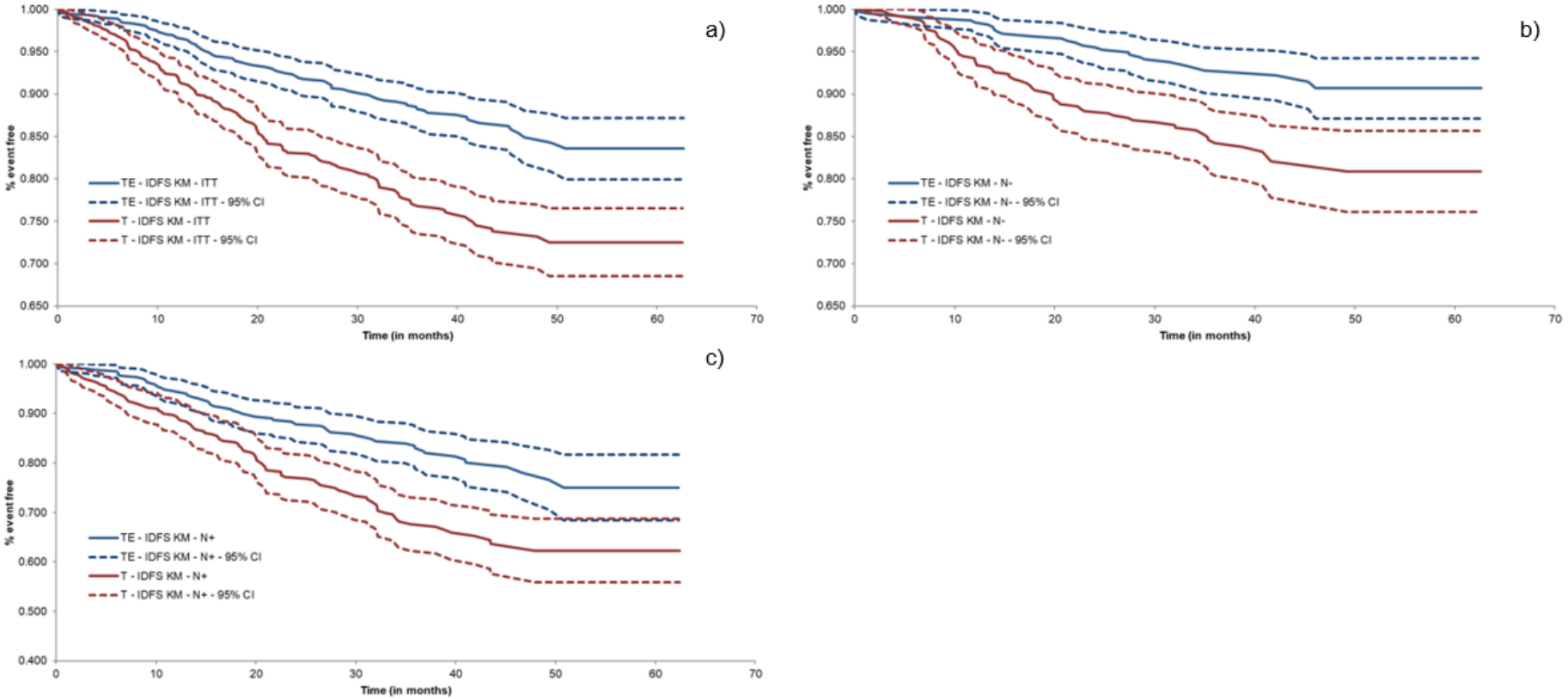
Appendix 1: Model updates

In response to the NICE Technical report, the company changed its cost effectiveness model. Most of these changes were related to using subgroup-specific data from KATHERINE to derive input parameters for subgroup cost effectiveness analyses (instead of using ITT data only for this). The changes made to the model are described below.

IDFS KM data

The model now contains IDFS KM data for the ITT, node-negative, and node-positive populations. Figure A1.1 presents these the KM curves.

Figure A1.1. IDFS KM data from KATHERINE trial in the a) ITT, b) node-negative and c) node-positive populations



Source: Figure 3 from the company response to the NICE technical engagement report.

Abbreviations: IDFS = Invasive disease-free survival; ITT = Intention to treat; KM = Kaplan-Meier; N- = Node-negative; N+ = Node-positive; T = trastuzumab; TE = trastuzumab.

* Y-axes have been adjusted to magnify curves.

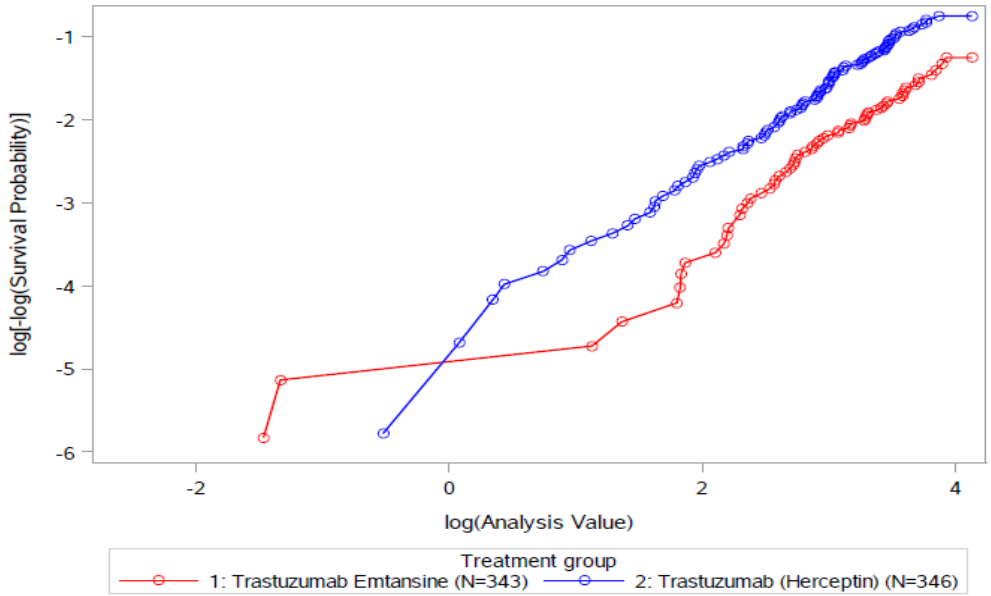
IDFS extrapolations based on KM data

Survival analyses have now been run on each of the KM curves presented in Figure A1.1. The IDFS extrapolations in the ITT and node-negative subgroups have been presented in the original company submission and the response to clarification questions, respectively. Only the node-positive extrapolation selection process is presented here.

Assessment of Proportional Hazards Assumption

The proportional hazards (PH) assumption can be tested graphically, using log-cumulative hazard plots. As shown in Figure A1.2, the two curves cross, which signals that the PH assumption may not hold. However, this crossing takes place at a time when minimal events have occurred. A similar situation was observed in the ITT population (Figure 16 of Document B – the company submission). The company decided not to assume the proportional hazards assumption holds and this was agreed reasonable by the ERG. The same approach has been taken here.

Figure A1.2. Log of negative log of estimated survivor functions – IDFS endpoint from the KATHERINE study – node-positive population



Source: Figure 4 from the company response to the NICE technical engagement report.

Statistical fit

Akaike information criterion (AIC) and Bayesian information criterion (BIC) values for the extrapolation of node-positive IDFS data are presented below in Table A1.1. Based on the values in Table A1.1 the Exponential appears to be the best statistical fit to the KM data.

Table A1.1. IDFS extrapolation – AIC and BIC values (relative ranking of goodness of fit shown in brackets) – node-positive population

	AIC		BIC	
	Trastuzumab emtansine arm	**Trastuzumab arm***	**Trastuzumab emtansine arm**	**Trastuzumab arm**
Exponential	438.44 (1)	619.47 (1)	442.28 (1)	623.32 (1)
Weibull	439.94 (3)	621.45 (5)	447.62 (3)	629.15 (4)

Log-normal	443.19 (6)	619.83 (2)	450.86 (5)	627.52 (2)
Gamma	441.88 (5)	621.39 (4)	453.39 (6)	632.93 (6)
Log-logistic	439.74 (2)	619.86 (3)	447.42 (2)	627.55 (3)
Gompertz	440.30 (4)	621.47 (6)	447.97 (4)	629.16 (5)
Source: Table 7 from the company response to the NICE technical engagement report. Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion.				

Extrapolation approach

The company has decided to adopt the ERG's preferred approach for the extrapolation of IDFS in the node-positive analysis (i.e. use of KM data until the point of the last observed event, then the best fitting function thereafter). Invasive disease-free survival in the node-positive subgroup analysis has been extrapolated by using KM data until 50.83 months (trastuzumab emtansine arm) and 47.97 months (trastuzumab arm) then the Exponential function thereafter. The choice of extrapolation function post-KM data has been evaluated in scenario analysis.

Rates of metastatic and non-metastatic recurrence

In their report, the ERG cited that there was potential uncertainty surrounding the model results in the node-negative subgroup analysis because the rates of metastatic and non-metastatic recurrence observed in the ITT population of KATHERINE were used, rather than those of the node-negative population. Table A1.2 presents the metastatic and non-metastatic recurrence rates used in the updated model for each of the subgroups.

Table A1.2. Proportion of recurrences which are non-metastatic by treatment arm in the "early" and "late" relapser population

	ITT		Node-negative		Node-positive	
	Trastuzumab emtansine (n=743)	**Trastuzumab (n=743)**	**Trastuzumab emtansine (n=400)**	**Trastuzumab (n=397)**	**Trastuzumab emtansine (n=343)**	**Trastuzumab* (n=346)**
IDFS event, n	91	165	29	62	62	103
Deaths without prior event, n (%)	2 (2.20%)	3 (1.82%)	2 (6.90%)	2 (3.23%)	0 (0.0%)	1 (0.97%)
IDFS event excluding deaths, n	89	162	27	60	62	102
"Early" relapser – pre-18 months[a]						
Metastatic recurrence, n (%)	36 (85.71%)	60 (72.29%)	9 (81.82%)	24 (72.73%)	30 (96.77%)	41 (78.85%)
Non-metastatic recurrence, n (%)	6 (14.29%)	23 (27.71%)	2 (18.18%)	9 (27.27%)	1 (3.23%)	11 (21.15%)
"Late" relapser – post-18 months[a]						
Metastatic recurrence, n (%)	42 (89.36%)	58 (73.42%)	12 (75.00%)	17 (62.96%)	27 (87.10%)	36 (72.00%)
Non-metastatic recurrence, n (%)	5 (10.64%)	21 (26.58%)	4 (25.00%)	10 (37.04%)	4 (12.90%)	14 (28.00%)

***** Given that trastuzumab is not a relevant comparator in the node-positive population, these figures have been presented for completeness.
Footnotes: [a]Deaths are not counted as IDFS events in these figures. Death is accounted for separately in the model.
Source: Table 8 from the company response to the NICE technical engagement report.
Abbreviations: IDFS = invasive disease-free survival; ITT = intention to treat.

The rates presented in Table A1.2 were applied by treatment arm. Rates seen in the node-positive and node-negative subgroups are broadly similar to those seen in the ITT. There are, however, some anomalies in these figures, for example, patients on trastuzumab emtansine arm in the early relapser node-positive population would expect their IDFS event to be metastatic in nature 97% of the time. This is likely an artefact of the data due to low event numbers.

In the node-positive population, the relevant comparator is pertuzumab + trastuzumab. Pertuzumab + trastuzumab was not included in the KATHERINE trial, it is therefore not possible to derive the rates of metastatic and non-metastatic recurrence from this data source. In the company's base-case analysis, the rates observed in both arms of the KATHERINE trial were pooled and applied to the pertuzumab + trastuzumab arm in the model.

The updated model includes the option to use the rates of metastatic and non-metastatic recurrences seen in the node-positive population of the pertuzumab + trastuzumab arm of APHINITY. Currently, there have been two data cuts of the APHINITY trial (primary analysis at ~4 years and interim OS analysis at ~6 years). The rates derived from each of these data cuts, along with the KATHERINE pooled values are presented below in Table A1.3.

Table A1.3. Proportion of recurrences which are non-metastatic by treatment arm in the "early" and "late" relapser population in the node-positive patients of pertuzumab + trastuzumab arms

	KATHERINE - Pooled	**APHINITY – 4-year**	**APHINITY – 6-year**
	Pertuzumab + trastuzumab (n=689)	**Pertuzumab + trastuzumab (n=1503)**	**Pertuzumab + trastuzumab (n=1503)**
IDFS event, n	165	139	173
Deaths without prior event, n (%)	1 (0.61%)	20 (14.39%)	26 (15.03%)
IDFS event excluding deaths, n	164	119	147
"Early" relapser – pre-18 months[a]			
Metastatic recurrence, n (%)	63 (77.78%)	31 (75.61%)	31 (75.61%)
Non-metastatic recurrence, n (%)	18 (22.22%)	10 (24.39%)	10 (24.39%)
"Late" relapser – post-18 months[a]			
Metastatic recurrence, n (%)	71 (85.54%)	67 (85.90%)	93 (87.74%)
Non-metastatic recurrence, n (%)	12 (14.46%)	11 (14.10%)	13 (12.26%)

Footnotes: [a]Deaths are not counted as IDFS events in these figures. Death is accounted for separately in the model.
Source: Table 9 from the company response to the NICE technical engagement report.
Abbreviations: IDFS = invasive disease-free survival.

IDFS health state utilities

In the company submission and response to clarification questions, all subgroup analyses used health state utilities derived from the ITT population in KATHERINE. It can be argued that for the node-negative and node-positive analyses, it is more appropriate to use health state utilities collected in these populations. IDFS state utilities for the ITT, node-negative, and node-positive populations are presented below in Table A1.4.

Table A1.4. IDFS health state utilities from KATHERINE

State	ITT (Utility (SE))			Node-negative (Utility (SE))			Node-positive (Utility (SE))			Source
	TE arm	T arm	Pooled	TE arm	T arm	Pooled	TE arm	T arm*	Pooled	
IDFS – On treatment	0.774 (0.009)	0.776 (0.010)	0.775 (0.009)	0.778 (0.013)	0.783 (0.012)	0.781 (0.012)	0.769 (0.013)	0.767 (0.017)	0.768 (0.015)	EQ-5D data from KATHERINE
IDFS – Off treatment	0.784 (0.010)	0.791 (0.009)	0.788 (0.010)	0.798 (0.012)	0.802 (0.011)	0.800 (0.012)	0.769 (0.015)	0.777 (0.015)	0.773 (0.015)	
Non metastatic recurrence	0.774 (0.009)	0.776 (0.010)	0.775 (0.009)	0.778 (0.013)	0.783 (0.012)	0.781 (0.012)	0.769 (0.013)	0.767 (0.017)	0.768 (0.015)	Assumption
Remission	0.784 (0.010)	0.791 (0.009)	0.788 (0.010)	0.798 (0.012)	0.802 (0.011)	0.800 (0.012)	0.769 (0.015)	0.777 (0.015)	0.773 (0.015)	

* Given that trastuzumab is not a relevant comparator in the node-positive population, these figures have been presented for completeness.
Source: Table 10 from the company response to the NICE technical engagement report.
Abbreviations: IDFS = Invasive disease-free survival; ITT = Intention to treat; SE = Standard error; T = trastuzumab; TE = trastuzumab emtansine.

As the company anticipated, there were minimal differences in the utility values, signalling that health-related quality of life (HRQoL) is not expected to vary according to nodal status alone. Upon further inspection, some of these utilities lack face validity. For example, in the trastuzumab emtansine arm of the node-positive population there is no difference in the utility values across the IDFS health states. It seems illogical to assume that being in IDFS and receiving no treatment (i.e. no treatment-related adverse events) is associated with the same level of health-related quality of life as a non-metastatic recurrence. Discrepancies in these figures are likely due to the limited number of observations in the EQ-5D data.

Due to the issues with face-validity and the fact that HRQoL does not appear to vary according to nodal status, the Company argues that it is still most appropriate to use the ITT values in all subgroup analyses for the purposes of decision-making. Scenario analyses using the subgroup-specific values are presented below. Please note, in the KATHERINE trial no EQ-5D data was collected after recurrence. Therefore, subgroup data for the utilities in metastatic health states are not available. Finally, as in the base case analysis, pertuzumab + trastuzumab utilities in the node-positive analysis are equal to the pooled values in the ITT population of KATHERINE. The ERG agrees with this approach.

Safety

Subgroup-specific safety analyses have now been run. As anticipated, no new safety signals were identified. The criteria set out in Document B meant that none of the AEs in either the node-negative or the node-positive subgroups qualified for inclusion in the economic model (i.e. all had an incidence of <2%). Consequently, no subgroup-specific safety data has been integrated into the model.

Time to-off Treatment (TTOT)

In the response to clarification questions, the company postulated that the time at which a patient remained on treatment would not be expected to vary according to nodal status. Nevertheless, the ERG argued that this point remained uncertain. The TTOT data for each of the relevant subgroups in KATHERINE is presented below in Table A1.5 and has now been integrated into the economic model. It seems clear that there practically difference between the times spent on treatment across the three subgroups. Therefore, the impact of using subgroup specific TTOT data in the model is negligible.

Table A1.5. Time to off-treatment data across relevant subgroups in the KATHERINE trial

Cycle number	ITT		Node-negative		Node-positive	
	TE arm	T arm	TE arm	T arm	TE arm	T arm*
Cycle 1	100.0%	99.9%	100.0%	100.0%	100.0%	99.7%
Cycle 2	97.8%	97.9%	97.5%	98.5%	98.2%	97.3%
Cycle 3	95.9%	96.3%	95.5%	96.9%	96.5%	95.5%
Cycle 4	94.3%	94.7%	93.5%	96.1%	95.3%	93.1%
Cycle 5	92.7%	93.9%	92.0%	95.9%	93.5%	91.5%
Cycle 6	91.9%	93.1%	91.3%	95.1%	92.6%	90.6%
Cycle 7	90.9%	92.1%	90.5%	94.3%	91.5%	89.4%
Cycle 8	90.0%	90.6%	89.8%	93.1%	90.3%	87.6%
Cycle 9	88.8%	89.7%	88.3%	92.8%	89.4%	86.1%
Cycle 10	87.7%	88.5%	87.3%	91.3%	88.2%	85.2%
Cycle 11	86.4%	85.8%	85.8%	88.7%	87.1%	82.5%
Cycle 12	84.7%	83.9%	83.5%	86.6%	86.2%	80.7%
Cycle 13	82.4%	82.5%	82.3%	84.3%	82.6%	80.4%
Cycle 14	80.1%	81.0%	80.5%	83.0%	79.7%	78.5%

* Given that trastuzumab is not a relevant comparator in the node-positive population, these figures have been presented for completeness. Pertuzumab + trastuzumab TToT data has been taken from the APHINITY trial – as outlined in the Company's original submission.
Source: Table 11 from the company response to the NICE technical engagement report.
Abbreviations: ITT = Intention to treat; T = trastuzumab; TE = trastuzumab emtansine.

Baseline characteristics

The model now incorporates subgroup specific baseline characteristics (see Table).

Table A1.6. Baseline characteristics across relevant subgroups in the KATHERINE trial

Baseline characteristic	ITT		Node-negative		Node-positive	
	Mean	Std. Err	Mean	Std. Err	Mean	Std. Err
Age (years)	49.10	10.65	48.85	10.80	49.35	10.5
Weight (kg)	70.91	15.15	70.05	14.71	71.93	15.61
Height (cm)	163.10	7.17	163.36	7.17	162.79	7.17

Source: Table 12 from the company response to the NICE technical engagement report.
Abbreviations: cm = Centimetre; ITT = Intention to treat; kg = Kilograms; Std. Err. = Standard error

Updated APHINITY data cut

In the node-positive subgroup analysis of this submission, pertuzumab + trastuzumab is the relevant comparator. The indirect treatment comparison used to derive comparative effectiveness of trastuzumab emtansine compared to pertuzumab + trastuzumab relies on the hazard ratios from the APHINITY trial. At the time of the original evidence submission, only the hazard ratios from the primary analysis of the APHINITY trial were available. However, in December 2019, the interim OS analysis from the APHINITY trial became available. As communicated on the Technical Engagement teleconference, the Company modified the ITC to include the updated hazard ratios. Outputs of the revised Bucher analysis are presented alongside the original figures in Table and Table below.

Table A1.7. Hazard ratios from Bucher analysis – 4-year APHINITY data cut

Scenario	APHINITY			KATHERINE			ITC	
	Population	HR (95% CI)	Log HR (±SE)	Population	HR (95% CI)	Log HR (±SE)	Log HR (±SE)	HR (95% CI)
A	Node-positive	0.77 (0.62–0.96)	-0.26 (0.11)	Node-positive	0.52 (0.38–0.71)	-0.65 (0.16)	-0.39 (0.19)	0.675 (0.461–0.989)
B	Node-positive	0.77 (0.62–0.96)	-0.26 (0.11)	ITT	0.50 (0.39–0.64)	-0.69 (0.13)	-0.43 (0.17)	0.649 (0.467–0.904)
C	ITT	0.81 (0.67–1.00)	-0.21 (0.10)	ITT	0.50 (0.39–0.64)	-0.69 (0.13)	-0.48 (0.16)	0.617 (0.449–0.849)

Source: Table 13 from the company response to the NICE technical engagement report.
Abbreviations: 95% CI = 95% confidence interval; HR = Hazard ratio; ITC = Indirect treatment comparison; ITT = Intention to treat; SE = Standard error.

Table A1.8. Hazard ratios from Bucher analysis – 6-year APHINITY data cut

Scenario	APHINITY			KATHERINE			ITC	
	Population	HR (95% CI)	Log HR (±SE)	Population	HR (95% CI)	Log HR (±SE)	Log HR (±SE)	HR (95% CI)
A	Node-positive	0.72 (0.59-0.87)	-0.33 (0.10)	Node-positive	0.52 (0.38–0.71)	-0.65 (0.16)	-0.33 (0.19)	0.722 (0.50-1.04)
B	Node-positive	0.72 (0.59-0.87)	-0.33 (0.10)	ITT	0.50 (0.39–0.64)	-0.69 (0.13)	-0.36 (0.16)	0.694 (0.51-0.95)
C	ITT	0.76 (0.64-0.91)	-0.27 (0.09)	ITT	0.50 (0.39–0.64)	-0.69 (0.13)	-0.42 (0.16)	0.658 (0.49-0.89)

Source: Table 14 from the company response to the NICE technical engagement report.
Abbreviations: 95% CI = 95% confidence interval; HR = Hazard ratio; ITC = Indirect treatment comparison; ITT = Intention to treat; SE = Standard error.

Both sets of outputs are available for use in the revised cost-effectiveness model. However, the values derived using the six-year APHINITY data are the most robust and should be preferred for the purposes of decision-making.