Single Technology Appraisal

Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after 1 or more anti-HER2 therapies [ID3909] Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after 1 or more anti-HER2 therapies [ID3909]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

Pre-technical engagement documents

1. **Company submission from Daiichi Sankyo UK**

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. Breast Cancer Now
   b. METUP UK
   c. NCRI-ACP-RCP-RCR

4. **External Assessment Report** prepared by Newcastle University
   a. Evidence Review Group Report
   b. Addendum

5. **External Assessment Report – factual accuracy check**

Post-technical engagement documents

6. **Technical engagement response from company**

7. **Technical engagement responses and statements from experts:**
   - Suki Kaur – patient expert, nominated by Breast Cancer Now

8. **External Assessment Group critique of company response to technical engagement** prepared by Newcastle University

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after trastuzumab and a taxane [ID3909]

Document B

Company evidence submission

April 2022

File name	Version	Contains confidential information	Date
ID3909_T-DXd_HER2+mBC_Document B_[redacted]	1.0	No	22/4/22

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Abbreviations

ABC	Advanced breast cancer
AE	Adverse events
ADC	Antibody Drug Conjugate
AIC	Aikake Information Criterion
AJCC	American Joint Cancer Committee
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AWMSG	All Wales Medicines Strategy Group
BC	Breast Cancer
BIC	Bayesian Information Criterion
BICR	Blinded Independent Central Review
BNF	British National Formulary
BSA	Body Surface Area
BTD	Breakthrough Therapy Designation
CBR	Clinical Benefit Rate
CDF	Cancer Drugs Fund
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence Interval
CNS	Central Nervous System
CR	Complete Response
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DALY	Disability-Adjusted Life Years
DCO	Data Cut Off
DoR	Duration of Response
DSU	Decision Support Unit
EAIR	Exposure-adjusted Incidence Rate
ECOG	Eastern Cooperative Oncology Group
ECG	Electrocardiogram
EMC	Electronic Medicines Compendium
EOL	End of Life
EORTC	European Organisation for Research and Treatment of Cancer
ER	Oestrogen receptor
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
FAD	Final Appraisal Determination
FAS	Full Analysis Set
FDA	Food and Drug Administration
GEE	Generalized Estimating Equations
HADS	Hospital Anxiety and Depression Scale
HEOR	Health Economics and Outcomes Research
HER2	Human Epidermal Growth Factor Receptor 2
HR	Hazard Ratio
HRG	Healthcare Resource Group
HRQoL	Health-related Quality of Life
HTA	Health Technology Assessment
IA	Investigator Assessment
ICER	Incremental Cost-effectiveness Ratio
ICU	Intensive Care Unit
IDMC	Independent Data Monitoring Committee
IHC	Immunohistochemistry
ILD	Interstitial Lung Disease
IMSS	el Instituto Mexicano del Seguro Social
ISH	*In Situ* Hybridisation
ISSSTE	Institute for Social Security and Services for State Workers
ITT	Intention-to-Treat
IXRS	Interactive Voice/Web Response System
KM	Kaplan-Meier
LC	Lapatinib/capecitabine
LCHP	Log-Cumulative Hazard Plots
LVEF	Left Ventricular Ejection Fraction
LY	Life-years
LYG	Life-year Gain
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines & Healthcare Products Regulatory Agency
MRI	Magnetic Resonance Imaging
MUGA	Multigated
MVH	Measuring and Valuing Health
NA	Not applicable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	Not estimable
NHB	Net-health benefit
NICE	National Institute for Health and Care Excellence
NR	Not reported
ONS	Office of National Statistics
ORR	Objective Response Rate
OS	Overall Survival
OWSA	One-way Sensitivity Analysis
PAR	Public Assessment Report
PartSA	Partitioned Survival Analysis
PAS	Patient Access Scheme
PD	Progressive Disease
PF	Progression Free
PFS	Progression-free survival
PH	Proportional Hazards
PK	Pharmacokinetic
PLD	Patient level Data
PPS	Per-protocol Analysis Set
PR	Progesterone Receptor

PRO	Patient-reported Outcome
PSA	Probabilistic Sensitivity Analysis
PSM	Parametric Survival Model
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALM	Quality-adjusted Life-month
QALY	Quality-adjusted Life-years
QLAS	Quality of Life in Adult Cancer Survivors
QLQ-C30	Quality-of-life Questionnaire Core 30
QLQ-BR45	Quality-of-life Questionnaire | Breast Cancer
QoL	Quality of Life
RCT	Randomised Controlled Trial
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumours
RU	Resource Use
SAE	Serious Adverse Events
SAS	Safety Analysis Set
SD	Stable Disease
SE	Standard Error
SLR	Systematic Literature Review
SmPC	Summary of Product Characteristics
SRE	Skeletal-related Events
TA	Technology Appraisal
TC	Trastuzumab/capecitabine
T-DM1	Trastuzumab emtansine
T-DXd	Trastuzumab deruxtecan
TEAE	Treatment-emergent Adverse Event
TKI	Tyrosine Kinase Inhibitor
THP	Docetaxel, trastuzumab and pertuzumab
TNM	Tumour, Node, and Metastasis
ToT	Time on Treatment
TSD	Technical Support Document
TTD	Time to Treatment Discontinuation
TTR	Time to Response
USD	United States Dollars
VAS	Visual Analogue Scale
WPAI	Work Productivity and Activity Impairment
WTP	Willingness-to-pay

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

B.1.1 Decision problem

A summary of the decision problem is shown in Table 1.

This submission focuses on trastuzumab deruxtecan (T-DXd) as a treatment for unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-positive breast cancer (BC) after trastuzumab and a taxane in accordance with the final scope issued by the National Institute for Health and Care Excellence (NICE). The proposed marketing authorisation for T-DXd is as [redacted]; in UK clinical practice, this is consistent with the final scope as two trastuzumab plus taxane regimens are recommended by NICE as first-line treatment options: pertuzumab plus trastuzumab and docetaxel; and trastuzumab and paclitaxel.[1,2]

T-DXd is currently recommended by NICE – via the Cancer Drugs Fund (CDF) – for treating HER2-positive unresectable or metastatic BC after 2 or more anti-HER2 therapies [TA704].[3]

The company submission is consistent with the final NICE scope and the NICE reference case.

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	People with HER2-positive unresectable or metastatic breast cancer who have received trastuzumab and a taxane	People with HER2-positive unresectable or metastatic breast cancer who have received trastuzumab and a taxane	NA
Intervention	Trastuzumab deruxtecan	Trastuzumab deruxtecan	NA
Comparator(s)	Trastuzumab emtansine	Trastuzumab emtansine	NA
Outcomes	The outcome measures to be considered include: • Progression free survival • Overall survival • Response rate • Duration of response • Adverse effects of treatment • HRQoL	As per final scope issued by NICE The outcome measures from DESTINY-Breast03 (the pivotal clinical trial) that are presented and included in the economic model are: • Progression-free survival (PFS) by blinded independent committee review (BICR) (primary endpoint) • Overall survival (OS) • HRQoL measured via the EQ-5D-5L • Response rates as confirmed by BICR • Adverse effects of treatment In addition, data from the following key secondary endpoints from the DESTINY-Breast03 trial are also presented: **Key secondary endpoints:** • PFS as confirmed by Investigator Assessment (IA) • Response rates as confirmed by IA • Clinical benefit rate as confirmed by BICR • Duration of response as confirmed by BICR • Time to response • HRQoL measured by the EORTC QLQ-C30 and EORTC QLQ-BR45	NA

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. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out. 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.	As per final scope issued by NICE A cost-utility analysis will be performed, with the key outcome being the incremental cost-effectiveness ratio (ICER) A lifetime time horizon will be used Costs will be considered from an NHS and PSS perspective The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account	NA

Abbreviations: BICR, blinded independent central review; EORTC QLQ, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L, EuroQol five-dimension, five level instrument; HER2, human epidermal growth factor receptor 2; HRQoL, health-related quality of life; IA, investigator assessment; ICER, incremental cost-effectiveness ratio; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PFS, progression-free survival; PSS, Personal Social Services; QALY, quality-adjusted life year.

B.1.2 Description of the technology being appraised

A description of T-DXd is presented in Table 2. The current summary of product characteristics (SmPC) is provided in Appendix C. The UK Public Assessment Report (PAR) was not available at the time of submission and will be provided when published.

Table 2: Technology being appraised

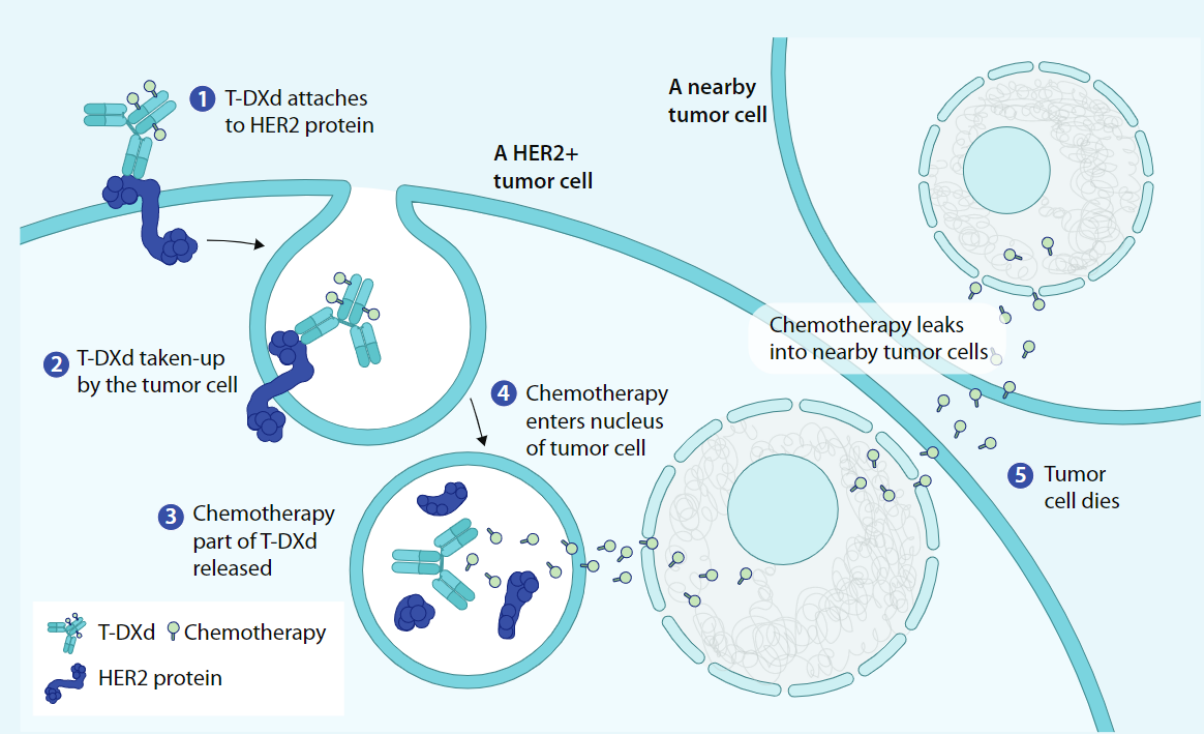
UK approved name and brand name	Trastuzumab deruxtecan (T-DXd; ENHERTU®)
Mechanism of action (see Figure 1 presents an overview of the mechanism of action of T-DXd. **Figure 1)**	Using optimised technology, DXd antibody drug conjugates (ADC) are composed of a monoclonal antibody (mAb) covalently linked to a potent membrane-permeable topoisomerase I inhibitor payload (an exatecan derivative, DXd) via a stable tetrapeptide-based linker selectively cleaved within tumour cells. Evidence supports the portability of DXd ADC technology to multiple tumour targets.[4] DXd ADCs are specifically designed to enhance selective tumour cell death and reduce systemic exposure to the topoisomerase I inhibitor payload. Intact DXd ADCs display long-term stability in plasma. The tetrapeptide-based cleavable linker and payload are stable in plasma.[5-8] The stable linker ensures minimal release of payload in circulation, reducing the risk of off-target toxicity. The linker is selectively cleaved by lysosomal enzymes typically upregulated in tumour cells.[5,6] The payload is cell membrane permeable, which enables a bystander antitumour effect resulting in elimination of both target and surrounding tumour cells.[6,9] The payload has a short half-life in systemic circulation.[5,6] T-DXd is composed of a humanised anti-HER2 IgG1 mAb with the same amino acid sequence as trastuzumab covalently linked to the membrane-permeable topoisomerase I inhibitor payload DXd via a stable tetrapeptide-based linker selectively cleaved within tumour cells.[5,6] The drug-to-antibody ratio of T-DXd is optimised and homogeneous and is approximately 8*. The HER2-directed mAb selectively binds to its target, HER2, which is expressed on the tumour cell surface.[5] The ADC is internalised by the tumour cell, where intracellular lysosomal enzymes typically upregulated in tumour cells selectively cleave the tetrapeptide-based linker.[10-12] The payload is released into the cytoplasm of the cell.[5] The released payload enters the cell nucleus and damages the tumour cell's DNA, which results in tumour cell death
Marketing authorisation/CE mark status	T-DXd is being assessed by the Medicines & Healthcare Products Regulatory Agency (MHRA) through the European Commission Decision Reliance Procedure. MHRA approval and GB launch is expected in [redacted]. [redacted]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The current licenced indication for T-DXd is: T-DXd as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens. The expected wording of the licence extension is: [redacted]

	[redacted]
Method of administration and dosage	T-DXd is administered as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity. The recommended dosage is 5.4 mg/kg
Additional tests or investigations	No additional tests or investigations are required to determine eligibility for T-DXd in this indication beyond those routinely conducted in NHS clinical practice
List price and average cost of a course of treatment	List price: £1,455.00 per 100 mg vial • Cost per cycle: £4,901† • Cost per course: £145,309‡ All costs exclude VAT
Patient access scheme (if applicable)	A simple discount patient access scheme (PAS) for T-DXd in the form of a fixed price has been approved by NHS England. PAS price: [redacted] per 100 mg vial • Cost per cycle: [redacted]† • Cost per course: [redacted]‡ All costs exclude VAT

*ADCs are a mixture of molecules in which the drug-to-antibody ratio is variable. Homogeneity of drug-to-antibody ratio refers to a mixture in which there is low variability of drug-to-antibody ratio; the payload number per antibody falls into a narrow range.
†Dose is dependent on patient weight, RDI and wastage.
‡Cost per course based on an average over a patient's lifetime, calculated in the cost-effectiveness analysis presented in Section B.3
Abbreviations: ADC, antibody-drug conjugate; EC, European Commission; HER2, human epidermal growth factor receptor 2; mAb, monoclonal antibody; MHRA, Medicines and Healthcare products Regulatory Agency; NHS, National Health Service; PAS, patient access scheme; RDI, relative dose intensity; T-DXd, trastuzumab deruxtecan.

Figure 1 presents an overview of the mechanism of action of T-DXd.

Figure 1: Trastuzumab deruxtecan mechanism of action[13]



Abbreviations: HER2, human epidermal growth factor receptor 2; T-DXd, trastuzumab deruxtecan.
Source: Modi et al, 2021[13]

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

HER2-positive (HER2+) unresectable or metastatic breast cancer (u/mBC) is an incurable, aggressive cancer with a high symptom and mortality burden[14-23]

- Breast cancer (BC) is the most common cancer type in the UK, with 48,387 new diagnoses in England in 2019.[24,25] Most cases (>85%) of BC are diagnosed at Stage I–II[26]
- For Stage I–II BC, and for many Stage III cases, therapy with curative potential is available,[27] and prognosis is good; 1-year survival for Stage I–III BC ranges from 95.7–100.0%, and 5-year survival from 73.8–98.7%[28]
- However, for patients diagnosed with – or who develop – unresectable or metastatic disease (inoperable Stage III, and all Stage IV, cases), no curative therapy is available. Patients diagnosed with metastatic BC (mBC) have a poor prognosis, with 1- and 5-year survival rates of 66.2% and 26.6%, respectively[28]
- The burden of mBC is high, predominantly due to symptoms caused by secondary tumours, which contribute substantial mental burden, impair quality of life (QoL), and increase hospital and treatment costs compared with early-stage disease[17-23]
- Moreover, 13–20% of patients have tumours overexpressing human epidermal growth factor receptor 2 (HER2), the presence of which is associated with aggressive disease and limited response to conventional therapies[14,15,29]
- No curative therapies are available for HER2+ u/mBC. The goal of treatment is to delay disease progression and extend the patient's life while managing toxicities and symptoms, to provide optimal QoL and wellbeing[30,31]
- NICE recommends first-line HER2-targeted treatment with pertuzumab, trastuzumab, and docetaxel (technology appraisal [TA]509) or trastuzumab and paclitaxel (TA34)[1,2]
- For patients who have previously received trastuzumab and a taxane, the standard of care is trastuzumab emtansine (T-DM1), currently the only HER2-targeted option in this setting recommended by NICE.[32] Outcomes for patients with aggressive, HER2+ u/mBC have not advanced since the introduction of T-DM1 in 2014, and there remains an unmet need for therapies that further improve outcomes in this setting
- T-DXd is an ADC that selectively binds to HER2 expressed on tumour cells and releases the highly potent cytotoxic DXd payload within the cell, causing cell death[5,6,9]
- T-DXd is anticipated to replace T-DM1 as standard of care after trastuzumab and a taxane for patients with HER2+ u/mBC

B.1.3.1 Disease overview

Breast cancer is the most common cancer in the UK,[24] with 48,387 cases recorded in England in 2019.[25] Breast cancer predominantly affects women, who comprise 99% of cases,[33,34] and prevalence increases with age.[34] Staging of BC categorises the disease according to extent of spread: early BC (Stage I–II) is still localised in the breast tissue, Stage III (locally advanced) disease has typically spread beyond the breast tissue to the lymph nodes, and Stage IV (advanced or metastatic) disease occurs when the tumour has metastasised to other organs.[35,36]

Over 70% of patients are diagnosed at Stage I–II BC,[25] and for these patients, and many with Stage III disease, tumour resection is the mainstay of therapy because it has curative

potential and provides good survival outcomes.[27,37] Historically, outcomes in BC have improved over time,[28] largely due to improved screening and early identification.[38] Early diagnosis allows treatment at an earlier disease stage, typically when the tumour remains localised to the breast tissue and surgical resection remains a treatment option.[38] Consequently, age-standardised 1-year survival for Stage I–III BC ranges from 95.7−100.0%, and 5-year survival from 73.8–98.7%.[28]

Despite the general improvement in BC outcomes over time, an unmet need remains for those patients with unresectable (inoperable) Stage III or metastatic (Stage IV) BC (Section B.1.3.4). Survival outcomes in these patients are poor: 1-year and 5-year age-standardised survival for patients diagnosed with Stage IV BC is 66.2% and 26.6%, respectively.[28] Patients with mBC also face a greater disease burden than patients with early BC,[20] as metastases impose symptoms such as seizures, jaundice, and pleural effusion.[17,18] Treatment resistance is frequent in advanced disease,[39] which effectively reduces available treatment options.

Prognosis and treatment of BC is based on various factors, including disease severity and presence of specific biomarkers.[40,41] Key biomarkers in BC are HER2 and hormone receptor expression (including oestrogen receptor [ER] and progesterone receptor [PR]).[40,42] Overexpression of HER2 – known as HER2-positive (HER2+) BC – results in an aggressive disease,[15] that responds poorly to conventional chemotherapy.[16] In total, 13–20% of patients with BC have HER2+ disease.[14] Unlike BC generally, HER2+ BC is more common in younger women[a].[43]

Because HER2+ disease is aggressive and can have limited response to conventional therapies, HER2 receptor-targeted treatments (e.g. trastuzumab and pertuzumab) are used in patients in whom curative resection is not possible to improve treatment efficacy vs. non-targeted chemotherapy.[39,44] The first-line standard of care recommended by NICE are regimens which include trastuzumab and a taxane. The most frequently used regimen (pertuzumab with trastuzumab and docetaxel) was associated with a median PFS and OS of 18.7 months and 56.5 months, respectively, in the CLEOPATRA trial.[2,45] T-DM1 is the current standard of care in the UK for HER2+ mBC in patients who have previously received trastuzumab and a taxane, and is the only HER2-targeted option in this line of therapy that is recommended by NICE.[32,46] In the T-DM1 registrational trial, EMILIA, T-DM1 provided a median PFS and OS of 9.6 and 29.9 months, respectively.[47,48] More recently, the KATE2 trial reported a lower median PFS of 6.8 months with T-DM1 plus placebo (the study control arm),[49] which may translate to lower OS than observed in EMILIA, although mature OS data are not available and the availability of more effective subsequent therapies may improve OS.

While HER2-targeted treatments have improved survival outcomes in HER2+ mBC,[39] PFS for patients who have received one or more prior anti-HER2 regimens is typically <10 months,[48,49] and an unmet need remains for improved survival outcomes for these patients.[50]

Epidemiology

In total, 48,387 new BC cases were recorded in England in 2019.[25] Late-stage BC accounts for a small proportion of BC diagnoses overall: in 2019, 9.2% of BC diagnoses in England were Stage III and 5.1% Stage IV.[26] In Wales in 2018, 6.8% of BC diagnoses were Stage IV.[26] Although no data are published on the specific proportion of patients with

[a] Younger: those aged <56 years; older: those aged ≥56 years.

Stage III unresectable disease, the majority of Stage III cases are expected to be suitable for surgery. Patients with unresectable BC for whom potentially curative therapy is not an option are therefore expected to be predominantly diagnosed with, or have progressed to, Stage IV metastatic disease. Based on the proportion of patients with distant recurrence after receiving adjuvant treatment with T-DM1 or trastuzumab in the KATHERINE study, the annual probability of progression from early to metastatic BC is expected to be 4.1%[b] in patients with HER2+ disease.[51]

Overall, 13–20% of UK patients with BC are reported to have HER2+ disease.[14] The proportion with HER2+ mBC who receive first-line therapy is 92.4%; of these patients, 43.2% subsequently receive second-line therapy.[52]

The estimated number of HER2+ patients who are either diagnosed with or progress to Stage IV disease, have received a first-line therapy and will subsequently receive their next line of treatment is 346 each year in England.

Diagnosis

Initial diagnosis of BC is through breast x-ray (mammogram) and ultrasound, with any breast tissue displaying abnormal characteristics under imaging subjected to biopsy or fine needle aspirates for laboratory diagnosis.[53]

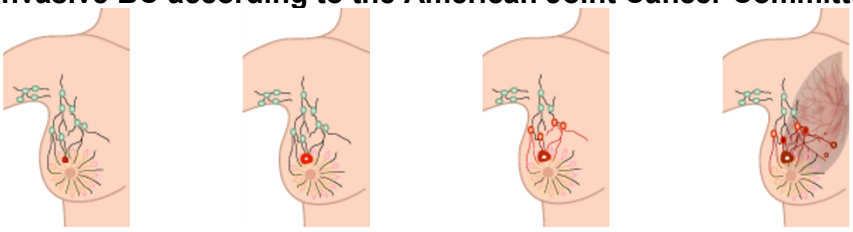
For patients with advanced/metastatic BC, diagnostic assessment is conducted to determine the extent of metastatic spread. Visceral metastases are assessed with a combination of plain radiography, ultrasound, magnetic resonance imaging (MRI), and computed tomography (CT) scans.[40] For bone metastases, CT scan with bone windows or MRI (for axial skeleton), bone scintigraphy (axial skeleton or proximal limbs) or plain radiography (proximal limbs) can be conducted. Patients with undiagnosed mBC, for whom imaging inconclusively suggests metastasis, should have positron emission tomography (PET)-CT.[40]

Staging and prognostication

Severity and invasiveness of BC is established through TNM (tumour, node, and metastasis) staging according to the American Joint Cancer Committee (AJCC), categorising disease as Stage 0 (non-invasive) or Stage I–IV (invasive; Figure 2).[35] Staging is based on tumour size (T), extent of spread to nearby lymph nodes (N), presence of metastases (M), and since 2018 also upon HER2 expression, hormone receptor expression, and the cancer grade.[35,54]

[b] Of 1,486 randomised patients, 196 patients experienced distant recurrence over a median follow-up of 3.4 years.

Figure 2: Staging of invasive BC according to the American Joint Cancer Committee



Stage		**I**		**II**		**III**			**IV**
		Early		Early		Locally-advanced			Metastatic/advanced
	Substage	IA	IB	IIA	IIB	IIIA	IIIB	IIIC	
TNM staging	T	1	0–1	0–2	2–3	0–3	4	Any	Any
	N	0	1	0–1	0–1	1–2	0–2	3	Any
	M	0		0		0			1
Survival by stage at diagnosis	1-year	100%		99.0%		95.7%			66.2%
	5-year	98.7%		90.2%		73.8%			26.6%

TNM staging categorises cancer stage by size and characteristics of primary tumour (T) and presence of nodal tumours (N), with increasing severity indicated by increasing numbers (from 0–4). Absence or presence of metastases (M) are indicated by M0 or M1, respectively.
Green bars represent the proportion surviving at each timepoint. Grey dashed bars indicate the proportion dead at that timepoint.
Abbreviations: M, metastasis; N, node, T, tumour.
Sources: adapted from American College of Surgeons, 2021 (diagram);[55] Cancer Research UK, 2020 (staging information);[36] Public Health England, 2020 (survival graphs).[28]

Although BC exhibits broad and diverse genetic characteristics, prognostication and treatment choice for BC is based on expression of HER2 and hormone receptors (oestrogen and progesterone): patients may be (i) HER2+/hormone receptor positive; (ii) HER2+/hormone receptor negative; (iii) HER2-negative (HER2–)/hormone receptor positive; or (iv) triple-negative disease (no expression of HER2 or either hormone receptor type).[56] HER2 and hormone receptor status is therefore routinely tested.[41,42] HER2+ BC is not defined only by higher expression of HER2 receptors, but by specific criteria related to HER2 receptor expression (assessed by immunohistochemistry [IHC]) and *HER2* gene copy number (assessed by *in situ* hybridisation [ISH]).[57] Positivity for HER2 is defined as a score of 3+ on IHC analysis or as IHC score of 2+ and a positive ISH result.[57]

B.1.3.2 Burden of HER2+ metastatic breast cancer

B.1.3.2.1 Clinical burden

As a progressive, terminal disease, people with mBC experience an increasing symptom burden and shorter time to next progression each time their disease progresses.[58]

Symptoms such as pain, breast or lymph node swelling, or changed appearance of the breast are typically experienced during all stages of BC.[59] However, unlike early-stage BC, mBC imposes a substantial additional symptom burden, including lethargy and low energy levels, reduced appetite, and unexplained weight loss, alongside symptoms specific to the location of the metastases (Table 3).[17,18]

Metastases in BC can involve visceral or non-visceral tissue. Visceral metastases are defined as metastases in the liver, lungs, abdominal cavity (leading to ascites), pleural space (leading to pleural effusion) and the central nervous system (CNS), while non-visceral

metastases are defined as bone, skin, and lymph node metastases.[60] In HER2+ disease, there is an increased risk (vs. HER2- BC) of experiencing metastatic spread to the visceral tissues,[61,62] with common sites including the liver, brain and lungs.[63-65] Related symptoms can vary substantially, from jaundice (liver metastases), to memory problems (brain metastases) and dyspnoea (lung metastases; Table 3).[17,18] Metastasis to the bone is common across all BC subtypes and is the first site of metastasis for more than half of women who develop Stage IV BC.[66] Rates of bone metastasis are especially high in HER2+ disease,[64] resulting in symptoms such as pain and impaired mobility, confusion (due to hypercalcaemia induced by the bone tumour), or if spinal metastases arise, symptoms such as poor bladder control (Table 3).[17,18,67] These symptoms may incur additional resource use and costs due to requirement for further treatment and monitoring (Section B.1.3.2.4) and can have a negative QoL impact, due to pain and difficulties for the patient in coping with symptoms (Section B.1.3.2.2).

Table 3: Site-specific symptoms of metastases in BC

Site of metastasis	Associated symptoms
General	Fatigue, difficulty sleeping, depression
Brain	Headache, confusion, weakness or numbness, seizure, altered mentation, memory problems, changes to eyesight, speech impairment, nausea or vomiting
Liver	Discomfort or pain, nausea, swollen abdomen, loss of appetite, jaundice
Lymph nodes	Brachial plexopathies, pain
Skin	Pain, infection, bleeding
Bone	Pain, hypercalcaemia, pathologic fracture, loss of mobility
Lungs	Pain, cough, dyspnoea, haemoptysis, weight loss, pleural effusion

Source: Irvin 2011;[17] Cancer Research UK 2017.[18]

B.1.3.2.2 Quality-of-life burden

As expected for a terminal disease with a high symptom burden, BC has a substantial and negative impact on patient quality and quantity of life. In a 2019 analysis in the UK, the total disability-adjusted life years (DALYs) lost to BC were 282,537 (95% confidence interval [CI]: 263,582, 301,298) and 17,358 (95% CI: 15,831, 19,046) in England and Wales, respectively, indicating substantial burden of disease at a population level.[68] Estimates from the Global Burden of Disease Study (1990–2017) indicated that BC contributes the greatest DALY loss of any cancer type in women.[69]

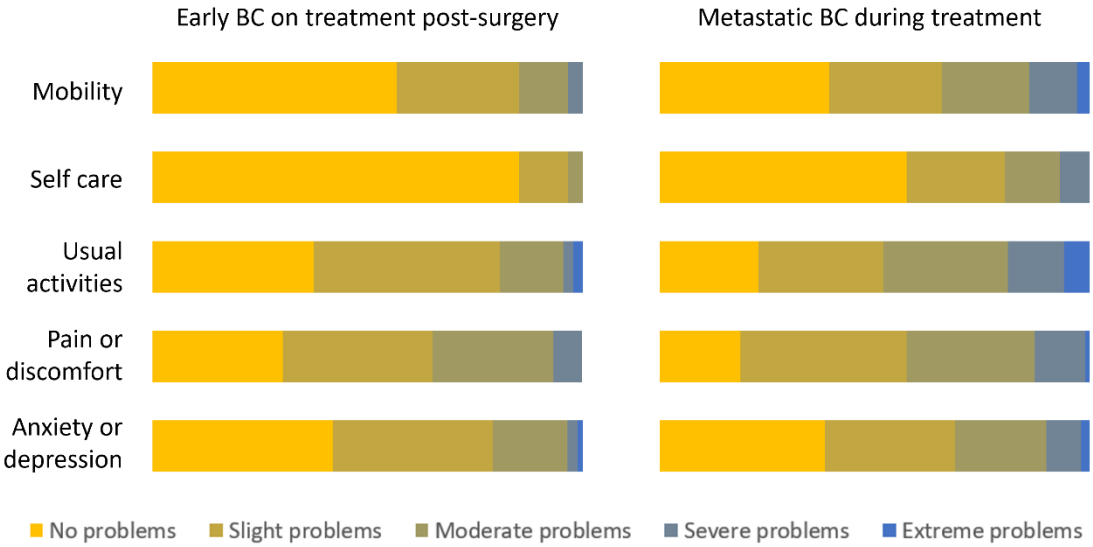
The high DALY loss in BC derives largely from years of life lost, accounting for 93% of the total,[69] and so are likely to be driven by the terminal or incurable stages of disease (unresectable Stage III and Stage IV) rather than the early stages which have good survival outcomes (Section B.1.3.2.6).

Impact of disease stage on QoL

Quality of life for patients with BC is lower than for the general population in similar age categories,[20,70] and loss of quality of life in UK patients with HER2+ BC is substantially greater if the disease is late-stage rather than early.[20] A UK study of HER2+ BC found that metastatic BC is associated with significantly lower health-related quality of life (HRQoL; measured by FACT-B and -G, and EQ-5D-5L) than both early BC in remission and early BC undergoing active treatment after surgery (all $p<0.001$).[20] Overall, patients with mBC reported significantly higher activity impairment – measured using the Work Productivity and

Activity Impairment (WPAI) activity impairment subscale – compared with patients with early BC on treatment post-surgery or after treatment completion (48.1% vs. 34.0% vs. 27.6%; p<0.001).[20] Moreover, mBC imposes restrictions on patients in terms of self-care and usual activities, with more patients reporting moderate or worse problems across EQ-5D-5L domains than in early BC (Figure 3).[20]

Figure 3: Patient QoL according to EQ-5D-5L by disease stage



Abbreviations: BC, breast cancer; QoL, quality of life.
Source: adapted from Verrill et al, 2020.[20]

Metastatic BC also impacts QoL in ways specific to the metastatic location. For example, in patients with bone metastases, skeletal-related events (SREs[c]) were found to cause substantial decrement in QoL – assessed using the Brief Pain Inventory – in a pooled analysis of 5,543 patients with solid tumours (including BC) from three Phase III trials.[71] In the BC population, the study reported a significant risk of clinically meaningful worsening[d] from baseline in pain interference overall and with physical activity in patients with SREs – specifically surgery to bone, radiation to bone, and pathological fractures – compared with patients without SREs (both p<0.05).[71]

Impact of metastatic disease on social functioning and mental health

The QoL impact of mBC in women varies by patient demographic, with younger patients[e] more likely to experience impaired social wellbeing than older patients.[72] Patients with children are more likely to have impaired functional wellbeing than those without, suggesting the disease impacts on their ability to parent actively and fulfil their social role.[72]

BC symptoms are also associated with a significant mental burden for patients.[19,21] Depressive symptoms were significantly associated with the symptom burden of disease in women with BC, regardless of age (p<0.01) in a US study using the Hospital Anxiety and

[c] Defined as fractures, the need for radiation to the bone to control pain or tumour burden, spinal cord compression, or bone surgery

[d] A clinically meaningful worsening in pain was a ≥2-point increase from baseline in pain scores according to the Brief Pain Inventory Short Form (BPI-SF).

[e] Unlike BC generally, HER2+ BC is more common in younger women (defined as those aged <56 years) than older women (defined as those aged ≥56 years).43. Dodson A, Parry S, Ibrahim M, *et al*. Breast cancer biomarkers in clinical testing: analysis of a UK national external quality assessment scheme for immunocytochemistry and in situ hybridisation database containing results from 199 300 patients. *J Pathol Clin Res*. 2018;4(4):262-273.

Depression Scale (HADS; N=125).[19] Another study in young North American women diagnosed with *de novo* mBC (N=54) reported a significant association between higher physical symptom scores and with higher HADS anxiety scores (p=0.005).[21]

B.1.3.2.3 Treatment burden

Beyond the clinical symptoms and quality of life impact for patients with u/mBC, treatment itself may be burdensome. While most patients with HER2+ u/mBC in England and Wales will receive T-DM1 after previously receiving trastuzumab and a taxane, for those patients unable to receive it, chemotherapy may be used as an alternative (Section B.1.3.3).

Patients with BC treated with chemotherapy report high symptom burden before receiving the next dose of chemotherapy, one week after receiving chemotherapy, and two weeks after receiving chemotherapy. The five highest occurring symptoms at the three timepoints are lack of energy (86.3%, 90.3% and 86.2, respectively), difficulty sleeping (74.5%, 72.2%, and 66.6%, respectively), hair loss (69.5%, 57.3%, and 54.4%, respectively), pain (60.7%, 69.7%, and, 62.4%, respectively), and feeling drowsy (60.3%, 65.6%, and 51.8%, respectively).[73]

Chemotherapy is also associated with reducing QoL and increased anxiety levels in patients with BC. In a UK study, chemotherapy was associated with a reduction in QoL – measured using the Quality of Life in Adult Cancer Survivors (QLAS) tool – across generic domains (HR: 8.70; 95% CI: 3.80, 13.70) and cancer-specific domains (HR: 10.90; 95% CI: 7.10, 14.70), as well as increased anxiety, measured using the HADS tool (HR: 1.10; 95% CI: 0.20, 2.00).[74] Across treatment types, chemotherapy is associated with significantly greater total toxicity than targeted or hormone therapies (p=0.03). Additionally, disease-limited social activity and a negative impact of BC on closest family are reported by 70% and 61%, respectively, of patients treated with chemotherapy, compared with 50% and 51%, respectively, of those treated with targeted therapy.[75]

By contrast, HER2-targeted therapies are associated with more favourable tolerability and fewer toxicities than conventional chemotherapy, meaning patients with HER2+ u/mBC administered anti-HER2 agents are likely to experience fewer side effects of treatment than those patients receiving conventional chemotherapy.[16,46]

B.1.3.2.4 Societal and economic burden of breast cancer

In general, the management of BC requires substantial resource use in England and Wales. In 2010, the total age-standardised cost of BC care in England was £371 million and £134 million for patients aged 18–64 and ≥65 years, respectively.[76]

Generally, the cost of treating and caring for patients with BC rises as the disease progresses: costs of disease-related hospital care and treatment increase as patients progress to locally-advanced or metastatic disease.[22,23] Hospital costs over 15 months were significantly associated with disease spread to lymph nodes and with how aggressive the cancer was (i.e. Grade 3 BC) in both univariate and multivariate regression analyses in a UK study (all p<0.001).[22] Treatment costs for distant BC were reported to be 165% higher than for local BC in a global systematic review,[23] and in the first year after diagnosis, Stage III–IV BC is associated with incremental care costs of £2,569 per patient vs. Stage I–II BC in England (the per-patient first-year cost of Stage I–II BC is £10,746).[76]

Cost drivers associated with HER2+ mBC include treatment type (HER2-targeted therapy, hormone therapy, chemotherapy, or radiation therapy), inpatient care, outpatient care, home care, surgery, continuous care, and laboratory tests.[77,78] Despite lower rates of surgery due

to the unresectable nature of many late-stage BC cases, later-stage BC is associated with an additional 2.93 inpatient days in the first 12 months, and more day case/regular admissions than early-stage BC.[76] The highest hospital care costs are those in the months prior to death (the 'terminal' phase of disease).[76]

Cost drivers vary based on the needs of individuals, and different metastases are associated with different costs. One example is increased use of analgesics, opioids and bisphosphonates in patients with bone metastases: SREs (i.e. fractures, treatment of bone with radiotherapy or surgery, and spinal cord compression) in BC were significantly associated with risk of progressing from no/low baseline analgesic use to opioids when compared with patients without SREs ($p<0.001$), with the greatest risk reported in patients with spinal cord compression (HR: 12.29), in a pooled analysis of three Phase III solid tumour studies.[71]

B.1.3.2.5 Caregiver burden

Caregivers of patients with mBC are also impacted by the disease as they may face economic difficulties, psychological problems, marital or familial anxieties, and worries about their loved one's wellbeing, disease status, and ability to maintain usual life activities.[79] The Global Status of Advanced/Metastatic Breast Cancer 2005–2015 Decade Report comprehensively assessed the caregiver burden of BC through surveys and a literature review.[79] As a consequence of the psychological and economic strain associated with caring for someone with the disease, caregivers may overlook their own needs, resulting in decreased wellbeing and an increase in symptoms of stress. Caring for a patient with mBC can also impact a caregiver's work, as they may need to take annual or special leave or quit work all together, leading to financial strain and increased indirect economic costs of mBC;[79] in a Canadian study in mBC, 69% of caregivers surveyed at the start of the palliative period reported that they had missed work due to caregiving (N=58).[80]

B.1.3.2.6 Mortality and prognosis

Survival outcomes in patients with mBC in England remain poor compared with patients at earlier stages of BC. According to Public Health England, the 5-year survival between 2014 and 2019 was 98.7% for Stage I BC, 90.2% for Stage II BC, 73.8% for Stage III BC, and only 26.6% for Stage IV (advanced/metastatic) BC (Figure 2).[28] The proportion of patients surviving their first year from diagnosis gives particular context to the poor prognosis of late-stage BC: whilst net survival is 95.7% in Stage III BC, for which curative resection is possible in some patients, it is 66.2% in Stage IV (unresectable) BC.[28] Presence of HER2+ disease confers tumour aggressiveness, worsening survival outcomes compared with a negative HER2 expression status.[81,82] In a 1991–2007 study, hormone receptor-positive mBC was associated with a 5-year OS of 31.3% if HER2–, compared with only 14.5% in HER2+ BC.[83]

The introduction of HER2-targeted therapies, supplementing or displacing treatment with untargeted chemotherapy, has substantially improved prognosis in the HER2+ population.[84] Initially, the introduction of trastuzumab in the first-line setting increased OS in HER2+ mBC resulting in 5-year OS of 29.7% and 17.7% in patients with hormone receptor positive and negative BC, respectively (vs. 14.5% and 8.9%, respectively, in patients who did not receive trastuzumab).[83] Subsequently, the CLEOPATRA trial established pertuzumab plus trastuzumab and docetaxel as a new first-line standard of care demonstrating 4-year OS of 57.6%.[45,85] The pertuzumab combination was associated with a median OS of 56.5 months (vs. 40.8 months for placebo plus trastuzumab and docetaxel), and median PFS of 18.7 months (vs. 12.4 months).[45,85] Regimens based around anti-HER2 therapies are now the mainstay of first-line treatment in HER2+ mBC in England rather than chemotherapy

alone (to which HER2+ disease has a poor response), with many patients treated with trastuzumab-based regimens (either the CLEOPATRA pertuzumab combination, or trastuzumab plus a taxane; see Section B.1.3.3 for further details of HER2+ u/mBC treatment strategies).[45,46]

After trastuzumab and a taxane, standard of care is T-DM1, currently the only HER2-targeted option recommended by NICE at this line.[32,46] Survival outcomes for T-DM1 (Section B.1.3.3) were assessed in the EMILIA trial which enrolled patients treated with prior trastuzumab and a taxane and was conducted between 2009–2012, prior to the introduction of pertuzumab.[2,86] In EMILIA, median PFS in the T-DM1 treatment arm was 9.6 months which translated into a median OS of 29.9 months.[47,48]

Subsequent studies confirm the efficacy of T-DM1 in this setting. In the KATE2 randomised controlled trial (RCT),[f] median PFS for T-DM1 (the trial comparator) was 6.8 months, although median OS was not estimable at the second interim analysis.[49] In the KAMILLA trial, designed to approximate the breadth of patients encountered in routine clinical practice[g], first- or second-line treatment with T-DM1 was associated with a median PFS of 8.3 months and median OS of 31.3 months.[87] Recent real-world studies of T-DM1 after one prior therapy report median PFS ranging from 3−11 months,[88-93] and median OS ranging from 12−27.3 months.[88,90,94]

Together these data highlight that most patients with HER2+ u/mBC progress within a year of starting treatment with T-DM1,[88-93] and that outcomes for patients with aggressive, HER2+ u/mBC have not advanced since the introduction of T-DM1 in 2014.

B.1.3.3 Current treatment pathway

Goals of treatment for mBC include improving or maintaining quality of life by reducing disease symptoms; delaying progression; reducing treatment toxicity and extension of life as much as possible.[30,31]

Current treatment guidelines

Europe

The Europe-wide treatment guideline of relevance to this submission is the 2021 European Society for Medical Oncology (ESMO) guideline for mBC.[85]

NICE

Recommendations for management of HER2+ advanced BC are included in NICE Clinical Guideline 81 (CG81). However, CG81 was published in 2009, was last updated in 2017,[40] and does not include two therapies recommended by NICE at first and second line, respectively: pertuzumab with trastuzumab and docetaxel, and T-DM1.[2,32] Therapies that received a positive recommendation from NICE at first, second and third line for populations that include patients with HER2+ metastatic BC are shown in Table 4. Relevant therapies for HER2+ u/mBC with a positive recommendation from NICE, or which are included in CG81, are shown in the treatment pathway in Figure 4.

[f] Like EMILIA, KATE2 enrolled patients who had previously been treated with trastuzumab and a taxane.

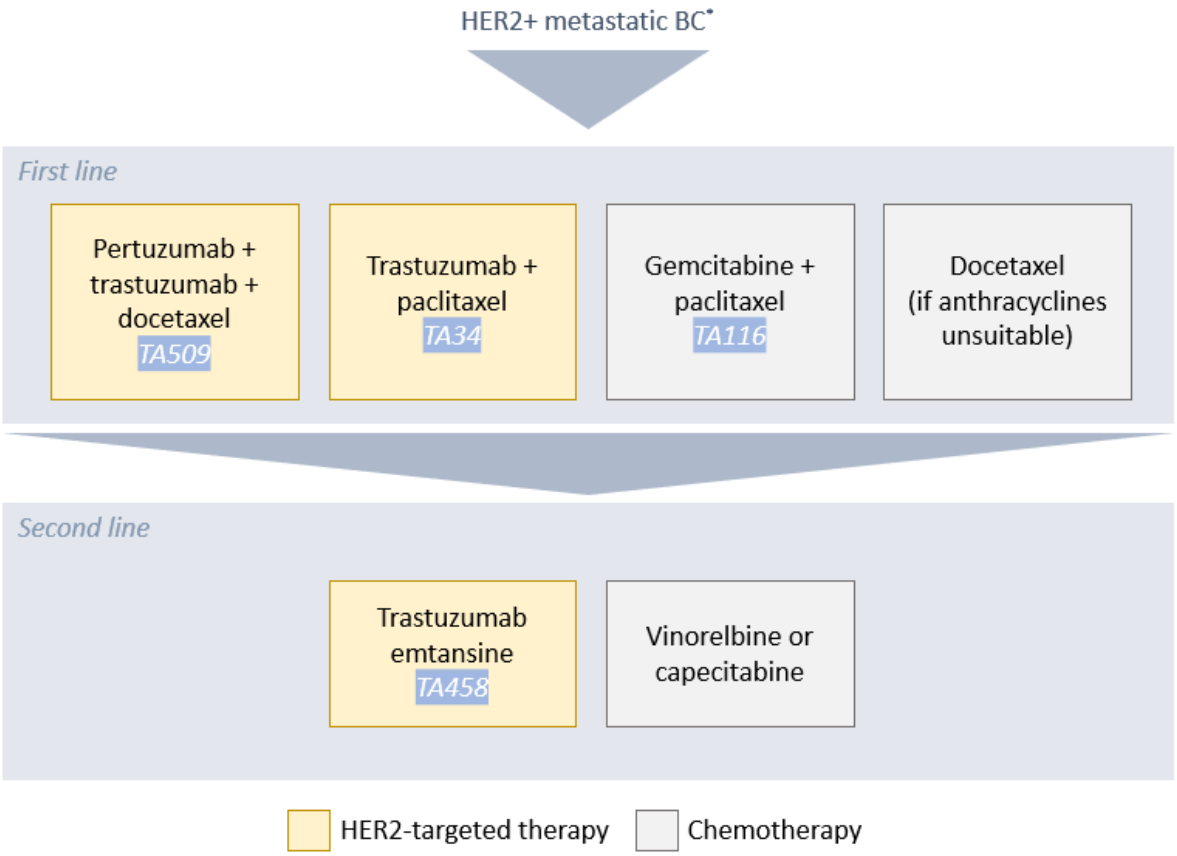
[g] Patients enrolled in KAMILLA had HER2+ recurrent, metastatic or unresectable BC and had received a prior anti-HER2 therapy and chemotherapy. Prior taxane was not required.

Table 4: Summary of published NICE technology appraisals with a positive recommendation in HER2+ metastatic BC

TA	Year	Intervention	LoT	Title
First line				
34	2002	Trastuzumab + paclitaxel	1†	Guidance on the use of trastuzumab for the treatment of advanced breast cancer
116	2007	Gemcitabine + paclitaxel	≥1	Gemcitabine for the treatment of metastatic breast cancer
509	2018	Pertuzumab + trastuzumab + docetaxel	1	Pertuzumab with trastuzumab and docetaxel for treating HER2-positive breast cancer
Second line				
458*	2017	Trastuzumab emtansine	≥2	Trastuzumab emtansine for treating HER2-positive advanced breast cancer after trastuzumab and a taxane
Third line				
34	2002	Trastuzumab	≥3	Guidance on the use of trastuzumab for the treatment of advanced breast cancer
423	2016	Eribulin	≥3	Eribulin for treating locally advanced or metastatic breast cancer after 2 or more chemotherapy regimens
704	2021	Trastuzumab deruxtecan	≥3	Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after 2 or more anti-HER2 therapies
[ID3828]‡	2022	Tucatinib + trastuzumab + capecitabine	≥3	Tucatinib with trastuzumab and capecitabine for treating HER2-positive advanced breast cancer after 2 or more anti-HER2 therapies

*Cancer Drugs Fund reconsideration of TA371.
†Although this regimen could potentially be used at second line, most patients would be expected to be excluded due to the requirement for no prior chemotherapy for metastatic BC.
‡ On 25 March 2022, tucatinib received a positive Final Appraisal Determination for this indication; however, a TA number had not been assigned.
Abbreviations: BC, breast cancer; HER2, human epidermal growth factor receptor 2; LoT, line of therapy; TA, technology appraisal.
Sources: NICE, 2002 (TA34);[1] NICE, 2007 (TA116);[95] NICE, 2017 (TA458);[32] NICE, 2018 (TA509);[2] NICE, 2022 (tucatinib final appraisal document).[96]

Figure 4: Current treatment pathway for HER2+ u/mBC in England



*Patients who are also hormone receptor-positive can receive add-on endocrine therapies.
Abbreviations: BC, breast cancer; HER2, human epidermal growth factor receptor 2; TA, technology appraisal.
Source: NICE, 2002 (TA34);[1] NICE, 2007 (TA116);[95] NICE, 2017 (CG81);[40] NICE, 2017 (TA458);[32] NICE, 2018 (TA509).[2]

First-line treatment for HER2+ advanced or metastatic BC

Two HER2-targeted first-line therapies are currently recommended by NICE. Current standard of care in this setting is pertuzumab with trastuzumab and docetaxel (TA509) which is recommended for adults with metastatic or locally recurrent unresectable HER2+ disease who have not had prior anti-HER2 therapy or chemotherapy.[2] Trastuzumab with paclitaxel (TA34) is also recommended by NICE for patients with HER2+ expression scores of 3+ who have not received chemotherapy for metastatic BC and for whom anthracycline treatment is inappropriate.[1]

For patients who are also hormone receptor-positive, endocrine therapy is included in CG81 as an option for first-line treatment for the majority of patients with ER-positive (ER+) BC.[40] However, clinical input at an expert validation meeting conducted by Daiichi Sankyo in March 2022 was that HER2-targeted therapies are the preferred treatment for HER2+ u/mBC.[46] Chemotherapy is also recommended more broadly in mBC irrespective of HER2-status (see Alternative Therapy Options below).[40]

The NICE first-line recommendations are consistent with the 2021 ESMO guideline, which recommends combinations of HER2-targeted agents and chemotherapy at first line. However, the ESMO guidelines allow a wider range of combinations than NICE, also

suggesting trastuzumab monotherapy or trastuzumab plus pertuzumab in patients contraindicated for chemotherapy.[85] If patient comorbidities, performance status, or personal preference make chemotherapy unsuitable, additional therapeutic options suggested by ESMO are trastuzumab and lapatinib, or lapatinib monotherapy (with endocrine therapy added if the patient also has hormone receptor-positive disease).[85] Endocrine monotherapy is not recommended unless anti-HER2 therapies are contraindicated due to cardiac disease.[85]

Second-line treatment for HER2+ advanced or metastatic BC

NICE CG81 recommends assessing ER and HER2 status on disease recurrence, if a change in receptor status could lead to a change in disease management.[40]

Current standard of care for patients with HER2+ BC after trasuzumab and a taxane is T-DM1 (TA458).[32] This is consistent with the 2021 ESMO guideline, which includes T-DM1 as the only NICE-approved targeted therapy for HER2+ unresectable or metastatic BC in this setting.[85]

Trastuzumab with paclitaxel may be used (TA34), but is only recommended for patients without prior chemotherapy for metastatic BC, and is therefore unlikely to be used in this setting, given the first-line NICE recommendations.[1,2,40]

The 2021 ESMO guideline includes two therapies that are not yet reimbursed in the UK. The guidelines state that T-DXd has replaced T-DM1 as the standard second-line therapy for HER2+ BC.[85] For selected patients who have known brain metastases, tucatinib with capecitabine and trastuzumab may also be considered, and is the preferred choice for active brain metastases.[85] As these therapies are not currently reimbursed in this setting in England and Wales, they are not in routine use.

Subsequent lines for HER2+ advanced or metastatic BC

Subsequent therapy (third line and beyond) recommended in the NICE pathway includes:

- T-DXd (TA704; reimbursed via CDF) in unresectable or metastatic BC after two or more anti-HER2 therapies[3]
- Trastuzumab monotherapy (TA34) in patients with HER2+ scores of 3+ and two or more prior chemotherapy regimens for metastatic BC[1]
- Tucatinib with trastuzumab and capecitabine (ID3828) in locally advanced or metastatic BC after two or more anti-HER2 therapies (FAD issued 25 March 2022)[h96]

In agreement with NICE recommendations, the ESMO guidelines also recommend third line and subsequent treatment with tucatinib with capecitabine and trastuzumab, or T-DXd depending on previous therapy and suitability.[85] ESMO also recommend trastuzumab in combination with chemotherapy, but only if other anti-HER2 therapies are unsuitable, have been used previously, or are not available.[85] Moreover, the ESMO guidelines recommend T-DM1 at third-line and subsequent therapy, given the prioritisation of T-DXd at second line, displacing T-DM1 as the second-line standard of care.[85] The guidelines also suggest lapatinib-based regimens, neratinib, and margetuximab as possible options in a late-line setting.[85]

[h] Vinorelbine and capecitabine were considered relevant comparators for these TAs and may also be widely used in clinical practice.

Alternative therapy options

HER2-targeted therapies are generally the preferred therapeutic options – vs. non-targeted options – in patients with HER2+ u/mBC due to better outcomes and tolerability, and are therefore likely to be the therapies of choice for clinicians (confirmed by clinical experts in an expert validation meeting).[46] However, chemotherapy is also broadly recommended across advanced BC by NICE, irrespective of HER2 status, and is therefore available as a therapeutic alternative for patients with HER2+ BC.[40]

- **First line |** Sequential chemotherapy can be used.[40] Combination chemotherapy should be considered where appropriate, or docetaxel used in patients unsuited to anthracyclines. Gemcitabine plus paclitaxel (TA116) is also recommended (stipulated to be only for patients for whom docetaxel plus capecitabine or docetaxel monotherapy are considered appropriate).[40,95]

- **Second line |** Patients may receive combination chemotherapy or single-agent vinorelbine or capecitabine.[40]

- **Third-line and subsequent therapy |** NICE recommends eribulin (TA423) after progression on at least two chemotherapy regimens.[97] As vinorelbine and capecitabine were listed as relevant comparators in TA704, TA423, and the tucatinib appraisal (ID3828), it is reasonable to assume these are in use beyond second line.[3,96,97]

B.1.3.4 Unmet need

Many patients present with, or develop, metastatic or unresectable BC for which no curative therapy is available. A substantial proportion of these patients also have HER2+ disease,[14] which results in a highly aggressive and chemotherapy-resistant disease with poor survival outcomes.[15,16,81,82] Symptom burden is very high in metastatic BC, largely due to metastases,[17,18,63-65,98] and QoL is often poor.[19,20]

The introduction of first-line pertuzumab in combination with trastuzumab and docetaxel after approval by NICE in 2018 improved outcomes in previously untreated unresectable HER2+ disease, demonstrating a median PFS of 18.7 months and median OS of 56.5 months in the CLEOPATRA trial.[2,45] Efficacy of T-DM1 in patients previously treated with trastuzumab and a taxane was demonstrated in the registration study EMILIA, with T-DM1 providing a median PFS of 9.6 months and median OS of 29.9 months.[47,48] T-DM1 also provided better tolerability than the comparator regimen – capecitabine plus lapatinib – with fewer patients experiencing Grade ≥3 symptomatic adverse events (AEs) such as diarrhoea, which may impose a substantial QoL decrement on patients.[47,48,75]

Subsequent studies confirm the efficacy of T-DM1 in this setting. In the KATE2 RCT,[i] median PFS for T-DM1 (the trial comparator) was 6.8 months, although median OS was not estimable at the second interim analysis.[49] In the KAMILLA trial, designed to approximate the breadth of patients encountered in routine clinical practice[j], first- or second-line treatment with T-DM1 was associated with a median PFS of 8.3 months and median OS of 31.3 months.[87] Recent real-world studies of T-DM1 after one prior therapy report median PFS ranging from 3−11 months,[88-93] and median OS ranging from 12−27.3 months.[88,90,94]

[i] Like EMILIA, KATE2 enrolled patients who had previously been treated with trastuzumab and a taxane. However, unlike EMILIA, 48% of patients in KATE2 had also received pertuzumab as a component of their previous treatment regimen, potentially better reflecting current UK clinical practice

[j] Patients enrolled in KAMILLA had HER2+ recurrent, metastatic or unresectable BC and had received a prior anti-HER2 therapy and chemotherapy. Prior taxane was not required.

However, while T-DM1 is an effective therapy, it is currently the only HER2-targeted NICE-recommended treatment for patients with HER2+ mBC who have previously received trastuzumab and a taxane, and outcomes for patients with aggressive, HER2+ u/mBC have not advanced since it was introduced to UK clinical practice in 2014.

The NHS Long Term Plan, published in 2019, outlined a number of commitments that aim to improve the diagnosis, treatment, care and outcomes for BC patients. This included the goal of – by 2028 – an extra 55,000 people each year surviving for five years or more, following a cancer diagnosis and improving QoL and patient experience outcomes.[99] The availability of a new, effective targeted treatment for a patient population with limited alternatives after trastuzumab and a taxane could help the NHS meet these long-term ambitions.

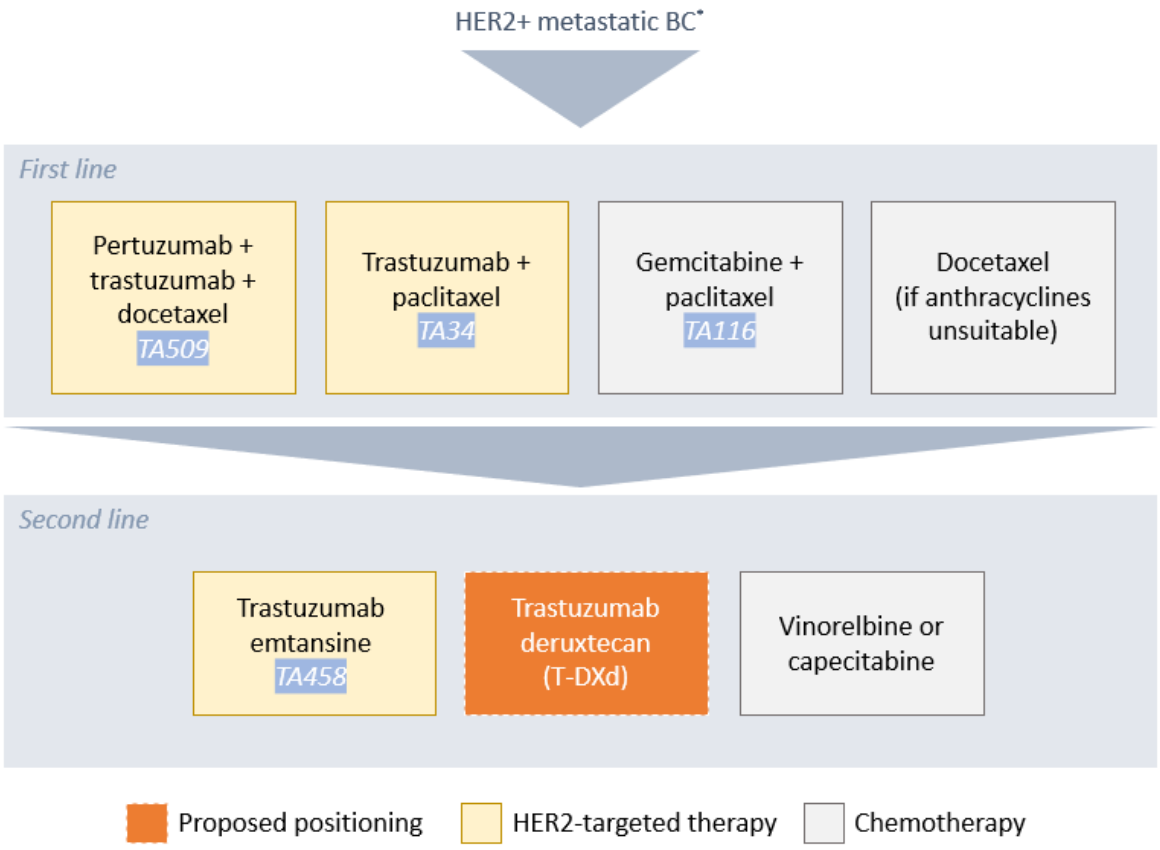
In summary, while HER2-targeted treatments have improved survival outcomes in HER2+ BC,[39] an unmet need remains for improved survival outcomes – both PFS and OS – for patients who have received one or more prior anti-HER2 regimens.[50] Treatments shown to increase PFS are highly valued by patients with incurable breast cancer, but where possible, should provide efficacy without the high levels of toxicity imposed by chemotherapy.[16,100]

B.1.3.5 Proposed place of T-DXd in therapy

T-DXd is currently reimbursed through the CDF for the treatment of HER2+ unresectable or metastatic BC after two or more prior anti-HER2 therapies i.e. the third-line setting and beyond.[3] This recommendation was based on data from DESTINY-Breast01 where patients were previously treated with T-DM1. Data from the DESTINY-Breast03 trial, in which patients were previously treated with trastuzumab and a taxane, supports the proposed positioning for T-DXd after trastuzumab and a taxane – i.e. after first-line treatment of HER2+ u/mBC – as an alternative to T-DM1 (Figure 5).

The 2021 ESMO guideline for mBC states that “it is reasonable to consider trastuzumab deruxtecan the new standard second-line therapy in regions where this drug is available, moving T-DM1 to a later-line setting”.[85] The National Comprehensive Cancer Network (NCCN) also recommends T-DXd as the preferred second-line option in unresectable or metastatic disease.[101] Patients receiving T-DXd at second line in the proposed pathway would be anticipated to receive T-DM1 as subsequent therapy, either at third or a later line of therapy.

Figure 5: Proposed positioning of T-DXd in HER2+ u/mBC in England and Wales



*Patients who are also hormone receptor-positive can receive add-on endocrine therapies.
Proposed positioning of T-DXd shown in orange.
Abbreviations: BC, breast cancer; HER2, human epidermal growth factor receptor 2; TA, technology appraisal; T-DXd, trastuzumab deruxtecan.
Source: NICE, 2002 (TA34);[1] NICE, 2007 (TA116);[95] NICE, 2017 (CG81);[40] NICE, 2017 (TA458);[32] NICE, 2018 (TA509).[2]

B.1.4 Equality considerations

No equality issues are anticipated for the appraisal of trastuzumab deruxtecan in this indication.

B.2 Clinical effectiveness

Evidence for this submission comes from the pivotal Phase III, multicentre, open-label, randomised, active-controlled DESTINY-Breast03 trial assessing the efficacy and safety of T-DXd vs. current standard of care, T-DM1, in patients with HER2+ u/mBC after treatment with trastuzumab and a taxane[102]

- The DESTINY-Breast03 trial is the only relevant evidence to support the evaluation of T-DXd in the HER2+ u/mBC indication after trastuzumab and a taxane[102-105]
- A systematic literature review (SLR) to identify evidence for the treatment of HER2+ u/mBC with T-DXd in this setting confirmed there is no additional evidence of relevance for this appraisal
- DESTINY-Breast03 is ongoing, with the evidence presented for this submission from the interim analysis for PFS (data cut-off [DCO]: 21st May 2021)[102]
- The median follow-up at DCO was 16.2 months with T-DXd and 15.3 months with T-DM1[102]

DESTINY-Breast03 provides evidence on treatment with T-DXd that is generalisable and highly relevant to UK patients with HER2+ u/mBC following treatment with trastuzumab and a taxane[46,102]

- DESTINY-Breast03 enrolled patients previously treated with trastuzumab and a taxane, and used T-DM1 as the active comparator. These therapies represent the UK standard of care at first- and second-line treatment, respectively[1,2,46,102]
- The generalisability of DESTINY-Breast03 to UK clinical practice was validated with UK clinical experts[46]

DESTINY-Breast03 met the primary endpoint of statistically significant PFS benefit by BICR, leading to early unblinding of DESTINY-Breast03[102,106]

- Median PFS by BICR was not reached (95% CI: 18.5, NE) in the T-DXd arm vs. 6.8 months (95% CI: 5.6, 8.2) in the T-DM1 arm[102]
- T-DXd provided a 72% lower risk of progression or death than treatment with T-DM1 for the primary efficacy endpoint (PFS by BICR; HR: 0.28; 95% CI: 0.22, 0.37 [$p=7.8\times10^{-22}$])[102,103]
- The Independent Data Monitoring Committee (IDMC) unblinded DESTINY-Breast03 early due to demonstrated superiority of T-DXd over T-DM1 for the primary endpoint (PFS by BICR)[106]
- Outcomes for the primary endpoint were confirmed via the secondary endpoint, PFS by investigator assessment (IA) (HR: 0.26 for T-DXd vs. T-DM1; 95% CI: 0.20, 0.35 [$p=6.5\times10^{-24}$])[102]

At DCO, OS data were immature but showed a numerical trend towards better survival with T-DXd as evidenced by an early and sustained separation of survival curves; this will be further evaluated in the ongoing trial[102]

- While median OS was not estimable (NE) in either treatment arm, the risk of death was numerically lower with T-DXd than T-DM1 (HR: 0.55; 95% CI: 0.36, 0.86 [p=0.007[k]]; pre-specified boundary of p<0.000265 not crossed)[102]
- The rate of survival at 12 months was 94.1% in the T-DXd arm compared with 85.9% in the T-DM1 arm[102]

[k] The pre-specified significance boundary for OS at the interim analysis for PFS was p<0.000265.

T-DXd was associated with a statistically significant confirmed objective response rate (ORR) and higher complete and partial response rates compared with T-DM1[103]

- T-DXd was associated with a significantly greater confirmed ORR by BICR (79.7%) compared with T-DM1 (34.2%) at DCO (p<0.0001)[102]
- 16.1% and 63.6% of patients in the T-DXd arm achieved complete response (CR) or partial response, respectively, vs. 8.7% and 25.5% with T-DM1 (response by BICR)[102]
- Confirmed ORR by IA [redacted] for T-DXd and T-DM1 ([redacted])[105]

T-DXd demonstrated benefit across key demographic and prognostic subgroups as measured by PFS (BICR) and ORR[102,104]

- PFS benefit (by BICR) was consistent across key subgroups, irrespective of hormone receptor mutation status, prior pertuzumab treatment, presence of visceral disease, lines of prior therapy, or stable brain metastases at baseline[102]
- A *post hoc* analysis of confirmed ORR demonstrated consistent benefit across subgroups with T-DXd compared with T-DM1[104]

T-DXd has an acceptable safety profile that was broadly similar to safety and tolerability observed in previous studies of T-DXd[102,107,108]

- Gastrointestinal and haematologic toxic effects were the most common TEAEs deemed drug-related in both treatment arms, but were mostly of low-grade severity[102,103]
- All events of interstitial lung disease (ILD), previously identified as an AE of special interest with T-DXd, were manageable and assessed as Grade ≤3 severity[102,103]

In DESTINY-Breast03, T-DXd was associated with [redacted][105]

- Compliance across HRQoL questionnaires was [redacted] and [redacted] at baseline in the T-DXd and T-DM1 arms, respectively, and a minimum of [redacted] and [redacted], respectively, from Cycle 3 onwards[105]
- HRQoL as measured by EQ-5D-5L (both index and visual analogue scale [VAS]) was [redacted][105]
- Median time to definitive deterioration for EQ-5D-5L VAS was [redacted] (HR: [redacted])[105]
- T-DXd was associated with [redacted] time to deterioration than T-DM1 for [redacted] of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30 and EORTC QLQ-BR45[105]

Clinical experts have described the efficacy of T-DXd in DESTINY-Breast03 as "unprecedented", and that it will lead to a "paradigm shift in the treatment of HER2-positive metastatic breast cancer"[109]

B.2.1 Identification and selection of relevant studies

An SLR was conducted to identify the existing clinical evidence detailing the efficacy, safety, and QoL for currently available and investigational therapies used at second line for patients with unresectable and/or metastatic HER2+ BC. See Appendix D.1 for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised.

Comprehensive literature searches for clinical evidence were undertaken in electronic databases (MEDLINE, Embase and The Cochrane Library [including the Cochrane Database of Systematic Reviews {CDSR} and the Cochrane Central Register of Controlled Trials {CENTRAL}]) for studies published prior to 20 August 2020, as well as conference proceedings and websites of national reimbursement and health technology assessment organisations (2018–2020). An update searched these databases from 21 August 2020 to 27 September 2021. Data from eligible studies were extracted and assessed for methodological quality and applicability. Following publication of the final scope for this submission, included studies were re-screened in March 2022 to restrict eligible treatments to T-DXd and T-DM1, the intervention and comparator for this appraisal, consistent with the decision problem.

In total, the SLR identified 187 unique publications. As some studies were associated with multiple publications, secondary publications were combined. Of these, 163 publications from 154 studies were not relevant for this submission because they did not investigate comparators of interest, did not have an appropriate study design, or did not present endpoint data for patients with one prior line of treatment. The SLR therefore identified a total of 24 relevant publications across 17 studies.

There was one study from four publications identified for T-DXd: DESTINY-Breast03. For the relevant comparator – T-DM1 – there were 16 studies (20 publications). These latter studies did not directly compare efficacy and safety vs. T-DXd. Consequently, this submission focuses primarily on the key evidence from the Phase III, head-to-head study, DESTINY-Breast03.

B.2.2 List of relevant clinical effectiveness evidence

Table 5: Clinical effectiveness evidence

Study	**DESTINY-Breast03 (NCT03529110)**
Study design	Phase III, multicentre, open-label, randomised, active-controlled, trial. 1:1 assignment was in parallel
Population	Adults with HER2-positive unresectable and/or metastatic BC previously treated with trastuzumab and taxane
Intervention(s)	T-DXd administered by IV infusion at a dose of 5.4 mg/kg (n=261)
Comparator(s)	T-DM1 administered by IV infusion at a dose of 3.6 mg/kg (n=263)
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale for use/non-use in the model	Pivotal trial in relevant patient population, vs. in-scope comparator

Reported outcomes specified in the decision problem	• **PFS** • **OS** • **Response rates** • Duration of response • **AEs** • **HRQoL**
All other reported outcomes	• Time to response • Hospitalisation
Key publication	Cortés et al, 2022[102]
Secondary sources	• Cortés et al, 2021 (presented at ESMO congress 2021)[103] • Hurvitz et al, 2021 (presented at SABCS 2021)[104] • Daiichi Sankyo Inc., 2021 (Clinical Study Report [CSR])[105]

Outcomes incorporated in the model are shown in **bold**.
Abbreviations: AE, adverse event; BC, breast cancer; CSR, clinical study report; ESMO, European Society for Medical Oncology; HER2, human epidermal growth factor receptor 2; HRQoL, health-related quality of life; IV, intravenous; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PROs, patient-reported outcomes; SABCS, San Antonio Breast Cancer Symposium; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Sources: Cortés et al, 2022;[102] Cortés et al, 2021;[103] Daiichi Sankyo Inc., 2021 (clinical study report [CSR]; Data on File).[105]

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

B.2.3.1 DESTINY-Breast03

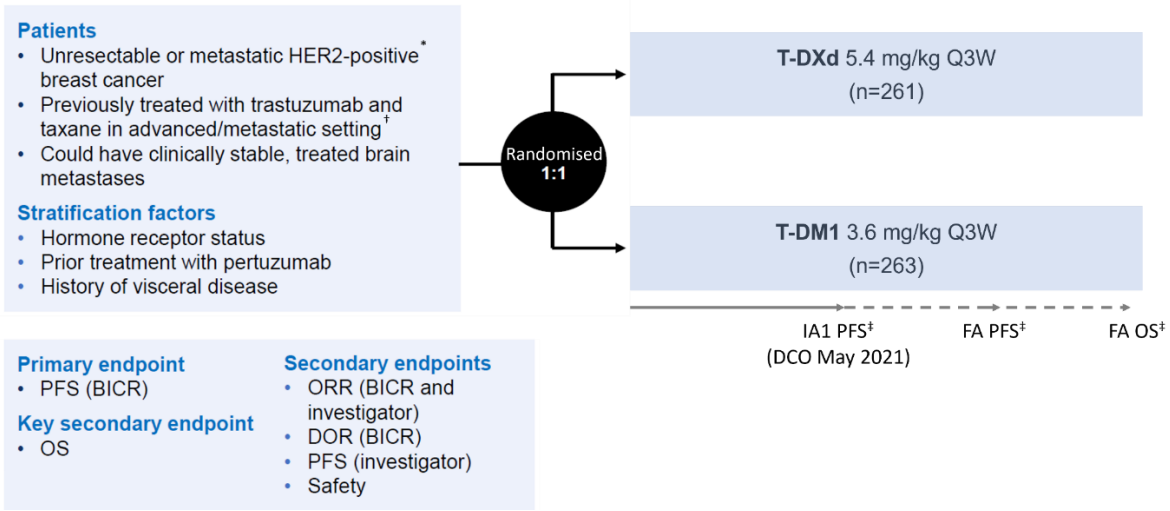
B.2.3.1.1 Study design

DESTINY-Breast03 is an ongoing Phase III, multicentre, open-label randomised active-controlled trial conducted across multiple countries including the UK (study design shown in Figure 6). Enrolled patients were adults with HER2+ u/mBC, previously treated with trastuzumab and a taxane in the advanced/metastatic setting or that had progressed within 6 months after neoadjuvant or adjuvant treatment with trastuzumab and a taxane.[102] Patients were randomised 1:1 by interactive web-based system and stratified by hormone receptor status (+/−), prior pertuzumab (yes/no), and history of visceral disease (yes/no).[102] The dose of T-DXd was based on conclusions from a previous dose-finding study.[110]

After superiority was demonstrated for the primary endpoint at the PFS interim analysis, the trial was unblinded early on the recommendation of the IDMC in 30 July 2021.[102,106] Evidence from DESTINY-Breast03 presented in this submission is from the PFS interim analysis data cut, for which the median follow-up was 16.2 (range: 0.0–32.7) and 15.3 (range: 0.0–31.3) months with T-DXd and T-DM1, respectively.[103] Details of planned analyses and statistical testing hierarchy are presented in Section B.2.4.2. DESTINY-Breast03 is anticipated to complete in 2023.[111]

A summary of the methodology of DESTINY-Breast03 is shown in Table 6.

Figure 6: DESTINY-Breast03 | Study design



*HER2 IHC3+ or IHC2+/ISH+ based on central confirmation.
†Progression during or <6 months after completing adjuvant therapy involving trastuzumab and taxane.
‡Planned analyses were: IA1 at [redacted] PFS by BICR events; FA of PFS by BICR at [redacted] PFS events; and FA OS at [redacted] OS events.[112]
Abbreviations: BC, breast cancer; BICR, blinded independent central review; DOR, duration of response; FA, final analysis; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IA1, interim analysis one; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3W, dosing every 3 weeks; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Sources: adapted from Cortés et al, 2021;[103] Cortés et al, 2022;[102]

Table 6: Summary of DESTINY-Breast03 methodology

Trial design	Phase III, multicentre, open-label, randomised, active-controlled trial. International study with parallel assignment
	Randomisation: 1:1 by Interactive Web/Voice Response System (IXRS) **Stratification factors:** hormone receptor status (+/−), prior pertuzumab (yes/no), history of visceral disease (yes/no) **Blinding:** open-label treatment allocation for individual participants and treating physicians.[102] [redacted].[105,112] The primary endpoint was assessed by blinded independent central review.[102] The randomisation schedule was [redacted][112]
Duration of study	Planned: approximately [redacted] months (at observation of approximately [redacted] OS events) Median at follow-up (DCO May 2021): • Overall: 15.9 months (range [redacted]) o T-DXd arm: 16.2 (range: 0.0–32.7) o T-DM1 arm: 15.3 (range: 0.0–31.3)
Settings and locations where data were collected	169 centres in 15 countries, including Europe (UK, France, Spain, Belgium, Italy, Germany), North America (US, Canada), Asia (Japan, Republic of Korea, China, Taiwan, Hong Kong), and other regions (Australia, Brazil)
Participant eligibility criteria	**Key inclusion criteria** • [redacted] • Pathologically documented BC that: o was unresectable or metastatic o had central-laboratory confirmed HER2-positive expression* o was previously treated with trastuzumab and taxane in the advanced/metastatic setting or progressed within 6 months after (neo)adjuvant treatment involving a regimen including trastuzumab and taxane • [redacted] • [redacted] • [redacted] • [redacted]
	Key exclusion criteria • Prior treatment with an anti-HER2 ADC in the metastatic setting† • [redacted] • History of (non-infectious) ILD/pneumonitis requiring steroids, current diagnosed or suspected ILD/pneumonitis, or clinically severe pulmonary compromise resulting from intercurrent pulmonary illnesses • Spinal cord compression or clinically active CNS metastases defined as untreated, symptomatic, or requiring therapy with corticosteroids or anticonvulsants to control associated symptoms‡ • [redacted] • [redacted] • [redacted]

	• [redacted] • [redacted] • [redacted]
Trial drugs	**Intervention:** T-DXd (n=261) was administered at a starting dose of 5.4 mg/kg (based on patient weight at screening), as IV infusion over 90 minutes for the first infusion. Subsequent doses were infused over a minimum of 30 minutes** every 21 days ([redacted]). Dosage was [redacted] weight value **Comparator:** T-DM1 (n=263) was administered at a starting dose of 3.6 mg/kg (based on patient weight at screening), as IV infusion over 90 minutes for the first infusion. Subsequent doses were infused over a minimum of 30 minutes** every 21 days ([redacted]). Dosage was [redacted] weight value Crossover at the end of treatment was not permitted within the trial. However, crossover post study completion may occur in markets where T-DXd/T-DM1 is commercially available
	Dose modifications for T-DXd in the event of toxicity were to be made on the basis of AE type, severity, and relatedness to study drug, outlined in the T-DXd management guideline (Appendix O) Dose modifications for T-DM1 were made in accordance with the approved label for T-DM1 **Dose interruption:** Study drug could be delayed/interrupted in the event of AEs, e.g. after any ILD event **Dose reduction:** Two dose reductions in the event of toxicity were permitted for each treatment arm (T-DXd: 4.4 kg/kg and 3.2 mg/kg; T-DM1: 3.0 mg/kg and 2.4 mg/kg). Continued toxicity after two dose reductions resulted in patient study drug discontinuation. **Study drug discontinuation:** Patients were to discontinue study drug in the event of [redacted], [redacted] ([redacted], but for which [redacted]), AEs (AEs requiring discontinuation are provided in Appendix M), or death††
Concomitant medication	**Permitted concomitant medication:** Prophylactic treatment of [redacted] was per [redacted] and [redacted]. [redacted] could be used for [redacted] based on [redacted] (except within [redacted]) Based on currently available clinical safety data, [redacted] were recommended [redacted] to T-DXd infusions Concomitant use of dietary supplements, medications [redacted], and [redacted] was discouraged but not prohibited **Prohibited concomitant medication:** Other anti-cancer therapy, [redacted], [redacted], [redacted], [redacted], or [redacted] (concurrent use of [redacted]); [redacted]; or [redacted]; or any [redacted]; [redacted] or [redacted],‡‡ or (for the T-DM1 arm) any products prohibited by the local label for T-DM1

Primary outcomes	**PFS by BICR** (analysis set was FAS; see Section B.2.3.1.2 for further details of outcomes and Section B.2.4.1 for details of analysis sets)
Other outcomes used in the model/specified in scope	• **OS** • **Response rates** • Duration of response • Safety **(AEs)** • **HRQoL assessed by EQ-5D**
Other outcomes of interest	• PFS (IA) • Time to response • HRQoL assessed by EORTC QLQ-C30 • HRQoL assessed by EORTC QLQ-BR45
Pre-planned subgroups	Subgroup analyses were planned for PFS according to BICR, [redacted], to be performed on the FAS Pre-specified subgroups were: hormone receptor status; ER status; PR status; prior pertuzumab treatment; lines of prior systemic therapy (not hormone therapy); lines of therapy prior to pertuzumab; baseline renal impairment; baseline hepatic impairment; baseline visceral disease; baseline lung metastases; baseline liver metastases; baseline CNS metastases; history of CNS metastases; age; race; region; ECOG performance status

Outcomes listed in **bold** are included in the economic model.
*According to American Society of Clinical Oncology/College of American Pathologists guidelines.[113,114]
†Anti-HER2 ADC such as T-DM1. Prior use in (neo)adjuvant setting [redacted].
‡Patients with brain metastases that were clinically inactive or no longer symptomatic and not requiring corticosteroids/anticonvulsants were eligible if recovered from acute toxic effects of radiotherapy.
§[redacted].
**Infusion time was reduced to ≥30 minutes only if no infusion-related reactions were observed in the patient.
††Additional reasons not listed above are: [redacted]. Patients could [redacted]
‡‡[redacted]
Abbreviations: ADC, antibody-drug conjugate; AE, adverse event; BC, breast cancer; BICR, blinded independent central review; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; ER, oestrogen receptor; FAS, full analysis set; HER2, human epidermal growth factor receptor 2; HIV, human immunodeficiency virus; IA, investigator assessment; ILD, interstitial lung disease; IV, intravenous; mAb, monoclonal antibody; OS, overall survival; PD, progressive disease; PR, progesterone receptor; RECIST, Response Evaluation Criteria in Solid Tumours; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Sources: Cortés et al, 2022;[102] Daiichi Sankyo Inc., 2021 (CSR; Data on File).[105]

Screening period assessments

During initial tissue screening, [redacted] were required. [112] During the screening period, from [redacted] From [redacted], and [redacted] were conducted/collected.[105,112]

[l] Unless documentation of other AEs were also recorded because of requirement by local law.

B.2.3.1.2 Trial outcomes

Trial endpoints, their definitions, and censoring rules are shown in Table 7.

Table 7: DESTINY-Breast03 | Summary of key endpoints

Endpoint/assessment	Details	Censoring rules
Primary endpoint		
Progression-free survival (by BICR)	Defined as the time from the date of [redacted] disease progression per BICR [redacted] or	No baseline evaluable tumour assessment: [redacted] No post-baseline tumour assessment: [redacted] Early death (within 14 weeks of randomisation) for no baseline or no post-baseline tumour assessment: [redacted] Patients with radiographic disease progression/death without missing ≥2 consecutive tumour assessments immediately preceding event: [redacted] Patients with disease progression or death after missing ≥2 consecutive scheduled tumour assessments: censored at date of last evaluable tumour assessment prior to earliest death/progression date and analysis cut-off date Patients with at least one post-baseline response assessment and no death or objective documentation of radiographic disease progression: censored at date of last evaluable tumour assessment (prior to analysis cut-off date)
Key secondary endpoint		
Overall survival (by IA)	Defined as the time from [redacted] to the date of death for any cause. If no death was reported for a patient before the data cut-off for overall survival analysis, overall survival was [redacted]	The [redacted]

Endpoint/assessment	Details	Censoring rules
		[redacted]
Secondary endpoints		
Progression-free survival (by IA)	Defined as the time from [redacted] disease progression via investigator-assessed disease progression [redacted] or [redacted]	Censoring rules were the same as described above for PFS by BICR
Objective response rate (by BICR; by IA)	Defined as the proportion of patients who achieved a best overall response of CR or PR, based on BICR and based on IA. Confirmation of CR or PR was required. Response definitions: • CR: disappearance of all target lesions • PR: ≥30% decrease in the sum of diameters of target lesions from baseline • PD: ≥20% increase in sum of diameters of target lesions, taking the smallest sum of diameters since study, or appearance of a new lesion • SD: response not fitting the criteria for PR or PD	NA

Endpoint/assessment	Details	Censoring rules
Duration of response (by BICR, by IA)	Defined as the time from the date of the first documentation of objective response (CR or PR) to the date of the first documentation of disease progression based on BICR or investigator's assessment or to the date of death due to any cause. Duration of response was to be measured for only patients with a response of CR or PR. Subjects who were progression-free at the time of the analyses were to be censored at the date of the last evaluable tumour assessment	Censoring rules were the same as described above for PFS by BICR
Quality of life endpoints (patient reported outcomes)	Endpoints included EORTC QLQ-C30, EORTC QLQ-BR45, EQ-5D-5L	If no baseline evaluable QoL and/or no post-baseline QoL assessment: • Death by first survival follow-up (3 months from 40-day visit): [redacted] • No death: [redacted] If baseline and at least one post-baseline QoL assessment: [redacted] • Death by first survival follow-up (3 months from 40-day visit): [redacted] Others: [redacted]
Resource use/hospitalisation endpoints	Hospitalisation-related endpoints, including: • Reasons for hospitalisation • Discharge status	NA

Endpoint/assessment	Details	Censoring rules
	• Length of hospital and/or ICU stay • Time to first hospitalisation, defined as the time from the date of randomisation to the date of the first hospitalisation during the study treatment	
Exploratory endpoints		
Time to response (by BICR)	Defined as the time from the date of randomisation to the date of the first documentation of objective response (CR or PR), based on BICR. Time to response was measured for only those patients who had a CR or PR	NA
Best percent change in the sum of the diameter of measurable tumours based on BICR and IA	The tumour measurement at the Screening Visit was used as the baseline tumour measurement	NA
Clinical benefit rate (by BICR)	Defined as the sum of CR rate, PR rate, and more than 6 months SD rate, based on BICR	Both of the following conditions must have been met for “more than 6 months SD”: • [redacted], and • [redacted]
Progression-free survival on the next line of therapy (by IA)	Defined as the time from date of randomisation to the first documented progression on next-line therapy or death due to any cause, whichever occurs first	If patients did not receive new systemic anti-cancer therapy: • Death: [redacted] • No death: [redacted] If patients received new systemic anti-cancer therapy: • Disease progression during next line therapy before/on the analysis cut-off date: [redacted] • Death during next line therapy and before/on the analysis cut-off date: [redacted]

Endpoint/assessment	Details	Censoring rules
		• No disease progression/death during next line therapy and received a second new systemic anti-cancer therapy before/on the analysis cut-off date: [redacted] • No disease progression/death during next line therapy did not receive a second new systemic anti-cancer therapy before/on the analysis cut-off date: [redacted]
Safety endpoints		
Assessment of adverse events (AEs) and serious adverse events (SAEs)	Safety endpoints included SAEs, treatment-emergent AEs (TEAEs), AEs of special interest, TEAEs associated with dose reduction and/or study drug interruption, TEAEs associated with discontinuation of study treatment, physical examination findings (including ECOG performance status), vital sign measurements, standard clinical laboratory parameters, ECG parameters, Echo/MUGA findings. All AEs were categorised using the MedDRA. AEs and abnormal laboratory test results, if applicable, were graded using NCI CTCAE Version 5.0	NA

Abbreviations: BICR, blinded independent central review; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; Echo, echocardiogram; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report from; EORTC, European Organisation for Research and Treatment of Cancer; IA, investigator assessment; ICU, intensive care unit; MedDRA, Medical Dictionary for Regulatory Activities; mRECIST, modified Response Evaluation Criteria in Solid Tumours; MUGA, multigated acquisition scan; NA, not applicable; NCI, National Cancer Institute; PD, progressive disease; PK, pharmacokinetics; PR, partial response; QLQ-BR45, Quality of Life Breast Cancer questionnaire; QLQ-C30, Quality of Life of Cancer Patients questionnaire; SAP, Statistical Analysis Plan; SD, stable disease; TEAE, treatment-emergent adverse event.
Source: Cortés et al, 2022;[102] Daiichi Sankyo, Inc., 2021 (SAP; Data on File).[115]

Assessment timepoints and follow-up

Throughout treatment, HRQoL questionnaires (EORTC QLQ-C30, EORTC QLQ-BR45, and EQ-5D-5L), [redacted], [redacted], and [redacted] were to be completed/assessed [redacted].[105] The HRQoL questionnaires were completed before any other assessments or procedures were done on the day.

Tumour assessment ([redacted][m] were to take place [redacted].[112] Unscheduled tumour assessments [redacted].[112] AEs were recorded [redacted].[105]

End of treatment assessments were to occur [redacted]. Follow-up assessments took place at [redacted] after administration of the last study treatment or before starting new anticancer treatment, [redacted], and in long-term follow-up thereafter, [redacted], until [redacted], [redacted], [redacted], or [redacted].[105]

Tumour assessment ([redacted]) and [redacted]. Questionnaires for HRQoL outcomes were to be completed at [redacted], at [redacted], and at the [redacted] which was the [redacted] for both questionnaires. Survival follow-up was assessed [redacted] follow-up timepoints.[105]

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

B.2.4.1 Analysis sets

Patient data sets analysed in DESTINY-Breast03 are described in Table 8. Efficacy analyses were performed on the full analysis set (FAS), and safety analyses on the safety analysis set (SAS).[102,105]

The per-protocol analysis set (PPS) [redacted]. Pharmacokinetic (PK) endpoints were to be evaluated using the PK analysis set.[115] Analyses based on the PPS and PK are not considered to be of relevance to this submission and are not presented here.

Table 8: DESTINY-Breast03 | Analysis sets

Analysis set	Definition	Number of patients, n (%)		
		T-DXd	T-DM1	Total
Full analysis set (FAS)	Included all patients randomised into the study. The FAS was [redacted] for all efficacy analysis. Following the intent-to-treat principle, patients were analysed [redacted]	261 (100.0)	263 (100.0)	524 (100.0)

[m] Mandatory for all patients with stable brain metastases at baseline; additional scans could be done for all other subjects if clinically indicated.

Analysis set	Definition	Number of patients, n (%)		
		T-DXd	T-DM1	Total
Safety analysis set (SAS)	Included all randomised patients who received [redacted] of study treatment (either T-DXd or T-DM1). [redacted]	257 (98.5)	261 (99.2)	518 (98.9)
Per-protocol analysis set (PPS)	Included [redacted] • [redacted]*	253 (96.9)	249 (94.7)	502 (95.8)
Pharmacokinetic (PK) analysis set	Included [redacted]	257 (98.5)	0	257 (49.0)

*Major protocol deviations included: not signing main consent form; violation of major inclusion/exclusion criteria; receipt of study drug regimen not assigned by randomisation.
Abbreviations: T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Source: Daiichi Sankyo Inc., 2021 (SAP and CSR; Data on File).[105,115]

B.2.4.2 Statistical analyses

Statistical methods used, or to be used, in DESTINY-Breast03 are summarised below (Table 9). A hierarchical testing procedure was proposed for analysis of the key secondary endpoint of OS, on the basis of confirmed efficacy for the primary endpoint (PFS by BICR):

1. **Interim PFS by BICR analysis | conducted at [redacted] PFS events:** the observed two-sided p-value threshold was p=0.000204 to conclude superiority of T-DXd over T-DM1 for the primary endpoint.[105]
   - **If PFS not statistically significant:** OS analysis not conducted.
   - **If PFS statistically significant:** first interim OS analysis conducted. Efficacy boundaries were scaled, such that for exactly [redacted] OS events, the two-sided significance boundaries would be p=0.001.
2. **Final PFS analysis | conducted at [redacted] PFS events:** the observed two-sided p-value threshold is [redacted] to conclude superiority of T-DXd over T-DM1 for the primary endpoint.[105]
   - **If PFS not statistically significant:** OS analysis not conducted.
   - **If PFS statistically significant and OS not significant at first interim analysis:** second interim OS analysis conducted. Efficacy boundaries were scaled, such that

for exactly [redacted] OS events, the two-sided significance boundaries would be [redacted].

3. **Final OS analysis | conducted at [redacted] OS events if any PFS analysis significant and OS not significant at either previous OS analysis:** the overall two-sided significance level for OS at final analysis is [redacted], based on an expected [redacted] events.[105]

Table 9: DESTINY-Breast03 | Summary of statistical analyses

Hypothesis objective	The study hypothesis was that [redacted]
Statistical analysis	**Primary endpoint (PFS by BICR)** was analysed through comparison of the distribution of PFS between the two treatment groups using a stratified log-rank test, with strata being the same as the randomisation stratification factors from IXRS, at an overall two-sided significance level of 0.05. The treatment effect HR of PFS and its two-sided 95% CI were estimated using a stratified Cox proportional hazards regression model with the same stratification factors as the randomisation stratification factors taken from IXRS. Median PFS time and the two-sided 95% CIs using the Brookmeyer and Crowley method were provided for each treatment group, as well as Kaplan-Meier estimates of PFS rates at fixed time points **Secondary efficacy endpoints:** • OS survival distribution was estimated by the Kaplan-Meier method. Median OS with two-sided 95% CIs was calculated with the Brookmeyer and Crowley method. A HR with two-sided 95% CIs was calculated with a stratified Cox proportional hazards regression model • PFS by IA survival distribution was estimated by the Kaplan-Meier method. Median PFS by IA with two-sided 95% CIs was calculated with the Brookmeyer and Crowley method. A HR with two-sided 95% CIs was calculated with a stratified Cox proportional hazards regression model • ORR was summarised by treatment group, [redacted] • Duration of response was summarised by median duration and its two-sided 95% CI calculated using the [redacted] **Exploratory endpoints** were assessed with descriptive statistics. The change of sum of diameters from baseline to post-baseline was summarised using a waterfall plot for each patient and each treatment group, with vertical lines representing the sorted values of percent changes. TTR was summarised using descriptive statistics and analyses for CBR was the same as the one described for ORR. The survival distribution of PFS2 was estimated using the Kaplan-Meier method. Median PFS2 with two-sided 95% CIs were calculated with the [redacted]. HRs and their two-sided 95% CIs for PFS2 were calculated with a [redacted] **Safety endpoints** were assessed with descriptive statistics **QoL and resource use/hospitalisation endpoints** were summarised by time point for each treatment group [redacted]EQ-5D-5L was assessed with descriptive statistics. Time to definitive deterioration on the VAS was assessed using the stratified log-rank test and at two-sided type I error rate of 5%. Survival distribution of time to definition deterioration was estimated by the [redacted]

	[redacted] • Changes from baseline in EORTC QLQ-C30 were assessed using a [redacted], and the descriptive p-values, differences in least square means, and the corresponding two-sided 95% CI was calculated. Time to definitive deterioration on the global QoL scale and physical functioning, emotional functioning, social functioning, and pain symptom subscales was assessed using [redacted] The survival distributions of time to definition deterioration were estimated by the [redacted] • Changes from baseline in EORTC QLQ-BR45 were assessed using a [redacted], and the descriptive p-values, differences in least square means, and the corresponding two-sided 95% CI was calculated. Time to definitive deterioration on the 'breast symptoms' and 'arm symptoms' subscales was assessed using the [redacted]. The survival distributions of time to definition deterioration were estimated by the [redacted] **Subgroup analysis of PFS by BICR** was carried out on all pre-specified patient subgroups (detailed in Section B.2.7) that had [redacted] PFS events. [redacted].
Sample size, power calculation	The study was planned with a group sequential design, which included an interim assessment for PFS using a [redacted]. It was hypothesised that treatment with T-DXd would result in an HR of 0.7, a 30% reduction in the hazard rate of PFS (disease progression or death), which would correspond to a 43% improvement in median PFS from 9.6 months in the T-DM1 arm (based on the results of the EMILIA study)[47] to [redacted] months in the T-DXd arm under the [redacted]. Approximately 500 patients were planned for randomisation (250 patients to T-DXd and 250 patients to T-DM1). An interim analysis that allowed the study to declare superiority of the primary efficacy endpoint was planned after approximately [redacted] PFS events ([redacted]) were documented. If superiority was not demonstrated at the interim analysis, the final PFS analysis was planned after approximately [redacted] PFS events were documented. With [redacted] PFS events in approximately 500 patients, the study had approximately [redacted]% power to detect an HR of 0.70 in PFS at an overall two-sided significance level of 0.05 to reject the null hypothesis (HR=1) using a log-rank test and [redacted].
Data management, patient withdrawals	In general, [redacted]. The rules for censored data for each endpoint are defined in Table 7.
Statistical analysis timepoints	The primary efficacy analysis was planned for after observation of approximately [redacted] BICR-assessed PFS events for the interim analysis, or after observation of approximately [redacted] BICR-assessed PFS events for final analysis. The interim analysis performed 21 May 2021 was interim analysis 1, performed after [redacted] events.

Abbreviations: BC, breast cancer; BICR, blinded independent central review; CBR, clinical benefit rate; CI, confidence interval; EORTC, European Organisation for Research and Treatment of Cancer; HR, hazard ratio; IA, investigator assessment; IXRS, Interactive Web/Voice Response System; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PFS2, progression-free survival 2; QLQ-BR45, Quality of Life

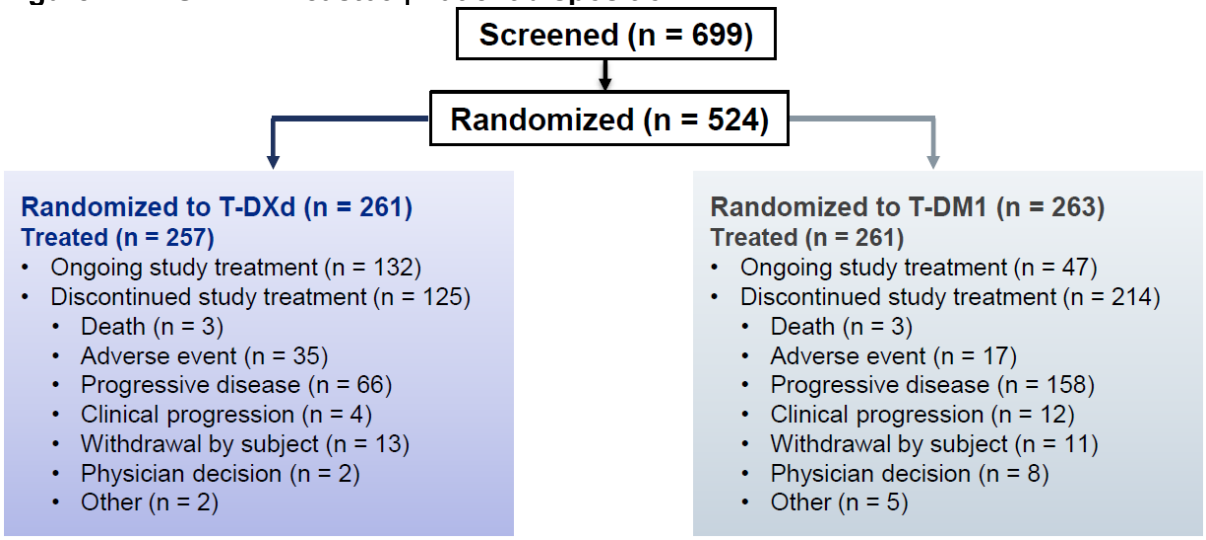
Breast Cancer questionnaire; QLQ-C30, Quality of Life of Cancer Patients questionnaire; QoL, quality of life; TTR, time to response; VAS, visual analogue scale.
Source: Daiichi Sankyo, 2021, (SAP; Data on File).[115]

B.2.4.3 Patient flow in DESTINY-Breast03

For full details of participant flow in DESTINY-Breast03, see Appendix D.2.

In total, 524 patients were randomised to treatment (Figure 7). Of the 261 patients randomised to T-DXd, 257 received treatment, and 261 patients of 263 randomised to T-DM1 received treatment.[102] At the first interim analysis for PFS (DCO, 21 May 2021) the median follow-up for T-DXd and T-DM1 was 16.2 and 15.3 months, respectively. A total of 132 and 47 patients, respectively, were ongoing treatment; 66 and 158 patients, respectively, discontinued due to progressive disease; 35 and 17 patients, respectively, discontinued due to AEs; and for three patients in each arm, the reason for discontinuation was death.[102]

Figure 7: DESTINY-Breast03 | Patient disposition



Abbreviations: T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Source: Cortés et al, 2022.[102]

B.2.4.4 Patient baseline characteristics

Patient baseline characteristics for DESTINY-Breast03 are presented in Table 10. Between July 20, 2018, and June 23, 2020, 524 patients with HER2+ mBC were enrolled at 169 centres in 15 countries.[102]

Patients were generally well-matched across treatment arms at baseline. Median age was similar in the T-DXd and T-DM1 treatment arms (54.3 vs. 54.2 years, respectively),[102] as was the proportion of patients who were female (99.6% in both treatment arms); only two male patients were enrolled (one in each treatment arm).[103]

Patients across the T-DXd and T-DM1 arms had similar HER2 immunohistochemistry recorded as 3+ status (89.7% vs. 88.2% respectively), or 2+ and HER2-amplified according to *in situ* hybridisation (9.6% vs. 11.4%, respectively).[102] The proportion of patients with positive hormone receptor status was also similar between arms (50.2% vs. 51.0% in the T-DXd and T-DM1 arms, respectively).

A greater proportion of patients in the T-DXd arm had a higher (worse) ECOG performance status of 1, compared with the T-DM1 arm (40.6% vs. 33.1%, respectively) and similar proportions in each arm had baseline visceral disease (70.5% vs. 70.3%, respectively).[102] A higher proportion of patients in the T-DXd arm had brain metastases (23.8% vs. 19.8%, respectively, had a reported history of CNS metastases; 16.5% vs. 14.8%, respectively, had stable metastases identified at baseline).[105]

The majority of patients (99.2% vs. 98.9% in the T-DXd and T-DM1 arms, respectively) had received at least one prior therapy in the metastatic setting, meaning their trial treatment was at second line or above.[102] Nearly all patients (99.6%) in both treatment arms had prior treatment with trastuzumab and a taxane[n].[103,105] Similarly, the majority of enrolled patients had received prior pertuzumab (62.1% vs. 60.1%, respectively).[102]

Table 10: DESTINY-Breast03 | Patient baseline characteristics | FAS

Characteristic	T-DXd (n=261)	T-DM1 (n=263)
Age, years		
Mean (standard deviation)	[redacted]	[redacted]
Median (range)	54.3 (27.9–83.1)	54.2 (20.2–83.0)
Female, %	99.6	99.6
Region, n (%)		
Europe	54 (20.7)	50 (19.0)
Asia	149 (57.1)	160 (60.8)
North America	17 (6.5)	17 (6.5)
Rest of world	41 (15.7)	36 (13.7)
Race, n (%)		
Asian	152 (58.2)	162 (61.6)
White	71 (27.2)	72 (27.4)
Black or African American	10 (3.8)	9 (3.4)
Multiple	2 (0.8)	0
Other	26 (10.0)	20 (7.6)
Smoking status, n (%)		
Never	[redacted]	[redacted]
Former	[redacted]	[redacted]
Current	[redacted]	[redacted]
Missing	[redacted]	[redacted]
HER2 IHC status,* n (%)		
3+	234 (89.7)	232 (88.2)
2+ (ISH amplified)	25 (9.6)	30 (11.4)
1+	1 (0.4)	0
ECOG PS, n (%)		
0	154 (59.0)	175 (66.5)
1	106 (40.6)	87 (33.1)
Missing	1 (0.4)	1 (0.4)

[n] [redacted]; all treated patients had received prior therapy with trastuzumab and a taxane.

Characteristic	T-DXd (n=261)	T-DM1 (n=263)
Hormone receptor, n (%)		
Positive	131 (50.2)	134 (51.0)
Negative	130 (49.8)	129 (49.0)
Stable brain metastases, n (%)	43 (16.5)	39 (14.8)
Stable brain metastases defined as a reported history of CNS metastases, n (%)	62 (23.8)	52 (19.8)
Visceral disease, n (%)		
Yes	184 (70.5)	185 (70.3)
No	77 (29.5)	78 (29.7)
Median number of lines (range)	1 (0–16)	2 (0–14)
Prior lines of therapy in the metastatic setting†, n (%)		
0	2 (0.8)	3 (1.1)
1	130 (49.8)	123 (46.8)
2	56 (21.5)	65 (24.7)
3	35 (13.4)	35 (13.3)
4	15 (5.7)	19 (7.2)
≥5	23 (8.8)	18 (6.8)
Prior cancer therapy‡, n (%)		
Trastuzumab	260 (99.6)	262 (99.6)
Pertuzumab	162 (62.1)	158 (60.1)
Taxane	260 (99.6)	262 (99.6)
Other anti-HER2		
Anti-HER2 TKI	42 (16.1)	36 (13.7)
Other anti-HER2 antibody or ADC§	2 (0.8)	3 (1.1)

*As evaluated by central lab.
†Includes rapid progressors (rapid progressors defined as progression within 6 months of (neo)adjuvant therapy or 12 months if regimen contained pertuzumab) as one line of treatment. Line of therapy does not include endocrine therapy.
‡All patients received at least one prior cancer therapy; prior cancer therapy was not recorded for two patients randomised in error and not treated.
§One patient with prior T-DM1 treatment was enrolled in error in the T-DXd arm.
Abbreviations: ADC, antibody-drug conjugate; BC, breast cancer; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridisation; PS, performance status; T-DM1, trastuzumab emtansine; TKI, tyrosine kinase inhibitor; T-DXd, trastuzumab deruxtecan.
Sources: Cortés et al, 2022;[102] Cortés et al, 2021;[103] Daiichi Sankyo Inc., 2021 (Data on File);[105] Hurvitz et al, 2021.[104]

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

Quality assessment of DESTINY-Breast03 was conducted using the NICE single technology assessment: User guide for company evidence submission template, adapted from Systematic reviews: Centre for Reviews and Dissemination's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination; Table 11).

Table 11: DESTINY-Breast03 | Quality assessment results

Questions	DESTINY-Breast03[103,105]
Was randomisation carried out appropriately?	**Yes:** Patients were randomised 1:1 by an interactive voice and web response system (IXRS), and stratified by hormone receptor status (positive/negative), prior treatment with pertuzumab (yes/no) and history of visceral disease (yes/no)
Was the concealment of treatment allocation adequate?	**Not applicable.** DESTINY-Breast03 is an open-label study. To minimize any risk of bias, the Sponsor was blinded to aggregate data by treatment arm, although the study participant and investigator would be aware of the study drug administered
Were the groups similar at the outset of the study in terms of prognostic factors?	**Yes:** There was no significant difference in the baseline characteristics reported between the treatment arms
Were the care providers, participants and outcome assessors blind to treatment allocation?	**No:** Open-label study design. However, outcome assessors for some endpoints – including the primary endpoint, PFS by BICR – were blinded to treatment allocation
Were there any unexpected imbalances in drop-outs between groups?	**No:** There were no unexpected imbalances in dropouts between groups. Withdrawals by subject were similar in both arms (T-DXd, n=13; T-DM1, n=11).
Is there any evidence to suggest that the authors measured more outcomes than they reported?	**No:** No evidence to suggest that the authors measured more outcomes than they reported
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	**Yes:** Efficacy analysis was performed using the Full Analysis Set (FAS) population. Following the intent-to-treat principle, subjects were analysed according to the treatments and strata to which they were assigned at randomisation. For missing data: In general, missing or dropout data were treated as missing, and were not imputed for the purpose of data analysis, unless otherwise specified

Abbreviations: AE, adverse event; RCT, randomised controlled trial.

B.2.5.1 Limitations of the evidence base

DESTINY-Breast03 is an ongoing trial and the data reported below are from the first interim analysis for PFS (DCO, 21 May 2021).[102] A high alpha for statistical significance for OS was chosen to avoid final conclusions on the basis of a small number of events. Despite a HR for OS that indicates a strong treatment effect favouring T-DXd (p=0.007172), OS data are nonetheless immature, with more events required to confirm a treatment effect, and future analyses are planned to collect these data.

B.2.6 Clinical effectiveness results of the relevant trials

B.2.6.1 DESTINY-Breast03

Data presented are from the interim analysis for PFS (DCO, 21 May 2021) with a median follow-up of 16.2 months (range: 0–32.7) in the T-DXd arm (n=261) and 15.3 months (range: 0–31.3) in the T-DM1 arm (n=263).[103] Efficacy analyses were conducted on the FAS, following the intent-to-treat principle (see Section B.2.4.1).[102,105]

DESTINY-Breast03 met its primary endpoint, demonstrating statistical significance for PFS by BICR in the T-DXd arm compared with T-DM1 (HR: 0.28; p<0.001).[102] T-DXd was also associated with a statistically significant HR for the secondary efficacy endpoint of ORR by BICR (p<0.0001), and for the [redacted].[102,105] The findings of both the primary endpoint and ORR by BICR were confirmed by a statistically significant HR for the secondary endpoint of PFS by IA (p<0.0001) and [redacted].[102,105] At DCO, OS data were immature, but showed a numerical trend towards better survival with T-DXd compared with T-DM1 as evidenced by an early and sustained separation of survival curves (HR: 0.55 [p=0.007]) though the reduction in risk did not meet the strict boundary for statistical significance (p<0.000265).[102]

Primary efficacy outcome | PFS by BICR

At follow-up, events of disease progression or death were reported in 87 patients (33.3%) in the T-DXd arm and 158 patients (60.1%) in the T-DM1 arm (Table 12; Figure 8).[105] In total, [redacted] patients ([redacted]) in the T-DXd arm and [redacted] patients ([redacted]) in the T-DM1 arm had disease progression.[105] Death was the recorded PFS event in [redacted] patients ([redacted]) in the T-DXd arm and [redacted] patients ([redacted]) in the T-DM1 arm.[105]

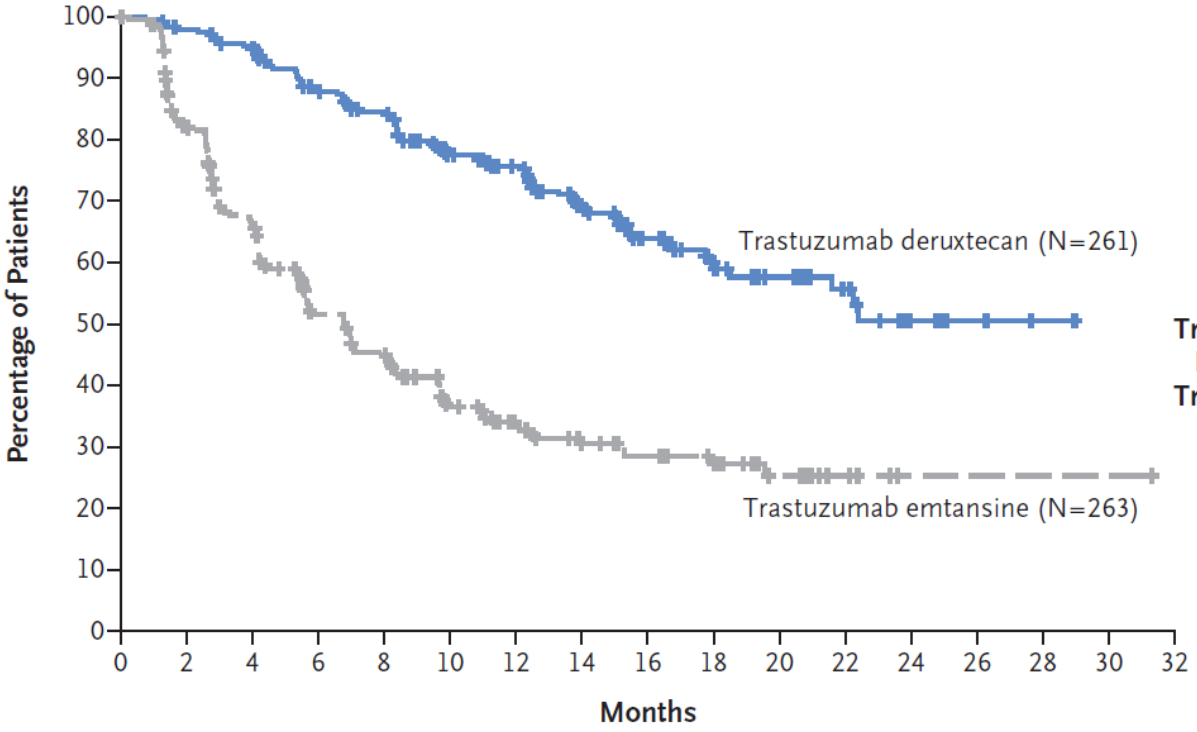
At DCO, [redacted] patients ([redacted]) in the T-DXd arm and [redacted] patients ([redacted]) in the T-DM1 arm were ongoing without events.[105] The remaining [redacted] patients ([redacted]) in the T-DXd arm and [redacted] patients ([redacted]) in the T-DM1 arm were censored for other reasons (Table 12).[105]

T-DXd was associated with a statistically significant 72% lower risk of progression or death compared with T-DM1 (HR: 0.28; 95% CI: 0.22, 0.37 [$p=7.8\times10^{-22}$]).[102,103] Superiority of T-DXd over T-DM1 was confirmed for the primary endpoint as the pre-specified efficacy boundary of p<0.000204 was surpassed.[102,103]

Median PFS by BICR with T-DXd was not reached (95% CI: 18.5 months, NE) compared with 6.8 months (95% CI: 5.6, 8.2) with T-DM1.[102] At 12 months, 75.8% (95% CI: 69.8, 80.7) and 34.1% (95% CI: 27.7, 40.5) of patients were alive and progression free in the T-DXd and T-DM1 arms, respectively (Figure 8).[102]

An additional analysis of PFS by BICR without censoring for missing two consecutive tumour assessments is provided in Appendix N.1.

Figure 8: DESTINY-Breast03 | Kaplan-Meier of PFS by BICR | FAS



	Median Progression-free Survival (95% CI)	12-Mo Progression-free Survival (95% CI)
	mo	%
Trastuzumab Deruxtecan	NR (18.5–NE)	75.8 (69.8–80.7)
Trastuzumab Emtansine	6.8 (5.6–8.2)	34.1 (27.7–40.5)

Hazard ratio for disease progression or death, 0.28 (95% CI, 0.22–0.37)
P<0.001

No. at Risk

Trastuzumab deruxtecan	261	250	240	214	200	168	150	112	79	53	36	25	10	5	2	
Trastuzumab emtansine	263	200	155	108	93	65	51	37	29	21	12	6	1	1	1	0

Abbreviations: BICR, blinded independent central review; CI, confidence interval; FAS, full analysis set; HR, hazard ratio; mo, months; NR, not reached; PFS, progression-free survival.
Source: Cortés et al, 2022.[102]

Table 12: DESTINY-Breast03 | Analysis of PFS by BICR | FAS

	T-DXd (n=261)	T-DM1 (n=263)
Subjects with events, n (%)	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]
Death	[redacted]	[redacted]
Subjects without events (censored), n (%)	[redacted]	[redacted]
Ongoing without event	[redacted]	[redacted]
Other reason*	[redacted]	[redacted]
Median PFS, months†	NE	6.8
(95% CI)†	(18.5, NE)	(5.6, 8.2)
Stratified Cox hazard ratio‡	0.28	
(95% CI)§	(0.22, 0.37)	
Stratified log-rank p-value	<0.001	
Proportion alive and progression-free at landmark (%)§		
3 months (95% CI)	[redacted]	[redacted]
6 months (95% CI)	[redacted]	[redacted]
9 months (95% CI)	[redacted]	[redacted]
12 months (95% CI)	75.8 (69.8, 80.7)	34.1 (27.7, 40.5)
18 months (95% CI)	[redacted]	[redacted]
24 months (95% CI)	[redacted]	[redacted]

*Censoring reasons included: adequate tumour assessment no longer available, event after missing two consecutive assessments, subject withdrew consent, no post-baseline tumour assessment, and no baseline evaluable tumour assessment.
†Median PFS is from the KM analysis. CI for median was computed using the Brookmeyer-Crowley method.
‡Two-sided p-value is from the stratified log-rank test; hazard ratio and 95% CI are from the stratified Cox proportional hazards model with stratification factors: Hormone receptor status, Prior treatment with pertuzumab, and History of visceral disease, as defined by the IXRS. §Estimate and CI for PFS rate at the specified time point are from the KM analysis.
Abbreviations: BICR, blinded independent central review; CI, confidence interval; FAS, full analysis set; IXRS, Interactive Web/Voice Response System; KM, Kaplan-Meier; NE, not estimable; PFS, progression-free survival; SAP, Statistical Analysis Plan; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Source: Cortés et al, 2022;[102] Daiichi Sankyo Inc., 2021 (Data on File).[105]

Key secondary efficacy outcomes

PFS by IA

The statistically significant result for the primary endpoint of PFS by BICR was confirmed by PFS by IA (Figure 9). At DCO, [redacted] and [redacted] patients had events of disease progression or death in the T-DXd and T-DM1 arms, respectively ([redacted] and [redacted], respectively). Of these, progressive disease was experienced by [redacted] patients ([redacted]) in the T-DXd arm and [redacted] patients ([redacted]) in the T-DM1 arm.[105] In total, [redacted] patients ([redacted]) in each arm died.[105]

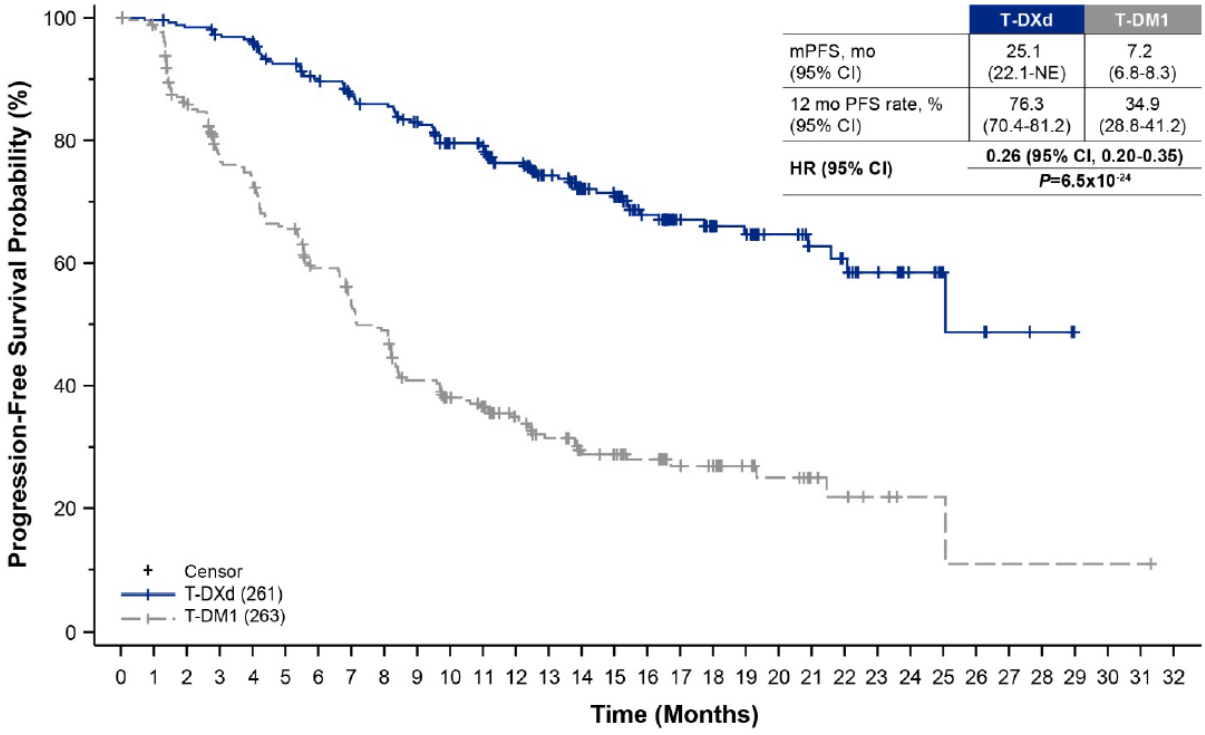
At DCO, [redacted] patients ([redacted]) in the T-DXd arm and [redacted] patients ([redacted]) in the T-DM1 arm were recorded as ongoing without an event.[105] In total, the remaining [redacted] patients ([redacted]) in the T-DXd arm and [redacted] patients ([redacted]) in the T-DM1 arm were censored for other reasons[o].[105]

[o] Censoring reasons included: [redacted], event after [redacted], [redacted], no [redacted], and no [redacted].

T-DXd was associated with a statistically significant 74% lower risk of progression or death by IA compared with T-DM1 (HR: 0.26; 95% CI: 0.20, 0.35 [p=6.5×10^{-24}]).[102] Median PFS by IA was 25.1 months (95% CI: 22.1, NE) with T-DXd compared with 7.2 months (95% CI: 6.8, 8.3) with T-DM1.[102] At 12 months, 76.3% and 34.9% of patients were alive and progression-free in the T-DXd and T-DM1 arms, respectively.[102]

A tabulated analysis of PFS by IA is presented in Appendix N.2.

Figure 9: DESTINY-Breast03 | Kaplan-Meier of PFS by IA | FAS



Patients Still at Risk:

T-DXd (261)	261	256	252	247	244	230	221	209	205	195	179	176	158	140	120	113	85	64	53	48	37	31	27	20	11	7	5	3	2	0
T-DM1 (263)	263	253	216	185	175	156	136	119	110	88	78	72	61	51	43	39	34	25	23	16	13	9	7	5	2	2	1	1	1	1	1	1	0

Abbreviations: CI, confidence interval; FAS, full analysis set; HR, hazard ratio; IA, investigator assessment; mo, months; mPFS, median progression-free survival; NE, not estimable; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Source: Cortés et al, 2022.[102]

Overall survival by IA

At DCO, 33 patients (12.6%) in the T-DXd arm and 53 patients (20.2%) in the T-DM1 arm had died (Figure 10; Table 13).[102]

In total, at the end of follow-up, [redacted] patients ([redacted]) in the T-DXd arm and [redacted] patients ([redacted]) in the T-DM1 arm were alive.[105] A further [redacted] patients ([redacted]) and [redacted] patients ([redacted]) in the T-DXd and T-DM1 arms, respectively, were lost to follow-up.[105]

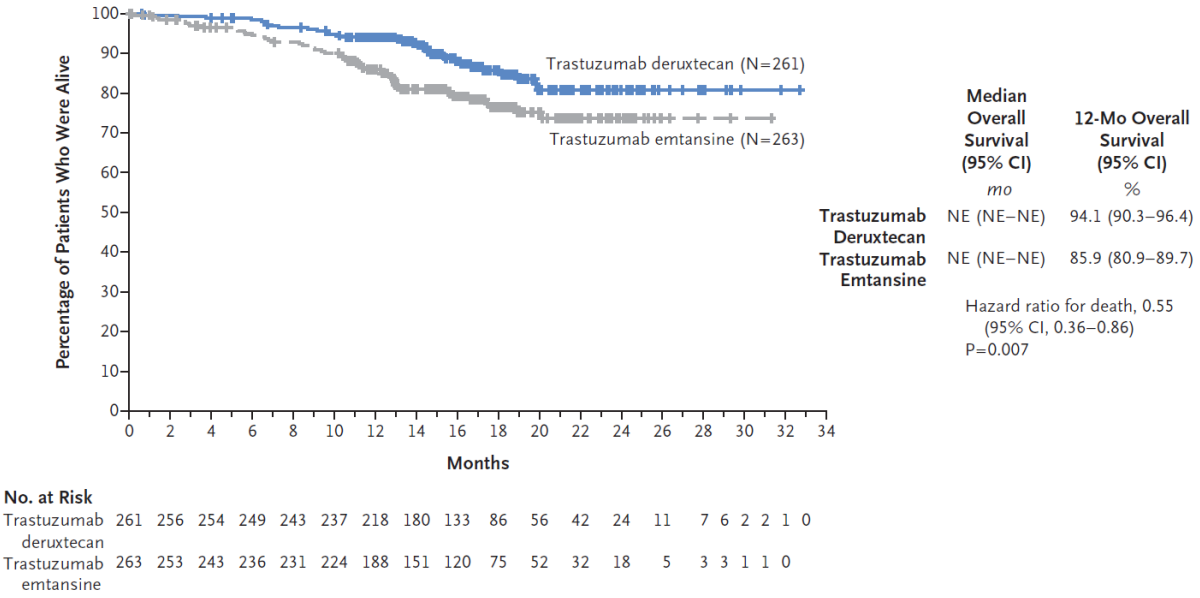
At the interim analysis for PFS (DCO May 2021), T-DXd was associated with a numerically lower risk of death compared with T-DM1 (HR: 0.55; 95% CI: 0.36, 0.86 [p=0.007]).[102] Median OS was NE (95% CI: NE, NE) for both treatment arms.[102]

While the reduction in risk did not cross the pre-specified significance boundary of p<0.000265, a trend in OS showing a benefit with T-DXd relative to T-DM1 is evidenced by

the early separation of Kaplan-Meier curves between treatment arms that is sustained to the end of follow-up.[102]

At 12 months, the OS rate was 94.1% and 85.9% in the T-DXd and T-DM1 treatment arms, respectively.[102]

Figure 10: DESTINY-Breast03 | Kaplan-Meier of OS | FAS



Pre-specified boundary for statistical significance was p<0.000265.
Abbreviations: CI, confidence interval; FAS, full analysis set; HR, hazard ratio; mo, months; NE, not estimable; OS, overall survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Source: Cortés et al, 2021.[102]

Table 13: DESTINY-Breast03 | Analysis of OS | FAS

	T-DXd (n=261)	T-DM1 (n=263)
Subjects with events (deaths), n (%)	33 (12.6)	53 (20.2)
Subjects without events (censored), n (%)	[redacted]	[redacted]
Alive	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
Median overall survival, months*	NE	NE
(95% CI)*	(NE, NE)	(NE, NE)
Stratified Cox proportional hazards model hazard ratio†	0.55	
(95% CI)†	(0.36, 0.86)	
Stratified log-rank test p-value†	0.007	
Proportion of patients alive at landmark, %‡		
3 months (95% CI)	[redacted]	[redacted]
6 months (95% CI)	[redacted]	[redacted]
9 months (95% CI)	[redacted]	[redacted]
12 months (95% CI)	94.1 (90.3, 96.4)	85.9 (80.9, 89.7)
18 months (95% CI)	[redacted]	[redacted]

	T-DXd (n=261)	T-DM1 (n=263)
24 months (95% CI)	[redacted]	[redacted]

*Median OS is from KM analysis. CI for median was computed using the Brookmeyer-Crowley method.
†Two-sided p-value is from the stratified log-rank test; hazard ratio and 95% CI are from the stratified Cox proportional hazards model with stratification factors: Hormone receptor status, Prior treatment with pertuzumab, and History of visceral disease, as defined by IXRS.
‡Estimate and CI for OS rate at the specified timepoint are from KM analysis.
Abbreviations: CI, confidence interval; FAS, full analysis set; IXRS, Interactive Web/Voice Response System; KM, Kaplan-Meier; NE, not estimable; OS, overall survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Source: Cortés et al, 2022;[102] Daiichi Sankyo Inc, 2021 (CSR; Data on File).[105]

Response rates

BICR-assessed response

At the interim analysis for PFS (DCO May 2021), the percentage of patients who had disease control (defined as CR, PR, or SD) was 96.6% (252 patients) in the T-DXd arm and 76.8% (202 patients) in the T-DM1 arm.[102] The confirmed ORR (CR + partial response) by BICR was 79.7% (208 of 261 patients) in the T-DXd arm compared with 34.2% (90 of 263 patients) in the T-DM1 arm (p<0.0001; Table 14).[102]

A best overall response of CR was observed in 16.1% (42 of 261 patients) in the T-DXd arm and 8.7% (23 of 263 patients) in the T-DM1 arm.[102] A best response of partial response was observed in 63.6% (166 patients) in the T-DXd arm and 25.5% (67 patients) in the T-DM1 arm.[102] A best response of SD was observed in 16.9% (44 patients) in the T-DXd arm and 42.6% (112 patients) in the T-DM1 arm.[102] Progressive disease (PD) was observed in 1.1% (3 patients) in the T-DXd arm compared with 17.5% (46 patients) in the T-DM1 arm.[102]

The clinical benefit rate (CBR; a best response of CR, partial response, or SD for ≥6 months) was [redacted]: [redacted] ([redacted] patients) in the T-DXd arm, compared with [redacted] ([redacted] patients) in the T-DM1 arm ([redacted]).[105]

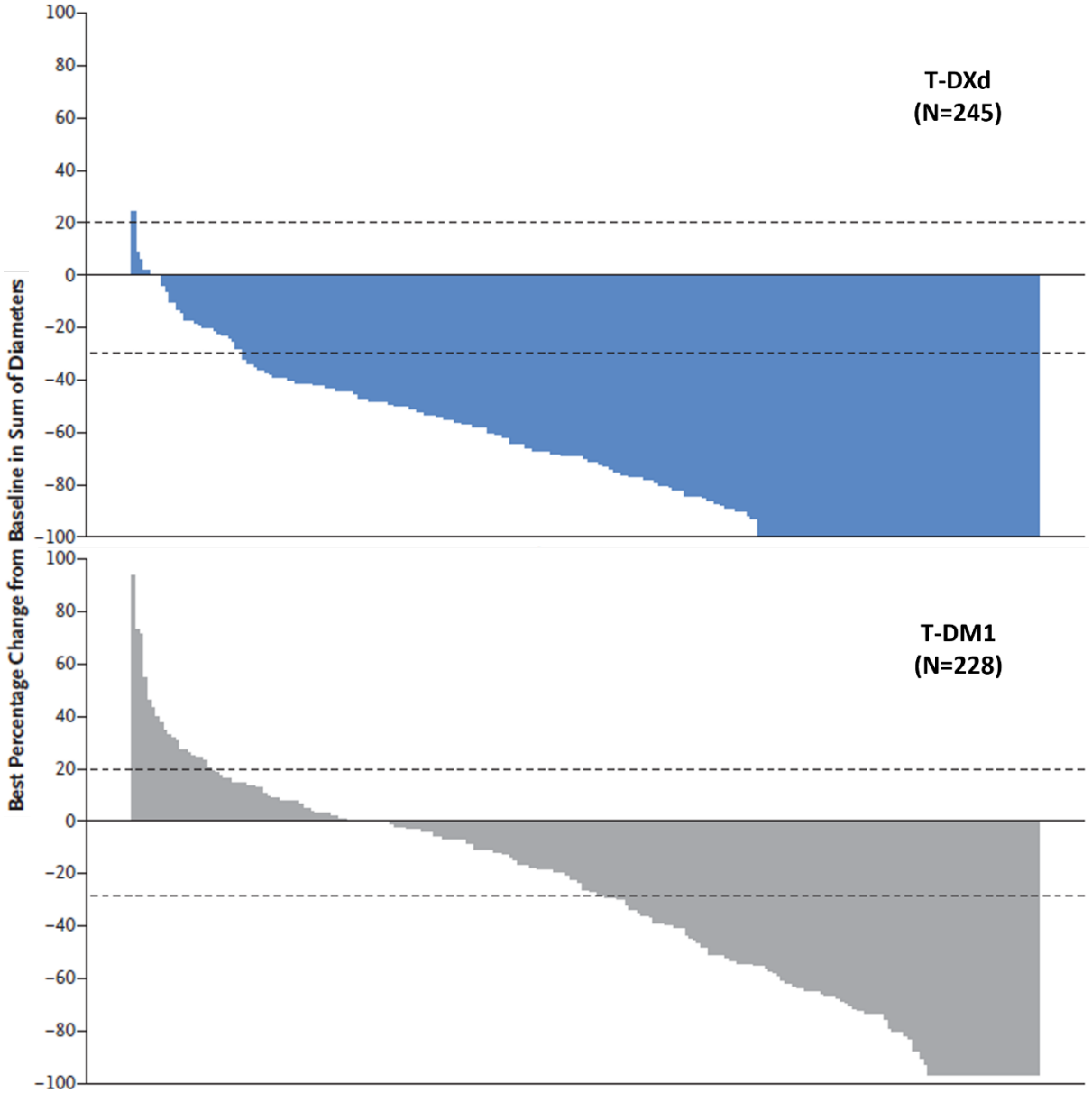
Table 14: DESTINY-Breast03 | Best overall response and ORR by BICR | FAS

	T-DXd (n=261)	T-DM1 (n=263)
Confirmed ORR by BICR, n (%)	208 (79.7)	90 (34.2)
95% CI	74.3, 84.4	28.5, 40.3
p-value	<0.0001	
Confirmed ORR by IA, n (%)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
p-value	[redacted]	
Disease control rate by BICR*, n (%)	252 (96.6)	202 (76.8)
Clinical benefit rate by BICR†, n (%)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
p-value	[redacted]	
Best overall response by BICR, n (%)		
CR	42 (16.1)	23 (8.7)
PR	166 (63.6)	67 (25.5)
SD	44 (16.9)	112 (42.6)
PD	3 (1.1)	46 (17.5)

	T-DXd (n=261)	T-DM1 (n=263)
Not evaluable	6 (2.3)	15 (5.7)
Best overall response by IA, n (%)		
CR	[redacted]	[redacted]
PR	[redacted]	[redacted]
SD	[redacted]	[redacted]
PD	[redacted]	[redacted]
Not evaluable	[redacted]	[redacted]

*CR + PR + SD.
†CR + PR + SD ≥6 months.
Abbreviations: CI, confidence interval; CR, complete response; FAS, full analysis set; IA, investigator assessment; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Source: Cortés et al, 2022;[102] Daiichi Sankyo Inc., 2021 (CSR; Data on File).[105]

Figure 11: DESTINY-Breast03 | Waterfall plot of percentage change in sum of diameters of target lesions from baseline to best post-baseline value based on BICR | FAS



Shown are the best percentage changes from baseline in the sum of the largest diameters of measurable tumours in patients for whom data from both baseline and postbaseline assessments of target lesions by BICR were available.
Red lines at 20% indicate PD; black lines at −30% indicate PR.
Abbreviations: BICR, blinded independent central review; FAS, full analysis set; PD, progressive disease; PR, partial response; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Source: adapted from Cortés et al, 2022.[102]

By IA

Response rates by IA [redacted] the assessment of response by BICR. The difference between treatment arms for confirmed ORR (CR + partial response) by IA was [redacted]: [redacted] ([redacted] patients) in the T-DXd arm vs. [redacted] ([redacted] patients) in the T-DM1 arm ([redacted]; Table 14).

The proportion of patients with CR was [redacted] ([redacted] patients) in the T-DXd arm and [redacted] ([redacted] patients) in the T-DM1 arm.[105] The proportion of patients with PR was [redacted] ([redacted] patients) in the T-DXd arm and [redacted] ([redacted] patients) in the T-DXd arm.[105] In total, [redacted] ([redacted] patients) in the T-DXd arm and [redacted] ([redacted] patients) in the T-DM1 arm had SD.[105] A best response of PD was observed in [redacted] ([redacted] patients) in the T-DXd arm and [redacted] ([redacted] patients) in the T-DM1 arm.[105]

Duration of confirmed response

The median duration of response in patients with a confirmed objective response (CR or partial response, by BICR or by IA) was [redacted].[105] At 12 months, the response rate based on BICR was [redacted] (95% CI: [redacted]) in the T-DXd arm and [redacted] (95% CI: [redacted]) in the T-DM1 arm.[105]

Time to response

The median time to response (TTR) based on BICR among responders (patients with CR or partial response) was 1.64 months (range: 1.1–17.1) in the T-DXd arm and 1.43 months (range: 1.2–9.5) in the T-DM1 arm.[102]

Patient-reported outcomes and hospitalisation

In DESTINY-Breast03 EQ-5D-5L, EORTC QlQ-BR45 and EORTC QLQ-C30 questionnaires were administered to patients to measure HRQoL. Questionnaires were completed by patients prior to infusion on day 1 of Cycles 1, 2 and 3 and then every 2 cycles thereafter until the end of treatment assessments. Patients were then followed up at the Day 40 (+7 days) first follow-up assessment (after last study drug administration) or before initiation of new anti-cancer treatment, whichever came first, and then at the first long-term/survival follow-up assessments three months later which was the last data collection point for both questionnaires. Patients were required to complete questionnaires before any other study assessments or procedures were performed on the day and prior to infusion.

At baseline, the HRQoL questionnaire completion compliance rate was [redacted] in the T-DXd arm and [redacted] in the T-DXd arm for the EQ-5D-5L questionnaire; [redacted] and [redacted], respectively, for the EORTC QLQ-C30; and [redacted] and [redacted], respectively, for the EORTC QLQ-BR45. From Cycle 3 onward, the minimum compliance rate across the questionnaires was [redacted] in the T-DXd arm and [redacted] in the T-DM1 arm.[105]

EQ-5D-5L

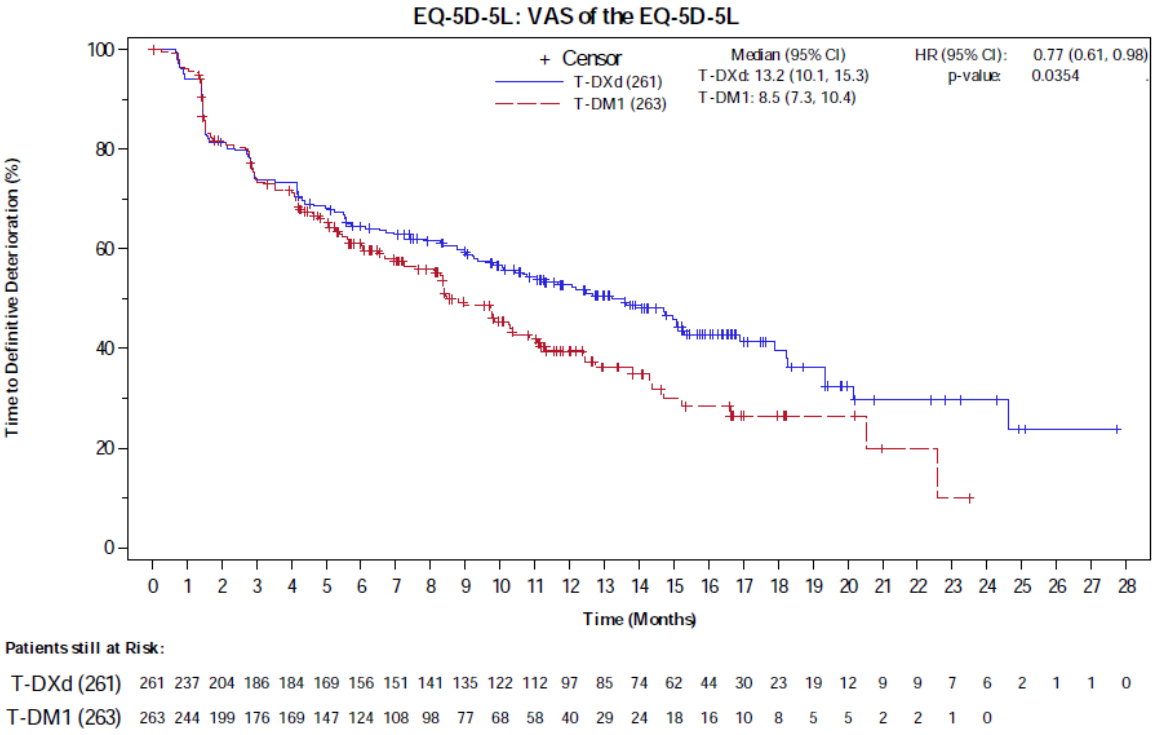
HRQoL as measured by EQ-5D-5L (both index and VAS) was [redacted].

At baseline, the mean EQ-5D-5L Index Score was [redacted] (standard deviation [std. dev.]: [redacted]; range: [redacted]) in the T-DXd arm [redacted] (std. dev.: [redacted]; range: [redacted]) in the T-DM1 arm.[105] In the T-DXd arm, the mean scores at end of treatment, at 40-day follow-up, and at 3 months' follow-up were [redacted] (std. dev.:[redacted]), [redacted] (std. dev.:[redacted]), and [redacted] (std. dev.:[redacted]), respectively.[105] In the T-DM1 arm, the mean scores at the same timepoints were [redacted] (std. dev.: [redacted]), [redacted] (std. dev.: [redacted]), and [redacted](std. dev.: [redacted]), respectively.[105] The mean change in score from baseline to end of treatment was [redacted] (std. dev.: [redacted]) in the T-DXd arm and [redacted] (std. dev.: [redacted]) in the T-DM1 arm.[105]

For the EQ-5D-5L VAS, the mean score at baseline was [redacted] (std. dev.: [redacted]) in the T-DXd arm and [redacted] (std. dev.: [redacted]) in the T-DM1 arm.[105] In the T-DXd arm, the mean scores at end of treatment, at 40-day follow-up, and at 3 months' follow-up were [redacted] (std. dev.: [redacted]), [redacted] (std. dev.: [redacted]), and [redacted] (std. dev.: [redacted]), respectively.[105] In the T-DM1 arm, the mean scores at end of treatment, at 40-day follow-up, and at 3 months' follow-up were [redacted] (std. dev.: [redacted]), [redacted] (std. dev.: [redacted]), and [redacted] (std. dev.: [redacted]), respectively.[105] At end of treatment, the mean change from baseline was [redacted] (std. dev.: [redacted]) in the T-DXd arm and [redacted](std. dev.: [redacted]) in the T-DM1 arm.[105]

Median time to definitive deterioration for the VAS (Figure 12) was 13.2 months in the T-DXd arm, which was statistically significantly longer when compared with the T-DM1 arm median of 8.5 months (HR: 0.77; 95% CI: 0.61, 0.98; p=0.0354).[105]

Figure 12: DESTINY-Breast03 | Kaplan-Meier plot of time to definitive deterioration of the EQ-5D-5L | FAS



Abbreviations: CI, confidence interval; FAS, full analysis set; HR, hazard ratio; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; VAS, visual analogue score.
Source: Daiichi Sankyo Inc., 2021 (CSR tables, figures, and graphs).[105]

EORTC QLQ-C30

At baseline, the median global health status score was [redacted] in the T-DXd arm and [redacted] in the T-DM1 arm.[105] At end of treatment, the median change from baseline was [redacted] in both arms; likewise, for [redacted] the median change from baseline to end of treatment was [redacted] in both arms.[105]

For global health status, treatment with T-DXd was associated with a numerically longer median time to definitive deterioration in (9.7 months) compared with T-DM1 (8.3 months).[105]

For all prespecified subscales, the HR for time to definitive deterioration favoured the T-DXd arm over the T-DM1 arm (HR: 0.69–0.90). The HR for the difference in median time to deterioration was statistically significant in favour of T-DXd compared with T-DM1 for the

subscales of emotional functioning (16.4 and 10.5 months, respectively; HR: 0.69; 95% CI: 0.53, 0.89; p=0.0049) and pain symptoms (10.8 and 8.3 months, respectively; HR: 0.75; 95% CI: 0.59, 0.95; p=0.0146).[105] The time to deterioration was numerically longer in the T-DXd arm than in the T-DM1 arm for the physical functioning and social functioning subscales, but did not reach statistical significance.[105]

EORTC QLQ-BR45

At baseline, the median score for the breast symptoms scale was [redacted] in both treatment arms, and at end of treatment, the median change from baseline was [redacted] in both arms.[105] For the arm symptoms scale, the HR for median time to definitive deterioration was statistically significantly in favour of T-DXd compared with T-DM1 (11.1 and 7.0 months, respectively; HR: 0.70; 95% CI: 0.55, 0.89; p=0.0033).[105] The difference between treatment arms was not significant for the breast symptoms subscale.[105]

Hospitalisation

At DCO (May 2021), 18 patients (6.9%) in the T-DXd arm and 19 patients (7.2%) in the T-DM1 arm had been hospitalised.[105] At DCO, median time to first hospitalisation was more than three times longer in the T-DXd arm compared with the T-DM1 arm (219.5 and 60.0 days, respectively), although interpretation is limited by low rates of hospitalisation in both arms.[105]

B.2.6.2 Efficacy conclusions

DESTINY-Breast03 is a head-to-head trial vs. the UK standard of care in patients previously treated with trastuzumab and a taxane, T-DM1. Most patients had previously received pertuzumab (61.1%), as well as trastuzumab and a taxane (99.6%), the first-line standard of care treatments in the UK.[1,2,46,102,105] A clinical expert consulted by Daiichi Sankyo as part of an expert validation meeting stated that DESTINY-Breast03 is generalisable to patients with HER2+ u/mBC treated after trastuzumab and a taxane in the UK.[46] DESTINY-Breast03 is therefore considered generalisable to UK clinical practice.

In DESTINY-Breast03, T-DXd demonstrated substantial, statistically and clinically significant superiority compared with T-DM1 for the primary endpoint of PFS by BICR in patients with HER2+ u/mBC after trastuzumab and a taxane ($p=7.8\times10^{-22}$).[102,103] At DCO, T-DXd treatment resulted in a 72% lower risk of progression or death compared with T-DM1, with median PFS by BICR not yet reached in the T-DXd arm vs. 6.8 months with T-DM1.[102] The findings of the primary endpoint were confirmed by analysis of PFS by IA with median PFS of 25.1 vs. 7.2 months ($p=6.5\times10^{-24}$).[102]

A significantly greater proportion of patients achieved a confirmed ORR (CR + PR) by BICR and [redacted] with T-DXd compared with T-DM1 (both p<0.0001).[102,105] A best overall response of CR was observed in twice as many patients in the T-DXd arm as the T-DM1 arm (16.1% vs. 8.7%, respectively).[102] A best response of PR was observed in 63.6% (166 patients) in the T-DXd arm and 25.5% (67 patients) in the T-DM1 arm, and 1.1% and 17.5%, respectively, had PD.[102] The median duration of confirmed CR or partial response was [redacted].[105] Progressive disease (PD) was observed in 1.1% (3 patients) in the T-DXd arm compared with 17.5% (46 patients) in the T-DM1 arm.[102] The clinical benefit rate by BICR was also greater with T-DXd treatment than in the T-DM1 arm (89.3% and 45.6%, respectively).[105]

At DCO, OS data were immature, but showed a numerical trend towards better survival with T-DXd compared with T-DM1 as evidenced by an early and sustained separation of survival

curves (HR: 0.55 [p=0.007]) that did not meet the strict boundary for statistical significance.[102] T-DXd was associated with a 94.1% 12-month OS rate, 8.2%-points higher than that provided by T-DM1 (85.9%).[32,46,102] OS will be further evaluated in the ongoing trial.[102]

QoL of patients in the T-DXd arm was [redacted].[105] The mean changes from baseline in EORTC QLQ-C30 global health status (the primary PRO variable) and EQ-5D [redacted].[105] Median time to definitive deterioration for HRQoL as measured by the EQ-5D-5L VAS was [redacted] (HR: [redacted]).[105] Moreover, for all prespecified subscales of the EORTC QLQ-C30 and EORTC QLQ-BR45, the HR for time to definitive deterioration [redacted] (HR ranging from [redacted]).[105] T-DXd was associated with a [redacted] HR for median time to deterioration compared with T-DM1 for the [redacted] and [redacted], and for the [redacted] of the [redacted] ([redacted]).[105] None of the assessed PRO time to deterioration endpoints were [redacted].[105]

Overall, the efficacy benefit demonstrated by T-DXd over T-DM1 in DESTINY-Breast03 (in terms of PFS by BICR and IA, confirmed ORR by BICR and IA, multiple PRO endpoints, and a numerical trend towards an OS benefit) indicates a substantial improvement in clinical outcomes with T-DXd compared with T-DM1, the current second-line standard of care for HER2+ mBC.[32,46,102,105]

B.2.7 Subgroup analysis

Pre-specified subgroups for analysis were:

- Hormone receptor status (either or both ER and PR positive, negative, indeterminate)
- ER status (positive, negative, indeterminate)
- PR status (positive, negative, indeterminate)
- Prior treatment with pertuzumab (yes, no, indeterminate)
- Lines of prior systemic therapy not including hormone therapy (<3, ≥3)
- Lines of therapy prior to pertuzumab treatment (<3, ≥3)
- Renal impairment at baseline (normal function, mild impairment, moderate impairment, severe impairment, end-stage renal disease)
- Hepatic impairment at baseline (normal function, mild impairment, moderate impairment, severe impairment)
- Baseline visceral disease (yes, no)
- Baseline lung metastases (yes, no)
- Baseline liver metastases (yes, no)
- Baseline CNS metastases (yes, no)
- Reported history of CNS metastases (yes, no)
- Age (<65, ≥65 years; <75, ≥75 years)
- Race (white, black/African-American, Asian, other)
- Region (Asia, North America, Europe, Rest of World)
- ECOG performance status (0, 1)

Daiichi Sankyo are not currently aware of any subgroups of people in whom T-DXd is expected to be more clinically effective and cost effective. Trial outcomes for the primary endpoint, PFS, are homogenous across key subgroups.

B.2.7.1 PFS by BICR | Pre-specified analysis in key subgroups

Key results for the subgroup analysis of PFS by BICR are shown in Figure 13.

A consistent and statistically significant PFS HR was observed with T-DXd compared with T-DM1 across key subgroups.[102,105] The benefit was observed across key sub-groups including number of prior lines of therapy, prior pertuzumab treatment, hormone receptor status, presence of visceral disease, and the presence of stable brain metastases defined as a reported history of CNS metastases.[102] Point estimate HRs for all key subgroups (except presence of stable brain metastases [HR: 0.38; 95% CI: 0.23, 0.64]) were within the 95% CI bounds of the HR for all patients (HR: 0.28; 95% CI: 0.22, 0.37) indicating no difference in treatment effect (Figure 13).[102] In patients with stable brain metastases, the CI was wide due to patient numbers and overlapped that of patients without brain metastases, indicating no difference in treatment effect between the subgroups.[102]

In patients with and without prior pertuzumab treatment, median PFS was NE for both subgroups in the T-DXd arm, and 6.8 and 7.0 months, respectively, in the T-DM1 arm, aligning with findings across the whole trial cohort (Section B.2.6.1).[102] The HR for PFS was 0.30 (95% CI: 0.22, 0.43) and 0.30 (95% CI: 0.19, 0.47) for prior pertuzumab and no prior pertuzumab, respectively, for T-DXd compared with T-DM1, which was similar to the HR for the whole trial cohort (HR: 0.28; 95% CI: 0.22, 0.37).[102]

In the subgroup of patients with 0–1 prior lines of therapy in the metastatic setting (n=258), PFS favoured T-DXd vs. T-DM1 (HR: 0.33; 95% CI: 0.23, 0.48). Likewise, for ≥2 prior lines of therapy (n=266), the HR was in favour of T-DXd vs. T-DM1 (HR: 0.28; 95% CI: 0.19, 0.41).[102] In patients treated with T-DXd, median PFS was 22.4 months after 0–1 prior therapies, and NE after ≥2 prior therapies; the treatment effect was similar to that for all

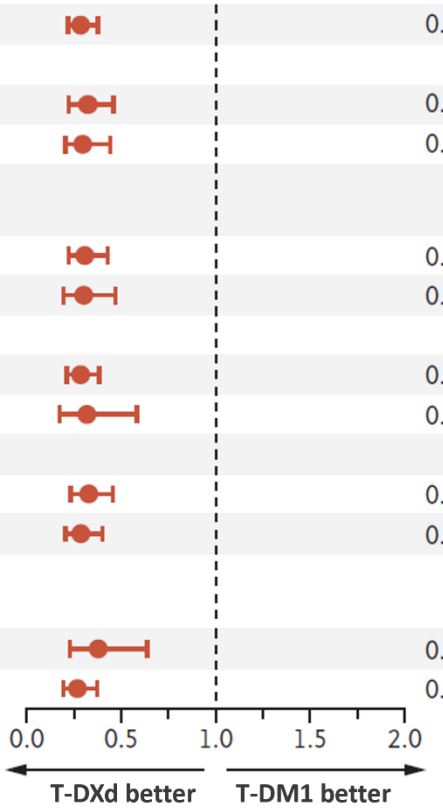
patients.[102] In patients treated with T-DM1, median PFS for patients treated with 0–1 or ≥2 prior therapies was 8.0 and 5.6 months, respectively.[102]

B.2.7.2 Confirmed ORR by BICR| *Post hoc* analysis in pre-specified subgroups

Confirmed ORR by BICR across all key subgroups, including prior lines of therapy, prior pertuzumab treatment, hormone receptor status, presence of visceral disease, and the presence of stable brain metastases at baseline, was greater with T-DXd than with T-DM1 (Figure 14).[104] In the T-DXd arm, ORR ranged from 67.4–86.4% across subgroups (the ORR in all patients was 79.7%). In the T-DM1 arm, ORR ranged from 20.5–47.3% across subgroups (the ORR in all patients was 34.2%).[104]

Figure 13: DESTINY-Breast03 | Forest plot of PFS by BICR subgroup analysis | FAS | Analysis in key subgroups

Subgroup	No. of Patients	No. of Events/No. of Patients		Median Progression-free Survival (95% CI)		Hazard Ratio for Disease Progression or Death (95% CI)
				months		
		Trastuzumab deruxtecan	Trastuzumab emtansine	Trastuzumab deruxtecan	Trastuzumab emtansine	
All patients		87/261	158/263	NE (18.5–NE)	6.8 (5.6–8.2)	0.28 (0.22–0.37)
Hormone-receptor status						
Positive	272	46/133	84/139	22.4 (17.7–NE)	6.9 (4.2–9.8)	0.32 (0.22–0.46)
Negative	248	41/126	73/122	NE (18.0–NE)	6.8 (5.4–8.3)	0.30 (0.20–0.44)
Previous pertuzumab treatment						
Yes	320	57/162	98/158	NE (18.5–NE)	6.8 (5.4–8.3)	0.30 (0.22–0.43)
No	204	30/99	60/105	NE (16.5–NE)	7.0 (4.2–9.7)	0.30 (0.19–0.47)
Visceral disease						
Yes	384	72/195	123/189	22.2 (16.5–NE)	5.7 (4.2–7.0)	0.28 (0.21–0.38)
No	140	15/66	35/74	NE (NE–NE)	11.3 (6.8–NE)	0.32 (0.17–0.58)
Lines of previous therapy						
0 or 1	258	46/132	75/126	22.4 (17.9–NE)	8.0 (5.7–9.7)	0.33 (0.23–0.48)
≥2	266	41/129	83/137	NE (16.8–NE)	5.6 (4.2–7.1)	0.28 (0.19–0.41)
Stable brain metastases defined by reported history of CNS metastases						
Yes	114	31/62	31/52	15.0 (12.6–22.2)	5.7 (2.9–7.1)	0.38 (0.23–0.64)
No	410	56/199	127/211	NE (22.4–NE)	7.0 (5.5–9.7)	0.27 (0.19–0.37)



Abbreviations: BICR, blinded independent central review; CI, confidence interval; CNS, central nervous system; FAS, full analysis set; NE, not estimable; No, number; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Source: Adapted from Cortés et al, 2022.

Figure 14: DESTINY-Breast03 | Forest plot of confirmed ORR by BICR subgroup analysis | FAS | *Post hoc* analysis

		T-DXd (n = 261)	T-DM1 (n = 263)	ORR, % (95% CI) ■ T-DXd ■ T-DM1	Difference of T-DXd vs T-DM1, % (95% CI)
		No. of Patients With Confirmed CR/PR	No. of Patients With Confirmed CR/PR		
All patients		208/261	90/263	79.7 / 34.2	45.5 (37.6-53.4)
Hormone receptor status	Positive (n = 272)	104/133	43/139	78.2 / 30.9	47.3 (36.1-58.4)
	Negative (n = 248)	103/126	47/122	81.7 / 38.5	43.2 (31.5-55.0)
Prior pertuzumab treatment	Yes (n = 320)	129/162	52/158	79.6 / 32.9	46.7 (36.5-56.9)
	No (n = 204)	79/99	38/105	79.8 / 36.2	43.6 (30.5-56.7)
Baseline visceral disease	Yes (n = 384)	151/195	55/189	77.4 / 29.1	48.3 (39.1-57.6)
	No (n = 140)	57/66	35/74	86.4 / 47.3	39.1 (23.6-54.6)
Prior lines of therapy*	0-1 (n = 258)	99/132	45/126	75.0 / 35.7	39.3 (27.3-51.2)
	≥2 (n = 266)	109/129	45/137	84.5 / 32.8	51.6 (40.9-62.4)
Baseline CNS metastases	Yes (n = 82)	29/43	8/39	67.4 / 20.5	46.9 (25.6-68.3)
	No (n = 442)	179/218	82/224	82.1 / 36.6	45.5 (36.9-54.1)

*Patients with rapid progression on (neo)adjuvant therapy were included. Line of therapy does not include endocrine therapy.
Abbreviations: BICR, blinded independent central review; BM, brain metastasis; CI, confidence interval; CR, complete response; ORR, objective response rate; PR, partial response; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Source: Adapted from Hurvitz et al, 2021.[104]

B.2.8 Meta-analysis

Not applicable.

B.2.9 Indirect and mixed treatment comparisons

Not applicable.

B.2.10 Adverse reactions

The safety of T-DXd in patients with HER2+ u/mBC after trastuzumab and a taxane was evaluated in the DESTINY-Breast03 study, as presented below.

B.2.10.1 DESTINY-Breast03

The data presented from the DESTINY-Breast03 study are from the May 2021 DCO, with a median follow-up of 16.2 months in the T-DXd arm and 15.3 months in the T-DM1 arm.[103] TEAEs were categorised with the use of the Medical Dictionary for Regulatory Activities (MedDRA), version 23.0, and graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. Potential episodes of ILD, an AE of special interest, were evaluated by an external independent adjudication committee, and grading was consistent with the NCI CTCAE version 5.0. Safety analyses were performed on the SAS.

In general, T-DXd had a safety profile similar to that observed in previous studies of T-DXd, with no new AEs of concern identified in DESTINY-Breast03.[102,107,108]

B.2.10.1.1 Exposure to T-DXd

At DCO (May 2021), the median treatment duration was 14.3 months (range: 0.7–29.8) for T-DXd and 6.9 months (range: 0.7–25.1) for T-DM1 (Table 15).[102] The mean study dose[p] was [redacted] mg/kg/3 weeks in the T-DXd arm and [redacted] mg/kg/3 weeks in the T-DM1 arm;[105] the mean relative dose intensity (RDI; the ratio of drug actually delivered vs. the planned starting dose of each study drug[p]) was [redacted] in the T-DXd arm and [redacted] in the T-DM1 arm (Table 15).[116]

At DCO, 132 patients in the T-DXd arm and 47 patients in the T-DM1 arm were continuing study treatment.[103]

Table 15: DESTINY-Breast03 | Study drug exposure | SAS

	T-DXd (n=257)	T-DM1 (n=261)
Median treatment duration, months (range)*	14.3 (0.7–29.8)	6.9 (0.7–25.1)
Patient-years of exposure†	[redacted]	[redacted]
Mean dose intensity, mg/kg/3 weeks (std. dev.)‡	[redacted]	[redacted]
Mean relative dose intensity, % (std. dev.)§	[redacted]	[redacted]
Duration of treatment as of data cut-off date, n (%) ≤3 months	[redacted]	[redacted]

[p] Starting doses were 5.4 mg/kg for T-DXd, and 3.6 mg/kg for T-DM1. Two dose reductions were permitted for each treatment arm in the event of toxicity, with withdrawal from study drug if toxicity continued after two dose reductions. Increases in study drug were not permitted.
Relative dose intensity (%)=dose intensity/planned dose intensity×100, where planned dose intensity is equal to the planned starting doses for T-DXd (5.4 mg/kg/3 weeks) and T-DM1 (3.6 mg/kg/3 weeks).

	T-DXd (n=257)	T-DM1 (n=261)
>3, ≤6 months	[redacted]	[redacted]
>6, ≤9 months	[redacted]	[redacted]
>9, ≤12 months	[redacted]	[redacted]
>12, ≤18 months	[redacted]	[redacted]
>18, ≤24 months	[redacted]	[redacted]
>24 months	[redacted]	[redacted]

*Treatment duration=(last dose date–first dose date+21)×12/365.25 (interruptions included).
†Patient-years of exposure=total of treatment duration of all patients within each treatment group.
‡Dose intensity (mg/kg/3 weeks)=total amount of drug taken/(treatment duration [days]/21).
§Relative dose intensity (%)=dose intensity/planned dose intensity×100, where planned dose intensity is equal to the planned starting doses for T-DXd (5.4 mg/kg/3 weeks) and T-DM1 (3.6 mg/kg/3 weeks).
Abbreviations: SAS, safety analysis set; std. dev., standard deviation; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Source: Cortés et al, 2022;[102] Daiichi Sankyo Inc., 2021 (CSR and post hoc RDI calculation; Data on File).[105,116]

B.2.10.1.2 Treatment-emergent adverse events

A summary of TEAEs reported in patients in the DESTINY-Breast03 study are shown in Table 16.

TEAEs were reported in 256 of 257 patients (99.6%) who received T-DXd and 249 of 261 patients (95.4%) who received T-DM1 (Table 16).[102] When the incidence of TEAEs were adjusted for patient-years of exposure, the event rate per patient year was [redacted] and [redacted] with T-DXd and T-DM1, respectively.[105] When assessed by the investigator for causality to treatment, TEAEs reported by 252 patients (98.1%) and 226 patients (86.6%) treated with T-DXd and T-DM1, respectively, were considered drug related.[102]

In total, CTCAE Grade ≥3 TEAEs were reported by 134 patients (52.1%) treated with T-DXd and 126 patients (48.3%) treated with T-DM1; in 116 patients (45.1%) and 104 patients (39.8%), respectively, the investigator deemed these drug related.[102] When adjusted by patient-years of exposure, the rate of Grade ≥3 AEs was [redacted] events per patient year in the T-DXd arm and [redacted] events per patient year in the T-DM1 arm.[105]

Serious TEAEs were reported by 49 patients (19.1%) treated with T-DXd and 47 patients (18.0%) treated with T-DM1.[102] Adjusted for drug exposure, serious TEAEs occurred at a rate of [redacted] and [redacted] events per patient-year of exposure in patients treated with T-DXd and T-DM1, respectively.[105] Serious drug-related TEAEs were reported by 28 patients (10.9%) in the T-DXd and 16 patients (6.1%) in the T-DM1 arm.[102]

In the T-DXd arm, TEAEs leading to discontinuation or dose reduction occurred in 35 patients (13.6%) and 55 patients (21.4%), respectively, and in the T-DM1 arm, 19 patients (7.3%) and 33 patients (12.6%), respectively, with most considered drug related (see Table 16).[102] The proportion of TEAEs [redacted] (Table 17).[105] No drug-related TEAEs led to death in either treatment arm (Table 16).[102] Overall, despite most patients experiencing TEAEs in earlier treatment cycles, this did not lead to significant levels of treatment discontinuation (Table 16).

Table 16: DESTINY-Breast03 | Summary of TEAEs | SAS

n (%)	T-DXd (n=257)	T-DM1 (n=261)
Any TEAE	256 (99.6)	249 (95.4)
EAIR per patient-year of exposure	[redacted]	[redacted]
Any drug-related TEAE	252 (98.1)	226 (86.6)
TEAE Grade ≥3	134 (52.1)	126 (48.3)
EAIR per patient-year of exposure	[redacted]	[redacted]
Drug-related TEAE Grade ≥3	116 (45.1)	104 (39.8)
Serious* TEAE	49 (19.1)	47 (18.0)
EAIR per patient-year of exposure	[redacted]	[redacted]
Serious* drug-related TEAE	28 (10.9)	16 (6.1)
TEAE associated with an outcome of death	5 (1.9)	5 (1.9)
Drug-related TEAE associated with an outcome of death	0	0
TEAE associated with study drug discontinuation	35 (13.6)	19 (7.3)
Drug-related TEAE associated with discontinuation	33 (12.8)	13 (5.0)
TEAE associated with dose reduction	55 (21.4)	33 (12.6)
Drug-related TEAE associated with dose reduction	55 (21.4)	33 (12.6)

*An AE that results in death, is life-threatening, requires inpatient/prolonged hospitalisation, results in persistent/significant disability/incapacity, is a congenital anomaly/birth defect, or is an important medical event.[112]
Abbreviations: EAIR, exposure-adjusted incidence rate; TEAE, treatment-emergent adverse event.
Sources: Cortés et al, 2022;[102] Daiichi Sankyo Inc., 2021 (CSR and protocol; Data on File).[105,112]

Table 17: DESTINY-Breast03 | TEAEs by cycle | SAS

	T-DXd (n=257)			T-DM1 (n=261)		
	Subjects with any TEAEs, n	Subjects at risk, n	Proportion with TEAEs, %	Subjects with any TEAEs, n	Subjects at risk, n	Proportion with TEAEs, %
Cycle 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle ≥8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle ≥18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Daiichi Sanko Inc., 2021 (CSR tables and figures; Data on File).[105]

Most common treatment-emergent adverse events

In patients treated with T-DXd, the most common TEAEs (any grade – reported by ≥50% of patients) were in the system organ classes of gastrointestinal disorders ([redacted] patients; [redacted]%), investigations ([redacted] patients; [redacted]%), general disorders and administration site conditions ([redacted] patients; [redacted]%), and skin and subcutaneous tissue disorders ([redacted] patients; [redacted]%).[105] In patients treated with T-DM1, the most common TEAEs were investigations

([redacted] patients; [redacted]%), gastrointestinal disorders ([redacted] patients; [redacted]%) and general disorders and administrative site conditions ([redacted] patients; [redacted]%).[105]

A summary of TEAEs (any grade) experienced by ≥20% of patients treated with T-DXd or T-DM1 in the DESTINY-Breast03 trial in order of decreasing frequency is presented in Table 18.

Most drug-related TEAEs (all grades) in both treatment arms were haematological or gastrointestinal in nature, or in the system organ class of investigations.[103]

Among the haematological events, neutropoenia was the most frequently reported TEAE in the T-DXd arm (110 patients; 42.8%), followed by anaemia (78 patients; 30.4%), leucopoenia (77 patients; 30.0%), and thrombocytopaenia (64 patients; 24.9%).[102] In patients treated with T-DM1, the most frequently reported haematological TEAE was thrombocytopaenia (135 patients; 51.7%), followed by anaemia (37 patients; 14.2%), neutropoenia (29 patients; 11.1%), and leucopoenia (20 patients; 7.7%).[102] The majority of haematological TEAEs reported were Grade 1 or Grade 2 (Table 18).[102]

Among the gastrointestinal events, nausea was the most frequently reported TEAE in both T-DXd and T-DM1 arms (187 patients [72.8%] and 72 patients [27.6%], respectively); events of nausea were mostly Grade 1 or Grade 2 (Table 18).[102] Similarly, most events of vomiting, diarrhoea, and constipation were Grades 1 or Grade 2 (Table 18).[102]

Among investigations events, AST increased was the most frequently reported TEAE in the T-DXd and T-DM1 arms (60 patients [23.3%] and 97 patients [37.2%], respectively), followed by ALT increased (50 patients [19.5%] and 71 patients [27.2%], respectively).[102]

The most common drug-related TEAEs of Grade ≥3 that occurred in more than 5% of the patients treated with T-DXd were neutropoenia (49 patients; 19.1%), thrombocytopaenia (18 patients; 7.0%), leucopoenia (17 patients; 6.6%), nausea (17 patients; 6.6%), anaemia (15 patients; 5.8%), and fatigue (13 patients; 5.1%). In patients treated with T-DM1, these were thrombocytopaenia (65 patients; 24.9%) and AST increased (13 patients; 5.0%).[105]

Overall, across the most common TEAEs and in both treatment arms, the proportion[q] of patients experiencing TEAEs was highest in Cycle 1.[105] Moreover, the proportion of patients experiencing TEAEs generally declined across subsequent cycles.[105]

Table 18: DESTINY-Breast03 | Drug-related TEAEs in ≥20% of patients | SAS

	T-DXd (n=257)		T-DM1 (n=261)	
Patient-years of exposure	[redacted]		[redacted]	
System organ class Preferred term, n (%)	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
Blood and lymphatic system disorders				
Neutropoenia*	110 (42.8)	49 (19.1)	29 (11.1)	8 (3.1)
Anaemia†	78 (30.4)	15 (5.8)	37 (14.2)	11 (4.2)
Leucopoenia‡	77 (30.0)	17 (6.6)	20 (7.7)	1 (0.4)
Thrombocytopaenia§	64 (24.9)	18 (7.0)	135 (51.7)	65 (24.9)

[q] The proportion was calculated from the number of patients at risk during the cycle window.

	T-DXd (n=257)		T-DM1 (n=261)	
Gastrointestinal disorders				
Nausea	187 (72.8)	17 (6.6)	72 (27.6)	1 (0.4)
Vomiting	113 (44.0)	4 (1.6)	15 (5.7)	1 (0.4)
Diarrhoea	61 (23.7)	1 (0.4)	10 (3.8)	1 (0.4)
Constipation	58 (22.6)	0	25 (9.6)	0
General disorders				
Fatigue**	115 (44.7)	13 (5.1)	77 (29.5)	2 (0.8)
Investigations				
AST increased	60 (23.3)	2 (0.8)	97 (37.2)	13 (5.0)
ALT increased	50 (19.5)	4 (1.6)	71 (27.2)	12 (4.6)
Metabolism and nutrition disorders				
Decreased appetite	67 (26.1)	3 (1.2)	33 (12.6)	0
Skin and subcutaneous tissue disorders				
Alopecia††	93 (36.2)	1 (0.4)	6 (2.3)	0

*This category includes the preferred terms neutrophil count decreased and neutropoenia.
†This category includes the preferred terms haemoglobin decreased, red blood cell count decreased, anaemia, and haematocrit decreased.
‡This category includes the preferred terms white blood cell count decreased and leucopoenia.
§This category includes platelet count decreased and thrombocytopaenia.
**This category includes the preferred terms fatigue, asthenia, and malaise.
††Grade 1 alopecia: T-DXd=26.5%, T-DM1=2.3%; Grade 2, T-DXd=9.3%.
Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; SAS, safety analysis set; T-DM1, trastuzumab emtansine; TEAE, treatment-emergent adverse event; T-DXd, trastuzumab deruxtecan.
Source: Cortés et al, 2022.[102]

Treatment-emergent adverse events associated with changes to treatment

The key TEAEs associated with study drug discontinuation, dose reduction, or treatment interruption are summarised in Table 19.

In total, 35 patients (13.6%) in the T-DXd arm and 19 patients (7.3%) in the T-DM1 arm had TEAEs associated with study drug discontinuation.[102] These TEAEs were considered drug related by the investigator in 33 patients (12.8%) treated with T-DXd and 13 patients (5.0%) treated with T-DM1,[102] including Grade ≥3 events reported by [redacted] patients ([redacted]%) and [redacted] patients ([redacted]%), respectively.[105] Of all TEAEs associated with study drug discontinuation, the key event associated with discontinuation was ILD in 21 patients (8.2%) treated with T-DXd and three patients (1.1%) treated with T-DM1.[102] Discontinuation was associated with [redacted] in [redacted] patients ([redacted]%) and [redacted] patients ([redacted]%), respectively (Table 19).[105]

A total of 55 patients (21.4%) in the T-DXd arm and 33 patients (12.6%) in the T-DM1 arm had TEAEs resulting in dose reduction[r].[102] The most common events leading to dose reduction were [redacted] ([redacted] patients; [redacted]%), [redacted] ([redacted] patients; [redacted]%), and [redacted] ([redacted] patients; [redacted]%) in the T-DXd arm, and [redacted] ([redacted] patients; [redacted]%) and [redacted] ([redacted] patients; [redacted]%) in the T-DM1 arm (Table 19).[105] In [redacted], the investigator considered the TEAE associated with dose reduction to be drug-related.[105]

[r] Two dose reductions were permitted for each treatment arm in the event of toxicity, with withdrawal from study drug if toxicity continued after two dose reductions.

TEAEs that led to study drug interruption[s] were reported for 113 patients (44.0%) in the T-DXd arm and 61 patients (23.4%) in the T-DM1 arm (Table 19).[102] The TEAE leading to study drug interruption was considered by the investigator to be drug related in 91 patients (35.4%) and 34 patients (13.0%), respectively.[102] Study drug interruption was due to Grade ≥3 events in [redacted] patients ([redacted]%) in the T-DXd arm and [redacted] patients ([redacted]%) in the T-DM1 arm, which were considered drug related in [redacted] patients ([redacted]%) and [redacted] patients ([redacted]%), respectively.[105] The most commonly reported TEAEs associated with study drug interruption in the T-DXd arm were [redacted] ([redacted] patients; [redacted]%) and [redacted] ([redacted] patients; [redacted]%); in the T-DM1 arm they were [redacted] ([redacted] patients; [redacted]%) and [redacted] ([redacted] patients; [redacted]%; Table 19).[105]

Table 19: TEAEs associated with changes to treatment occurring in ≥2% of patients in either arm | SAS

Preferred term or grouped term, n (%)	T-DXd (n=257)	T-DM1 (n=261)
TEAEs associated with study drug discontinuation	35 (13.6)	19 (7.3)
ILD*	21 (8.2)	3 (1.1)
[redacted]	[redacted]	[redacted]
TEAEs associated with study drug reduction	55 (21.4)	33 (12.6)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
TEAEs associated with study drug interruption	113 (44.0)	61 (23.4)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

*ILD includes events that were adjudicated as ILD and related to use of T-DXd or T-DM1.
Abbreviations: ILD, interstitial lung disease; TEAE, treatment-emergent adverse event.
Source: Cortés et al, 2022;[102] Daiichi Sankyo Inc., 2021 (CSR; Data on File).[105]

Treatment-emergent adverse events of special interest

Adverse events identified as of special interest in DESTINY-Breast03 were ILD/pneumonitis and left ventricular ejection fraction (LVEF) decrease, which are summarised in Table 20 and Table 21, respectively. Cases of potential ILD or pneumonitis in either study arm were reviewed by an independent ILD adjudication committee.[102]

[s] Doses could be interrupted for ≤28 days from the planned date of administration. If a subject was assessed as requiring a dose delay ≥28 days (≥49 days from last infusion date) the subject was permanently discontinued from study treatment and followed for survival.

A total of 27 patients (10.5%) in the T-DXd arm and five patients (1.9%) in the T-DM1 arm had events adjudicated as being drug-related ILD of any grade.[102] All ILD events were manageable using the established risk management plan for ILD (Appendix O.2).[102,105] None were adjudicated as Grade 4 or Grade 5 (Events of ILD associated with study drug interruption, dose reduction, or discontinuation were reported in XXX X (XXX%), XXX (XXX %) and 21 patients (8.2%), respectively, across patients treated with T-DXd.102,105 In patients treated with T-DM1, interruptions, dose reductions, or discontinuations were reported in XXX ([redacted]%), [redacted], and three patients (1.1%), respectively.[102,105]

In the T-DXd arm, the outcome of the worst adjudicated drug-related ILD event experienced by the patient was recovered/resolved in 15 patients (55.6%), recovered/resolved with sequelae in two patients (7.4%), recovering/resolving in two patients (7.4%), and not recovered/not resolved in eight patients (29.6%), with no fatal events.[102] In the T-DM1 arm, four patients (80.0%) had recovered/resolved events, and one patient (20.0%) had an ILD event with a fatal outcome, for which the death was not evaluable for adjudication.[102]

Table 20).[102] Median time to onset of the first adjudicated drug-related ILD event was [redacted] days (range: [redacted]) in the T-DXd arm and [redacted] days (range: [redacted]) in the T-DM1 arm.[105]

Events of ILD associated with study drug interruption, dose reduction, or discontinuation were reported in [redacted] ([redacted]%), [redacted] ([redacted] %) and 21 patients (8.2%), respectively, across patients treated with T-DXd.[102,105] In patients treated with T-DM1, interruptions, dose reductions, or discontinuations were reported in [redacted] ([redacted]%), [redacted], and three patients (1.1%), respectively.[102,105]

In the T-DXd arm, the outcome of the worst adjudicated drug-related ILD event experienced by the patient was recovered/resolved in 15 patients (55.6%), recovered/resolved with sequelae in two patients (7.4%), recovering/resolving in two patients (7.4%), and not recovered/not resolved in eight patients (29.6%), with no fatal events.[102] In the T-DM1 arm, four patients (80.0%) had recovered/resolved events, and one patient (20.0%) had an ILD event with a fatal outcome, for which the death was not evaluable for adjudication[t].[102]

Table 20: TEAEs adjudicated as drug-related ILD/pneumonitis* by CTCAE v5.0 grade

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
T-DXd (n=257)	7 (2.7)	18 (7.0)	2 (0.8)	0	0	27 (10.5)
T-DM1 (n=261)	4 (1.5)	1 (0.4)	0	0	0	5 (1.9)

*Patients with prior history of ILD/pneumonitis requiring steroids were excluded.
Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; ILD, interstitial lung disease; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Source: Cortés et al, 2022.[102]

Left ventricular dysfunction (Grade 1) was reported in one patient in the T-DXd arm (Table 21), which was resolved with no action taken.[102] Grade 2 events of left ventricular ejection fraction decreased were reported in six patients (2.3%) in the T-DXd arm and one patient (0.4%) in the T-DM1 arm (Table 21); no events of higher severity were reported in either

[t] This subject had an event of pulmonary embolism that the investigator considered to be grade 5. This event was initially reported as respiratory failure; however, the patient was subsequently updated to pulmonary embolism. The interstitial lung disease adjudication committee adjudicated this event as drug-related grade 1 interstitial lung disease/pneumonitis. The death was not evaluable for adjudication. The investigator recorded disease progression as the primary cause of death.

arm.[102] All but one event of left ejection fraction decreased were resolved, and no [redacted] for any events.[102,105]

Table 21: TEAEs of LVEF decrease by CTCAE v5.0 grade

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
T-DXd (n=257)	1 (0.4)*	6 (2.3)†	0	0	0	7 (2.7)
T-DM1 (n=261)	0	1 (0.4)†	0	0	0	1 (0.4)

*Left ventricular dysfunction.
†Decreased ejection fraction.
Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; LVEF, left ventricular ejection fraction; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Source: Cortés et al, 2022.[102]

B.2.10.2 Safety conclusions

The safety profiles of T-DXd and T-DM1 in the DESTINY-Breast03 study were generally manageable and tolerable. In general, T-DXd had a safety profile similar to that observed in previous studies of T-DXd, with no new AEs of concern identified in DESTINY-Breast03.[102,107,108]

Gastrointestinal, haematologic, and investigation-related toxic effects were the most common TEAEs in both treatment arms deemed drug-related, but were mostly low grade (CTCAE Grade 1–2).[103,105] The most common Grade ≥3 drug-related TEAE was neutropoenia (19.1%) in the T-DXd arm, and thrombocytopenia (24.9%) in the T-DM1 arm.[105] Drug-related TEAEs with T-DXd were manageable in routine clinical practice.[102,105] No deaths due to drug-related AEs were reported in the study.[102]

AEs of special interest (ILD/pneumonitis and LVEF decrease) were well managed during the study.[102] No Grade 4−5 ILD/pneumonitis events were identified.[102]

Rates of TEAEs and drug-related Grade ≥3 TEAEs were as expected; the proportion of patients experiencing TEAEs and drug-related Grade ≥3 TEAEs was higher in the T-DXd arm than in the T-DM1 arm.[102] The difference in incidence rates between the treatment arms may be driven by the longer median treatment duration in patients treated with T-DXd than in patients treated with T-DM1 (14.3 and 6.9 months, respectively) despite similar median follow-up (16.2 and 15.3 months, respectively).[102,103,105] Exposure-adjusted incidence rates for all TEAEs and Grade ≥3 TEAEs were lower in patients treated with T-DXd ([redacted] events per patient-year of exposure, respectively) than in those treated with T-DM1 ([redacted] events per patient-year of exposure, respectively).[105] The proportion of patients reporting TEAEs was highest in [redacted] in both treatment arms, and generally [redacted].[105]

Drug-related TEAEs with T-DXd [redacted] in most patients.[105] The most commonly reported TEAE associated with study drug discontinuation in the T-DXd arm was ILD; in the T-DM1 arm, thrombocytopenia was the TEAE most commonly associated with discontinuation.[102] Few patients discontinued study drug due to TEAEs, although the proportion of patients discontinuing treatment due to TEAEs was higher in the T-DXd arm than in the T-DM1 arm (13.6% and 7.3%, respectively).[102] Discontinuation due to drug-related TEAEs was reported in 12.8% of patients treated with T-DXd, and 5.0% of patients treated with T-DM1.[102]

B.2.11 Ongoing studies

DESTINY-Breast03 trial data referenced in this submission are from the first interim analysis for PFS (DCO May 2021).[102] Further analyses are planned based on the accumulation of survival events. A second interim analysis is expected in [redacted], after [redacted] PFS events, when the final PFS analysis and second interim OS analysis will be conducted.[105] A final OS analysis is also planned at [redacted] OS events.[105]

B.2.12 Interpretation of clinical effectiveness and safety evidence

B.2.12.1 Principal interim findings from the clinical evidence base

The pivotal DESTINY-Breast03 RCT demonstrated unprecedented efficacy vs. T-DM1, the only NICE-approved therapeutic option at second line for the target patient population. In DESTINY-Breast03, T-DXd significantly and substantially delayed progression of disease (median PFS by BICR; not reached vs. 6.8 months for T-DM1; HR=0.28; $p=7.8\times10^{-22}$).[102,103] PFS benefit was confirmed by the secondary endpoint of PFS by IA where median PFS was 25.1 months vs. 7.2 months for T-DXd and T-DM1, respectively.[102] Clinical experts have described the efficacy of T-DXd in DESTINY-Breast03 as “unprecedented”, and that it will lead to a “paradigm shift in the treatment of HER2+ mBC”.[109]

Standard of care for HER2+ u/mBC after trastuzumab and a taxane in UK clinical practice is T-DM1, currently the only NICE-recommended HER2-targeted therapy; Table 22 provides a summary of survival data for T-DM1 from both RCT and real-world studies. Median PFS for T-DM1 in DESTINY-Breast03 (7.2 months) is similar to that reported in the recent KATE2 trial (6.8 months) but lower than the EMILIA trial which was conducted 2009–2012 (9.6 months by independent review). These differences may be due to developments in clinical practice such as earlier diagnosis, improvements in clinical care and the availability of more effective therapies at earlier lines including pertuzumab-based regimens.[48,49,103] More efficacious therapies at earlier treatment lines may mean patients receiving treatment after trastuzumab and a taxane have delayed progression and potentially worse prognosis when initiating therapy. Median PFS for T-DM1 in DESTINY-Breast03 is in a similar range to that reported in real-world clinical practice (3−11 months),[88-93] although there is, as expected, greater variability across studies due to the differences between real-world and clinical studies (e.g. patient characteristics and performance status, and number of prior lines of therapy). Together, these data highlight that most patients with HER2+ u/mBC receiving T-DM1 after trastuzumab and a taxane progress within a year.

The magnitude of PFS benefit observed with T-DXd in DESTINY-Breast03 is unprecedented in HER2+ u/mBC setting after trastuzumab and a taxane.[46,48,49,87] No therapy has demonstrated a median PFS greater than that seen with T-DXd in DESTINY-Breast03 (PFS by IA), and the PFS observed for T-DXd after trastuzumab and a taxane is greater than that reported for pertuzumab plus trastuzumab and docetaxel at first line in the pivotal CLEOPATRA trial (median PFS of 25.1 months vs 18.7 months, respectively).[45]

A trend in overall survival showing a benefit with T-DXd relative to T-DM1 is evidenced by an early and sustained separation of the survival curves.[102] While median OS was not estimable in either treatment arm and the pre-specified threshold for statistical significance has not yet been crossed, the risk of death with T-DXd was numerically lower than with T-DM1 at DCO (HR: 0.55; 95% CI: 0.36, 0.86 [p=0.007]); 407 patients are still being followed across both study arms.[102] While median OS was not estimable in both treatment arms due to the low number of deaths, T-DXd and T-DM1 demonstrated 12-month survival rates of 94.1% and

85.9%, respectively.[102] DESTINY-Breast03 is ongoing, and clinical experts expect the PFS benefit at the first interim analysis to translate into an OS benefit at future DCOs.[46]

Efficacy of T-DXd was confirmed through multiple clinically meaningful endpoints, including response rates. DESTINY-Breast03 demonstrated a statistically significant 45.5%-points greater confirmed ORR by BICR with T-DXd than T-DM1 (79.7% and 34.2%, respectively).[102] A best overall response of CR was observed in twice as many patients in the T-DXd arm as the T-DM1 arm (16.1% vs. 8.7%, respectively).[102] A best response of PR was observed in 63.6% (166 patients) in the T-DXd arm and 25.5% (67 patients) in the T-DM1 arm.[102] The median duration of confirmed CR or partial response was [redacted].[105]

Subgroup analyses confirmed a consistent treatment effect of T-DXd vs. T-DM1 for PFS and ORR, across a range of key pre-specified prognostic and demographic subgroups. T-DXd was associated with a statistically significant HR for PFS by BICR in key subgroups including: patients with 0–1 and ≥2 prior lines of therapy; prior or no prior pertuzumab; patients with or without stable CNS metastases; patients with or without baseline visceral disease; and positive or negative hormone receptor status. Notably, patients with baseline CNS metastases had a median PFS of 15.0 months in the T-DXd arm, compared with 5.7 months in the T-DM1 arm – a substantial difference meaning many patients in this subgroup with very poor outcomes on the second-line standard of care can experience over a year without progression if treated with T-DXd.[102] Likewise, subgroup analysis of ORR across patients with baseline visceral disease demonstrated a greater difference in ORR between T-DXd and T-DM1, due to the low ORR in patients with visceral disease treated with T-DM1 (a difference of 48.3%-points).[104]

Table 22: Summary of survival outcomes in key studies of T-DM1 for patients with HER2+ u/mBC

Study, intervention	N	Prior therapy		Median PFS*, months	OS	
		Lines	Type		Median, months	1-year
RCT						
DESTINY-Breast03[102]						
T-DXd	261	1†	Trastuzumab + taxane	25.1	NE	94.1%
T-DM1	263	2†		7.2	NE	85.9%
EMILIA[47,48,117]						
T-DM1	495	3†	Trastuzumab + taxane	9.4	29.9	85.2%
Lapatinib + capecitabine	496	3†		5.8	25.9	78.4%
KATE2[49]						
T-DM1 + atezolizumab	133	3†	Trastuzumab + taxane	8.2	NE	89%
T-DM1 + placebo	69	4†		6.8	NE	89%
RWE						
KAMILLA[87] T-DM1	594	0–1	Chemotherapy + anti-HER2 or adjuvant therapy	8.3	31.3	~82%‡

Study, intervention	N	Prior therapy		Median PFS*, months	OS	
		Lines	Type		Median, months	1-year
Ramagopalan, 2021[94]						
T-DM1	278	1	Trastuzumab combination or monotherapy	-	27.3	-
Lapatinib + chemotherapy	34	1		-	14.5	-
Bon, 2020[91]						
T-DM1	177	1	Pertuzumab	6	§	-
T-DM1	194	1	No pertuzumab	10	§	-
Conte, 2020[92] T-DM1	77	1	Pertuzumab + trastuzumab + taxane	6.3	NR	82%
Michel, 2020[93] T-DM1	39	1	Pertuzumab	7.7	NR	80%
Vici, 2017[88]						
T-DM1	98	1	Any	6	26	-
T-DM1	39	1	Pertuzumab	3	12	-
T-DM1	62	1	Anti-HER2; no pertuzumab	8	26	-
Fabi, 2017[89]						
T-DM1	34	1	Pertuzumab + trastuzumab	5.0	-	-
T-DM1	73	1	Trastuzumab	11.0	-	-

*PFS presented for RCTs is PFS by investigator assessment.
†Median prior lines in the advanced/metastatic setting.
‡Estimated from Kaplan-Meier.
§OS for second-line therapy was not reported; OS from diagnosis of mBC was 52 and 74 months, for patients treated with and without pertuzumab at first line, respectively, followed by second-line T-DM1.
Abbreviations: ADC, antibody-drug conjugates; HER2, human epidermal growth factor receptor 2; NE, not estimable; NR, not reached; OS, overall survival; PFS, progression-free survival; RCT, randomised controlled trial; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Sources: As referenced in table.

T-DXd demonstrated an acceptable safety profile in DESTINY-Breast03 that was consistent with previous studies of T-DXd, with no new safety concerns identified; most TEAE were Grade 1 or 2 and were manageable in routine care.[102,107,108] Few patients discontinued study drug due to TEAEs, although the proportion of patients discontinuing treatment due to TEAEs was higher in the T-DXd arm than in the T-DM1 arm.[102] Despite higher rates of TEAEs in the T-DXd arm than the T-DM1 arm, the [redacted] was [redacted].[105] Most TEAEs were reported [redacted], with the proportion reporting AEs [redacted].[105] Events of ILD, identified as an AE of special interest with T-DXd, were all Grade ≤3 and manageable in the clinical setting.[102] Overall, the safety profile for T-DXd was similar to T-DM1, and was as expected based on previous studies of T-DXd; AEs – including events relating to ILD – were manageable.

B.2.12.2 Strengths and limitations of the clinical evidence base for T-DXd

Strengths of the evidence base

The key strength of the T-DXd evidence base is the DESTINY-Breast03 study which is a Phase III, multicentre, open-label, randomised trial vs.T-DM1, the current standard-of-care in the UK after trastuzumab and a taxane and the relevant comparator for this appraisal.[32,40,46] DESTINY-Breast03 provides the first head-to-head data on the efficacy, safety, and QoL of treatment with T-DXd after trastuzumab and a taxane in HER2+ u/mBC, vs. T-DM1, supporting use at second line.[102] The findings of DESTINY-Breast03 are reinforced by previous safety and efficacy data from the Phase II DESTINY-Breast01 trial, through which T-DXd gained a recommendation from NICE for reimbursement at third line and beyond via the CDF.[3]

The number of patients randomised in DESTINY-Breast03 was large (N=524) despite the relatively small proportion of patients with HER2+ u/mBC in the BC setting.[102] Treatment arms in DESTINY-Breast03 were well-balanced in terms of baseline characteristics, performance status and prior therapies, and clinical experts have confirmed that the patient population and study design is generalisable to UK clinical practice.[46] The clinical experts consulted by Daiichi Sankyo at an expert validation meeting also stated that HER2-targeted therapies are the preferred treatment for HER2+ u/mBC, meaning the DESTINY-Breast03 inclusion criteria of prior trastuzumab and a taxane are aligned with clinical practice.[1,2,46] In DESTINY-Breast03, 49.8% and 46.8% of patients in the T-DXd and T-DM1 arms, respectively, had been treated with 1 prior line of therapy.[105] The majority of patients in DESTINY-Breast03 had received pertuzumab-based regimens at first line (61.1% in the T-DXd arm, and 60.1% in the T-DM1 arm) , and 99.6% had received trastuzumab, consistent with NICE-recommended first-line therapies.

The magnitude of the PFS benefit, and maturity of PFS data, observed in DESTINY-Breast03 is also a key strength of the trial. DESTINY-Breast03 demonstrated a superior PFS (by BICR) with T-DXd compared with the current standard-of care T-DM1, and which led to the IDMC issuing a recommendation of early unblinding at the first interim analysis for PFS.[46,102,106] Robustness of the primary endpoint was confirmed by supporting, pre-specified analyses of investigator-assessed PFS (which found a similar HR to the primary endpoint) and consistent PFS by BICR across subgroups, demonstrating the broad applicability to the second-line HER2+ u/mBC population.[102] T-DXd also showed benefit vs T-DM1 for other clinically meaningful endpoints, including response rates, and QoL was maintained across a range of PROs, with a lower time to deterioration compared with T-DM1.

Potential limitations

Potential limitations of DESTINY-Breast03 include the open-label nature of the trial. Although this is unlikely to have substantially affected interpretation of the primary endpoint (PFS for the primary endpoint was analysed by a blinded assessor) it should be considered when interpreting efficacy and safety findings from the trial.[102]

The low number of deaths within the trial at the first DCO means that the OS data are currently immature; consequently, the pre-specified significance threshold for OS was not crossed.[102] DESTINY-Breast03 is ongoing, and clinical experts expect the PFS benefit at the first interim analysis to translate into an OS benefit at future DCOs.[46] Median PFS by BICR was also not reached with T-DXd due to a small number of events in the intervention arm, unlike T-DM1. However, PFS data are mature, showing statistical significance in favour of T-DXd for the risk of progression or death.[102]

Improved PFS has been established as a surrogate for OS in mBC in multiple studies.[118-120] Beauchemin et al, 2014, reported a correlation coefficient for treatment effect on PFS/time to progression and OS of 0.427 (p<0.01) for patients with mBC.[120] Likewise, Adunlin et al, 2015, reported a model coefficient of 0.40 (p<0.001) for the HR of PFS and the HR of OS for mBC at second line and beyond.[118] The correlation between HRs of PFS and OS was reported to be even stronger in HER2+ mBC (correlation coefficient: 0.9515; 95% CI: 0.7009, 1.0000) than for mBC generally in the second-line setting, in a meta-analysis by Liu et al, 2016.[119]

Based on their algorithm, Beauchemin et al suggest that a difference in median PFS of 5, 10, 15, and 20 months between an intervention and comparator would be expected to translate into approximately 8.7, 17.4, 26.2, and 35.0 months' additional median OS for the intervention. This approach, and all estimates of OS deriving from it, should be interpreted with caution due to heterogeneity between trials and differences in setting (the Beauchemin et al, 2014 analysis was not specific for HER2+ BC at second line of treatment).[120] Nevertheless, the 17.9-month increase in median PFS (by investigator assessment[u]) observed in DESTINY-Breast03 for T-DXd vs. T-DM1,[102] is expected to translate into a clinically significant OS advantage, potentially providing OS outcomes similar to the current first-line setting.

B.2.12.3 Summary

The introduction of the HER2-targeted therapy trastuzumab transformed care for people with HER2+ BC when it was approved in 1998, altering the natural history of the disease.[83] Since then, the development of additional HER2-targeted therapies has further improved survival. First-line pertuzumab in combination with trastuzumab and docetaxel was approved by NICE in 2018 and improved outcomes in previously untreated unresectable HER2+ disease, demonstrating a median PFS of 18.7 months and median OS of 56.5 months in the CLEOPATRA trial.[2,45]

For patients who had previously received trastuzumab and a taxane, T-DM1 was approved by NICE based on the EMILIA trial in which T-DM1 provided a median PFS of 9.6 months and median OS of 29.9 months.[47,48] More recently, the KATE2 study reported a median PFS of 6.8 months with T-DM1 plus placebo (the trial comparator),[49] and other studies confirm the efficacy of T-DM1 in this setting. In the KAMILLA trial, designed to approximate the breadth of patients encountered in routine clinical practice[v], first- or second-line treatment with T-DM1 was associated with a median PFS of 8.3 months and median OS of 31.3 months.[87] Recent real-world studies of T-DM1 report median PFS ranging from 3−11 months,[88-93] and median OS ranging from 12−27.3 months.[88,90,94]

However, while T-DM1 is an effective therapy, it is currently the only NICE-recommended HER2-targeted treatment for patients with HER2+ mBC after trastuzumab and a taxane, and outcomes for patients with aggressive, HER2+ u/mBC have not advanced since it was introduced to UK clinical practice in 2014.

T-DXd is a targeted ADC monotherapy that combines unprecedented PFS outcomes with a manageable safety profile.[102] In the DESTINY-Breast01 trial, T-DXd demonstrated strong efficacy in HER2+ u/mBC as third-line or subsequent therapy (median PFS 19.4 months), leading to a recommendation by NICE for reimbursement through the CDF.[3] In DESTINY-

[u] Note that median PFS by BICR is not available for T-DXd at the first interim analysis.

[v] Patients enrolled in KAMILLA had HER2+ recurrent, metastatic or unresectable BC and had received a prior anti-HER2 therapy and chemotherapy. Prior taxane was not required.

Breast03, T-DXd demonstrated unprecedented, superior efficacy in a head-to-head trial vs. the NICE-approved UK standard of care after trastuzumab and a taxane, T-DM1.[32,46,102,106] Treatment benefit was consistent across key pre-specified subgroups, irrespective of whether patients had received prior pertuzumab, the number of prior lines of therapy, or the presence of absence of stable brain metastases.[102] PFS is a highly relevant primary endpoint that is valued by patients as well as healthcare professionals, and often preferred over OS, perhaps because of the potential for extending quality of life.[100] Treatment sequences enabling consecutive periods of PFS or cumulative PFS were rated positively[w] by 100% and 89% of patients with mBC in a US study, respectively, and OS by 75%.[100] The PFS outcomes observed with T-DXd also substantially exceed findings from any previous T-DM1 studies (Table 22).

The proportion of patients achieving a CR or PR was greater with T-DXd than T-DM1 according to BICR [redacted].[102,105] A best overall response of CR was observed in twice as many patients in the T-DXd arm as the T-DM1 arm (16.1% vs. 8.7%, respectively).[102] A best response of PR was observed in 63.6% (166 patients) in the T-DXd arm and 25.5% (67 patients) in the T-DM1 arm.[102] QoL for patients in the T-DXd arm was [redacted].[105] For all prespecified subscales, the HR for time to definitive deterioration [redacted] (HR ranging from [redacted]).[105] No PRO time to deterioration endpoints were [redacted].[105]

A trend in OS showing a benefit with T-DXd relative to T-DM1 is evidenced by the early separation of Kaplan-Meier curves for each treatment arm that is sustained to the end of follow-up.[102] However, this was not deemed statistically significant.[102] Immaturity of OS data, a limitation of DESTINY-Breast03 at the interim data cut, will be addressed by future analyses at prespecified event levels. The significant and clinically meaningful PFS extension vs. T-DM1 is anticipated to translate into an OS benefit, based on the link between PFS and OS in this disease setting.[118-120] In light of the suboptimal survival outcomes in HER2+ u/mBC, the OS and PFS benefits provided by T-DXd represent a step-change in treatment and offer intangible benefits of hope of extended life and associated QoL benefits for patients, carers, and families.

The safety profile of T-DXd in DESTINY-Breast03 was acceptable and in line with expectations for ADCs in this patient population, with few drug-related TEAEs leading to treatment discontinuation; most AEs were Grade 1 or 2 in severity.[102] Toxicities reported in DESTINY-Breast03 were consistent with previous studies of T-DXd.[107,108] Despite higher rates of TEAEs in the T-DXd treatment arm than with T-DM1, overall rates were low, and safety of T-DXd should be seen in the context of the unprecedented efficacy offered to patients with HER2+ u/mBC after trastuzumab and a taxane, with a higher proportion of patients surviving to 12 months from treatment initiation vs. T-DM1.[102] Events of ILD, previously identified as a potential safety signal with T-DXd, were all manageable, with no Grade ≥4 or fatal events reported.[102] Introduction of an ILD management programme, utilised in DESTINY-Breast03, has led to progressive improvements in managing ILD events with T-DXd in the clinical setting.

Overall, these data showed the superiority of T-DXd over T-DM1 in reducing the risk of progression or death in patients with HER2+ u/mBC who have been previously treated with trastuzumab and a taxane.[102] The strong efficacy findings for T-DXd in DESTINY-Breast03,

[w] Positive rating denotes participants granting a positive utility rating to that aspect of treatment sequencing; N=299.

coupled with the acceptable safety profile, support T-DXd becoming the new standard of care treatment for patients with HER2+ u/mBC in this treatment setting.

Recognising the innovative nature of T-DXd, the US Food and Drug Administration (FDA) granted Breakthrough Therapy Designation (BTD) in HER2+ mBC in this setting based on the interim PFS data from the pivotal DESTINY-Breast03 trial.[121] Based on the DESTINY-Breast03 study, T-DXd has been recommended by ESMO in their 2021 guidelines as the preferred second-line treatment option for patients with HER2+ mBC.[85] ESMO also suggest that T-DXd is the new standard second-line therapy, displacing T-DM1 to a later line of therapy.[85] Clinical experts have described the efficacy of T-DXd in DESTINY-Breast03 as "unprecedented", and that it will lead to a "paradigm shift in the treatment of HER2+ mBC".[109]

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

An SLR was conducted to identify relevant economic evaluations of treatments for patients with HER2+ u/mBC breast cancer in the second-line setting. A detailed description of the review methods and results are reported in Appendix G.

Eighteen publications were identified from the review and are summarised in Table 23. A quality assessment of the identified studies is presented in Appendix G.

The majority of models identified in the SLR used a Markov model structure, however the models used for HTA submissions utilised a partitioned survival approach. Lifetime horizons were the most common, with a few shorter time horizons of 5 to 10 years also published.

Table 23: Summary list of published cost-effectiveness studies

Study	Cost year (currency)	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)
Delea et al. 2012[122]	2008 (£)	Cost-utility analysis PartSA Cycle length: 1 day Time horizon: 5 years	Women with HER2+ metastatic breast cancer who have received prior therapy with trastuzumab	L+C vs. C: 0.190 L+C vs. T+C: 0.031.	L+C vs. C: 14,831 L+C vs. T+C: -107	L+C vs. C: £77,993 L+C vs. T+C: dominant
Diaby et al. 2020[123]	2018 (USD)	Cost-utility analysis Markov Cycle length: 1 week Time horizon: lifetime	HER2+ mBC in Taiwan	The 3rd sequence is the baseline. Without wastage consideration: 4th: 0.132 2nd: 0.506 1st: 0.534 With wastage consideration: 4th: 0.132 2nd: 0.506 1st: 0.534	The 3rd sequence is the baseline. Without wastage consideration: 4th: 8434.28 2nd: 82,434.33 1st: 84,252.69 With wastage consideration: 4th: 9359.55 2nd: 80,431.45 1st: 82,630.86	The 3rd sequence is the baseline. Without wastage consideration: 4th: 63,887.71 2nd: 162,919.8 1st: 157,888.1 With wastage consideration: 4th: 70,896.37 2nd: 158,961.4 1st: 154,848.9
Diaby et al. 2017[124]	2016 (USD)	Cost-utility analysis Markov Cycle length: 1 week Time horizon: lifetime	Newly diagnosed with HER2+ MBC, treated in Mexico	IMSS and ISSSTE perspective: 4th vs. 1st sequence: 0.401 4th vs. 3rd sequence: -0.132 4th vs. 2nd sequence: 0.374 SP perspective: 4th vs. 1st sequence: 0.401	IMSS and ISSSTE perspective: 4th vs. 1st sequence: 10,5621.26 4th vs. 3rd sequence: 3529.40 4th vs. 2nd sequence: 100,066.95 SP perspective: 4th vs. 1st sequence: 104,994.44	IMSS and ISSSTE perspective: 4th vs. 1st sequence: 263,113.955 4th vs. 3rd sequence: -26,736.680 4th vs. 2nd sequence: 267,671.722 SP perspective:

Study	Cost year (currency)	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)
				4th vs. 3rd sequence: -0.132 4th vs. 2nd sequence: 0.374	4th vs. 3rd sequence: 3741.11 4th vs. 2nd sequence: 99,485.15	4th vs. 1st sequence: 261,552.476 4th vs. 3rd sequence: -28,340.541 4th vs. 2nd sequence: 266,115.45
Mosegui et al. 2017[125]	NR (BRL)	Cost-utility analysis Markov Cycle length: 1 month Time horizon: 3 years	Women, aged 50 year old or older, with mBC and HER2 overexpression previously treated with trastuzumab (>50 years)	T-DM1 vs L+C: 1.32	T-DM1 vs L+C: 192,842.62	T-DM1 vs L+C: 145,668.94
Diaby et al. 2016[126]	2015 (USD)	Cost-utility analysis Markov Cycle length: 1 week Time horizon: lifetime	Newly diagnosed HER2+ mBC, treated in the US.	3rd vs. 4th sequence: 0.13 3rd vs. 2nd sequence: 0.51 3rd vs. 1st sequence: 0.53 Excluding dominated 3rd vs. 4th sequence: 0.13 3rd vs. 1st sequence: 0.40	3rd vs. 4th sequence: 25,990.50 3rd vs. 2nd sequence: 18,4547.01 3rd vs. 1st sequence: 185,981.16 Excluding dominated 3rd vs. 4th sequence: 25,990.50 3rd vs. 1st sequence: 159,990.66	3rd vs. 4th sequence: 197,012.54 3rd vs. 2nd sequence: 364,883.82 3rd vs. 1st sequence: 348,630.87 Excluding dominated 3rd vs. 4th sequence: 197,012.54 3rd vs. 1st sequence: 398,444.17

Study	Cost year (currency)	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)
Le et al. 2016[127]	2015 (USD)	Cost-utility analysis Markov Cycle length: 6 weeks Time horizon: lifetime	Progressive, HER2+, locally advanced or metastatic, previously treated with trastuzumab and a taxane (53 years)	NR	NR	T-DM1 vs. L+C: Payer: 220,385 Societal: 183,828 T-DM1 vs. C: Payer: 168,355 Societal: 126,001
Diaby et al. 2016[128]	NR (USD)	Cost-utility analysis NR Cycle length: NR Time horizon: lifetime	HER2+ mBC	NR	T+D -> T+L -> T+C: 159,500	THP -> T-DM1 -> L+C: 322,913 per QALY THP without subsequent T-DM1: 459,100 per QALY
Le et al. 2015[129]	2014 (USD)	Cost-utility analysis Markov Cycle length: 6 weeks Time horizon: lifetime	HER2+, ABC, previously treated with trastuzumab and a taxane	NR	NR	T-DM1 vs. L+C: Payer: 205,598 Societal: 172,152 T-DM1 vs. C: Payer: 164,628 Societal: 126,251
Gor et al. 2015[130]	2014 (USD)	Cost-utility analysis Markov Cycle length: 21 days Time horizon: 6.9 years	HER2+ mBC	NR	NR	T-DM1 vs L+C: 124,247
Elsisi et al. 2014[131]	2013 (EGP)	Cost-utility analysis Markov Cycle length: NR Time horizon: 10 years	HER2+ mBC	L+C vs C: 5.7	L+C vs C: 1,597,796	L+C vs C: 277,169
Danese et al. 2014[132]	NR	Life-years gained PartSA	Women, HER2+ MBC, de novo stage IV, metastatic recurrences,	NR	NR	NR

Study	Cost year (currency)	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)
		Cycle length: NR Time horizon: 15 years	adjuvant trastuzumab use			
Chicaíza-Becerra et al. 2014[133]	2009 (COP)	Cost-utility analysis Markov Cycle length: NR Time horizon: 5 years	Women, ErbB2+ mBC, progressed after a trastuzumab first scheme	NR	L+C vs. T+C: 29,661,798 L+C vs. T+P: 18,267,686 L+C vs. T+D: 22,577,386 L+C vs. T+V: 23,296,404	L+C vs. T+C: Dominated L+C vs. T+P: Dominated L+C vs. T+D: Dominated L+C vs. T+V: Dominated
Machado et al. 2012[134]	2010 (BRL)	Cost-utility analysis PartSA Cycle length: 1 month Time horizon: 5 years	Brazilian women, HER2+ mBC, failed trastuzumab therapy	L+C vs. C: 0.189 L+C vs. T+C: 0.131	L+C vs. C: 53,861 L+C vs. T+C: -18,430	L+C vs. C: 284,864 L+C vs. T+C: dominant
Chicaiza et al. 2012[135]	NR (COP)	Cost-utility analysis Markov Cycle length: 1 week Time horizon: 5 years	HER2+ mBC, progressed after trastuzumab	NR	Less expensive	NR
Anaya et al. 2011[136]	NR (USD)	Cost-utility analysis Markov Cycle length: 1 month Time horizon: lifetime	HER2+ mBC, progressed on first scheme of trastuzumab	NR	L+C vs T+C: 371.74	L+C vs T+C: 49.74 per week
NICE 2017[32]	2013 (£)	Cost-utility analysis PartSA Cycle length: 1 week Time horizon: 15 years	HER2+, unresectable, locally advanced or metastatic breast cancer; adults; previously received trastuzumab and a taxane, separately or in combination	T-DM1 vs. L+C: 0.53 T-DM1 vs. T+C: 0.63 T-DM1 vs. C: 0.89	T-DM1 vs. L+C: 66,705 T-DM1 vs. T+C: 62,313 T-DM1 vs. C: 84,331	T-DM1 vs. L+C: 125,567 T-DM1 vs. T+C: 98,244 T-DM1 vs. C: 95,279

Study	Cost year (currency)	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)
AWMSG 2013[137]	NR (£)	Cost-utility analysis PartSA Cycle length: NR Time horizon: 10 years	Female, HER+, advanced or metastatic BC, prior therapy of anthracyclines, taxanes and trastuzumab in the metastatic setting	L+C vs. T+C: 0.031 L+C vs. T+V: 0.031	L+C vs. T+C: -3,578 L+C vs. T+V: -5,121	Lapatinib + capecitabine is both less costly and more effective than the comparators
CADTH 2014[138]	NR (CAD)	Cost-utility analysis PartSA Cycle length: NR Time horizon: 7 years	HER2+, unresectable locally advanced or metastatic BC, previously treated with trastuzumab and a taxane	T-DM1 vs. L+C: 0.398 T-DM1 vs. T+C: 0.725	T-DM1 vs. L+C: 57,835 T-DM1 vs. T+C: 65,618	T-DM1 vs. L+C: 145,403 T-DM1 vs. T+C: 90,540

Abbreviations: BRL, Brazilian real; C, Capecitabine; CAD – Canadian dollars; COP, Colombian peso; EGP, Egyptian pound; ErbB2+, epidermal growth factor receptor 2-positive; QALYs, quality-adjusted life years; QALM, quality-adjusted life-month; ICER, incremental cost-effectiveness ratio; IMSS, el Instituto Mexicano del Seguro Social; ISSSTE, Institute for Social Security and Services for State Workers; L+C, lapatinib + capecitabine; mBC, metastatic breast cancer; NR, not reported; PartSA, partitioned survival analysis; T+C, trastuzumab + capecitabine; T+D, trastuzumab + docetaxel; T+L, trastuzumab + lapatinib; T+P, trastuzumab + paclitaxel; T+V, trastuzumab + vinorelbine; THP, pertuzumab + trastuzumab + docetaxel; USD, United States dollars.

B.3.2 Economic analysis

No published economic evaluations of T-DXd were identified in the cost-effectiveness SLR within the second-line setting (see Section B.3.1 and Appendix G). Therefore, a *de novo* economic model was developed to assess the cost-effectiveness of T-DXd vs. T-DM1 for treating patients with HER2+ u/mBC who have previously received trastuzumab and a taxane. Previous economic evaluations submitted to NICE within the HER2+ u/mBC setting were used alongside publications identified within the economic SLR to inform the *de novo* model structure, assumptions and data sources.[2,3,32,96,97] These are discussed henceforth throughout the dossier where relevant.

B.3.2.1 Patient population

The cost-effectiveness analysis presented considers patients with HER2+ u/mBC who have previously received trastuzumab and a taxane. This is in line with the population in the pivotal DESTINY-Breast03 clinical trial, and the final scope issued by NICE.

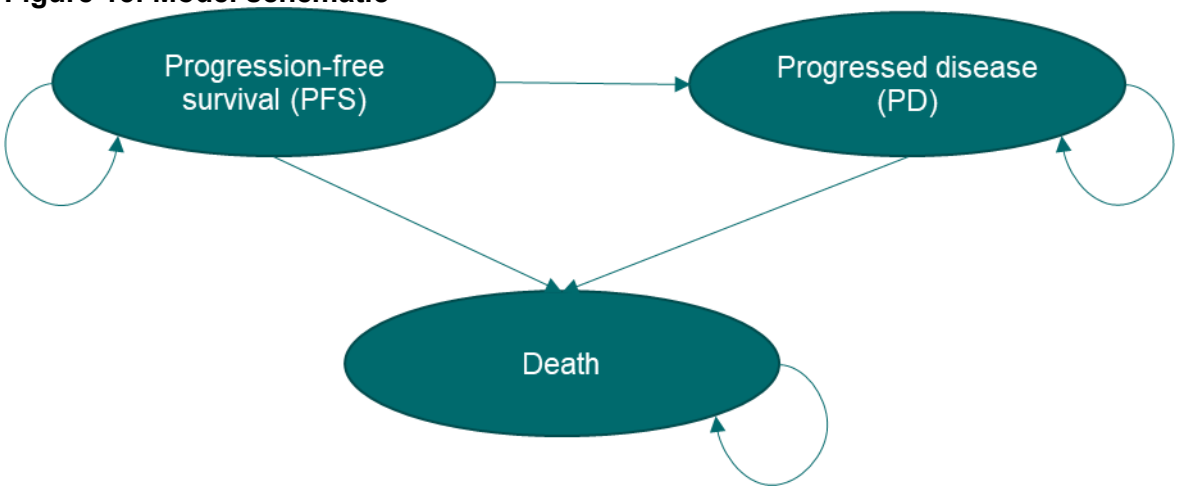
B.3.2.2 Model structure

The de novo cost-effectiveness model was developed in Microsoft Excel® using an area-under-the-curve, partitioned survival analysis (PartSA) structure in both deterministic and probabilistic (Monte Carlo simulation) frameworks. The model structure has three health states*; 'progression-free'*, *'progressed disease'* and *'death'*. This model structure was selected based on the following reasons:

- This structure is in line with the primary outcome (PFS) and key secondary outcome (OS) in the DESTINY-Breast03 trial.
- Progression-based models are commonly used within oncology cost-effectiveness models because they provide an intuitive application of the outcomes seen in cancer-based trials and accurately reflect the progressive nature of BC.
- This structure is consistent with that used in previous HER2+ BC NICE appraisals which have been accepted as appropriate for decision making by the respective committees.[2,3,32,96,97]

The model structure and permitted flow of patients is shown in Figure 15. All patients begin in the *'progression-free'* health state and receive treatment with either T-DXd or T-DM1, and within this health state patients are at risk of disease progression or death. Patients in the *'progressed disease'* health state are also at risk of transitioning to *'death'*, which is an absorbing state.

Figure 15: Model schematic



The occupancy of the '*progression-free'* state is calculated as the area underneath the PFS curve (informed by patient-level data from DESTINY-Breast03), while the *'progressed disease'* state is calculated as the area between the OS curve and the PFS curve. The proportion of patients in each health state at any time point (per cycle) is therefore calculated as follows:

- Progression-free = PFS
- Progressed disease = OS – PFS
- Death = 1 – OS

A time to treatment discontinuation (TTD) curve is used (informed by individual patient-level data from DESTINY-Breast03) to calculate the proportion of patients within the '*progression-free'* health state who are on treatment and is used for the calculation of drug costs. Details of how the TTD, PFS and OS curves are derived is provided in Section B.3.3.2. Extrapolated OS curves are adjusted for general population mortality informed by life tables for England and Wales to ensure that the probability of death never falls below that of the general population.[139]

B.3.2.2.1 Time horizon and cycle length

The base case analysis adopts a 'lifetime' horizon of 30 years, which is considered long enough to adequately capture the lifetime of patients in this setting (the mean start age is [redacted] years which is aligned with the baseline characteristics in DESTINY-Breast03). By this time point <1.5% of patients remain alive in the model. A cycle length of 1 week is used to adequately capture and reflect changes in health and is short enough to capture the dosing schedules of T-DXd and T-DM1. Given the short cycle length, the application of a half cycle correction is not considered necessary to account for uncertainty in the timing of transitions within the cycle period.

B.3.2.2.2 Discount rate and perspective

As per the NICE reference case, all health effects were measured in quality-adjusted life years (QALYs) and a 3.5% discount rate is used for QALYs and costs. The analysis is conducted from the perspective of the NHS and Personal Social Services (PSS) for costs and health effects.[140]

B.3.2.2.3 Features of the economic analysis

Table 24 presents the key features of the economic analysis in comparison to TA458, the only other previous NICE submission in HER2+ mBC after trastuzumab and a taxane.[32] T-DM1 (assessed in TA458) is also the relevant in scope comparator for this appraisal.

Table 24: Features of the economic analysis

	Previous appraisals		Current appraisal
Factor	**TA458**	**Chosen values**	**Justification**
Model type	PartSA	PartSA	This approach is consistent with previous models in mBC and other oncology indications
Perspective	NHS and PSS	NHS and PSS	As per NICE reference case
Time horizon	15 years	30 years	As per NICE reference case: lifetime horizon for the patient population
Cycle length	1 week	1 week	Considered short enough to capture changes in health and captures the dosing schedules
Discount rate	3.5% for costs and QALYs	3.5% for costs and QALYs	As per the NICE reference case
Outcome measure	QALYs	QALYs	As per the NICE reference case
Source of utilities	Lloyd et al 2006 regression model applied based on response rates	DESTINY-Breast-03 (PFS) Lloyd et al 2006 (PD)	EQ-5D utilities collected from the relevant population within the clinical study, as per the NICE reference case. Literature values used for *'progressed disease'* and scenarios.
Source of costs	BNF PSSRU NHS Cost Collection	BNF PSSRU NHS Cost Collection	As per the NICE reference case

Abbreviations: BNF, British National Formulary; mBC, metastatic breast cancer; NHS, National Health Service; PartSA, partitioned survival analysis; PD, progressed disease; PFS, progression-free survival; PSSRU, Personal Social Services Research Unit; QALY, quality-adjusted adjusted life-years.

B.3.2.3 Intervention technology and comparators

The intervention modelled in the analysis is T-DXd, administered at a dose of 5.4 mg/kg once per 21-day cycle. Treatment is administered until disease progression or toxicity, as per the SmPC and dose received in DESTINY-Breast03 (as outlined in Section B.1).[102,141] Dose adjustments and modifications have been included as per the DESTINY-Breast03 trial which is in line with the licensed dose reductions and dosing in routine clinical practice (see Section B.3.5.1).

Consistent with the NICE final scope, the modelled comparator is T-DM1, administered at a dose of 3.6 mg/kg once per 21-day cycle. T-DM1 is administered until disease progression or unmanageable toxicity as per the SmPC and DESTINY-Breast03.[102,142] Dose adjustments and modifications have been included as per DESTINY-Breast03 which is aligned with the SmPC for T-DM1.

T-DM1 is the most common treatment for HER2+ mBC patients after treatment with trastuzumab and a taxane in routine NHS practice and is the only NICE approved HER2-targeted treatment option at this point in the treatment pathway (see Section B.1.3). This is consistent with the NICE final scope and aligned with the control arm of the DESTINY-Breast03 trial allowing a head-to-head comparison of the two treatments relevant to this appraisal.[143] Clinical experts confirmed that for HER2+ mBC patients, T-DM1 was the relevant comparator after treatment with trastuzumab and a taxane.[46]

B.3.3 Clinical parameters and variables

The principal source of data used to inform the economic analysis is the pivotal DESTINY-Breast03 trial. This data comprises the key evidence base concerning the use of T-DXd as a treatment for patients with HER2+ u/mBC following treatment with trastuzumab and a taxane (see Section B.2). Clinical data for the following inputs/endpoints/events are used to inform the estimation of costs and effects within the model:

- Baseline characteristics (Section B.3.3.1)
- Efficacy (Section B.3.3.2)
    - OS
    - PFS
    - TTD
- Safety (Section B.3.3.3)

B.3.3.1 Baseline patient characteristics

The baseline characteristics used to inform the economic analysis are presented in Table 25. A more detailed summary of baseline patient demographics is provided within Section B.3.3.1. The baseline characteristics were considered generalisable to the UK population by UK clinical experts.[46]

Table 25: Baseline patients characteristics informing the economic analysis

Characteristic	Value	SD	Source	Use in model
Mean age	[redacted] years	[redacted]	DESTINY-Breast03[105]	Used to inform estimation of background mortality and adjustment of HRQoL over time
Proportion female	99.6%	13.30		
Mean weight	[redacted] kg	-		Used to inform estimation of drug costs (those dosed according to weight)

Abbreviations: HRQoL, health-related quality of life; kg, kilograms; SD, standard deviation.

B.3.3.2 Efficacy

Due to the specification of a lifetime horizon over which modelled costs and QALYs are required to be estimated (in line with the NICE reference case), survival modelling was required to extrapolate outcomes beyond those observed within the DESTINY-Breast03 trial. The approach taken to extrapolating the data are in line with the best practice guidance set out in the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14.[144]

- Data and statistical tests from DESTINY-Breast03
    - Inspection of the Kaplan-Meier (KM) curves
    - Inspection of the log-cumulative hazard plots (LCHP) to determine potentially suitable approaches to fitting parametric models
- Inspection of statistical goodness-of-fit scores for fitted models (i.e., the Aikake Information Criterion [AIC] and the Bayesian Information Criterion [BIC])
- Visual inspection of suitable fitting models compared to the KM curves
- Assessment of the plausibility of fitted models after the end of the follow-up period for DESTINY-Breast03 via clinical validation and external data sources

The following section outlines the approach taken to inform OS, PFS and TTD in turn. The principal source of data used to inform the model is the DESTINY-Breast03 trial, however other external data has been used to explore OS uncertainty where possible and methods are outlined in respective sections.

B.3.3.2.1 Overall survival

Despite a median follow-up of 15.9 months, at the first interim analysis for PFS (DCO May 2021), the data available for the DESTINY-Breast03 study is still relatively immature with median OS not yet reached in either treatment arm of the study.

As such, two distinct methods have been implemented to fully explore OS (and the uncertainty associated with OS) within the economic model. A summary of the approaches considered are presented within Table 26, and each method is discussed in turn through this section.

Table 26: Summary of methods explored to derive OS

Label	Summary	OS for T-DM1 informed by	OS for T-DXd informed by
Method 1	Direct extrapolation of DB03	Parametric curves fitted to DB03 data (with a treatment covariate for T-DXd)	
Method 2	Extrapolation of replicated data from EMILIA + HR	Parametric curves fitted to replicated data from the T-DM1 arm of the EMILIA study	DB03 OS HR applied to T-DM1 OS

Abbreviations: DB03, DESTINY-Breast03; HR, Hazard Ratio; OS, overall survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

As the DESTINY-Breast03 study provides evidence for T-DXd and the relevant comparator from a well conducted RCT, and clinicians considered the trial and outcomes generalisable to UK practice, direct extrapolation using the DESTINY-Breast03 data has been used to inform the model base case.[46] The alternative method explored using the EMILIA data is provided as a supporting analysis (see Section B.3.3.2.1.2). Both methods are discussed in turn through this section.

For both OS approaches, to ensure that the model projections do not lead to an estimated hazard of death below that of the age- and sex- adjusted general population, an adjustment is made to the OS projections in both arms of the economic model. This approach is common where extrapolations provide long-term estimates which exceed general population mortality. National life tables from the Office of National Statistics were used to populate this adjustment and this ensures that the hazard of death is, at a minimum, that of the general population.[145]

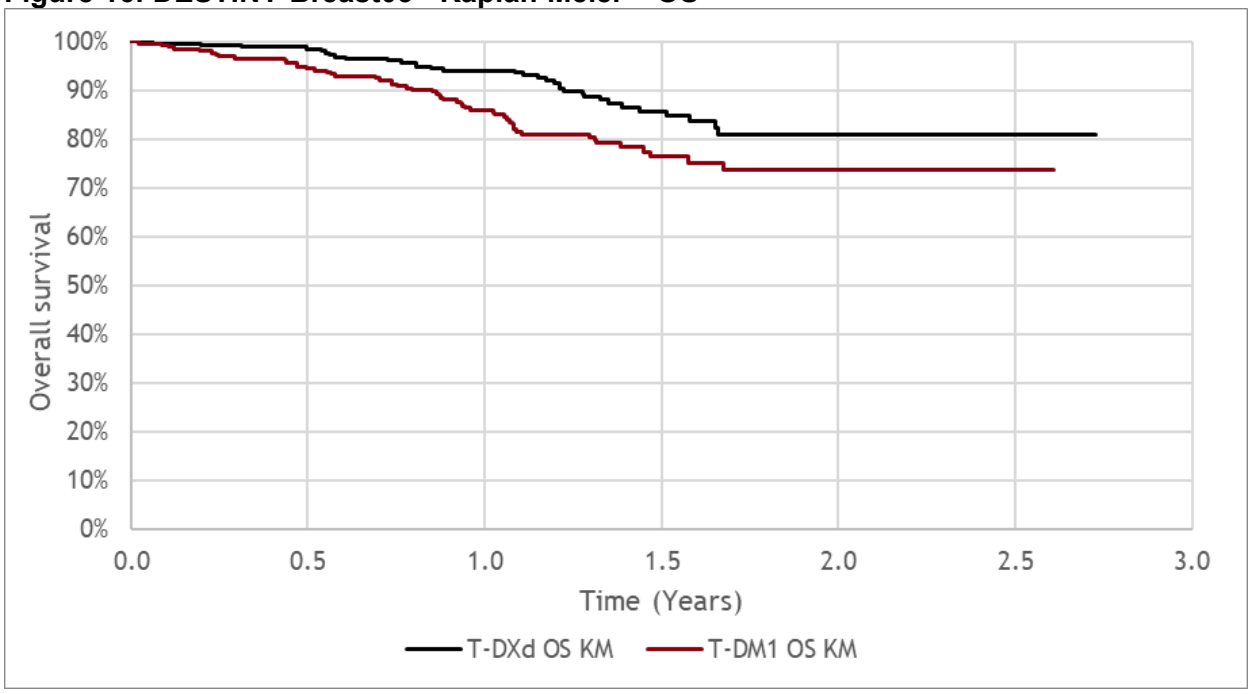
B.3.3.2.1.1 OS Method 1 – DESTINY-Breast03 direct extrapolation

Method 1 directly extrapolates the OS data from the DESTINY-Breast03 trial for T-DXd and T-DM1.

Assessment of data from DESTINY-Breast03

A summary of the OS data from DESTINY-Breast03 is provided in Section B.2.6.1 (and Figure 16 below). T-DXd was associated with a numerically lower risk of death compared with T-DM1 (HR: 0.55; 95% CI: 0.36, 0.86 [p=0.007] using a stratified Cox proportional hazard model).[102] The reduction in risk did not cross the pre-specified significance boundary of p<0.000265.[102] As can be seen from the KM curves, OS data are immature with medians not reached in either arm, as such extrapolation of outcomes was required to inform cost-effectiveness estimates.

Figure 16: DESTINY-Breast03 - Kaplan-Meier – OS



Abbreviations: KM, Kaplan-Meier; OS, overall survival.

Prior to the fitting of parametric models, a LCHP was produced to assess whether the proportional hazards (PH) assumption may hold. Figure 17 presents the LCHP based on OS data from DESTINY-Breast03. As can be seen from the LCHP, the plots exhibit a linear trend in both treatment arms and are approximately parallel indicating that the ratio of the hazards between the two treatment arms may be considered constant. The Therneau and Grambsch's non-proportionality test has a p-value of 0.0531 (failing to reject the null hypothesis that PH holds at the 5% significance level).

Given the assessment that PH may hold for the OS data, it was concluded that dependent models (i.e., a joint model with a treatment covariate) would be appropriate to provide a sufficient basis for informing the cost-effectiveness analysis. In addition, the use of dependent curves may allow for better use of the OS data, where very few OS events have been observed in either arm. This option means one parametric model is fitted to the entire dataset with T-DXd included as a treatment covariate assuming proportional hazards throughout the extrapolation. The use of dependent models would also reduce the potential for implausible extrapolations of data (i.e., crossing of curves).

Figure 17: Log-cumulative hazard plot of OS from DB03

Abbreviations: DB03, DESTINY-Breast03; LCHP, log-cumulative hazard plot; OS, overall survival.

Assessment of the statistical goodness-of-fit scores for fitted models

Dependent parametric survival models (PSMs) were fitted in R® using the '*flexsurv*' package. Six standard parametric forms discussed in NICE DSU TSD 14 were fitted for completeness:

- Exponential
- Generalised Gamma
- Gompertz
- Log-logistic
- Log-normal
- Weibull

AIC and BIC scores provide informative statistical tests which determine the relative fit of alternative parametric models to the observed data. AIC and BIC scores for the extrapolated OS for DESTINY-Breast03 data are presented in Table 27. Based on the goodness-of-fit statistics, the log-logistic provides the best statistical fit to the DESTINY-Breast03 data with the lowest AIC and BIC values, however all fit statistics are within 10 points and provide relatively close statistical fits to one another.

Table 27: Statistical goodness-of-fit scores (OS – Method 1)

	Joint T-DXd/T-DM1 dependent models	
Model	**AIC**	**BIC**
Exponential	953.05	961.58
Weibull	945.44	958.22
Gompertz	949.14	961.93
Log-logistic	944.44	957.22
Log-normal	947.91	960.69
Generalised gamma	946.98	964.02

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion.

Fitting of parametric models

Figure 18 presents the model fits for T-DXd and T-DM1 across the observed period and over the 30-year time horizon.

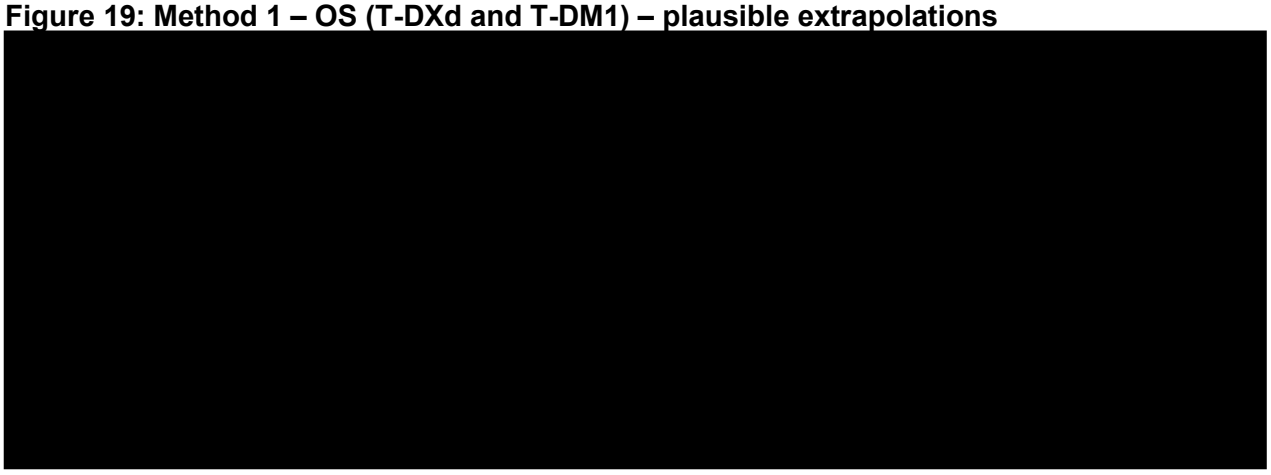
Figure 18: Method 1 – OS (T-DXd and T-DM1)

Abbreviations: KM, Kaplan-Meier; OS, overall survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

Figure 18 was used to determine the suitability of the different PSMs. Across the observed period, all curves appeared to fit the data well however there are large differences in the long-term projections. Clinical experts consulted by Daiichi Sankyo at an expert validation meeting advised that 25–35% of patients treated with T-DM1 would be alive at 5 years and 5–10% by 10 years, and therefore considered that the exponential, log-normal and Gompertz curves could be excluded. The clinical experts considered that survival would likely be somewhere between the range provided by the Weibull which may be considered

pessimistic at 10 years (with [redacted] of patients alive) and the log-logistic which may be considered optimistic at 10 years ([redacted] alive). Therefore the log-logistic, Weibull and generalised gamma curves were considered most appropriate. The resulting T-DXd curves were also considered by the clinicians to provide plausible estimates of expected survival (a comparison is provided in Figure 19).

Figure 19: Method 1 – OS (T-DXd and T-DM1) – plausible extrapolations



Abbreviations: KM, Kaplan-Meier; OS, overall survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

The generalised gamma was considered the most reasonable curve to inform the base case for extrapolation of OS. The generalised gamma has a reasonable fit to the KM data with AIC/BIC statistics which are not dissimilar to the best fitting log-logistic curve (within 3 points for AIC and 7 points for BIC) and provides a clinically plausible long-term extrapolation of T-DM1 survival, with 5- and 10-year survival estimates in line with ranges provided by clinicians ([redacted] and [redacted], respectively). The curve also lies centre between the three extrapolations which were considered the most appropriate by clinical experts. Survival in the T-DXd arm was also considered reasonable by clinical experts. To ensure uncertainty is fully explored, the alternative plausible PSMs are explored in sensitivity analysis (see Section B.3.11).

Summary of base-case model

Figure 20 provides a summary of the base-case extrapolation for OS applied within the model (using the generalised gamma extrapolation). Internal and external validation of the base case curves are presented in Section B.3.11.

Figure 20: Base-case extrapolations for OS (T-DXd and T-DM1)

Abbreviations: KM, Kaplan-Meier; OS, overall survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Note: The generalised gamma curve was selected as the base case to inform the OS models

B.3.3.2.1.2 OS Method 2 – Replicated EMILIA data + HR

Given that median OS has not yet been reached in DESTINY-Breast03, the approach taken to inform Method 2 utilises data from DESTINY-Breast03 and replicated patient level data (PLD) from the EMILIA study of T-DM1.[48]

The EMILIA study compared T-DM1 with lapatinib plus capecitabine in patients with HER2+ advanced BC who had previously been treated with trastuzumab and a taxane. The co-primary endpoints of the study were PFS and OS (in line with DESTINY-Breast03 and the model structure). The EMILIA study was considered the most relevant source of clinical evidence to inform decision making in the prior NICE assessment for T-DM1 (TA458 – the same indication as this appraisal) and was considered generalisable to UK clinical practice.[146] After a median follow-up of 47.8 months, the final OS analysis of EMILIA has been published demonstrating median OS of 29.9 months (95% confidence interval [CI] 26.3–34.1) in the T-DM1 arm.[47]

Method 2 seeks to utilise the longer follow-up data provided in EMILIA to inform the extrapolation of OS on the T-DM1 arm (and subsequently the T-DXd arm). This is done in three key steps:

1. The PLD from the EMILIA study was replicated using digitisation software and the Guyot algorithm.[147]
2. PSMs were then fitted to the replicated EMILIA study data to project OS for the T-DM1 comparator arm within the economic model.
3. To obtain a relevant estimate of T-DXd the hazard ratio (HR) observed within the DESTINY-Breast03 study is used and applied to the EMILIA replicated comparator arm (HR: 0.55; 95% confidence interval [CI] 0.36–0.86).[102]

A comparison of key patient characteristics in the T-DM1 arm of each trial is provided in Table 28. The two cohorts appear similar in terms of median age and ECOG status while a greater proportion of patients in EMILIA received 0–1 prior therapies than in DESTINY-Breast03 (60.4% vs 47.9%). The proportion of patients who had received prior pertuzumab was greater in DESTINY-Breast03 than EMILIA (60.1% vs. 10.3%). This is likely because pertuzumab was not commercially available when the EMILIA study was conducted between 2009 and 2011. DESTINY-Breast03 is considered more generalisable to the UK given NICE recommend a pertuzumab based regimen as a first-line option in this population (TA509).[2] Subgroup analysis of DESTINY-Breast03 in patients with prior pertuzumab treatment vs. those without shows no difference in treatment effect and similar median PFS in the T-DM1 arm (median not reached in T-DXd arm for both groups). Clinical experts also confirmed there is no clinical reason as to why prior pertuzumab may impact effectiveness of T-DM1 and therefore both trials were considered generalisable to UK clinical practice.

Table 28: Comparison of patient characteristics of T-DM1 arms between DESTINY-Breast03 and EMILIA

Component	DESTINY-Breast03 – T-DM1 arm	EMILIA – T-DM1 arm
Phase	3	3
Population	HER2+ advanced/metastatic unresectable or metastatic HER2+ BC previously treated with trastuzumab and a taxane	HER2+ aBC who have had been previously treated with trastuzumab and a taxane

Component	DESTINY-Breast03 – T-DM1 arm	EMILIA – T-DM1 arm
N	263	495
Median age	54 (20 – 83)	53 (25 – 84)
Median PFS	6.8 months	9.4 months
Prior pertuzumab	158 (60.1%)	51 (10.3%)
Prior lines of therapy		
0-1	126 (47.9%)	304 (61.4%)
≥ 2	137 (52.1%)	191 (38.6%)
ECOG		
0	175 (66.5%)	299 (60.4%)
1	87 (33.0%)	194 (39.1%)
Not available	1 (<1%)	2 (<1%)

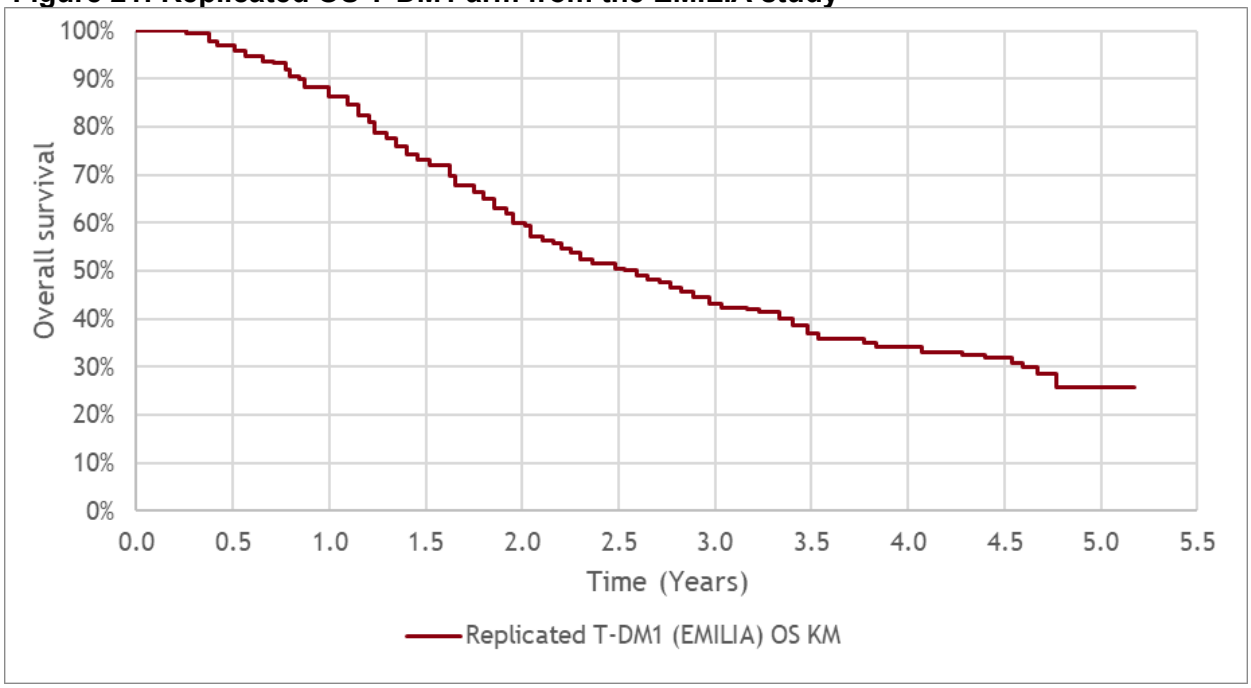
Abbreviations: aBC, advanced breast cancer; BC, breast cancer; PFS, progression-free survival.

Although this method moves away from direct extrapolation of the pivotal trial evidence, it allows use of longer-term, more mature OS data for T-DM1 in the relevant patient population than is currently available from DESTINY-Breast03. This approach therefore reduces uncertainty around long-term T-DM1 OS and subsequently, T-DXd OS due to the inferred relationship with T-DM1. This approach also makes use of evidence from DESTINY-Breast03, as the observed HR is applied to the EMILIA based T-DM1 arm, with the assumption that the HR relationship would hold across trials. Given the similarity in trial design, patient characteristics and support from expert clinicians that both trials were generalisable to UK practice, this assumption was considered appropriate.

Assessment of data from the EMILIA study

A summary of the replicated OS from the EMILIA study is provided in Figure 21 (which was digitised and replicated using the Guyot algorithm).[147]

Figure 21: Replicated OS T-DM1 arm from the EMILIA study



Abbreviations: KM, Kaplan-Meier; OS, Overall Survival; T-DM1, trastuzumab emtansine.

Assessment of the statistical goodness-of-fit scores for fitted models for T-DM1

Similar to the approach taken in Method 1, PSMs were then fitted to the replicated data in R® using the '*flexsurv*' package. AIC and BIC scores for the extrapolated OS for the replicated EMILIA data are presented in Table 29. Based on the goodness-of-fit statistics, the generalised gamma and log-normal curves provided the best statistical fits for AIC and BIC, respectively.

Table 29: Statistical goodness-of-fit scores (OS EMILIA T-DM1 arm – Method 2)

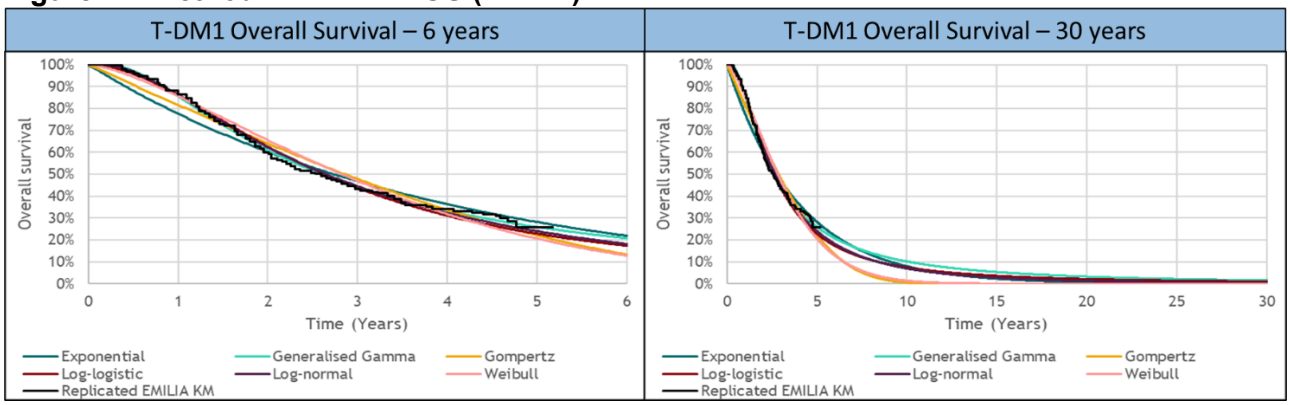
Model	AIC	BIC
Exponential	2910.37	2914.57
Weibull	2864.08	2872.49
Gompertz	2896.76	2905.17
Log-logistic	2838.28	2846.69
Log-normal	2829.30	2837.71
Generalised gamma	2828.44	2841.05

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; PSM, parametric survival model.

Fitting of parametric models

The aforementioned six standard parametric models were considered (Figure 22).

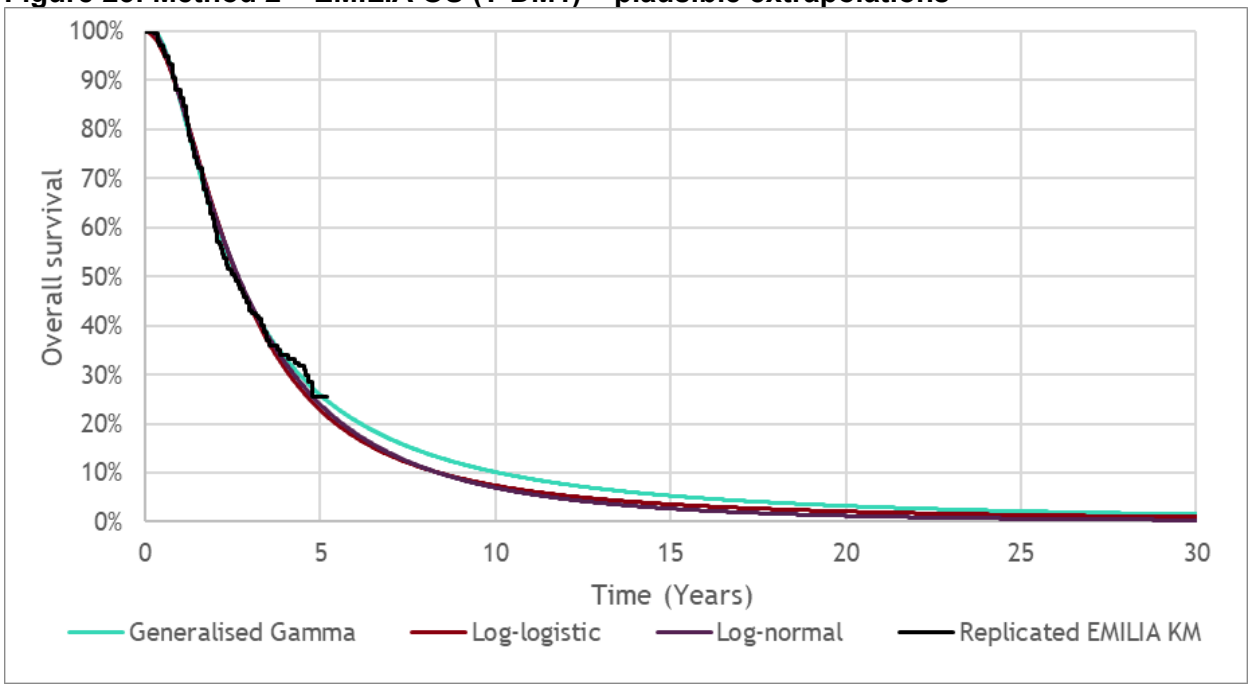
Figure 22: Method 2 – EMILIA OS (T-DM1)



Abbreviations: KM, Kaplan-Meier; OS, Overall Survival; T-DM1, trastuzumab emtansine.

Figure 22 was used to determine the suitability of the six PSMs. Clinical experts consulted as part of an expert validation meeting estimated that 25–35% of patients would be alive at 5 years and 5–10% of patients would be alive at 10 years when treated with T-DM1. Three curves, the Gompertz, exponential and Weibull, were excluded based on the visual fit, as they provided a poor visual fit to the replicated EMILIA KM and/or did not sit within the clinically plausible range provided by the clinical experts. Therefore, the log-logistic, log-normal, and generalised gamma were considered most appropriate for further consideration to inform OS estimates in Method 2. A comparison is provided in Figure 23. Of the plausible curves, generalised gamma provides the most optimistic (~10%) survival at 10 years, at the upper end of the clinical estimates. The log-normal and log-logistic sit between the estimates provided by clinicians at 10 years (6.97% and 7.40% respectively). With a good fit to the replicated data, a better goodness-of-fit score, plausible long-term extrapolations, and better visual fit, the log-normal was selected as the most pragmatic curve to inform scenarios using Method 2, with alternative plausible extrapolations also investigated.

Figure 23: Method 2 – EMILIA OS (T-DM1) – plausible extrapolations



Abbreviations: KM, Kaplan-Meier; OS, Overall Survival; T-DM1, trastuzumab emtansine.

Estimating T-DXd OS

Method 2 incorporates data for T-DM1 informed by EMILIA (which compared T-DM1 with lapatinib plus capecitabine). As the EMILIA study did not consider the use of T-DXd, the relationship between T-DM1 and T-DXd Method 2 is informed by applying a HR derived from DESTINY-Breast03 to the extrapolated T-DM1 comparator arm. The HR calculated from DESTINY-Breast03 data is 0.55 (95% CI: 0.36 – 0.86) (see Section B.2.6.1).

Summary of selected model

Figure 24 provides a summary of the selected OS curves within the model when Method 2 is applied, extrapolating EMILIA T-DM1 trial data and applying the DESTINY-Breast03 HR to the extrapolated data to inform T-DXd. The KM presented curves are from DESTINY-Breast03 and illustrate the visual fit of this approach in comparison to the observed data. As illustrated, the approach taken in Method 2 provides a good fit to the DESTINY-Breast03 data for both the T-DM1 and T-DXd arms.

Figure 24: Method 2: EMILIA OS + HR (T-DXd and T-DM1)

Abbreviations: DB03. DESTINY-Breast03; HR, hazard ratio; KM, Kaplan-Meier; OS, Overall Survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

B.3.3.2.1.3 Strengths and limitations of the OS methods

Both approaches have key strengths and limitations which are highlighted in Table 30. As a generalisable trial with a relevant head-to-head comparison, direct extrapolation of OS from DESTINY-Breast03 (Method 1), although immature, was considered the most appropriate to inform the model base case, and was supported by consulted external experts. Given the immaturity of OS within the DESTINY-Breast03 study, Method 2 is used to explore uncertainty in scenario analysis (see Section B.3.11.3). The extrapolations derived from Method 2 (with longer-term OS) provide a supporting analysis with projections in line with the less mature DESTINY-Breast 03 trial extrapolations.

Table 30: Strengths and limitations of the OS approaches

Method	Summary	Strengths	Limitations
Method 1 (base case)	Direct extrapolation of DB03	• Uses all pivotal trial data • Relevant head-to-head comparison • DB03 trial is generalisable to UK practice • Efficacy aligned to other inputs	• Immature survival data • Greater variability in long-term outcomes

Method	Summary	Strengths	Limitations
Method 2 (scenario)	Replicated data from EMILIA + HR	• Considered generalisable to UK practice and DESTINY-Breast03 • Uses longer-term mature OS data • Incorporates within trial comparison of T-DXd to T-DM1 via application of HR • Extrapolations provide a good fit to the DB03 data	• Assumes PH holds • Assumes relationship within DB03 trial would apply within the EMILIA trial/population • Re-created PLD from EMILIA • Different efficacy sources between PFS and OS

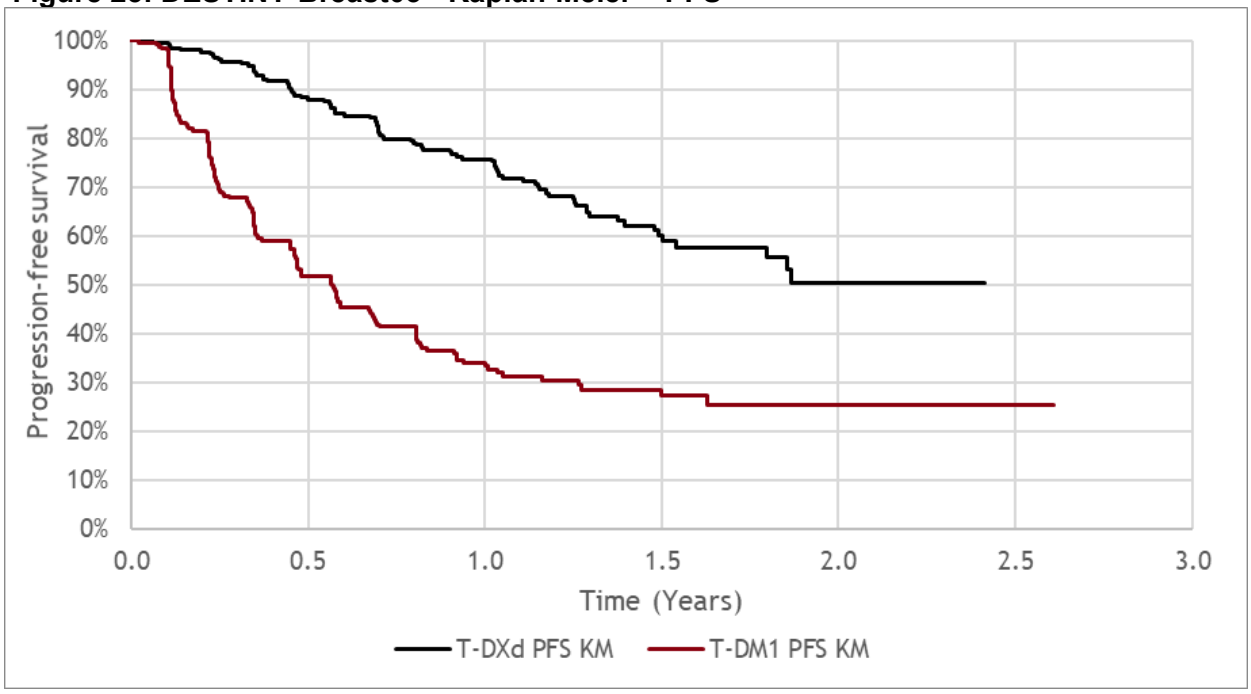
Abbreviations: DB03, DESTINY-Breast03; HR, hazard ratio; OS, overall survival; PH, proportional hazards; PFS, progression-free survival; PLD, patient-level data; TTD, time to treatment discontinuation.

B.3.3.2.2 Progression-free survival

Assessment of data from DESTINY-Breast03

A summary of the PFS data from DESTINY-Breast03 is provided in Section B.2.6.1 (and Figure 25 below). T-DXd was associated with a statistically significant 72% lower risk of progression or death compared with T-DM1 (HR: 0.28; 95% CI: 0.22, 0.37 [$p=7.8\times10^{-22}$]).[102,103] PFS data are relatively mature (33.3% .vs. 60.1% for T-DXd and T-DM1, respectively) however, extrapolation of outcomes was required to inform cost-effectiveness estimates.

Figure 25: DESTINY-Breast03 - Kaplan-Meier – PFS



Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival.

For all analyses within the cost-effectiveness model, the BICR definition of PFS has been used, which is the primary efficacy outcome in the trial (in line with Section B.2.3).

As with the OS data from DESTINY-Breast03, a LCHP was produced for PFS (Figure 26). The LCHP shows that the curves are not parallel over time (converging at the start and then

diverging), indicating that there is no clear evidence that the PH assumption holds. This is further supported by the Therneau and Grambsch's test of non-proportionality that rejects the null hypothesis (p-value <0.0001). As such, given the results of the PH tests and the number of PFS events, independent parametric model fits were concluded to be the most suitable approach for informing the cost-effectiveness analysis.

Figure 26: Log-cumulative hazard plot of PFS from DB03

Abbreviations: BICR, blinded independent central review; DB03, DESTINY-Breast03; LCHP, log-cumulative hazard plot; PFS, progression-free survival.

Assessment of the statistical goodness-of-fit scores for fitted models

PSMs were fitted in R® using the '*flexsurv*' package. As per the OS estimates, six standard parametric forms discussed in NICE DSU TSD 14 were fitted for completeness.

AIC and BIC scores for the extrapolated PFS for DESTINY-Breast03 data are presented in Table 31. Based on the goodness-of-fit statistics, it may be concluded that the log-normal provides the best fit to the T-DXd arm, while the generalised gamma provides the best fit to the T-DM1 arm.

Table 31: Statistical goodness-of-fit scores (PFS)

	T-DXd		T-DM1	
Model	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	811.15	814.72	1091.10	1094.67
Weibull	804.18	811.31	1093.03	1100.17
Gompertz	809.64	816.77	1081.18	1088.33
Log-logistic	802.00	809.13	1067.40	1074.54
Log-normal	800.83	807.96	1058.42	1065.56
Generalised gamma	802.77	813.46	1045.19	1055.91

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; PSM, parametric survival model; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

Fitting of parametric models

Figure 27 presents the model fits for T-DXd and T-DM1 across the observed period and 30-year time horizon.

Figure 27: PFS (T-DXd and T-DM1)

Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

Figure 27 was used to determine the suitability of the different PSMs. Clinical advice indicated that 1-2% and 0% of T-DM1 patients would be progression-free at 5 and 10 years, respectively. As such, expert clinical advice indicated that the Gompertz and generalised gamma curves could be excluded as they were not clinically plausible for T-DM1 with 5-year estimates substantially above this range. For T-DXd, the Gompertz was considered too pessimistic. Further, both the Gompertz and generalised gamma curves produced extrapolations for T-DXd which crossed with T-DM1 at [redacted] and [redacted] years respectively. Clinicians considered this unlikely given the large PFS benefit observed within DESTINY-Breast03 and the clear separation of KM OS curves. Therefore, based on the visual fit and the plausibility of the long-term extrapolation, the log-logistic, log-normal, Weibull and exponential were considered most appropriate for further consideration to inform PFS estimates (a comparison is provided in Figure 28).

Figure 28: PFS (T-DXd and T-DM1) – plausible extrapolations

Abbreviations: KM, Kaplan-Meier; OS, overall survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

Based on the clinical advice received, the Weibull distribution was selected to inform the base case extrapolations for T-DM1 and, in line with NICE guidance, other plausible curves were explored in sensitivity analysis (see Section B.3.11.3). Applying the Weibull may be considered pessimistic in comparison to the alternative plausible extrapolations, however, clinical experts agreed that the Weibull curve for T-DM1 would provide the most clinically plausible fit with 5- and 10 year PFS of [redacted] (which closely matches the clinical experts feedback of between 1–2% and 0%).[46] The log-normal and log-logistic curves also projected slightly higher PFS with T-DM1 than expected at both time points.

Given the similar mechanisms of action of T-DXd and T-DM1 and in line with TSD guidance, it was also considered appropriate to assume the same base case PFS distribution across arms.[144] The clinicians agreed that the Weibull distributions for both T-DXd and T-DM1 provided an appropriate curve choice with a consistently higher PFS estimate for T-DXd.

Summary of base-case models

Figure 29 provides a summary of the base-case extrapolation for PFS applied within the model (applying a Weibull curve to both T-DM1 and T-DXd).

Figure 29: Base-case extrapolations for PFS (T-DXd and T-DM1)

Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

B.3.3.2.3 Time to treatment discontinuation

Assessment of data from DESTINY-Breast03

As with PFS and OS, PSMs were also required to inform the estimation of the treatment duration within the economic analysis. Patient-level TTD data is used within the model to determine the drug and administration costs associated with T-DXd and T-DM1. A summary of the TTD data from the DESTINY-Breast03 is provided below in Figure 30.

Figure 30: TTD KM from DESTINY-Breast03

Abbreviations: KM, Kaplan-Meier; T-DM1, trastuzumab emtansine; TTD, time-to-treatment discontinuation; T-DXd, trastuzumab deruxtecan.

Similar to PFS and OS, a LCHP was produced for TTD (Figure 31). The LCHP shows that the curves are not parallel over time (and converging), indicating that there is no clear evidence that the PH assumption holds. This is supported by the Therneau and Grambsch's test of non-proportionality that rejects the null hypothesis (p = 0.0004). Therefore, similar to PFS, independent curves were fitted to the DESTINY-Breast03 data to inform TTD for T-DXd and T-DM1. Given the maturity of the data (events for both arms) and likely independence of treatment discontinuation across both treatment arms (i.e., due to different adverse event profiles, or progression), and the relationship with PFS, independent curves were deemed the most appropriate to inform TTD.

Figure 31: Log-cumulative hazard plot of TTD from DB03

Abbreviations: DB03, DESTINY-Breast03; T-DM1, trastuzumab emtansine; TTD, time-to-treatment discontinuation; T-DXd, trastuzumab deruxtecan.

Assessment of the statistical goodness-of-fit scores for fitted models

As with PFS and OS, the same six standard parametric forms were fitted to TTD data from the DESTINY-Breast03 trial. AIC and BIC scores for the extrapolated TTD curves are presented in Table 32.

Table 32: Statistical goodness-of-fit scores (TTD, independent models)

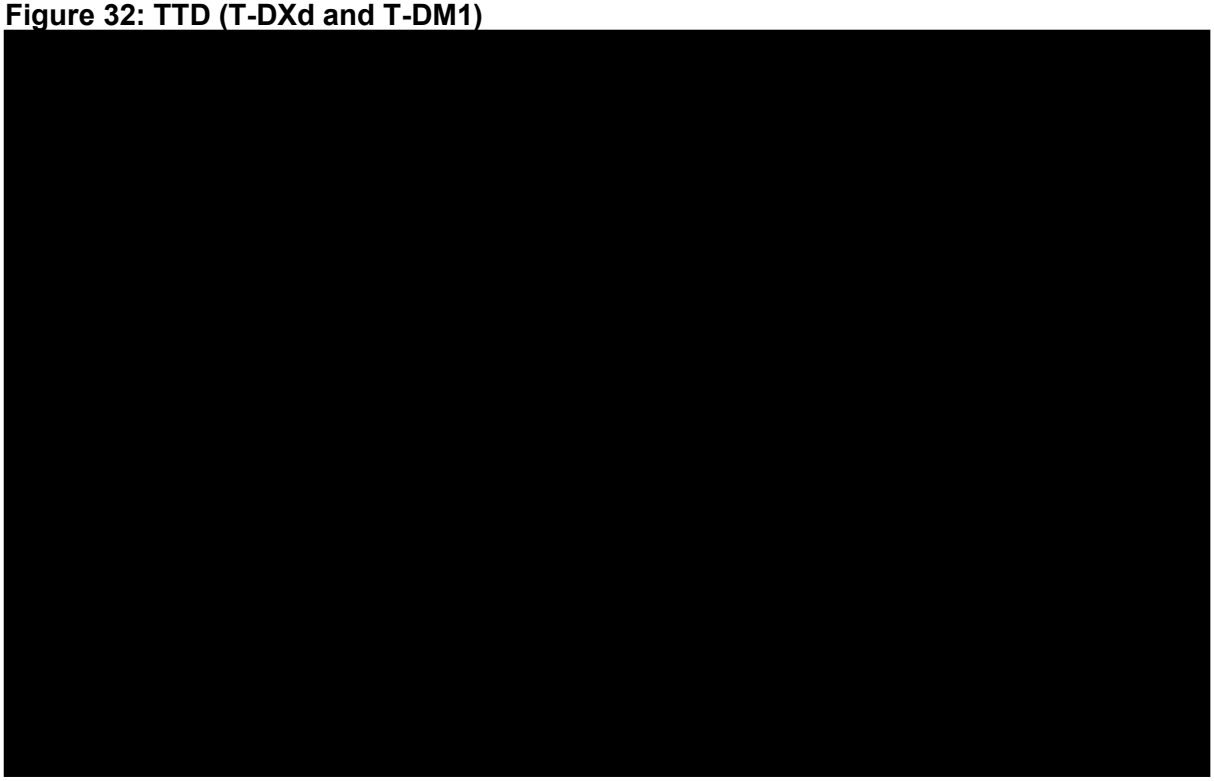
	T-DXd		T-DM1	
Model	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	1084.75	1088.31	1409.80	1413.38
Weibull	1066.07	1073.20	1405.39	1412.53
Gompertz	1077.34	1084.47	1411.80	1418.94
Log-logistic	1061.20	1068.33	1386.80	1393.95
Log-normal	1059.57	1066.70	1384.04	1391.19
Generalised gamma	1061.39	1072.09	1386.01	1396.72

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; TOT, Time-on-treatment; T-DM1, trastuzumab emtansine; TTD, time-to-treatment discontinuation; T-DXd, trastuzumab deruxtecan.

Fitting of parametric models

Figure 32 presents the model fits for T-DXd and T-DM1 across the observed period and longer-term extrapolations (across the 30-year time horizon).

Figure 32: TTD (T-DXd and T-DM1)



Abbreviations: KM, Kaplan-Meier; T-DM1, trastuzumab emtansine; TTD, time-to-treatment discontinuation; T-DXd, trastuzumab deruxtecan.

Figure 32 was used to determine the suitability of the different PSMs. As the TTD data for T-DM1 is very mature, little difference is seen between the curves. As data are less mature

for T-DXd, there is slightly more variability amongst fitted curves, however this is limited. Based on the visual fits, all curves were considered plausible for the base case selection.

In line with the SmPC, patients are treated until progression, and the majority of patients will discontinue treatment due to progression (as observed in both treatment arms of DESTINY-Breast03). However some may discontinue treatment due to other reasons such as unacceptable toxicity and so the TTD curve should not rise above PFS at any time. Clinical experts confirmed TTD and PFS should therefore follow a similar shaped extrapolation and curves should not cross.[46]

The Weibull curve was therefore selected to inform the model base case. This is consistent with the PFS base case curve (given the expectation of similar shapes) and provides a good fit to the data. In addition, this curve aligns with the clinical feedback received for PFS whereby very few patients are expected to be progression-free at 5 years (and therefore on treatment) and no patients expected to be on treatment by 10 years. In line with TSD guidance[144], the same parametric curves were considered for both treatment arms and alternative curve choices are explored in sensitivity analysis (see Section B.3.11.3).

Summary of base case models

Figure 33 provides a summary of the base-case extrapolation for TTD applied within the model (Weibull curves considered for both T-DM1 and T-DXd).

Figure 33: Base-case extrapolations for TTD (T-DXd and T-DM1)

Abbreviations: KM, Kaplan-Meier; T-DM1, trastuzumab emtansine; TTD, time-to-treatment discontinuation; T-DXd, trastuzumab deruxtecan.

B.3.3.3 Safety

Adverse events (AEs) that occurred in the DESTINY-Breast03 study are reported in Section B.2.10. Grade ≥3 AEs with an incidence of greater than 5% in either treatment arm of the DESTINY-Breast03 trial were included in the economic model.

The economic model also accounts for adverse events of special interest identified in the DESTINY-Breast03 CSR (at any grade).[105] These were interstitial lung disease (ILD) and left ventricular ejection fraction (LVEF) decrease.

Table 33 presents the AEs from DESTINY-Breast03 included within the economic model.[102]

Table 33: Adverse event incidence included in the economic model

Adverse event	T-DXd N=257	T-DM1 N=261
Anaemia	15 (5.8%)	11 (4.2%)
Fatigue	13 (5.1%)	2 (0.8%)
Interstitial lung disease (any grade)	27 (10.5%)	5 (1.9%)
Left ventricular ejection fraction decrease (any grade)	5 (1.9%)	1 (0.4%)
Nausea	17 (6.6%)	1 (0.4%)
Neutropenia	49 (19.1%)	8 (3.1%)
Thrombocytopenia	18 (7%)	65 (24.9%)
Leukopenia	17 (6.6%)	1 (0.4%)

Abbreviations: T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

B.3.3.4 Efficacy summary

A summary of the main clinical parameters and variables applied in the economic model is provided in Table 34. The base case survival models (OS, PFS and TTD) used to inform the cost-effectiveness are provided in Figure 34.

Table 34: Summary of clinical model parameters and variables used in economic model base case

Parameter	Value	Rationale	Section
Baseline characteristics	As presented in Table 25 informed by DB03	Aligned to the observed efficacy in DB03 and considered generalisable to UK practice	B.3.3.1
OS method	Direct DB03 extrapolation	Using direct evidence from DB03 in the relevant population with the relevant comparator	B.3.3.2
OS models	Dependent generalised gamma model	Good visual fit to KM, and provided middle estimate of OS based on clinically plausible range	B.3.3.2
PFS models	Independent Weibull models applied to both arms	Good visual fit to KM, reasonable extrapolation of longer-term PFS and considered clinically most plausible	B.3.3.2
TTD models	Independent Weibull models applied to both arms	Good visual fit to KM, consistent with PFS and clinically plausible	B.3.3.2

Parameter	Value	Rationale	Section
Adverse events	Grade ≥3 AEs occurring in ≥5% of patients in either treatment arm and AEs of special interest (any grade)	Considered to reflect the main AEs experienced by patients and those that could impact the economic analysis	B.3.3.3

Abbreviations: AE, adverse event; DB03, DESTINY-Breast03; KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TTD, time-to-treatment discontinuation.

Figure 34: Summary of base case efficacy (T-DXd and T-DM1)

Abbreviations: KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; T-DM1, trastuzumab emtansine; TTD, time-to-treatment discontinuation; T-DXd, trastuzumab deruxtecan.

B.3.4 Measurement and valuation of health effects

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

In DESTINY-Breast03, EQ-5D-5L, EORTC QlQ-BR45 and EORTC QLQ-C30 questionnaires were administered to patients to measure HRQoL.[105] EQ-5D-5L questionnaires were completed by patients on day 1 of cycles 1, 2 and 3 and then every 2 cycles thereafter until the end of treatment assessments. Patients were then followed up at the Day 40 (+ 7 days) first follow-up assessment (after last study drug administration) or before initiation of new anti-cancer treatment, whichever came first, and then at the first long-term/survival follow-up assessments three months later. Patients were required to complete questionnaires before any other study assessments or procedures were performed on the day.

B.3.4.2 Mapping of EQ-5D-5L to EQ-5D-3L

In line with NICE methods guidance, the EQ-5D-5L responses were 'crosswalked' to produce EQ-5D-3L values.[140] The responses were 'crosswalked' using the algorithm developed by Van Hout et al, 2012.[148]

In total, 4,644 EQ-5D-5L observations were available from 734 patients. Of these, 3,974 observations were recorded while progression-free with the remaining 670 recorded post-progression. A tabulated summary of the EQ-5D-5L 'crosswalked' to EQ-5D-3L utility values by progression status is provided in Table 35.

Table 35: Summary of utility values by progression status

Health state	Number of patients	Number of observations	Mean	Median
Progression-free	517	3,974	[redacted]	[redacted]
Progressed disease	217	670	[redacted]	[redacted]

EQ-5D-3L utility scores based on *'progression-free'* and *'progressed disease'* health states were derived using generalized estimating equations (GEE) regressions. EQ-5D-5L scores from all available time points, including baseline, were included in the GEE as dependent variables. Treatment and treatment response status (progressed disease vs. progression-free) were included as independent variables. The mean utility values and associated 95% confidence intervals for the progression-free and progressed health states for each treatment group are derived from the model using least squares means. The GEEs are fitted with an independence working correlation structure and a robust sandwich variance estimator. Two regression models were considered:

1. Utility ~ progressed
2. Utility ~ progressed + treatment

An overview of the statistical goodness of fit (by quasi-likelihood under the independence model criterion [QIC]) and results of the GEE regression estimates are provided in Table 36.

Table 36: GEE regression coefficients

Coefficient	Value	95% CI	p-value	QIC
Model 1				
Intercept	[redacted]	[redacted]	[redacted]	[redacted]
Progressed	[redacted]	[redacted]	[redacted]	
Model 2				
Intercept	[redacted]	[redacted]	[redacted]	[redacted]
Treatment (T-DXd)	[redacted]	[redacted]	[redacted]	
Progressed	[redacted]	[redacted]	[redacted]	

Abbreviations: CI, confidence interval; QIC, quasi-likelihood.

Table 37 presents the resulting crosswalked EQ-5D-3L utility values from the DESTINY-Breast03 study by progression status and treatment arm using models 1 and 2, respectively.

Table 37: Mapped EQ-5D-3L utility values from DESTINY-Breast03

Health state	T-DXd (SE) (95% CI)	T-DM1 (SE) (95% CI)	Overall (SE) (95% CI)
Progression-free	[redacted]	[redacted]	[redacted]
Progressed	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; SE, standard error.

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

An SLR to identify relevant HRQoL studies was conducted. Appendix H provides full details of the methods, overview of studies and results of the identified studies, together with the quality assessments. The SLR identified 15 studies, however, none of the identified studies fully qualified for the preferred NICE reference case or used EQ-5D values.

Nevertheless, the majority of studies referred to Lloyd et al, 2006 from which the values used in these studies were based on. This was also the case for the majority of prior HER2+ BC NICE appraisals (see Section B.3.4.3.1 below). As such, this study has been included within the model as an option to derive utility estimates.

Lloyd et al, 2006 is a preference-based study estimating utilities at distinct stages of mBC in the general population. The health state valuations were analysed using a mixed model analysis with random effects which revealed that all disease states and toxicities were independently significant predictors of utility. Using the coefficients of the mixed model the utility values were calculated specifically for the patient population within this submission using the following equation:

$$\frac{e^{(sum\ of\ coefficiants)}}{1 + e^{(sum\ of\ coefficients)}}$$

The coefficients used to calculate the treatment specific and combined utilities for T-DXd and T-DM1 were age, response rates and progression status based on data from DESTINYBreast-03. Details of how these were derived are presented in Table 38. First, the responder and non-responder utilities were calculated using the coefficients and the equation above. Then the responder and non-responder utilities were weighted by response rates from the DESTINY-Breast03 study. This approach is consistent with the preferred approach outlined by the Evidence Review Group (ERG) in TA458.[32]

Table 38: Utilities derived from Lloyd et al

Parameter	Coefficient value	T-DXd multiplier	T-DM1 multiplier	Pooled multiplier
Intercept	0.008871	-	-	-
Age	0.0239	[redacted]	[redacted]	[redacted]
Treatment response	0.4063	79.7%	34.2%	56.9%
Progression	-1.1477	-	-	-
Resulting utility [a]	PF responder: 0.848 PF non responder: 0.787 PD responder: 0.638 PD non responder: 0.540	**PF: 0.835** **PD: 0.618**	**PF: 0.808** **PD: 0.574**	**PF: 0.822** **PD: 0.596**

Abbreviations: PD, progressed disease; PF, progression-free.
Note: [a] Resulting utilities after applying the coefficients to the equation

B.3.4.3.1 Utilities used in previous appraisals

As well as consideration of the utilities reported within the literature, utilities reported within prior NICE appraisals in HER2+ mBC were also assessed for appropriateness of inclusion within the economic model. TA509[2] (pertuzumab – first line) and TA458[32] (T-DM1 – second line) implemented utility values based on the Lloyd et al regression.[149]

In TA704[3] (T-DXd – third line), *'progression-free'* utilities were derived using the approach in TA423[97] (eribulin – third line) where objective response from the EMBRACE clinical trial was used as a function of the calculated utilities. In TA704, the baseline utility value (0.704), tumour response utility (0.780) and the incremental utility of response (0.076) were taken from TA423. *'Progression-free, off-treatment'* used the baseline utility value. For *'progression-free, on treatment'*, to calculate treatment specific utilities, the baseline value, and tumour response utility were used to derive the utilities on treatment incorporating the ORR for each treatment from the DESTINY-Breast01 trial and the literature. For *'progressed disease'*, TA704 used the accepted value in TA423. In TA423, the ERG stated that the value used by the company for *'progressed disease'* from Study 301 (0.679) was unrealistic as it did not represent a large enough reduction in utility after patients experienced disease progression, and proposed a value of 0.496 from Lloyd et al. The committee stated that the true utility value was likely somewhere between the company and ERG values, as clinicians stated that the reduction in utility was likely smaller than suggested by the ERG. Therefore, for *'progressed disease'* the average of the company and ERG preferred values from TA423 was used (0.588).

In ID3828 (tucatinib – third line), the most recent mBC NICE appraisal, the company assigned treatment specific utilities in the *'pre-progression'* health state. Utilities for the intervention arm were derived directly from the HER2CLIMB study and declined over time until disease progression. Comparator utilities were taken from TA458. The ERG believed the use of treatment specific utilities was inappropriate due to the non-comparative nature of the evidence. While the committee agreed that utility values were uncertain due to a lack of comparative evidence it concluded that treatment specific pre-progression values were plausible. The committee also concluded that the difference seen in progressed utilities is plausible but uncertain, and that evidence-based utilities were preferred.

A summary of final utility values used in previous submissions are presented in Table 39.

Table 39: Summary of final utility values in previous submissions

Submission (treatment line)	Treatment	Progression-free	Progressed disease
TA598 (1L)	Pertuzumab + trastuzumab + docetaxel	0.772 (during docetaxel) 0.785 (after docetaxel)	0.769
	Trastuzumab + docetaxel	0.769 (during docetaxel) 0.777 (after docetaxel)	
TA458 (2L)	T-DM1	0.807	0.53
	Lapatinib + capecitabine/ herceptin + capecitabine/ capecitabine	0.80/ 0.80 / 0.792	
TA704 (3L)	T-DXd	0.750 0.704 (off treatment)	0.588
	Eribulin/ capecitabine/ vinorelbine	0.715/0.718/0.728 0.704 (off treatment)	
ID3828 (3L)	Tucatinib + trastuzumab + capecitabine	0.748 (cycles 1-2) 0.763 (cycles 3-4) 0.792 (cycles 5-6) 0.807 (cycles 7+)	0.698
	Eribulin	0.782	0.588

Abbreviations: 1L, first-line; 2L, second line; 3L, third line; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

B.3.4.4 Adverse reactions

The impact of adverse events on HRQoL was explored in the cost-effectiveness model. As trial-based treatment specific utilities derived from DESTINY-Breast03 are applied in the model across both arms in the base case analysis (see Section B.3.4.5), these are expected to capture the impact of toxicities. As such, AE disutilities are only applied in a scenario analysis (see Section B.3.11.3).

The disutility values and expected duration of AEs used in scenario analysis were identified from published sources and are presented in Table 40. The frequency of AEs for both arms was obtained from DESTINY-Breast03 (as outlined in Section B.3.3.3).

Table 40: Disutilities for adverse events

Adverse event	Disutility	Duration (days)	Source	
			Disutility	Duration
Anaemia	-0.010	42.90	Hudgens et al, 2014[150]	TA704[3]
Fatigue	-0.0290	58.30	Hudgens et al, 2014[150]	
Interstitial lung disease	-0.170	51.10	Doyle et al[151]	
Left ventricular ejection fraction decrease	-0.059	31.00	Sandhu et al, 2016[152]	
Nausea	-0.021	36.20	Hudgens et al, 2014[150]	
Neutropenia	-0.007	40.10	Hudgens et al, 2014[150]	
Thrombocytopenia	-0.066	42.20	ID3828[153]	Assumption
Leukopenia	-0.003	42.20	Hudgens et al, 2014[150]	TA704[3]

Abbreviations: TA, technology appraisal.

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

For the model base case, utilities derived from DESTINY-Breast03 have been used directly to inform treatment specific values for the *'progression-free'* health state (see Section B.3.4.1). The values derived from DESTINY-Breast03 are based directly on the relevant population and treatments and measure the health states using EQ-5D-5L crosswalked to EQ-5D-3L which is the preferred measure in the NICE Reference Case.

Clinical advice to the company indicated that the pre-progression utility values derived from the DESTINY-Breast03 trial may be slightly higher than expected in clinical practice. However, this could be due to the known paradigm that trial patients are considered in better health than real-world patients, for example, patients with poorer performance status (ECOG 2+) are generally excluded from clinical trials. Nevertheless, trial-based utilities were considered the most appropriate source of evidence by both clinical and economic experts for the *'progression-free'* health state in this submission as they are derived directly from a relevant patient population using the NICE preferred EQ-5D values.[140] Alternative utility values from the published literature for the *'progression-free'* health state are explored in scenario analysis (see Table 41).

For the '*progressed disease'* health state, the number of post-progression observations from DESTINY-Breast03 were limited (n=670) and the resulting values were considered implausibly high by clinical experts in comparison to previously accepted '*progressed disease'* utility values within the same population (see Table 39). As outlined in Section B.3.4.1, HRQoL data collection after progression was limited with assessments taken after last study drug administration or before initiation of further treatment, and then again 3 months later. This means that no long-term data for HRQoL for progressed patients was collected, which may be reason for implausibly high progressed disease utility values.

Therefore, the values derived from Lloyd et al, 2006 are used to inform the model base case for the *'progressed disease'* health state. Treatment specific progressed disease utility

values are used to inform the base case as there is an expectation that patients who progress on T-DXd have a better QoL than those who progress on T-DM1 due to the improved and longer response rates and disease control. Hence, patients progressing on T-DXd will be starting with a 'higher' utility upon progression than those patients progressing on T-DM1 which has been observed in the utility values derived from DESTINY-Breast03 (see Table 37). This is also consistent with the approach taken in ID3828 where differences in *'progressed disease'* utility values between arms were considered plausible (though the committee acknowledged the uncertainty in the actual values).[153]

Scenario analyses exploring alternative utility data from the literature are also explored using information provided in Lloyd et al, 2006.[149]

Age-related utility decrements have also been included in the model base case to account for the natural decline in quality of life associated with age. Utility values from the general population at each age were calculated using the algorithm by Ara and Brazier, 2010.[154] The utility multiplier was the calculated per increase in age and applied in each cycle throughout the model time horizon.

$$General\ population\ utility\ value = 0.9508566 + 0.0212126 \times male - 0.0002587 \times age - 0.0000332 \times age^2$$

Table 41 summarises the utility values included within the cost-effectiveness analysis base case and scenarios.

Table 41: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
Base case				
Progression-free T-DXd T-DM1	[redacted]	[redacted]	B.3.4.1, Page 114	Derived from DESTINY-Breast03 study
Progressed disease T-DXd T-DM1	0.6183 0.5738		B.3.4.3, Page 116	Previously accepted algorithm from Lloyd et al
Scenario – Lloyd et al (treatment specific)				
Progression-free T-DXd T-DM1	0.8353 0.8079		B.3.4.3, Page 116	Explore using alternative utility values from the literature (treatment specific)
Progressed disease T-DXd T-DM1	0.6183 0.5738			
Scenario – Lloyd et al (combined)				
Progression-free	0.8216		B.3.4.3, Page 116	Explore using alternative utility values from the literature (combined)
Progressed disease	0.5960			

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
Scenario – DB03 (PF combined); Lloyd et al (PD combined)				
Progression-free on treatment	[redacted]	[redacted]	B.3.4.3, Page 116	Explore using alternative utility values from the literature
Progressed disease	0.5960			

Abbreviations: DB03, DESTINY-Breast03; PD, progressed disease; PFS, progression-free; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

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

An SLR was undertaken to identify cost and resource use studies for HER2+ mBC in the second line or later setting. Full details of the SLR methods, identified studies and results are presented in Appendix I.

B.3.5.1 Intervention and comparators' costs and resource use

B.3.5.1.1 Drug acquisition costs

The drug unit costs for each treatment included in the model were sourced from the British National Formulary (BNF) and are presented in Table 42. There is an approved confidential simple discount Patient Access Scheme (PAS) for T-DXd resulting in a fixed net price of [redacted] per 100mg vial (equivalent to a discount of [redacted] to the list price). As the PAS in place for T-DM1 is commercial in confidence, no other discounts are applied within the analysis.

Table 42: Unit drug costs

Drug	Size	List price (with PAS)	Source
T-DXd	100mg	£1,455.00 [redacted]	BNF 2022
T-DM1	100mg	£1,641.01	BNF 2022
	160mg	£2,625.62	

Abbreviations: PAS, patient access scheme; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

The dosing schedule for each treatment was taken from DESTINY-Breast03 which is in line with the proposed license and SmPC for T-DXd and the SmPC for T-DM1.[142] T-DXd is administered at a dose of 5.4 mg/kg once per 21-day cycle.[102] T-DM1 is administered at a dose of 3.6 mg/kg once per 21-day cycle.[102,142]

In DESTINY-Breast03, no dose modifications were permitted for Grade 1 and 2 AEs unless specified in the protocol. For Grade ≥3 toxicities, two dose reductions were permitted which is in line with the SmPC for both drugs.[141] For T-DXd, the dose could be reduced to 4.4 mg/kg (Level-1) then further to 3.2 mg/kg if required (Level-2) and then withdrawal. For T-DM1, the dose could be reduced to 3.0 mg/kg then 2.4 mg/kg and then withdrawal.[102,142] Once the dose of study treatment had been reduced because of toxicity, all subsequent

cycles were to be administered at that lower dose level unless further dose reduction was required. If toxicity continued after 2 dose reductions, then the subject was withdrawn from study treatment. Study treatment dose increases were not allowed in DESTINY-Breast03.

Therefore, to account for dose reductions, missed doses and treatment interruptions, the RDI from DESTINY-Breast03 is included in the base case; [redacted]% for T-DXd and [redacted]% for T-DM1. RDI was calculated as the dose intensity over the planned dose intensity (i.e., planned starting dose).

Drug wastage was calculated through the method of moments approach to calculate the average number of vials that would be required per one administration of treatment.[155] The method of moments first derives a log-normal distribution for the average patient's weight based on the mean and standard deviation measured at baseline from DESTINY-Breast03. The log-normal distribution is then used to predict the proportion of patients requiring each number of vials to administer the required dose. This method assumes that patients only receive whole vials (i.e., no vial sharing), and thus accounts for drug wastage. As vial sharing is available in some UK centres, the model also includes an option to assume a proportion of patients vial share. In the base case, 50% vial sharing was assumed in line with the assumptions accepted in previous BC appraisals.[3,156] A hybrid approach is therefore taken within the model base case which accounts for 50% of patients vial sharing (and is applied to both treatment arms).

Table 43 presents the dosing schedules, dose intensity and final cost per treatment cycle used in the model base case. The cost per dose is then applied within the model to patients on treatment every 3 weeks as per the administration frequency.

Table 43: Dosing schedules and cost per 21-day treatment cycle

Treatment	Dose	Relative dose intensity (RDI)	% vial sharing	Cost per dose [a]	Source
T-DXd	5.4 mg/kg Q3W	[redacted]	50%	[redacted]	DESTINY-Breast03[102]
T-DM1	3.6 mg/kg Q3W	[redacted]	50%	[redacted]	DESTINY-Breast03[102] SmPC[142]

Abbreviations: Q3W, every 3 weeks; RDI, Relative dose intensity; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Note: [a] Includes T-DXd PAS, RDI and assuming 50% vial sharing.

B.3.5.1.2 Administration costs

T-DXd and T-DM1 are both administered via intravenous infusion. The initial dose should be administered as a 90-minute infusion. If the prior infusion is well tolerated subsequent doses may be administered over 30 minutes. The cost per administration used in the model was sourced from the National Schedule of NHS Costs 2019/20 using Healthcare Resource Group (HRG) code SB12Z: deliver simple parenteral chemotherapy. This includes an overall time of 30 minutes nurse time and 30 to 60 minutes chair time for the delivery of a complete cycle.[157] The cost per administration is provided in Table 44 and is applied in the model as a single cost per treatment dose (every 21 days) to both T-DXd and T-DM1.

Table 44: Administration costs

Method	Cost	Source
IV infusion	£221.35	NHS Cost Collection 19/20. SB12Z (Outpatient)

Abbreviations: IV, intravenous.

B.3.5.2 Health-state unit costs and resource use

Disease monitoring healthcare resource use costs are based on frequencies reported in TA704, TA458 and ID3828.[3,32,153] Disease monitoring resource use is split by health state ('*progression-free'* and '*progressed disease'*) and all three appraisals assume the same resource use across health states and treatment arms. Advice to the company from clinical experts was that disease-related resource use was unlikely to differ by health state or treatment and therefore the approaches taken in the aforementioned TA's were considered appropriate for the economic model.

Table 45 presents resource use for monitoring and disease management in *the 'progression-free'* and *'progressed'* health states. Unit costs were sourced from the NHS Cost Collection costs 19/20[157] and the PSSRU 2021[158] based on the setting of care.

Table 45: Monitoring costs and frequencies

Resource	Frequency (per cycle)		Unit cost	Frequency source	Cost source
	PF	PD			
Medical oncologist	0.230	0.230	£201.33	TA704[3]	NHS Cost Collection 19/20[157] – 370 – medical oncologist – consultant led
GP contact	0.230	0.230	£39.23	TA704[3]/ ID3828[153]	PSSRU 2021[158] - GP Per patient contact lasting 9.22 minutes with qualifications
CT scan	0.077	0.077	£88.31	TA704[3]	NHS Cost Collection 19/20[157] - RD20A - Computerised Tomography Scan of One Area, without Contrast, 19 years and over - Outpatient
Community nurse	0.500	0.500	£25.00	TA458[32]/ ID3828[153]	PSSRU 2021[158] - Nurses - band 8a - 20 minutes assumed
Clinical nurse specialist	0.230	0.230	£88.00	TA458[32]/ ID3828[153]	PSSRU 2021[158] - Hospital based nurses - band 8b - 1 hour assumed
LVEF follow-up	0.077	0.077	£140.03	TA458[32]	£130 suggested by TA458 ERG uplifted to 2021 costs
Total cost	**£105.57**	**£105.57**			

Abbreviations: CT, Computerised Tomography; GP, general practitioner; LVEF, left ventricular ejection fraction; PD, progressed disease; PF, progression-free.

B.3.5.3 Adverse reaction unit costs and resource use

The unit costs associated with the management of AEs were sourced from the NHS Cost Collection 19/20 and PSSRU 2021.[157,158] Table 46 summarises the costs associated with each adverse event. The unit cost of each adverse event is applied to the incidence rate within each treatment (as outlined in Section B.3.3.3 and Table 33). The total weighted cost per treatment arm was calculated and applied as a one-off cost within the first cycle of the

economic model as the greatest proportion of TEAEs in DESTINY-Breast03 occurred in the first cycle and subsequently declined through cycles (see Section B.2.10.1.2). The total costs associated with the AEs are shown in Table 47.

Table 46: Adverse event costs included in the model

Adverse event	Cost per event	Source
Anaemia	£557.98	NHS Cost Collection 19/20 - SA04K - Iron deficiency anaemia with cc score 2-5 non-elective short stay
Fatigue	£44.00	PSSRU 2021. Nurse cost per 1 hour (Band 5)
Interstitial lung disease (any grade)	£3,401.08	NHS Cost Collection 19/20 - DZ11M - Lobar, Atypical or Viral Pneumonia, with Multiple Interventions, with CC Score 0-8
Left ventricular ejection fraction decrease (any grade)	£505.68	NHS Cost Collection 19/20 - EB03E, Heart failure or shock, with CC score 0-3, non-elective short stay
Nausea	£467.06	NHS Cost Collection 19/20 - JA12L - Malignant breast disorders without Interventions, with CC score 0-1 non-elective short stay
Neutrophil count decreased	£641.11	NHS Cost Collection 19/20 - SA35D - Agranulocytosis with CC Score 2-4. Non elective short stay
Thrombocytopenia	£735.96	NHS Cost Collection 19/20 - SA12H, Thrombocytopenia with CC Score 5-7 non-elective short stay
Leukopenia	£641.11	NHS Cost Collection 19/20 - SA35D - Agranulocytosis with CC Score 2-4. Non elective short stay

Table 47: Total adverse event costs

Treatment	Total cost
T-DXd	£649.03
T-DM1	£298.13

B.3.5.4 Miscellaneous unit costs and resource use

B.3.5.4.1 Subsequent treatments

Subsequent treatment costs were included in the model as an average cost per patient applied as a one-off cost to patients leaving the '*progression-free'* health state. In the base case, the distribution of subsequent treatments is aligned with the treatments received in DESTINY-Breast03 in each treatment arm to align modelled costs with efficacy. The cost of subsequent treatments is modelled as a weighted distribution of these treatments and accounts for the expected time on treatment based on published sources using third-line trials where possible.

The DESTINY-Breast03 CSR grouped subsequent treatments into treatment categories. The most representative treatment for the UK setting was selected for costing purposes. For example, treatments grouped as 'hormone therapies' in DESTINY-Breast03 were costed in the model as tamoxifen given that this is the most commonly used hormone therapy for mBC patients. Treatments categorised as Anti-HER2 were assumed to receive the recently approved combination treatment (tucatinib, trastuzumab and capecitabine). Treatments categorised as 'other' in DESTINY-Breast03 are costed as non-targeted chemotherapy (capecitabine). These assumptions were based on clinical advice.

In the DESTINY-Breast03 study, a large proportion of patients went on to receive subsequent treatment. The high proportions observed in DESTINY-Breast03, particularly in the T-DM1 arm, may be due to a higher number of disease progression events in this arm and drug discontinuation events in both arms due to reasons other than disease progression such as unacceptable toxicity. It may be observed at later data cuts that the proportion of patients receiving subsequent treatments in the two arms becomes more balanced as more T-DXd patients progress. Clinical advice also suggested that the proportion of progressed patients receiving subsequent treatment in DESTINY-Breast03 was higher than expected and that approximately two-thirds of progressed patients would receive subsequent therapy in UK clinical practice after second-line treatment. Although a conservative assumption (as a higher proportion of patients received subsequent treatment after progression in the T-DM1 arm vs T-DXd), to align with more closely with UK clinical practice, it is assumed that 66.7% of patients who leave the '*progression-free'* health state go onto receive subsequent treatment in the base case.

A UK based scenario analysis for subsequent treatment distributions was explored based on clinical advice,[46] which provided estimates of subsequent treatment use by category and by treatment arm. Given the recent acceptance of tucatinib in combination with trastuzumab and capecitabine (ID3828),[153] the use of tucatinib is also explored within this UK scenario, alongside other treatments (T-DM1, T-DXd, trastuzumab and a taxane, tamoxifen and paclitaxel). However, adjustments to the model inputs applied here which deviate from the DESTINY-Breast03 trial only impact the modelled costs associated with subsequent treatment and not efficacy as it would not be practical to adjust OS extrapolations.

Table 48 presents the subsequent treatment distributions, cost per treatment and duration of therapy applied within the economic model base case. Unit costs for the subsequent therapies are provided in Appendix K. Table 49 presents the total subsequent therapy cost applied per arm.

Table 48: Subsequent therapy costs

Treatment		T-DXd distribution	T-DM1 distribution	Dose	Cost per cycle (week)	Admin cost per cycle (week)	Duration of treatment (weeks)	Source for duration
Proportion receiving subsequent treatment		66.7%	66.7%					
Trastuzumab (subcutaneous)		[redacted]	[redacted]	6 mg/kg Q3W	£254.22	£73.78	20	HER2CLIMB[153]
T-DXd		[redacted]	[redacted]	5.4 mg/kg Q3W	[redacted]	£73.78	43	DESTINYBreast01[107]
T-DM1		[redacted]	[redacted]	3.6 mg/kg Q3W	£1,228.79	£73.78	23	TH3RESA
Pertuzumab		[redacted]	[redacted]	420 mg Q3W	£798.33	£73.78	45	Urruticoechea et al. 2017[159]
Taxane (paclitaxel)		[redacted]	[redacted]	175 mg/m^2 Q3W	£5.12	£73.78	12	John et al, 2012[160]
Taxane + trastuzumab		[redacted]	[redacted]	-	£259.34	£143.91	42	John et al, 2012[160]
Other anti-HER2	Tucatinib	[redacted]	[redacted]	300 mg twice daily	£1,878.95	£3.06	25	HER2CLIMB[153]
	Trastuzumab			6 mg/kg Q3W	£254.22	£73.78	20	HER2CLIMB[153]
	Capecitabine			2000 mg daily	£6.04	£7.13	25	HER2CLIMB[153]
Hormone therapy (tamoxifen)		[redacted]	[redacted]	20 mg daily	£1.65	£2.14	70	Manni et al 1981
Other systemic therapy (capecitabine)		[redacted]	[redacted]	2,000 mg/m^2 for 2 weeks Q3W	£6.65	£9.80	19	HER2CLIMB[153]

Note: Distributions are based on data from DESTINY-Breast03 for the base case. [a] Using vial cost of [redacted] per 100mg which is consistent with current operational 3L T-DXd PAS price

Table 49: Total subsequent therapy costs applied in the model

	T-DXd	T-DM1
Total subsequent therapy cost per progressed patient	[redacted]	[redacted]
Proportion receiving subsequent treatment	66.7%	66.7%
Total subsequent therapy cost applied	[redacted]	[redacted]

B.3.5.4.2 Terminal care costs

A one-off terminal care cost was applied within the economic model which was assumed to cover costs of supporting patients in a palliative (end-of-life) stage before death. The same cost is applied to both treatment arms based on the proportion of patients who enter the death health state in each cycle.

The end-of-life cost was based on Round et al (2015).[161] Round et al was a modelling study estimating the cost of caring for cancer patients at the end of their life. The study reports a mean cost among four cancer types (breast, colorectal, lung and prostate). The total end of life health care cost associated with BC care was reported as £4,346 which was then uplifted to 2021 prices using the PSSRU inflation indices (£4,782).

B.3.6 Severity

While HER2-targeted treatments have improved survival outcomes in HER2+ mBC,[39] there is only one NICE-recommended therapy – T-DM1 – for patients after trastuzumab and a taxane,[32] providing a PFS of typically <10 months.[48,49] Given the importance of improving PFS and OS, there remains a clear unmet need for treatments that provide improved efficacy and outcomes for patients with HER2+ u/mBC who have previously received trastuzumab and a taxane.[50]

In line with the new NICE manual, the severity of the condition, measured by the QALY shortfall has been calculated to understand the absolute and proportional QALY shortfall associated with current standard of care, T-DM1, in patients with HER2+ u/mBC who have previously received trastuzumab and a taxane.[140] Within the new framework, differential QALY weights may be applied if the absolute or proportional shortfalls estimated lie within given cut-off ranges (see Table 50). A variety of sources have been considered to inform the total expected QALYs of patients with the disease treated with established NHS practice, T-DM1, and this was then compared to the total expected QALYs in patients with no disease to evaluate the QALY shortfall and the applicability of a QALY severity modifier. The following sources were used for T-DM1:

1. Using the base case from the economic analysis (scenarios considered in Section B.3.11.3)
2. Exploring the secondary OS analysis using Method 2 (extrapolated EMILIA data – see Section B.3.3.2.1.2 for a full description of efficacy assumed)
3. Assessing outcomes associated from the prior TA458 appraisal for T-DM1 after trastuzumab and a taxane [32]

Table 50: QALY weights referenced within the new NICE manual

QALY weight	Absolute shortfall	Proportional shortfall
1 x	Less than 12	Less than 0.85
1.2 x	12 – 18	0.85 – 0.95
1.7 x	At least 18	At least 0.95

Abbreviations: QALY, quality-adjusted life-year.

To estimate the shortfall, the Schneider et al. (2021) estimator tool was used, which was cited by NICE as a potential option for exploring the appropriateness of applying a severity modifier.[162] This tool uses the Office of National Statistics (ONS) data from England to generate the general population survival.[163] with various sources of data to inform utility estimates. Given NICE DSU guidance indicates that the EQ-5D-3L is a preferred method of capturing utility values, EQ-5D-3L data from health state profiles from the Health Survey for England (HSE) 2012 and 2014 data and the Measuring and Valuing Health Study (MVH) value set were used to estimate HRQoL and inform shortfall calculations (also recommended by the NICE DSU) as this was considered to represent a recent and robust source.[164-167]

Table 51 summarises the data used in the Schneider et al tool to calculate the base case QALY shortfall calculations.

Table 51: Summary features of QALY shortfall analysis

Factor	Value	Reference to section in submission
Sex distribution	100.0% female	Section B.3.3.1 (Table 25)
Starting age	[redacted] years	Section B.3.3.1 (Table 25)

Abbreviations: QALY, quality-adjusted life-year.

Assuming a cohort age of [redacted] and 100% female (as per the DESTINY-Breast03 study) and using the base case discounted QALYs for T-DM1 from the economic analysis (method 1 outlined above), the absolute shortfall is estimated to be [redacted] with a proportional shortfall of [redacted]. The absolute QALY shortfall values obtained from the base case meets the threshold of a QALY weight of 1.2 (see Table 52).

Table 52: Summary of QALY shortfall analysis using data from economic analysis

Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	QALY shortfall
14.63	T-DM1: [redacted] (discounted)	Absolute: [redacted] Proportional: [redacted]

Abbreviations: QALY, quality-adjusted life-year.

Assuming the same cohort age and sex distribution, but using the EMILIA replicated data to inform the QALY shortfall calculations (Method 2 above and methodology outlined in Section B.3.3.2.1.2) produced an absolute shortfall of [redacted], and a proportional shortfall of [redacted]. Within this scenario, the QALY shortfall estimates meet the 1.2x QALY weighted category, further supporting that a QALY weighting is applicable (see Table 54).

Table 53: Summary of QALY shortfall analysis using data from the EMILIA replicated data

Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	QALY shortfall
14.63	T-DM1: [redacted] (discounted)	Absolute: [redacted] Proportional: [redacted]

Abbreviations: QALY, quality-adjusted life-year; T-DM1, trastuzumab emtansine.

The final approach considered was using the information from TA458 (i.e., the relevant prior TA for the standard of care for this appraisal based on the mature EMILIA study), the estimated absolute QALY shortfall was 12.84 and the proportional shortfall was 86.00%. which, similar to the prior methods, indicates that a QALY weight of 1.2 is applicable (Table 54).

Table 54: Summary list of QALY shortfall from previous evaluations

TA	Expected total QALYs for the general population	Expected total QALYs that people living with a condition would be expected to have with current treatment	QALY shortfall
TA458	Age = 53 years 100% female QALYs = 14.93	T-DM1: 2.09	Absolute: 12.84 Proportional: 86.00%

Abbreviations: QALY, quality-adjusted life-year, TA, technology appraisal; T-DM1, trastuzumab emtansine.

The base case economic analysis (utilising data from the DESTINY-Breast03 OS extrapolations) and alternative methods explored, consistently demonstrate that a 1.2x QALY weight is appropriate for decision making in this appraisal. In addition, scenario analysis demonstrates that the majority meet the 1.2x QALY weight showing robustness to different assumptions (see Section B.3.11.3). Hence, the methods explored provide rationale that a 1.2x QALY weight is appropriate for decision making in this appraisal.

Table 55 presents the health state values used to calculate the base case QALY shortfall analysis.

Table 55: Summary of health state benefits and utility values for QALY shortfall analysis

State	Utility value	Undiscounted life years
Progression-free	[redacted]	[redacted]
Progressed	0.5738	[redacted]

Abbreviations: QALY, quality-adjusted life-year.

B.3.7 Uncertainty

In the first interim analysis of DESTINY-Breast03, T-DXd demonstrated a highly statistically significant reduction in progression vs. T-DM1 (HR = 0.2840, p<0.001) which is consistent across subgroups. Clinical experts have described the efficacy of T-DXd in DESTINY-Breast03 as “unprecedented”, and that it will lead to a “paradigm shift in the treatment of HER2+ mBC”.[109]

While T-DXd has also demonstrated a substantial gain in survival vs. T-DM1, overall survival is still relatively immature resulting in uncertainty in the long-term outcomes. The model base case has been informed by clinical and health economic expert opinion as well as external validation and exploration of uncertainty through the use of alternative mature data. This approach incorporating more mature data supported the extrapolations used in the model base case.

Extensive sensitivity analyses have also been performed to test the structural and parameter uncertainty with a summary of components and approaches tested provided in Table 56 (see Section B.3.11 for results). More conservative assumptions continue to demonstrate the clinical and cost-effectiveness of T-DXd vs. T-DM1.

Table 56: Summary of variables applied and tested in economic model

Component	Parameter grouping	Tested in OWSA?	Tested in PSA?	Testing in Scenario analysis?
Model settings	Time horizon			✓
	Cycle length			
	Discount rates			✓
Patient characteristics	Patient age	✓	✓	
	Patient weight	✓	✓	
Efficacy	OS		✓	✓
	PFS		✓	✓
	TTD		✓	✓
Safety	AE rates	✓	✓	
Utilities	Progression-free	✓	✓	
	Progressed	✓	✓	
	AE disutilities			✓
Costs	Drug costs			
	Administration costs	✓	✓	
	Resource use costs	✓	✓	
	AE costs	✓	✓	
	Subsequent treatment assumptions			✓
	Subsequent treatment costs	✓	✓	✓
	EOL costs	✓	✓	

Abbreviations: AE, Adverse event; EOL, end-of-life; OS, overall survival; OWSA, one-way sensitivity analysis; PFS, progression-free survival; PSA, probabilistic sensitivity analysis; TTD, time-to-treatment discontinuation.

B.3.8 Managed access proposal

Daiichi Sankyo consider the Phase III RCT DESTINY-Breast03 (comparing T-DXd with the relevant UK standard of care after trastuzumab and a taxane, T-DM1) to be a suitable basis for a routine commissioning decision.

B.3.9 Summary of base-case analysis inputs and assumptions

B.3.9.1 Summary of base-case analysis inputs

In line with the NICE reference case, the analysis was conducted from the NHS and PSS perspective using a lifetime horizon (30 years) and with costs and QALYs discounted at 3.5% (see Section B.3.2). Table 57 summarises base case variables and ranges used for probabilistic and one-way sensitivity analysis.

Table 57: Summary of base case variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Patient characteristics			
Age	[redacted] (Table 25)	Not varied	Section B.3.2.1
% female	99.6% (Table 25)	Not varied	
BSA	1.65 (Table 25)	1.33 – 1.97 (Normal)	
Weight	[redacted] kg (Table 25)	[redacted] (Log-normal)	
Efficacy			
T-DXd/T-DM1 curves - OS	Generalised gamma	Multinormal distribution	Section B.3.3.2
T-DXd curves - PFS	Weibull		
T-DXd curves - TTD	Weibull		
T-DM1 curves - PFS	Weibull		
T-DM1 curves - TTD	Weibull		
Utilities			
DB03 T-DXd PFS utility	[redacted] (Table 41)	[redacted] (Beta)	Section B.3.4.1
DB03 T-DM1 PFS utility	[redacted] (Table 41)	[redacted] (Beta)	
Lloyd et al 2006 – PF responder	0.85 (Table 38)	0.65 – 0.97 (Beta)	Section B.3.4.3
Lloyd et al 2006 – PD responder	0.64 (Table 38)	0.51 – 0.76 (Beta)	
Lloyd et al 2006 – PF non responder	0.79 (Table 38)	0.61 – 0.92 (Beta)	
Lloyd et al 2006 – PD non responder	0.54 (Table 38)	0.43 – 0.65 (Beta)	
T-DXd - % responders	80% (Table 38)	74.30% - 84.40% (Beta)	
T-DM1 - % responders	34% (Table 38)	28.50% - 40.30% (Beta)	
Drug costs			
T-DXd - 100 mg	£1,455.00 (Table 42) [redacted]	Not varied	Section B.3.5.1.1 and Appendix K
T-DM1 - 100 mg	£1,641.01 (Table 42)	Not varied	
T-DM1 - 160 mg	£2,625.62 (Table 42)	Not varied	
Trastuzumab - 600 mg	£1,222.20 (Appendix K)	Not varied	
Trastuzumab - 150 mg	£366.65 (Appendix K)	Not varied	
Trastuzumab - 420 mg	£1,026.65 (Appendix K)	Not varied	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Pertuzumab - 420 mg	£2,395.00 (Appendix K)	Not varied	
Paclitaxel - 100 mg	£8.06 (Appendix K)	£7.96 - £8.16 (Normal)	
Paclitaxel - 150 mg	£10.15 (Appendix K)	£10.12 - £10.18 (Normal)	
Paclitaxel - 300 mg	£15.97 (Appendix K)	£15.92 - £16.02 (Normal)	
Paclitaxel - 30 mg	£4.15 (Appendix K)	£3.23 - £5.08 (Normal)	
Tamoxifen - 10 mg	£4.20 (Appendix K)	£4.08 - £4.33 (Normal)	
Tamoxifen - 20 mg	£7.07 (Appendix K)	Not varied	
Tamoxifen - 40 mg	£76.72 (Appendix K)	Not varied	
Capecitabine - 150 mg	£4.43 (Appendix K)	£4.40 - £4.45 (Normal)	
Capecitabine - 300 mg	£7.77 (Appendix K)	£7.70 – £7.83 (Normal)	
Capecitabine - 500 mg	£26.30 (Appendix K)	£26.21 - £26.40 (Normal)	
T-DXd - RDI	[redacted]	[redacted]	Section B.3.5.1.1
T-DM1 - RDI	[redacted]	[redacted]	
Admin cost – simple infusion	£221.35	£177.96 - £264.73 (Normal)	Section B.3.5.1.1
Adverse events			
T-DXd - Anaemia	5.84% (Table 33)	3.32% - 9.01% (Beta)	Section B.3.3.3
T-DXd - Fatigue	5.06% (Table 33)	2.73% - 8.04% (Beta)	
T-DXd - Interstitial lung disease (any grade)	10.51% (Table 33)	7.07% - 14.53% (Beta)	
T-DXd - Left ventricular ejection fraction decrease (any grade)	1.95% (Table 33)	0.64% - 3.95% (Beta)	
T-DXd - Nausea	6.61% (Table 33)	3.92% - 9.95% (Beta)	
T-DXd - Neutropenia	19.07% (Table 33)	14.51% - 24.08% (Beta)	
T-DXd - Thrombocytopenia	7.00% (Table 33)	4.22% - 10.42% (Beta)	
T-DXd - Leukopenia	6.61% (Table 33)	3.92% - 9.95% (Beta)	
T-DM1 - Anaemia	4.21% (Table 33)	2.13% - 6.96% (Beta)	
T-DM1 - Fatigue	0.77% (Table 33)	0.09% - 2.12% (Beta)	
T-DM1 - Interstitial lung disease (any grade)	1.92% (Table 33)	0.63% - 3.89% (Beta)	
T-DM1 - Left ventricular ejection fraction decrease (any grade)	0.38% (Table 33)	00.01% - 1.41% (Beta)	
T-DM1 - Nausea	0.38% (Table 33)	0.01% - 1.41% (Beta)	
T-DM1 - Neutropenia	3.07% (Table 33)	1.34% - 5.47% (Beta)	
T-DM1 - Thrombocytopenia	24.90% (Table 33)	19.86% - 30.32% (Beta)	
T-DM1 - Leukopenia	0.38% (Table 33)	0.0% - 1.41% (Beta)	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Anaemia - cost	£557.98 (Table 46)	£448.62 - £667.34 (Normal)	Section B.3.5.3
Fatigue - cost	£44.00 (Table 46)	£35.38 - £52.62 (Normal)	
Interstitial lung disease (any grade) - cost	£3,401.08 (Table 46)	£2,734 .48- £4,068.68 (Normal)	
Left ventricular ejection fraction decrease (any grade) - cost	£505.68 (Table 46)	£406.57 - £604.80 (Normal)	
Nausea - cost	£467.06 (Table 46)	£375.52 - £558.61 (Normal)	
Neutropenia - cost	£641.11 (Table 46)	£515.46 - £766.77 (Normal)	
Thrombocytopenia - cost	£735.96 (Table 46)	£591.72 - £880.21 (Normal)	
Leukopenia - cost	£641.11 (Table 46)	£515.46 - £766.77 (Normal)	
Resource use			
Terminal care	£4,782 (page 127)	£3,844.88 - £5,719.45 (Normal)	Section B.3.5.4.2
RU - PF - Medical oncologist	0.23 (Table 45)	0.18 - 0.28 (Normal)	Section B.3.5.2
RU - PF - GP contact	0.23 (Table 45)	0.18 - 0.28 (Normal)	
RU - PF - CT scan	0.08 (Table 45)	0.06 - 0.09 (Normal)	
RU - PF - Community nurse	0.50 (Table 45)	0.40 - 0.60 (Normal)	
RU - PF - Clinical nurse specialist	0.23 (Table 45)	0.18 - 0.28 (Normal)	
RU - PF - LVEF follow-up	0.08 (Table 45)	0.06 - 0.09 (Normal)	
RU - PD - Medical oncologist	0.23 (Table 45)	0.18 - 0.28 (Normal)	
RU - PD - GP contact	0.23 (Table 45)	0.18 - 0.28 (Normal)	
RU - PD - CT scan	0.08 (Table 45)	0.06 - 0.09 (Normal)	
RU - PD - Community nurse	0.50 (Table 45)	0.4 - 0.6 (Normal)	
RU - PD - Clinical nurse specialist	0.23 (Table 45)	0.18 - 0.28 (Normal)	
RU - PD - LVEF follow-up	0.08 (Table 45)	0.06 - 0.09 (Normal)	
RU - unit cost - Medical oncologist	£201.33 (Table 45)	£161.87 - £240 79 (Normal)	
RU - unit cost - GP contact	£39.23 (Table 45)	£31.54 - £46.92 (Normal)	
RU - unit cost - CT scan	£88.31 (Table 45)	£71.00 - £105.62 (Normal)	
RU - unit cost - Community nurse	£25.00 (Table 45)	£20.10 - £29.90 (Normal)	
RU - unit cost - Clinical nurse specialist	£88.00 (Table 45)	£70.75- £105.25 (Normal)	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
RU - unit cost - LVEF follow-up	£140.03 (Table 45)	£112.58 - £167.47 (Normal)	
Subsequent treatment			
Sub trt - T-DXd - Trastuzumab	[redacted] (Table 48)	Not varied in OWSA. Dirichlet used for PSA	Section B.3.5.4.1
Sub trt - T-DXd - T-DXd	[redacted] (Table 48)		
Sub trt - T-DXd - T-DM1	[redacted] (Table 48)		
Sub trt - T-DXd - Pertuzumab	[redacted] (Table 48)		
Sub trt - T-DXd - Taxane	[redacted] (Table 48)		
Sub trt - T-DXd - Trastuzumab + taxane	[redacted] (Table 48)		
Sub trt - T-DXd - Anti-HER2	[redacted] (Table 48)		
Sub trt - T-DXd - Hormone therapy	[redacted] (Table 48)		
Sub trt - T-DXd - Other (capecitabine)	[redacted] (Table 48)		
Sub trt - T-DM1 - Trastuzumab	[redacted] (Table 48)	Not varied in OWSA. Dirichlet used for PSA	
Sub trt - T-DM1 - T-DXd	[redacted] (Table 48)		
Sub trt - T-DM1 - T-DM1	[redacted] (Table 48)		
Sub trt - T-DM1 - Pertuzumab	[redacted] (Table 48)		
Sub trt - T-DM1 - Taxane	[redacted] (Table 48)		
Sub trt - T-DM1 - Trastuzumab + taxane	[redacted] (Table 48)		
Sub trt - T-DM1 - Anti-HER2	[redacted] (Table 48)		
Sub trt - T-DM1 - Hormone therapy	[redacted] (Table 48)		
Sub trt - T-DM1 - Other (capecitabine)	[redacted] (Table 48)		
T-DXd - Proportion receiving subsequent treatment	66.67% (Table 48)	53.03% - 79.02% (Beta)	
T-DM1 - Proportion receiving subsequent treatment	66.67% (Table 48)	53.03% - 79.02% (Beta)	

Abbreviations: BSA, body surface area; CT, computerised tomography; GP, general practitioner; LVEF, Left ventricular ejection fraction; OS, overall survival; PD, progressed disease; PF, progression-free; PFS, progression-free survival; Sub trt, subsequent treatment; TTD, time to treatment discontinuation; RDI, relative dose intensity; RU, resource use.

B.3.9.2 Assumptions

Assumptions underlying the base case analysis are summarised in Table 58. The table also outlines a summary of how each assumption was tested in sensitivity or scenario analyses.

Table 58: Summary of key model assumptions

Topic	Assumption	Justification/reason	Sensitivity
Cycle length	Model cycle length of 1 week	A weekly cycle length is assumed to be sufficiently short to represent the frequency of clinical events and interventions. Further, one week is aligned with the administration of the multiple subsequent treatments included within the model (treatment cycles in weeks)	Not tested
Time horizon	A lifetime horizon of 30 years	Reflects the lifetime of patients based on a starting age of [redacted]. Less than 1.5% are alive after this time horizon	**Scenario analysis** The impact of alternative time horizons on the results was tested
Efficacy	Direct extrapolation of DESTINY-Breast03 is the most appropriate OS approach for the base case	Uses available data from a head-to-head randomised control trial vs the relevant comparator. Validated by clinical and economic experts as the preferred approach	**Scenario Analysis** Alternative OS method utilising mature OS data from the EMILIA trial which is considered generalisable to UK practice and DESTINY-Breast03 study
	Dependent models are appropriate for OS	Log cumulative hazard plots and proportionality test showed support for the proportional hazard assumption. Using dependent models also allows more data to be used for the parametric models	NA
	Independent models are appropriate for PFS and TTD	Log cumulative hazard plots and proportionality test rejected the assumption of proportional hazards. In addition, given the availability of patient-level data for each treatment and maturity of the data, the reliance on the proportional hazard assumption was considered unnecessary and therefore, independent models were considered more appropriate. TTD approach consistent with PFS as majority of discontinuations were due to progression	NA
	Identification of the most appropriate survival curves describing OS, PFS and TTD	Extensive analyses have been undertaken to identify appropriate survival curves describing the long-term efficacy of each treatment, with reference to the guidance from the NICE DSU. The approach and	**Scenario Analysis** Evaluation of clinically plausible alternative extrapolations **PSA**

Topic	Assumption	Justification/reason	Sensitivity
		identified survival extrapolations have been validated by clinical experts and external data	Variation of base case distribution parameters via variance co-variance matrix
Utilities	Utility values were assumed to differ by treatment arm and health state	Direct EQ-5D data collected within DB03 show a difference between treatment arms in utilities in both *'progression-free'* and *'progressed'* health states. This may be due to the higher response rates. Based on the response rates of T-DXd and T-DM1, utility values are expected to be greater for T-DXd which is demonstrated by the observed direct evidence from DESTINY-Breast03. Patients on T-DXd are expected to have greater utility when progressing which follows into the progression health state. Similar assumptions have been made in prior appraisals	**Scenario Analysis** Use of alternative utility sources and alternative assumptions around treatment-specific utility differences **OWSA, PSA** Variation of utility value through confidence intervals
Vial sharing	50% of centres vial share and therefore have no wastage	Clinical experts during the TA458 appraisal noted that some centres do vial share and therefore 100% wastage is not reflective of current practice. In line with assumptions made in TA704, 50% was assumed as this was accepted by the committee	**Scenario analysis** 0% and 100% vial sharing tested in scenario analysis **OWSA, PSA** OWSA and assuming a beta distribution
Subsequent treatments	66.7% of patients who progress will receive subsequent treatments	Clinical opinion at expert validation meeting that two-thirds of patients who progress will receive subsequent treatments in UK practice	**Scenario Analysis** Alternative values based on the DESTINY-Breast03 study **OWSA and PSA** Varied across confidence interval and assuming a beta distribution
	Subsequent treatments from DB03 are costed	The trial was considered generalisable to UK practice, and without adjusting OS efficacy for alternative subsequent treatments, aligning with the trial was considered the most appropriate way of costing subsequent treatments within the model base case	**Scenario analysis** Alternative subsequent treatment proportions based on clinical expert advice **OWSA and PSA** Varied across confidence interval and assuming a Dirichlet distribution

Topic	Assumption	Justification/reason	Sensitivity
	Subsequent treatments listed as 'Other' in DB03 are costed as capecitabine	In line with clinical practice as capecitabine is the most common non-targeted chemotherapy used in third-line HER2+ mBC	**OWSA and PSA** Varied across confidence interval and assuming a Dirichlet distribution

Abbreviations: DB03, DESTINY-Breast03; OS, overall survival; OWSA, one-way sensitivity analysis; PFS, progression-free survival; PSA, probabilistic sensitivity analysis; TTD, time to treatment discontinuation.

B.3.10 Base-case results

B.3.10.1 Base-case incremental cost-effectiveness analysis results

The base case deterministic cost-effectiveness results for T-DXd vs. T-DM1 are presented in Table 59 (at the PAS price). The results demonstrate that, compared with T-DM1, T-DXd is associated with LY and QALY gains of [redacted] and [redacted], respectively. This suggests a substantial improvement in survival and quality-of-life in the mBC setting. This benefit is associated with incremental costs of [redacted] per patient over a lifetime translating into an ICER of [redacted]. Table 60 presents the net-health benefit (NHB) at the £20,000/QALY and £30,000/QALY willingness-to-pay (WTP) thresholds.

As discussed in Section B.3.6, based on the calculated QALY shortfall, this appraisal meets criteria for the severity modifier with a QALY weighting of 1.2. Deterministic base case results are presented including and excluding the 1.2x QALY weighting (Table 59 and Table 60). Application of the 1.2x QALY weight results in an incremental QALY gain of [redacted] and an ICER of [redacted]. Alternatively, the 1.2x QALY weighting also translates into a WTP threshold of £36,000/QALY and so consideration of this threshold has been described in all sensitivity and scenario analyses.

Results demonstrate that at a WTP threshold of £30,000/QALY, when applying the severity modifier, the NHB is greater than zero and thus the introduction of T-DXd would increase the overall population health. This demonstrates that T-DXd is a cost-effective use of NHS resources.

Table 59: Base-case results (with PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs (x1.2 modifier)	ICER vs. baseline (x1.2 modifier)
T-DM1	[redacted]	[redacted]	[redacted]				
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years.

Table 60: Net health benefit (with PAS)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs (x1.2 modifier)	NHB at £20,000 (x1.2 modifier)	NHB at £30,000 (x1.2 modifier)
T-DM1	[redacted]	[redacted]				
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years; NHB, net health benefit.

B.3.11 Exploring uncertainty

B.3.11.1 Probabilistic sensitivity analysis

Joint parameter uncertainty was explored through probabilistic sensitivity analysis (PSA) where all parameters are assigned probability distributions and varied jointly (see Table 57). PSA was run for 10,000 iterations, by which point, results had stabilised and therefore considered reliable to explore the uncertainty.

The mean results from the probabilistic analysis are presented in Table 61 and the cost-effectiveness plane (CE-plane) in Figure 35. The probabilistic results show consistency with the deterministic analysis providing a mean QALY gain of [redacted] at an incremental cost of [redacted], resulting in a probabilistic ICER of [redacted]. All iterations in the CE-plane remain within the North-East quadrant demonstrating a positive QALY gain and confirming the clinical benefit of T-DXd vs. T-DM1 when parameter uncertainty is evaluated. Probabilistic results confirm that T-DXd is a cost-effective use of NHS resources at the £30,000/QALY and £36,000/QALY WTP thresholds and results are consistent with the deterministic evaluation.

Table 61: Mean PSA results (with PAS)

Technologies	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
T-DM1	[redacted]	[redacted]	[redacted]				
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient-access scheme; QALYs, quality-adjusted life years.

Figure 35: Cost-effectiveness plane – T-DXd vs. T-DM1

Abbreviations: PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year.

Figure 36 presents the cost-effectiveness acceptability curve for T-DXd vs. T-DM1. At a WTP threshold of £30,000/QALY and £36,000/QALY the probability that T-DXd is the cost-effective treatment option is [redacted] and [redacted], respectively.

Figure 36: Cost-effective acceptability curve (with PAS)

B.3.11.2 Deterministic sensitivity analysis

One-way sensitivity analysis (OWSA) was conducted to test the impact of individual parameters when their values are set to the lower and upper limits of the confidence intervals (presented in Table 57) while all other parameters are maintained at the base case setting. If the variance in any inputs was not available, a simplified assumption was made assuming that the standard error was 10% of the mean value. Table 62 and Figure 37 present the ICERs and the tornado plot showing the 10 parameters which had the largest impact on the ICER.

Utility values for the *'progressed disease'* health state had the largest impact on the ICER followed by the proportion of patients receiving subsequent treatments. Other parameters had a marginal impact on the ICER when varied between their upper and lower bounds. For all scenarios, T-DXd remained cost-effective at the £30,000/QALY and £36,000/QALY thresholds.

Table 62: OWSA results (with PAS)

Parameter	ICER at lower bound	ICER at upper bound
Lloyd 2006: PD - original responders	[redacted]	[redacted]
Lloyd 2006: PD - original non-responders	[redacted]	[redacted]
T-DM1 - Proportion receiving subsequent treatment	[redacted]	[redacted]
T-DXd - Proportion receiving subsequent treatment	[redacted]	[redacted]
RDI - T-DXd	[redacted]	[redacted]
RU - unit cost - Medical oncologist	[redacted]	[redacted]
DB03 PFS T-DXd utility	[redacted]	[redacted]
Sub trt - duration (weeks) - T-DM1	[redacted]	[redacted]
Administration cost - simple infusion	[redacted]	[redacted]
RU - PF - Medical oncologist	[redacted]	[redacted]

Abbreviations: DB03, DESTINY-Breas03; ICER, incremental cost-effectiveness ratio; OWSA, one-way sensitivity analysis; PD, progressed disease; PF, progression-free; PFS, progression-free survival; RDI, relative dose intensity; RU, resource use; Sub trt, subsequent treatment.

Figure 37: Tornado plot showing OWSA results on the ICER (with PAS)

Abbreviations: DB03, DESTINY-Breast03; ICER, incremental cost-effectiveness ratio; OWSA, one-way sensitivity analysis; PD, progressed disease; PF, progression-free; PFS, progression-free survival; RDI, relative dose intensity; RU, resource use; Sub trt, subsequent treatment.

B.3.11.3 Scenario analysis

The key scenario analysis where an alternative OS approach utilising data from the mature EMILIA study (see Section B.3.3.2.1.2) is presented in Table 63 and Table 64. Results using this alternative OS approach demonstrate that T-DXd is cost-effective at the £30,000/QALY and £36,000/QALY thresholds.

Other scenario analyses were performed in order to test key structural and inputs assumptions. Results of the scenario analysis are presented in Table 65 with an indication of whether each scenario meets the criteria for the 1.2x QALY weighting translating to a WTP threshold of £36,000/QALY. In the case of OS, PFS and TTD survival curves, only curves considered clinically plausible (as validated by clinical experts and external data) were included in scenario analysis (see Section B.3.3.2). Furthermore, any curve which crossed

with another curve at an implausible timepoint was also excluded, this captures the following rules:

- If T-DXd and T-DM1 PFS or OS curves cross each other (between treatment arms)
- If T-DXd or T-DM1 PFS crosses with the OS curve (within treatment arms)
- If T-DXd or T-DM1 TTD crosses with the PFS curve (within treatment arms)

The results of the scenarios analyses are presented together within the cost-effectiveness plane (Figure 38). The results show that for all plausible scenarios explored, T-DXd remains cost-effective under the £30,000/QALY and £36,000/QALY thresholds. The majority of scenarios also meet the 1.2x QALY weighting threshold reinforcing that T-DXd meets the criteria for the severity modifier. Scenario results demonstrate the robustness of the base case results.

Table 63: Key scenario analysis: EMILIA + HR OS approach (with PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs (x1.2 modifier)	ICER vs. baseline (x1.2 modifier)
T-DM1	[redacted]	[redacted]	[redacted]				
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years.

Table 64: Key scenario analysis: EMILIA + HR OS approach - Net health benefit (with PAS)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs (x1.2 modifier)	NHB at £20,000 (x1.2 modifier)	NHB at £30,000 (x1.2 modifier)
T-DM1	[redacted]	[redacted]				
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years; NHB, net health benefit.

Table 65: Scenario analysis (with PAS)

Parameter	Base case	Scenario	Incremental costs	Incremental QALYs	ICER	Difference from base case	x1.2 QALY weighting threshold met
Base case			[redacted]	[redacted]	[redacted]	**-**	**Yes**
Time horizon	30 years	20 years	[redacted]	[redacted]	[redacted]	£356	Yes
		40 years	[redacted]	[redacted]	[redacted]	-£49	Yes
Discount rates	Costs and health effects = 3.5%	1.5%	[redacted]	[redacted]	[redacted]	-£692	No
Utility source*	PFS = DB03 (treatment specific) PD = Lloyd et al (treatment specific)	PFS = Lloyd et al – treatment specific utilities PD = Lloyd et al – treatment specific utilities	[redacted]	[redacted]	[redacted]	-£422	Yes
		PFS = Lloyd et al – combined utilities PD = Lloyd et al – combined utilities	[redacted]	[redacted]	[redacted]	£2,481	Yes
		PFS = DB03 utilities combined PD = Lloyd et al combined	[redacted]	[redacted]	[redacted]	£2,696	Yes
Disutilities	Excluded	Included	[redacted]	[redacted]	[redacted]	£18	Yes
Age-related disutilities	Included	Excluded	[redacted]	[redacted]	[redacted]	-£742	Yes
RDI	Included	Excluded	[redacted]	[redacted]	[redacted]	£2,453	Yes
Proportion vial sharing	50%	0%	[redacted]	[redacted]	[redacted]	£1,573	Yes
		100%	[redacted]	[redacted]	[redacted]	-£1,573	Yes
Subsequent treatment distributions	DB03 data	UK practice	[redacted]	[redacted]	[redacted]	£757	Yes
		DB03 pooled	[redacted]	[redacted]	[redacted]	£734	Yes

Parameter	Base case	Scenario	Incremental costs	Incremental QALYs	ICER	Difference from base case	x1.2 QALY weighting threshold met
Base case			[redacted]	[redacted]	[redacted]	**-**	**Yes**
Subsequent treatment proportions	UK practice	DB03 data	[redacted]	[redacted]	[redacted]	-£2,236	Yes
		DB03 pooled	[redacted]	[redacted]	[redacted]	-£534	Yes
Subsequent treatments T-DXd and T-DM1	Include costs	Exclude costs	[redacted]	[redacted]	[redacted]	-£692	Yes
OS plausible extrapolations	Generalised gamma	Log-logistic	[redacted]	[redacted]	[redacted]	-£55	No
		Weibull	[redacted]	[redacted]	[redacted]	£1,879	Yes
PFS plausible extrapolations	Weibull	Log-logistic	[redacted]	[redacted]	[redacted]	-£1,705	Yes
		Log-normal	[redacted]	[redacted]	[redacted]	-£2,623	Yes
		Exponential	[redacted]	[redacted]	[redacted]	-£1,979	Yes
TTD extrapolations	Weibull	Gompertz	[redacted]	[redacted]	[redacted]	-£4,127	Yes
OS (EMILIA + HR)	OS = log-normal	Generalised gamma	[redacted]	[redacted]	[redacted]	-£2,836	Yes
		Log-logistic	[redacted]	[redacted]	[redacted]	-£2,081	Yes
		Weibull	[redacted]	[redacted]	[redacted]	£3,193	Yes

Abbreviations: DB03, DESTINY-Breast03; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; PD, progressed disease; PFS, progression-free survival; QALYs, quality adjusted life-years; RDI, relative dose intensity; TTD, time to treatment discontinuation.
Note: * Source applicable for both PFS and PD utility values

Figure 38: Cost-effectiveness plane for the scenario analysis (based on results with PAS)

Abbreviations: WTP, willingness-to-pay; QALYs, quality-adjusted life-years.

B.3.12 Subgroup analysis

A consistent treatment effect was observed in all subgroups in DESTINY-Breast03 (see Figure 13), therefore subgroup analyses were not considered relevant for the economic analysis.

B.3.13 Benefits not captured in the QALY calculation

HER2+ mBC has a considerable impact on patients' quality of life and their ability to conduct usual activities (Section B.1.3.2). The majority of patients diagnosed with mBC are of working age with the impact of disease and effects of treatment having substantial consequences on productivity and ability to work. A recent study investigating the relationship between disease and treatment stage found that metastatic patients had lower employment rates in comparison to early BC after surgery or adjuvant therapy (27.5% vs 50.6% or 50.9%, respectively).[20] The study also found that metastatic patients most often reported not being able to attend work and that poor HRQoL was significantly associated with high work impairment ($p<0.001$). The results of this study support the premise that being able to delay or prevent the metastatic recurrence of breast cancer, for example by extending the time patients are in remission, has wider benefits in terms of patient productivity. Although the EQ-5D has a 'Usual activities' domain which refers to elements such as work, family activities or leisure activities, the questionnaire is unable to detect the more subtle differences in HRQoL which may impact a patients' ability to attend work and productivity when at work. In addition, the wider societal and economic impact of disease for these patients is unable to be captured in the current EQ-5D-5L framework.

Caregivers of patients with mBC are also impacted by the disease which is not captured within the QALY calculation. As a consequence of the psychological and economic strain

associated with caring for someone with the disease, caregivers may overlook their own needs, resulting in decreased wellbeing and an increase in symptoms of stress (Section B.1.3.2.5). Caring for a patient with mBC can also impact a caregiver's work, leading to financial strain and increased indirect economic costs.[79] A treatment that allows patients to lead a near normal life for longer by improving response rates and reducing progression rates will therefore substantially improve caregiver and patient quality of life and productivity.

There is a large unmet need for effective HER2-targeted therapies as outcomes for patients with aggressive, HER2+ u/mBC have not advanced since T-DM1 was introduced to UK clinical practice in 2014. While HER2-targeted treatments have improved survival outcomes in HER2+ BC,[39] an unmet need remains for improved survival outcomes – both PFS and OS – for patients who have received trastuzumab and a taxane.[50] Treatments shown to increase PFS are highly valued by patients with incurable breast cancer, but where possible, should provide efficacy without the high levels of toxicity imposed by chemotherapy.[16,100]

DESTINY-Breast03 demonstrated that T-DXd significantly improves response rates, progression-free and overall survival, which would inherently allow more patients to perform their usual activities including the ability to work. As such, T-DXd not only greatly improves patients overall QALYs (see Section B.3.10) but can also have a substantial benefit in terms of societal gains and economic production as well as cover the unmet need for more effective and tolerable HER2+ targeted therapies.

T-DXd is an innovative treatment based on its potential to make a significant and substantial impact on health-related benefits, representing a step-change in management vs. T-DM1. [redacted]

B.3.14 Validation

B.3.14.1 Independent technical cost-effectiveness model QC

The cost-effectiveness model was quality assured by a senior health economist not involved in the model building who reviewed the model for coding errors, inconsistencies, and plausibility of inputs and outputs. The model was also subject to stress testing of extreme scenarios to test for technical modelling errors and plausibility of results

B.3.14.2 Expert validation of cost-effectiveness analysis

Clinical validation was sought for the cost-effectiveness analysis consisting of a UK expert validation meeting.

The UK expert validation meeting was held in February 2022 and consisted of two clinical experts and two HEOR experts. The two clinical experts were leading breast cancer medical oncologists from different centres in the UK and provided clinical input into the modelling assumptions and outputs. The two HEOR experts were from UK universities with relevant and vast experience in health economics methods. Both were past or present NICE committee members and provided input and validation of health economic methodology applied in the economic modelling given the available data.

The following key aspects were discussed and validated:

- DESTINY-Breast03 trial generalisability, efficacy and safety

- Generalisability of external data sources
- UK treatment pathway
- The model structure and appropriateness to the decision problem
- Overall survival methods
- Extrapolation of OS and PFS beyond the observed period
- Validity of model inputs including resource use, costs and utilities
- Subsequent treatment usage

Feedback from the clinical validation meeting has been used throughout the dossier and referenced where appropriate.

B.3.14.3 Internal validation

PFS, OS and TTD Kaplan-Meier data from DESTINY-Breast03 trial were compared with the PFS, OS and TTD outputs from the model (see Appendix J).

For both T-DXd and T-DM1, the model survival projections appear in line with the observed trial data for all outcomes; OS, PFS and TTD.

B.3.14.4 External validation

External data sources reporting OS and PFS outcomes of T-DM1 in other trials with longer follow-up have been used to compare the modelled outcomes from DESTINY-Breast03:

- EMILIA was a Phase III study which compared T-DM1 with lapatinib plus capecitabine in patients with HER2+ advanced BC who had previously been treated with trastuzumab and a taxane.[48] The EMILIA study has a median follow-up 47.8 months and reports mature OS data. The trial was considered generalisable to UK clinical practice by clinical experts in TA458[146] and at an expert validation meeting undertaken by Daiichi Sankyo.[46]
- KATE2 was a randomised placebo-controlled Phase II study comparing T-DM1 plus atezolizumab vs. T-DM1 plus placebo in HER2+ patients with advanced BC previously treated with trastuzumab and a taxane. Median follow-up of 8.4 months for the T-DM1 arm although median OS was not estimable.
- KAMILLA was a Phase IIIb study of T-DM1 in patients with HER2+ locally advanced or mBC with prior HER2-targeted therapy and chemotherapy. The study has median follow-up of 20.6 months and reports both PFS and OS.[87]

Figure 39 and Figure 40 present the base case T-DM1 progression-free and overall survival curves extrapolated from DESTINY-Breast03 compared with the external sources listed above. As discussed in Section B.3.14.3, the modelled outcomes are consistent with the observed outcomes in DESTINY-Breast03 as well as considered clinically plausible in the long-term from the clinical validation meeting.[46]

For PFS (Figure 39), the modelled outcomes from DESTINY-Breast03 are aligned with the observed external data sources until just after one-year, after which they appear to best follow KAMILLA. Compared to the EMILIA study, a difference in PFS is seen in the observed KM curves where EMILIA shows higher PFS through the observed period. This difference could be due to a number of factors, mainly relating to changes in overall clinical care since

the EMILIA study was conducted between 2009 and 2011. For example, earlier diagnosis and the availability of better, more efficacious, treatment options at earlier lines, in the adjuvant and metastatic settings, in current practice could provide better outcomes including delayed progression and prolonging of life for patients in these settings. This, in turn, could lead to poorer outcomes when initiating later lines of treatment as delayed progression may mean patients are less well or have poorer performance resulting in differences in PFS compared with older trials. Further, a greater proportion of patients in DESTINY-Breast03 received two or more lines of treatment than in EMILIA (see Table 28) which is associated with lower PFS. Observed PFS data from DESTINY-Breast03 are consistent with KAMILLA and KATE2 which were both conducted more recently.

The choice of base case PFS curve in the model was based on the longer-term 5- and 10-year outcomes expected in clinical practice as advised by UK clinical experts. Implausible curves not aligned to clinical expectations were ruled out while alternative plausible extrapolations are tested in scenario analysis. Overall, the modelled PFS outcomes are considered to be aligned with clinical expectations and current practice.

Figure 39: External validation – T-DM1 – PFS

Abbreviations: ITT, intention to treat; KM, Kaplan-Meier; PFS, progression-free survival

For T-DM1, the modelled OS (Figure 40) outcomes appear similar to the external data although slightly higher over time. It is anticipated that the better OS in the modelled T-DM1 arm is a result of the availability of more effective subsequent therapies within the third-line and beyond setting in current practice (and consequently in DESTINY-Breast03). Notably, in DESTINY-Breast03, [redacted]% of patients received T-DXd as subsequent therapy after T-DM1 which was not available when the EMILIA, KATE2 and KAMILLA studies were conducted. This is consistent with clinical practice given changes in the UK treatment pathway for mBC, for example the availability of T-DXd and tucatinib in the third-line and beyond. Therefore, overall survival could be expected to be improved than was observed within EMILIA and the other prior studies. UK clinicians consulted by Daiichi Sankyo advised that EMILIA is a

generalisable trial where outcomes are similar to UK practice, with differences in OS likely a result of changes in treatment practice, particularly the availability of more effective HER2-targeted subsequent therapies. As such, the modelled OS outcomes are considered to be in line with expectations. To mitigate uncertainty associated OS and naïve comparisons to external data, the alternative OS method (see Section B.3.3.2 for details) was conducted using replicated EMILIA data which incorporates external data into the economic analysis via a more formal mechanism. This approach produced extrapolated outcomes similar to the observed KM for T-DM1 in DESTINY-Breast03 further validating the base case extrapolations.

Figure 40: External validation – T-DM1 – OS

Abbreviations: ITT, intention to treat; KM, Kaplan-Meier; OS, overall survival

B.3.15 Interpretation and conclusions of economic evidence

DESTINY-Breast03 is a randomised controlled Phase III trial in the relevant population directly comparing T-DXd to the relevant comparator and was considered generalisable to UK clinical practice. The efficacy benefit indicates a substantial improvement in clinical outcomes with T-DXd compared with T-DM1 (PFS HR 0.28; 95% CI: 0.22, 0.37); an outcome which clinicians have described as ‘unprecedented’ in the mBC setting.

The economic analysis is based on a *de novo* economic model with a structure designed to reflect the natural history of u/m HER2+ BC. The model structure is consistent with prior breast cancer appraisals and brings together the most relevant clinical efficacy and safety data.

In line with the new NICE manual, the severity of the condition was assessed by calculating the QALY shortfall to understand the absolute and proportional QALY shortfall associated with T-DM1 in HER2+ mBC versus the general population. Calculations showed that this appraisal met the threshold for a QALY weighting of 1.2 in the base case and majority of

scenarios. The 1.2x QALY weighting threshold was also met when basing calculations on the alternative OS approach using the EMILIA + HR method and when using information from the relevant previous NICE appraisal for T-DM1 (TA458).

Base case results demonstrate that T-DXd is a cost-effective option at WTP thresholds of £30,000/QALY and £36,000/QALY with a substantial QALY gain of [redacted] at an incremental cost of [redacted], resulting in an ICER of [redacted].

In line with the guidance from the NICE methods manual, both structural and parameter uncertainty has been extensively explored. The robustness of base case results was assessed via comprehensive probabilistic, deterministic, and scenario analyses with results demonstrating the stability of base case with a high level of certainty:

- PSA was performed to explore joint parameter uncertainty. The probabilistic results are consistent with the deterministic results with a probabilistic QALY gain of [redacted] and ICER of [redacted]. T-DXd has a [redacted] and [redacted] probability of being cost-effective at £30,000/QALY and £36,000/QALY WTP thresholds, respectively.
- Parameter uncertainty was evaluated through OWSA. Results show that the cost-effectiveness results were not sensitive to these parameters when varied within their 95% confidence intervals, with all results consistently showing T-DXd is cost-effective at a £30,000/QALY and £36,000/QALY thresholds.
- A wide range of scenario analyses were performed to evaluate key model assumptions and alternative choices of inputs to test the robustness of the base case results. T-DXd is cost-effective under all scenarios at £30,000/QALY and £36,000/QALY thresholds, with the majority of scenarios meeting the criteria for the 1.2x QALY weighting.
- Throughout all the deterministic sensitivity analysis, the incremental QALYs attributable to treatment with T-DXd ranged from [redacted] to [redacted] showing the substantial impact T-DXd could offer for mBC patients.

A strength of the analysis is that key inputs for the economic model are taken from DESTINY-Breast03 which provides a head-to-head comparison between the in scope intervention and comparator for this appraisal.

The key limitation of the economic analysis is the immature OS data from the IA of DESTINY-Breast03 which informs the long-term estimates of patient survival. However, outcomes were validated by UK based clinical experts and against external data sources; outputs were considered appropriate and plausible, with differences likely justified by nuances in the patient population or changes in treatment practice over time. In addition a range of plausible extrapolations as well as an alternative approach to inform OS utilising longer follow-up data have been explored and outcomes quantified. Outcomes consistently demonstrate that T-DXd offers a cost-effective treatment option in comparison to the current standard of care, T-DM1.

Overall, T-DXd represents both a clinically and cost-effective treatment that is expected to replace the current standard of care for patients with unresectable or metastatic HER2+ BC after trastuzumab and a taxane, addressing an unmet need for more effective targeted therapies in this setting by improving response rates, PFS, OS and HRQoL.

B.4 References

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after trastuzumab and a taxane [ID3909]

Response to clarification questions

May 2022

File name	Version	Contains confidential information	Date
ID3909_T-DXd_HER2+mBC_ Response to EAG clarifications_[redacted]	1.0	No	26/05/2022

Section A: Clarification on effectiveness data

Literature Searches

A1. Priority question: In Appendix E, section E.1.1.3 (pages 10 to 13) – the company presents only partial search strategies for a subset of the databases listed in E.1.1 as having been searched. The MEDLINE strategy (in Embase.com) is missing. In order for the EAG to be able to fully critically appraise all the searches performed please could the company supply, for both the original searches "for studies published prior to 20 August 2020" and for the updated searches "from 21 August 2020 to 27 September 2021", the following:

a. The dates of coverage of each of the databases searched;

For studies captured in the initial searches, PubMed was searched on 12 August 2020 and Embase and Cochrane were both searched on 13 August 2020. MEDLINE was included in both the Embase searches, and via PubMed. No limitations were imposed on these searches, so all dates are covered.

For efficiency reasons, each of the database searches for the update were split in two. The hits shown in the table below are summed from both updated searches:

- Embase was first searched on 23 August 2021, using filters covering 08-08-2020 to 23-08-2021 (by adding AND [08-08-2020]/sd NOT [24-08-2021]/sd to the final line). The subsequent search on 27 September 2021 used filters covering 24-08-2021 to 27-09-2021 (by adding AND [24-08-2021]/sd NOT [28-09-2021]/sd to the final line).
- PubMed was first searched on 23 August 2021, using filters covering publication dates from 2020-08-08 to 3000-12-12 (by adding AND (2020/8/8:3000/12/12[pdat]) to the final line). The subsequent search on 27 September 2021 used filters covering publications dates from 2021-08-24 to 3000-12-12 (by adding AND (2021/8/24:3000/12/12[pdat]) to the final line).
- Cochrane was first searched on 23 August 2021, filtering for publication dates from August 2020 to September 2021. The subsequent search on

27 September 2021 filtered for publication dates from August 2021 to October 2021.

b. The date(s) on which each search was performed;

Please see response to A1(a) above.

c. The complete search strategies for all the databases listed in E.1.1 (i.e. MEDLINE on Embase.com, Embase on Embase.com, MEDLINE In-Process on 'PubMed.com' [*sic*], the Cochrane Library on Wiley), exactly as run, including the number of records (hits) retrieved by each line of the search;

The complete search strategies are provided in the tables below. Please note that MEDLINE was included within both the Embase and the PubMed searches.

Table 1: Embase and MEDLINE initial search strategy via Embase.com (searched 13 August 2020)

String Number	Query	Hits
1	'breast cancer'/exp OR ((breast NEAR/2 (cancer* OR neoplas* OR tumour* OR tumor* OR carcinoma* OR sarcoma* OR adenocarcinoma* OR malignan*)):ab,ti) OR ((mammary NEAR/2 (cancer* OR neoplas* OR tumour* OR tumor* OR carcinoma* OR sarcoma* OR adenocarcinoma* OR malignan*)):ab,ti)	600,105
2	'cancer recurrence'/exp OR 'relapse'/exp OR 'cancer resistance'/exp OR '2nd line':ab,ti OR 'second line':ab,ti OR '2 l':ab,ti OR '2 line':ab,ti OR 2l:ab,ti OR relaps*:ab,ti OR refrac*:ab,ti OR resist*:ab,ti OR recurr*:ab,ti OR progress*:ab,ti OR (((previ* OR prior* OR heav* OR post*) NEAR/4 (chemo* OR line* OR therap* OR treat* OR regim* OR fail*)):ab,ti) OR treated:ab,ti OR pretreat*:ab,ti OR 'pre treat*':ab,ti OR failed:ab,ti OR failure:ab,ti OR reocur*:ab,ti OR 're ocur*':ab,ti OR reoccur*:ab,ti OR 're occur*':ab,ti	7,096,351
3	'epidermal growth factor receptor 2'/exp OR 'epidermal growth factor receptor 2':ab,ti OR cd340:ab,ti OR erbb2*:ab,ti OR 'erbb 2*':ab,ti OR her2*:ab,ti OR 'her 2*':ab,ti OR ((neu NEAR/1 (protein* OR oncoprotein* OR receptor*)):ab,ti) OR 'differentiation factor receptor':ab,ti OR 'neuregulin receptor':ab,ti OR (((immunohistochemistry OR ihc) NEAR/2 (3 OR 2)):ab,ti) OR 'hr positive':ab,ti OR 'hormone receptor positive':ab,ti	100,450
4	'case report'/exp OR 'case study'/exp OR 'editorial'/exp OR 'veterinary clinical trial'/exp OR 'abstract report'/exp OR letter/exp OR note/exp OR 'case study':it OR 'case report':it OR 'abstract report':it OR editorial:it OR letter:it OR note:it OR 'veterinary clinical trial':it OR 'case study':ab,ti OR 'case report':ab,ti OR 'abstract report':ab,ti OR editorial:ab,ti OR letter:ab,ti OR comment:ab,ti OR note:ab,ti OR 'veterinary clinical trial':ab,ti	5,376,549
5	animal/exp NOT (animal/exp AND human/exp)	5,476,743

6	(review:it OR 'literature review':it) NOT 'meta-analysis':it OR 'meta-analysis (topic)':it OR 'systematic review':it OR 'systematic literature review':it OR 'meta-analysis':ab,ti OR 'systematic review':ab,ti OR 'systematic literature review':ab,ti	2,838,778
7	#4 OR #5 OR #6	13,302,309
8	stages:ab,ti OR ((stage* NEAR/2 ('3' OR 'iii' OR '3c' OR 'iiic' OR '3b' OR 'iiib' OR '4' OR 'iv')):ab,ti)	621,265
9	metasta*:ab,ti OR advanc*:ab,ti OR unresect*:ab,ti OR 'un resect*':ab,ti OR nonresect*:ab,ti OR 'non resect*':ab,ti OR inoperable:ab,ti OR (((non OR 'not') NEAR/2 (amenabl* OR suit*) NEAR/2 (surge* OR surgi* OR opera*)):ab,ti)	1,774,391
10	#8 OR #9	2,265,464
11	#1 AND #2 AND #3 AND #10	22,060
12	'european quality of life 5 dimensions questionnaire'/exp OR 'short form 36'/exp OR 'patient preference'/exp OR 'visual analog scale'/exp OR 'quality of life'/exp OR utilit*:ab,ti OR disutilit*:ab,ti OR 'sf 6':ab,ti OR sf6:ab,ti OR 'short form 6':ab,ti OR 'shortform 6':ab,ti OR 'sf six':ab,ti OR 'sfsix':ab,ti OR 'shortform six':ab,ti OR 'short form six':ab,ti OR 'sf 36':ab,ti OR sf36:ab,ti OR 'short form 36':ab,ti OR 'shortform 36':ab,ti OR 'sf thirtysix':ab,ti OR 'sfthirtysix':ab,ti OR 'shortform thirtysix':ab,ti OR 'short form thirtysix':ab,ti OR euroqol:ab,ti OR 'euro qol':ab,ti OR eq5d:ab,ti OR 'eq 5d':ab,ti OR 'health utilities index':ab,ti OR hui:ab,ti OR hui1:ab,ti OR hui2:ab,ti OR hui3:ab,ti OR ((standard NEXT/1 gamble*):ab,ti) OR 'quality of life*':ab,ti OR 'time trade off':ab,ti OR 'time tradeoff':ab,ti OR tto:ab,ti OR 'visual analog scale':ab,ti OR 'patient preference':ab,ti OR 'european quality of life 5 dimensions questionnaire':ab,ti	972,875
13	price*:ti OR pricing:ti OR economic*:ti OR cost:ti OR costs:ti OR 'cost control':ti	219,235
14	'health economics':ti OR 'quality adjusted life year':ti OR 'decision tree':ti OR 'hidden markov model':ti OR 'economic model':ti OR 'markov chain':ti OR qaly*:ti OR (((cost OR costs) NEAR/1 (variable* OR unit* OR estimate*)):ti) OR (((cost OR costs) NEAR/3 (increment* OR conseq* OR minim*)):ti) OR icer:ti OR 'incremental cost effectiveness ratio':ti OR ((decision NEXT/2 (analy* OR tree*)):ti) OR ((model* NEAR/3 (simulat* OR decisio* OR analy* OR 'area under curve' OR partition* OR transitio* OR state* OR discrete* OR individual* OR cohort*)):ti) OR (monte:ti AND carlo:ti) OR economic:ti OR pharmacoeconomic:ti OR markov:ti OR 'cost effect*':ti OR 'cost utilit*':ti OR 'cost benefit*':ti	143,397
15	(#14 OR #13) NOT #12	226,305
16	#15 OR #7	13,481,763
17	#11 NOT #16	17,391

Table 2: Embase and MEDLINE updated search strategy via Embase.com (searched 27 September 2021)

String Number	Query	Hits
1	'breast cancer'/exp OR ((breast NEAR/2 (cancer* OR neoplas* OR tumour* OR tumor* OR carcinoma* OR sarcoma* OR adenocarcinoma* OR malignan*)):ab,ti) OR ((mammary NEAR/2 (cancer* OR neoplas* OR tumour* OR tumor* OR carcinoma* OR sarcoma* OR adenocarcinoma* OR malignan*)):ab,ti)	59,871

String Number	Query	Hits
2	'cancer recurrence'/exp OR relapse/exp OR 'cancer resistance'/exp OR '2nd line':ab,ti OR 'second line':ab,ti OR '2 l':ab,ti OR '2 line':ab,ti OR 2l:ab,ti OR relaps*:ab,ti OR refrac*:ab,ti OR resist*:ab,ti OR recurr*:ab,ti OR progress*:ab,ti OR (((previ* OR prior* OR heav* OR post*) NEAR/4 (chemo* OR line* OR therap* OR treat* OR regim* OR fail*)):ab,ti) OR treated:ab,ti OR pretreat*:ab,ti OR pre-treat*:ab,ti OR failed:ab,ti OR failure:ab,ti OR reocur*:ab,ti OR 're ocur*':ab,ti OR reoccur*:ab,ti OR 're occur*':ab,ti	717,818
3	'epidermal growth factor receptor 2'/exp OR 'epidermal growth factor receptor 2':ab,ti OR cd340:ab,ti OR erbb2*:ab,ti OR 'erbb 2*':ab,ti OR her2*:ab,ti OR 'her 2*':ab,ti OR ((neu NEAR/1 (protein* OR oncoprotein* OR receptor*)):ab,ti) OR 'differentiation factor receptor':ab,ti OR 'neuregulin receptor':ab,ti OR (((immunohistochemistry OR ihc) NEAR/2 (3 OR 2)):ab,ti) OR 'hr positive':ab,ti OR 'hormone receptor positive':ab,ti	13,147
4	'case report'/exp OR 'case study'/exp OR 'editorial'/exp OR 'veterinary clinical trial'/exp OR 'abstract report'/exp OR letter/exp OR note/exp OR 'case study':it OR 'case report':it OR 'abstract report':it OR editorial:it OR letter:it OR note:it OR 'veterinary clinical trial':it OR 'case study':ab,ti OR 'case report':ab,ti OR 'abstract report':ab,ti OR editorial:ab,ti OR letter:ab,ti OR comment:ab,ti OR note:ab,ti OR 'veterinary clinical trial':ab,ti	450,234
5	animal/exp NOT (animal/exp AND human/exp)	260,726
6	(review:it OR 'literature review':it) NOT 'meta-analysis':it OR 'meta-analysis (topic)':it OR 'systematic review':it OR 'systematic literature review':it OR 'meta-analysis':ab,ti OR 'systematic review':ab,ti OR 'systematic literature review':ab,ti	272,352
7	#4 OR #5 OR #6	958,599
8	stages:ab,ti OR ((stage* NEAR/2 ('3' OR 'iii' OR '3c' OR 'iiic' OR '3b' OR 'iiib' OR '4' OR 'iv')):ab,ti)	66,858
9	metasta*:ab,ti OR advanc*:ab,ti OR unresect*:ab,ti OR 'un resect*':ab,ti OR nonresect*:ab,ti OR 'non resect*':ab,ti OR inoperable:ab,ti OR (((non OR 'not') NEAR/2 (amenabl* OR suit*) NEAR/2 (surge* OR surgi* OR opera*)):ab,ti)	222,297
10	#8 OR #9	273,248
11	#1 AND #2 AND #3 AND #10	3,458
12	#11 NOT #7	2,701

Table 3: PubMed and MEDLINE In-Process search strategy via PubMed at National Library https://pubmed.ncbi.nlm.nih.gov/ (searched 12 August 2020)

String Number	Query	Hits
1	"breast neoplasms"[MeSH Terms] OR (breast[tiab] AND (cancer*[tiab] OR neoplas*[tiab] OR tumor*[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR sarcoma*[tiab] OR adenocarcinoma*[tiab] OR malignan*[tiab])) OR (mammary[tiab] AND (cancer*[tiab] OR neoplas*[tiab] OR tumor*[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR sarcoma*[tiab] OR adenocarcinoma*[tiab] OR malignan*[tiab]))	431,870
2	"Neoplasm Recurrence, local"[MeSH] OR recurrence[MeSH] OR "disease resistance"[MeSH] OR "2nd line"[tiab] OR "second line"[tiab] OR "2 l"[tiab]	6,066,971

String Number	Query	Hits
	OR “2 line”[tiab] OR 2l[tiab] OR relaps*[tiab] OR refrac*[tiab] OR resis*[tiab] OR recurr*[tiab] OR progress*[tiab] OR (previ*[tiab] AND (chemo*[tiab] OR line*[tiab] OR therap*[tiab] OR treat*[tiab] OR regim*[tiab] OR fail*[tiab])) OR (prior*[tiab] AND (chemo*[tiab] OR line[tiab] OR therap*[tiab] OR treat*[tiab] OR regim*[tiab] OR fail*[tiab])) OR (heav*[tiab] AND (chemo*[tiab] OR line[tiab] OR therap*[tiab] OR treat*[tiab] OR regim*[tiab] OR fail*[tiab])) OR (post*[tiab] AND (chemo*[tiab] OR line[tiab] OR therap*[tiab] OR treat*[tiab] OR regim*[tiab] OR fail*[tiab])) OR treated[tiab] OR pretreat*[tiab] OR pre-treat*[tiab] OR failed[tiab] OR failure[tiab] OR reoccur*[tiab] OR reocur*[tiab] OR “re occur”[tiab]	
3	“receptor, erbb-2”[MeSH] OR “genes, erbb-2”[MeSH] OR “epidermal growth factor receptor 2”[tiab] OR cd340[tiab] OR erbb2*[tiab] OR “erbb 2*”[tiab] OR her2*[tiab] OR “her 2*”[tiab] OR (neu[tiab] AND protein*[tiab]) OR (neu[tiab] AND oncoprotein*[tiab]) OR (neu[tiab] AND receptor*[tiab]) OR “differentiation factor receptor”[tiab] OR “neuregulin receptor”[tiab] OR “neu receptor”[tiab] OR (immunohistochemistry[tiab] AND (2[tiab] OR 3[tiab])) OR (ihc[tiab] AND (2[tiab] OR 3[tiab])) OR hr positive[tiab] OR “hormone receptor positive”[tiab]	132,727
4	“case reports”[pt] OR editorial[pt] OR letter[pt] OR comment[pt] OR “clinical trial, veterinary”[pt]	3,772,728
5	Animals[MeSH] NOT (animals[MeSH] AND humans[MeSH])	4,725,488
6	review[pt] NOT (“meta-analysis”[pt] OR “systematic review”[pt] OR meta-analysis[tiab] OR “systematic review”[tiab] OR “systematic literature review”[tiab])	2,543,079
7	#4 OR #5 OR #6	10,634,492
8	Stages[tiab] OR (stage*[tiab] AND (3[tiab] OR iii[tiab] OR 3c[tiab] OR iiic[tiab] OR 3b[tiab] OR iiib[tiab] OR 4[tiab] OR iv[tiab]))	659,157
9	metasta*[tiab] OR advance*[tiab] OR unresect*[tiab] OR “un resect*”[tiab] OR nonresect*[tiab] OR “non resect*”[tiab] OR inoperable[tiab] OR (non[tiab] AND amenabl*[tiab] AND surg*[tiab]) OR (non[tiab] AND suit*[tiab] AND surg*[tiab]) OR (non[tiab] AND amenabl*[tiab] AND opera*[tiab]) OR (non[tiab] AND suit*[tiab] AND opera*[tiab]) OR (not[tiab] AND amenabl*[tiab] AND surg*[tiab]) OR (not[tiab] AND suit*[tiab] AND surg*[tiab]) OR (not[tiab] AND amenabl*[tiab] AND opera*[tiab]) OR (not[tiab] AND suit*[tiab] AND opera*[tiab])	1,270,256
10	#8 OR #9	1,812,845
11	#1 AND #2 AND #3 AND #10	10,993
12	“Patient Health Questionnaire”[MeSH] OR “patient preference”[MeSH] OR “quality of life”[MeSH] OR “visual analog scale”[MeSH] OR utilit*[Title/Abstract] OR disutilit*[Title/Abstract] OR ”sf 6”[Title/Abstract] OR sf6[Title/Abstract] OR ”short form 6”[Title/Abstract] OR ”shortform 6”[Title/Abstract] OR ”sf six”[Title/Abstract] OR ”sfsix”[Title/Abstract] OR ”shortform six”[Title/Abstract] OR ”short form six”[Title/Abstract] OR ”sf 36”[Title/Abstract] OR sf36[Title/Abstract] OR ”short form 36”[Title/Abstract] OR ”shortform 36”[Title/Abstract] OR ”sf thirtysix”[Title/Abstract] OR ”sfthirtysix”[Title/Abstract] OR ”shortform thirtysix”[Title/Abstract] OR ”short form thirtysix”[Title/Abstract] OR euroqol[Title/Abstract] OR ”euro qol”[Title/Abstract] OR eq5d[Title/Abstract] OR ”eq 5d”[Title/Abstract] OR ”health utilities index”[Title/Abstract] OR hui[Title/Abstract] OR hui1[Title/Abstract] OR hui2[Title/Abstract] OR hui3[Title/Abstract] OR ((standard NEXT/1 gamble*)[Title/Abstract]) OR ”quality of life*”[Title/Abstract] OR ”time trade off”[Title/Abstract] OR ”time	579,446

String Number	Query	Hits
	tradeoff"[Title/Abstract] OR tto[Title/Abstract] OR "visual analog scale"[Title/Abstract] OR "patient preference"[Title/Abstract] OR "european quality of life 5 dimensions questionnaire"[Title/Abstract]	
13	price*[Title] OR pricing[Title] OR economic*[Title] OR cost[Title] OR costs[Title] OR "cost control"[Title]	163,215
14	"health economics"[Title] OR "quality adjusted life year"[Title] OR "decision tree"[Title] OR "hidden markov model"[Title] OR "economic model"[Title] OR "markov chain"[Title] OR qaly*[Title] OR (((cost OR costs) NEAR/1 (variable* OR unit* OR estimate*))[Title]) OR (((cost OR costs) NEAR/3 (increment* OR conseq* OR minim*))[Title]) OR icer[Title] OR "incremental cost effectiveness ratio"[Title] OR ((decision NEXT/2 (analy* OR tree*))[Title]) OR ((model* NEAR/3 (simulat* OR decisio* OR analy* OR "area under curve" OR partition* OR transitio* OR state* OR discrete* OR individual* OR cohort*))[Title]) OR (monte[Title] AND carlo[Title]) OR economic[Title] OR pharmacoeconomic[Title] OR markov[Title] OR "cost effect*"[Title] OR "cost utilit*"[Title] OR "cost benefit*"[Title]	86,787
15	(#14 OR #13) NOT #12	164,163
16	#15 OR #7	10,770,703
17	#11 NOT #16	8,396

Table 4: PubMed and MEDLINE In-Process updated search strategy via PubMed at National Library https://pubmed.ncbi.nlm.nih.gov/ (searched 27 September 2021)

String Number	Query	Hits
1	"breast neoplasms"[MeSH Terms] OR (breast[tiab] AND (cancer*[tiab] OR neoplas*[tiab] OR tumor*[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR sarcoma*[tiab] OR adenocarcinoma*[tiab] OR malignan*[tiab])) OR (mammary[tiab] AND (cancer*[tiab] OR neoplas*[tiab] OR tumor*[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR sarcoma*[tiab] OR adenocarcinoma*[tiab] OR malignan*[tiab]))	32,877
2	"Neoplasm Recurrence, local"[MeSH] OR recurrence[MeSH] OR "disease resistance"[MeSH] OR "2nd line"[tiab] OR "second line"[tiab] OR "2 l"[tiab] OR "2 line"[tiab] OR 2l[tiab] OR relaps*[tiab] OR refrac*[tiab] OR resis*[tiab] OR recurr*[tiab] OR progress*[tiab] OR (previ*[tiab] AND (chemo*[tiab] OR line*[tiab] OR therap*[tiab] OR treat*[tiab] OR regim*[tiab] OR fail*[tiab])) OR (prior*[tiab] AND (chemo*[tiab] OR line[tiab] OR therap*[tiab] OR treat*[tiab] OR regim*[tiab] OR fail*[tiab])) OR (heav*[tiab] AND (chemo*[tiab] OR line[tiab] OR therap*[tiab] OR treat*[tiab] OR regim*[tiab] OR fail*[tiab])) OR (post*[tiab] AND (chemo*[tiab] OR line[tiab] OR therap*[tiab] OR treat*[tiab] OR regim*[tiab] OR fail*[tiab])) OR treated[tiab] OR pretreat*[tiab] OR pre-treat*[tiab] OR failed[tiab] OR failure[tiab] OR reoccur*[tiab] OR reocur*[tiab] OR "re occur"[tiab]	520,660
3	"receptor, erbb-2"[MeSH] OR "genes, erbb-2"[MeSH] OR "epidermal growth factor receptor 2"[tiab] OR cd340[tiab] OR erbb2*[tiab] OR "erbb 2*"[tiab] OR her2*[tiab] OR "her 2*"[tiab] OR (neu[tiab] AND protein*[tiab]) OR (neu[tiab] AND oncoprotein*[tiab]) OR (neu[tiab] AND receptor*[tiab]) OR "differentiation factor receptor"[tiab] OR "neuregulin receptor"[tiab] OR "neu receptor"[tiab] OR (immunohistochemistry[tiab]	13,567

String Number	Query	Hits
	AND (2[tiab] OR 3[tiab])) OR (ihc[tiab] AND (2[tiab] OR 3[tiab])) OR hr positive[tiab] OR "hormone receptor positive"[tiab]	
4	"case reports"[pt] OR editorial[pt] OR letter[pt] OR comment[pt] OR "clinical trial, veterinary"[pt]	194,002
5	Animals[MeSH] NOT (animals[MeSH] AND humans[MeSH])	86,127
6	review[pt] NOT ("meta-analysis"[pt] OR "systematic review"[pt] OR meta-analysis[tiab] OR "systematic review"[tiab] OR "systematic literature review"[tiab])	164,154
7	#4 OR #5 OR #6	434,971
8	"clinical study"[pt] OR "random allocation"[MeSH] OR "placebo effect"[MeSH] OR placebos[MeSH] OR "control groups"[MeSH] OR "single-blind method"[MeSH] OR "cross-over studies"[MeSH] OR "double-blind method"[MeSH] OR "cohort studies"[MeSH] OR "comparative study"[pt] OR "follow-up studies"[MeSH] OR "medical records"[MeSH] OR "cross-sectional studies"[MeSH] OR "observational study"[pt] OR registries[MeSH] OR randomization[tiab] OR "control group"[tiab] OR "crossover procedure"[tiab] OR "cohort analysis"[tiab] OR "comparative study"[tiab] OR "follow up"[tiab]	276,670
9	"clinical audit"[MeSH] OR "clinical trials data monitoring committees"[MeSH] OR ("case control"[tiab] AND stud*[tiab]) OR ("case control"[tiab] AND trial*[tiab]) OR (observational[tiab] AND stud*[tiab]) OR (observational[tiab] AND trial*[tiab]) OR ("cross sectional"[tiab] AND stud*[tiab]) OR ("cross sectional"[tiab] AND trial*[tiab]) OR retrospectiv*[tiab] OR registry[tiab] OR (hospital[tiab] AND record*[tiab]) OR (hospital[tiab] AND chart*[tiab]) OR (medical[tiab] AND record*[tiab]) OR (medical[tiab] AND chart*[tiab]) OR (electronic[tiab] AND record*[tiab]) OR (electronic[tiab] AND chart*[tiab]) OR "non random"[tiab] OR "single arm"[tiab] OR "real world"[tiab] OR "real life"[tiab] OR "controlled clinical trial"[tiab] OR "randomized controlled trial"[tiab] OR "randomised controlled trial"[tiab] OR rct[tiab] OR (random[tiab] AND alloca*[tiab]) OR (random[tiab] AND assign*[tiab]) OR (single[tiab] AND blind*[tiab]) OR (double[tiab] AND blind*[tiab]) OR (triple[tiab] AND blind*[tiab]) OR (treble[tiab] AND blind*[tiab]) OR (single[tiab] AND mask*[tiab]) OR (double[tiab] AND mask*[tiab]) OR (triple[tiab] AND mask*[tiab]) OR (treble[tiab] AND mask*[tiab]) OR placebo[tiab] OR "clinical study"[tiab] OR "clinical article"[tiab]	293,494
10	#8 OR #9	433,020
11	#10 NOT #7	396,321
12	Stages[tiab] OR (stage*[tiab] AND (3[tiab] OR iii[tiab] OR 3c[tiab] OR iiic[tiab] OR 3b[tiab] OR iiib[tiab] OR 4[tiab] OR iv[tiab]))	66,515
13	metasta*[tiab] OR advance*[tiab] OR unresect*[tiab] OR "un resect*"[tiab] OR nonresect*[tiab] OR "non resect*"[tiab] OR inoperable[tiab] OR (non[tiab] AND amenabl*[tiab] AND surg*[tiab]) OR (non[tiab] AND suit*[tiab] AND surg*[tiab]) OR (non[tiab] AND amenabl*[tiab] AND opera*[tiab]) OR (non[tiab] AND suit*[tiab] AND opera*[tiab]) OR (not[tiab] AND amenabl*[tiab] AND surg*[tiab]) OR (not[tiab] AND suit*[tiab] AND surg*[tiab]) OR (not[tiab] AND amenabl*[tiab] AND opera*[tiab]) OR (not[tiab] AND suit*[tiab] AND opera*[tiab])	141,009
14	#12 OR #13	194,074
15	#1 AND #2 AND #3 AND #14	1,638
16	#11 AND #15	735

Table 5: Cochrane search strategy via Cochrane Library on Wiley (searched 13 August 2020, and 28 September 2021)

String Number	Query	Hits
1	MeSH descriptor: [Breast neoplasm] explode all trees	12,895 Update: 13,736*
2	((breast NEAR/2 (cancer* OR neoplas* OR tumour* OR tumor* OR carcinoma* OR sarcoma* OR adenocarcinoma* OR malignan*)):ab,ti) OR ((mammary NEAR/2 (cancer* OR neoplas* OR tumour* OR tumor* OR carcinoma* OR sarcoma* OR adenocarcinoma* OR malignan*)):ab,ti)	32,691 Update: 2,758
3	#1 OR #2	33,993 Update: 2,819
4	MeSH descriptor: [Recurrence] explode all trees	11,975 Update: 12,806*
5	'2nd line':ab,ti OR 'second line':ab,ti OR '2 l':ab,ti OR '2 line':ab,ti OR 2l:ab,ti OR relaps*:ab,ti OR refrac*:ab,ti OR resist*:ab,ti OR recurr*:ab,ti OR progress*:ab,ti OR (((previ* OR prior* OR heav* OR post*) NEAR/4 (chemo* OR line* OR therap* OR treat* OR regim* OR fail*)):ab,ti) OR treated:ab,ti OR pretreat*:ab,ti OR 'pre treat*':ab,ti OR failed:ab,ti OR failure:ab,ti OR reocur*:ab,ti OR 're ocur*':ab,ti OR reoccur*:ab,ti OR 're occur*':ab,ti	586,204 Update: 55,883
6	#4 OR #5	587,978 Update: 55,918
7	MeSH descriptor: [ErbB Receptors] explode all trees	1,220 Update: 1,368*
8	'epidermal growth factor receptor 2':ab,ti OR cd340:ab,ti OR erbb2*:ab,ti OR 'erbb 2*':ab,ti OR her2*:ab,ti OR 'her 2*':ab,ti OR ((neu NEAR/1 (protein* OR oncoprotein* OR receptor*)):ab,ti) OR 'differentiation factor receptor':ab,ti OR 'neuregulin receptor':ab,ti OR (((immunohistochemistry OR ihc) NEAR/2 (3 OR 2)):ab,ti) OR 'hr positive':ab,ti OR 'hormone receptor positive':ab,ti	21,427 Update: 2,689
9	#7 OR #8	21,512 Update: 2,690
10	stages:ab,ti OR ((stage* NEAR/2 ('3' OR 'iii' OR '3c' OR 'iiic' OR '3b' OR 'iiib' OR '4' OR 'iv')):ab,ti)	31,911 Update:

String Number	Query	Hits
		3,790
11	metasta*:ab,ti OR advanc*:ab,ti OR unresect*:ab,ti OR 'un resect*':ab,ti OR nonresect*:ab,ti OR 'non resect*':ab,ti OR inoperable:ab,ti OR (((non OR 'not') NEAR/2 (amenabl* OR suit*) NEAR/2 (surge* OR surgi* OR opera*)):ab,ti)	96,882 Update: 9,990
12	#10 OR #11	118,206 Update: 12,667
13	#3 AND #6 AND #9 AND #12	3,604 Update: 486
14	MeSH descriptor: [Surveys and Questionnaires] explode all trees	53,508 Update: 56,442*
15	MeSH descriptor: [Quality of Life] explode all trees	23,523 Update: 26,983*
16	MeSH descriptor: [Patient Preference] explode all trees	741 Update: 879*
17	MeSH descriptor: [Visual Analog Scale] explode all trees	848 Update: 1,286*
18	utilit*:ab,ti OR disutilit*:ab,ti OR 'sf 6':ab,ti OR sf6:ab,ti OR 'short form 6':ab,ti OR 'shortform 6':ab,ti OR 'sf six':ab,ti OR 'sfsix':ab,ti OR 'shortform six':ab,ti OR 'short form six':ab,ti OR 'sf 36':ab,ti OR sf36:ab,ti OR 'short form 36':ab,ti OR 'shortform 36':ab,ti OR 'sf thirtysix':ab,ti OR 'sfthirtysix':ab,ti OR 'shortform thirtysix':ab,ti OR 'short form thirtysix':ab,ti OR euroqol:ab,ti OR 'euro qol':ab,ti OR eq5d:ab,ti OR 'eq 5d':ab,ti OR 'health utilities index':ab,ti OR hui:ab,ti OR hui1:ab,ti OR hui2:ab,ti OR hui3:ab,ti OR ((standard NEXT/1 gamble*):ab,ti) OR 'quality of life*':ab,ti OR 'time trade off':ab,ti OR 'time tradeoff':ab,ti OR tto:ab,ti OR 'visual analog scale':ab,ti OR 'patient preference':ab,ti OR 'european quality of life 5 dimensions questionnaire':ab,ti	164,547 Update: 22,666
19	#14 OR #15 OR #16 OR #17 OR #18	208,733 Update: 24,197
20	price*:ti OR pricing:ti OR economic*:ti OR cost:ti OR costs:ti OR 'cost control':ti	16,496 Update:

String Number	Query	Hits
		1,372
21	'health economics':ti OR 'quality adjusted life year':ti OR 'decision tree':ti OR 'hidden markov model':ti OR 'economic model':ti OR 'markov chain':ti OR qaly*:ti OR (((cost OR costs) NEAR/1 (variable* OR unit* OR estimate*)):ti) OR (((cost OR costs) NEAR/3 (increment* OR conseq* OR minim*)):ti) OR icer:ti OR 'incremental cost effectiveness ratio':ti OR ((decision NEXT/2 (analy* OR tree*)):ti) OR ((model* NEAR/3 (simulat* OR decisio* OR analy* OR 'area under curve' OR partition* OR transitio* OR state* OR discrete* OR individual* OR cohort*)):ti) OR (monte:ti AND carlo:ti) OR economic:ti OR pharmacoeconomic:ti OR markov:ti OR 'cost effect*':ti OR 'cost utilit*':ti OR 'cost benefit*':ti	18,483 Update: 1,881
22	(#20 OR #21) NOT #19	14,875 Update: 1,326
23	#13 NOT #22	3,595 Update: 484

*No limits were applied to the MeSH terms included in the chains for the update performed on 23 August 2021.

d. The strategies should please include any limitations imposed on the search and for updated searches should also include any terms/syntax/limits applied and/or any date fields specifically searched.

Please see response to A1(a) above.

A2. Regarding the EMBASE strategy (Appendix E, section E.1.1.3, Table 1, page 10 Embase strategy), the version presented raises concerns regarding the ability of this strategy to retrieve relevant studies. Could the company please explain the following:

a. Why a strategy that would result in retrieval of zero records (in line 12, the final line of the search) has been presented rather than the strategy as actually run (and hence one of the most important reasons for priority question A1)? (this is due to the 'knock-on' effect of an error in line 11, please see point A2.c below)

The EAG is correct that the reporting of the search strategy as presented in the initial submission includes this error. In line #12, line #6 has erroneously been added with the Boolean 'AND' instead of the intended line #10. However, when the literature search was actually executed, line #12 was run correctly as #1 AND #2 AND #3 AND #10.

b. The important loss to the effectiveness of this strategy in retrieving records from Embase related to their full 'Population' due to the missing Emtree term from line 1 ('breast tumor'/exp)

The EAG is correct the inclusion of a 'breast tumor'/exp in line #1 could broaden the review. At the time of the review it was anticipated that the search terms proposed would identify all the relevant clinical evidence.

To check this assumption, an updated search with 'breast tumor'/exp added to line #1 was run on 17 May 2022. Of the 19 additional records found, none met the review inclusion criteria. Therefore the exclusion of this Emtree term did not affect the effectiveness of the search strategy.

c. The erroneous line combination (see line 11)

Please see response to A2(a) above.

d. Missing lines from the population search (line 10 is not combined)

Please see response to A2(a) above.

e. The loss to the effectiveness of this strategy in retrieving records from Embase related to their full 'Population' due to not allowing for plural of 'mammary' in line 1.

Terms using the plural of mammary (e.g. mammaries cancer, mammaries carcinoma) are not commonly used when referring to breast cancer. An Embase search on 17 May 2022 using only an adapted line #1 in which the term mammary was replaced with mammar* yielded 13 extra records; however, once this modified line was combined with the subsequent search terms in the Embase search strategy, these records were not present in the final list of studies. Therefore, no relevant records were missed, and there is no loss to the effectiveness of this strategy.

f. The rationale for including a general set of terms (line 3) related to any HER/epidermal growth factor receptors, regardless of status (only the last two terms relate to positive status)

The systematic literature review detailed in the submission was originally conducted to support multiple purposes, one of which was the NICE submission. The Company took the approach of conducting the review according to the NICE methods, so that it could subsequently be adapted to the Final Scope for this appraisal, a common approach for NICE appraisals.

The consequence of this approach was that the global review was – initially – broader in scope than required for the NICE decision problem. Subsequently, the hits identified by the searches were screened to identify those studies relating to patients with HER2/EGFR-positive disease. While this strategy increases the number of hits to be screened, it is comprehensive, and has a low likelihood of missing key clinical data.

g. Regarding line 4, why have 'abstract reports' been specifically removed and yet conference proceedings have been hand searched in order to pick up abstracts?

The terms for 'abstract report' could have been removed from line #4 to provide a more comprehensive search string. When running the complete search with line #4 adapted to remove mention of 'abstract report', no additional records were identified. Therefore, no relevant records were missed.

h. Regarding line 6, how successful will this line be with a set of brackets missing (from around the terms given after the Boolean 'NOT')?

The EAG has correctly identified that this is an error. However, systematic literature reviews identified by this search were not used for evidence generation but for bibliographic corroboration — bibliographies from the reviews were cross-referenced with the included studies to ensure that all relevant studies were captured. Considering the breadth of relevant clinical evidence studies found through this literature search, it is unlikely that the bibliographic searches would have yielded further relevant studies.

i. Whether any limits were imposed on this search?

For the initial searches, no limits were imposed. For the updated searches, limits were imposed on dates of publication (08-08-2020 to 23-08-2021 and 24-08-2021 to 27-09-2021) to prevent duplication of search results.

A3. Regarding the reported PubMED strategy (Appendix E, section E.1.1.3. Table 2, pages. 11-12), please could the company:

a. Clarify whether when they state that they searched 'PubMed.com' they mean PubMed at National Library https://pubmed.ncbi.nlm.nih.gov/? If not correct please could the company give the main webpage for this resource.

The EAG is correct that the PubMed database erroneously referred to as PubMed.com is PubMed at National Library https://pubmed.ncbi.nlm.nih.gov/.

b. Clarify whether this strategy relates only to 'In-Process' records within PubMed – if so please include in your strategies (as requested in A1 above) search lines related to this limit.

The search strategy refers to the entire search performed in PubMed, not only In-Process records (which were captured by searching PubMed on https://pubmed.ncbi.nlm.nih.gov/).

c. With regard to line 1, explain the negative effect on the search of having not exploded the MeSH term "breast neoplasms" (or picked all the relevant terms below this one individually) as they will have missed important MeSH terms such as 'breast neoplasms, male', and 'inflammatory breast neoplasms'.

With regard to line #1, breast neoplasms[MeSH] was not exploded as PubMed automatically explodes MeSH terms. Therefore, no important MeSH terms have been omitted from our searches in PubMed.

d. With regard to Line 2 – explain why recurrence[MeSH] was not exploded here when it was exploded in the Cochrane Library search.

With regard to line #2, recurrence[MeSH] was not exploded as PubMed automatically explodes MeSH terms. Therefore, no important MeSH terms have been omitted from our searches in PubMed.

e. Comment on the negative impact on this strategy's ability to retrieve records related to their full 'Population' due to not allowing for plural of 'mammary' in line 1.

Terms using the plural of mammary (e.g. mammaries cancer, mammaries carcinoma) are not commonly used when referring to breast cancer. An adapted PubMed search using only line #1 in which mammary[tiab] was replaced by mammar*[tiab] yielded 17 extra records; however, these records were not relevant

for the clinical evidence of HER2+ breast cancer because they were included due to matches with “mammarian gland”, “mammarian artery”, and “mammarenavirus”. Therefore, no relevant records were missed, and searches omitting these terms would not be expected have a negative impact on this strategy's ability to retrieve relevant records.

f. Regarding Lines 8 and 9 - could the company please clarify whether these are validated filters (or are broadly based on validated filters) and, if 'yes' please could they provide the reference(s) for these filters (as is good practice)

The search string was developed internally in collaboration with librarians from the University Medical Center Gronigen. These specific lines are broadly based on the validated sensitivity-maximizing version of the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in PubMed. The strategy employed for the search is broader than the Cochrane strategy.

g. Whether any limits were imposed on this search?

For the initial searches, no limits were used. For the updated searches, custom publication date filters were used to prevent duplication of search hits. The dates filters were applied were from 2020/08/20 to 3000/12/12 and from 2021/8/24 to 3000/12/12).

A4. Regarding the reported Cochrane (CDSR and CENTRAL) search strategy Appendix E, section E.1.1.3. Table 3, pages. 12-13, please could the Company:

a. Comment on the loss to the effectiveness of this strategy in retrieving records from CDSR and CENTRAL related to their full ‘Population’ due to not allowing for plural of ‘mammary’ in line 2.

Terms using the plural of mammary (e.g. mammaries cancer, mammaries carcinoma) are not commonly used when referring to breast cancer. A Cochrane search using only an adapted line #2 in which mammary was replaced by mammar* yielded 1 extra record; however, once this modified line was combined with the subsequent search terms in the Cochrane search strategy, this record was not present in the final list of studies. Therefore, no relevant records were missed, and there is no loss to the effectiveness of this strategy.

b. Comment on the effect on the search (Line 7) – where they have exploded the MeSH term ‘ErbB Receptors’ when they could have used a narrower MeSH term instead (e.g., receptor, erbb-2).

The EAG is correct that a narrower search term could potentially have been used. As outlined in the Company’s response to clarification question A2 (f) above, the approach for the broader global review – prior to adaptation for the NICE decision problem – was to take a broad approach to the searches, and to refine hits via the screening stages.

The Company developed a comprehensive search strategy for the review, and the broader search terms highlighted in the clarification question above are not anticipated to have an impact on the ability of the review to identify relevant evidence given that they are broader than may be necessary. The broad search strings provide confidence that there is low likelihood that relevant clinical studies would not have been captured by the review.

c. Comment on the effect on the search, in Line 8, in helping to retrieve more (relevant) records related to their population if the Company had added in "erbb-2" as an additional term to search in title and abstract.

The Company’s approach to the search strategy was to take a broad approach, and to refine the hits at screening. It is possible that a more targeted search strategy would have been equally valid in identifying the relevant clinical evidence. To ensure all relevant studies were identified in the original and updated reviews, the Company re-ran Line 8 from the search strategies highlighted by the EAG, including the ”erbb-2”. No additional hits were identified. Therefore the Company is confident that the search strategy identified the clinical evidence of relevance to the submission.

d. Regarding line 19 – please clarify if this is a validated filter (or based on a validated filter) - if 'yes' please give the reference (as is good practice)

While this is not a validated filter, the entire search string was checked by a librarian from the University Medical Center Groningen and deemed exceptionally broad. Therefore, the Company is confident that this search string captured all relevant evidence.

e. Regarding lines 20 and 21 - Is this a validated filter (or based on a validated filter) - if 'yes' please give the reference (as is good practice)

Please see response to A4(e) above

f. Line 23 - please could the company clarify why they have removed from the set of population-related records the subset of records that are related (roughly) to health economics/costs that do not cover QoL?

As outlined in the Company's response to clarification question A2 (f) above, the approach for the broader global review – prior to adaptation for the NICE decision problem – was to take a broad approach to the searches, and to refine hits via the screening stages. While health economic studies were out of scope for the clinical literature review, QoL outcomes were an outcome of interest for clinical studies. Therefore, the search strings for the clinical review were developed to exclude health economic studies, while still allowing for the inclusion of clinical trials that reported QoL outcomes. Separate reviews were conducted for resource use, costs and other health economics studies.

A5. Sources searched. In Appendix E, sections E.1.1, E.1.1.1 and E.1.1.2, pages 9-10, a number of different sources that were searched for clinical effectiveness studies are detailed. Could the company please:

a. Provide a rationale for not searching clinical trial registers, in particular WHO ICTRP, ClinicalTrials.gov and EudraCT?

Clinicaltrials.gov (and other clinical trial registries) do not systematically report trial outcomes beyond study design and eligibility. Our search strategies for the identified sources (Appendix D, Section D1.1, D.1.1.1 and D.1.1.2, p9-10) were designed to be comprehensive and capture all relevant resources, evidence and outcomes from recent clinical trials. This search strategy and its results – the broad range of trials captured up to and including the ESMO 2021 results from DESTINY-Breast03 – are reason to expect that a clinical trial register database search will not yield additional relevant trials with published relevant outcomes beyond those already captured. As such these clinical trial register searches were not conducted.

b. Provide clarity on which segments of MEDLINE were searched (as e.g., Epub Ahead of Print appears not to have been covered) and the rationale for omitting any MEDLINE segments?

MEDLINE and MEDLINE In-Process were included within the Embase and PubMed PubMed searches, respectively. In PubMed, status subsets can be used to restrict records by subject, citation status, and journal category. No status subsets were utilised for the review to ensure that the searches were as broad as possible. For example, when combining pubstatusaheadofprint or inprocess[sb] with our search in PubMed, the records found were included in our literature search. Therefore, the Company is confident that ahead of print articles were captured.

A6. Regarding the congress searches (Appendix E, section E.1.1.1, listed on pages 9-10), could the company please:

a. Clarify if the congress searches were updated in 2021 and on which date they were run?

The grey literature search for conference abstracts was updated at multiple timepoints in 2021. Updates were performed of individual conferences following their 2021 edition, with ASCO 2021 searched on 13-09-2021, ESMO 2020 searched on 04-10-2021, ESMO May 2021 searched on 16-09-2021, ESMO September 2021 searched on 01-10-2021, EBCC 2020 searched on 17-09-2021, SABCS 2020 searched on 22-09-2021, JSCO 2020 searched on 15-09-2021, ISPOR Europe 2020 searched on 20-09-2021, ISPOR US 2021 search on 17-09-2021.

b. Provide a rationale for the time limits used in the conference searches (2018-2020)?

The EAG is correct that a 2-year time limit was used for conference searches for the original review for studies published prior to 20 August 2020; this was subsequently extended to 2021, based on the search dates described in the response to A6(a) above. The Company anticipated that any high-quality studies published in abstract form prior to 2018 would have been published as a peer-reviewed journal article in the intervening period. This is a typical for to identifying relevant clinical evidence for HTA from conferences.

A7. In Appendix E, section E.1, page 9 (2nd para, 1st sentence) mention is made of "searches… [of] websites of national reimbursement and health technology assessment

organisations". Please could the company give details of each of these websites and organisations and how they were searched; i.e. please provide:

a. Urls for each site/organisation (if possible the exact webpages searched)

b. The dates covered by the searches

c. The date on which each search was conducted

d. For each site - how they were searched eg please present any search terms/strings used

e. The number of records retrieved from each source

f. Please include details for the original search and for each search update performed for each website/organisation

g. Please specifically state whether these searches were updated beyond 2020

URLs for each site/organisation (equal in original search and search update) are shown in the table below.

ICER	https://icer.org/
Chuikyo*	
EMA	https://www.ema.europa.eu/en
HAS	https://www.has-sante.fr/jcms/pprd_2986129/en/home
DAHTA	http://vortal.htai.org/index.php?q=node/72
AIFA	https://www.aifa.gov.it/en/web/guest/home
AEMPS	https://www.aemps.gob.es/informa-en/the-spanish-agency-of-medicines-and-medical-devices-aemps-recommends-using-voluntary-harmonisation-procedure-before-the-official-submission-of-a-multi-state-ct-application/?lang=en
NICE	https://www.nice.org.uk/
SMC	https://www.scottishmedicines.org.uk/search/?page=all&keywords=breast+cancer&from=&to=
AWMSG	https://awmsg.nhs.wales/
ZIN	https://english.zorginstituutnederland.nl/
CADTH	https://www.cadth.ca/
MSAC	http://www.msac.gov.au/
CONITEC	http://conitec.gov.br/
SFDA	https://www.sfdachina.com/
NECA**	http://neca.re.kr/eng/index.jsp
BNHI	https://www.nhi.gov.tw/english/
SBU	https://www.sbu.se/en/
Medicinrådet	https://medicinraadet.dk/om-os/in-english

The Norwegian Knowledge centre for health services	https://www.fhi.no/en/
FinCCHTAn	https://www.ppshp.fi/Tutkimus-ja-opetus/FinCCHTA/Sivut/In_other_languages.aspx

*No website found
**No access

Dates of searches, limits, search strings and hits returned for the 2020 searches are provided in the table below for the original review.

	A7b	A7c (all searches conducted in 2020)	A7d	A7e
ICER	Until date of search	02/Oct	"breast cancer"; "HER2"	0
Chuikyo*				
EMA	Until date of search	05/Oct	"breast cancer"; "HER2"	3
HAS	Until date of search	05/Oct	"breast cancer"; "HER2"	0
DAHTA	Until date of search	05/Oct	"HER2"	4
AIFA	Until date of search	05/Oct	"breast cancer"; "HER2"	1
AEMPS	Until date of search	05/Oct	"breast cancer"; "HER2"	0
NICE	Until date of search	05/Oct	"HER2"	8
SMC	Until date of search	05/Oct	"HER2"	0
AWMSG	Until date of search	05/Oct	"HER2"	2
ZIN	Until date of search	05/Oct	"HER2"	8
CADTH	Until date of search	05/Oct	"HER2"	5
MSAC	Until date of search	05/Oct	"breast"; "HER2"	0
CONITEC	Until date of search	05/Oct	"breast"; "HER2"	4
SFDA	Until date of search	05/Oct	"breast"; "HER2"	0
NECA**	Until date of search			
BNHI	Until date of search	05/Oct	"HER2"	0
SBU	Until date of search	05/Oct	"breast"	1
Medicinrådet	Until date of search	05/Oct	"breast"	3
The Norwegian Knowledge centre for health services	Until date of search	05/Oct	"breast"	1
FinCCHTAn	Until date of search	05/Oct	"breast"	0

*No website found
**No access

Dates of searches, limits, search strings and hits returned for the updated, 2021 searches are provided in the table below for the original review.

	A7b	A7c (all searches conducted in 2021)	A7d	A7e
ICER	01/10/2020 - 28/12/2021	18/Dec	"breast cancer"	0
Chuikyo*	01/10/2020 - 28/12/2021	18/Dec	"breast cancer"; "HER2"	0

EMA	01/10/2020 - 28/12/2021	18/Dec	"breast cancer"; "HER2-positive"	3
HAS	01/10/2020 - 28/12/2021	18/Dec	"breast cancer" "le cancer du sein + HER2"	0
DAHTA	01/10/2020 - 28/12/2021	18/Dec	"breast cancer" "Brustkrebs"	0
AIFA	01/10/2020 - 28/12/2021	18/Dec	"breast cancer" "Cancro al seno"	0
AEMPS	01/10/2020 - 28/12/2021	18/Dec	"breast cancer" "Cáncer de mama"	5
NICE	01/10/2020 - 28/12/2021	18/Dec	"breast cancer"	1
SMC	01/10/2020 - 28/12/2021	18/Dec	"HER2"	1
AWMSG	01/10/2020 - 28/12/2021	18/Dec	"HER2"	2
ZIN	01/10/2020 - 28/12/2021	18/Dec	"breast cancer"; "HER2"	1
CADTH	01/10/2020 - 28/12/2021	18/Dec	"breast cancer"; "HER2"	1
MSAC	01/10/2020 - 28/12/2021	18/Dec	"HER2"	0
CONITEC	01/10/2020 - 28/12/2021	18/Dec	"breast"; "HER2"	0
SFDA	01/10/2020 - 28/12/2021	18/Dec		0
NECA**	01/10/2020 - 28/12/2021	18/Dec		0
BNHI	01/10/2020 - 28/12/2021	18/Dec	"breast" "HER2"	0
SBU	01/10/2020 - 28/12/2021	18/Dec	"breast" "brystkræft"	4
Medicinrådet	01/10/2020 - 28/12/2021	18/Dec	"breast" "brystkreft"	0
The Norwegian Knowledge centre for health services	01/10/2020 - 28/12/2021	18/Dec	"breast" "rintasyöpä"	0
FinCCHTAn	01/10/2020 - 28/12/2021	18/Dec	"breast cancer"	0

*No website found
**No access

A8. Can the company provide details for the “Additional hand searching” that took place after the NICE scope was made public that contributed to the identification of 3 studies and 1 CSR as reported in the PRISMA flowchart (Appendix E, figure 1, page 17). Could the company please provide details of which resources were hand searched and on which date(s) these hand searches were performed?

Hand-searching for relevant clinical evidence relating to T-DXd efficacy and safety was conducted on the congress sites for The San Antonio Breast Cancer

Symposium (SABCS) 2021, and the European Society for Medical Oncology (ESMO) 2021 meetings, via the following weblinks:

- SABCS | https://www.sabcs.org/2021-SABCS
- ESMO | https://www.esmo.org/meetings/past-meetings/esmo-congress-2021

These sites were targeted for hand-searching based on known external presentation of the DESTINY-Breast03 study. Search strings comprised “T-DXd”, “TDXd”, “deruxtecan” and “DESTINY”. Searches were conducted in March 2022, on or around the 14th March. These searches identified the two conference presentations included in the included studies reference list.

Shortly before the initial submission to NICE, the Company published the primary manuscript for the DESTINY-Breast03 study in the New England Journal of Medicine (publication date 24 March, 2022). This was subsequently added to the included studies, although a formal hand search of NEJM was not deemed necessary.

Finally, the Clinical Study Report (CSR) was provided by the Company and added to the included studies. Hand searching was not required for the identification of the CSR.

A9. For the cost-effectiveness searches (Appendix H, section H.1.1, page 25), no search strategies are presented. In order for the EAG to be able to fully critically appraise all the searches performed for all the electronic databases listed could the company please present, for both the original searches “conducted on 11th August 2020” and for the further updated searches on 24 November 2021 the following:

a. The full details (i.e. dates/dates of coverage of the databases searched);

b. The date(s) on which each search was performed;

c. The complete search strategies for all the databases listed in H.1.1 (i.e. MEDLINE on Embase.com, Embase on Embase.com, MEDLINE In-Process on ‘PubMed.com’ [*sic*], EconLit (on which platform?), School of Health and Related Research Health Utilities Database (ScHARRHUD), Centre for Reviews and Dissemination (CRD) –

HTA and NHS EED), exactly as run, including the number of records (hits) retrieved by each line of the search;

d. The strategies should please include any limitations imposed on the search and for updated searches should also include any terms/syntax/limits applied and/or any date fields specifically searched.

Full details of the search strategies are presented in turn below. MEDLINE was included in both the Embase searches, and via PubMed.

Embase and MEDLINE

The searches were conducted on August 11, 2020 (No limits) and updated on November 24, 2021 (limitation on time: Aug 12, 2020 – Nov 24, 2021).

Table 6: Embase and MEDLINE search strategy via Embase.com (cost-effectiveness)

String Number	Query	Hits
1	'breast cancer'/exp OR ((breast NEAR/2 (cancer* OR neoplas* OR tumour* OR tumor* OR carcinoma* OR sarcoma* OR adenocarcinoma* OR malignan*)):ab,ti) OR ((mammary NEAR/2 (cancer* OR neoplas* OR tumour* OR tumor* OR carcinoma* OR sarcoma* OR adenocarcinoma* OR malignan*)):ab,ti)	585,148 Update: 63,654
2	metasta*:ab,ti OR advanc*:ab,ti OR unresect*:ab,ti OR 'un resect*':ab,ti OR nonresect*:ab,ti OR 'non resect*':ab,ti OR inoperable:ab,ti OR (((non OR 'not') NEAR/2 (amenabl* OR suit*) NEAR/2 (surge* OR surgi* OR opera*)):ab,ti)	1,773,747 Update: 237,888
3	'cancer recurrence'/exp OR relapse/exp OR 'cancer resistance'/exp OR relaps*:ab,ti OR refrac*:ab,ti OR resist*:ab,ti OR recurr*:ab,ti OR progress*:ab,ti OR (((previ* OR prior* OR heav* OR post*) NEAR/4 (chemo* OR line* OR therap* OR treat* OR regim* OR fail*)):ab,ti) OR treated:ab,ti OR pretreat*:ab,ti OR pre-treat*:ab,ti OR failed:ab,ti OR failure:ab,ti OR reocur*:ab,ti OR 're ocur*':ab,ti OR reoccur*:ab,ti OR 're occur*':ab,ti	7,074,288 Update: 761,845
4	'epidermal growth factor receptor 2'/exp OR 'epidermal growth factor receptor 2':ab,ti ORcd340:ab,ti OR erbb2*:ab,ti OR 'erbb 2*':ab,ti OR her2*:ab,ti OR 'her 2*':ab,ti OR ((neu NEAR/1 (protein* OR oncoprotein* OR receptor*)):ab,ti) OR 'differentiation factor receptor':ab,ti OR 'neuregulin receptor':ab,ti OR(((immunohistochemistry OR ihc) NEAR/2 (3 OR 2)):ab,ti) OR 'hr positive':ab,ti OR 'hormone receptor positive':ab,ti	100,420 Update: 14,029
5	'case report'/exp OR 'case study'/exp OR 'abstract report'/exp OR 'editorial'/exp OR 'veterinary clinical trial'/exp OR letter/exp OR note/exp OR (animal/exp NOT (animal/exp AND human/exp)) OR 'meta-analysis (topic)'/exp OR 'case study':it OR 'case study':ab,ti OR 'case report':it OR 'case report':ab,ti OR 'abstract report':it OR 'abstract report':ab,ti OR editorial:it OR editorial:ab,ti OR 'veterinary clinical trial':it OR 'veterinary clinical trial':ab,ti OR letter:it OR letter:ab,ti OR note:it OR note:ab,ti OR ((review:it OR review:ab,ti OR 'literature review':it OR 'literature review':ab,ti) NOT ('meta-analysis':it OR 'meta-analysis':ab,ti OR 'meta-analysis (topic)':it OR 'systematic review':it OR 'systematic literature review':it OR 'meta-analysis':ab,ti OR 'meta analysis':ab,ti))	13,886,323 Update: 1,090,134

String Number	Query	Hits
6	'health economics'/exp OR 'quality adjusted life year'/exp OR 'decision tree'/exp OR 'monte carlo method'/exp OR 'survival analysis'/exp OR 'hidden markov model'/exp OR 'sensitivity analysis'/exp OR 'economic model'/exp OR 'markov chain'/exp OR simulation/exp OR 'health economics':ab,ti OR 'quality adjusted life year':ab,ti OR 'decision tree':ab,ti OR 'monte carlo method':ab,ti OR 'survival analysis':ab,ti OR 'hidden markov model':ab,ti OR 'sensitivity analysis':ab,ti OR 'economic model':ab,ti OR 'markov chain':ab,ti OR simulation:ab,ti OR qaly*:ab,ti OR ly:ab,ti OR lys:ab,ti OR 'life year*':ab,ti OR (((cost OR costs) NEAR/1 (variable* OR unit* OR estimate*)):ab,ti) OR (((cost OR costs) NEAR/3 (increment* OR effect* OR utilit* OR benefit* OR conseq* OR minim*)):ab,ti) OR icer:ab,ti OR 'incremental cost effectiveness ratio':ab,ti OR ((decision NEXT/2 (analy* OR tree*)):ab,ti) OR ((survival* NEAR/2 analy*):ab,ti) OR ((model* NEAR/3 (simulat* OR decisio* OR analy* OR 'area under curve' OR partition* OR survival* OR transitio* OR state* OR discrete* OR individual* OR cohort*)):ab,ti) OR (monte:ab,ti AND carlo:ab,ti) OR economic:ab,ti OR pharmacoeconomic:ab,ti OR markov:ab,ti	2,026,344 Update: 269,677
7	#1 AND #2 AND #3 AND #4 AND #6 NOT #5	1,410 Update: 282

PubMed and MEDLINE In-Process

The searches were conducted on August 11, 2020 (No limits) and updated on November 24, 2021 (limitation on time: Aug 12, 2020 – Nov 24, 2021).

Table 7: PubMed and MEDLINE In-Process search strategy via PubMed at National Library https://pubmed.ncbi.nlm.nih.gov/ (cost-effectiveness)

String Number	Query	Hits
1	"breast neoplasms"[MeSH Terms] OR (breast[tiab] AND (cancer*[tiab] OR neoplas*[tiab] OR tumor*[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR sarcoma*[tiab] OR adenocarcinoma*[tiab] OR malignan*[tiab])) OR (mammary[tiab] AND (cancer*[tiab] OR neoplas*[tiab] OR tumor*[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR sarcoma*[tiab] OR adenocarcinoma*[tiab] OR malignan*[tiab]))	431,753 Update: 36,169
2	metasta*[tiab] OR advance*[tiab] OR unresect*[tiab] OR "un resect*"[tiab] OR nonresect*[tiab] OR "non resect*"[tiab] OR inoperable[tiab] OR (non[tiab] AND amenabl*[tiab] AND surg*[tiab]) OR (non[tiab] AND suit*[tiab] AND surg*[tiab]) OR (non[tiab] AND amenabl*[tiab] AND opera*[tiab]) OR (non[tiab] AND suit*[tiab] AND opera*[tiab]) OR (not[tiab] AND amenabl*[tiab] AND surg*[tiab]) OR (not[tiab] AND suit*[tiab] AND surg*[tiab]) OR (not[tiab] AND amenabl*[tiab] AND opera*[tiab]) OR (not[tiab] AND suit*[tiab] AND opera*[tiab])	1,269,826 Update: 155,452
3	"Neoplasm Recurrence, local"[MeSH] OR recurrence[MeSH] OR "disease resistance"[MeSH] OR "2nd line"[tiab] OR "second line"[tiab] OR "2 l"[tiab] OR "2 line"[tiab] OR 2l[tiab] OR relaps*[tiab] OR 24tiliza*[tiab] OR resis*[tiab] OR 24tili*[tiab] OR progress*[tiab] OR (previ*[tiab] AND (chemo*[tiab] OR line*[tiab] OR therap*[tiab] OR treat*[tiab] OR regim*[tiab] OR fail*[tiab])) OR (prior*[tiab] AND (chemo*[tiab] OR line[tiab] OR therap*[tiab] OR treat*[tiab] OR regim*[tiab] OR fail*[tiab])) OR (heav*[tiab] AND (chemo*[tiab] OR line[tiab] OR therap*[tiab] OR	6,065,425 Update: 571,756

String Number	Query	Hits
	treat*[tiab] OR regim*[tiab] OR fail*[tiab])) OR (post*[tiab] AND (chemo*[tiab] OR line[tiab] OR therap*[tiab] OR treat*[tiab] OR regim*[tiab] OR fail*[tiab])) OR treated[tiab] OR pretreat*[tiab] OR pre-treat*[tiab] OR failed[tiab] OR failure[tiab] OR reoccur*[tiab] OR 25tiliza*[tiab] OR "re occur"[tiab]	
4	"receptor, erbb-2"[MeSH] OR "genes, erbb-2"[MeSH] OR "epidermal growth factor receptor 2"[tiab] OR cd340[tiab] OR erbb2*[tiab] OR "erbb 2*"[tiab] OR her2*[tiab] OR "her 2*"[tiab] OR (neu[tiab] AND protein*[tiab]) OR (neu[tiab] AND oncoprotein*[tiab]) OR (neu[tiab] AND receptor*[tiab]) OR "differentiation factor receptor"[tiab] OR "neuregulin receptor"[tiab] OR "neu receptor"[tiab] OR (immunohistochemistry[tiab] AND (2[tiab] OR 3[tiab])) OR (ihc[tiab] AND (2[tiab] OR 3[tiab])) OR hr positive[tiab] OR "hormone receptor positive"[tiab]	132,672 Update: 14,785
5	"case reports"[pt] OR editorial[pt] OR letter[pt] OR comment[pt] OR "clinical trial, veterinary"[pt]	3,771,946 Update: 224,136
6	"economics, medical"[MeSH] OR "Economics, Pharmaceutical"[MeSH] OR "Economics, Hospital"[MeSH] OR "economics, nursing"[MeSH] OR "models, economic"[MeSH] OR "quality-adjusted life years"[MeSH] OR "decision trees"[MeSH] OR "monte carlo method"[MeSH] OR "survival analysis"[MeSH] OR "computer simulation"[MeSH] OR "patient simulation"[MeSH] OR "sensitivity and specificity"[MeSH] OR "markov chains"[MeSH] OR "health economics"[tiab] OR "quality adjusted life year"[tiab] OR "decision tree"[tiab] OR "monte carlo method"[tiab] OR "survival analysis"[tiab] OR "hidden markov model"[tiab] OR "sensitivity analysis"[tiab] OR "economic model"[tiab] OR "markov chain"[tiab] OR simulation[tiab] OR qaly*[tiab] OR ly[tiab] OR lys[tiab] OR "life year*"[tiab] OR ((cost[tiab] OR costs[tiab]) AND (variable*[tiab] OR unit*[tiab] OR estimate*[tiab])) OR ((cost[tiab] OR costs[tiab]) AND (increment*[tiab] OR effect*[tiab] OR 25tiliza*[tiab] OR benefit*[tiab] OR conseq*[tiab] OR minim*[tiab])) OR icer[tiab] OR "incremental cost effectiveness ratio"[tiab] OR (decision AND (analy*[tiab] OR tree*[tiab])) OR (survival*[tiab] AND analy*[tiab]) OR (model*[tiab] AND (simulat*[tiab] OR 25tilizat*[tiab] OR analy*[tiab] OR "area under curve"[tiab] OR partition*[tiab] OR survival*[tiab] OR 25tilizatio*[tiab] OR state*[tiab] OR discrete*[tiab] OR individual*[tiab] OR cohort*[tiab])) OR (monte[tiab] AND carlo[tiab]) OR economic[tiab] OR pharmacoeconomic[tiab] OR markov[tiab]	3,442,404 Update: 430,822
7	#1 AND #2 AND #3 AND #4 AND #6 NOT #5	4,427 Update: 702

EconLit (platform: EBSCOhost)

The searches were conducted on August 11, 2020 (No limits) and updated on November 24, 2021 (limitation on time: Aug 12, 2020 – Nov 24, 2021).

Table 8: EconLit search strategy via EBSCOhost (cost-effectiveness)

String Number	Query	Limiters/Expanders	Last Run Via	Results
S1	AB (breast N2 (cancer* OR neoplas* OR tumour* OR tumor* OR carcinoma* OR sarcoma* OR adenocarcinoma* OR malignan*)) AND TI (breast N2 (cancer* OR neoplas* OR tumour* OR tumor* OR carcinoma* OR sarcoma* OR adenocarcinoma* OR malignan*)) OR AB (mammary N2 (cancer* OR neoplas* OR tumour* OR tumor* OR carcinoma* OR sarcoma* OR adenocarcinoma* OR malignan*)) AND TI (mammary N2 (cancer* OR neoplas* OR tumour* OR tumor* OR carcinoma* OR sarcoma* OR adenocarcinoma* OR malignan*))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit	103 Update: 7
S2	AB (metasta* OR advanc* OR unresect* OR 'un resect*' OR nonresect* OR 'non resect*' OR inoperable OR (((non OR 'not') N2 (amenabl* OR suit*) N2 (surge* OR surgi* OR opera*)))) AND TI (metasta* OR advanc* OR unresect* OR 'un resect*' OR nonresect* OR 'non resect*' OR inoperable OR (((non OR 'not') N2 (amenabl* OR suit*) N2 (surge* OR surgi* OR opera*))))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit	1,290 Update: 95
S3	AB ('cancer recurrence' OR relapse OR 'cancer resistance' OR relaps* OR refrac* OR resist* OR recurr* OR progress* OR (((previ* OR prior* OR heav* OR post*) N4 (chemo* OR line* OR therap* OR treat* OR regim* OR fail*))) OR treated OR pretreat* OR pre-treat* OR failed OR failure OR reocur* OR 're ocur*' OR reoccur* OR 're occur*') AND TI ('cancer recurrence' OR relapse OR 'cancer resistance' OR relaps* OR refrac* OR resist* OR recurr* OR progress* OR (((previ* OR prior* OR heav* OR post*) N4 (chemo* OR line* OR therap* OR treat* OR regim* OR fail*))) OR treated OR pretreat* OR pre-treat* OR failed OR failure OR reocur* OR 're ocur*' OR reoccur* OR 're occur*')	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit	4,664 Update: 290
S4	AB ('epidermal growth factor receptor 2' OR 'epidermal growth factor receptor 2' OR cd340 OR erbb2* OR ‘erbb 2*’ OR her2* OR ‘her 2*’ OR ((neu N1 (protein* OR oncoprotein* OR receptor*))) OR 'differentiation factor receptor' OR 'neuregulin receptor' OR (((immunohistochemistry OR ihc) N2 (3 OR 2))) OR ‘hr positive’ OR 'hormone receptor positive') AND TI ('epidermal	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit	4 Update: 0

String Number	Query	Limiters/Expanders	Last Run Via	Results
	growth factor receptor 2' OR 'epidermal growth factor receptor 2' OR cd340 OR erbb2* OR ‘erbb 2*’ OR her2* OR ‘her 2*’ OR ((neu N1 (protein* OR oncoprotein* OR receptor*))) OR 'differentiation factor receptor' OR 'neuregulin receptor' OR (((immunohistochemistry OR ihc) N2 (3 OR 2))) OR ‘hr positive’ OR 'hormone receptor positive')			
S5	AB ('health economics' OR 'quality adjusted life year' OR 'decision tree' OR 'monte carlo method' OR 'survival analysis' OR 'hidden markov model' OR 'sensitivity analysis' OR 'economic model' OR 'markov chain' OR simulation OR 'health economics' OR 'quality adjusted life year' OR 'decision tree' OR 'monte carlo method' OR 'survival analysis' OR 'hidden markov model' OR 'sensitivity analysis' OR 'economic model' OR 'markov chain' OR simulation OR qaly* OR ly OR lys OR 'life year*' OR (((cost OR costs) N1 (variable* OR unit* OR estimate*))) OR (((cost OR costs) N3 (increment* OR effect* OR utilit* OR benefit* OR conseq* OR minim*))) OR icer OR 'incremental cost effectiveness ratio' OR ((decision N2 (analy* OR tree*))) OR ((survival* N2 analy*)) OR ((model* N3 (simulat* OR decisio* OR analy* OR 'area under curve' OR partition* OR survival* OR transitio* OR state* OR discrete* OR individual* OR cohort*))) OR (monte AND carlo) OR economic OR pharmacoeconomic OR markov) AND TI ('health economics' OR 'quality adjusted life year' OR 'decision tree' OR 'monte carlo method' OR 'survival analysis' OR 'hidden markov model' OR 'sensitivity analysis' OR 'economic model' OR 'markov chain' OR simulation OR 'health economics' OR 'quality adjusted life year' OR 'decision tree' OR 'monte carlo method' OR 'survival analysis' OR 'hidden markov model' OR 'sensitivity analysis' OR 'economic model' OR 'markov chain' OR simulation OR qaly* OR ly OR lys OR 'life year*' OR (((cost OR costs) N1 (variable* OR unit* OR estimate*))) OR (((cost OR costs) N3 (increment* OR effect* OR utilit* OR benefit* OR conseq* OR minim*))) OR icer OR 'incremental cost effectiveness ratio'	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit	64,874 Update: 3,375

String Number	Query	Limiters/Expanders	Last Run Via	Results
	OR ((decision N2 (analy* OR tree*))) OR ((survival* N2 analy*)) OR ((model* N3 (simulat* OR decisio* OR analy* OR 'area under curve' OR partition* OR survival* OR transitio* OR state* OR discrete* OR individual* OR cohort*))) OR (monte AND carlo) OR economic OR pharmacoeconomic OR markov)			
S6	S1 AND S2 AND S3 AND S4 AND S5	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit	1 Update: 0

CRD

The searches were conducted on August 11, 2020 (No limits). An update was not executed. The CRD statement for the rationale for not updating is:

"CRD would like to reassure our many thousands of users that we are committed to maintaining archive versions of DARE and NHSEED until at least the end of March 2022 (the point to which we have funds to support maintenance). [Bibliographic records were published on DARE and NHS EED until 31st March 2015. Searches of MEDLINE, Embase, CINAHL, PsycINFO and PubMed were continued until the end of the 2014.]"

Table 9: CRD search strategy (cost-effectiveness)

String Number	Query	Hits
1	(MeSH DESCRIPTOR breast neoplasms EXPLODE ALL TREES) OR ((breast NEAR2 (cancer* OR neoplas* OR tumour* OR tumor* OR carcinoma* OR sarcoma* OR adenocarcinoma* OR malignan*)):ti) OR ((mammary NEAR2 (cancer* OR neoplas* OR tumour* OR tumor* OR carcinoma* OR sarcoma* OR adenocarcinoma* OR malignan*)):ti)	1,978
2	metasta*:ti OR advanc*:ti OR unresect*:ti OR un resect*:ti OR nonresect*:ti OR non resect*:ti OR inoperable:ti OR ((non OR 'not') NEAR2 (amenabl* OR suit*) NEAR2 (surge* OR surgi* OR opera*)):ti	2,197
3	(MeSH DESCRIPTOR neoplasm recurrence, local EXPLODE ALL TREES) OR (MeSH DESCRIPTOR recurrence EXPLODE ALL TREES) OR (MeSH DESCRIPTOR disease resistance EXPLODE ALL TREES) OR relaps*:ti OR refrac*:ti OR resist*:ti OR recurr*:ti OR progress*:ti OR (((previ* OR prior* OR heav* OR post*) NEAR4 (chemo* OR line* OR therap* OR treat* OR regim* OR fail*)):ti) OR treated:ti OR pretreat*:ti OR	4,650

String Number	Query	Hits
	pre-treat*:ti OR failed:ti OR failure:ti OR reocur*:ti OR re ocur*:ti OR reoccur*:ti OR re occur*:ti	
4	(MeSH DESCRIPTOR receptor, erbb-2 EXPLODE ALL TREES) OR (MeSH DESCRIPTOR genes, erbb-2 EXPLODE ALL TREES) OR epidermal growth factor receptor 2:ti OR cd340:ti OR erbb2*:ti OR erbb 2*:ti OR her2*:ti OR her 2*:ti OR ((neu NEAR1 (protein* OR oncoprotein* OR receptor*)):ti) OR differentiation factor receptor:ti OR neuregulin receptor:ti OR (((immunohistochemistry OR ihc) NEAR2 (3 OR 2)):ti) OR hr positive:ti OR hormone receptor positive:ti	165
5	(MeSH DESCRIPTOR case reports EXPLODE ALL TREES) OR (MeSH DESCRIPTOR editorial EXPLODE ALL TREES) OR (MeSH DESCRIPTOR letter EXPLODE ALL TREES) OR ((MeSH DESCRIPTOR animal EXPLODE ALL TREES) NOT ((MeSH DESCRIPTOR animal EXPLODE ALL TREES) AND (MeSH DESCRIPTOR human EXPLODE ALL TREES))) OR (MeSH DESCRIPTOR meta-analysis as topic EXPLODE ALL TREES) OR case study:ti OR case report:ti OR abstract report:ti OR editorial:ti OR veterinary clinical trial:ti OR letter:ti OR note:ti OR ((review:ti OR literature review:ti) NOT (meta-analysis:ti OR systematic review:ti OR systematic literature review:ti OR meta analysis:ti))	3,574
6	(MeSH DESCRIPTOR economics, medical EXPLODE ALL TREES) OR (MeSH DESCRIPTOR Economics, Pharmaceutical EXPLODE ALL TREES) OR (MeSH DESCRIPTOR Economics, Hospital EXPLODE ALL TREES) OR (MeSH DESCRIPTOR economics, nursing EXPLODE ALL TREES) OR (MeSH DESCRIPTOR models, economic EXPLODE ALL TREES) OR (MeSH DESCRIPTOR quality-adjusted life years EXPLODE ALL TREES) OR (MeSH DESCRIPTOR decision trees EXPLODE ALL TREES) OR (MeSH DESCRIPTOR monte carlo method EXPLODE ALL TREES) OR (MeSH DESCRIPTOR survival analysis EXPLODE ALL TREES) OR (MeSH DESCRIPTOR computer simulation EXPLODE ALL TREES) OR (MeSH DESCRIPTOR patient simulation EXPLODE ALL TREES) OR (MeSH DESCRIPTOR sensitivity and specificity EXPLODE ALL TREES) OR (MeSH DESCRIPTOR markov chains EXPLODE ALL TREES) OR health economics:ti OR quality adjusted life year:ti OR decision tree:ti OR monte carlo method:ti OR survival analysis:ti OR hidden markov model:ti OR sensitivity analysis:ti OR economic model:ti OR markov chain:ti OR simulation:ti OR qaly*:ti OR ly:ti OR lys:ti OR life year*:ti OR (((cost OR costs) NEAR1 (variable* OR unit* OR estimate*)):ti) OR (((cost OR costs) NEAR3 (increment* OR effect* OR utilit* OR benefit* OR conseq* OR minim*)):ti) OR icer:ti OR incremental cost effectiveness ratio:ti OR ((decision NEAR2 (analy* OR tree*)):ti) OR ((survival* NEAR2 analy*):ti) OR ((model* NEAR3 (simulat* OR decisio* OR analy* OR area under curve OR partition* OR survival* OR transitio* OR state* OR discrete* OR individual* OR cohort*)):ti) OR (monte:ti AND carlo:ti) OR economic:ti OR pharmacoeconomic:ti OR markov:ti	17,944
7	#1 AND #2 AND #3 AND #4 AND #6 NOT #5	3

ScHARRHUD

The searches were run on August 11, 2020 for the relevant status of HER2 and HR, which returned zero results in the initial search. The update was not executed as in the ScHARRHUD database, the most recent published study was from 2017. No

studies after 2017 are found in the ScHARRHUD database, therefore ScHARRHUD was not included in the update.

Table 10: ScHARRHUD search strategy (cost-effectiveness)

String Number	Query	Hits
1	'epidermal growth factor receptor 2':AB,TI OR cd340:AB,TI OR erbb2*:AB,TI OR 'erbb 2*':AB,TI OR her2*:AB,TI OR 'her 2*':AB,TI OR ((neu NEAR (protein* OR oncoprotein* OR receptor*)):AB,TI) OR 'differentiation factor receptor':AB,TI OR 'neuregulin receptor':AB,TI OR (((immunohistochemistry OR ihc) NEAR (3 OR 2)):AB,TI) OR 'hr positive':AB,TI OR 'hormone receptor positive':AB,TI	0

A10. Regarding the conference searches conducted for cost-effectiveness studies (Appendix H, section H.1.1, page 25), could the company please provide a rationale for the time limits used in the conference searches (2018-2021)?

Please refer to the response to A6 above.

A11. Regarding the other sources searched for cost effectiveness information (as described in Appendix H, section H.1.1, page 25) the company states that data were available on HTA body websites for clinical trials on which manufacturer submissions are based". Please could the company provide details of the dates of the search and the exact HTA bodies and the urls for the webpages where data were sought?

Please refer to the response to A7 above. The search was performed at once and articles were assessed to be eligible for either of the three economic SLR sub searches

A12. HRQoL Appendix I section I.1.1, page 31 refers the reader to 'Appendix G**,** Section G.1.1**'** for the search strategy. This is the wrong appendix (see C1)? Could the company please provide the full search details and the full search strategies in order that the EAG can

fully critically appraise the searches performed. For HRQoL - could the company please provide:

a. The full details (i.e., dates/dates of coverage of the databases searched);

b. The date(s) on which each search was performed;

c. The complete search strategies for all the databases (none are listed in I.1.1), exactly as run, including the number of records (hits) retrieved by each line of the search;

d. The strategies should please include any limitations imposed on the search and for updated searches should also include any terms/syntax/limits applied and/or any date fields specifically searched.

Full details of the search strategies are presented in turn below. MEDLINE was included in both the Embase searches, and via PubMed.

Embase and MEDLINE

The searches were conducted on August 11, 2020 (No limits) and updated on November 24, 2021 (limitation on time: Aug 12, 2020 – Nov 24, 2021).

Table 11: Embase and MEDLINE search strategy via Embase.com (HRQoL)

String Number	Query	Hits
1	'breast cancer'/exp OR ((breast NEAR/2 (cancer* OR neoplas* OR tumour* OR tumor* OR carcinoma* OR sarcoma* OR adenocarcinoma* OR malignan*)):ab,ti) OR ((mammary NEAR/2 (cancer* OR neoplas* OR tumour* OR tumor* OR carcinoma* OR sarcoma* OR adenocarcinoma* OR malignan*)):ab,ti)	585,148 Update: 63,654
2	metasta*:ab,ti OR advanc*:ab,ti OR unresect*:ab,ti OR 'un resect*':ab,ti OR nonresect*:ab,ti OR 'non resect*':ab,ti OR inoperable:ab,ti OR (((non OR 'not') NEAR/2 (amenabl* OR suit*) NEAR/2 (surge* OR surgi* OR opera*)):ab,ti)	1,773,747 Update: 237,888
3	'cancer recurrence'/exp OR relapse/exp OR 'cancer resistance'/exp OR relaps*:ab,ti OR refrac*:ab,ti OR resist*:ab,ti OR recurr*:ab,ti OR progress*:ab,ti OR (((previ* OR prior* OR heav* OR post*) NEAR/4 (chemo* OR line* OR therap* OR treat* OR regim* OR fail*)):ab,ti) OR treated:ab,ti OR pretreat*:ab,ti OR pre-treat*:ab,ti OR failed:ab,ti OR failure:ab,ti OR reocur*:ab,ti OR 're ocur*':ab,ti OR reoccur*:ab,ti OR 're occur*':ab,ti	7,074,288 Update: 761,845
4	'epidermal growth factor receptor 2'/exp OR 'epidermal growth factor receptor 2':ab,ti OR cd340:ab,ti OR erbb2*:ab,ti OR ‘erbb 2*’:ab,ti OR her2*:ab,ti OR ‘her 2*’:ab,ti OR ((neu NEAR/1 (protein* OR oncoprotein* OR receptor*)):ab,ti) OR 'differentiation factor receptor':ab,ti OR 'neuregulin receptor':ab,ti OR (((immunohistochemistry OR ihc) NEAR/2 (3 OR 2)):ab,ti) OR ‘hr positive’:ab,ti OR 'hormone receptor positive':ab,ti	100,420 Update: 14,029

String Number	Query	Hits
5	'case report'/exp OR 'case study'/exp OR 'abstract report'/exp OR 'editorial'/exp OR 'veterinary clinical trial'/exp OR letter/exp OR note/exp OR (animal/exp NOT (animal/exp AND human/exp)) OR 'meta-analysis (topic)'/exp OR 'case study':it OR 'case study':ab,ti OR 'case report':it OR 'case report':ab,ti OR 'abstract report':it OR 'abstract report':ab,ti OR editorial:it OR editorial:ab,ti OR 'veterinary clinical trial':it OR 'veterinary clinical trial':ab,ti OR letter:it OR letter:ab,ti OR note:it OR note:ab,ti OR ((review:it OR review:ab,ti OR 'literature review':it OR 'literature review':ab,ti) NOT ('meta-analysis':it OR 'meta-analysis':ab,ti OR 'meta-analysis (topic)':it OR 'systematic review':it OR 'systematic literature review':it OR 'meta-analysis':ab,ti OR 'meta analysis':ab,ti))	13,886,323 Update: 1,090,134
6	'european quality of life 5 dimensions questionnaire'/exp OR 'short form 36'/exp OR 'patient preference'/exp OR 'visual analog scale'/exp OR 'quality of life'/exp OR utilit*:ab,ti OR disutilit*:ab,ti OR 'sf 6':ab,ti OR sf6:ab,ti OR 'short form 6':ab,ti OR 'shortform 6':ab,ti OR 'sf six':ab,ti OR 'sfsix':ab,ti OR 'shortform six':ab,ti OR 'short form six':ab,ti OR 'sf 36':ab,ti OR sf36:ab,ti OR 'short form 36':ab,ti OR 'shortform 36':ab,ti OR 'sf thirtysix':ab,ti OR 'sfthirtysix':ab,ti OR 'shortform thirtysix':ab,ti OR 'short form thirtysix':ab,ti OR euroqol:ab,ti OR 'euro qol':ab,ti OR eq5d:ab,ti OR 'eq 5d':ab,ti OR 'health utilities index':ab,ti OR hui:ab,ti OR hui1:ab,ti OR hui2:ab,ti OR hui3:ab,ti OR ((standard NEXT/1 gamble*):ab,ti) OR 'quality of life*':ab,ti OR 'time trade off':ab,ti OR 'time tradeoff':ab,ti OR tto:ab,ti OR 'visual analog scale':ab,ti OR 'patient preference':ab,ti OR 'european quality of life 5 dimensions questionnaire':ab,ti	972,401 Update: 148,839
7	#1 AND #2 AND #3 AND #4 AND #6 NOT #5	1,101 Update: 235

PubMed and MEDLINE In-Process

The searches were conducted on August 7, 2020 (No limits) and updated on November 24, 2021 (limitation on time: Aug 8, 2020 – Nov 24, 2021).

Table 12: PubMed and MEDLINE In-Process search strategy via PubMed at National Library https://pubmed.ncbi.nlm.nih.gov/ (HRQoL)

String Number	Query	Hits
1	"breast neoplasms"[MeSH Terms] OR (breast[tiab] AND (cancer*[tiab] OR neoplas*[tiab] OR tumor*[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR sarcoma*[tiab] OR adenocarcinoma*[tiab] OR malignan*[tiab])) OR (mammary[tiab] AND (cancer*[tiab] OR neoplas*[tiab] OR tumor*[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR sarcoma*[tiab] OR adenocarcinoma*[tiab] OR malignan*[tiab]))	431,753 Update: 36,169
2	metasta*[tiab] OR advance*[tiab] OR unresect*[tiab] OR "un resect*"[tiab] OR nonresect*[tiab] OR "non resect*"[tiab] OR inoperable[tiab] OR (non[tiab] AND amenabl*[tiab] AND surg*[tiab]) OR (non[tiab] AND suit*[tiab] AND surg*[tiab]) OR (non[tiab] AND amenabl*[tiab] AND opera*[tiab]) OR (non[tiab] AND suit*[tiab] AND opera*[tiab]) OR (not[tiab] AND amenabl*[tiab] AND surg*[tiab]) OR (not[tiab] AND suit*[tiab] AND	1,269,826 Update: 155,452

String Number	Query	Hits
	surg*[tiab]) OR (not[tiab] AND amenabl*[tiab] AND opera*[tiab]) OR (not[tiab] AND suit*[tiab] AND opera*[tiab])	
3	"Neoplasm Recurrence, local"[MeSH] OR recurrence[MeSH] OR "disease resistance"[MeSH] OR "2nd line"[tiab] OR "second line"[tiab] OR "2 l"[tiab] OR "2 line"[tiab] OR 2l[tiab] OR relaps*[tiab] OR refrac*[tiab] OR resis*[tiab] OR recurr*[tiab] OR progress*[tiab] OR (previ*[tiab] AND (chemo*[tiab] OR line*[tiab] OR therap*[tiab] OR treat*[tiab] OR regim*[tiab] OR fail*[tiab])) OR (prior*[tiab] AND (chemo*[tiab] OR line[tiab] OR therap*[tiab] OR treat*[tiab] OR regim*[tiab] OR fail*[tiab])) OR (heav*[tiab] AND (chemo*[tiab] OR line[tiab] OR therap*[tiab] OR treat*[tiab] OR regim*[tiab] OR fail*[tiab])) OR (post*[tiab] AND (chemo*[tiab] OR line[tiab] OR therap*[tiab] OR treat*[tiab] OR regim*[tiab] OR fail*[tiab])) OR treated[tiab] OR pretreat*[tiab] OR pre-treat*[tiab] OR failed[tiab] OR failure[tiab] OR reoccur*[tiab] OR reocur*[tiab] OR "re occur"[tiab]	6,060,425 Update: 571,756
4	"receptor, erbb-2"[MeSH] OR "genes, erbb-2"[MeSH] OR "epidermal growth factor receptor 2"[tiab] OR cd340[tiab] OR erbb2*[tiab] OR "erbb 2*"[tiab] OR her2*[tiab] OR "her 2*"[tiab] OR (neu[tiab] AND protein*[tiab]) OR (neu[tiab] AND oncoprotein*[tiab]) OR (neu[tiab] AND receptor*[tiab]) OR "differentiation factor receptor"[tiab] OR "neuregulin receptor"[tiab] OR "neu receptor"[tiab] OR (immunohistochemistry[tiab] AND (2[tiab] OR 3[tiab])) OR (ihc[tiab] AND (2[tiab] OR 3[tiab])) OR hr positive[tiab] OR "hormone receptor positive"[tiab]	132,672 Update: 14,785
5	"case reports"[pt] OR editorial[pt] OR letter[pt] OR comment[pt] OR "clinical trial, veterinary"[pt]	3,771,946 Update: 224,136
6	"Patient Health Questionnaire"[MeSH] OR "patient preference"[MeSH] OR "quality of life"[MeSH] OR "visual analog scale"[MeSH] OR utilit*[tiab] OR disutilit*[tiab] OR "sf 6"[tiab] OR sf6[tiab] OR "short form 6"[tiab] OR "sf six"[tiab] OR "sfsix"[tiab] OR "short form six"[tiab] OR "sf 36"[tiab] OR sf36[tiab] OR "short form 36"[tiab] OR "shortform 36"[tiab] OR euroqol[tiab] OR "euro qol"[tiab] OR eq5d[tiab] OR "eq 5d"[tiab] OR "health utilities index"[tiab] OR hui[tiab] OR hui1[tiab] OR hui2[tiab] OR hui3[tiab] OR (standard[tiab] AND gamble*[tiab]) OR "quality of life*"[tiab] OR "time trade off"[tiab] OR "time tradeoff"[tiab] OR tto[tiab] OR "visual analog scale"[tiab] OR "patient preference"[tiab]	579,413 Update: 78,260
7	#1 AND #2 AND #3 AND #4 AND #6 NOT #5	512 Update: 99

EconLit (platform: via EBSCOhost)

The searches were conducted on August 11, 2020 (No limits) and updated on November 24, 2021 (limitation on time: Aug 12, 2020 – Nov 24, 2021).

Table 13: EconLit search strategy via EBSCOhost (HRQoL)

String Number	Query			Hits
S1	AB ('breast cancer' OR ((breast N2 (cancer* OR neoplas* OR tumour* OR tumor* OR carcinoma* OR sarcoma* OR adenocarcinoma* OR malignan*))) OR ((mammary N2 (cancer* OR neoplas* OR tumour* OR tumor* OR carcinoma* OR sarcoma* OR adenocarcinoma* OR malignan*)))) AND TI ('breast cancer' OR ((breast N2 (cancer* OR neoplas* OR tumour* OR tumor* OR carcinoma* OR sarcoma* OR adenocarcinoma* OR malignan*))) OR ((mammary N2 (cancer* OR neoplas* OR tumour* OR tumor* OR carcinoma* OR sarcoma* OR adenocarcinoma* OR malignan*))))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit	103 Update; 7
S2	AB (metasta* OR advanc* OR unresect* OR 'un resect*' OR nonresect* OR 'non resect*' OR inoperable OR (((non OR 'not') N2 (amenabl* OR suit*) N2 (surge* OR surgi* OR opera*)))) AND TI (metasta* OR advanc* OR unresect* OR 'un resect*' OR nonresect* OR 'non resect*' OR inoperable OR (((non OR 'not') N2 (amenabl* OR suit*) N2 (surge* OR surgi* OR opera*))))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit	1,290 Update: 95
S3	AB ('cancer recurrence' OR relapse OR 'cancer resistance' OR relaps* OR refrac* OR resist* OR recurr* OR progress* OR (((previ* OR prior* OR heav* OR post*) N4 (chemo* OR line* OR therap* OR treat* OR regim* OR fail*))) OR treated OR pretreat* OR pre-treat* OR failed OR failure OR reocur* OR 're ocur*' OR reoccur* OR 're occur*') AND TI ('cancer recurrence' OR relapse OR 'cancer resistance' OR relaps* OR refrac* OR resist* OR recurr* OR progress* OR (((previ* OR prior* OR heav* OR post*) N4 (chemo* OR line* OR therap* OR treat* OR regim* OR fail*))) OR treated OR pretreat* OR pre-treat* OR failed OR failure OR reocur* OR 're ocur*' OR reoccur* OR 're occur*')	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit	4,664 Update: 290
S4	AB ('epidermal growth factor receptor 2' OR 'epidermal growth factor receptor 2' OR cd340 OR erbb2* OR ‘erbb 2*’ OR her2* OR ‘her 2*’ OR ((neu N1 (protein* OR oncoprotein* OR receptor*))) OR 'differentiation factor receptor' OR 'neuregulin receptor' OR (((immunohistochemistry OR ihc) N2 (3 OR 2))) OR ‘hr positive’ OR 'hormone receptor positive') AND TI ('epidermal growth factor receptor 2' OR 'epidermal growth factor	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit	4 Update: 0

String Number	Query			Hits
	receptor 2' OR cd340 OR erbb2* OR 'erbb 2*' OR her2* OR 'her 2*' OR ((neu N1 (protein* OR oncoprotein* OR receptor*))) OR 'differentiation factor receptor' OR 'neuregulin receptor' OR (((immunohistochemistry OR ihc) N2 (3 OR 2))) OR 'hr positive' OR 'hormone receptor positive')			
S5	AB ('european quality of life 5 dimensions questionnaire' OR 'short form 36' OR 'patient preference' OR 'visual analog scale' OR 'quality of life' OR utilit* OR disutilit* OR 'sf 6' OR sf6 OR 'short form 6' OR 'shortform 6' OR 'sf six' OR 'sfsix' OR 'shortform six' OR 'short form six' OR 'sf 36' OR sf36 OR 'short form 36' OR 'shortform 36' OR 'sf thirtysix' OR 'sfthirtysix' OR 'shortform thirtysix' OR 'short form thirtysix' OR euroqol OR 'euro qol' OR eq5d OR 'eq 5d' OR 'health utilities index' OR hui OR hui1 OR hui2 OR hui3 OR ((standard N1 gamble*)) OR 'quality of life*' OR 'time trade off' OR 'time tradeoff' OR tto OR 'visual analog scale' OR 'patient preference' OR 'european quality of life 5 dimensions questionnaire') AND TI ('european quality of life 5 dimensions questionnaire' OR 'short form 36' OR 'patient preference' OR 'visual analog scale' OR 'quality of life' OR utilit* OR disutilit* OR 'sf 6' OR sf6 OR 'short form 6' OR 'shortform 6' OR 'sf six' OR 'sfsix' OR 'shortform six' OR 'short form six' OR 'sf 36' OR sf36 OR 'short form 36' OR 'shortform 36' OR 'sf thirtysix' OR 'sfthirtysix' OR 'shortform thirtysix' OR 'short form thirtysix' OR euroqol OR 'euro qol' OR eq5d OR 'eq 5d' OR 'health utilities index' OR hui OR hui1 OR hui2 OR hui3 OR ((standard N1 gamble*)) OR 'quality of life*' OR 'time trade off' OR 'time tradeoff' OR tto OR 'visual analog scale' OR 'patient preference' OR 'european quality of life 5 dimensions questionnaire')	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit	4,233 Update: 197
S6	S1 AND S2 AND S3 AND S4 AND S5	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit	0 Update: 0

CRD

The searches were conducted on August 11, 2020 (No limits). An update was not executed. The CRD statement for the rationale for not updating is:

"CRD would like to reassure our many thousands of users that we are committed to maintaining archive versions of DARE and NHSEED until at least the end of March 2022 (the point to which we have funds to support maintenance). [Bibliographic records were published on DARE and NHS EED until 31st March 2015. Searches of MEDLINE, Embase, CINAHL, PsycINFO and PubMed were continued until the end of the 2014.]"

Table 14: CRD search strategy (HRQoL)

String Number	Query	Hits
1	(MeSH DESCRIPTOR breast neoplasms EXPLODE ALL TREES) OR ((breast NEAR2 (cancer* OR neoplas* OR tumour* OR tumor* OR carcinoma* OR sarcoma* OR adenocarcinoma* OR malignan*)):ti) OR ((mammary NEAR2 (cancer* OR neoplas* OR tumour* OR tumor* OR carcinoma* OR sarcoma* OR adenocarcinoma* OR malignan*)):ti)	1,978
2	metasta*:ti OR advanc*:ti OR unresect*:ti OR un resect*:ti OR nonresect*:ti OR non resect*:ti OR inoperable:ti OR ((non OR 'not') NEAR2 (amenabl* OR suit*) NEAR2 (surge* OR surgi* OR opera*)):ti	2,197
3	(MeSH DESCRIPTOR neoplasm recurrence, local EXPLODE ALL TREES) OR (MeSH DESCRIPTOR recurrence EXPLODE ALL TREES) OR (MeSH DESCRIPTOR disease resistance EXPLODE ALL TREES) OR relaps*:ti OR refrac*:ti OR resist*:ti OR recurr*:ti OR progress*:ti OR (((previ* OR prior* OR heav* OR post*) NEAR4 (chemo* OR line* OR therap* OR treat* OR regim* OR fail*)):ti) OR treated:ti OR pretreat*:ti OR pre-treat*:ti OR failed:ti OR failure:ti OR reocur*:ti OR re ocur*:ti OR reoccur*:ti OR re occur*:ti	4,650
4	(MeSH DESCRIPTOR receptor, erbb-2 EXPLODE ALL TREES) OR (MeSH DESCRIPTOR genes, erbb-2 EXPLODE ALL TREES) OR epidermal growth factor receptor 2:ti OR cd340:ti OR erbb2*:ti OR erbb 2*:ti OR her2*:ti OR her 2*:ti OR ((neu NEAR1 (protein* OR oncoprotein* OR receptor*)):ti) OR differentiation factor receptor:ti OR neuregulin receptor:ti OR (((immunohistochemistry OR ihc) NEAR2 (3 OR 2)):ti) OR hr positive:ti OR hormone receptor positive:ti	165
5	(MeSH DESCRIPTOR case reports EXPLODE ALL TREES) OR (MeSH DESCRIPTOR editorial EXPLODE ALL TREES) OR (MeSH DESCRIPTOR letter EXPLODE ALL TREES) OR ((MeSH DESCRIPTOR animal EXPLODE ALL TREES) NOT ((MeSH DESCRIPTOR animal EXPLODE ALL TREES) AND (MeSH DESCRIPTOR human EXPLODE ALL TREES))) OR (MeSH DESCRIPTOR meta-analysis as topic EXPLODE ALL TREES) OR case study:ti OR case report:ti OR abstract report:ti OR editorial:ti OR veterinary clinical trial:ti OR letter:ti OR note:ti OR ((review:ti OR literature review:ti) NOT (meta-analysis:ti OR systematic review:ti OR systematic literature review:ti OR meta analysis:ti))	3,574
6	(MeSH DESCRIPTOR surveys and questionnaires EXPLODE ALL TREES) OR (MeSH DESCRIPTOR patient preference EXPLODE ALL	7,553

String Number	Query	Hits
	TREES) OR (MeSH DESCRIPTOR quality of life EXPLODE ALL TREES) OR (MeSH DESCRIPTOR visual analog scale EXPLODE ALL TREES) OR utilit*:ti OR disutilit*:ti OR sf 6:ti OR sf6:ti OR short form 6:ti OR shortform 6:ti OR sf six:ti OR sfsix:ti OR shortform six:ti OR short form six:ti OR sf 36:ti OR sf36:ti OR short form 36:ti OR shortform 36:ti OR sf thirtysix:ti OR sfthirtysix:ti OR shortform thirtysix:ti OR short form thirtysix:ti OR euroqol:ti OR euro qol:ti OR eq5d:ti OR eq 5d:ti OR health utilities index:ti OR hui:ti OR hui1:ti OR hui2:ti OR hui3:ti OR ((standard NEAR1 gamble*):ti) OR quality of life*:ti OR time trade off:ti OR time tradeoff:ti OR tto:ti OR visual analog scale:ti OR patient preference:ti OR european quality of life 5 dimensions questionnaire:ti	
7	#1 AND #2 AND #3 AND #4 AND #6 NOT #5	0

ScHARRHUD

The searches were run on August 11, 2020 for the relevant status of HER2 and HR, which returned zero results in the initial search. The update was not executed as in the ScHARRHUD database, the most recent published study was from 2017. No studies after 2017 are found in the ScHARRHUD database, therefore ScHARRHUD was not included in the update.

Table 15: ScHARRHUD search strategy (HRQoL)

String Number	Query	Hits
1	'epidermal growth factor receptor 2':AB,TI OR cd340:AB,TI OR erbb2*:AB,TI OR ‘erbb 2*’:AB,TI OR her2*:AB,TI OR ‘her 2*’:AB,TI OR ((neu NEAR (protein* OR oncoprotein* OR receptor*)):AB,TI) OR 'differentiation factor receptor':AB,TI OR 'neuregulin receptor':AB,TI OR (((immunohistochemistry OR ihc) NEAR (3 OR 2)):AB,TI) OR ‘hr positive’:AB,TI OR 'hormone receptor positive':AB,TI	0

A13. For the cost and resource use searches (Appendix J, section J.1.1, page 53), could the company please provide a detailed list of databases used and complete search strategies

"as run" with hits per line and date of searching for the cost and resource use evidence search?

a. The full details (i.e. dates/dates of coverage of the databases searched);

b. The date(s) on which each search was performed?

c. The complete search strategies for all the databases (none are listed in J.1.1), exactly as run, including the number of records (hits) retrieved by each line of the search;

d. The strategies should please include any limitations imposed on the search and for updated searches should also include any terms/syntax/limits applied and/or any date fields specifically searched.

Full details of the search strategies are presented in turn below. MEDLINE was included in both the Embase searches, and via PubMed.

Embase and MEDLINE

The searches were conducted on August 11, 2020 (No limits) and updated on November 24, 2021 (limitation on time: Aug 12, 2020 – Nov 24, 2021).

Table 16: Embase and MEDLINE search strategy via Embase.com (cost and resource use)

String Number	Query	Hits
1	'breast cancer'/exp OR ((breast NEAR/2 (cancer* OR neoplas* OR tumour* OR tumor* OR carcinoma* OR sarcoma* OR adenocarcinoma* OR malignan*)):ab,ti) OR ((mammary NEAR/2 (cancer* OR neoplas* OR tumour* OR tumor* OR carcinoma* OR sarcoma* OR adenocarcinoma* OR malignan*)):ab,ti)	585,148 Update: 63,654
2	metasta*:ab,ti OR 38tiliza*:ab,ti OR unresect*:ab,ti OR 'un resect*':ab,ti OR nonresect*:ab,ti OR 'non resect*':ab,ti OR inoperable:ab,ti OR (((non OR 'not') NEAR/2 (amenabl* OR suit*) NEAR/2 (surge* OR surgi* OR opera*)):ab,ti)	1,773,747 Update: 237,888
3	'cancer recurrence'/exp OR relapse/exp OR 'cancer resistance'/exp OR relaps*:ab,ti OR 38tiliza*:ab,ti OR resist*:ab,ti OR 38tili*:ab,ti OR progress*:ab,ti OR (((previ* OR prior* OR heav* OR post*) NEAR/4 (chemo* OR line* OR therap* OR treat* OR regim* OR fail*)):ab,ti) OR treated:ab,ti OR pretreat*:ab,ti OR pre-treat*:ab,ti OR failed:ab,ti OR failure:ab,ti OR 38tiliza*:ab,ti OR 're occur*':ab,ti OR reoccur*:ab,ti OR 're occur*':ab,ti	7,074,288 Update: 761,845
4	'epidermal growth factor receptor 2'/exp OR 'epidermal growth factor receptor 2':ab,ti OR cd340:ab,ti OR erbb2*:ab,ti OR 'erbb 2*':ab,ti OR her2*:ab,ti OR 'her 2*':ab,ti OR ((neu NEAR/1 (protein* OR oncoprotein* OR receptor*)):ab,ti) OR 'differentiation factor receptor':ab,ti OR	100,420 Update: 14,029

String Number	Query	Hits
	'neuregulin receptor':ab,ti OR (((immunohistochemistry OR ihc) NEAR/2 (3 OR 2)):ab,ti) OR 'hr positive':ab,ti OR 'hormone receptor positive':ab,ti	
5	'case report'/exp OR 'case study'/exp OR 'abstract report'/exp OR 'editorial'/exp OR 'veterinary clinical trial'/exp OR letter/exp OR note/exp OR (animal/exp NOT (animal/exp AND human/exp)) OR 'meta-analysis (topic)'/exp OR 'case study':it OR 'case study':ab,ti OR 'case report':it OR 'case report':ab,ti OR 'abstract report':it OR 'abstract report':ab,ti OR editorial:it OR editorial:ab,ti OR 'veterinary clinical trial':it OR 'veterinary clinical trial':ab,ti OR letter:it OR letter:ab,ti OR note:it OR note:ab,ti OR ((review:it OR review:ab,ti OR 'literature review':it OR 'literature review':ab,ti) NOT ('meta-analysis':it OR 'meta-analysis':ab,ti OR 'meta-analysis (topic)':it OR 'systematic review':it OR 'systematic literature review':it OR 'meta-analysis':ab,ti OR 'meta analysis':ab,ti))	13,886,323 Update: 1,090,134
6	'cost control'/exp OR 'cost of illness'/exp OR 'health care cost'/exp OR 'health care utilization'/exp OR 'resource management'/exp OR 'length of stay'/exp OR 'economic aspect'/exp OR ((('health care' OR healthcare) NEXT/1 (cost OR costs OR utilization OR utilisation)):ab,ti) OR ((resource NEXT/2 (allocat* OR utilization OR utilisation OR use OR management)):ab,ti) OR price*:ab,ti OR pricing:ab,ti OR economic*:ab,ti OR cost:ab,ti OR costs:ab,ti OR 'cost control':ab,ti OR 'cost of illness':ab,ti OR 'length of stay':ab,ti OR 'economic aspect':ab,ti	2,443,411 Update: 307,542
7	#1 AND #2 AND #3 AND #4 AND #6 NOT #5	882 Update: 264

PubMed an dMEDLINE In-Process

The searches were conducted on August 11, 2020 (No limits) and updated on November 24, 2021 (limitation on time: Aug 12, 2020 – Nov 24, 2021).

Table 17: PubMed and MEDLINE In-Process search strategy via PubMed at National Library https://pubmed.ncbi.nlm.nih.gov/ (cost and resource use)

String Number	Query	Hits
1	"breast neoplasms"[MeSH Terms] OR (breast[tiab] AND (cancer*[tiab] OR neoplas*[tiab] OR tumor*[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR sarcoma*[tiab] OR adenocarcinoma*[tiab] OR malignan*[tiab])) OR (mammary[tiab] AND (cancer*[tiab] OR neoplas*[tiab] OR tumor*[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR sarcoma*[tiab] OR adenocarcinoma*[tiab] OR malignan*[tiab]))	431,753 Update: 36,169
2	metasta*[tiab] OR advance*[tiab] OR unresect*[tiab] OR "un resect*"[tiab] OR nonresect*[tiab] OR "non resect*"[tiab] OR inoperable[tiab] OR (non[tiab] AND amenabl*[tiab] AND surg*[tiab]) OR (non[tiab] AND suit*[tiab] AND surg*[tiab]) OR (non[tiab] AND amenabl*[tiab] AND opera*[tiab]) OR (non[tiab] AND suit*[tiab] AND opera*[tiab]) OR (not[tiab] AND amenabl*[tiab] AND surg*[tiab]) OR (not[tiab] AND suit*[tiab] AND surg*[tiab]) OR (not[tiab] AND amenabl*[tiab] AND opera*[tiab]) OR (not[tiab] AND suit*[tiab] AND opera*[tiab])	1,269,826 Update: 155,452
3	"Neoplasm Recurrence, local"[MeSH] OR recurrence[MeSH] OR "disease resistance"[MeSH] OR "2nd line"[tiab] OR "second line"[tiab] OR "2 l"[tiab]	6,065,425

String Number	Query	Hits
	OR “2 line”[tiab] OR 2l[tiab] OR relaps*[tiab] OR refrac*[tiab] OR resis*[tiab] OR recurr*[tiab] OR progress*[tiab] OR (previ*[tiab] AND (chemo*[tiab] OR line*[tiab] OR therap*[tiab] OR treat*[tiab] OR regim*[tiab] OR fail*[tiab])) OR (prior*[tiab] AND (chemo*[tiab] OR line[tiab] OR therap*[tiab] OR treat*[tiab] OR regim*[tiab] OR fail*[tiab])) OR (heav*[tiab] AND (chemo*[tiab] OR line[tiab] OR therap*[tiab] OR treat*[tiab] OR regim*[tiab] OR fail*[tiab])) OR (post*[tiab] AND (chemo*[tiab] OR line[tiab] OR therap*[tiab] OR treat*[tiab] OR regim*[tiab] OR fail*[tiab])) OR treated[tiab] OR pretreat*[tiab] OR pre-treat*[tiab] OR failed[tiab] OR failure[tiab] OR reoccur*[tiab] OR reocur*[tiab] OR “re occur”[tiab]	Update: 571,756
4	“receptor, erbb-2”[MeSH] OR “genes, erbb-2”[MeSH] OR “epidermal growth factor receptor 2”[tiab] OR cd340[tiab] OR erbb2*[tiab] OR “erbb 2*”[tiab] OR her2*[tiab] OR “her 2*”[tiab] OR (neu[tiab] AND protein*[tiab]) OR (neu[tiab] AND oncoprotein*[tiab]) OR (neu[tiab] AND receptor*[tiab]) OR “differentiation factor receptor”[tiab] OR “neuregulin receptor”[tiab] OR “neu receptor”[tiab] OR (immunohistochemistry[tiab] AND (2[tiab] OR 3[tiab])) OR (ihc[tiab] AND (2[tiab] OR 3[tiab])) OR hr positive[tiab] OR “hormone receptor positive”[tiab]	132,672 Update: 14,785
5	“case reports”[pt] OR editorial[pt] OR letter[pt] OR comment[pt] OR “clinical trial, veterinary”[pt]	3,771,946 Update: 224,136
6	“cost control”[MeSH] OR “cost of illness”[MeSH] OR “health care costs”[MeSH] OR “health care economics and organizations”[MeSH] OR “Patient Acceptance of Health Care”[MeSH] OR “health resources”[MeSH] OR “length of stay”[MeSH] OR (((“Delivery of Health Care”[tiab]) AND (cost[tiab] OR costs[tiab] OR utilization[tiab] OR utilization[tiab]))) OR (resource[tiab] AND (allocat*[tiab] OR utilization[tiab] OR utilization[tiab] OR use[tiab] OR management[tiab])) OR price*[tiab] OR pricing[tiab] OR economic*[tiab] OR cost[tiab] OR costs[tiab] OR “cost control”[tiab] OR “cost of illness”[tiab] OR “length of stay”[tiab] OR “economic aspect”[tiab]	2,308,543 Update: 166,516
7	#1 AND #2 AND #3 AND #4 AND #6 NOT #5	368 Update: 60

EconLit (platform: via EBSCOhost)

The searches were conducted on August 11, 2020 (No limits) and updated on November 24, 2021 (limitation on time: Aug 12, 2020 – Nov 24, 2021).

Table 18: EconLit search strategy via via EBSCOhost (cost and resource use)

String Number	Query			Hits
S1	AB ('breast cancer' OR ((breast N2 (cancer* OR neoplas* OR tumour* OR tumor* OR carcinoma* OR sarcoma* OR adenocarcinoma* OR malignan*))) OR ((mammary N2 (cancer* OR neoplas* OR tumour* OR tumor* OR carcinoma* OR sarcoma* OR adenocarcinoma* OR malignan*)))) AND TI ('breast cancer' OR ((breast N2 (cancer* OR neoplas* OR tumour* OR tumor* OR carcinoma* OR sarcoma* OR adenocarcinoma* OR malignan*))) OR ((mammary N2 (cancer* OR neoplas* OR tumour* OR tumor* OR carcinoma* OR sarcoma* OR adenocarcinoma* OR malignan*))))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit	103 Update: 7
S2	AB (metasta* OR advanc* OR unresect* OR 'un resect*' OR nonresect* OR 'non resect*' OR inoperable OR (((non OR 'not') N2 (amenabl* OR suit*) N2 (surge* OR surgi* OR opera*)))) AND TI (metasta* OR advanc* OR unresect* OR 'un resect*' OR nonresect* OR 'non resect*' OR inoperable OR (((non OR 'not') N2 (amenabl* OR suit*) N2 (surge* OR surgi* OR opera*))))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit	1,290 Update: 95
S3	AB ('cancer recurrence' OR relapse OR 'cancer resistance' OR relaps* OR refrac* OR resist* OR recurr* OR progress* OR (((previ* OR prior* OR heav* OR post*) N4 (chemo* OR line* OR therap* OR treat* OR regim* OR fail*))) OR treated OR pretreat* OR pre-treat* OR failed OR failure OR reocur* OR 're ocur*' OR reoccur* OR 're occur*') AND TI ('cancer recurrence' OR relapse OR 'cancer resistance' OR relaps* OR refrac* OR resist* OR recurr* OR progress* OR (((previ* OR prior* OR heav* OR post*) N4 (chemo* OR line* OR therap* OR treat* OR regim* OR fail*))) OR treated OR pretreat* OR pre-treat* OR failed OR failure OR reocur* OR 're ocur*' OR reoccur* OR 're occur*')	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit	4,664 Update: 290
S4	AB ('epidermal growth factor receptor 2' OR 'epidermal growth factor receptor 2' OR cd340 OR erbb2* OR ‘erbb 2*’ OR her2* OR ‘her 2*’ OR ((neu N1 (protein* OR oncoprotein* OR receptor*))) OR 'differentiation factor receptor' OR 'neuregulin receptor' OR (((immunohistochemistry OR ihc) N2 (3 OR 2))) OR ‘hr positive’ OR 'hormone receptor positive') AND TI ('epidermal growth factor receptor 2' OR 'epidermal growth factor receptor 2' OR cd340 OR erbb2* OR ‘erbb 2*’ OR her2* OR ‘her 2*’ OR ((neu N1	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit	4 Update: 0

String Number	Query			Hits
	(protein* OR oncoprotein* OR receptor*))) OR 'differentiation factor receptor' OR 'neuregulin receptor' OR (((immunohistochemistry OR ihc) N2 (3 OR 2))) OR ‘hr positive’ OR 'hormone receptor positive')			
S5	AB ('cost control' OR 'cost of illness' OR 'health care cost' OR 'health care utilization' OR 'resource management' OR 'length of stay' OR 'economic aspect' OR ((('health care' OR healthcare) N1 (cost OR costs OR utilization OR utilisation))) OR ((resource N2 (allocat* OR utilization OR utilisation OR use OR management))) OR price* OR pricing OR economic* OR cost OR costs OR ‘cost control’ OR ‘cost of illness’ OR ‘length of stay’ OR ‘economic aspect’) AND TI ('cost control' OR 'cost of illness' OR 'health care cost' OR 'health care utilization' OR 'resource management' OR 'length of stay' OR 'economic aspect' OR ((('health care' OR healthcare) N1 (cost OR costs OR utilization OR utilisation))) OR ((resource N2 (allocat* OR utilization OR utilisation OR use OR management))) OR price* OR pricing OR economic* OR cost OR costs OR ‘cost control’ OR ‘cost of illness’ OR ‘length of stay’ OR ‘economic aspect’)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit	117,020 Update: 6,067
S6	S1 AND S2 AND S3 AND S4 AND S5	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit	1 Update: 0

CRD

The searches were conducted on August 11, 2020 (No limits). An update was not executed. The CRD statement for the rationale for not updating is:

“CRD would like to reassure our many thousands of users that we are committed to maintaining archive versions of DARE and NHSEED until at least the end of March 2022 (the point to which we have funds to support maintenance). [Bibliographic

records were published on DARE and NHS EED until 31st March 2015. Searches of MEDLINE, Embase, CINAHL, PsycINFO and PubMed were continued until the end of the 2014.]"

Table 19: CRD search strategy (cost and resource use)

String Number	Query	Hits
1	(MeSH DESCRIPTOR breast neoplasms EXPLODE ALL TREES) OR ((breast NEAR2 (cancer* OR neoplas* OR tumour* OR tumor* OR carcinoma* OR sarcoma* OR adenocarcinoma* OR malignan*)):ti) OR ((mammary NEAR2 (cancer* OR neoplas* OR tumour* OR tumor* OR carcinoma* OR sarcoma* OR adenocarcinoma* OR malignan*)):ti)	1,978
2	metasta*:ti OR advanc*:ti OR unresect*:ti OR un resect*:ti OR nonresect*:ti OR non resect*:ti OR inoperable:ti OR ((non OR 'not') NEAR2 (amenabl* OR suit*) NEAR2 (surge* OR surgi* OR opera*)):ti	2,197
3	(MeSH DESCRIPTOR neoplasm recurrence, local EXPLODE ALL TREES) OR (MeSH DESCRIPTOR recurrence EXPLODE ALL TREES) OR (MeSH DESCRIPTOR disease resistance EXPLODE ALL TREES) OR relaps*:ti OR refrac*:ti OR resist*:ti OR recurr*:ti OR progress*:ti OR (((previ* OR prior* OR heav* OR post*) NEAR4 (chemo* OR line* OR therap* OR treat* OR regim* OR fail*)):ti) OR treated:ti OR pretreat*:ti OR pre-treat*:ti OR failed:ti OR failure:ti OR reocur*:ti OR re ocur*:ti OR reoccur*:ti OR re occur*:ti	4,650
4	(MeSH DESCRIPTOR receptor, erbb-2 EXPLODE ALL TREES) OR (MeSH DESCRIPTOR genes, erbb-2 EXPLODE ALL TREES) OR epidermal growth factor receptor 2:ti OR cd340:ti OR erbb2*:ti OR erbb 2*:ti OR her2*:ti OR her 2*:ti OR ((neu NEAR1 (protein* OR oncoprotein* OR receptor*)):ti) OR differentiation factor receptor:ti OR neuregulin receptor:ti OR (((immunohistochemistry OR ihc) NEAR2 (3 OR 2)):ti) OR hr positive:ti OR hormone receptor positive:ti	165
5	(MeSH DESCRIPTOR case reports EXPLODE ALL TREES) OR (MeSH DESCRIPTOR editorial EXPLODE ALL TREES) OR (MeSH DESCRIPTOR letter EXPLODE ALL TREES) OR ((MeSH DESCRIPTOR animal EXPLODE ALL TREES) NOT ((MeSH DESCRIPTOR animal EXPLODE ALL TREES) AND (MeSH DESCRIPTOR human EXPLODE ALL TREES))) OR (MeSH DESCRIPTOR meta-analysis as topic EXPLODE ALL TREES) OR case study:ti OR case report:ti OR abstract report:ti OR editorial:ti OR veterinary clinical trial:ti OR letter:ti OR note:ti OR ((review:ti OR literature review:ti) NOT (meta-analysis:ti OR systematic review:ti OR systematic literature review:ti OR meta analysis:ti))	3,574
6	(MeSH DESCRIPTOR cost control EXPLODE ALL TREES) OR (MeSH DESCRIPTOR cost of illness EXPLODE ALL TREES) OR (MeSH DESCRIPTOR health care costs EXPLODE ALL TREES) OR (MeSH DESCRIPTOR health care economics and organizations EXPLODE ALL TREES) OR (MeSH DESCRIPTOR Patient Acceptance of Health Care EXPLODE ALL TREES) OR (MeSH DESCRIPTOR health resources EXPLODE ALL TREES) OR (MeSH DESCRIPTOR length of stay EXPLODE ALL TREES) OR (((health care OR healthcare) NEAR1 (cost OR costs OR utilization OR utilisation)):ti) OR ((resource NEAR2 (allocat* OR utilization OR utilisation OR use OR management)):ti) OR price*:ti OR pricing:ti OR economic*:ti OR cost:ti OR costs:ti OR cost control:ti OR cost of illness:ti OR length of stay:ti OR economic aspect:ti	22,482
7	#1 AND #2 AND #3 AND #4 AND #6 NOT #5	2

ScHARRHUD

The searches were run on August 11, 2020 for the relevant status of HER2 and HR, which returned zero results in the initial search. The update was not executed as in the ScHARRHUD database, the most recent published study was from 2017. No studies after 2017 are found in the ScHARRHUD database, therefore ScHARRHUD was not included in the update.

Table 20: ScHARRHUD search strategy (cost and resource use)

String Number	Query	Hits
1	'epidermal growth factor receptor 2':AB,TI OR cd340:AB,TI OR erbb2*:AB,TI OR 'erbb 2*':AB,TI OR her2*:AB,TI OR 'her 2*':AB,TI OR ((neu NEAR (protein* OR oncoprotein* OR receptor*)):AB,TI) OR 'differentiation factor receptor':AB,TI OR 'neuregulin receptor':AB,TI OR (((immunohistochemistry OR ihc) NEAR (3 OR 2)):AB,TI) OR 'hr positive':AB,TI OR 'hormone receptor positive':AB,TI	0

Decision problem

A14. According to the Final Scope, trastuzumab deruxtecan is to be used for HER2+ unresectable or metastatic breast cancer after trastuzumab and a taxane. Could the company provide the number and percentage of subjects in each study arm in the DESTINY-BREAST03 trial that are unresectable and the number and percentage of subjects that are metastatic? It would also be useful to identify those initially diagnosed with AJCC stage 3 vs stage 4 by treatment arm of the trial.

In total, [redacted] patients ([redacted]%) in the T-DXd arm and [redacted] patients ([redacted]%) in the T-DM1 arm had metastatic (Stage IV) disease at study entry; [redacted] patients ([redacted]%) and [redacted] patients ([redacted]%), respectively, had unresectable disease. A further two patients – one in each arm – had 'missing' status for their baseline disease stage.

Tumour stage at initial diagnosis (note: this did not necessarily remain the tumour stage of the patients at the time they entered the trial) was collected in DESTINY-Breast03, and is presented in Table 21 below.

Table 21: Tumour stage at initial diagnosis | FAS

Stage, n (%)	T-DXd (N=261)	T-DM1 (N=263)	Total (N=524)
I	[redacted]	[redacted]	[redacted]

Stage, n (%)	T-DXd (N=261)	T-DM1 (N=263)	Total (N=524)
IA	[redacted]	[redacted]	[redacted]
IB	[redacted]	[redacted]	[redacted]
II	[redacted]	[redacted]	[redacted]
IIA	[redacted]	[redacted]	[redacted]
IIB	[redacted]	[redacted]	[redacted]
III	[redacted]	[redacted]	[redacted]
IIIA	[redacted]	[redacted]	[redacted]
IIIB	[redacted]	[redacted]	[redacted]
IIIC	[redacted]	[redacted]	[redacted]
IV	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]

Abbreviations: FAS, full analysis set; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Source: File of tables, figures, and graphs for DESTINY-Breast03 (Table 14.1.3.1; p20).

Systematic review

A15. Priority question: The NICE health technology manual recommends the systematic review relating to evidence should be completed using a pre-defined protocol. Could the company please provide the protocol, give details of whether it was registered in the public domain (e.g., PROSPERO), and list any deviations?

The protocols have been provided as separate, confidential documents.

- ID3909_DS8201a_Final_Protocol_cSLR_HER2-positive 2L mBC
- ID3909_DS8201a_Final_Protocol_eSLR_HER2-positive 2L mBC

Protocols were not registered in the public domain.

Protocol deviations | Clinical SLR

Original SLR:

No protocol deviations.

Updated SLR:

1. The Embase and PubMed search strategies were slightly adjusted: They no longer include specific lines on quality of life and health economics, thereby broadening the search slightly.

2. “Studies that report a population with a median treatment line >2 will be excluded.” In phase II screening of the update to the cSLR, we previously excluded 18 articles using "median prior lines >1". Upon review, all but 6 could be excluded for other reasons that had previously remained unidentified. The last 6 would all fit the exclusion criterion "median prior lines >2". This means that the total number of articles included would not change.

Protocol deviations | Economic SLR

There were no protocol deviations for the economic SLR.

A16. There appears to be an inappropriate application of exclusion criteria. Abstracts were excluded at ’full-text’ level 2 screening (see Appendix figure 1, page 16) but this does not adhere to the inclusion and exclusion criteria specified in Appendix Table 4. Could the company explain the deviation from the listed inclusion and exclusion criteria.

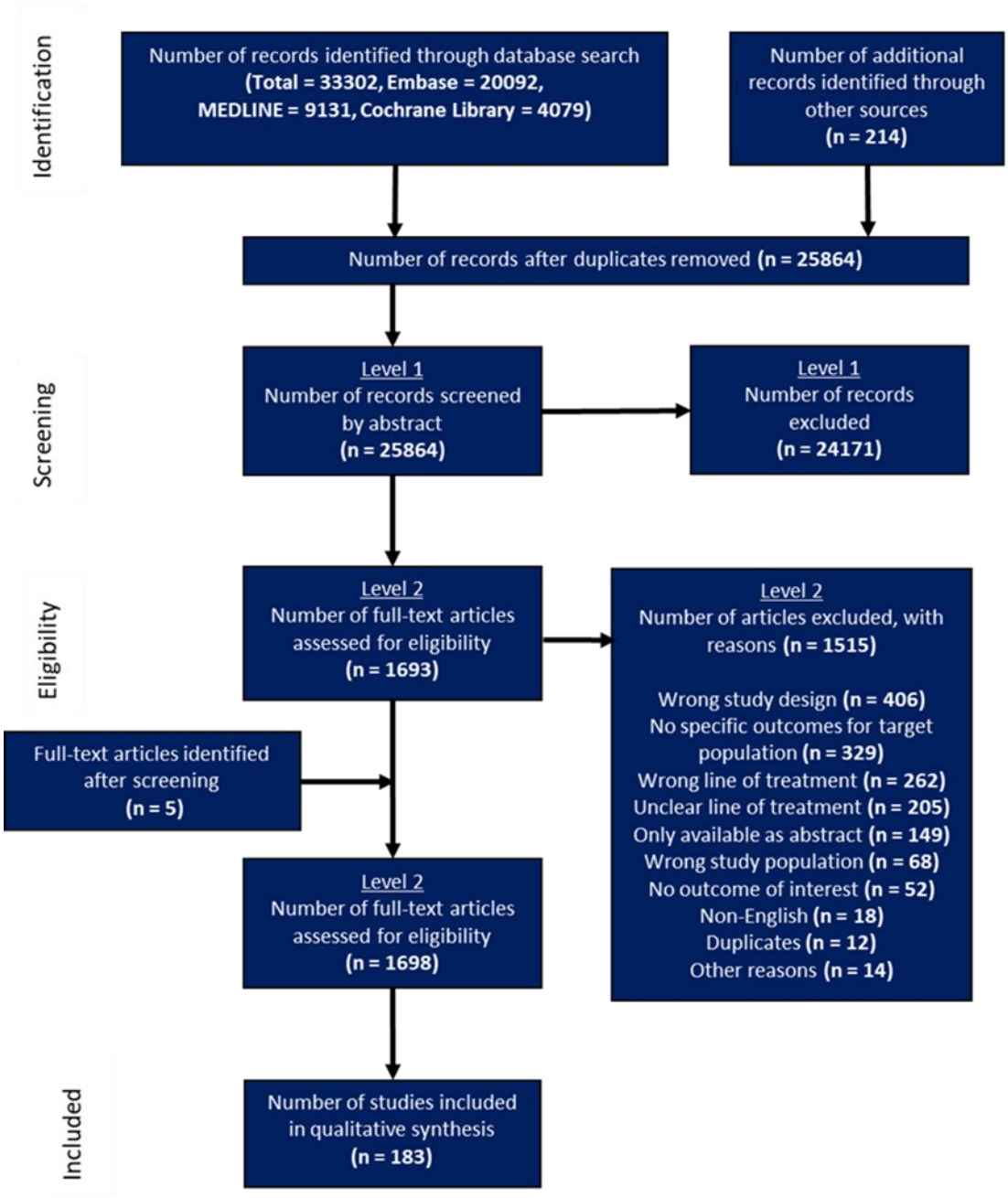
Thank you for the opportunity to clarify this point. The EAG is correct that Appendix Table 4 does not explicitly state that studies published in abstract form only would be excluded from the review. In practice, Level 2 screening was restricted to hits identified in the searches where a full-text review was possible i.e. where a full study text was available. For the 149 studies identified by the EAG in the PRISMA diagram, no full texts were available and it was not possible to conduct a full-text review for those studies.

A17. The following questions relate to the flow of information through the different phases of the systematic review:

a. In Appendix figure 1 (page 16), regarding the identification of evidence, could the company please provide a full breakdown of records identified when all individual databases were searched. Please display the number of records retrieved for each database in a revised Prisma flow chart (including the records identified from the updated search reported alongside).

A breakdown of records between the databases (PubMed, Embase, Cochrane) is provided in the PRISMA diagram below.

Figure 1: Revised PRISMA flow chart of the updated clinical literature review (before the final update to adapt to the Final Scope)



b. In Appendix figure 1 (page 16), the number of records screened by abstract was given as 25,861 and the number of records excluded was given as 24,178. This leaves 1,683 records for further eligibility assessment (as full texts). However, 1690

records are reported as being assessed for eligibility as full texts within the Prisma flow chart. Could the company please account for this discrepancy?

The EAG is correct that there was an error in the PRISMA diagram. A revised PRISMA has been provided above.

c. There is a lack of transparency regarding the studies excluded at the full text screening stage. Could the company please detail the full bibliographic references and exclusion reasons for the 163 articles excluded after the NICE review eligibility criterion were applied (as detailed in Appendix figure 1, page 16). An Excel file is mentioned in relation to this but is missing, could the Company please provide this.

The full bibliographic references and exclusion reasons for the 163 articles excluded after the NICE review eligibility criterion were applied are provided in an Excel file "ID3909_T-DXd_cSLR-NICE-screen_21-Mar-22". This file has been provided to the EAG separately.

d. There is no detail given on the identification of records through the review process post the search undertaken on the 27th September 2021. Could the Company please state how they sought and obtained such reports (and whether similar efforts were made for the comparator)?

The systematic review described in Appendix D in the Company submission, and last updated on 27th September 2021, was intended to be the final update required to support the NICE submission. However, given publication timings for the DESTINY-Breast03 trial data at the SABCS 2021 and ESMO 2021 congresses, and the lag between congress presentation and search database indexing, the 27 September 2021 searches did not identify any relevant T-DXd studies. It was therefore necessary to supplement the 27 September 2021 searches with those known publications that were not indexed at the time of the last search. The process and timings for identification of the four publications relating to T-DXd is described in the response to clarification question A8.

The Company was not aware of any relevant data that had been published for the comparator, T-DM1, within the timeframes covered by the review; additional searches were not therefore conducted for T-DM1.

A18. The methods of data extraction for the reviews are unclear. Please specify:

a. If data extraction for the effectiveness review was completed independently or if data were extracted, then checked in full by a second reviewer.

While data were extracted from the included studies as part of the broader review, these data extractions were not used for developing the Company submission. Where data were extracted for the wider review, this was conducted by a reviewer, and all extractions were independently checked by a different reviewer.

b. How any disagreements in data extraction were resolved for the effectiveness review?

Disagreements were resolved by discussion between the two reviewers.

c. Please also detail (b) with reference to the cost-effective review/health-related quality-of-life review and cost and resource use review (listed in the Appendices, sections H.1.4, I.1.4, J.1.4).

The same data extraction strategy as described in A18(a) and A19(b) above was used for the cost-effectiveness review, health-related quality-of-life review, and cost and resource use review.

A19. In section D.3 (Appendices, page 22), the company submission states that 'Quality assessment of DESTINY-Breast03 was conducted using the NICE STA: 'User guide for company evidence submission template'. Could the company please indicate how many reviewers undertook the quality assessment, whether this was done in a blinded manner, what the assessment decisions made were, and how disagreements in assessment decisions were resolved?

The quality assessment review was initially conducted by NL (an agency consultant used by the Company to support submission development), and subsequently independently and separately checked by two representatives from the Company. Any disagreements were resolved through discussion between the reviewers. It was not possible to conduct the review in a blinded manner, as all reviewers were aware that DESTINY-Breast03 was the only head-to-head RCT identified by the systematic review. The assessment decisions are as described in the Company submission (Appendix D.2, Table 7, p22).

Clinical trial

A20. Priority question: In section B.2.12.2 (Document B, page 79), the CS states that 'clinical experts have confirmed that the patient population and study design is generalisable to UK clinical practice.' Expert opinion is also elicited for survival estimates for use in the selection of parametric models in survival analysis (section B.3.3.2). Clinical expert opinion was derived from a consultation validation meeting undertaken by Daiichi Sankyo Inc. Please outline the methods used to:

a. **Recruit clinicians to the validation meeting.**

Clinicians were selected for recruitment to the validation meeting based on their extensive experience in treating metastatic breast cancer, involvement in prior NICE appraisals and experience of using T-DXd in breast cancer; both clinicians have used T-DXd in their respective clinical centres and one of the clinicians is part of the DESTINY clinical trial program.

b. **Elicit opinions in the validation meeting.**

Opinions were elicited at the meeting by means of open-ended questions and discussion between the advisors and the Company. The Company answered factual questions on the evidence base when required. For elicitation of values around model assumptions – for example survival estimates at 5- and 10-years – clinical advisors were presented with an empty grid which they then completed, either verbally (n=1) or in written form (independently) after the meeting (n=1). Formal elicitation methods were not utilised.

c. **Please also provide the minuted discussions of opinions shared during this meeting to assess how generalisable findings are to UK clinical practice.**

Consultancy contracts for the meeting stated that the meeting outputs would be confidential and anonymised. To provide the additional detail requested by the EAG, the Company has re-contacted the experts and requested their permission to share a summary of the meeting. A confidential document summarising the discussions from the meeting (filename "ID3909_T-DXd-NICE_Expert-validation-meeting-summary_CONFIDENTIAL") will be provided to the EAG as a separate document.

A21. Priority question: In Table 6 (section B.2.3.1.1) it states that the DESTINY-Breast03 trial took place in 169 centres in 15 countries, including the UK.

a. **Please clarify how many participants were recruited from the UK.**

In total, [redacted] participants were recruited from the UK.

b. **Please provide baseline characteristics of the UK and European population (as detailed in Table 10).**

Baseline characteristics of the European subpopulation are provided in Table 22.

[redacted]

Table 22: Baseline characteristics of the European subpopulation | DESTINY-Breast03 | FAS

		T-DXd (N=[redacted]) n (%)			T-DM1 (N=[redacted]) n (%)			Total (N=[redacted]) n (%)		
	N	[redacted]			[redacted]			[redacted]		
Age (years)	Mean	[redacted]			[redacted]			[redacted]		
	Standard Deviation	[redacted]			[redacted]			[redacted]		
	Median	[redacted]			[redacted]			[redacted]		
	Min, Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sex	Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race	White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Smoking status	Current	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Former	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Never	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HER2 Expression (IHC) - Central	1+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	2+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	3+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG Performance Status	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hormone Receptor	Positive	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Negative	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]		[redacted]
	Missing	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]		[redacted]

		T-DXd (N=[redacted]) n (%)		T-DM1 (N=[redacted]) n (%)		Total (N=[redacted]) n (%)	
Baseline CNS metastases	Yes No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reported history of CNS metastases	Yes No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline Visceral Disease	Yes No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lines of prior systemic therapy not including hormone therapy in the metastatic setting	N Mean Median Std Dev Maximum	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lines of prior systemic therapy not including hormone therapy in the metastatic setting	0 1 2 3 4 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior cancer therapy	Trastuzumab Pertuzumab Taxane Anti-HER2 TKI Other anti-HER2 or ADC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADC, antibody-drug conjugate; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; HER2, human epidermal growth factor receptor; IHC, immunohistochemistry; TKI, tyrosine kinase inhibitor; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

A22. Priority question: As reported in B.2 page 52 (Document B, clinical effectiveness), DESTINY-Breat03 has immature follow up particularly for overall survival (16.2 months with T-DXd and 15.3 months with T-DM1) owing to the trial achieving statistically significance of the primary endpoint of PFS by BICR. Could the company please provide any more up-to-date analyses or the next anticipated data cut point dates for when further PFS and OS data will be made available?

Consistent with B.2.4.2 (Document B, Clinical effectiveness, p45), the next interim analysis is planned at [redacted] PFS events; OS will be analysed if the result of the PFS

analysis is statistically significant. A final analysis of OS is also planned at [redacted] OS events. As per B.2.11 (Document B, p76), the next interim analysis (after [redacted] PFS events) is anticipated in [redacted]; however, as timings are event-driven, the date of the next analysis is subject to change.

There are no data cuts available that are more recent than the data presented in the submission, as the data presented in the submission uses the latest available data cut.

Since the CS was submitted to NICE, and following the Innovation Passport meeting on 24-March 2022 and further consideration by the Innovative Licensing and Access Pathway (ILAP) Steering Group (AWTTC, MHRA, NICE, SMC, and representatives from the ILAP Patient and Public Reference Group), the partners have informed Daiichi Sankyo UK Ltd that [redacted] for trastuzumab deruxtecan as monotherapy for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received one or more prior anti-HER2-based regimens.

A23. In section B.3.3.2.1.2 page 99 (Document B) of the CS, it states that 'Clinical experts also confirmed there is no clinical reason as to why prior pertuzumab may impact effectiveness of T-DM1 and therefore both trials were considered generalisable to UK clinical practice.' Prior pertuzumab treatment was one of three stratification factors in the DESTINY-Breast03 trial. Could the company please clarify why prior pertuzumab treatment may affect treatment effectiveness of T-DXd but not T-DM1? Please also provide the minuted discussions of this assumption within the consultation validation meeting undertaken by Daiichi Sankyo Inc.

The sentence identified by the EAG is within a section of Document B (Section B.3.3.2.1.2, p99) which explicitly explores the generalisability of the EMILIA study to UK clinical practice. T-DXd was not included as intervention or comparator in the EMILIA study.

The text as written above was not intended to imply that prior pertuzumab does impact T-DXd efficacy, and indeed the subgroup analyses for DESTINY-Breast03 (Document B, Figure 13, p66) demonstrates that there is no significant impact of prior pertuzumab on T-DXd or T-DM1 efficacy.

A summary of the discussion with clinical experts on this topic has been included in the supplemental confidential reference (filename "ID3909_T-DXd-NICE_Expert-validation-meeting-summary_CONFIDENTIAL") submitted with the response to the EAG's clarification questions.

A24. Approximately half of patients enrolled in DESTINY-Breast03 had two or more prior lines of therapy in the metastatic setting (Table 10, Document B). Please provide the following details:

a. The number and demographic variables of patients by all prior lines of therapy within each treatment arm.

The number and demographic variables by 0–1, 2–5, and 6–10 lines of prior therapy (not including hormone therapy) are shown in Table 23 to Table 25. Lines of prior therapies include *all* prior lines of systemic treatment since BC diagnosis. Only [redacted] patients in the T-DXd arm and [redacted] patient in the T-DM1 arm had received ≥11 lines of prior therapy (not including hormone therapy); therefore data for this subgroup is uninformative and not presented. This is consistent with the SAP, in which PFS analyses were only conducted for [redacted] events.

The Company would like to clarify that, while these data have been presented as requested by the EAG, these subgroup analyses should be viewed as explorative only and advise caution in interpretation due to small patient numbers in some subgroups. The only relevant subgroups included in the SAP and published in the DESTINY-Breast03 manuscript (Cortes *et al*, 2022) are patients with 0-1 prior therapies and 2+ prior therapies,[1] which is consistent with the NICE decision problem for this appraisal.

Table 23: Baseline characteristics and demographics | Patients with 0–1 lines of prior systemic therapy excluding hormone therapy | DESTINY-Breast03 | FAS

		T-DXd (N=[redacted])		T-DM1 (N=[redacted])		Total (N=[redacted])	
	N	[redacted]		[redacted]		[redacted]	
Age (years)	Mean	[redacted]		[redacted]		[redacted]	
	Standard Deviation	[redacted]		[redacted]		[redacted]	
	Median	[redacted]		[redacted]		[redacted]	
	Min, Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sex, n (%)	Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race, n (%)	White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Black or African American	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Smoking status, n (%)	Current	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Former	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Never	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HER2 Expression (IHC) – Central, n (%)	1+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	2+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	3+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Not Evaluable	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG Performance Status, n (%)	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hormone Receptor, n (%)	Indeterminate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Positive	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Negative	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

		T-DXd (N=[redacted])		T-DM1 (N=[redacted])		Total (N=[redacted])	
	Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline CNS metastases, n (%)	Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reported history of CNS metastases, n (%)	Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline Visceral Disease, n (%)	Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lines of prior systemic therapy not including hormone therapy in the metastatic setting	N	[redacted]		[redacted]		[redacted]	
	Mean	[redacted]		[redacted]		[redacted]	
	Standard Deviation	[redacted]		[redacted]		[redacted]	
	Median	[redacted]		[redacted]		[redacted]	
	Min, Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lines of prior systemic therapy not including hormone therapy in the metastatic setting, n (%)	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior cancer therapy, n (%)	Trastuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Pertuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Taxane	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lines of prior systemic therapy not including hormone therapy in the metastatic setting, n (%)	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: FAS, full analysis set; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

Table 24: Baseline characteristics and demographics | Patients with 2–5 lines of prior systemic therapy excluding hormone therapy | DESTINY-Breast03 | FAS

		T-DXd (N=[redacted]) n (%)		T-DM1 (N=[redacted]) n (%)		Total (N=[redacted]) n (%)	
	N	[redacted]		[redacted]		[redacted]	
Age (years)	Mean	[redacted]		[redacted]		[redacted]	
	Standard Deviation	[redacted]		[redacted]		[redacted]	
	Median	[redacted]		[redacted]		[redacted]	
	Min, Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sex, n (%)	Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race, n (%)	White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Black or African American	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Smoking status, n (%)	Current	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Former	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Never	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HER2 Expression (IHC) – Central, n (%)	2+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	3+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Not Evaluable	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG Performance Status, n (%)	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hormone Receptor, n (%)	Indeterminate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Positive	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Negative	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

		T-DXd (N=[redacted]) n (%)		T-DM1 (N=[redacted]) n (%)		Total (N=[redacted]) n (%)	
Baseline CNS metastases, n (%)	Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reported history of CNS metastases, n (%)	Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline Visceral Disease, n (%)	Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lines of prior systemic therapy not including hormone therapy in the metastatic setting	N	[redacted]		[redacted]		[redacted]	
	Mean	[redacted]		[redacted]		[redacted]	
	Standard Deviation	[redacted]		[redacted]		[redacted]	
	Median	[redacted]		[redacted]		[redacted]	
	Min, Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lines of prior systemic therapy not including hormone therapy in the metastatic setting, n (%)	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior cancer therapy, n (%)	Trastuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Pertuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Taxane	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Anti-HER2 TKI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Other anti-HER2 or ADC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: FAS, full analysis set; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

Table 25: Baseline characteristics and demographics | Patients with 6–10 lines of prior systemic therapy excluding hormone therapy | DESTINY-Breast03 | FAS

		T-DXd (N=[redacted])		T-DM1 (N=[redacted])		Total (N=[redacted])	
	N	[redacted]		[redacted]		[redacted]	
Age (years)	Mean	[redacted]		[redacted]		[redacted]	
	Standard Deviation	[redacted]		[redacted]		[redacted]	
	Median	[redacted]		[redacted]		[redacted]	
	Min, Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sex, n (%)	Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race, n (%)	White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Black or African American	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Smoking status, n (%)	Current	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Former	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Never	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HER2 Expression (IHC) - Central, n (%)	2+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	3+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG Performance Status, n (%)	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hormone Receptor, n (%)	Positive	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Negative	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline CNS metastases, n (%)	Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reported history of CNS metastases, n (%)	Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline Visceral Disease, n (%)	Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

		T-DXd (N=[redacted])		T-DM1 (N=[redacted])		Total (N=[redacted])	
	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lines of prior systemic therapy not including hormone therapy in the metastatic setting	N	[redacted]		[redacted]		[redacted]	
	Mean	[redacted]		[redacted]		[redacted]	
	Standard Deviation	[redacted]		[redacted]		[redacted]	
	Median	[redacted]		[redacted]		[redacted]	
	Min, Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lines of prior systemic therapy not including hormone therapy in the metastatic setting, n (%)	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior cancer therapy, n (%)	Trastuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Pertuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Taxane	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Anti-HER2 TKI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Other anti-HER2 or ADC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: FAS, full analysis set; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

b. Subgroup analyses by the number of prior lines of therapy within each treatment arm for Progression Free Survival and confirmed Objective Response Rate using the following cut points 2-5, 6-10, 11+.

A PFS (by BICR) analysis by subgroups of number of prior lines of therapy is shown in Table 26. A confirmed ORR (by BICR) analysis by subgroups of number of prior lines of therapy is shown in Table 27. Only [redacted] patients in the T-Dxd arm and [redacted] in the T-DM1 arm had received ≥11 lines of prior therapy (not including hormone therapy); therefore data for this subgroup is uninformative and not presented. This is consistent with the SAP, in which PFS analyses were only conducted for [redacted] events.

Forest plots showing subgroup analyses are shown in Figure 2 and Figure 3.

Analyses should be viewed as explorative only, given that they were not pre-defined and patient numbers were small for subgroups ≥6 prior lines of therapy. The only relevant subgroups included in the SAP are patients with 0-1 prior therapies and 2+ prior therapies which is consistent with the NICE decision problem for this appraisal.

Table 26: Subgroup analysis of PFS by BICR | Prior lines of therapy not including hormone therapy | DESTINY-Breast03 | FAS

Prior lines	T-DXd (N=261)			T-DM1 (N=263)			Hazard Ratio (95% CI)
	n	No. of events (%)	Median PFS, months (95% CI)	n	No. of events (%)	Median PFS, months (95% CI)	
0-1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2-5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6-10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

PFS is defined as the time from the date of randomization to the date of the first radiographic disease progression or death due to any cause, whichever comes first. See SAP for the handling of censored cases. Subgroup values are as defined at baseline. Median PFS is from Kaplan-Meier analysis. CI for median was computed using the Brookmeyer-Crowley method. Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate.
Abbreviations: CI, confidence interval; FAS, full analysis set; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

Table 27: Subgroup analysis of ORR by BICR | Prior lines of therapy not including hormone therapy | DESTINY-Breast03 | FAS

Prior lines	T-DXd (N=261)	T-DM1 (N=263)
	Confirmed ORR n (%) (95% CI)*	Confirmed ORR n (%) (95% CI)*
0-1	[redacted]	[redacted]
2-5	[redacted]	[redacted]
6-10	[redacted]	[redacted]

*Based on Clopper-Pearson method for single proportion. †OR and 95% CI obtained from unadjusted logistic regression models. ‡Derived using the Cochran-Mantel-Haenszel method.

Figure 2: Forest plot of subgroup analysis by lines of prior systemic therapy not including hormone therapy | PFS by BICR | DESTINY-Breast03 | FAS

Abbreviations: BICR, blinded independent central review; CI, confidence interval; FAS, full analysis set; NE, not estimable; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

Figure 3: Forest plot of subgroup analysis by lines of prior systemic therapy not including hormone therapy | Confirmed ORR by BICR | DESTINY-Breast03 | FAS

Abbreviations: BICR, blinded independent central review; CI, confidence interval; FAS, full analysis set; ORR, objective response rate; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

c. The number and demographic variables of patients by all prior lines of therapy in the metastatic setting within each treatment arm.

The number and demographic variables by 0–1, 2–3, 4–5, and ≥6 lines of prior therapy in the metastatic setting (not including hormone therapy) are shown in Table 28 to Table 31. Prior lines of therapy in the metastatic setting were defined as those received in the metastatic setting as well as patients who were fast progressors (following the definition in the DESTINY-Breast03 SAP).

The Company would like to clarify that, while these data have been presented as requested by the EAG, these subgroup analyses should be viewed as explorative only. The only relevant subgroups included in the SAP are patients with 0-1 prior therapies and 2+ prior therapies which is consistent with the NICE decision problem for this appraisal.

Table 28: Baseline characteristics and demographics | Patients with 0–1 lines of prior systemic therapy in the metastatic setting, excluding hormone therapy | DESTINY-Breast03 | FAS

		T-DXd (N=[redacted])		T-DM1 (N=[redacted])		Total (N=[redacted])	
	N	[redacted]		[redacted]		[redacted]	
Age (years)	Mean	[redacted]		[redacted]		[redacted]	
	Standard Deviation	[redacted]		[redacted]		[redacted]	
	Median	[redacted]		[redacted]		[redacted]	
	Min, Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sex, n (%)	Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race, n (%)	White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Black or African American	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Smoking status, n (%)	Current	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Former	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Never	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HER2 Expression (IHC) - Central, n (%)	1+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	2+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	3+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Not Evaluable	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG Performance Status, n (%)	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hormone Receptor, n (%)	Indeterminate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Positive	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Negative	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

		T-DXd (N=[redacted])		T-DM1 (N=[redacted])		Total (N=[redacted])	
Baseline CNS metastases, n (%)	Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reported history of CNS metastases, n (%)	Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline Visceral Disease, n (%)	Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lines of prior systemic therapy not including hormone therapy in the metastatic setting, n (%)	N	[redacted]		[redacted]		[redacted]	
	Mean	[redacted]		[redacted]		[redacted]	
	Standard Deviation	[redacted]		[redacted]		[redacted]	
	Median	[redacted]		[redacted]		[redacted]	
	Min, Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lines of prior systemic therapy not including hormone therapy in the metastatic setting, n (%)	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior cancer therapy, n (%)	Trastuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Pertuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Taxane	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Anti-HER2 TKI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor.

Table 29: Baseline characteristics and demographics | Patients with 2–3 lines of prior systemic therapy in the metastatic setting, excluding hormone therapy | DESTINY-Breast03 | FAS

		T-DXd (N=[redacted])		T-DM1 (N=[redacted])		Total (N=[redacted])	
	N	[redacted]		[redacted]		[redacted]	
Age (years)	Mean	[redacted]		[redacted]		[redacted]	
	Standard Deviation	[redacted]		[redacted]		[redacted]	
	Median	[redacted]		[redacted]		[redacted]	

		T-DXd (N=[redacted])		T-DM1 (N=[redacted])		Total (N=[redacted])	
	Min, Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sex, n (%)	Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race, n (%)	White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Black or African American	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Smoking status, n (%)	Current	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Former	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Never	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HER2 Expression (IHC) - Central, n (%)	2+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	3+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Not Evaluable	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG Performance Status, n (%)	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hormone Receptor, n (%)	Indeterminate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Positive	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Negative	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline CNS metastases, n (%)	Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reported history of CNS metastases, n (%)	Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline Visceral Disease, n (%)	Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lines of prior systemic therapy not including hormone therapy in the metastatic setting	N	[redacted]		[redacted]		[redacted]	
	Mean	[redacted]		[redacted]		[redacted]	
	Standard Deviation	[redacted]		[redacted]		[redacted]	

		T-DXd (N=[redacted])		T-DM1 (N=[redacted])		Total (N=[redacted])	
	Median	[redacted]		[redacted]		[redacted]	
	Min, Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lines of prior systemic therapy not including hormone therapy in the metastatic setting, n (%)	2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior cancer therapy, n (%)	Trastuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Pertuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Taxane	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Anti-HER2 TKI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Other anti-HER2 or ADC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor.

Table 30: Baseline characteristics and demographics | Patients with 4–5 lines of prior systemic therapy in the metastatic setting, excluding hormone therapy | DESTINY-Breast03 | FAS

		T-DXd (N=[redacted])		T-DM1 (N=[redacted])		Total (N=[redacted])	
	N	[redacted]		[redacted]		[redacted]	
Age (years)	Mean	[redacted]		[redacted]		[redacted]	
	Standard Deviation	[redacted]		[redacted]		[redacted]	
	Median	[redacted]		[redacted]		[redacted]	
	Min, Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sex, n (%)	Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race, n (%)	White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Black or African American	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Smoking status, n (%)	Current	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Former	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Never	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

		T-DXd (N=[redacted])		T-DM1 (N=[redacted])		Total (N=[redacted])	
	Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HER2 Expression (IHC) – Central, n (%)	2+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	3+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG Performance Status, n (%)	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hormone Receptor, n (%)	Positive	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Negative	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline CNS metastases, n (%)	Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reported history of CNS metastases, n (%)	Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline Visceral Disease, n (%)	Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lines of prior systemic therapy not including hormone therapy in the metastatic setting	N	[redacted]		[redacted]		[redacted]	
	Mean	[redacted]		[redacted]		[redacted]	
	Standard Deviation	[redacted]		[redacted]		[redacted]	
	Median	[redacted]		[redacted]		[redacted]	
	Min, Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lines of prior systemic therapy not including hormone therapy in the metastatic setting, n (%)	4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior cancer therapy, n (%)	Trastuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Pertuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Taxane	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Anti-HER2 TKI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Other anti-HER2 or ADC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor.

Table 31: Baseline characteristics and demographics | Patients with 6+ lines of prior systemic therapy in the metastatic setting, excluding hormone therapy | DESTINY-Breast03 | FAS

		T-DXd (N=[redacted])		T-DM1 (N=[redacted])		Total (N=[redacted])	
	N	[redacted]		[redacted]		[redacted]	
Age (years)	Mean	[redacted]		[redacted]		[redacted]	
	Standard Deviation	[redacted]		[redacted]		[redacted]	
	Median	[redacted]		[redacted]		[redacted]	
	Min, Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sex, n (%)	Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race, n (%)	White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Black or African American	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Smoking status, n (%)	Current	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Never	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HER2 Expression (IHC) - Central, n (%)	2+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	3+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG performance status, n (%)	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hormone Receptor	Positive	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Negative	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline CNS metastases	Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reported history of CNS metastases	Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline Visceral Disease	Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lines of prior systemic therapy not including hormone therapy in the metastatic setting	N	[redacted]		[redacted]		[redacted]	
	Mean	[redacted]		[redacted]		[redacted]	
	Standard Deviation	[redacted]		[redacted]		[redacted]	

		T-DXd (N=[redacted])		T-DM1 (N=[redacted])		Total (N=[redacted])	
	Median	[redacted]		[redacted]		[redacted]	
	Min, Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lines of prior systemic therapy not including hormone therapy in the metastatic setting	6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior cancer therapy	Trastuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Pertuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Taxane	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Anti-HER2 TKI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Other anti-HER2 or ADC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor.

d. Subgroup analyses by the number of prior lines of therapy in the metastatic setting within each treatment arm for Progression Free Survival and confirmed Objective Response Rate using the following cut-points 0-1, 2-3, 4-5, 6+.

A PFS (by BICR) analysis by subgroups of number of prior lines of therapy in the metastatic setting is shown in Table 32. A confirmed ORR (by BICR) analysis by subgroups of number of prior lines of therapy in the metastatic setting is shown in Table 33. Forest plots showing subgroup analyses are shown in Figure 4 and Figure 5.

Analyses should be viewed as explorative only, given that they were not predefined, and patient numbers were small for subgroups ≥4 prior lines of therapy. The informative subgroup analyses with regards to the decision problem are those conducted in patients with 0–1 prior lines of therapy.

Prior lines of therapy in the metastatic setting were defined as those received in the metastatic setting and patients who were fast progressors.

Table 32: Subgroup analysis of PFS by BICR | Prior lines of therapy in metastatic setting, not including hormone therapy | DESTINY-Breast03 | FAS

Prior lines	T-DXd (N=261)			T-DM1 (N=263)			Hazard Ratio (95% CI)
	n	No. of events (%)	Median PFS, months (95% CI)	n	No. of events (%)	Median PFS, months (95% CI)	
0-1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2-3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4-5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

PFS is defined as the time from the date of randomization to the date of the first radiographic disease progression or death due to any cause, whichever comes first. See SAP for the handling of censored cases. Subgroup values are as defined at baseline. Median PFS is from Kaplan-Meier analysis. CI for median was computed using the Brookmeyer-Crowley method. Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate.
Abbreviations: CI, confidence interval; FAS, full analysis set; NE, not estimable; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

Table 33: Subgroup analysis of ORR by BICR | Prior lines of therapy in metastatic setting, not including hormone therapy | DESTINY-Breast03 | FAS

Prior lines	T-DXd (N=261)	T-DM1 (N=263)
	Confirmed ORR n (%) (95% CI)*	Confirmed ORR n (%) (95% CI)*
0-1	[redacted]	[redacted]
2-3	[redacted]	[redacted]
4-5	[redacted]	[redacted]
6+	[redacted]	[redacted]

*Based on Clopper-Pearson method for single proportion. †OR and 95% CI obtained from unadjusted logistic regression models. ‡Derived using the Cochran-Mantel-Haenszel method.

Figure 4: Forest plot of subgroup analysis by lines of prior systemic therapy in the metastatic setting not including hormone therapy | PFS by BICR | DESTINY-Breast03 | FAS

Abbreviations: BICR, blinded independent central review; CI, confidence interval; FAS, full analysis set; NE, not estimable; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

Figure 5: Forest plot of subgroup analysis by lines of prior systemic therapy in the metastatic setting not including hormone therapy | Confirmed ORR by BICR | DESTINY-Breast03 | FAS

Abbreviations: BICR, blinded independent central review; CI, confidence interval; FAS, full analysis set; ORR, objective response rate; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

A25. In section B.2.4.4 (Document B), the CS states, 'Similarly, the majority of enrolled patients had received prior pertuzumab (62.1% vs. 60.1%, respectively)'. Confirm how many subjects had two trastuzumab plus taxane regimens as recommended by NICE as first-line treatment options (pertuzumab plus trastuzumab and docetaxel; and trastuzumab and paclitaxel, page 10).

As per the inclusion criteria, all patients enrolled in DESTINY-Breast03 were required to have previously received trastuzumab and a taxane.

In total, [redacted] patients ([redacted]%) in the T-DXd arm and [redacted] patients ([redacted]%) in the T-DM1 arm had either of these NICE-recommended first-line regimens prior to their trial treatment, and [redacted] patients ([redacted]%) in each arm had both regimens as prior treatment.

Pertuzumab plus trastuzumab and docetaxel was a prior regimen in [redacted] patients ([redacted]%) in the T-DXd arm and [redacted] patients ([redacted]%) in the T-DM1 arm. Prior trastuzumab and paclitaxel was a prior regimen in [redacted] patients ([redacted]%) and [redacted] patients ([redacted]%), respectively. Please note that these numbers include patients who had either/or and therefore may be counted in both.

A26. In section B.2.4.4 (Document B), Table 10 page 50 states that 42 and 36 participants in the T-DXd and T-DM1 arms respectively had prior cancer therapy with an anti-HER2 TKI. Could the company please specify what types of anti-HER2 TKIs were given to these participants?

The following therapies were anti-HER2 TKIs recorded as administered as prior therapy to patients enrolled in DESTINY-Breast03:

[redacted]

[redacted]

A27. In section B.3.3.2.1.2 (page 99) of the CS (Document B), it states that 'The two cohorts appear similar in terms of median age and ECOG status while a greater proportion of patients in EMILIA received 0–1 prior therapies than in DESTINY-Breast03 (60.4% vs 47.9%)' Could the company please comment on why there may be this difference in number of prior therapies?

A higher proportion of patients in the EMILIA study received 0-1 prior therapies compared with the DESTINY-Breast03 study. This may be due to the availability of additional therapies in the more recent DESTINY-Breast03 trial. The first line standard of care at the time of the EMILIA study (2012) was trastuzumab and a taxane. Subsequently, the CLEOPATRA study led to the approval of the trastuzumab, pertuzumab and taxane combination. In addition, further treatments have become available globally. The availability of more earlier line treatment options at the time that DESTINY-Breast03 recruited may explain the greater proportion of patients having had >1 prior line of therapy.

It should be noted that there is a wealth of evidence showing poorer outcomes through successive lines of therapy in both breast cancer and other cancers,[2-7] thus it is likely that the more prior lines a patient has had, the harder they are to effectively treat. Evidence from previous studies, including DESTINY-Breast01 and 03, show additional prior lines are associated with poorer outcomes. This was also confirmed by clinicians at a validation meeting held by Daiichi Sankyo, thus results from DESTINY-Breast03 may be more conservative relative to the EMILIA study.

A28. A range of subgroup analyses were planned (Document B, Table 6 page 38) which included: hormone receptor status; ER status; PR status; prior pertuzumab treatment; lines of prior systemic therapy (not hormone therapy); lines of therapy prior to pertuzumab; baseline renal impairment; baseline hepatic impairment; baseline visceral disease; baseline lung metastases; baseline liver metastases; baseline CNS metastases; history of CNS metastases; age; race; region; ECOG performance status.

In section B.2.7.2 (page 65) and Figures 13 and 14 (Document B), only subgroup analyses relating to including prior lines of therapy, prior pertuzumab treatment, hormone receptor

status, presence of visceral disease, and the presence of stable brain metastases at baseline were undertaken.

Could the company please detail the results of other subgroup analyses reported in Table 6 that were omitted from Figures 13/14 for PFS and for OS? Or, if these subgroup analyses have not been undertaken explain the deviation from planned analysis?

The Company presented subgroup analysis by key subgroups of interest in Document B, aligned with those presented in the primary publication for DESTINY-Breast03, and data published via conference presentations. The full set of subgroup analyses undertaken as per the protocol can be found in the DESTINY-Breast03 CSR, submitted by the Company as an accompanying reference with the initial submission, Section 8.2.1.5 (starting on p90). Forest plots of subgroup analyses are presented in Figure 8.3 of the CSR (p91–94). Please note that prespecified subgroups with sparse data (<10 events) were not analysed at this data cut.

A29. Priority question: In Table 6 (Document B, page 37) the CS states that 'Crossover at the end of treatment was not permitted within the trial. However, crossover post study completion may occur in markets where TDXd/TDM1 is commercially available'.

Section D.2.1 (Appendices) states that 78 subjects in the T-DXd arm and 164 subjects in the T-DM1 arm received a new systemic anticancer treatment, which included either T-DM1 or T-DXd. The numbers receiving 'Post study treatment' stated in Section D.2.1 (Appendices) appear consistent with the numbers in Table 48, page 126 in the CS (Document B).

a. **Please clarify whether control subjects could switch to T-DXd before disease progression following the first interim analysis data-cut point due to a statistically significant benefit in progression-free survival found at the first interim analysis.**

The 78 subjects in the T-DXd arm and 164 subjects in the T-DM1 arm refer to patients who received at least one systemic anti-cancer therapy. Patients may have received more than one line of subsequent treatment therefore the total number of subsequent treatments exceeds the number of patients receiving subsequent treatments.

Treatment crossover was not permitted before protocol defined drug discontinuation or within the trial. Patients in the control arm could therefore not switch to the T-DXd

arm following the first interim analysis as per protocol. Patients could however receive T-DXd or T-DM1 as a subsequent therapy outside of DESTINY-Breast03 in those markets where it was commercially available following protocol defined discontinuation.

b. **Please clarify whether subjects could receive the study treatment allocated to the other arm of DESTINY-Breast03 following discontinuation of the randomly allocated study treatment according to the trial protocol.**

As per the DESTINY-Breast03 protocol, subjects could not receive the study treatment allocated to the other arm of the trial following discontinuation; however, the protocol did not outline any restrictions on subsequent therapies outside of DESTINY-Breast03. Patients were therefore able to receive either treatment outside of the trial in those countries where either T-DM1 or T-DXd were commercially available following protocol-defined discontinuation.

c. **Please clarify whether the 78 subjects in the T-DXd arm and 164 subjects in the T-DM1 arm who received a new systemic anticancer treatment, which could include either T-DM1 or T-DXd, and the subsequent treatment statistics in Table 48 (page 126) are for those who started to receive these treatments before the interim analysis data-cut point.**

All subjects recorded as receiving a new systemic anticancer treatment (and the accompanying statistics) did so before the interim analysis data cut point, following protocol defined discontinuation of the randomly allocated study treatment.

Please note the number of subsequent treatments received will be greater than the number of patients receiving subsequent treatments, due to some patients receiving more than one subsequent line.

d. **On page 63 in the CS (Document B), it states that further analysis of OS will be conducted as statistical significance at the required level was not achieved at the first interim analysis time point. Please report the statistical analysis method planned for further analysis. Please comment on any bias that may be present if subjects switch treatments before progression when using the statistical analysis method planned.**

Statistical analysis of OS (see Document B, Section B.2.4.2, p45–46) will be conducted by estimating survival distribution by the Kaplan–Meier method. Median

OS with two-sized 95% confidence intervals will be calculated with the Brookmeyer and Crowley method, and a hazard ratio with two-sided confidence intervals calculated with a stratified Cox proportional hazards regression model. The boundary for efficacy will be scaled, such that for exactly [redacted] OS events, the two-sided significance boundaries would be [redacted], and at the final analysis, [redacted], based on an expected [redacted] events.

Although treatment switching was not permitted in the study protocol, some patients may, after discontinuing their study treatment, receive either T-DXd or T-DM1, in markets where these therapies are commercially available. This subsequent treatment is outside of the trial setting and an option only in markets where the therapies are available. The analysis planned follows the ITT principle, in which patients who receive subsequent treatment after protocol defined drug discontinuation will remain in the analysis as randomised. If patients receiving T-DM1 in DESTINY-Breast03 subsequently receive commercially available T-DXd, the OS benefit of T-DXd may be underestimated given its known efficacy in the third-line setting via DESTINY-Breast01.

e. **Please report how many of the 43 subjects in the T-DXd arm that received T-DM1 as subsequent treatment did so because of discontinuation due to disease progression and how many were due to adverse events. Please report how many of the 30 subjects in the T-DM1 arm that received T-DXd as subsequent treatment did so because of discontinuation due to disease progression and how many were due to adverse events.**

A summary of patients who discontinued due to disease progression or adverse events (see Table 7.2 in the CSR for patient disposition) and the subsequent treatments received is presented in Table 34.

The majority of patients who switched treatments at subsequent treatment (i.e., from T-DXd to T-DM1, or vice versa) did so after discontinuing due to disease progression.

Of the 43 and 30 patients in the T-DXd and T-DM1 arms, respectively, who crossed over to the other therapy after discontinuing their study drug, [redacted] in the T-DXd arm received subsequent T-DM1, and [redacted] in the T-DM1 arm received subsequent T-DXd.

Of the patients who discontinued due to adverse events, [redacted] and [redacted] patients, respectively, received the other treatment after discontinuing their study drug. [redacted] patient in the T-DXd arm who crossed over to T-DM1 discontinued study drug for other reasons.

Table 34: Summary of key discontinuation reasons in patients who crossed over to T-DXd or T-DM1 as subsequent therapy | DESTINY-Breast03 | FAS

	T-DXd (N=43)	T-DM1 (N=30)
Progressive disease per RECIST	[redacted]	[redacted]
Clinical progression per investigator	[redacted]	[redacted]
Adverse event	[redacted]	[redacted]
Other	[redacted]	[redacted]

Next line therapy is defined as the first systemic anti-cancer treatment initiated before/on the analysis cut-off date (DCO).
Abbreviations: T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

f. Please comment on whether the reason for discontinuation (due to adverse effects or disease progression) may have an influence on choice of subsequent treatment.

Discontinuation of a treatment due to adverse events may have an influence on choice of subsequent treatment in circumstances where the subsequent treatment has a similar adverse event profile to the treatment that was discontinued. For example, if the treatment had been discontinued due to a particular adverse event, and the subsequent treatment is associated with a similar common adverse event then it may be less likely to be chosen.

Disease progression does not normally influence a subsequent treatment decision, however with regards to targeted therapy, if a patient progresses rapidly on treatment this could then lead to an investigation to reconfirm that target (e.g. HER2) prior to initiating subsequent therapy.

Table 34 shows a greater proportion of patients who discontinued T-DXd in DESTINY-Breast03 received subsequent T-DM1 than vice versa. These results should be interpreted with caution given the significantly lower proportion of patients in the T-DXd arm moving to subsequent therapy (due to lower rates of disease progression) and because T-DXd is not currently available as a subsequent therapy across all markets in this setting.

g. **Regarding the subsequent treatment categories, the 'most representative treatment for the UK setting was selected for costing purposes' (page124 in CS, Document B). Please clarify how the most representative treatment was identified.**

For costing purposes, the most representative treatment for the UK setting was selected for each drug class. Selection was firstly based on clinician feedback (at the global level) to reflect clinical guidelines, drugs available at this line of therapy and usage. Based on feedback, the following assumptions were initially made:

- Taxanes to be costed as paclitaxel
- Anti-HER2 therapies to be costed as lapatinib
- Hormone therapy to be costed as tamoxifen
- Other to be costed as capecitabine

These were then presented to the UK clinical experts at the validation meeting held by Daiichi Sankyo UK and during follow-up via email (see response to CQ A29 i). At the follow-up, the clinical expert confirmed that, based on usage in this setting, paclitaxel, capecitabine and tamoxifen are the most appropriate taxane, chemotherapy and hormone therapy agents, respectively. They also confirmed that lapatinib is not re-imbursed in the NHS and that the most appropriate anti-HER2 agent would be the tucatinib combination as it is now reimbursed in this setting. Therefore, within the economic model, these assumptions are considered appropriate and validated.

h. **It was stated in section B.3.5.4.1 page 125 in the CS (Document B) that 'Clinical advice also suggested that the proportion of progressed patients receiving subsequent treatment in DESTINY-Breast03 was higher than expected and that approximately two-thirds of progressed patients would receive subsequent therapy in UK clinical practice after second-line treatment.' What proportion of progressed patients received subsequent treatment in the DESTINY-Breast03 trial at the first interim data-cut point for each trial arm?**

The proportion of progressed patients who received subsequent treatment was assessed for the patients who had BICR-assessed progression including those censored due to missing two consecutive tumour assessments in the PFS analysis.

Of the [redacted] and [redacted] progressed patients eligible for analysis in the T-DXd and T-DM1 arms, respectively, [redacted] and [redacted] patients, respectively, received subsequent treatment, or proportionally, [redacted]% and [redacted]% of patients, respectively.

i. **If proportion of progressed patients received subsequent treatment in each study arm mentioned A29 (h) do not correspond to 78 subjects in the T-DXd arm and 164 subjects in the T-DM1 arm who received a new systemic anticancer treatment, please explain the difference. Please comment on the possible reasons for the difference between the DESTINY-Breast03 trial and UK clinical practice, in relation to subsequent lines of treatment.**

The data presented above (A29[h]) only includes patients with BICR-assessed progression, and does not include patients who were censored for other reasons, such as adequate tumour assessment no longer available (for a full list of censoring reasons, see the footnote below Table 12 in Document B, Section B.2.6.1, p54). Moreover, as A29[e] states, a small proportion of patients discontinued due to adverse events or other reasons and received a subsequent treatment.

Possible reasons for the difference in proportions of patients receiving subsequent treatment between DESTINY-Breast03 and UK clinical practice were not directly addressed in the clinical validation meeting conducted by the Company; however, the experts consulted mentioned two aspects that may be of relevance:

1) The extensive progression-free survival observed in the T-DXd arm of DESTINY-Breast03 means that many of these patients will not have experienced disease progression and subsequently received their next treatment. As DESTINY-Breast03 is an ongoing trial the data for subsequent therapies are immature at this data cut. Consequently, the base case assumption has been chosen to be conservative (a high proportion) for the T-DXd arm, which currently has a much lower rate of subsequent therapy uptake.
2) Caution by physicians treating clinical trial patients potentially resulting in high rates of discontinuation due to TEAEs, largely in the face of TEAEs they may be less familiar with (e.g., interstitial lung disease). This effect is anticipated to decrease in clinical practice as clinicians gain familiarity with the safety profile of T-DXd.

j. **On page 63 in the CS (Document B), it states that further analysis of OS will be conducted as statistical significance at the required level was not achieved at the first interim analysis time point. Please report the statistical analysis method planned for further analysis. Please comment on any bias that may be present if subjects switch treatments before progression when using the statistical analysis method planned.**

Duplicate question (Please see response to A29[d])

k. **In Table 48, page 126, it states that [redacted] subjects in the T-DM1 arm received T-DXd as subsequent therapy. Since the number of subjects in the T-DM1 arm was 263, for the purpose of calculating the number of patients who receive T-DXd in the T-DM1 arm of the model, should the percentage not be [redacted], which is then multiplied by the unit cost in Costs!G115 in the Excel model, then multiplied by the proportion receiving subsequent (66.7%- clinical expert opinion), Costs!G117?**

To calculate the subsequent treatment costs, for the economic model, the following steps were taken:

1. Firstly, the distribution of subsequent treatments was calculated. The denominator was taken as the total number of subsequent treatments in each arm of DESTINY-Breast03. For the T-DM1 arm, a total of 389 subsequent treatments were received after discontinuation of T-DM1. The proportion of those subsequent treatments which were T-DXd was [redacted] This approach is used within the economic model in favour of using the total number of patients in each arm as the denominator (i.e., 263 for T-DM1), to avoid the subsequent treatment costs being dependent on the maturity of trial data i.e., the proportion of patients receiving subsequent treatment will increase with further, more mature data from DESTINY-Breast03 as more patients discontinue study drug.

2. The next step was to calculate the average cost of subsequent treatment per patient by multiplying the distributions in Step 1 by the drug cost per cycle. This is then multiplied by the anticipated duration for each subsequent treatment based on external data to calculate the 'average total cost of subsequent treatment per patient receiving a subsequent treatment' – see CS Section B.3.5.4.1 table 48).

3. The final step is to multiply the 'average total cost of subsequent treatment per patient receiving a subsequent treatment' by the proportion of patients who are estimated to receive subsequent treatment (i.e., 66.7% in the CS base case informed by clinical opinion). If the total number of patients was used as the denominator in Step 1, then applying this step would lead to double counting as the subsequent treatment distribution would already be accounted for. The current approach allows use of an alternative source to inform the proportion of patients receiving subsequent treatments which align more closely with current UK practice.

I. **Please clarify in detail how the distribution of UK clinical practice subsequent treatment categories used in scenario analysis, referenced on page 125 in the CS and reported in Costs!O128:P138 in the Excel model, was derived. This should include the source and the methods, and whether the denominator in the % calculation was (i) the number of patients who received 2nd-line treatment, (ii) the number of patients who experienced disease progression following 2nd-line treatment, or (iii) the number of patients who experienced disease progression following 2nd-line treatment and that received a subsequent treatment. Please clarify whether the denominator is the same as that used in point (g) in determining the percentages in the DESTINY-Breast03 trial.**

Following the expert validation meeting (see response to CQ B5), clinical experts were asked to complete a table via email with estimates of the proportion of patients who receive each treatment after progressing on either T-DM1 or T-DXd. One of the clinical experts filled in the table answering the following questions:

'Following T-DM1, of those that receive subsequent therapy, what proportion receive each treatment?'

and

'Should T-DXd be reimbursed, what proportion of patients that progress on T-DXd would receive each subsequent treatment?'

During the validation meeting, the clinical experts confirmed that approximately two-thirds is a reasonable assumption moving into third-line. The clinical expert who responded to the follow-up questions, estimated that around 65%-75% of patients

would receive subsequent treatment following T-DM1 and this may be slightly higher (~+5%) after T-DXd. General consensus during the validation meeting was that around two-thirds of patients would receive subsequent treatment (hence why this was used as the base case). Of the proportions estimated by the clinical expert, the figures were re-calibrated such that they totalled 100% to align with the approach described in CQ response A29 (k) Step 1, and incorporated within the economic model as a scenario analysis. Table 35 presents the actual values estimated by the clinical expert and the subsequent uplifted values used within the economic model.

Table 35: Clinical expert subsequent treatment usage

Subsequent treatment	Clinical expert opinion		Uplifted values	
	Following T-DM1	Following T-DXd	Following T-DM1	Following T-DXd
T-DXd	30%	-	40.0%	-
T-DM1	-	10%	-	12.5%
Taxane	5% (weekly paclitaxel)	5%	6.7%	6.3%
Trastuzumab + taxane	5%	-	6.7%	-
Anti-HER2	30% (trastuzumab + tucatinib, capecitabine)	60%	40.0%	75.0%
Hormone therapy	5%	5%	6.7%	6.3%
Total	75%	80%	100.0%	100.0%

Abbreviations: T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan

A30. The following questions relate to EORTC QLQ-30 in section B.2.6.1 (Document B):

a. On page 61, the CS states 'For global health status, treatment with TDXd was associated with a numerically longer median time to definitive deterioration in (9.7 months) compared with TDM1 (8.3 months).' This sentence is incomplete. Please clarify in what deterioration was occurring?

The wording in Document B.2.6.1 is in error, and should instead read: 'For global health status, treatment with T-DXd was associated with a numerically longer median time to definitive deterioration (9.7 months) compared with T-DM1 (8.3 months).'

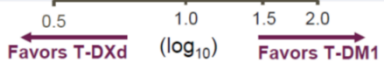
b. On page 62, the CS states "The time to deterioration was numerically longer in the TDXd arm than in the TDM1 arm for the physical functioning and social functioning

subscales, but did not reach statistical significance." Please provide data for these outcomes.

The data for time to definitive deterioration across patient-reported outcome measures of interest are presented in Figure 6.

Figure 6: Forest plot of time to definitive deterioration in PRO measures of interest

		Median (95% CI) TDD, months		HR (95% CI)	Nominal *P* value
		T-DXd (n = 261)	T-DM1 (n = 263)		
EORTC QLQ-C30	Global health status/QoL[a]	9.7 (7.3-12.5)	8.3 (7.0-10.3)	0.88 (0.70-1.11)	0.2829
	Pain symptoms[b]	10.8 (8.3-14.0)	8.3 (6.6-9.8)	0.75 (0.59-0.95)	0.0146
	Physical functioning[b]	16.7 (14.5-NE)	10.3 (8.3-21.0)	0.77 (0.59-1.01)	0.0529
	Emotional functioning[b]	16.4 (14.1-19.9)	10.5 (9.0-13.8)	0.69 (0.53-0.89)	0.0049
	Social functioning[b]	11.1 (7.3-13.4)	9.0 (7.1-11.3)	0.90 (0.71-1.14)	0.3577
EORTC QLQ-BR45	Arm symptoms[b]	11.1 (8.5-14.8)	7.0 (5.6-9.3)	0.70 (0.55-0.89)	0.0033
	Breast symptoms[b]	26.4 (26.4-NE)	NE (NE-NE)	0.76 (0.53-1.09)	0.1329
EQ-5D-5L	VAS[b]	13.2 (10.1-15.3)	8.5 (7.3-10.4)	0.77 (0.61-0.98)	0.0354



a primary PRO variable of interest.
b Secondary PRO variable of interest.
Abbreviations: CI, confidence interval; EORTC, European Organization for Research and Treatment of Cancer; HR, hazard ratio; NE, not estimable; QLQ-BR45, Quality of Life Breast cancer questionnaire; QLQ-C30, Quality of Life Core 30 questionnaire; QoL, quality of life; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TTD, time to deterioration; VAS, visual analogue scale.
Source: Curigliano et al; 2022. Presented at ESMO 2022 congress (oral presentation 1630).[8]

c. On page 62, the CS states 'The difference between treatment arms was not significant for the breast symptoms subscale.' Please provide the data for this outcome.

The data for time to definitive deterioration in the breast symptoms scale are presented in Figure 6 above.

A30. The following questions relate to TEAEs in section B.2.10.1.2 (Document B):

a. In Table 16, numbers within specific TEAE categories listed do not match the overall participant numbers who had TEAEs. Could the company provide an explanatory footnote to explain why this is the case or revise the table?

Table 16 is a summary table and is not intended to be an exhaustive list of all TEAEs. It presents patients with TEAEs of each category (e.g., the table does not present the number and proportion of patients who did not report serious TEAEs, which can be inferred from the total number of patients with TEAEs and the number

with serious TEAEs). Moreover, it is expected that there will be a degree of overlap between categories (e.g., serious TEAEs and TEAEs associated with an outcome of death).

The Company proposes the following explanatory note:

"TEAE categories presented above are a summary of key safety findings, and not an exhaustive list of all TEAEs; patient numbers will not sum to the total given for patients with 'any TEAE'."

b. In Table 19, specific TEAEs listed do not match the overall participant numbers who had TEAEs associated with study drug discontinuation, drug reduction and drug interruption. Could the company provide an explanatory footnote to explain why this is the case or revise the table?

Table 19 presents the most frequently occurring TEAEs associated with changes to treatment (i.e. those occurring in ≥2% of patients in either arm) and is not an exhaustive list. The Company proposes the following explanatory note:

"TEAEs shown are those reported by ≥2% of patients in either treatment arm, and are not an exhaustive list of TEAEs associated with changes to treatment."

d. The CS states, 'events of ILD associated with study drug interruption, dose reduction, or discontinuation were reported in [redacted] ([redacted]%), [redacted] ([redacted]%) and 21 patients (8.2%), respectively, across patients treated with T-DXd.' These numbers appear inconsistent with those provided in Table 19. Please rectify the statement made or the table.

Table 19 presents TEAEs occurring in ≥2% of patients in either arm. The proportion of patients with ILD leading to dose reduction is less than 2% for both treatment arms (including the [redacted]% value highlighted above), and are therefore not presented in Table 19. The other two values highlighted above ([redacted]% and 8.2%) are both included in Table 19. The Company therefore believes that the text as presented in the CS is correct.

e. The CS states 'the proportion of patients experiencing TEAEs generally declined across subsequent cycles' (page 71). However, in Table 17 the proportion of patients with TEAEs in cycles ≥8 was [redacted]. Could the company provide a breakdown of TEAEs by cycle and specific TEAE category and type?

TEAEs by cycle and selected preferred term are shown in Table 36. Please note that TEAEs for Cycles ≥8 and ≥18 are collated across multiple cycles, and would therefore be expected to include a larger proportion of affected patients than for a single cycle. A gradual decline in the proportion of patients experiencing a TEAE can be observed in individual cycles 1 to 7.

Table 36: Treatment-emergent adverse events by selected preferred term and cycle | SAS

MedDRA preferred term	T-DXd (N = 257)			T-DM1 (N = 261)		
Cycle	n	n at risk	%	n	n at risk	%
Any TEAE						
Cycle1	[redacted]					
Cycle2	[redacted]					
Cycle3	[redacted]					
Cycle4	[redacted]					
Cycle5	[redacted]					
Cycle6	[redacted]					
Cycle7	[redacted]					
Cycle>=8	[redacted]					
Cycle>=18	[redacted]					
Nausea						
Cycle1	[redacted]					
Cycle2	[redacted]					
Cycle3	[redacted]					
Cycle4	[redacted]					
Cycle5	[redacted]					
Cycle6	[redacted]					
Cycle7	[redacted]					
Cycle>=8	[redacted]					
Cycle>=18	[redacted]					
Vomiting						
Cycle1	[redacted]					
Cycle2	[redacted]					
Cycle3	[redacted]					
Cycle4	[redacted]					
Cycle5	[redacted]					
Cycle6	[redacted]					
Cycle7	[redacted]					
Cycle>=8	[redacted]					
Cycle>=18	[redacted]					
Fatigue						
Cycle1	[redacted]					
Cycle2	[redacted]					

MedDRA preferred term	T-DXd (N = 257)			T-DM1 (N = 261)		
Cycle	n	n at risk	%	n	n at risk	%
Cycle3	[redacted]					
Cycle4						
Cycle5						
Cycle6						
Cycle7						
Cycle>=8						
Cycle>=18						
Decreased appetite						
Cycle1						
Cycle2						
Cycle3						
Cycle4						
Cycle5						
Cycle6						
Cycle7						
Cycle>=8						
Cycle>=18						
Diarrhoea						
Cycle1						
Cycle2						
Cycle3						
Cycle4						
Cycle5						
Cycle6						
Cycle7						
Cycle>=8						
Cycle>=18						
Neutropenia						
Cycle1						
Cycle2						
Cycle3						
Cycle4						
Cycle5						
Cycle6						
Cycle7						
Cycle>=8						
Cycle>=18						
Anaemia						
Cycle1						
Cycle2						
Cycle3						
Cycle4						
Cycle5						

MedDRA preferred term	T-DXd (N = 257)			T-DM1 (N = 261)		
Cycle	n	n at risk	%	n	n at risk	%
Cycle6	[redacted]					
Cycle7						
Cycle>=8						
Cycle>=18						
Thrombocytopenia						
Cycle1						
Cycle2						
Cycle3						
Cycle4						
Cycle5						
Cycle6						
Cycle7						
Cycle>=8						
Cycle>=18						
Constipation						
Cycle1						
Cycle2						
Cycle3						
Cycle4						
Cycle5						
Cycle6						
Cycle7						
Cycle>=8						
Cycle>=18						
Leukopenia						
Cycle1						
Cycle2						
Cycle3						
Cycle4						
Cycle5						
Cycle6						
Cycle7						
Cycle>=8						
Cycle>=18						
Abdominal pain						
Cycle1						
Cycle2						
Cycle3						
Cycle4						
Cycle5						
Cycle6						
Cycle7						
Cycle>=8						

MedDRA preferred term	T-DXd (N = 257)			T-DM1 (N = 261)		
Cycle	n	n at risk	%	n	n at risk	%
Cycle>=18	[redacted]					
Headache						
Cycle1						
Cycle2						
Cycle3						
Cycle4						
Cycle5						
Cycle6						
Cycle7						
Cycle>=8						
Cycle>=18						
Stomatitis						
Cycle1						
Cycle2						
Cycle3						
Cycle4						
Cycle5						
Cycle6						
Cycle7						
Cycle>=8						
Cycle>=18						
Rash						
Cycle1						
Cycle2						
Cycle3						
Cycle4						
Cycle5						
Cycle6						
Cycle7						
Cycle>=8						
Cycle>=18						
Upper respiratory tract infection						
Cycle1						
Cycle2						
Cycle3						
Cycle4						
Cycle5						
Cycle6						
Cycle7						
Cycle>=8						
Cycle>=18						
Lymphopenia						

MedDRA preferred term	T-DXd (N = 257)			T-DM1 (N = 261)		
Cycle	n	n at risk	%	n	n at risk	%
Cycle1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Cycle6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Cycle7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle>=8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle>=18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Febrile neutropenia						
Cycle1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Cycle2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Cycle3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Cycle4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Cycle5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Cycle6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Cycle7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Cycle>=8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Cycle>=18	[redacted]	[redacted]		[redacted]	[redacted]	

Percents are based on the number of subjects at risk at any point in the cycle window as the denominator.
Abbreviations: SAS, safety analysis set; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

f. Table 19 in section B.2.10.1.2 (Document B) states that 44% of participants in the T-DXd trial arm had their doses interrupted due to TEAEs. Can the company provide additional data on length of interruptions in dose?

Duration of interruption was not collected in DESTINY-Breast03 and cannot be provided. However, the protocol stipulates that dose can be interrupted for up to 28 days from the planned date of administration (DESTINY-Breast03 protocol, Section 5.6.1, p52).

Additionally, as a contingency measure for the COVID-19 pandemic, dose interruptions were limited to 49 days after the last dose date and a dosing extension form required to be filled in for any such delay that occurred. Dosing extensions due to COVID-19 occurred in seven patients, with a maximum dosing extension of 25 days (DESTINY-Breast03 CSR, Section 6.8.2, p65).

A31. Could the Company please provide a list of the adverse events that qualify as Serious Treatment Emergent Adverse Events (serious TEAEs)?

Serious adverse events (SAEs) were defined in the DESTINY-Breast03 protocol by the standard definition[9,10] of SAEs (see DESTINY-Breast03 protocol, section 9.4.2, p84):

An SAE is any untoward medical occurrence that at any dose:

- *Results in death,*
- *Is life-threatening,*
- *Requires inpatient hospitalization or prolongation of existing hospitalization,*
- *Results in persistent or significant disability/incapacity,*
- *Is a congenital anomaly/birth defect, or*
- *Is an important medical event.*

Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

A list of serious TEAEs by arm, reported in DESTINY-Breast03, is provided below in Table 37.

Table 37: Treatment-emergent serious adverse events by preferred term | SAS

MedDRA preferred term	T-DXd (N = 257)	T-DM1 (N = 261)
Subjects with any serious TEAE, n (%)	49 (19.1)	47 (18.0)
Vomiting	[redacted]	[redacted]
Interstitial lung disease	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Disease progression	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Cellulitis	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Seizure	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]

MedDRA preferred term	T-DXd (N = 257)	T-DM1 (N = 261)
Abdominal pain	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
Acute respiratory failure	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Bone lesion	[redacted]	[redacted]
Breast cellulitis	[redacted]	[redacted]
Campylobacter gastroenteritis	[redacted]	[redacted]
Colitis	[redacted]	[redacted]
Cytomegalovirus infection	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]
Dehydration	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Ejection fraction decreased	[redacted]	[redacted]

Abbreviations: SAS, safety analysis set; T-DM1, trastuzumab emtansine; TEAE, treatment-emergent adverse event; T-DXd, trastuzumab deruxtecan.
Source: Tables, graphs, and figures for DESTINY-Breast03 CSR (Table 14.3.1.5; p521).

Section B: Clarification on cost-effectiveness data

General

B1. There is a description of the QALY severity modifier in the CS (Document B Section B3.6 page 127). Please provide

a. The details where NICE cite the Schneider et al. (2021) estimator tool to estimate the shortfall;

NICE do not specifically recommend the Schneider et al. (2021) tool, or any other tool, as a way of estimating the QALY shortfall, however they do acknowledge the Schneider estimator as a useful tool. As part of the review of the NICE methods, NICE published a document titled "*Review of methods, processes and topic selection for health technology evaluation programmes: conclusions and final update. Appendix: Further discussion and rationale for conclusions – methods*". The link is available as a Word document download which can be found here. Under the section on the '*Severity of disease'* on page 15, NICE state "*In addition, Schneider et al. (2021) have presented a further data source in a preprint paper, using EQ 5D 5L data from HSE in 2017 and 2018 (mapped to EQ-5D-3L using the tool by van Hout et al. 2012). They also present a tool for calculating shortfall automatically, which could be a helpful resource for stakeholders".*

b. Justification for preference in using the Measuring and Valuing Health Study (MVH) HRQoL norms (Alternative C) in the Schneider et al. (2021);

For the calculation of health benefits, NICE recommend the use of EQ-5D-3L over EQ-5D-5L.[11] A recent (12th January 2022) document published by the NICE Decision Support Unit (DSU) titled 'Estimating EQ-5D by age and sex for the UK' provided a description of existing estimates for general population utilities as well as outlining datasets available using more recent data which still utilises the EQ-5D-3L (referring to the Health Survey for England [HSE] 2014 data and the Economic Methods of Evaluation in Health and Social Care Policy Research Unit [EEPRU] dataset). Within this document it was stated that NICE still recommends the use of the EQ-5D-3L for the calculation of health benefits, and that the EQ-5D-3L utilities are preferred to those derived from the EQ-5D-5L tool (link here).[12] When considering the estimation of quality of life of the general population the DSU advised that "for the sake of consistency our recommendation to NICE is to use the most up to date information available that has direct observation of the EQ-5D-3L from the HSE (2014)."

As part of the Schneider et al 2021 tool, Alternative C (i.e., 'MVH, EQ-5D-3L value set + HSE 2012+14') refers to utilising data from the EQ-5D-3L health state profiles from the Health Survey for England (HSE) 2012 and 2014, and the 3L value set from the 1993 MVH study. This option incorporates the latest two datasets available from the HSE where the EQ-5D-3L was collected to capture quality of life. After 2014, the EQ-5D-5L was collected. Within the Schneider 2021 tool, all options except for 'MVH, EQ-5D-3L value set + HSE 2012+14' incorporate later data from HSE 2017 and 2018 labelled as 'Health survey for England 2017 and 2018 (pooled). These data are based on EQ-5D-5L estimates and are then cross-walked. Based on the preference stated by NICE for the EQ-5D-3L and based on guidance from the DSU, 'MVH, EQ-5D-3L value set + HSE 2012+14' was considered the most robust source and most appropriate to inform the shortfall estimates from the publicly available Schneider et al 2021 tool.

To further support the QALY shortfall calculations, since the CS was made, the Schneider et al tool has been specifically adapted for the Company to include two further utility options:

- MVH, EQ-5D-3L value set + HSE 2014

- Ara and Brazier 2010 3L value set + HSE 2003+06

These include other 3L value set sources and includes an option to use just HSE 2014 data set which is recommended in the DSU guidance. Results using these two further options are presented in the response below.

c. Sensitivity analysis using the reference case (Hernandez Alava et al. EQ-5d-5l to 3L mapping + HSE 2017-2018).

Table 38 and

Table 39 reports the requested EAG sensitivity analysis estimating the absolute and proportional QALY shortfall using Hernandez Alava et al. EQ-5D-5L to 3L mapping + HSE 2017-2018 for the base case using OS Method 1 and scenario using OS Method 2. Results from previous submissions (i.e., TA458) are also presented in Table 40. Results from two additional EQ-5D-3L utility sources are also included to reflect NICE's preference for using EQ-5D-3L for the calculation of health benefits.

Table 38: Summary of QALY shortfall analysis using data from economic analysis – base case

Schneider shortfall calculator	Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	QALY shortfall
Hernandez Alava et al., EQ-5D-5L to 3L mapping + HSE 2017-2018	14.33	T-DM1: [redacted] (discounted)	Absolute: [redacted] Proportional: [redacted]
MVH, EQ-5D-3L value set + health state profiles	14.61		Absolute: [redacted] Proportional: [redacted]
MVH, EQ-5D-3L value set + HSE 2012+14	14.63		Absolute: [redacted] Proportional: [redacted]
MVH, EQ-5D-3L value set + HSE 2014	14.70		Absolute: [redacted] Proportional: [redacted]
Ara & Brazier 2010 (3L + HSE 2003+06)	14.63		Absolute: [redacted] Proportional: [redacted]

Abbreviations: HSE, Health Survey for England; MVH, Measuring and Valuing Health Study; QALY, quality-adjusted life-year.

Table 39: Summary of QALY shortfall analysis using data from economic analysis – OS Method 2

Schneider shortfall calculator	Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	QALY shortfall
Hernandez Alava et al., EQ-5D-5L to 3L mapping + HSE 2017-2018	14.33	T-DM1: [redacted] (discounted)	Absolute: [redacted] Proportional: [redacted]
MVH, EQ-5D-3L value set + health state profiles	14.61		Absolute: [redacted] Proportional: [redacted]
MVH, EQ-5D-3L value set + HSE 2012+14	14.63		Absolute: [redacted] Proportional: [redacted]
MVH, EQ-5D-3L value set + HSE 2014	14.70		Absolute: [redacted] Proportional: [redacted]
Ara & Brazier 2010 (3L + HSE 2003+06)	14.63		Absolute: [redacted] Proportional: [redacted]

Abbreviations: HSE, Health Survey for England; MVH, Measuring and Valuing Health Study; QALY, quality-adjusted life-year.

Table 40: Summary of QALY shortfall analysis using data from economic analysis - previous evaluations (TA458)

Schneider shortfall calculator	Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	QALY shortfall
Hernandez Alava et al., EQ-5D-5L to 3L mapping + HSE 2017-2018	14.60	T-DM1: 2.09 S(discounted) Age: 53 years Female: 100%	Absolute: 12.51 Proportional: 85.69%
MVH, EQ-5D-3L value set + health state profiles	14.93		Absolute: 12.84 Proportional: 86.00%
MVH, EQ-5D-3L value set + HSE 2012+14	14.93		Absolute: 12.84 Proportional: 86.00%
MVH, EQ-5D-3L value set + HSE 2014	15.01		Absolute: 12.92 Proportional: 86.07%
Ara & Brazier 2010 (3L + HSE 2003+06)	2.09		Absolute: 12.85 Proportional: 86.02%

Abbreviations: HSE, Health Survey for England; MVH, Measuring and Valuing Health Study; QALY, quality-adjusted life-year.

Based on the rationale outlined in the response to B1 (b), Daiichi Sankyo considers that the MVH, EQ-5D-3L value set + HSE 2012+14 or the MVH, EQ-5D-3L + HSE 2014 to be the most robust data sets to inform the QALY shortfall calculation and aligned to DSU and NICE recommendations.

d. The full evidence details used in the calculation. This may include for example a graph showing the survival curves for the general population and the decision population, and details on utility estimates.

Two fundamental components are needed to inform the QALY shortfall. These are:

1. Discounted QALYs for patients with the disease (for this decision problem this is reflected by the total QALYs for T-DM1)

2. Discounted QALYs for patients without the disease (i.e., general population)

This response summarises how each component was estimated in turn and then provides results presented within the Schneider et al. RShiny tool.[13]

Discounted QALYs for T-DM1:

To estimate the discounted QALYs for T-DM1 the survival (PFS and OS outcomes) and corresponding health-related quality of life (HRQoL) values were required. In both instances the economic model was used and the headline outcomes from the economic model estimated the total discounted QALYs ([redacted] for T-DM1 as reported in CS Section B.3.10 Table 59 in the base case).

Figure 6 shows the modelled PFS and OS T-DM1 outcomes that were used in the model base case. A starting age of [redacted] (based on the starting age of the cohort in DESTINY-Breast03) was applied and a time horizon of 30 years was considered (after which ~0.1% of patients remained alive). All QALYs were discounted at 3.5% per annum in line with the NICE reference case.

Figure 7: Modelled PFS and OS outcomes for T-DM1 - model base case

Abbreviations: KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; T-DM1, trastuzumab emtansine

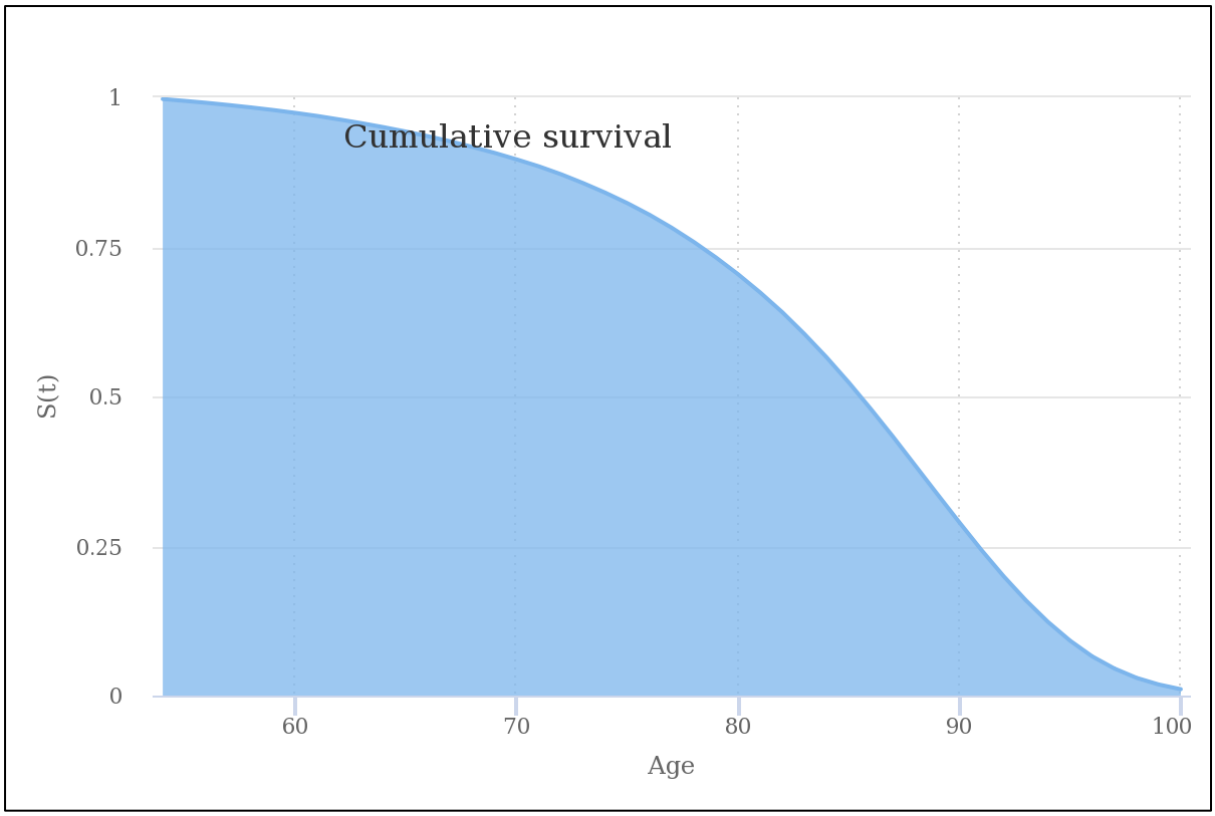
A total of [redacted] discounted QALYs were estimated in the T-DM1 arm of the model and this was based on PFS and OS outcomes combined with utility values incorporated into the model (details for which can be found in the CS Section B.3.4.4). Figure 8 shows how the QALYs were accrued over the modelled time horizon.

Figure 8: Cumulative QALYs for T-DM1 over the modelled time horizon

Discounted QALYs for the general population:

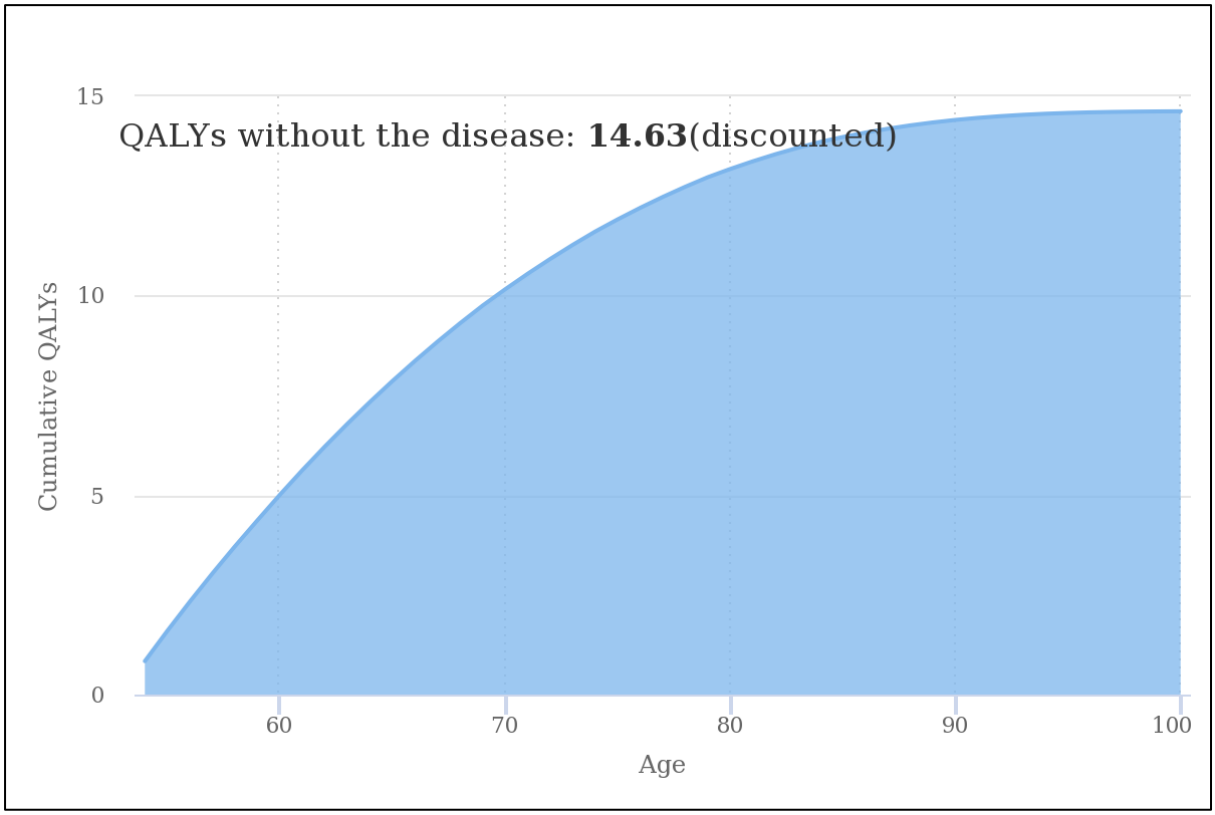
The Schneider et al. 2021 RShiny tool was used to calculate the total discounted QALYs for the general population.[13] As outlined in the CS, 'MVH, EQ-5D-3L value set + HSE 2012+14' was selected to inform the estimates which was based on information using the EQ-5D-3L health state profiles from the Health Survey for England pooled from 2012 and 2014, and the 3L value set from the 1993 MVH study. The tool allows the user to input an integer for age and proportion of patients who are female; [redacted] and 100% were imputed respectively. The tool then calculates the general population survival which is shown in Figure 9 and estimated based on national life tables from 2017-2019 (please note this is available as a download from the Schneider 2021 RShiny app). HRQoL is then estimated using information from the HSE 2012 and 2014 data using the 3L value set from the 1993 MVH study. In total the tool estimates 14.63 QALYs for the general population based on the baseline characteristics applied. The cumulative QALYs are shown in Figure 10.

Figure 9: Cumulative survival in the Schneider 2021 tool based on a population with age [redacted] who are 100% female using data from National Life Tables



Note: Please note that this image is available as a download option from the Schneider et al. 2021 RShiny tool and has not been developed by Daiichi Sankyo

Figure 10: Cumulative QALYs for the general population using MVH, EQ-5D-3L value set + HSE 2012+14 in the Schneider 2021 tool based on a population with age [redacted] who are 100% female



Note: Please note that this image is available as a download option from the Schneider et al. 2021 RShiny tool and has not been developed by Daiichi Sankyo

From the two key components of information (expected QALYs for T-DM1 and expected QALYs for the general population with the same baseline age and sex distribution), the absolute and proportional QALY shortfall can be calculated. The Schneider tool has an option to input the expected discounted QALYs associated with the disease (in this case the T-DM1 discounted QALYs were imputed with a value of [redacted]). The tool then provides the estimated shortfall and reports them in a graphical format as shown in Figure 11 and Figure 12.

Figure 11: Absolute QALY shortfall estimated by Schenider et al. 2021 tool using 'MVH, EQ-5D-3L value set + HSE 2012+14'

Abbreviations: QALY, quality adjusted life-year

Note: Please note that this image is available as a download option from the Schneider et al. 2021 RShiny tool and has not been developed by Daiichi Sankyo

Figure 12: Proportional QALY shortfall estimated by Schneider et al. 2021 tool using 'MVH, EQ-5D-3L value set + HSE 2012+14'

Abbreviations: QALY, quality adjusted life-year

Note: Please note that this image is available as a download option from the Schneider et al. 2021 RShiny tool and has not been developed by Daiichi Sankyo

Model structure

B2. Please clarify how the model was validated, and whether a checklist such as ADVISHE was used.

As presented in CS Section B.3.14, the model was validated using a number of approaches:

- During model development, the economic model was subject to rigorous quality control (QC) by a senior health economist independent from the model development team. The QC involved checking the model for coding errors, inconsistencies, and plausibility of inputs and outputs at key stages of model development including the final stage before submission.
    - The purpose of the QC was to stress test the cost-effectiveness results subject to the relevant settings and assumptions, as well as highlight any errors inadvertently implemented throughout model

development. Internal (non-published) QC checklists were used which have been designed to thoroughly assess the model in addition to completing a tailored sheet-by-sheet check of model calculations. A 4-stage approach to a thorough QC was conducted which is based on black-box testing, white-box testing, sheet-by-sheet checks, and replication-based checks. The objective of the QC was to identify any programming errors or issues relating to model functionality that would hinder the ability for others to reliably use the model.

- The UK expert validation meeting was used to discuss various aspects of the model structure and cost-effectiveness analyses including validation of the chosen model structure to inform the decision problem (see response to CQ A20 for further details). Details of the discussion topics are presented in Section B.3.14.2 with separate notes summarising the discussion points.[14] Feedback from the validation meeting was used throughout the analysis and informed the Company's base case.

- Internal validation of the model outcomes was conducted which compared the modelled OS, PFS and TTD outcomes with the observed outcomes in the trial (presented in Appendix J). The modelled outcomes appeared consistent with the observed trial data.

- External validation using external sources reporting OS and PFS outcomes of T-DM1 in other trials (with longer follow-up) was used to compare the modelled outcomes from DESTINY-Breast03. Details of the external sources used, and results of the external validation are presented Section B.3.14.4.

B3. Please provide a justification for the use of a Partitioned Survival Model other than that such models have previously been used and accepted in submissions to NICE. Please comment on the pros and cons vis-à-vis a Markov model.

Justification for the partitioned survival model (PartSA) was based on two key factors which are inherently linked (with both undoubtedly leading to a third which is prior acceptance at the HTA level). Firstly, the structure is aligned with the primary outcome measure (PFS) and key secondary outcomes measure (OS) in the DESTINY-Breast03 trial. This is a clear benefit, as there is a direct correspondence

between the clinical outcomes and the survival functions incorporated to derive health state membership. Secondly, as HER2+ mBC is a progressive disease, the partitioned survival structure captures the patient pathway in an intuitive way which is clinically relevant, easily interpretable and understandable to patients, clinicians, decision makers and other stakeholders. The PartSA framework also allows for a varying risk of progression and death over time which increases flexibility in the modelling approach as the hazards of events may vary over time due to factors such as subsequent treatment. These differential risks may be observed within a clinical trial setting, be an artefact of parametric survival curve fits or could be based on expectation in a real-world setting. The flexibility of varying risk of events over time is a benefit over alternative approaches such as a traditional Markov model with underlying constant transition probabilities. As outlined in DSU TSD19 the use of a PartSA makes the model easy to communicate, construct and intuitively appealing.[15] These reasons likely contribute to the common use of PartSA within oncology cost-effectiveness models at NICE and wider HTAs.

The main limitations of a PartSA structure are two-fold. Firstly, it is not possible to determine within the framework the proportion of patients who move to death from a pre/post-progression health state, the occupancy of the progressed health state is instead inferred from the difference between the OS and PFS extrapolations. Secondly, the PartSA structure does not lend itself easily to the inclusion of external evidence.

A Markov (state-transition) modelling framework could be an alternative mechanism to model oncology indications however it was considered that the limitations of doing so outweighed the benefits in the context of the decision problem for T-DXd for this appraisal. The strengths of the Markov framework would be that explicit transitions to and from the progressed disease health state could be modelled and that external evidence can be introduced more easily within this framework than within a PartSA (arguably a limitation of a PartSA). However, in light of the immaturity of OS within DESTINY-Breast03, explicitly modelling constant transition probabilities may introduce bias, as patients who have progressed first (e.g., due to more severe disease or older age, etc.) would inform a non-varying transition to death from both the PFS and PD health states. Given that the data available within DESTINY-

Breast03 is relatively immature, the extrapolations of post-progression survival could be misleading and create additional uncertainty in the extrapolated outcomes for later model transitions. To avoid this, a three-health state model using time-dependencies in event rates would need to be built, which in turn would add substantial complexity based on the number of tunnel states that would be required to accurately model the transitions (i.e., tunnel state per cycle). This would again be based on limited information and also create unnecessary computational complexity that would potentially make the model calculations a burden to calculate, review and meaningfully interpret. PartSA's could be considered limited due to the need to extrapolate data beyond the observed period, however a state-transition model does not negate the need to extrapolate data, therefore, when extrapolating immature data (such as explicitly modelling movements to/from post-progression survival), the information available (for which there are already limited number of events) are further split, which in turn could create further uncertainty in final model outputs. In this instance, it was considered that the benefits of a Markov model would not outweigh the PartSA framework. Although the Company acknowledge limitations regarding the PartSA approach, this was considered more appropriate in comparison to a Markov/state-transition model. HEOR experts consulted as part of the validation meeting also supported the use of a partitioned-survival model.

B4. Priority question: In the Excel model Costs!F122:K122 please clarify the calculation and meaning of the values. For example, what does [redacted] represent?

The value of [redacted] represents the proportion of 'progressed' patients who received subsequent treatments. The reason this is over 100% is due to the denominator only considering progression events, and not including patients who discontinued treatment for reasons other than progression (e.g., due to adverse events or withdrawal).

Within the Excel model, Costs!F122:K122 models the proportion of patients who have progressed and receive at least one subsequent therapy. The purpose of these calculations is to estimate the proportion of progressed patients receiving subsequent therapy from the DESTINY-Breast03 study, which is then used in scenario analysis. The [redacted] is calculated from the 164 T-DM1 patients

that received at least one subsequent therapy in DESTINY-Breast03 (CSR Table 14.4.3.5) regardless of progression status, while the [redacted] refers to the number of progression events on the T-DM1 arm in DESTINY-Breast03 (CSR Table 14.2.1.1).

The Excel model assumes that the cost of subsequent treatment is applied to patients that progress (which is in line with clinical expectation that most patients would receive subsequent therapy after disease progression). The calculations in Costs!J122 and Costs!K122 utilise the evidence available from the DESTINY-Breast03 trial to estimate a proportion that receive subsequent treatment based on two components: the proportion of patients that experience a progression event, and the proportion of all patients that receive subsequent treatment. Please note that including 164 patients from DESTINY-Breast03 T-DM1 arm means that the small number of patients who received subsequent treatment prior to experiencing progression (due to adverse events or withdrawal) are included in the calculation. This avoids underestimating the costs of subsequent treatment as these patients are still included within the cost-calculations when DESTINY-Breast03 is selected as the source (Controls!G80). This is the reason why the value exceeds 100%. The two values obtained from this calculation ([redacted] for T-DXd and [redacted] for T-DM1) estimate the proportions of progressed patients who would receive subsequent therapy. Based on advice received at a validation meeting from two clinical experts, these percentages were considered slightly higher than UK clinical practice and clinicians considered, of the patients that progress, approximately two-thirds would go on to receive subsequent treatment (see response to CQ A29 (i). This is therefore reflected in the model base case and shown in the Excel model in Costs!K122:M122.

Clinical effectiveness variables (Time to event, metastatic health states, etc.)

B5. Priority question: In section B.3.3.2 (Document B), the CS states that 'clinical experts have confirmed that the patient population and study design is generalisable to UK clinical practice.' Clinical expert opinion was derived from a consultation

validation meeting undertaken by Daiichi Sankyo Inc. Please outline the methods used to:

a. **Recruit clinicians to the validation meeting.**

Please see the response to clarification question A20.

b. **Elicit opinions in the validation meeting.**

Please see the response to clarification question A20.

c. **Please also provide the minuted discussions of opinions shared during this meeting to assess how generalisable findings are to UK clinical practice.**

Please see the response to clarification question A20.

B6. Priority question: Could the company please provide a graph plotting the overall survival curves over 10-year time horizon for trastuzumab emtansine using method 1 and method 2, and for trastuzumab deruxtecan using method 1 and method 2? Could the company also please report the percentage survival at 3 years, 5 years, 10 years and 20 years?

Figure 13 and Figure 14 provide a comparison of modelled base case OS for Methods 1 and 2 for T-DXd for up to 10- and 30-years (to align with the life-time horizon), respectively. Both diagrams also plot the T-DXd Kaplan-Meier (KM) from DESTINY-Breast03. The diagrams show that the modelled estimates provide a reasonable fit to the KM data and provide similar outcomes in the long-term.

Figure 13: Overall survival comparing Method 1 and Method 2 – T-DXd (10-years)

Abbre*viations: DB03, DESTINY-Breast03; KM, Kaplan-Meier; T-DXd, trastuzumab deruxtecan*

Figure 14: Overall survival comparing Method 1 and Method 2 – T-DXd (30-years)

Abbre*viations: DB03, DESTINY-Breast03; KM, Kaplan-Meier; T-DXd, trastuzumab deruxtecan*

Figure 15 and Figure 16 provide a comparison of modelled OS for Methods 1 and 2 for T-DM1 illustrating up to 10- and 30-years, respectively. Both diagrams also plot the KM from the DESTINY-Breast03 T-DM1 arm. Similar to T-DXd, both diagrams show that the modelled estimates provide a reasonable fit to the T-DM1 KM data and provide similar outcomes in the long term.

Figure 15: Overall survival comparing Method 1 and Method 2 – T-DM1 (10-years)

Abbreviations: DB03, DESTINY-Breast03; KM, Kaplan-Meier; T-DM1, trastuzumab emtansine

Figure 16: Overall survival comparing Method 1 and Method 2 – T-DM1 (30-years)

Abbreviations: DB03, DESTINY-Breast03; KM, Kaplan-Meier; T-DM1, trastuzumab emtansine

Table 41 provides a comparison in survival estimates at 3-, 5-, 10- and 20-year time points. UK clinical experts anticipated that at 5-years 25-35% of patients would be alive after being treated with T-DM1. This is in line with the estimates provided in Table 41 for Method 1 ( ), although Method 2 may be on the lower end of the of OS ( ) based on clinician estimates. At 10-years clinicians anticipated that 5-10% of patients treated with T-DM1 would be alive. Both Methods are in line with these estimates with (and for Methods 1 and 2 respectively). For further details of validation with UK clinical experts please see the response to clarification question A20.

Table 41: Survival percentages at 3, 5, 10 and 20 years for T-DXd and T-DM1 across OS Method 1 and OS Method 2

	T-DXd		T-DM1	
Time	Method 1	Method 2	Method 1	Method 2
3 years	[redacted]	[redacted]	[redacted]	[redacted]
5 years	[redacted]	[redacted]	[redacted]	[redacted]
10 years	[redacted]	[redacted]	[redacted]	[redacted]
20 years	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan

B7. On page 95 of the CS (Document B), it states that "Given the assessment that PH may hold for the OS data, it was concluded that dependent models (i.e., a joint model with a treatment covariate) would be appropriate to provide a sufficient basis for informing the cost-effectiveness analysis". It is further stated on page 105/6 that "The LCHP shows that the curves are not parallel over time (converging at the start and then diverging), indicating that there is no clear evidence that the PH assumption holds. This is further supported by the Therneau and Grambsch's test of non-proportionality that rejects the null hypothesis (p-value <0.0001). As such, given the results of the PH tests and the number of PFS events, independent parametric model fits were concluded to be the most suitable approach for informing the cost-effectiveness analysis."

Whether or not the proportional hazards assumption holds appears to significantly influence the choice made in the CS of whether to fit dependent parametric models jointly estimating hazard rate functions (e.g. a Weibull model with an intervention covariate that affects a shape parameter) or to fit parametric models independently for the intervention and control (e.g. a Weibull model for T-DXd and an exponential model for T-DM1). One of the benefits of jointly estimating the hazard rate functions using a dependent parametric model is that time-varying hazard ratios can be modelled (i.e. the proportional hazards assumption does not hold). If non-proportional hazards is suspected it does not follow that independent parametric models should be fit. A benefit of using a dependent parametric model over independent parametric models is minimising the introduction of any bias associated with model selection based on clinical expert opinion around predicted survival. A disadvantage is that the fit to each treatment arm may not be as good.

Could the company please clarify the arguments around whether dependent parametric models should be selected rather than a Cox-proportional hazard model, and the arguments around whether dependent or independent parametric models should be fitted to the intervention and the control arms? Please provide the relevant diagnostic plots with

commentary to support the argument that independent parametric models should be fitted to the progression-free data.

The approach used to decide whether to model dependent or independent parametric models is in line with the process outlined in TSD 14.[16] The log-cumulative hazard plots (LCHP) were used to assess whether the proportional hazard assumption holds, if the plots appeared parallel then dependent models were considered appropriate. If not parallel, then individual models were considered more appropriate. In response to the EAG clarification question, quantile-quantile (Q-Q) plots have also been produced to assess the appropriateness of acceleration-failure time (AFT) models in addition to proportional hazard (PH) models.

To provide a response to this question, the Company outline considerations for OS and PFS separately.

Overall Survival

As discussed in the CS Section B.3.3.2.1.1, prior to the fitting of parametric models, a LCHP was produced to assess whether the PH assumption may hold. Figure 17 presents the LCHP based on OS data from DESTINY-Breast03 (also presented in CS Figure 17). As can be seen from the LCHP, the plots exhibit a linear trend in both treatment arms and are approximately parallel indicating that the ratio of the hazards between the two treatment arms may be considered constant. The Therneau and Grambsch's non-proportionality test has a p-value of 0.0531 (failing to reject the null hypothesis that PH holds at the 5% significance level). As such, the PH assumption was considered to hold.

Figure 17: LCHP of OS from DB03 (CS Figure 17)

Abbreviations: DB03, DESTINY-Breast03; CS, company submission; LCHP, log cumulative hazard plot; OS, overall survival

The Q-Q plot of $t_0(p)$ vs. $t_1(p)$ – quantiles of the survival function of T-DXd and T-DM1 at specific probabilities p - where

$$t_0(p) = S^{-1}_{T-DM1}\left(\frac{100-p}{100}\right),$$

$$t_1(p) = S^{-1}_{\text{T-DXd}}\left(\frac{100-p}{100}\right).$$

is displayed in Figure 18. For OS, the Q-Q plot displays a reasonably straight line, indicating that an AFT model could be plausible.

Figure 18: Q-Q plot of OS from DB03

Abbreviations: DB03, DESTINY-Breast03; OS, overall survival; Q-Q, Quantile-Quantile

Given the assessment that PH and AFT models may be appropriate for the OS data, it was concluded that dependent models (i.e., a joint model with a treatment covariate) would be appropriate to provide a sufficient basis for informing the cost-effectiveness analysis. In addition, the use of dependent curves may allow for better use of the OS data, where very few OS events have been observed in either arm. The use of dependent models would also reduce the potential for implausible extrapolations of data (i.e., crossing of curves).

Given that PH may hold for OS, the Cox-proportional hazard model may also be appropriate, however given the availability of Individual Patient-level Data (IPD) for both treatment arms from DESTINY-Breast03, dependent parametric models were considered the most appropriate approach as they allowed the flexibility to

extrapolate the treatments using both PH and AFT models both of which have been considered appropriate.

Progression-free survival

As with the OS data from DESTINY-Breast03, a LCHP was produced for PFS (Figure 19). The LCHP shows that the curves are not parallel over time (converging at the start and then diverging), indicating that there is no clear evidence that the PH assumption holds. This is further supported by the Therneau and Grambsch's test of non-proportionality that rejects the null hypothesis (p-value <0.0001).

Figure 19: LCHP of PFS from DB03 (CS Figure 26)

Abbreviations: DB03, DESTINY-Breast03; CS, company submission; LCHP, log cumulative hazard plot; PFS, progression-free survival

The Q-Q plot presented in Figure 20 shows a reasonably straight line, suggesting that an AFT model could be appropriate.

Figure 20: Q-Q plot of PFS from DB03

Abbreviations: DB03, DESTINY-Breast03; PFS, progression-free survival; Q-Q, Quantile-Quantile

As the results of the PH tests indicate that PH does not hold, and as per TSD 14 (page 42) *"…if they [LCHPs] are not parallel, individual model fitting for each treatment arm should be undertaken using a suitable model and assessed further",*[16] independent parametric model fits were concluded to be the most suitable approach for PFS. This is also considered appropriate due to the number of PFS events and availability of patient-level data where it is generally *"unnecessary to rely upon the proportion hazards assumption…if the proportional hazards assumption does not seem appropriate it is likely to be most sensible to fit separate parametric models of the same type…".*[16]

While more flexible models, such as restricted cubic splines including an interaction between treatment and time, would permit fitting of dependent models with time-dependent treatment effects (DSU TSD 21),[17,18] the Company argue that that this would not lead to simpler models in terms of degrees of freedom compared to independent less complex parametric models. Furthermore, the shape of the hazard functions for PFS does not warrant the use of complex parametric models (see response to CQ B9). Thus, following Occam's razor, simpler, independent models were preferred.

Even though the economic base case uses independent models to inform PFS, the same parametric distribution has been selected for T-DXd and T-DM1 to ensure consistency between treatments.

B8. Priority question: Please provide a graph of the hazard ratio over 10 years and a graph of the hazard rate for both T-DXd and T-DM1 over 10 years for methods 1 and 2 for OS, for PFS and TTD.

To provide a response to this question, three steps were conducted.

1. The cumulative hazards were calculated for each treatment arm
2. The incremental differences between the cumulative hazard between each cycle length (7-days) were calculated for each treatment arm to estimate the hazard rate
3. The relative difference between T-DXd and T-DM1 was calculated at each cycle to obtain the hazard ratio

Figure 21, Figure 23, Figure 25 and Figure 27 show graphs of the hazard ratio of T-DXd versus T-DM1 for OS Method 1, OS Method 2, PFS and TTD, respectively (i.e., step 3 above).

Figure 22, Figure 24, Figure 26 and Figure 28 show hazard rates (i.e., step 2 above) over 10 years for OS Method 1, OS Method 2, PFS and TTD, respectively for both T-DXd and T-DM1.

Please note that to ensure consistency within the economic model calculations, the inclusion of background mortality is considered in the OS estimates.

Figure 21: Implied hazard ratio over 10 years for OS – Method 1 (generalised gamma)

Abbreviations: HR, hazard ratio; OS, overall survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan

Figure 22: Implied hazard rate over 10 years for OS – Method 1 (generalised gamma)

Abbreviations: OS, overall survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan

Figure 23: Implied hazard ratio over 10 years for OS – Method 2 (log-normal)

Abbreviations: HR, hazard ratio; OS, overall survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan
Note: Hazard ratio = 1 in the first section of the curve is due to adjustment for general population mortality (i.e., gen pop mortality was estimated to be higher than the log-normal curve at this time point).

Figure 24: Implied hazard rate over 10 years for OS – Method 2 (log-normal)

Abbreviations: HR, hazard ratio; OS, overall survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan

Figure 25: Implied hazard ratio over 10 years for PFS (Weibull)

Abbreviations: HR, hazard ratio; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan

Figure 26: Implied hazard rate over 10 years for PFS (Weibull)

Abbreviations: PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan

Figure 27: Implied hazard ratio over 10 years for TTD (Weibull)

Abbreviations: HR, hazard ratio; TTD, time-to-treatment discontinuation; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan

Figure 28: Implied hazard rate over 10 years for TTD (Weibull)

Abbreviations: HR, hazard ratio; TTD, time-to-treatment discontinuation; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan

B9. The log-cumulative hazard diagnostic plot is reported in the CS.

a. Please provide logit survival, inverse normal survival, smoothed hazard diagnostic plots for OS from DB03, PFS DB03, and TTD from DB03.

b. Please comment on the implication of the smoothed hazard plot, i.e. does it indicate whether a more flexible model should have been fitted.

The requested plots are presented in turn below for OS, PFS and TTD, respectively.

Overall Survival

Figure 29 shows $log\left(S(t)/\left(1-S(t)\right)\right)$ vs. $log(t)$, permitting assessment of the adequacy of the log-logistic model and Figure 30 displays the inverse.normal(1 - S(t)) vs. $log(t)$, to assess the adequacy of the log-normal distribution.[19]

For both logit survival and inverse normal, plots are approximately linear for both treatment arms. Thus, both log-logistic and log-normal data appear to fit the data well. This is supported by the AIC and BIC fit statistics which suggested that log-logistic had the best statistical fit to the DESTINY-Breast03 Kaplan-Meier (CS Section B.3.3.2.1.1 Table 27). However, based on clinical plausibility of long-term estimates, log-normal was considered too optimistic and log-logistic was at the upper end of the curves considered clinically plausible. Therefore, generalised gamma (which also had a good visual and statistical fit) was considered a more appropriate and conservative approach to inform the base case.

Figure 29: Logit survival – DESTINY-Breast03 – (log(S(t)))/(1-S(t))) vs log(t) of OS

Abbreviations: OS, overall survival

Figure 30: Inverse.normal(S(t)) vs log(t) of OS

Abbreviations: OS, overall survival

Smoothed and unsmoothed hazard plots of OS for T-DXd and T-DM1 arms are displayed in Figure 31. Both hazard functions initially increase before decreasing at later timepoints. Such hazard shapes are amenable to being correctly modelled by simple parametric models.

Figure 31: Smoothed hazard function of OS

Abbreviations: OS, overall survival

Progression-free survival

Figure 32 and Figure 33 provide goodness-of-fit plots for the log-logistic and the log-normal distributions, respectively. In both figures, for T-DXd, the curves are mostly linear, which may support the use of a log-logistic or log-normal distribution. For T-DM1, however, the curves deviate from a straight line, indicating that a log-logistic or log-normal distribution may not fit the observed data well. As discussed in the CS (Section B.3.3.2.2), the log-logistic and log-normal curves were both considered clinically plausible, however projected slightly higher estimates of PFS than expected for T-DM1 compared to clinical feedback. Therefore, the Weibull distribution was considered the most appropriate to inform the base case.

Figure 32: Logit survival – DESTINY-Breast03 – (log(S(t)))/(1-S(t))) vs log(t) of PFS based on BICR

Abbreviations: BICR, blinded independent central review; PFS, progression-free survival

Figure 33: Inverse.normal(S(t)) vs log(t) of PFS based on BICR

Abbreviations: BICR, blinded independent central review; PFS, progression-free survival

Smoothed and unsmoothed hazard plots of PFS for T-DXd and T-DM1 arms are displayed in Figure 34. Both hazard functions initially increase before decreasing at later timepoints. Such hazard shapes are amenable to being correctly modelled by simple parametric models therefore flexible models are not required.

Figure 34: Smoothed hazard function of PFS based on BICR

Abbreviations: BICR, blinded independent central review; PFS, progression-free survival

Time to treatment discontinuation

Figure 35 and Figure 36 are goodness-of-fit plots for the log-logistic and the log-normal distributions, respectively. Similar to PFS, for T-DXd, the curve is mostly linear with some departure at the beginning, which may support the use of a log-logistic or log-normal distribution. For T-DM1 however, the curve shows clear departure from a straight line, indicating that log-logistic and log-normal distributions may not fit the data well.

The log-normal and log-logistic curves appeared to visually fit the data well which is supported by the AIC and BIC fit statistics where the log-normal is statistically the best fitting. However, as discussed in the CS Section B.3.3.2.3, the Weibull distribution was considered the most appropriate to inform the base case due to the consistency with the PFS base case curve (given the expectation of similar shapes due to progression being the predominant reason for treatment discontinuation) and also provides a good fit to the data. In addition, Weibull aligns with the clinical feedback received for PFS whereby very few patients are expected to be progression-free at 5 years (and therefore on treatment) and no patients expected to be on treatment by 10 years. Using a log-normal and log-logistic distribution, [redacted] and [redacted] would be estimated to be alive and progression-free on T-DM1 at 10 years which was considered too optimistic.

Figure 35: Logit survival – DESTINY-Breast03 – log(S(t)))/(1-S(t)) vs log(t) of TTD

Abbreviations: TTD, time to treatment discontinuation

Figure 36: Inverse.normal(S(t)) vs log(t) TTD

Abbreviations: TTD, time to treatment discontinuation

Smoothed and unsmoothed hazard plots of TTD for T-DXd and T-DM1 arms are displayed in Figure 37. The hazard of discontinuation for T-DM1 initially increases before decreasing at later times. A slight increase in hazard is seen starting at around month 20, when some events are observed while very few patients are at risk. The TTD hazard of T-DXd monotonically increases over time. Such hazard

shapes are amenable to being correctly modelled by simple parametric models, therefore more flexible models are not required.

Figure 37: Smoothed hazard function of TTD

Abbreviations: TTD, time to treatment discontinuation

B10. Please provide more details on the digitisation software that was used to replicate the patient-level data (PLD) from the EMILIA study and discuss its reliability.

Two software-programs were used to create pseudo-IPD. The online application WebPlotDigitizer was used to create point estimates of the percentages alive within specific time intervals of the Kaplan-Meier curves. WebPlotDigitizer is the recommended software to apply for this data extraction because it has high inter-investigator reliability and multiple options for extraction.[20,21] The created point estimates were loaded into R and further converted into pseudo-IPD using the algorithm written by Guyot et al. 2012.[22]

B11. Baseline characteristics of the DESTINY-Breast03 and EMILIA trials are reported in Table 28, Page 99-100 of the CS (Document B). Other baseline characteristics may be useful to know. If there are other baseline characteristics available for both DESTINY-Breast03 and EMILIA trials, could the company please provide an updated table with these characteristics added?

Additional baseline characteristics published from the EMILIA study are presented below in Table 42 in comparison to the DESTINY-Breast03 study T-DM1 arm.[23,24]

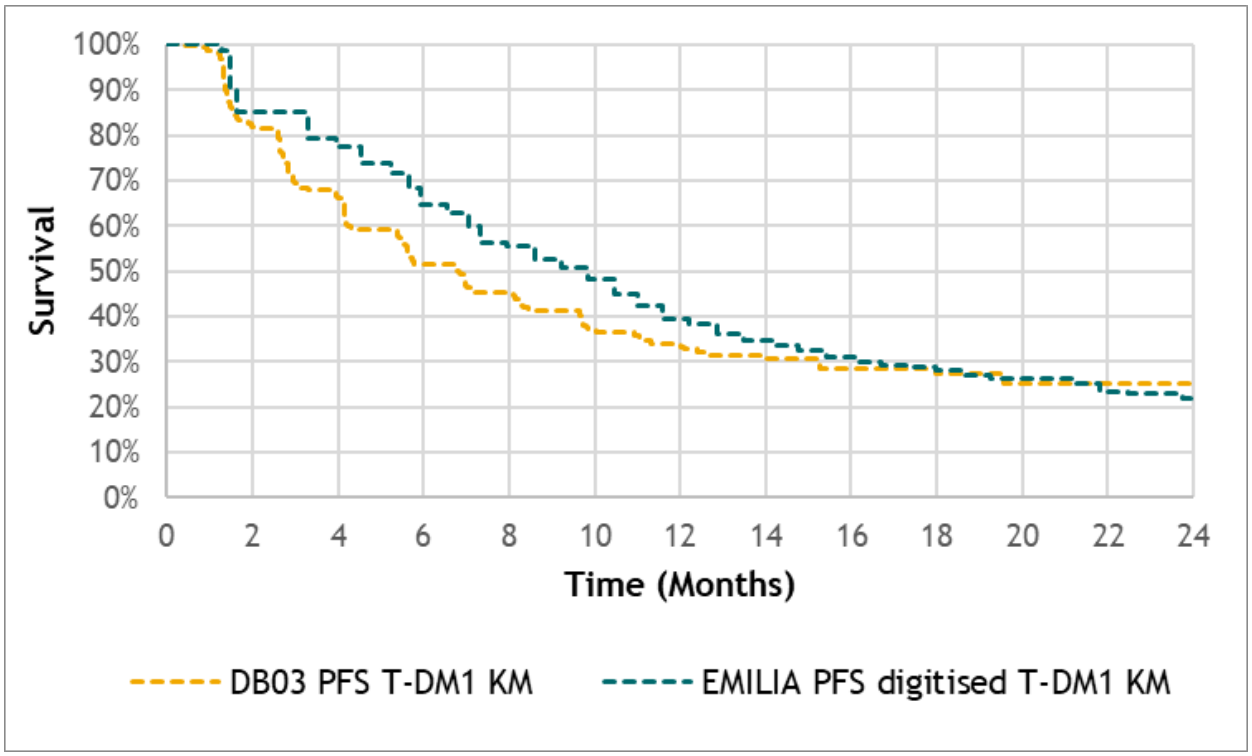
Table 42: Comparison of patient characteristics of T-DM1 arms between DESTINY-Breast03 and EMILIA

Component	DESTINY-Breast03 – T-DM1 arm	EMILIA – T-DM1 arm
Phase	3	3
Population	HER2+ advanced/metastatic unresectable or metastatic HER2+ BC previously treated with trastuzumab and a taxane	HER2+ aBC who have had been previously treated with trastuzumab and a taxane
N	263	495
Median PFS	6.8 months	9.4 months
Median age (years)	54 (20 – 83)	53 (25 – 84)
Race		
White	72 (27%)	358 (72%)
Asian	162 (62%)	94 (19%)
Black	9 (3%)	29 (6%)
Other	20 (8%)	7 (1%)
NA	-	7 (1%)
World region		
USA	17 (7%)	134 (27%)
Western Europe	50 (19%)	157 (32%)
Asia	160 (61%)	82 (17%)
Other	36 (14%)	122 (25%)
ECOG		
0	175 (67%)	299 (60%)
1	87 (33%)	194 (39%)
NA	1 (<1%)	2 (<1%)
Site of disease involvement		
Visceral	185 (70%)	334 (67%)
Non-Visceral	78 (30%)	161 (33%)
Hormone receptor status		
Oestrogen receptor positive, progesterone receptor positive, or both	134 (51%)	282 (57%)
Oestrogen receptor negative and progesterone receptor negative	129 (49%)	202 (41%)
Unknown	-	11 (2%)
Prior lines of therapy		
0 or 1	126 (48%)	304 (61%)
≥1	137 (52%)	191 (39%)

B12. Please provide graphs comparing the Kaplan-Meier plots for OS and PFS in the EMILIA and DESTINY-Breast03 trials for the first 24 months to see how well their observed outcomes fit.

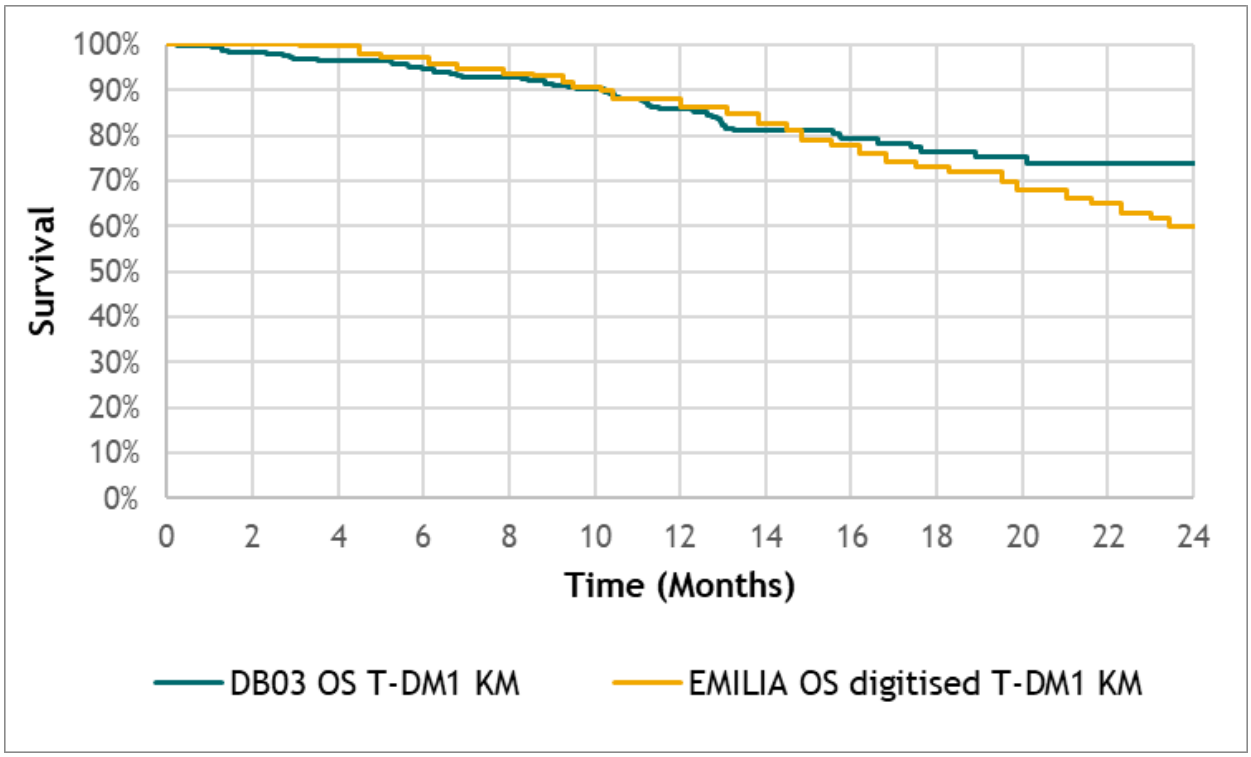
Figure 38 presents the Kaplan-Meier plots for PFS comparing T-DM1 outcomes from EMILIA and DESTINY-Breast03 for the first 24 months. Figure 39 presents the OS Kaplan-Meier plots, and Figure 40 presents a combined figure showing OS and PFS outcomes.

Figure 38: T-DM1 PFS outcomes from EMILIA and DESTINY-Breast03 – up to 24 months



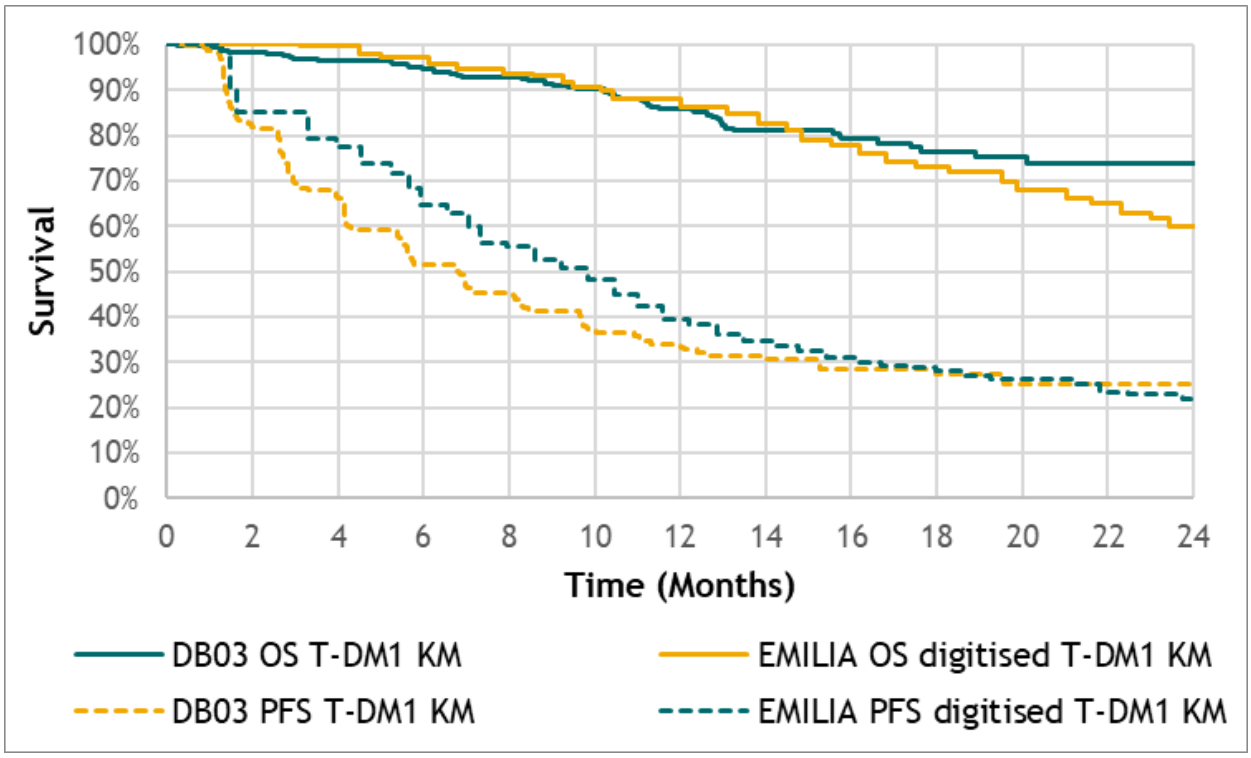
Abbreviations: DB03, DESTINY-Breast03; KM, Kaplan-Meier; PFS, progression-free survival; T-DM1, trastuzumab emtansine

Figure 39: T-DM1 OS outcomes from EMILIA and DESTINY-Breast03 – up to 24 months



Abbreviations: DB03, DESTINY-Breast03; KM, Kaplan-Meier; OS, overall survival; T-DM1, trastuzumab emtansine

Figure 40: T-DM1 PFS and OS outcomes from EMILIA and DESTINY-Breast03 – up to 24 months



Abbreviations: DB03, DESTINY-Breast03; KM, Kaplan-Meier; OS, overall survival; T-DM1, trastuzumab emtansine

B13. Please present the plots in Figures 18, 19, 22, 27, 28, 32, 34 in the CS (Document B) individually as they are too small.

Company submission Figure 18

Figure 41 to Figure 44 present enlarged versions of the plots presented within the Company submission Figure 18.

Figure 41: T-DXd Overall Survival (5-years) presented in CS: Figure 18 – titled 'Method 1 – OS (T-DXd and T-DM1)'

Abbreviations: CS = company submission; KM = Kaplan-Meier, T-DXd, trastuzumab deruxtecan

Figure 42:T-DXd Overall Survival (30-years) presented in CS: Figure 18– titled ‘Method 1 – OS (T-DXd and T-DM1)’

Abbreviations: CS = company submission; KM = Kaplan-Meier, T-DXd, trastuzumab deruxtecan

Figure 43: T-DM1 Overall Survival (5-years) presented in CS: Figure 18– titled ‘Method 1 – OS (T-DXd and T-DM1)’

Abbreviations: CS = company submission; KM = Kaplan-Meier, T-DM1, trastuzumab emtansine

Figure 44: T-DM1 Overall Survival (30-years) presented in CS: Figure 18– titled 'Method 1 – OS (T-DXd and T-DM1)'

Abbreviations: CS = company submission; KM = Kaplan-Meier, T-DM1, trastuzumab emtansine

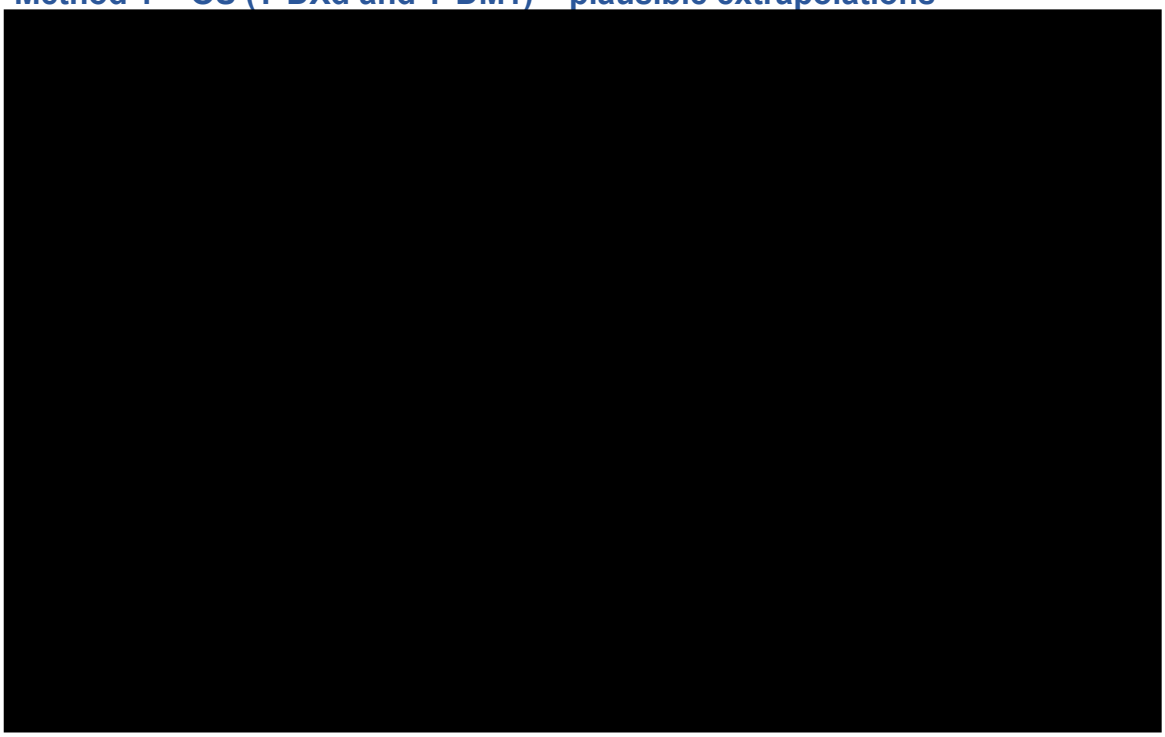
Company submission Figure 19

Figure 45 and Figure 46 present enlarged versions of the plots presented within the Company submission Figure 19.

Figure 45: T-DXd Overall Survival (30-years) presented in CS: Figure 19 – titled 'Method 1 – OS (T-DXd and T-DM1) – plausible extrapolations'

Abbreviations: CS = company submission; KM = Kaplan-Meier, T-DXd, trastuzumab deruxtecan

Figure 46: T-DM1 Overall Survival (30-years) presented in CS: Figure 19 – titled 'Method 1 – OS (T-DXd and T-DM1) – plausible extrapolations'



Abbreviations: CS = company submission; KM = Kaplan-Meier, T-DM1, trastuzumab emtansine

Company submission Figure 22

Figure 47 and Figure 48 present enlarged versions of the plots presented within the Company submission Figure 22.

Figure 47: T-DM1 Overall Survival (6-years) presented in CS: Figure 22 – titled 'Method 2 – EMILIA OS (T-DM1)'

Abbreviations: CS = company submission; KM = Kaplan-Meier, T-DM1, trastuzumab emtansine

Figure 48: T-DM1 Overall Survival (30-years) presented in CS: Figure 22 – titled 'Method 2 – EMILIA OS (T-DM1)'

Abbreviations: CS = company submission; KM = Kaplan-Meier, T-DM1, trastuzumab emtansine

Company submission Figure 27

Figure 49 to Figure 53 present enlarged versions of the plots presented within the Company submission Figure 27.

Figure 49: T-DXd PFS (5-years) presented in CS: Figure 27 – titled 'PFS (T-DXd and T-DM1)'

Abbreviations: CS = company submission; KM = Kaplan-Meier; PFS = progression-free survival, T-DXd, trastuzumab deruxtecan

Figure 50: T-DXd PFS (30-years) presented in CS: Figure 27 – titled 'PFS (T-DXd and T-DM1)'

Abbreviations: CS = company submission; KM = Kaplan-Meier; PFS = progression-free survival, T-DXd, trastuzumab deruxtecan

Figure 51: 52: T-DM1 PFS (5-years) presented in CS: Figure 27 – titled 'PFS (T-DXd and T-DM1)'

Abbreviations: CS = company submission; KM = Kaplan-Meier; PFS = progression-free survival, T-DM1, trastuzumab emtansine

Figure 53: T-DM1 PFS (30-years) presented in CS: Figure 27 – titled 'PFS (T-DXd and T-DM1)'

Abbreviations: CS = company submission; KM = Kaplan-Meier; PFS = progression-free survival, T-DM1, trastuzumab emtansine

Company submission Figure 28

Figure 54 and Figure 55 present enlarged versions of the plots presented within the Company submission Figure 28.

Figure 54: T-DXd PFS (30-years) presented in CS: Figure 28 – titled 'PFS (T-DXd and T-DM1) – plausible extrapolations'

Abbreviations: CS = company submission; KM = Kaplan-Meier; PFS = progression-free survival, T-DXd, trastuzumab deruxtecan

Figure 55: T-DM1 PFS (30-years) presented in CS: Figure 28 – titled 'PFS (T-DXd and T-DM1) – plausible extrapolations'

Abbreviations: CS = company submission; KM = Kaplan-Meier; PFS = progression-free survival, *T-DM1, trastuzumab emtansine*

Company submission Figure 32

Figure 56 to Figure 59 present enlarged versions of the plots presented within the Company submission Figure 32.

Figure 56: T-DXd TTD (5-years) presented in CS: Figure 32 – titled 'TTD (T-DXd and T-DM1)'

Abbreviations: CS, company submission; KM,, Kaplan-Meier; T-DXd, trastuzumab deruxtecan; TTD, time to treatment discontinuation

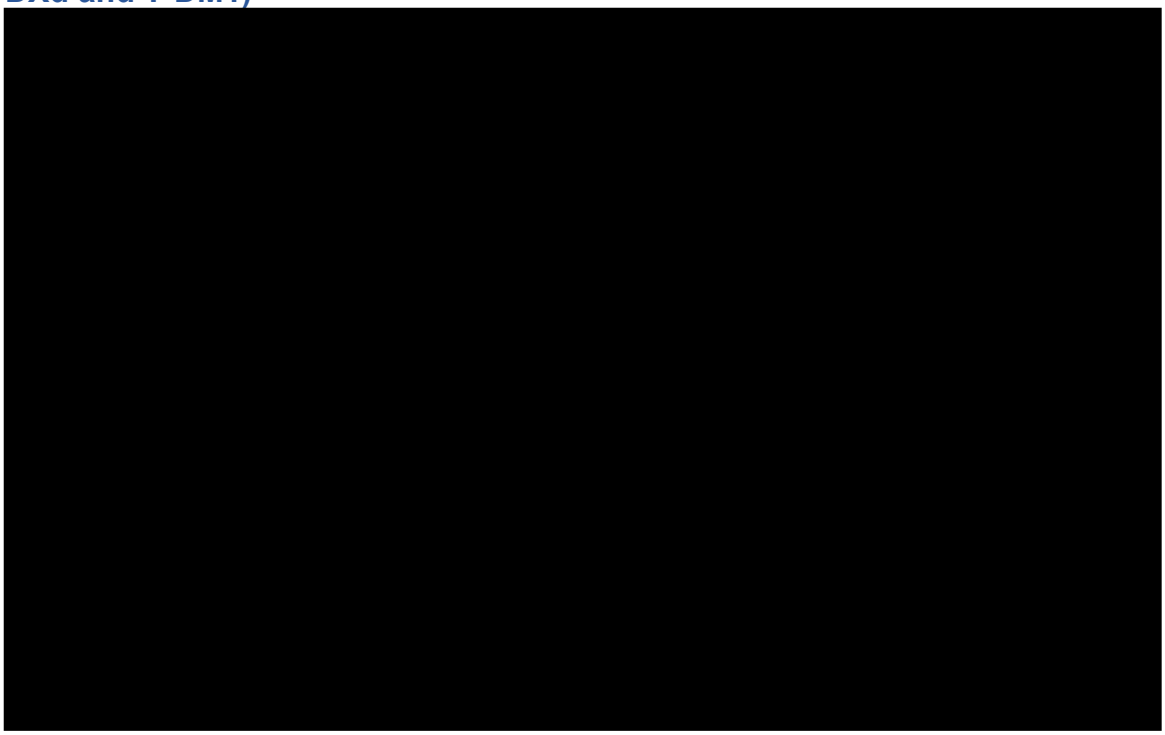
Figure 57: T-DXd TTD (30-years) presented in CS: Figure 32 – titled 'TTD (T-DXd and T-DM1)'

Abbreviations: CS, company submission; KM, Kaplan-Meier; T-DXd, trastuzumab deruxtecan; TTD, time to treatment discontinuation

Figure 58: T-DM1 TTD (5-years) presented in CS: Figure 32 – titled 'TTD (T-DXd and T-DM1)'

Abbreviations: CS, company submission; KM, Kaplan-Meier; T-DM1, trastuzumab emtansine; TTD, time to treatment discontinuation

Figure 59: T-DM1 TTD (30-years) presented in CS: Figure 32 – titled 'TTD (T-DXd and T-DM1)'



Abbreviations: CS, company submission; KM,, Kaplan-Meier;T-DM1, trastuzumab emtansine; TTD, time to treatment discontinuation

Company submission Figure 34

Figure 60 to Figure 62Figure 61 present enlarged versions of the plots presented within the Company submission Figure 34.

Figure 60: T-DXd (30-years) presented in CS: Figure 34 – titled 'Summary of base case efficacy (T-DXd and T-DM1)'

Abbreviations: CS, company submission; KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TTD, time to treatment discontinuation

Note: Please note that the original submission image labelled T*TD as ToT (time-on-treatment)*

Figure 61: T-DM1 (30-years) presented in CS: Figure 34 – titled 'Summary of base case efficacy (T-DXd and T-DM1)'

Abbreviations: CS, company submission; KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TTD, time to treatment discontinuation

Note: Please note that the original submission image labelled TTD as ToT (time-on-treatment)

Figure 62: T-DXd and T-DM1 (30-years) presented in CS: Figure 34 – titled 'Summary of base case efficacy (T-DXd and T-DM1)'

Abbreviations: CS, company submission; KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TTD, time to treatment discontinuation

Health related quality of life

B14. As per NICE reference case, the EQ-5D utilities were collected from the relevant population within the clinical study (DESTINY-Breast03). Please clarify if the CS used UK population value set tariffs or, if not, which population tariffs were used. Source of utilities (Document B, page 91, Table 24)

NICE recommends the use of the EQ-5D-3L for the calculation of health benefits.[11] In line with NICE methods guidance, the directly collected EQ-5D-5L clinical study responses were 'cross-walked' to produce EQ-5D-3L values.[25] The responses were 'cross-walked' using the UK algorithm developed by Van Hout et al, 2012.

B15. Priority question: it is stated in the CS (Document B, page 115): "EQ-5D-3L utility scores based on 'progression-free' and 'progressed disease' health states were derived using generalized estimating equations (GEE) regressions. EQ-5D-5L scores from all available time points, including baseline, were included in the GEE as dependent variables.".

a. **Please clarify if should be 'EQ-5D-3L' in the second sentence.**

The original sentence is correct, however for clarity the first and second sentence should read ‘EQ-5D-5L cross-walked to EQ-5D-3L’, as this is what was collected within DESTINY-Breast03. The revised text should read “EQ-5D-5L cross-walked to EQ-5D-3L utility scores based on ‘progression-free’ and ‘progressed disease’ health states were derived using generalized estimating equations (GEE) regressions. EQ-5D-5L cross-walked to EQ-5D-3L scores from all available time points, including baseline, were included in the GEE as dependent variables.”

b. Please justify using baseline EQ-5D utility score as a dependent variable in the regression

EQ-5D-5L ‘cross-walked’ to EQ-5D-3L utility scores from all available timepoints, i.e., baseline and follow-up visits, were included in a longitudinal model (GEE) as dependent variables.

The GEEs were used to estimate population-averaged utility values for the health-states ‘progression-free’ and ‘progressed disease’. Thus, including baseline utility values in addition to values observed at follow-up visits as a dependent variable in the model allows to use all the data available from the clinical trial. Note that the utility values were included in the model rather than using a change from baseline.

c. Please justify the selection of the regression model (e.g. longitudinal analysis or cross-sectional analysis using a pooled sample)

EQ-5D-5L ‘cross-walked’ to EQ-5D-3L utility score from all available timepoints, i.e., baseline and follow-up visits, were included in a longitudinal model (GEE) as dependent variable. A longitudinal model was chosen over cross-sectional analysis using a pooled sample as it better aligns with the design of the clinical study where multiple observations are collected per patient at multiple time-points.

d. Please explain how the utility scores were estimated by clarifying independent variables used in the GEE regression and if considering data structure.

EQ-5D-5L utility scores from all available timepoints, including baseline, were included in the GEE as dependent variables. Health state status (progressed versus progression-free) at the corresponding visit and treatment arm were included as independent variables in a stepwise fashion, starting with the progression status. The model with lowest quasi-likelihood under the independence model criterion

(QIC) was selected for inclusion in the economic model. The GEEs are fitted with an independence working correlation structure and a robust sandwich variance estimator to account for the fact that we considered several visits per patient.

B16. Please provide a summary table (frequency, completion rate, mean, SD, median, and range) of the EQ-5D index results at different time points by study arm. A plot of EQ-5D index over time by study arm would be helpful.

The summary table of EQ-5D index results are presented in Table 43. The plot of EQ-5D index over time is presented in Figure 63.

Table 43: Summary of EQ-5D-5L index score – UK value set (Van Hout)

Time point	Value	T-DXd N=261	T-DM1 N=263	Total N=524
Baseline	n (%)[a]	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]	[redacted]
	Standard Deviation	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]
Cycle 2 Day 1	n (%)[a]	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]	[redacted]
	Standard Deviation	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]
Cycle 3 Day 1	n (%)[a]	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]	[redacted]
	Standard Deviation	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]
Cycle 5 Day 1	n (%)[a]	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]	[redacted]
	Standard Deviation	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]
Cycle 7 Day 1	n (%)[a]	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]	[redacted]
	Standard Deviation	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]
Cycle 9 Day 1	n (%)[a]	[redacted]	[redacted]	[redacted]

Time point	Value	T-DXd N=261	T-DM1 N=263	Total N=524
	Mean	[redacted]	[redacted]	[redacted]
	Standard Deviation	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]
Cycle 11 Day 1	n (%)[a]	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]	[redacted]
	Standard Deviation	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]
Cycle 13 Day 1	n (%)[a]	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]	[redacted]
	Standard Deviation	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]
Cycle 15 Day 1	n (%)[a]	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]	[redacted]
	Standard Deviation	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]
Cycle 17 Day 1	n (%)[a]	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]	[redacted]
	Standard Deviation	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]
Cycle 19 Day 1	n (%)[a]	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]	[redacted]
	Standard Deviation	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]

Time point	Value	T-DXd N=261	T-DM1 N=263	Total N=524
	Min, Max	[redacted]	[redacted]	[redacted]
Cycle 21 Day 1	n (%)[a]	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]	[redacted]
	Standard Deviation	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]
Cycle 23 Day 1	n (%)[a]	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]	[redacted]
	Standard Deviation	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]
Cycle 25 Day 1	n (%)[a]	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]	[redacted]
	Standard Deviation	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]
Cycle 27 Day 1	n (%)[a]	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]	[redacted]
	Standard Deviation	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]
Cycle 29 Day 1	n (%)[a]	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]	[redacted]
	Standard Deviation	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]
Cycle 31 Day 1	n (%)[a]	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]	[redacted]

Time point	Value	T-DXd N=261	T-DM1 N=263	Total N=524
	Standard Deviation	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]
Cycle 33 Day 1	n (%)[a]	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]	[redacted]
	Standard Deviation	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]
Cycle 35 Day 1	n (%)[a]	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]	[redacted]
	Standard Deviation	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]
Cycle 37 Day 1	n (%)[a]	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]	[redacted]
	Standard Deviation	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]
Cycle 39 Day 1	n (%)[a]	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]	[redacted]
	Standard Deviation	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]
Cycle 41 Day 1	n (%)[a]	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]	[redacted]
	Standard Deviation	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]

Time point	Value	T-DXd N=261	T-DM1 N=263	Total N=524
End of treatment	n (%)[a]	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]	[redacted]
	Standard Deviation	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]
40 day follow-up	n (%)[a]	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]	[redacted]
	Standard Deviation	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]
3 months follow-up	n (%)[a]	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]	[redacted]
	Standard Deviation	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]

Notes: [a] percentage based on number of patients alive and under observation at each visit

Figure 63: EQ-5D-5L index score over time – UK value set (Van Hout)

Resource use and costs

B17. Priority question: Could the company please summarise the costs used in the progression-free state and in the progressed disease state?

Resource use and disease monitoring incorporated into the economic model are based on the frequencies reported from three prior technology appraisals:

1. TA704: Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after 2 or more anti-HER2 therapies
2. TA458: Trastuzumab emtansine for treating HER2-positive advanced breast cancer after trastuzumab and a taxane
3. ID3828 (TA786): Tucatinib with trastuzumab and capecitabine for treating HER2-positive advanced breast cancer after 2 or more anti-HER2 therapies

Disease monitoring was split by health state (*'progression-free'* and *'progressed disease'*) however in all three appraisals, the same pre-progression and post-progression resource use was applied, which was the same across treatment arms. As such, the same approach was taken to inform the economic model within the CS, applying the same resource use across disease states and treatment arms, this was also validated with clinical experts at the validation meeting. A summary of the resource use frequencies applied are provided in Table 44.

Table 44: Resource use frequencies used to inform the economic model split by health state

Resource use	Frequency PFS	Frequency per weekly cycle (3.d.p)	Frequency PD	Frequency per weekly cycle (3.d.p)	Source
Medical oncologist	Monthly	0.230	Monthly	0.230	TA704
GP contact	Monthly	0.230	Monthly	0.230	TA704
CT scan	Every 3 months	0.077	Every 3 months	0.077	TA704
Community nurse	Every 2 weeks	0.500	Every 2 weeks	0.500	TA458
Clinical nurse specialist	Monthly	0.230	Monthly	0.230	TA458
LVEF follow-up	Every 3 months	0.077	Every 3 months	0.077	TA458

Abbreviations: CT, Computerised Tomography; GP, general practitioner; LVEF, left ventricular ejection fraction; PD, progressed disease; PF, progression-free.

The relevant frequencies informed from past technology appraisals were re-estimated to align with the economic models weekly cycle length. Unit costs for each resource were applied based on NHS reference costs or PSSRU 2021. Weekly frequencies were multiplied by relevant unit costs to obtain a cost per model cycle for each component of resource use. The individual weighted component costs are thereafter summated to calculate the total resource use cost per cycle. The total resource use per cycle cost is then applied to the PFS and PD health states. A breakdown is provided in Table 45. A total cost of £105.57 is calculated for progression-free and progressed patients and applied in each model cycle.

Table 45: Resource use estimates and costs used to inform economic model split by health state

Resource use	PFS cycle frequency	PD cycle frequency	Unit cost	PFS cycle cost	PD cycle cost	Unit Cost source
Medical oncologist	0.230	0.230	£201.33	£46.30	£46.30	NHS Cost Collection 19/20[26] – 370 – medical oncologist – consultant led
GP contact	0.230	0.230	£39.23	£9.02	£9.02	PSSRU 2021[27] - GP Per patient contact lasting 9.22 minutes with qualifications
CT scan	0.077	0.077	£88.31	£6.77	£6.77	NHS Cost Collection 19/20[26] - RD20A - Computerised Tomography Scan of One Area, without Contrast, 19 years and over - Outpatient
Community nurse	0.500	0.500	£25.00	£12.50	£12.50	PSSRU 2021[27] - Nurses - band 8a - 20 minutes assumed
Clinical nurse specialist	0.230	0.230	£88.00	£20.24	£20.24	PSSRU 2021[27] - Hospital based nurses - band 8b - 1 hour assumed
LVEF follow-up	0.077	0.077	£140.03	£10.73	£10.73	£130 suggested by TA458 ERG uplifted to 2021 costs
Total				£105.57	£105.57	

Abbreviations: CT, Computerised Tomography; GP, general practitioner; LVEF, left ventricular ejection fraction; PD, progressed disease; PF, progression-free.

B18. On page 122 of the CS (Document B) it states, “Study treatment dose increases were not allowed in DESTINY-Breast03.” Please clarify if it reflects current UK clinical practice.

The T-DXd SmPC states that the recommended dose of T-DXd is 5.4mg/kg once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity. The SmPC allows for dose reductions to either 4.4 mg/kg or 3.2 mg/kg before discontinuation and that the dose should not be re-escalated after a dose reduction is made. This is also consistent with the study protocol. Dosing of T-DXd in current UK practice is expected to be in accordance with the SmPC.

B19. In Table 45 page 123 please clarify the unit of the frequency per cycle. For example, what does the value of 0.23 per cycle mean?

The unit of frequency per cycle refers to how often the resource component is expected to be used per model cycle (with each cycle representing 1-week as outlined in Section B.3.2.2.1 - page 90). Table 44 and Table 45 provide further details of how the resource use estimates have been derived and calculated.

From the estimates available from prior appraisals, a conversion had to be applied to adjust monthly frequencies into weekly frequencies (to align with the model cycle length). Using the example above, a medical oncologist visit every month (Table 44) equates to 0.23 per model cycle (every week), which is then applied within the model.

$$Cycle\ frequency = monthly\ frequency\ \times \left(\frac{months\ per\ year}{weeks\ per\ year}\right)$$

Therefore,

$$0.23\ = 1\ \times \left(\frac{12}{52.18}\right)$$

The resource use frequency is multiplied by the unit cost and is applied as a weekly cost in the model (in line with the cycle length of 7-days).

The frequencies for each resource use component are presented in Table 44.

B20. In section B3.5.4.1 of the CS (Document B) page 124, it states that the costs of adverse events are applied as a one-off cost after leaving the disease-free state. In the

Excel model, costs (and dis-utilities) are applied in the first cycle of the model. Is this method of application in the model due to the fact the adverse event costs are based on the percentage of total subjects in each study arm experiencing the adverse events rather than the percentage of subjects that move into the disease-progressed state (everyone leaves the progression-free state by progression or death)?

Please note that the description of how adverse events (costs and disutilities) are applied in the economic model - as stated in CS Section B.3.5.3 page 123 and 124 - is correct and aligned with the economic model, i.e., in the first model cycle. The text in CS pages 123–124 states *"the total weighted cost per treatment arm was calculated and applied as a one-off cost to all patients within the first cycle of the economic model as the greatest proportion of TEAEs in DESTINY-Breast03 occurred in the first cycle and subsequently declined through cycles (see Section B.2.10.1.2)".* Section B.3.5.4.1 mentioned by the EAG, refers to the miscellaneous unit costs and resource use section and is in reference to subsequent treatment costs. Subsequent treatment costs are applied in the Excel model as a one-off cost after leaving the progression-free health state.

B21. The CS assumed the cost of subsequent treatments is one-off, then the cost for patients who stayed at progression state longer may be underestimated. Could it be re-estimated by deriving the unit cost using the one-off cost and the average time at progression state, then calculating the subsequent treatment cost for each patient?

The cost of subsequent treatment is, as the EAG note, applied as a one-off cost. The cost is applied on progression within the model (calculated as the difference between the PFS between each cycle). Although the cost is applied as a one-off (as a simplification to avoid the need to track patients and costs into the progression-state), the cost is calculated based on an informed duration of treatment for each individual subsequent treatment based on reported mean or median treatment durations from appropriate trials. These durations are shown in CS Section B.3.5.4.1 Table 48 and are summarised in Table 46 below.

Table 46: Subsequent treatment proportion and durations applied in the model base case

Treatment		T-DXd distribution	T-DM1 distribution	Dose	Duration of treatment (weeks)	Source for duration
Trastuzumab (subcutaneous)		[redacted]	[redacted]	6 mg/kg Q3W	20	HER2CLIMB[28]
T-DXd		[redacted]	[redacted]	5.4 mg/kg Q3W	43	DESTINYBreast01[29]
T-DM1		[redacted]	[redacted]	3.6 mg/kg Q3W	23	TH3RESA
Pertuzumab		[redacted]	[redacted]	420 mg Q3W	45	Urruticoechea et al. 2017[30]
Taxane (paclitaxel)		[redacted]	[redacted]	175 mg/m^2 Q3W	12	John et al, 2012[31]
Taxane + trastuzumab		[redacted]	[redacted]	-	42	John et al, 2012[31]
Other anti-HER2	Tucatinib	[redacted]	[redacted]	300 mg twice daily	25	HER2CLIMB[28]
	Trastuzumab			6 mg/kg Q3W	20	HER2CLIMB[28]
	Capecitabine			2000 mg daily	25	HER2CLIMB[28]
Hormone therapy (tamoxifen)		[redacted]	[redacted]	20 mg daily	70	Manni et al 1981
Other systemic therapy (capecitabine)		[redacted]	[redacted]	2,000 mg/m^2 for 2 weeks Q3W	19	HER2CLIMB[28]

Note: Distributions are based on data from DESTINY-Breast03 for the base case.

The same duration for each subsequent treatment is applied across the T-DXd and T-DM1 arms as there is no clinical rationale for why patients would receive specific subsequent treatment regimens for different durations based on their prior treatment. For example, subsequent hormone therapy is assumed to be used for 70 weeks – this 70-week cost is applied to both T-DXd and T-DM1 arms and does not differ by treatment arm, the difference instead is driven by the proportion of patients in each arm that progress and receive hormone therapy. The total cost for the average course of each subsequent treatment is estimated and then weighted by the

proportion of patients in each arm assumed to receive that subsequent therapy. The total weighted cost of all subsequent treatments is then applied as a one-off cost. Whilst this method is a simplification, using an assumed duration of treatment (predominantly based on information sourced from prior clinical trials), there is a risk that the costs of subsequent therapy could overestimate or underestimate the subsequent treatment cost – the direction of which is wholly unknown. This is a common limitation in cost-effectiveness modelling where the clinical trial is not yet complete, and the duration of subsequent therapy is not known. This pragmatic approach has been considered and accepted in multiple prior NICE appraisals.[32-35]

Whilst the Company agree that using the a one-off cost estimated by the average duration of time spent in the progressed health state is possible, the Company believe this is likely to grossly overestimate the costs associated with subsequent treatment as it assumes that patients in both arms of the model would be on subsequent treatment for the remainder of their lives (and further assumes that the duration of treatment of each individual subsequent therapy would be the same). This assumption seems unrealistic in an oncology indication and for HER2+ mBC which is progression-based, where patients are known to discontinue treatment and move to alternative therapies and eventually move to palliative care at the end of their lives (which as noted in the CS, is costed for separately as an end-of-life cost).

Further to this, to calculate an average between the two treatment arms will mean that this cost will be an overestimate for one arm of the model and an underestimate for the other. For example, because the progressed LYs are greater in the T-DXd arm than the T-DM1 arm, using an average would mean that the corresponding cost would assume the duration of treatment for T-DM1 is longer than the average time in the progressed disease state, thereby applying treatment costs for longer than the patient is alive – this lacks face validity and clinical plausibility. Conversely, if separate subsequent treatment durations were applied within the model based on the average progressed LYs based on each individual treatment arm, an inherent assumption would be made that the ability for patients to tolerate subsequent treatment is greater post treatment with T-DXd than T-DM1. Whilst this may be possible, the magnitude of this is unknown and as outlined above there is no current expectation or clinical rationale that treatments would be different. A simplified

scenario is provided below for illustrative purposes applying an average duration based on the LYs between the two arms but the Company would emphasise that this scenario should be treated with caution.

Within the model base case there is an average of 4.21 LYs gained in the progression states ([redacted] for T-DXd and [redacted] T-DM1 respectively). This equates to [redacted] weeks which is substantially longer than the treatment durations obtained from the literature. Table 47 summarises the difference that this method has on the one-off costs applied to both arms of the model.

Table 47: Comparison of subsequent treatment costs between CS model base case and applying the average progressed LYs within the model

	CS approach	EAG suggested approach	Difference
Duration of Subs tx informed by	Literature and prior trials	Total progressed average LYs in the model	N/A
T-DXd subs tx cost	[redacted]	[redacted]	[redacted]
T-DM1 subs tx cost	[redacted]	[redacted]	[redacted]

Abbreviations: CS, company submission; LY, life-year; subs tx, subsequent treatment; T-DM1, trastuzumab emtansine; T-DXd trastuzumab deruxtecan

Table 48 presents the model results when applying the method outlined by the EAG. Despite the difference in estimated subsequent treatment costs, this alternative method is not a key driver in the cost-effectiveness results and the ICER obtained ([redacted]) remains cost-effective at a willingness to pay threshold of £30,000/QALY. Although the impact on the ICER is small and is very close to the base case ICER, the Company would still like to emphasise caution when considering this approach given the aforementioned reasons relating to assumption that all HER2+ mBC patients would be receiving treatment for the remainder of their lives.

Table 48: Scenario analysis using total progressed average LYs to inform subsequent therapy duration - results (with PAS)

Technologies	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
T-DM1	[redacted]	[redacted]	[redacted]				
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient-access scheme; QALYs, quality-adjusted life years.

Base case summary and assumptions

B22. B.3.5.1.1 It is stated on page 122 in the CS (Document B) that "RDI was calculated as the dose intensity over the planned dose intensity." Please clarify how the RDI values of [redacted] and [redacted] for T-DXd and T-DM1 were calculated and reflected dose modifications due to Grade>=3 toxicities. Also, referring to Table 57, the CS assumed normal distribution for RDI, which made value more than 100%. Please clarify if it is possible a patient could receive a dose more than planned in clinical practices?

The RDI values of [redacted] and [redacted] were calculated using the following formula:

$$\frac{dose\ intensity\ received}{planned\ dose\ intensity} \times 100$$

Where 'planned dose intensity' is in line with the licensed dosing (and planned starting doses in DESTINY-Breast03):

$$planned\ dose\ intensity\ for\ T-DXd\ = 5.4mg/kg(QW3)$$

$$planned\ dose\ intensity\ for\ T-DM1\ = 3.6mg/kg(QW3)$$

As such, any dose modification such as due to grade 3+ toxicities or modifications/ interruptions are inherently captured within the numerator of the RDI calculation. The RDI results from DESTINY-Breast03 are presented in Table 49.

Table 49: Relative Dose Intensity (Full Analysis Set)

Relative Dose Intensity (%)	T-DXd (N=261)	T-DM1 (N=263)
N	[redacted]	[redacted]
Mean	[redacted]	[redacted]
Standard Deviation	[redacted]	[redacted]
Median	[redacted]	[redacted]
Average dose (mg/kg)*	[redacted]	[redacted]

Note: * Average dose = starting dose*RDI

Given the approach used to calculate RDI, and the approach to weight-based dosing, it is possible that some patients estimated RDI is greater than 1 (possibly due to 10% weight tolerance).[36] As such, a Normal distribution was considered relevant for the purposes of the parameter. A beta distribution may also be considered appropriate, and this would cap the maximum RDI percentage at 100%.

However, when running the PSA for 10,000 iterations, none of the RDI values for both T-DXd and T-DM1 actually went higher than 1, therefore the likelihood of this occurring in the model is extremely small.

It is not possible for a patient to receive a dose which is higher than the planned dose in clinical practice due to the guidance in the SmPC which states that the dose of T-DXd should not be re-escalated after a dose reduction is made due to adverse reactions.

Section C: Textual clarification and additional points

General Clarification/Comments

C1. In the Appendices document, one or two appendices appear to be incorrectly labelled. For example, in Appendix I.1.1, the search strategy is referenced to G.1.1, however Appendix G relates to 'Adverse Events' and has no information. Could the company please update the Appendices (and Document B where necessary) to ensure correct labelling.

Thank you for the thorough review of the Company submission. In the versions submitted by the Company to NICE, the documents and appendices were labelled as follows:

- Document A
- Document B
- Appendix C | SmPC and UK PAR
- Appendix D | Identification, selection, and synthesis of clinical evidence
- Appendix E | Subgroup analyses (no data, but appendix title included to ensure consistency of appendix naming with the NICE template)
- Appendix F | Adverse reactions (no data, but appendix title included to ensure consistency of appendix naming with the NICE template)
- Appendix G | Published cost-effectiveness studies
- Appendix H | Health-related quality-of-life studies
- Appendix I | Cost and healthcare resource identification, measurement, and valuation
- Appendix J | Clinical outcomes and disaggregated results from the model
- Appendix K | Price details of treatments included in the submission

- Appendix L | Checklist of confidential information
- Appendix M | Dose adjustments guideline for T DXd
- Appendix N | DESTINY-Breast03 | Additional clinical effectiveness results
- Appendix O | Additional evidence relating to ILD

The appendix labelling in the initial Company submission is therefore consistent with the text the EAG quotes above, and the Company does not believe that any changes to labelling are required.

C2. In Appendix D (page 16), the CS states that one study (three publications) were identified that reported data on T-DXd (DESTINY-Breast03). However, in Appendix figure 1, (page 16) and Appendix table 6, four linked publications are given. Could the company please account for the discrepancy?

This is a typographical error in the text on page 16. At the time the review was conducted, there were three publications available from the DESTINY-Breast03 study, excluding the CSR. In total, therefore, four documents were identified, and these are listed correctly in Appendix Table 6.

C3. In section D.1.2.2 (Appendices), the CS states that 25,856 publications were excluded at secondary screening. Could the company please clarify where this number relates to on the PRISMA flow chart (Appendix Figure 1, page 16)?

The EAG has correctly identified this typographical error. The number should be 1,515 as stated in the PRISMA flow chart.

C4. In section B.2.3.1.1 page 37 (Document B), Table 6 notes that the dosage of the intervention and comparator in the DESTINY-Breast03 trial could be modified if the patient's weight rose or fell by more than 10%. How many participants in each arm underwent dose modification due to a plus or minus 10% fluctuation in weight?

In the DESTINY-Breast03 study, [redacted] on the T-DXd arm and [redacted] on the T-DM1 arm had dose modifications due to a plus or minus 10% fluctuation in weight.

C5. In section B.2.5 Table 11 page 51 (Document B), the company notes that allocation concealment for the DESTINY-Breast03 study is "not applicable". The justification provided

refers to blinding of participants, personnel and sponsor, not to blinding of allocation. Please clarify.

In Section 6.4.6 of the DESTINY-Breast03 CSR it states: “Treatment allocations were not blinded for subjects or treating physicians. The Sponsor was blinded to aggregate data by treatment arm and the study team did not perform efficacy analysis or have access to summary data during the study.” Methods of concealed allocation to study arms (via IXRS) is stated in the uppermost row of the table body in Table 11 (Document B, Section B.2.5, p51).

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

[ID3909] - Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after trastuzumab or a taxane

Patient Organisation Submission

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. [Please note that declarations of interests relevant to this topic are compulsory].

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

NICE National Institute for Health and Care Excellence

1.Your name	[redacted]
2. Name of organisation	Breast Cancer Now
3. Job title or position	Senior Policy Officer
4a. Brief description of the organisation (including who funds it). How many members does it have?	From research to care, Breast Cancer Now has people affected by breast cancer at its heart – providing support for today and hope for the future. All of our funding comes from the public and our partners.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	Breast Cancer Now has received funding from a number of drug companies towards our support services, however, we do not receive any pharmaceutical funding for our Policy, Evidence and Influencing work, which includes our work on access to drugs. In the last 12 months (from 11 April 2021- 11 April 2022) we have received the following from the relevant pharmaceutical companies to this appraisal: - Roche - £100,826 towards Breast Cancer Now's Living with Secondary Breast Cancer Online and Face to Face services - Daiichi Sankyo - £45,000 towards Breast Cancer Now's Living with Secondary Breast Cancer Face to Face service

If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	At Breast Cancer Now we utilise our various networks of people affected by breast cancer to gather information about patient experience, including our online Breast Cancer Now Forum, as well as our online and face to face services. Trastuzumab emtansine (Kadcyla) is the current standard of care for treating patients with HER2-positive unresectable or metastatic breast cancer after trastuzumab or a taxane. Breast Cancer Now was involved during all stages of the NICE appraisal of trastuzumab emtansine throughout 2016-17. In April 2021, trastuzumab deruxtecan (Enhertu) was approved for use on the Cancer Drugs Fund (CDF) for treating HER2-positive unresectable or secondary breast cancer after 2 or more anti-HER2 therapies. Breast Cancer Now was involved throughout this NICE appraisal and we have spoken to a number of patients who have direct experience of this this treatment. We struggled to find patients with experience of trastuzumab deruxtecan in this new indication.
Living with the condition	
6. What is it like to live with the condition? What do carers	Secondary (also known as advanced, metastatic or stage 4) breast cancer is when cancer originating in the breast has spread to other parts of the body; most commonly the lungs, brain, bones or liver. There is no cure for secondary breast cancer, so treatment aims to control and slow down the spread of the

experience when caring for someone with the condition?	cancer, relieve symptoms and give patients the best quality of life for as long as possible. A patient can be diagnosed with secondary cancer from the start (de novo metastatic), or they can develop the condition months or years after treatment for their primary breast cancer has ended. When breast cancer cells have a higher than normal level of a protein called HER2 (human epidermal growth factor receptor 2) on their surface, which stimulates them to grow, this is known as HER2 positive breast cancer. Around one in five invasive breast cancers (breast cancer that has the potential to spread to other parts of the body) are HER2 positive. Brain metastases can also be more common with HER2 positive breast cancer which can negatively impact on quality of life. The symptoms of secondary breast cancer can vary depending on where the cancer has spread to. For example, if it has spread to the bones the main symptoms can include pain in the bones or bone fractures. If breast cancer has spread to the lungs, someone may experience symptoms such as breathlessness or pain when breathing. In addition, all breast cancer treatments can cause some side effects and although everyone reacts differently to drugs, for those people who experience more side effects than others, it can cause a significant impact on their day to day lives and health and wellbeing. Being diagnosed with secondary breast cancer is extremely difficult to come to terms with both for patients and their family and friends and it can affect patients in different ways. Many people may feel upset and shocked or anxious, as well as angry and alone. These common feelings can have a huge impact on people's mental health. As well as the huge emotional toll of living with secondary breast cancer, patients often have to cope with numerous practical concerns, such as managing their day-to-day activities, which may include working, household and parental responsibilities as well as travelling to and from regular hospital appointments. Patients are keen to find treatments that will halt progression and extend life for as long as possible. As patients' time is limited, people tell us that quality of life is just as important to take into account as length of life, as this enables them to spend quality time with their loved ones. Therefore, the type and severity of treatment side effects are also important for patients. A patient with HER2-positive secondary breast cancer told us what it is like to live with this condition:

	"I was diagnosed with HER2+ primary breast cancer in 2013 and then, in 2015, with metastatic breast cancer that has spread to the bones. *The cumulative effect of the treatment is mentally & physically exhausting. I struggle to sleep – often with pain, sometimes with menopausal symptoms brought on by the treatment, sometimes with anxiety & fear.* *My views about treatment, progression free survival & the level of side effects and quality of life issues I am prepared to tolerate have been hugely shaped by my experience over the past 7 years. I am so much better informed than in the early years of my treatment for primary breast cancer. Cancer has impacted every aspect of my life, family, work & relationships, but I have learnt that I can cope with the level of side effects from targeted therapy & still have a quality of life that is worth fighting for. My best hope continues to be to live long enough for the science to come up with something else that can keep me going for longer."* Another patient with HER2-positive secondary breast cancer told us what it is like to live with this condition: *"Living with SBC had a big impact on my day to day. Somedays I feel "normal" and can achieve everything I could do pre diagnosis. Somedays i maybe slower at getting task completed. Then there are days where I can just about do the minimum as I am exhausted or due to severe neuropathy my mobility is impacted. Every day is unpredictable and I have to plan everything in advanced and prepare for the bad days.* *I have lived with de novo secondary breast cancer for 9years. The past 2 years with covid have been the hardest to deal with and left me at times regretful because I have so much I want to achieve. These things are not big elaborate things but things that are important to me."*

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	The current first-line treatment is the combination of a taxane with trastuzumab and pertuzumab. Trastuzumab emtansine is currently the standard of care for treating HER2-positive unresectable or secondary breast cancer after trastuzumab or a taxane. It was recommended by NICE for routine use on the NHS in 2017 following its time on the old CDF. Trastuzumab emtansine is given intravenously, as an infusion. Prior to trastuzumab emtansine, once current treatments had stopped working, patients did not have any further targeted treatments options available to them. Despite advances in the treatments available to patients with HER2 secondary breast cancer, such as pertuzumab and trastuzumab emtansine, there is still a need for new treatments, which can extend progression free survival and overall survival. There also continues to be a need for kinder treatments which can improve patients' quality of life. A HER2-positive secondary breast cancer patient on trastuzumab emtansine told us: *"It's kept me alive for 6 years – it's a pretty phenomenal drug. When I started Kadcyla it was the only treatment that was an option for me, and it continues to work for me. Next week will be my 100th dose of Kadcyla, I think that makes me one of the people in the UK who has been on this drug for the longest time. I experience many side effects including extreme nausea, for which I take steroids. I'm also really fatigued in the first week of the cycle, I'm so wiped out that I often end up going to bed in the afternoon - people who know me would find this shocking as it's not something I'd normally do. I get neuropathic pain in my hands and feet, which is like being stung by a thousand bees. It can come on suddenly and at any time and I haven't found anything that eases the pain.* *I also have low immunity during the first couple of weeks of taking Kadcyla. This means I'm prone to mouth ulcers, skin infections, problems with my nails and my hair doesn't grow. I also get ear infections and UTIs, and during periods of low immunity I avoid going out. It has struck me during the pandemic that people have all of a sudden become aware of their immunity, but I've been aware of mine for years – Covid-19 is the least of my worries.*

	I have echo scans to make sure there's no impact of Kadcyla on my heart. *I go through this consistently every three weeks, it's relentless and messes with your mind. You get used it and you normalise it but actually this isn't normal. I've had to stop working because with the side effects I experience, work just isn't manageable.* *For me to switch to another drug, obviously it needs to be as efficacious, but side effects and quality of life are also really important to me. The mode of delivery of a drug is also important to me. I take Kadcyla intravenously, in hospital, on a three- weekly cycle. I'm in the hospital for a whole day - it's quite an arduous process so a drug that is easier to take would be better."* *A patient with HER2-positive secondary breast cancer with experience of trastuzumab deruxtecan in the indication it is currently approved for via the CDF shared her experience:* *"I have been fortunate with my side effects that they have been manageable and in comparison to how I was feeling before enhertu. I will take these side effects as what I have gained in quality of life is exceptional and I really didn't think after so long I would feel "this well" again."*
8. Is there an unmet need for patients with this condition?	New treatments with improved outcomes are needed for patients with HER2-positive secondary breast cancer after trastuzumab or a taxane. Trastuzumab emtansine is the current standard of care for this group of patients, but as with all breast cancer treatments we know that patients can experience a number of side effects.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Given the difficulties finding patients with experience of this treatment in this new indication, we do not have any additional data beyond what is published in the clinical trial. Phase 3 of the DESTINY-Breast03 trial, compared trastuzumab deruxtecan directly with Trastuzumab emtansine. The first interim results of the ongoing trial, published in the New England Journal of Medicine in March 2022, showed that at 12 months, 75.8% of the patients receiving trastuzumab deruxtecan were alive without progression as compared with 34.1% of those receiving trastuzumab emtansine. This is a significant improvement and patients have told us that they value this extra time, as delaying disease progression means more quality time to spend with relatives and friends. Maintaining a good quality of life for as long as possible is currently the best outcome for this patient group. Delaying progression can have a positive impact on patients' emotional wellbeing and mental health, as it may mean that patients may be able to continue to work and do the activities they enjoy. Increasing the time until a patient's disease progresses is also likely to bring some comfort to their relatives and friends. This in turn could help to reduce any stress the patient is experiencing as a result of worrying about any burden on their friends and family. Overall survival data is not yet mature, however, it is noted that there is a trend towards overall survival benefit with trastuzumab deruxtecan. An interim analysis showed that the percentage of patients who were alive at 12 months was 94.1% with trastuzumab deruxtecan and 85.9% with trastuzumab emtansine, although this did not cross the prespecified boundary for significance. The study also looked at response to treatment. An overall response (a complete or partial response) occurred in 79.7% of the patients who received trastuzumab deruxtecan compared to 34.2% of those who received trastuzumab emtansine. Given that trastuzumab emtansine is currently the standard of care for this group of patients, trastuzumab deruxtecan, with its improved treatment response rate could provide a more effective treatment option for this group of patients as an improved response can be associated with an improvement in cancer related symptoms which is an important factor for patients as it can improve quality of life.

	We understand that there is no added burden (or improvement) for patients in terms of administration method – as trastuzumab deruxtecan is delivered by IV every three weeks as is trastuzumab emtansine.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	One of the main disadvantages of this treatment is the side effects associated with it. The DESTINY-Breast03 trial showed that the occurrence of side effects of any grade was 98.1% with trastuzumab deruxtecan and 86.6% with trastuzumab emtansine, and the occurrence of side effects of grade 3 or 4 was 45.1% for trastuzumab deruxtecan and 39.8% for trastuzumab emtansine. The most common side effects of any grade reported amongst the trastuzumab deruxtecan group were nausea (72.8%), fatigue (44.7%) and vomiting (44%). The occurrence of these side effects was lower in the trastuzumab emtansine group: nausea (27.6%), fatigue (29.5%) and vomiting (5.7%). Alopecia of any grade was higher in trastuzumab deruxtecan (36.2%) compared to trastuzumab emtansine (2.3%). Drug-related interstitial lung disease or pneumonitis occurred in 10.5% of the patients in the trastuzumab deruxtecan group and in 1.9% of those in the trastuzumab emtansine group; none of these events were of grade 4 or 5. As trastuzumab deruxtecan is already available via the CDF in another indication many clinicians are familiar with these side effects. However, it is important that there is close monitoring to identify early warning signs of any patients developing signs or symptoms of interstitial lung disease or pneumonia so they can be managed effectively. Every treatment for breast cancer has some side effects and each patient's situation will be different, with side effects affecting some patients more than others. Patients' willingness to have treatment will understandably vary. If trastuzumab deruxtecan were to be approved, it would be important for clinicians to clearly discuss its specific potential side effects with patients, so that they can make informed decisions, regarding treatment options with the support of their clinician. A patient with HER2-positive secondary breast cancer explained to us the importance of new treatments for this patient group: *"I've progressed from primary to secondary breast cancer, so it's important to me that any drug I take doesn't have horrific side effects. I've been through such a long period of time on different treatments, that*

	I think my choices are more conservative now. Dugs coming down the line for secondary breast cancer need to ensure quality of life. By the time of a secondary breast cancer diagnosis, we've been through so much, we're not pin cushions, there's only so much we can take."
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.	This treatment may not be appropriate for patients who are at increased risk of experiencing lung disease or pneumonia.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None that we are aware of

Other issues	
13. Are there any other issues that you would like the committee to consider?	Subgroup analysis published in December 2021 suggests that progression-free survival and objective response rate were consistent, including those with brain metastases.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- A diagnosis of secondary breast cancer can cause considerable anxiety and fear for people and their loved ones, impacting on all aspects of their lives. The uncertainty can be the hardest part for many people. There is no cure for secondary breast cancer, so the aim of treatment is to extend the length of life, whilst providing a good quality of life.
- Interim results from the DESTINY-Breast03 trial have shown that at 12 months 75.8% of the patients receiving trastuzumab deruxtecan were alive without progression as compared with 34.1% of those receiving trastuzumab emtansine. This is a significant improvement and patients have told us that they value this extra time, as delaying disease progression means more quality time to spend with their relatives and friends.
- Whilst we await final overall survival data, the Destiny-Breast03 trial also showed that interim results for overall survival for trastuzumab deruxtecan was 94.1% compared to 85.9% for trastuzumab emtansine, although this did not cross the prespecified boundary for significance.
- There are some increased side effects with trastuzumab deruxtecan compared to trastuzumab emtansine. Every treatment for breast cancer has some side effects and each patient's situation will be different, with side effects affecting some patients more than others. If trastuzumab deruxtecan were to be approved, it would be important for clinicians to clearly discuss its specific potential side effects with patients, so that they can make informed decisions, regarding treatment options, with the support of their clinician.

Thank you for your time.

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Single Technology Appraisal

[ID3909] - Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after trastuzumab or a taxane

Patient Organisation Submission

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. [Please note that declarations of interests relevant to this topic are compulsory].

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	METUPUK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	METUPUK is a volunteer led patient advocacy organisation working for the unmet needs of patients with metastatic breast cancer. Our three main objectives are raising MBC awareness and education, campaigning for equitable treatment including access to drugs and improvements in patient care. Our services aim to inform patients with primary breast cancer, their family and friends and clinicians of the red flag signs and symptoms of secondary breast cancer. For patients with metastatic breast cancer we campaign for improved access to drugs and treatments. This may include addressing disparities in accessing treatment and clinical trials in the four nations of the UK, or between different commissioning groups within a given nation. We also campaign for access to new therapeutics and radiotherapy treatments so NHS and private patients have the same access to treatment. We call on Trusts to collect accurate and timely data on their patients with MBC. Through our social media channels offer we offer signposting for peer support. We became a registered charity in 2021, but the organisation began as a small group of patients frustrated by the poor prognosis for MBC in 2016 and has grown since then. We are not a membership organisation, but do reach out to the metastatic patient community with over 4000 followers on social media platforms. Our funding is entirely from public donations, and all our trustees and volunteers are unpaid.
4b. Has the organisation received any funding from the	No

manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We used our social media channels of Facebook, Instagram and Twitter to gather experiences of patients on trastuzumab deruxtecan. Currently this treatment is available after two or more lines of treatment on the Cancer Drug Fund, while it is being assessed. We have also reached out to a smaller WhatsApp group of active volunteers, some of whom are taking this treatment, either for later line HER2-positive MBC or as part of a trial for HER2-low MBC.

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?	Living with MBC is living with uncertainty. We live scan to scan, and even if our treatment appears to be working well, we never know if our cancer is progressing. It is incredibly difficult to plan anything beyond three or six months in the future. Even with the best available drug therapy, for most patients decades of life will be lost. Many of us mourn the loss of jobs and the future loss of families including children or even children that were planned but now will never be born. Patient advocate Ann describes living with MBC in these words: Living with MBC brings a level of sadness (associated with loss) which is always there and cannot be shifted. You are constantly aware that your life is time limited and planning of any kind is exceptionally difficult. You feel helpless and despair that you have no control over your illness, and are wholly dependent on the availability of drugs to keep you alive. The psychological benefits of knowing that medical advancements continue to be pursued and will be made available cannot be emphasised enough- it reduces the mental stress of MBC and brings real hope. MBC is also incredibly difficult for carers. Partners find their role in a family changes quite suddenly from lover to carer for the patient, often balancing this with the financial need to work and sometimes manage childcare. Patients' parents face the awful prospect of their children dying before them, with very little support. Many patients have children under 18 living with them, and these children also face the considerable difficulties of being a young carer while balancing their studies. Alessandro's wife has an aggressive form of MBC. He writes: It's much easier to take care of someone who has stability on their drug regime; my wife has not had that yet and it's been a struggle. Also when drugs are denied by NICE it feels that the system doesn't care about patients like my wife.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and	At the time of writing, patients have access to four lines of targeted anti-HER2 treatment, which is a massive improvement on a year ago, when only two lines of anti-HER2 treatment were available. However, trastuzumab deruxtecan is only available provisionally on the cancer drug fund after two lines of

care available on the NHS?	treatment. We are very conscious that this could be removed at short notice. This proposal is to move trastuzumab deruxtecan into the second line, and trial evidence is encouraging. However, we are concerned about losing access to trastuzumab emtansine, which would then reduce patients to only having three lines of anti-HER2 therapy. Patients hope that all four lines of anti-HER2 treatment will be retained. Patients would strongly prefer trastuzumab beyond progression to be offered at all treatment lines if their oncologist recommends this. Many patients are aware that the ESMO guidelines recommend trastuzumab to be given with chemotherapy beyond progression. They are also aware that patients treated in the UK privately are given trastuzumab with chemotherapy beyond progression, but in most cases NHS patients are not.
8. Is there an unmet need for patients with this condition?	Yes. HER2-positive MBC is an incurable and life-limiting disease. Even with best available care disease progression occurs and patients require new treatments to extend their lives. The provision of second line trastuzumab deruxtecan is important, because clinical trials indicate that second line is where it is most effective and best tolerated by patients. It is also important that oncologists can choose at which line to use trastuzumab deruxtecan. Every patient has different needs, and these are best assessed by their medical team.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Each line of treatment for MBC takes a toll on patients general fitness. Accessing trastuzumab deruxtecan earlier, means many patients may tolerate the treatment better and have a lower burden of disease to live with. Patients taking trastuzumab deruxtecan have a longer PFS compared to trastuzumab emtansine, which for most patients will translate into a better quality of life for a longer period of time.

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Patients are concerned that accessing trastuzumab deruxtecan earlier may reduce the total number of targeted anti-HER2 treatments offered by the NHS. Specifically patients are concerned that they will lose access to trastuzumab emtansine. Not every patient will respond to trastuzumab deruxtecan, and these patients will value having drugs such as trastuzumab emtansine as an option for their oncologist to prescribe. Patients are concerned that trastuzumab deruxtecan has more side effects that trastuzumab emtansine and that there will be more “bad days” in treatment cycles. Patients are also worried by the risks of interstitial lung disease. They are concerned that this side effect may be life threatening, and also that they will need to stop a treatment which could be working well on their cancer.
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.	No comment. Patient selection is a clinical decision.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None noted.
Other issues	
13. Are there any other issues that you would like the committee to consider?	Another unmet need for HER2-positive MBC is the lack of availability of trastuzumab beyond progression, particularly in later treatment lines. The approval of trastuzumab deruxtecan and the tucatinib combination goes some way to addressing this, but not fully. Now that trastuzumab is a generic drug, there does not seem to be a mechanism to appraise if it is beneficial in later treatment lines. We believe this is a failing of the regulatory system. Regulatory systems should be run to benefit patients, and should be flexible enough to adapt to changes when drugs become generic. Patients value the clinical acumen of their oncologist, and would like them to have a large toolkit of drugs. Only then can the NHS provide personalised care for patients.
Key messages	
14. In up to 5 bullet points, please summarise the key messages of your submission: • Evidence suggests trastuzumab deruxtecan is best placed in the second line. • Oncologists should be given flexibility to decide which treatment line to use trastuzumab deruxtecan for their patient.	

- Patients are excited by the results of trastuzumab deruxtecan because they can live for longer without progression.
- Patients are concerned about the side effects. That there will be more “bad days” per cycle, and by the risk of ILD.
- Patients do not want to lose trastuzumab emtansine, because there are limited lines of anti-HER2 therapies available on the NHS.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

[ID3909] - Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after trastuzumab or a taxane

Professional organisation submission

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.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Dr Cathryn Edwards**
2. Name of organisation	**NCRI-ACP-RCP-RCR**

3. Job title or position	**RCP registrar**
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? X ☐ 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).	**NCRI-ACP-RCP-RCR**
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	**No**

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
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.)	To control disease, stop progression, improve symptoms and quality of life, expand life expectancy.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	Clinically significant treatment response depends on the perspective and cannot be encapsulated with a single metric. Improvement of the PFS and/or OS when compared to standard treatment is a significant treatment response. A reduction in tumour size is also important if this reduction is maintained for reasonable time.

x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Metastatic breast cancer is an incurable progressive disease with a poor prognosis and limited effective treatment options for patients with HER2-positive disease. Current practice includes TDM1 at the 2nd line following progression on taxanes and antiHER2 treatment. There is an unmet need for therapies that control disease progression for longer periods (by increasing progression free survival), extend life (by increasing overall survival) and have an acceptable tolerability and safety.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	HER2-positive breast cancer is an aggressive disease that presents more often in younger patients. The current standard of care in the MBC HER2+ve pathway involves a trastuzumab-containing regimen first-line (for example, trastuzumab-pertuzumab-taxane for first-line HER2-positive metastatic breast cancer) followed by trastuzumab emtansine monotherapy second-line for HER2-positive, unresectable or metastatic breast cancer previously treated with trastuzumab and a taxane.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE ESMO NCCN
• Is the pathway of care well defined? Does it vary or are there differences of opinion	Currently the defined standard of care for patients with unresectable or metastatic HER2-positive breast cancer after progressing on taxanes and antiHER2 treatment is TDM1. Some of the approved antiHER2-based regimens have moved to the setting of early breast cancer, such as trastuzumab emtansine (Katharine trial) and pertuzumab.

between professionals across the NHS? (Please state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	Trastuzumab deruxtecan is a HER2-targeted treatment that fills an unmet need in the 2nd line treatment after a trastuzumab-containing regimen. It is believed to be a therapeutic advancement due to its improved PFS rates and duration of response compared with current standard of care which is TDM1.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	It will be used if approved on the 2nd line following PD on taxane and trastuzumab containing regimen.
• How does healthcare resource use differ between the technology and current care?	As mentioned above current standard treatment on the 2nd line is Trastuzumab emtansine for patients with human epidermal growth factor receptor 2 (HER2)–positive metastatic breast cancer whose disease progresses after treatment with a combination of anti-HER2 antibodies and a taxane. Trastuzumab deruxtecan is an antibody-drug conjugate, and the first to combine an anti-HER2 antibody (trastuzumab) with a topoisomerase inhibitor licensed in the UK. It is a HER2-targeted therapy currently licensed for use in HER2-positive unresectable or metastatic breast cancer after two lines of HER2-targeted therapy, including trastuzumab emtansine. Destiny Breast 03 study is a phase 3, multicenter, open-label, randomized trial conducted to compare the efficacy and safety of trastuzumab deruxtecan with those of trastuzumab emtansine in patients with HER2-positive metastatic breast cancer previously treated with trastuzumab and a taxane. The primary end point was progression-free survival (as determined by blinded independent central review); secondary end points included overall survival, objective response, and safety.

	Treatment with T-DXd led to a highly significant 72% reduction in the risk of progression vs ado-trastuzumab emtansine (T-DM1) in patients who had received treatment with a taxane and trastuzumab (hazard ratio [HR] = 0.2840; P = 7.8 × 10−22). The percentage of patients who were alive at 12 months was 94.1% (95% CI, 90.3 to 96.4) with trastuzumab deruxtecan and 85.9% (95% CI, 80.9 to 89.7) with trastuzumab emtansine (hazard ratio for death, 0.55; 95% CI, 0.36 to 0.86; prespecified significance boundary not reached). An overall response (a complete or partial response) occurred in 79.7% (95% CI, 74.3 to 84.4) of the patients who received trastuzumab deruxtecan and in 34.2% (95% CI, 28.5 to 40.3) of those who received trastuzumab emtansine**.** The efficacy/benefit of TdxD was seen across subgroups and in other secondary endpoints. Very importantly, TDxd in this setting was associated with less lung toxicity than in Destiny 01, resetting the risk/benefit analysis in its favour.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Second-line treatment after a taxane and trastuzumab-containing regimen.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Training and education as with all new drugs introduced in the standard of care will be required. The focus of the training/education should be the adverse events of TDxd. Interstitial Lung Disease / Pneumonitis Severe, life-threatening, or fatal interstitial lung disease (ILD), including pneumonitis, can occur in patients treated with TDxd. Advise patients to immediately report cough, dyspnea, fever, and/or any new or worsening respiratory symptoms. Monitor patients for signs and symptoms of ILD. Promptly investigate evidence of ILD. Evaluate patients with suspected ILD by radiographic imaging. Consider consultation with a pulmonologist. For asymptomatic ILD/pneumonitis (Grade 1), interrupt TDxd until resolved to Grade 0, then if resolved in ≤28 days from date of onset, maintain dose. If resolved in >28 days from date of onset, reduce dose one level. Consider corticosteroid treatment as soon as ILD/pneumonitis is suspected (e.g., ≥0.5 mg/kg/day prednisolone or equivalent). For symptomatic ILD/pneumonitis (Grade 2 or greater), permanently discontinue TDxd. Promptly initiate systemic corticosteroid treatment as soon as

	ILD/pneumonitis is suspected (e.g., ≥1 mg/kg/day prednisolone or equivalent) and continue for at least 14 days followed by gradual taper for at least 4 weeks. The rest of AEs are commonly seen with most chemotherapy agents.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Trastuzumab deruxtecan produces unprecedented response rates and may offer survival improvements for patients with HER2-positive metastatic breast cancer (OS data still immature but a trend was seen) that has progressed after taxane and trastuzumab containing regimens. No similar response rates or PFS results in this setting have been seen previously.
• Do you expect the technology to increase length of life more than current care?	OS data are not available yet but and a trend has emerged in overall survival, though these data remain immature.
• Do you expect the technology to increase health-related quality of life more than current care?	The data show that trastuzumab deruxtecan could lead to a prolonged period when the patient's disease is controlled with patients remaining well and able to participate in family, work and social activities. Based on clinical experience, improvement of PFS and tumour responses relate to symptom control and subsequently better quality of life. Accessing TdXD may provide reassurance to patients that they are receiving the optimum treatment for their condition and this can have psychological benefits. Some patients may derive hope that any prolonged progression-free and overall survival may provide a bridge to a time when other new medicines become available.

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Forest plot analysis showed every subgroup favoured and derived benefit from trastuzumab deruxtecan over T-DM1. This applied to hormone receptor-positive or hormone receptor-negative tumours, to patients who had pertuzumab before, those who were naïve to pertuzumab, and to patients who had or lacked visceral disease. About half of these patients were treated in the second-line setting, and the other half were third line and later, both of which favoured benefit from TdXD. The subset of patients with stable treated brain metastases (115 patients on study) also had a significant benefit from TdXD and the hazard ratio was 0.37. Every subgroup examined favoured TdXD as per subgroup analysis.
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.)	Special attention needs to be given to the risk of ILD as described above. Education is key for patients and clinicians. There should be an agreement in place regarding lung imaging in each institute. Other than that, our experts do not anticipate any additional clinical requirements.

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	This is relevant to ILD as mentioned above. Severe, life-threatening, or fatal interstitial lung disease (ILD), including pneumonitis, can occur in patients treated with TDxd. Advise patients to immediately report cough, dyspnea, fever, and/or any new or worsening respiratory symptoms. Monitor patients for signs and symptoms of ILD. Promptly investigate evidence of ILD. Evaluate patients with suspected ILD by radiographic imaging. Consider consultation with a pulmonologist. For asymptomatic ILD/pneumonitis (Grade 1), interrupt TDxd until resolved to Grade 0, then if resolved in ≤28 days from date of onset, maintain dose. If resolved in >28 days from date of onset, reduce dose one level. Consider corticosteroid treatment as soon as ILD/pneumonitis is suspected (e.g., ≥0.5 mg/kg/day prednisolone or equivalent). For symptomatic ILD/pneumonitis (Grade 2 or greater), permanently discontinue TDxd. Promptly initiate systemic corticosteroid treatment as soon as ILD/pneumonitis is suspected (e.g., ≥1 mg/kg/day prednisolone or equivalent) and continue for at least 14 days followed by gradual taper for at least 4 weeks.
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?	N/A
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	Trastuzumab deruxtecan produces unprecedented PFS rates for patients with HER2-positive metastatic breast cancer that have progressed after taxanes and trastuzumab. No similar PFS and response rate results in this setting have been seen previously in HER2+ve tumours. The Destiny 03 data show that trastuzumab deruxtecan could lead to a prolonged period when the patient's disease is controlled with patients remaining well and able to participate in family, work, and social activities.

improve the way that current need is met?	Accessing trastuzumab deruxtecan may provide reassurance to patients that they are receiving the optimum treatment for their condition, and this can have psychological benefits. Some patients may derive hope that any prolonged progression-free and overall survival may provide a bridge to a time when other new medicines become available.
• Is the technology a 'step-change' in the management of the condition?	Yes, it is. Based on Destiny 03 data, T-DXd should replace T-DM1 as the standard of care for patients who have previously received trastuzumab and a taxane. It is believed to be a therapeutic advancement due to its improved PFS rates compared with TDM1 which is the current standard of care**.**
• Does the use of the technology address any particular unmet need of the patient population?	As above
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?	Please see above re ILD. All other AEs are commonly seen.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes

• 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?	Among 524 randomly assigned patients, the percentage of those who were alive without disease progression at 12 months was 75.8% (95% confidence interval [CI], 69.8 to 80.7) with trastuzumab deruxtecan and 34.1% (95% CI, 27.7 to 40.5) with trastuzumab emtansine (**hazard ratio for progression or death from any cause, 0.28; 95% CI, 0.22 to 0.37; P<0.001**). The percentage of patients who were alive at 12 months was 94.1% (95% CI, 90.3 to 96.4) with trastuzumab deruxtecan and 85.9% (95% CI, 80.9 to 89.7) with trastuzumab emtansine (hazard ratio for death, 0.55; 95% CI, 0.36 to 0.86; prespecified significance boundary not reached). **An overall response (a complete or partial response) occurred in 79.7% (95% CI, 74.3 to 84.4) of the patients who received trastuzumab deruxtecan and in 34.2% (95% CI, 28.5 to 40.3) of those who received trastuzumab emtansine**. The incidence of drug-related adverse events of any grade was 98.1% with trastuzumab deruxtecan and 86.6% with trastuzumab emtansine, and the incidence of drug-related adverse events of grade 3 or 4 was 45.1% and 39.8%, respectively. Adjudicated drug-related interstitial lung disease or pneumonitis occurred in 10.5% of the patients in the trastuzumab deruxtecan group and in 1.9% of those in the trastuzumab emtansine group; none of these events were of grade 4 or 5.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Our experts have extensively used TDxd both on the trials setting for a few years as well as through patient access scheme and then as a standard of care following SMC approval on 3rd line setting. Our experts confirm that no new AEs came to light that are different to the ones recorded in the DESTINY trials.
19. Are you aware of any relevant evidence that might	No

not be found by a systematic review of the trial evidence?	
21. How do data on real-world experience compare with the trial data?	The trial compared the efficacy and safety of trastuzumab deruxtecan with those of trastuzumab emtansine which is the current standard of practice on the 2nd line setting and in patients with HER2-positive metastatic breast cancer previously treated with trastuzumab and a taxane. We don't have any real-world data on this setting for TdxD at the moment but we have published data on RWE from single institutes about TDM1 PFS and efficacy that confirm the rates we see for TDM1 on the study. Experts are currently collecting RWE on the use of Tdxd on the 3rd line on a national level as well as a local level.
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.

1. Metastatic breast cancer is an incurable progressive disease with a poor prognosis and limited effective treatment options for patients with HER2-positive disease. Current practice includes TDM1 at the 2nd line following progression on taxanes and antiHER2 treatment. There is an unmet need for therapies that control disease progression for longer periods (by increasing progression free survival), extend life (by increasing overall survival) and have an acceptable tolerability and safety.
2. Trastuzumab deruxtecan is a HER2-targeted treatment that fills an unmet need in the 2nd line treatment after a trastuzumab-containing regimen. It is believed to be a therapeutic advancement due to its improved rates and duration of response compared with current SOC (TDM1).
3. Trastuzumab deruxtecan produces unprecedented response and PFS rates and may offer survival improvements for patients with HER2-positive metastatic breast cancer that have progressed after taxanes and trastuzumab containing regimen (OS data are still premature). No similar response rates or PFS results in this setting have been seen previously in HER2+ve tumours.
4. The data show that trastuzumab deruxtecan on the 2nd line could lead to a prolonged period when the patient's disease is controlled with patients remaining well and able to participate in family, work and social activities.
5. Special attention needs to be given to the risk of ILD as described above. Education is key for patients and clinicians. It is reassuring that the risk of ILD does not correlate with the cumulative dose of the TDxd.

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Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after trastuzumab and a taxane [ID3909]

Produced by Newcastle University

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Commercial in confidence (CiC) data are highlighted in blue throughout the report.

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Any de-personalised data are highlighted in pink throughout the report.

Rider on responsibility for report

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

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Contributions of authors

Stephen Rice acted as project lead. Katie Thomson and Fiona Pearson acted as lead effectiveness reviewers. Ge Yu acted as lead health economist. Sheila Wallace acted as lead reviewer of the literature search methods. Oluwatomi Arisa acted as assistant effectiveness reviewer. Diarmuid Coughlan and Ashleigh Kernohan acted as assistant health economists. Sonia Garcia Gonzalez-Moral assisted in reviewing the literature search methods. Amit Goyal provided clinical expert opinion.

Abbreviations

ADC	Antibody-drug conjugate
AEs	Adverse events
AIC	Akaike Information Criterion
ALT	Alanine Transaminase
AST	Aspartate Transferase
BC	Breast Cancer
BCS	Best case scenario
BI	Budget impact
BIC	Bayesian information criterion
BICR	Blinded independent central review
CBR	Clinical Benefit Rate
CDF	Cancer Drug Fund
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
CS	Company submission
CR	Complete Response
CSR	Clinical study report
CT	Computerised tomography
CTR	Clinical trial results
DCO	Data Cut off
DoR	Duration of Response
DSU	Decision Support Unit
EAG	External Assessment Group
eBC	Early breast cancer
ECOG	Eastern Cooperative Oncology Group
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-5L	EuroQol 5 Dimension 5 Level
EQ-5D-3L	EuroQol 5 Dimension 3 Level
ER	Oestrogen receptor
ESMO	European Society for Medical Oncology
EUR	Erasmus University Rotterdam
FAS	Full analysis set
FDA	Food and Drug Administration
GG	Generalised gamma
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
IA	Investigator assessment
ICD	International Statistical Classification of Diseases and Related Health Problems
ICER	Incremental cost effectiveness ratio
ILD	Interstitial Lung Disease

ITT	Intention to treat
IV	Intravenous
IXRS	Interactive Web/Voice Response System
KM	Kaplan-Meier
LVEF	Left ventricular ejection fraction
LYs	Life years
LYG	Life years gained
mAB	Monoclonal Antibody
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
NA	Not applicable
NCCN	National Comprehensive Cancer Network
NCRI	National Cancer Research Institute
NE	Not Evaluable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NR	Not reported
ORR	Objective Response Rate
OS	Overall survival
PartSA	Partitioned survival model
PAS	Patient access scheme
Pcr	Pathological complete response
PD	Progressive Disease
PFS	Progression-free survival
PH	Proportional hazards
PR	Partial Response
P4R	Progesterone Receptor
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
PSM	Parametric survival model
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
Q3W	Every three weeks
Q4	Quarter 4
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
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumours
RID	Residual invasive disease
RR	Response Rate
SABCS	San Antonio Breast Cancer Symposium
SAEs	Serious Adverse Events
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SC	Subcutaneous
SD	Stable Disease

SE	Standard error
SITC	Society for Immunotherapy of Cancer
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
SoC	Standard of care
STA	Single technology appraisal
STD DEV	Standard Deviation
STEEP	Standardised definitions for efficacy endpoints
TA	Technology assessment
T-DM1	Trastuzumab emtansine
T-DXd	Trastuzumab deruxtecan
TEAEs	Treatment emergent adverse events
TKI	Tyrosine Kinase Inhibitor
TTD	Time-to-treatment discontinuation
tpCR	Total pathological complete response
ToT	Time on Treatment
TTO	Time trade-off
TTOT	Time-to-off treatment
TTR	Time to response
uBC	Unresectable Breast Cancer
UK	United Kingdom
UMC	University Medical Centre
USA	United States of America
WHO	World Health Organization
WTP	Willingness-to-pay
VAS	Visual Analogue Scale

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1. EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 presents the key model outcomes. Section 1.3 discusses the decision problem, Section 1.4 presents issues related to the clinical effectiveness, and Section 1.5 discusses issues related to the cost effectiveness. Other key issues are discussed in Section 1.6, while a summary is presented in Section 1.7.

Background information on the condition, technology and evidence and information on key as well as non-key issues are in the main EAG report, see Sections 2 (background), 3 (decision problem), 4 (clinical effectiveness) and 5 (cost effectiveness) for more details.

All issues identified represent the EAG's views, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

Table 1.1: Summary of key issues

ID3909	Summary of issue	Report sections
1	Data from the included randomised control trial is from an interim cut-point	3.2.4, 3.2.4.2
2	Background characteristic of participants in randomised control trial may not be reflective of those seen in clinical practice within England	3.2.1, 3.2.4.1 and 3.2.4.2
3	Uncertainty in the proportion of progressed patients receiving subsequent treatment and the distribution of subsequent treatments	3.2.4.1 and 3.2.4.2
4	Adverse events (AEs) monitored within the randomised control trial are higher in the T-DXd arm compared to the T-DM1 arm	3.2.4.7
5	Uncertain PFS predictions for T-DXd	4.2.6
6	Uncertain OS predictions for T-DXd	4.2.6
7	Crosswalking EQ-5D-5L to EQ-5D-3L with the recommended algorithm	4.2.8
8	Post-progression utility values	4.2.8
Abbreviations: AEs, adverse events; EQ-5D-5L, EuroQol 5 Dimension 5 Level; EQ-5D-3L, EuroQol 5 Dimension 3 Level; T-DM1, trastuzumab emtansine; T-Dxd, trastuzumab deruxtecan		

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are:

- The company assumes a treatment benefit in reducing mortality over the lifetime, whereas the EAG assumes a conservative scenario with no treatment effect beyond progression.
- The company Treatment-specific utility values for progressed disease health state versus a single combined utility estimate
- Vial-sharing occurs for 50% of patients versus for 10% of patients

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled by the company to affect QALYs by:

- Difference in progression-free survival (PFS)
- Difference in overall survival (OS)
- Difference in utilities in the PFS and the disease progression health states

Overall, the technology is modelled by the company to affect costs by:

- Higher drug cost
- Longer time on treatment
- Different relative dose intensities
- Different incidences of adverse events
- Different distributions of subsequent treatments
- Different time periods in the progression-free and the disease progression health states affecting the duration of monitoring and receiving subsequent treatment

The modelling assumptions and values that have the greatest effect on the ICER are:

- A significant treatment benefit in terms of reducing mortality is sustained across the 30-year time horizon of the model
- Utility values for the progression-free survival and the disease progression health states
- The percentage of patients receiving subsequent treatment

1.3 The decision problem: summary of the EAG's key issues

The decision problem addressed in the company submission (CS) is in line with the final scope issued by NICE, trastuzumab deruxtecan (T-DXd) to be used for human epidermal growth factor receptor 2 positive (HER2+) unresectable or metastatic breast cancer after trastuzumab and a taxane.[1,2] There are no key issues arising from the decision problem.

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

The EAG identified the following concerns with evidence presented on clinical effectiveness of T-DXd which may lead to uncertainty regarding treatment effects, benefits and risks or harms:

1. Interim OS data were immature with insufficient precision to conclude superiority for T-DXd, right censoring of patients contributed to imprecision, although censoring appears balanced across groups.
2. Background characteristics, including prior lines of treatment, of those included in the randomised control trial may not reflect characteristics of those seen in clinical practice in England.
3. There is uncertainty in the proportion of progressed patients who receive subsequent treatment and in the distribution of subsequent treatments due to a high percentage of patients who have not yet progressed. There is also uncertainty in the generalisability to the English setting. .

4. There is a higher number of AEs in the T-DXd trial arm compared to the trastuzumab emtansine (T-DM1) trial arm.

Table 1.2: Key issue [1] - Effectiveness data from the included randomised control trial is from an interim data cut point

Report section	3.2.4 and 3.2.4.2
Description of issue and why the EAG has identified it as important	Interim analyses of T-DXd are presented within the company submission.[1] The evidence presented is derived from the DESTINY-Breast03 trial using the interim cut off point of the 21st of May 2021 with right censoring. Sufficient PFS events occurred to conduct the interim analysis with [redacted] events across both treatment arms combined ([redacted]% of patients). However, the OS data are not near maturity with 86 events across both treatment arms ([redacted]% of patients). Interim analyses of clinical trial data are often used to provide evidence for marketing authorization submissions; however, the results from such analyses may not reflect the true estimates of relative effectiveness that will become estimable when trial follow-up is complete.
What alternative approach has the EAG suggested?	The EAG suggest no alternative approach be undertaken at this point. The company has indicated that the next data cut-point is likely to be undertaken in [redacted]. Final PFS analysis is planned at [redacted] PFS events and this is when the second interim OS analysis will be conducted. Final OS analysis will be undertaken at [redacted] OS events. The right censoring appears to be balanced across groups of patients and uses a commonly employed censoring rule so is unlikely to lead to censoring bias.
What is the expected effect on the cost effectiveness estimates?	The immaturity of the data results in considerable uncertainty in the PFS and OS extrapolations used in the economic model. See Key Issue [5] and Key Issue [6].
What additional evidence or analyses might help to resolve this key issue?	We believe this to be a currently unresolvable issue that is a cause of uncertainty. Longer-term DESTINY-Breast03 OS data are required.
Abbreviations: EAG, Evidence assessment group; OS, Overall survival; PFS, Progression free survival; T-DXd, Trastuzumab deruxtecan; Q4, quarter four	

Table 1.3: Key issue [2] – Background characteristics of trial participants may not reflect characteristics of those that would be seen in English clinical practice

Report section	3.2.1, 3.2.4.1 and 3.2.4.2
Description of issue and why the EAG has identified it as important	Background characteristics of patients enrolled in DESTINY-Breast03 may not reflect characteristics of those that would be seen in clinical practice in England. Patients enrolled in DESTINY-Breast03 are more likely to be Asian, smokers and to have received a higher number of prior treatment lines. This threatens the external validity of the randomised control trial findings. There is uncertainty as to whether the clinical trial results generalise to NHS settings.
What alternative approach has the EAG suggested?	The EAG considers that the background characteristics of the European subgroup in DESTINY-Breast03 are likely to be more

	generalisable to an English clinical setting. However, the sample size for this subgroup is not large so findings derived from this subgroup are impacted by high uncertainty.
What is the expected effect on the cost effectiveness estimates?	It is unclear if the estimates of clinical benefit are likely to be applicable to an English clinical setting. The expected impact on the cost effectiveness estimates is unknown.
What additional evidence or analyses might help to resolve this key issue?	We believe this to be an unresolvable issue that is a limited cause of uncertainty.
Abbreviations: EAG, Evidence assessment group; NHS, National Health Service	

Table 1.4: Key issue [3] – Uncertainty in the proportion of progressed patients receiving subsequent treatment and the distribution of subsequent treatments

Report section	3.2.4.1 and 3.2.4.2
Description of issue and why the EAG has identified it as important	Of patients enrolled in DESTINY-Breast03 who experienced disease progression, [redacted]% and [redacted]% of patients in the T-DXd and T-DM1 arms received subsequent treatment respectively. The company clinical experts stated that the percentages were higher than expected. The clinical experts estimated the percentages for T-DXd and T-DM1 to be 66.7% in English clinical practice. It is possible that as the trial progresses the percentages of progressed patients receiving subsequent treatment will be higher than at the first interim data cut point. Further complicating the issue, a high percentage of patients in DESTINY-Breast03 received treatment subsequent to their allocated treatment having discontinued treatment due to adverse events or otherwise in addition to disease progression: in total, [redacted] in the T-DXd arm and [redacted] in the T-DM1 arm (calculated as a percentage from the total number of patients who received subsequent treatment divided by the number of patients who had experienced a progression event, i.e. not including those who discontinued treatment for other reasons than progression). Also, the subsequent treatments received by those in DESTINY-Breast03 may not wholly be reflective of the subsequent therapies that would be used in English clinical practice after second-line treatment. As the trial progresses, the subsequent treatment distribution could potentially change.
What alternative approach has the EAG suggested?	No alternative approach is suggested for the percentage of progressed patients receiving subsequent treatment. The EAG considers that the distribution of subsequent treatments in the European subgroup in DESTINY-Breast03 is likely to be more reflective of the distribution of subsequent treatments used in an English clinical setting. However, the sample size for this subgroup is not large, so findings derived from this subgroup are impacted by high uncertainty.
What is the expected effect on the cost effectiveness estimates?	The company used clinical expert opinion on percentages of progressed patients receiving subsequent treatment in the base case

	economic model. The distribution of subsequent treatments was informed by DESTINY-Breast03. The effect of the alternative approaches on cost-effectiveness is unknown.
What additional evidence or analyses might help to resolve this key issue?	European subgroup data on subsequent treatment distribution could have been informative. The issue of the proportion of patients receiving subsequent treatment is currently unresolvable. Data from a later data cut point would provide more information on the percentage of patients receiving subsequent treatment and on the subsequent treatment distribution, although the issue of generalisability to the English setting remains.
Abbreviations: EAG, Evidence Assessment Group; T-DM1, Trastuzumab emtansine; T-DXd, Trastuzumab deruxtecan	

Table 1.5: **Key issue [4] - Higher AEs in the T-DXd arm compared to T-DM1 arm**

Report section	3.2.4.7
Description of issue and why the EAG has identified it as important	Treatment-emergent adverse events (TEAEs) of any grade were more common in the T-DXd arm than in the T-DM1 arm (99.6% vs 95.4%, respectively), as were TEAEs associated with study drug discontinuation (13.6% vs 7.3%, respectively) and dose reduction (21.4% vs 12.6%, respectively). Higher drug discontinuation and dose reduction could potentially affect the acceptability of T-DXd relative to T-DM1.
What alternative approach has the EAG suggested?	No alternative approach is required. This issue highlights uncertainty in acceptability rather than in the evidence base.
What is the expected effect on the cost effectiveness estimates?	No effect is expected. This issue highlights uncertainty in acceptability rather than in the evidence base.
What additional evidence or analyses might help to resolve this key issue?	No further evidence or analyses are required.
Abbreviations: EAG, Evidence Assessment Group; ICER, Incremental cost-effectiveness ratio; T-DM1, Trastuzumab emtansine; T-DXd, Trastuzumab deruxtecan; TEAEs, treatment emergent adverse events;	

1.5 The cost effectiveness evidence: summary of the EAG's key issues

The company's cost effectiveness results are presented in Section 5, the EAG's summary and detailed critique in Section 4, and the EAG's amendments to the company's model and results will be presented in Section 6. The main EAG results will be reproduced using confidential Patient Access Schemes (PASs) in a confidential Appendix. The key issues in the cost effectiveness evidence are discussed in Table 1.6 to 1.8.

Table 1.6: Key Issue [5] – Uncertain PFS predictions for T-DXd

Report section	4.2.6

Description of issue and why the EAG has identified it as important	Key Issue [5] links to Key Issue [1] The PFS prediction in the economic model is uncertain, particularly for T-DXd given that approximately 50% of patients were still progression-free at the first interim data cut point (i.e., ongoing without event or censoring).
What alternative approach has the EAG suggested?	To conduct scenario analyses around the parametric model selected to model PFS. The company has done this.
What is the expected effect on the cost effectiveness estimates?	The alternative parametric models had little effect on the cost-effectiveness estimates.
What additional evidence or analyses might help to resolve this key issue?	Additional data from the next expected data cut off point would provide considerably more data on PFS.
Abbreviations: EAG, Evidence Assessment Group; EQ-5D-5L, EuroQol 5 Dimension 5 Level; EQ-5D-3L, EuroQol 5 Dimension 3 Level	

Table 1.7: Key Issue [6] – Uncertain OS predictions for T-DXd

Report section	4.2.6
Description of issue and why the EAG has identified it as important	Key Issue [6] links to Key Issue [1] Approximately 80% of patients were still alive at the first interim data cut point. As a result, the T-DXd OS predictions for use in the economic model are highly uncertain. This is exacerbated by the fact that approximately 50% of patients in the T-DXd arm were still progression-free at the interim cut off point of 21st May 2021. The company produced a partitioned-survival analysis model; and changing proportions of patients across states over time along with the associated changes in treatment increases the uncertainty in the hazard rate and implied hazard ratio extrapolations. The company base case model includes an implied hazard ratio of mortality from [redacted] to [redacted] across the first 10 years of the model. In scenario analysis, a constant hazard rate estimate of 0.55 was used over the course of the model. The OS prediction for T-DM1 was plausible given the clinical expert opinion on survival and the EMILIA trial data.
What alternative approach has the EAG suggested?	The impact of assuming no treatment effect or declining treatment effect of T-DXd after treatment cessation when they have experienced disease progression on the cost-effectiveness results could be investigated.
What is the expected effect on the cost effectiveness estimates?	The total QALYs and incremental QALYs associated with T-DXd are expected to reduce when assuming no treatment effect after disease progression.

What additional evidence or analyses might help to resolve this key issue?	The EAG has undertaken this analysis that explores the effect of these assumptions in the extrapolation of OS beyond 2 years on the cost-effectiveness results.
Abbreviations: EAG, Evidence Assessment Group; EQ-5D-5L, EuroQol 5 Dimension 5 Level; EQ-5D-3L, EuroQol 5 Dimension 3 Level	

Table 1.8: Key Issue [7] - Crosswalking EQ-5D-5L to EQ-5D-3L with the recommended algorithm

Report section	4.2.8
Description of issue and why the EAG has identified it as important	The methodology underpinning utility values was not in line with NICE methods and process guidance. The 2022 '*NICE Health Technology Evaluations: The Manual*' (PMG36) states the preferred method of crosswalking EQ-5D-5L to EQ-5D-3L is to use the algorithm developed by Hernández et al. (2017).[3]
What alternative approach has the EAG suggested?	The company could use the Hernández et al. (2017) algorithm rather than the Van Hout et al. (2012) algorithm to calculate the PFS utility values from the DESTINY-Breast03 trial. The same algorithm could then be used to calculate the HRQoL population norms in order to calculate the severity of the condition.
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	The company could adapt its base-case analysis to utilise the NICE recommended preferred crosswalk method.
Abbreviations: EAG, Evidence Assessment Group; EQ-5D-5L, EuroQol 5 Dimension 5 Level; EQ-5D-3L, EuroQol 5 Dimension 3 Level	

Table 1.9: Key issue [8] - Post-progression utility values

Report section	4.2.8
Description of issue and why the EAG has identified it as important	The company used treatment-specific utility values for the post-progression health states from the DESTINY-Breast03 trial. It is uncertain that the difference in utility values, accounting for uncertainty in the estimates, would be generalisable to the English setting. There does not appear to be evidence in Lloyd et al. (which was used as the source for PD utility estimates in the company's base case model) or in the CS for a difference in PD utility values across treatment groups.
What alternative approach has the EAG suggested?	A common utility value for both arms could be used, referred to as combined or pooled value in the submission.
What is the expected effect on the cost effectiveness estimates?	It is expected that the common utility value would increase the ICER of the company's base-case.

What additional evidence or analyses might help to resolve this key issue?	The combined value based on Lloyd et al. (2006) could be used for the base-case analysis. The EAG has adopted this approach in the EAG base case analysis. However, there is uncertainty in the applicability of the Lloyd et al. (2006) values too. In scenario analyses, other values from the literature can also be used.
Abbreviations: EAG, Evidence Assessment Group; ICER, incremental cost-effectiveness ratio	

1.6 Other key issues: summary of the EAG's view

There are no other key issues.

1.7 Summary of the EAG's view

The EAG base-case analysis includes the EAG preferred assumptions. The estimated ICER from the deterministic analysis is [redacted] per QALY gained for T-DXd compared to T-DM1. If the disease severity 1.2x QALY weighting is considered eligible, the ICER is [redacted]. The probabilistic analysis indicated cost-effectiveness probabilities of [redacted] and [redacted] at willingness-to-pay thresholds of £30,000 and £36,000 per QALY gained respectively. The £36,000 per QALY gained threshold is used in place of the £30,000 per QALY gained threshold if disease severity 1.2x QALY weighting is considered eligible. The most influential adjustments to the company base case analysis in ranked order were: 1) assuming no treatment effect or declining treatment effect for the progressed disease state, 2) equating the utility values in the progressed disease (PD) health state and 3) modifying vial-sharing assumption.

The EAG base-case probabilistic analysis results suggest that the 1.0x QALY weighting criteria are not met, and the EAG base-case deterministic analysis results suggest that the 1.2x QALY weighting criteria are met if the Van Hout algorithm HRQoL norms are used. The absolute shortfall in QALYs is very close to 12, so the eligibility for the 1.2x QALY weighting is very sensitive to the utility estimates, analysis method, and survival assumptions.

It should be noted that the EAG analyses are based on the company's use of a partitioned-survival model and immature PFS and OS data. As further data accrue from the DESTINY-Breast03 trial immature PFS and OS data will begin to be resolved. The baseline characteristics and treatment of trial participants in DESTINY-Breast03 after progression are not comparable to what would likely be seen amongst patients in an NHS setting. The impact of generalisability on effectiveness and the impact of increased TEAEs (including those associated with drug discontinuation and dose reduction) in the T-DXd arm relative to the T-DM1 arm on acceptability is unknown. Key uncertainties remain about the effectiveness and cost-effectiveness of T-DXd.

Table 1.10: Summary of EAG's preferred assumptions and ICER

Scenario	Incremental cost	Incremental QALYs (1.2x weighting)	ICER £/QALY, (1.2x weighting)
Company's base case after clarification	[redacted]	[redacted]	[redacted]
Company's base-case after clarifications and including EAG corrections	[redacted]	[redacted]	[redacted]

Scenario	Incremental cost	Incremental QALYs (1.2x weighting)	ICER £/QALY, (1.2x weighting)
Matters of Judgement 1: no treatment effect beyond progression (Key issue 6)	[redacted]	[redacted]	[redacted]
Matters of Judgement 2: a single combined utility for progressed disease health state (Key issue 5)	[redacted]	[redacted]	[redacted]
Matters of Judgement 3: assuming 90% wastage rate	[redacted]	[redacted]	[redacted]
EAG's preferred base-case deterministic	[redacted]	[redacted]	[redacted]
EAG's preferred base-case probabilistic	[redacted]	[redacted]	[redacted]
Abbreviations: EAG: Evidence Assessment Group; ICER: Incremental Cost-Effectiveness Ratio; QALY: Quality Adjusted Life Year			

2. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 2.1: 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	EAG Comment
Population	People with HER2-positive unresectable or metastatic breast cancer who have received trastuzumab and a taxane.	People with HER2-positive unresectable or metastatic breast cancer who have received trastuzumab and a taxane.	NA.	The population is in line with the NICE scope.
Intervention	Trastuzumab deruxtecan.	Trastuzumab deruxtecan.	NA.	The intervention is in line with the NICE scope.
Comparator(s)	Trastuzumab emtansine.	Trastuzumab emtansine.	NA.	The comparators are in line with the NICE scope.
Outcomes	The outcome measures to be considered include: • PFS • OS • RR (Response rate) • Duration of response (DoR) • Adverse effects of treatment • Health Related Quality of Life (HRQoL)	As per final scope issued by NICE. The outcome measures from DESTINY-Breast03 (the pivotal clinical trial) that is presented and included in the economic model are: • PFS by blinded independent central review (BICR) (primary endpoint) • OS • HRQoL measured via the EQ-5D-5L • RR as confirmed by BICR • Adverse effects of treatment In addition, data from the following key secondary endpoints from the DESTINY-	NA.	The outcomes reported are in line with the NICE scope.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG Comment
		Breast03 trial are also presented: **Key secondary endpoints:** • PFS as confirmed by Investigator Assessment (IA) • RR as confirmed by IA • Clinical benefit rate (CBR) as confirmed by BICR • DoR as confirmed by BICR • Time to response (TTR) • HRQoL measured by the EORTC QLQ-C30 and EORTC QLQ-BR45		
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. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any	As per final scope issued by NICE. A cost-utility analysis will be performed, with the key outcome being the ICER. A lifetime time horizon will be used. Costs will be considered from an NHS and PSS perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be considered	NA.	The economic analysis undertaken is in line with the elements of the reference case listed in the NICE scope. The only recommended method included in NICE 2022 (PMG36) guidance that was not used in the Company Submission (CS), but not explicitly mentioned in the NICE scope, was the use of the Hernandez et al. algorithm to conduct the EQ-5D crosswalk to calculate utility values.[3]

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG Comment
	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 considered.			

Source: Based on Table 1 and pages 11 to 12 of the CS[1]

Abbreviations: BICR, blinded independent central review; CBR, Clinical Benefit Rate; CS, company submission; EORTC QLQ, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L, EuroQol 5 Dimension 5 Level; EQ-5D-3L, EuroQol 5 Dimension 3 Level; HER2, human epidermal growth factor receptor 2; HRQoL, health-related quality of life; IA, investigator assessment; ICER, incremental cost-effectiveness ratio; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; OS, Overall survival; PFS, progression-free survival; PSS, Personal Social Services; RR, Response rate; QALY, quality-adjusted life year

2.1 Population

The population defined in the NICE scope is: Adults with HER2-positive unresectable or metastatic breast cancer after trastuzumab and a taxane.[2] The population outlined in the CS is in line with that specified in the final scope issued by NICE, *"trastuzumab deruxtecan (T-DXd) as a treatment for unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-positive breast cancer (BC) after trastuzumab and a taxane".*[1] This is in line with the clinical trial for T-DXd in this indication, the DESTINY-Breast03 trial, in which patients with HER2-positive unresectable or metastatic breast cancer were required to have experienced disease progression after receiving trastuzumab and a taxane (CS, Table 1, page 11).[1] The Phase II DESTINY-Breast01[4,5] trial enabled T-DXd to gain a recommendation from NICE for reimbursement at third line and beyond via the Cancer Drug Fund (CDF).[6]

According to NICE CG81,[7] HER2 status is reassessed on disease reoccurrence if a change in receptor status could lead to a change in the management of disease in second line treatment. During initial tissue screening in DESTINY-Breast03, the company stated, *"*[redacted]*"* (CS, page 38).[1]

EAG Comment:

The population in the CS is in line with the NICE scope.[2]

2.2 Intervention

The intervention defined in the NICE scope is T-DXd.[2] The intervention outlined within the CS is in line with this: T-DXd administered as an intravenous (IV) infusion at 5.4 mg/kg of body weight every 21 days, with patients being treated with T-DXd until disease progression or toxicity.

EAG Comment:

The intervention in the CS is in line with the NICE scope.[2]

2.3 Comparators

The description of the comparator detailed in the NICE Scope is T-DM1.[2] The comparator in the CS is in line with the NICE scope.[2] T-DM1 is the comparator for the whole population in the DESTINY BREAST-03 trial. T-DM1 is administered to patients as an intravenous (IV) infusion at 3.6 mg/kg of body weight every 21 days. Patients should receive treatment for a total of 14 cycles (early breast cancer), or until disease progression or unacceptable toxicity (early breast cancer and metastatic breast cancer). The infusion rate of T-DM1 should be slowed or interrupted if the patient develops infusion-related symptoms (including increased aspartate transferase (ASTs)/alanine transaminase (ALTs), thrombocytopenia, hyperbilirubinemia, left ventricle dysfunction or peripheral neuropathy), as outlined in the summary of product characteristics (SmPC).[8] T-DM1 should be discontinued in case of life-threatening infusion reactions.

EAG comment:

The comparator in the CS is in line with the NICE scope.[2]

2.4 Outcomes

The NICE final scope lists the following outcome measures:[2]

- PFS
- OS
- RR
- DoR
- Adverse effect of treatment
- HRQoL

These were all assessed in the DESTINY-Breast03 trial (CS, Table 5, page 34). In addition, the company also assessed TTR and hospitalisation.[1]

EAG comment:

The outcomes in the CS are in line with the NICE scope with additional relevant outcomes captured.[2]

2.5 Other relevant factors

In January 2021, T-DXd was granted a conditional European Market Authorisation as a monotherapy for the treatment of adult patients with metastatic or unresectable HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens.[6,9] T-DXd has subsequently been awarded the [redacted] as monotherapy for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received one or more prior anti-HER2-based regimens.[10]

In May 2022, the US Food and Drug Administration (FDA) approved T-DXd for adult patients with unresectable or metastatic HER2-positive breast cancer who have received a prior anti-HER2-based regimen either in the metastatic setting, or in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within 6 months of completing therapy.[11] In December 2019, T-DXd received accelerated approval for adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting.[12]

3. CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The CS describes a systematic literature review (SLR) of the clinical effectiveness and safety of T-DXd and T-DM1, as a treatment for unresectable or metastatic HER2 positive breast cancer (BC) after receiving one or more anti-HER2 therapy(s). The methods of the SLR are detailed in Appendix D of the CS. The CS details a global SLR which was undertaken initially, with an additional exclusion criterion applied to the included references (for intervention and line of therapy) to identify evidence that met the NICE scope.[2]

3.1.1 Searches

There was a lack of transparency in the search description presented in the CS (Appendix D.1.1) due to incomplete reporting of search strategies. The EAG were therefore, initially, not able to undertake a full critical appraisal of the searches performed for the SLR using the following tools and guidance: the PRESS checklist[13] and the latest NICE methods manual (NICE 2022, PMG36).[3] In response to the clarification letter, the company submitted full search strategies and other relevant information for each of the sources searched which the EAG critically appraised.

The company undertook a search of electronic bibliographic databases "for studies published prior to 20 August 2020" (date of search: 12-13 August 2020) and updated these searches on 23 August 2021 and on 27 September 2021. Websites of national reimbursement and health technology assessment organisations were searched (initial searches were conducted from 2-5 October 2020 and updated on 18 December 2021) and the reference lists of included studies and systematic reviews in the area were checked for additional studies. The company state that no limitations were imposed on the initial searches. Tables 3.1 and 3.2 below present a summary of the search-related information provided in the CS supplemented by information supplied by the company in the clarification letter in compliance with standard literature search reporting guidance.[14] The company stated that in March 2022 *post hoc* identification of all 4 reports of the one included intervention study were added to the SLR (see Table 3.3 for details). Updated searches for the comparator were not conducted after 27 September 2021.

The search approach taken was to search only for the 'population' ('P' of e.g., PICO) concept of the decision problem. This meant that the set of population terms needed to be very comprehensive in order to capture all potentially relevant records. The EAG is uncertain whether all potentially relevant studies will have been captured by the searches mainly due to clinical trials registers/platforms not being searched, the use of multiple search filters that are not reported as validated and the combination of the 'breast cancer'-related set of terms being combined with 'AND' with other sets of terms that would have narrowed rather than widened the search. Conference abstracts were hand-searched but then excluded during the screening process. The EAG have not verified whether these factors would have directly affected the retrieval of relevant studies. Presented below are the EAG's main comments regarding the searches.

Table 3.1: Resources searched for the clinical effectiveness 'SLR' ("for studies published prior to 20 August 2020")

Resource - category	Resource	Host source	Date Range	Date of search	Search strategy/string/ terms reported	N hits per line	Reported in PRISMA flowchart[a]
Electronic bibliographic databases	Embase	Embase.com	NR#	13.08.20	Yes	Yes[b]	Yes[a]
	MEDLINE	Embase.com	NR#	13.08.20	Yes		Reported as MEDLINE[a]
	MEDLINE (including In-Process)[c]	PubMed[c]	NR#	12.08.20	Yes	Yes	
	CDSR	Wiley.com	NR#	13.08.20	Yes	NR	Reported as Cochrane Library[a]
	CENTRAL	Wiley.com	NR#	13.08.20	Yes	NR	
Conference proceedings*	ASCO Annual Meeting	NR	2018-2020	NR	NR	NR	Abstracts excluded
	ASCO/SITC Clinical Immuno-Oncology Symposium	NR	2018-2020	NR	NR	NR	Abstracts excluded
	ASCO Quality Care Symposium	NR	2018-2020	NR	NR	NR	Abstracts excluded
	ESMO	NR	2018-2020	NR	NR	NR	Abstracts excluded
	EBCC	NR	2018-2020	NR	NR	NR	Abstracts excluded
	SABCS	NR	2018-2020	NR	NR	NR	Abstracts excluded
	JSCO Annual meetings	NR	2018-2020	NR	NR	NR	Abstracts excluded
	ISPOR Europe	NR	2018-2020	NR	NR	NR	Abstracts excluded
	ISPOR-FDA	NR	2018-2020	NR	NR	NR	Abstracts excluded
	ISPOR Asia Pacific	NR	2018-2020	NR	NR	NR	Abstracts excluded

	ISPOR Latin America	NR	2018-2020	NR	NR	NR	Abstracts excluded
	ISPOR Warsaw	NR	2018-2020	NR	NR	NR	Abstracts excluded
	ISPOR Dubai	NR	2018-2020	NR	NR	NR	Abstracts excluded
National reimbursement and HTA organisations websites~	Yes~	Yes~	2020	Yes~	Yes~	Yes~	NR
Other sources	Reference lists (included studies + additional studies)	NA	NA	NA	NA	NA	NR
	Reference lists (SLRs and MAs)	NA	NA	NA	NA	NA	NR

Source: Based on information presented in Appendix D, CS and responses to clarification questions.[1,10,15]

Footnote:

* Conference proceedings searched to 'capture the most recent unpublished or ongoing trials' (as reported in CS Appendix D pg.11), however abstracts were excluded at a later stage in the PRISMA flow diagram, (Appendix D, figure 1, page 17)[15]

Not reported in the original CS but in responses to clarification questions "all dates" (in Responses to PfC questions)[10]

~ Full list provided – see responses to clarification questions A7, pages 19-20[10]

a Reported for all search dates combined (original searches and search updates)

b Combined result presented

c Originally reported in CS as MEDLINE In-Process via 'Pubmed.com' in responses to clarification questions it was stated that no limitations were imposed on the searches which were actually undertaken in PubMed via NLM was searched.[1,10,15]

Abbreviations: AACR = American Association for Cancer Research; ASCO = American Society of Clinical Oncology; CDSR = Cochrane Database of Systematic Reviews; CENTRAL = Cochrane Central Register of Controlled Clinical Trials; EBCC = European Breast Cancer Conference; ESMO = European Society for Medical Oncology; HTA = health technology assessment; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; JSCO = Japan Society of Clinical Oncology; N = number; NA = not applicable; NR = not reported; PfC = points for clarification; SABCS = San Antonio Breast Cancer Symposium; SITC = Society for Immunotherapy of Cancer

Table 3.2: Resources searched for the clinical effectiveness 'SLR' (for updated search "from 21 August 2020 to 27 September 2021")

Resource - category	Resource	Host source	Date range	Date of search#	Search strategy/string/ terms reported	N hits per line	Reported in PRISMA flowchart[a]
Electronic bibliographic databases	Embase	Embase.com	NR	23.08.21 27.09.21	NR Yes	NR Yes	Yes [a]
	MEDLINE	Embase.com	NR	23.08.21 27.09.21	NR Yes	NR Yes	Reported as MEDLINE[a]
	MEDLINE (including In-Process)[c]	PubMed[c]	NR	23.08.21 27.09.21	NR Yes	NR	
	CDSR	Wiley.com	NR	23.08.21 27.09.21[d]	NR	NR	Reported as Cochrane Library[a]
	CENTRAL	Wiley.com	NR	23.08.21 27.09.21 [d]	NR	NR	
Conference proceedings*	ASCO 2021 Annual Meeting	NR	2021	13.09.21	NR	NR	Abstracts excluded
	ASCO/SITC Clinical Immuno-Oncology Symposium	NR	NR	NR	NR	NR	Abstracts excluded
	ASCO Quality Care Symposium	NR	NR	NR	NR	NR	Abstracts excluded
	ESMO 2020 ESMO May 2021 ESMO Sept 2021	NR	2021 2021 2021	04.10.21 16.09.21 01.10.21	NR	NR	Abstracts excluded
	EBCC 2020	NR	2020	17.09.21	NR	NR	Abstracts excluded
	SABCS 2020	NR	2020	22.09.21	NR	NR	Abstracts excluded
	JSCO 2020 Annual meetings	NR	2020	15.09.21	NR	NR	Abstracts excluded
	ISPOR Europe 2020	NR	2020`	20.09.21	NR	NR	Abstracts excluded

	ISPOR-FDA 2021	NR	2021	17.09.21	NR	NR	Abstracts excluded
	ISPOR Asia Pacific	NR	NR	NR	NR	NR	Abstracts excluded
	ISPOR Latin America	NR	NR	NR	NR	NR	Abstracts excluded
	ISPOR Warsaw	NR	NR	NR	NR	NR	Abstracts excluded
	ISPOR Dubai	NR	NR	NR	NR	NR	Abstracts excluded
National reimbursement and HTA organisations	Yes~	Yes~	2021	Yes~	Yes~	Yes~	NR
Other sources	Reference lists (inc. studies + additional studies)	NA	NA	NA	NA	NA	NR
	Reference lists (SLRs and MAs)	NA	NA	NA	NA	NA	NR

Source: Based on information presented in Appendix D, CS and responses to clarification questions.[1,10,15]

Footnote:

* Conference proceedings searched to 'capture the most recent unpublished or ongoing trials' (as reported in CS Appendix D pg.11), all excluded at later stage in PRISMA flow diagram, Appendix D, figure 1, page 17)[15]

Not reported in the original CS but in responses to clarification questions the company reported that 2 update searches of the electronic bibliographic databases were performed – on 23 August 2021 and on 27 September 2021 (in Responses to PfC questions)[10]

~ Full list provided – see responses to clarification questions A7, pages 19-21[10]

a Reported for all search dates combined (original searches and search updates)

b Combined result presented

c Originally reported in CS as MEDLINE In-Process via 'Pubmed.com' in responses to clarification questions it was stated that no limitations were imposed on the searches which were actually undertaken in PubMed via NLM was searched[1,10,15]

d although Table 5, responses to clarification questions gives a date of 28 September 2021[10]

Abbreviations: AACR = American Association for Cancer Research; ASCO = American Society of Clinical Oncology; CDSR = Cochrane Database of Systematic Reviews; CENTRAL = Cochrane Central Register of Controlled Clinical Trials; EBCC = European Breast Cancer Conference; ESMO = European Society for Medical Oncology; HTA = health technology assessment; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; JSCO = Japan Society of Clinical Oncology; NA = not applicable; NR = not reported; PfC = points for clarification; SABCS = San Antonio Breast Cancer Symposium; SITC = Society for Immunotherapy of Cancer

Table 3.3: 'Additional hand searching' and other targeted (post hoc, i.e. conducted after the systematic searching was completed) acquisition of reports of studies for the intervention T-DXd only - for the clinical effectiveness 'SLR' to identify the 4 reports of the one included study for the intervention

Resource - category	Resource	Host source	Date Range	Date of search	Search strategy/string/ terms reported	N hits per line	Reported in PRISMA flowchart
Conference proceedings#	SABCS 2021#	www.sabcs.org/2021-SABCS #	2021#	14.03.22 (approx)#	Yes#	NR	Yes
	ESMO 2021	www.esmo.org/meetings/past-meetings/esmo-congress-2021 #	2021#	14.03.22 (approx)#	Yes#	NR	Yes
Company's primary publication for their DESTINY-Breast03 study[16]	NA	NA	NA	24.03.22	NA	NA	Yes
Clinical Study Report (provided by the company)[17]	NA	NA	NA	NR	NA	NA	Yes

Source: Based on information presented in Appendix D, CS and responses to clarification questions.[1,10,15]
Footnote:
Full details of the post hoc retrieval of the 4 reports of the one included study for the intervention were not reported in the original CS however in responses to clarification questions the company reported these details in their response to question A8 (pages 21-2)[1,10]
Abbreviations: ESMO = European Society for Medical Oncology; NA = not applicable; NR = not reported; PfC = points for clarification; SABCS = San Antonio Breast Cancer Symposium

EAG comment:

The flow of studies in the SLR seems to be appropriate. The CS describes the search strategy used in Appendix D1.1.[15] Several specific issues with the company search strategy are noted and presented in Appendix 1. A full breakdown of the numbers of search hits provided by each database was provided in response to the clarification letter (Question A17.[10] Whilst search methods and reporting of the SLR were of variable quality, the studies the SLR identified are likely to be those relevant. Of the 24 publications identified, only those related to DESTINY-Breast03 provide evidence comparing T-DXd versus the NICE approved standard of care, T-DM1. The EAG acknowledges that the company, as the developer of T-DXd are likely aware of, and have reported, all relevant studies related to T-DXd.

The EAG know of one other head-to-head comparison between T-DXd and T-DM1 in participants with high-risk HER2-positive primary BC who have residual invasive disease in breast or axillary lymph nodes following neoadjuvant therapy (DESTINY-Breast05).[18] However, this trial is still in recruitment and its population is different to the NICE scope.[2]

3.1.2 Inclusion criteria

The full inclusion and exclusion criteria for the global SLR and the narrowed NICE scope SLR are detailed in Tables 4 and 5 of the CS Appendices respectively.[2,15] Studies were limited to those reported in English language only. There were no other limitations set upon the studies included. Following best practice as outlined by Cochrane,[19] two reviewers independently performed title and abstract screening (Level 1), and full text screening (Level 2) using the inclusion criteria stated below in Table 3.4. Any uncertainty or disagreements were resolved by a third independent reviewer.

Table 3.4: Eligibility criteria used in search strategy for RCT and non-RCT evidence

	Description	Justification
Inclusion criteria		
Population	Adult (age ≥18 years) HER2-positive uBC and/or mBC patients who had 1 prior systemic treatment in the metastatic setting or have progressed within 6 months after receipt of neoadjuvant or adjuvant treatment involving a regimen including trastuzumab and a taxane.	Patients with HER2-positive unresectable or metastatic breast cancer had received prior systemic therapy or progressed after trastuzumab and a taxane treatment as specified in the NICE scope.
Interventions	Studies assessing at least one of the below mentioned interventions as monotherapy and/or combination therapy were included: • TDX-d • TDM-1	Consistent with final scope.
Outcomes	• PFS • Event-free survival • Disease-free survival • OS • TTR • DoR • Time to progression • Time on treatment (ToT) • Objective response rate (ORR) • Best overall response (complete response (CR), partial response (PR), stable disease (SD), PD, CBR) • AEs • HRQoL	Consistent with final scope.

	Description	Justification
Study design	• Randomised control trails (RCTs) – both parallel-group and crossover (double-blind, single-blind, open-label) • Non-Randomised comparative studies • Retrospective and prospective cohort studies • Single-arm trials • Real-world evidence studies	Separate searches were conducted for RCTs and non-RCTs.
Language restrictions	English language only.	Reduced sensitivity of the search but pragmatically lowered the number of records identified.
Exclusion criteria		
Population	• Healthy volunteers • Patients <18 years • Diseases other than unresectable and/or metastatic HER2-positive breast cancer • Patients with HER2-negative breast cancer • Non-invasive or Stage 0 breast cancer	Excludes populations not relevant to final NICE scope.
Interventions	Any interventions not listed as included.	Excludes studies of interventions not relevant to final NICE scope.
Outcomes	Studies that do not report at least one of the outcomes of interest.	Excludes studies of outcomes not relevant to final NICE scope.
Study design	• In vitro studies • Preclinical studies • Reviews, comments, letters, and editorials • Case reports, case series • Dose-escalation studies	Separate searches were conducted for RCTs and non-RCTs.
Language restrictions	Publications with abstracts published in non-English language.	To reduce number of hits and to identify studies in patient populations relevant to the United Kingdom (UK) setting.

	Description	Justification
Source: Table 5 of the CS Appendices[15] Abbreviations: AEs = adverse events; BOR = best overall response; CBR = clinical benefit rate; CR = complete response; DoR = duration of response; HER2, human epidermal growth factor receptor 2; mBC = metastatic breast cancer; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; QoL = quality of life; RCT = randomized clinical trial; RR = response rate; SD = stable disease; ToT = time on treatment; TTR = time to response; uBC = unresectable breast cancer.		

EAG Comment: The additional inclusion criteria applied to the global SLR ensured relevance to the NICE scope.[2] The EAG considers this appropriate. Whilst there were some errors in original reporting, clarification was provided by the company detailing the flow of studies outlined in a PRISMA flow chart. Language restrictions mean that the risk of missing relevant non-English language studies cannot be excluded.[20] However, the EAG acknowledge these limitations are unlikely to have a major impact on the SLR findings and company submission.[1]

3.1.3 Critique of data extraction

The CS stated *"data from eligible studies were extracted and assessed for methodological quality and applicability."*[1] The company did not provide detailed information on their method of data extraction, and the EAG asked for further clarification. In response to the clarification letter (Question A18), the company detailed that for the global review (which was subsequently modified for relevance to the NICE scope),[2] data was extracted by one reviewer and independently checked by a second reviewer with any disagreements resolved between the two reviewers.

After applying additional inclusion criteria relevant to the NICE scope only reports of the DESTINY-Breast03 trial which provides a direct comparison of the intervention T-DXd and the comparator of interest T-DM1 were relevant.[2] The company have direct access to this trial data as the sponsors of the DESTINY-Breast03 trial.

EAG Comment: Methods of 'data extraction' employed for the SLR relevant to the NICE scope are unlikely to impact on the validity of SLR findings and company submission.[1,2] The EAG finds this approach acceptable.

3.1.4 Quality assessment

The company conducted quality assessment using the NICE '*Single technology appraisal and highly specialised technologies evaluation: User guide for company evidence submission template'*.[21] Each assessment made was appropriately linked to a supporting statement.

EAG Comment: The quality assessment tool used by the company and implementation of assessments were considered appropriate by the EAG. A more detailed appraisal of the quality of the DESTINY-Breast03 trial evidence is presented in Section 3.2.1 below.

3.1.5 Evidence synthesis

One hundred and eighty-three publications were identified in the global review. Following the application of the additional exclusion criteria relevant to the NICE scope, 24 publications were identified in total.[2] Twenty publications were identified that reported data on T-DM1 (the current standard of care as a second-line therapy in the population under consideration). Four publications were identified which reported data from a single trial, the DESTINY-Breast03 trial which compared efficacy and safety for T-DXd and T-DM1.[15] As such, no synthesis of evidence was undertaken.

EAG Comment: The flow of studies in the SLR and resultant lack of synthesis seem appropriate. The response to the clarification letter, gave detail on flow of studies through the SLR, the final number of studies identified and the synthesis.[15]

Although the description of methods and reporting of the SLR were of variable quality, the EAG considers these methodological limitations of minimal concern owing to the direct comparison of T-DXd and T-DM1 provided by the DESTINY-Breast03 trial.

3.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

The company identified one RCT for T-DXd for which published data was available, DESTINY-Breast03. This phase III trial compared the efficacy and safety of T-DXd with T-DM1 in patients with HER2-positive, unresectable and/or metastatic breast cancer (u/mBC) previously treated with trastuzumab and a taxane.

3.2.1 DESTINY-Breast03 design and quality assessment

The evidence for the effectiveness of T-DXd against T-DM1 came from the DESTINY-Breast03 (NCT03529110) study.[22] This is a phase III, ongoing, parallel-arm, open label study in 524 adults with HER2-positive, u/mBC patients previously treated with trastuzumab and a taxane. T-DXd and T-DM1 were administered as a sterile intravenous solution at a dose of 5.4 mg/kg or 3.6 mg/kg every 3 weeks respectively until progression of the disease or unacceptable toxicity. The study was conducted in 169 centres from 15 countries worldwide. Ten centres were included from the UK (8 from England), from which [redacted] patients were enrolled. A summary of the methodology of the trial is shown in Table 3.5.

Table 3.5: DESTINY-Breast03 design

Category of design	Details
Trial design	Phase III, multicentre, open-label, randomised, active-controlled trial. International study with parallel assignment.
Population	Patients were adults with HER2+ u/mBC, previously treated with trastuzumab and a taxane in the advanced/metastatic setting or that had progressed within 6 months after neoadjuvant or adjuvant treatment with trastuzumab and a taxane.
Intervention(s)	Intervention: T-DXd (n=261) was administered at a starting dose of 5.4 mg/kg (based on patient weight at screening), as IV infusion over 90 minutes for the first infusion. Subsequent doses were infused over a minimum of 30 minutes** every 21 days ([redacted]). Dosage was [redacted] weight value.
Comparator(s)	Comparator: T-DM1 (n=263) was administered at a starting dose of 3.6 mg/kg (based on patient weight at screening), as IV infusion over 90 minutes for the first infusion. Subsequent doses were infused over a minimum of 30 minutes** every 21 days ([redacted]). Dosage was [redacted] weight value.
Location	DESTINY-Breast03 was an international, multicentre trial conducted in 169 centres across 15 countries: Europe (UK, France, Spain, Belgium, Italy, Germany), North America (US, Canada), Asia (Japan, Republic of Korea, China, Taiwan, Hong Kong), and other regions (Australia, Brazil). Ten centres were included from the UK (8 from England), with [redacted] patients enrolled.
Duration of study	Planned duration: approximately [redacted] months (at observation of approximately [redacted] OS events). Median duration at follow-up (Data cut off (DCO) May 2021): Overall: 15.9 months (range [redacted]) T-DXd arm: 16.2 (range: 0.0–32.7)

	T-DM1 arm: 15.3 (range: 0.0–31.3)
Method of randomisation	1:1 by Interactive Web/Voice Response System (IXRS) and stratified by hormone receptor status (+/−), prior pertuzumab (yes/no), and history of visceral disease (yes/no).
Methods of blinding	This was an open label study for individual participants and treating physicians. To maintain the study integrity, the XXXXX [redacted]
Primary endpoints (including scoring methods and timings of assessments)	The primary effectiveness measure was PFS by BICR (analysis set was full analysis set (FAS)). Time Frame: Up to 33 months (DCO) End of treatment assessments were to occur [redacted]
Secondary endpoints (including scoring methods and timings of assessments)	PFS (IA) Time Frame: Up to 33 months (DCO) OS (IA) Time Frame: Up to 33 months (DCO) TTR HRQoL assessed by EORTC QLQ-C30, EORTC QLQ-BR45, EQ-5D-5L HRQoL questionnaires were to be completed by patients [redacted] of [redacted] and then [redacted] until the end of treatment assessments. The first follow up assessment was at day 40 (+7 days). The first and only long-term HRQoL follow-up assessment was conducted three months later.

Source: Modified from Table 6 of the CS,[1] ClinicalTrials.gov[22]

Abbreviations: BC, breast cancer; BICR, blinded independent central review; DCO, Data cut off; EORTC QLQ, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L, EuroQol 5 Dimension 5 Level; HER2, human epidermal growth factor receptor 2; FAS, full analysis set; HRQoL, Health-related quality of life; IA, investigator assessment; IV, intravenous; IXRS, Interactive Web/Voice Response System; OS, overall survival; PFS, Progression free survival; TTR, time to response; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; u/mBC, unresectable and/or metastatic breast cancer.

Quality assessment of DESTINY-Breast03 was presented in Table 11 of the company submission.[1] It was unclear how 'concealment of treatment allocation' was interpreted in the company submission.[1] In response to the clarification letter (Question C5)[10], the company confirmed that allocation to study arms utilised interactive response technology (IXRS), so the question asking whether the concealment of treatment allocation was adequate should read 'yes'. The EAG finds this response acceptable.

EAG comment: The EAG agreed the DESTINY-Breast03 study was useful for decision-making. The trial was randomised, had an adequate sample size, and evaluated the intervention and comparator in the NICE scope.[2] Ten centres were from the UK, and in total [redacted] patients were enrolled from UK centres. Further discussion on the generalisability of the DESTINY-Breast03 trial population to clinical practice in England is provided in Section 3.2.3. There is some concern regarding risk of bias due to the open label trial design. It is unclear whether knowledge of the intervention may have affected treatment. However, PFS and overall response were assessed by BICR, which reduces risk of bias for these outcomes. Lack of blinding for objective outcomes, such as OS were of less concern, as knowledge of intervention status was unlikely to bias these data.

3.2.2 Statistical approach adopted for the analysis of DESTINY-Breast03 study data

Information about the statistical approach taken by the company is reported within the Clinical Study Report (CSR), the statistical analysis plan (SAP), the study protocol and the CS.[1,23-25] A summary of the statistical analyses undertaken for DESTINY-Breast03 is described in Table 9 of the CS.[1]

The company took a sequential approach to analyses, setting out *a priori* thresholds for conducting interim (PFS [redacted] events; interim analysis of OS conducted if the analysis of PFS was statistically significant) and full analyses of PFS and OS. Interim PFS by BICR analysis was to be conducted at [redacted] PFS events, with final P08FS analysis conducted at [redacted] PFS events.[1] The first interim analysis of OS was to be conducted if PFS was statistically significant. Final OS analysis will be conducted at [redacted] OS events if any PFS analysis was significant and OS analysis not significant at either previous OS analysis.[1]

The company set *a priori* stopping boundaries (Haybittle-Peto approach) for interim analyses to control for multiple testing. This involved setting more stringent thresholds of statistical significance for interim analyses (for PFS: p=[redacted]; first OS interim analysis: p=[redacted] if [redacted] OS events occurred; second interim analysis: p=[redacted]) (B.2.4.2 CS).[1]

EAG comment: The statistical approaches used in the analysis of study data were considered appropriate by the EAG. With Haybittle-Peto boundaries an appropriately conservative approach to adjusting for multiple testing.

3.2.3 DESTINY-Breast03 eligibility criteria and baseline characteristics including treatments received

A summary of the DESTINY-Breast03 baseline characteristics and eligibility criteria are detailed in Table 3.6 and **Error! Reference source not found.** The majority of patients were females (99.6%) and the median age of the population was [redacted] years ([redacted]). Most patients were from Asia: 57.1% in the T-DXd arm and 60.8% in the T-DM1 arm of the study. One hundred and four patients in the trial were from Europe (T-DXd arm, n=54/261, 20.7%; T-DM1, n=50/263, 19.0%). Baseline characteristics of the European subpopulation are provided in **Error! Reference source not found.**. In response to the clarification letter (Question A21), the company reported that [redacted] patients in DESTINY-Breast03 were from the UK.[10] The baseline characteristics of the UK population were not provided [redacted]

There are noticeable differences between the full trial population and the European subpopulation. Firstly, as expected, there is a considerably greater proportion of 'white' ethnicity amongst the European subpopulation, [redacted]% and [redacted]% in the T-DXd and T-DM1 arms respectively. The population defined as 'other' for their ethnicity is also a particularly large proportion of the European subpopulation, accounting for [redacted]% in the T-DXd arm and [redacted]% in the T-DM1 arm. Secondly, there are also more smokers in the European subpopulation, which more closely represents practice in England. However, trial arms are somewhat unbalanced (current smokers account for [redacted]% of patients in the T-DXd arm and [redacted]% in the T-DM1 arm).

Table 3.6: Key eligibility criteria for DESTINY-BREAST03

Inclusion	Exclusion
[redacted]	Prior treatment with an anti-HER2 antibody-drug conjugate (ADC) in the metastatic setting.†
Pathologically documented BC that: • was unresectable or metastatic • had central-laboratory confirmed HER2-positive expression* • was previously treated with trastuzumab and taxane in the advanced/metastatic setting or progressed within 6 months after (neo)adjuvant treatment involving a regimen including trastuzumab and taxane	[redacted]
[redacted]	History of (non-infectious) interstitial lung disease (ILD)/pneumonitis requiring steroids, current diagnosed or suspected ILD/pneumonitis, or clinically severe pulmonary compromise resulting from intercurrent pulmonary illnesses.
[redacted]	Spinal cord compression or clinically active CNS metastases defined as untreated, symptomatic, or requiring therapy with corticosteroids or anticonvulsants to control associated symptoms.‡
[redacted]	[redacted]
[redacted]	[redacted]
	[redacted]
	[redacted]
	[redacted]
	[redacted]

Source: Table 6 of the CS[1]

*According to American Society of Clinical Oncology/College of American Pathologists guidelines.

[redacted]

Abbreviations: ADC, antibody-drug conjugate; BC, breast cancer; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; HIV, human immunodeficiency virus; ILD, interstitial lung disease; IV, intravenous; mAb, monoclonal antibody; RECIST, Response Evaluation Criteria in Solid Tumours

Table 3.7: Baseline characteristics of the DESTINY-Breast03 trial, and European population

Characteristic	**All population**		**European sub-population FAS**	
	T-DXd (n=261)	T-DM1 (n=263)	T-DXd (n=[redacted])	T-DM1 (n=[redacted])
Age, years				
Mean (standard deviation)	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	54.3 (27.9–83.1)	54.2 (20.2–83.0)	[redacted]	[redacted]
Female, %	99.6	99.6	[redacted]	[redacted]
Region, n (%)				
Europe	54 (20.7)	50 (19.0)	[redacted]	[redacted]
Asia	149 (57.1)	160 (60.8)		
North America	17 (6.5)	17 (6.5)		
Rest of world	41 (15.7)	36 (13.7)		
Race, n (%)				
Asian	152 (58.2)	162 (61.6)	[redacted]	[redacted]
White	71 (27.2)	72 (27.4)	[redacted]	[redacted]
Black or African American	10 (3.8)	9 (3.4)		
Multiple	2 (0.8)	0		
Other	26 (10.0)	20 (7.6)	[redacted]	[redacted]
Smoking status, n (%)				
Never	[redacted]	[redacted]	[redacted]	[redacted]
Former	[redacted]	[redacted]	[redacted]	[redacted]
Current	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]
Hormone receptor, n (%)				
Positive	131 (50.2)	134 (51.0)	[redacted]	[redacted]
Negative	130 (49.8)	129 (49.0)	[redacted]	[redacted]

Median number of lines (range)	1 (0–16)	2 (0–14)		
Prior lines of therapy in the metastatic setting†, n (%)				
0	2 (0.8)	3 (1.1)	[redacted]	[redacted]
1	130 (49.8)	123 (46.8)	[redacted]	[redacted]
2	56 (21.5)	65 (24.7)	[redacted]	[redacted]
3	35 (13.4)	35 (13.3)	[redacted]	[redacted]
4	15 (5.7)	19 (7.2)	[redacted]	[redacted]
≥5	23 (8.8)	18 (6.8)	[redacted]	[redacted]
Prior cancer therapy‡, n (%)				
Trastuzumab	260 (99.6)	262 (99.6)	[redacted]	[redacted]
Pertuzumab	162 (62.1)	158 (60.1)	[redacted]	[redacted]
Taxane	260 (99.6)	262 (99.6)	[redacted]	[redacted]

Source: Table 10, CS and CSR[1,17]

†Includes rapid progressors (rapid progressors defined as progression within 6 months of (neo)adjuvant therapy or 12 months if regimen contained pertuzumab) as one line of treatment. Line of therapy does not include endocrine therapy.

‡All patients received at least one prior cancer therapy; prior cancer therapy was not recorded for two patients randomised in error and not treated.

Abbreviations: FAS, full analysis set; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

In the current treatment pathway, people with HER2+ u/mBC in England can receive one of two HER2-targeted first line regimens (TA509 and TA34)[26,27,28] or gemcitabine and paclitaxel chemotherapy (TA116).[28] Additionally, endocrine therapy may be administered to patients who are also hormone receptor-positive (CG81).[7] As a second-line treatment, current standard of care guidance recommends T-DM1 for patients with HER2+ BC after trastuzumab and a taxane (TA458).[29] In total, [redacted] patients ([redacted] patients in the T-DXd arm and [redacted] patients in the T-DM1 arm) had either of these NICE-recommended first-line regimens prior to their trial treatment, and [redacted] patients ([redacted]%) in each arm had both regimens as prior treatment.[1,10] In response to the clarification letter (Question A25), the company detailed that pertuzumab plus trastuzumab and docetaxel was a prior regimen in [redacted] patients ([redacted]%) in the T-DXd arm and [redacted] patients ([redacted]%) in the T-DM1 arm. Prior trastuzumab and paclitaxel was a prior regimen in [redacted] patients ([redacted]%) and [redacted] patients ([redacted]%), respectively.

All patients in DESTINY-Breast03 were required to have previously received trastuzumab and a taxane. However, the number of patients who have had >2 lines of prior therapy in the metastatic setting is lower in the European subpopulation (which is more indicative of clinical practice in England) compared with all participants in DESTINY-Breast03. In response to the clarification letter (Question A25), approximately [redacted] of patients ([redacted]% in the TDXd arm and [redacted]% in the TDM1 arm) had either of the NICE-recommended first-line regimens prior to their trial treatment.[10]

Fewer European participants have had >2 lines of prior therapy in the metastatic setting. In the full DESTINY-Breast03 population, 49.2% of patients had 0-1 line of prior therapy in the metastatic setting, compared to [redacted]% in the European subpopulation. In addition to receiving two lines of anti-HER2

therapy that are recommended by NICE, [redacted] and [redacted] patients in the T-DXd and T-DM1 arms respectively received an anti-HER2 tyrosine kinase inhibitor (TKI) therapy which is not currently recommended by NICE.[1] In response to the clarification letter (Question A26),[10] the company confirmed these included [redacted]

A high percentage of patients in DESTINY-Breast03 received subsequent treatment, reported in Question A29 of the clarification letter[10] and Section 3.2.4.2 detailed below.

Lastly, the inclusion criteria of DESTINY-Breast03 excluded some patients who are likely to receive treatment in English clinical practice. Clinical advice to the EAG indicated that:

- only uncontrolled/not treated spinal cord compression or clinically active central nervous system (CNS) metastases would be a contraindication
- prior treatment with an anti-HER2 ADC in the metastatic setting would be permitted. However, this patient population is included in NICE TA704 (trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after 2 or more anti-HER2 therapies)[6]
- multiple primary malignancies within three years and unresolved non-alopecia toxicities from prior anti-cancer therapy would be considered a contraindication

The trial population likely had fewer and less severe contraindications than those who will receive T-DXd in NHS care.

EAG Comment:

Clinical advice to the EAG suggested differences exist between those excluded from the study and those eligible for second line therapy in England for HER2+ unresectable or metastatic breast cancer. In addition, the age of the patients included in DESTINY-Breast03 are similar to patients treated in clinical practice within England. However, there are important differences between the DESTINY-Breast03 population and those typically seen in an NHS setting. The number of female smokers also differs; clinical advice to the EAG suggests the number of female smokers is likely higher in England. Data for 2020 from the Office for National Statistics suggests 13.4% of women (aged over 16 years) smoke, however rates are higher for those women aged 35-49 years (15.5%) and those 50-59 years (15.6%).[30] The number of Asian patients in DESTINY-Breast03 (59.9%) is considerably higher than typically seen in clinical practice within England although there is no evidence that the targeted treatment would behave differently in such populations. However, the EAG are aware of known differences between Asian and Caucasian populations in terms of side effects and toxicities[31,32] which may impact the applicability of the AEs detailed in the CS.[1] Subgroup analysis suggests there could be a difference in findings although this is not implausibly due to chance.

[redacted] patients enrolled in DESTINY-Breast03 were drawn from the UK.[10] The CS states, "*clinical experts have confirmed that the patient population and study design is generalisable to UK clinical practice*".[1] The company have not provided specific baseline characteristics of UK participants, although European baseline characteristics have been provided (**Error! Reference source not found.**) which are likely to be more generalisable to an English clinical setting. However, the sample size for this subgroup is small so findings derived from this subgroup are impacted by high uncertainty. Therefore, the EAG have difficultly assessing the generalisability of the DESTINY-Breast03 trial within the context of clinical practice in England.

Overall, it is possible after further trial follow-up, rates of subsequent treatment in the trial may be higher than the 66.7% of patients who are likely to be eligible for subsequent therapy in UK clinical practice after second-line treatment, as indicated to the company by clinical experts.[1] Also, the subsequent treatments received by those in DESTINY-Breast03 were not wholly reflective of the subsequent therapies that would be used in English clinical practice after second-line treatment. The EAG considers that the subsequent therapy the European subgroup in DESTINY-Breast03 receive is likely to be more reflective of the subsequent treatments used in an English clinical setting. However, as stated, the sample size for this subgroup is not large and derived findings are impacted by high uncertainty. Clinical expert opinion to the company was used to identify percentages of patients receiving subsequent treatment and the distribution of subsequent treatments in the company base case economic model. This might affect the cost estimate of subsequent treatment. Differences in subsequent treatment may affect the generalisability of overall survival estimates to English clinical practice.

3.2.4 DESTINY-Breast03 efficacy

The evidence presented by the company is derived from the DESTINY-Breast03 trial using the first PFS interim analysis (DCO 21 of May 2021). The final analyses for PFS and OS have yet to reach maturity using the pre-specified number of events; final PFS analysis is planned at [redacted] PFS events, and the first interim OS was to be conducted if PFS is statistically significant.[1] Final OS analysis will be undertaken at [redacted] OS events.[1] In response to the clarification letter (Question A22), the company anticipates this is likely to be in [redacted], although there is some uncertainty surrounding this as timings are event-driven.[10]

Results for PFS (by BICR), OS, HRQoL (measured via the EQ-5D-5L), RR (by BICR) and adverse effects of treatment are presented in this Section. In addition, the company provided other secondary endpoints: PFS (by IA), RR (by IA), [redacted], DoR (by BICR), TTR and HRQoL (EORTC QLQ-C30 and EORTC QLQ-BR45). Results are presented from the interim analysis (DCO, 21 May 2021) with a median follow-up of 16.2 months (range: 0–32.7) in the T-DXd arm (n=261) and 15.3 months (range: 0–31.3) in the T-DM1 arm (n=263). By this time point, the trial had achieved statistical significance of the primary endpoint of PFS by BICR in the T-DXd arm compared with T-DM1 (Hazard ratio (HR): 0.28; p<0.001). Efficacy results are presented for the full analysis set (following the intention-to-treat (ITT) principle).

At the planned interim analysis, DESTINY-Breast03 was unblinded early as it met the primary endpoint of statistically significant PFS benefit by BICR.[1] However, the trial was an open label study, so moving forward this only concerns the outcome data assessed by BICR and the sponsor's unblinding to the aggregate data by treatment arm and the running of efficacy analysis and access to summary data. The EAG finds this approach acceptable.

No subgroup analyses were specified in the final scope issued by NICE.[2] Analyses of PFS for prespecified subgroups is described in section 8.2.1.5 of the CSR, and shown in Figure 3.1.[17] The company reports findings from the following pre-specified DESTINY-Breast03 study subgroups:

- hormone receptor status;
- oestrogen receptor (ER) status;
- progesterone receptor (P4R) status;
- prior pertuzumab treatment;
- lines of prior systemic therapy (not hormone therapy);

- lines of therapy prior to pertuzumab;
- baseline renal impairment;
- baseline hepatic impairment;
- baseline visceral disease;
- baseline lung metastases;
- baseline liver metastases;
- baseline CNS metastases;
- history of CNS metastases;
- age;
- race;
- region;
- eastern cooperative oncology group (ECOG) performance status.[1]

Figure 3.1: Forest plot of treatment comparison for PFS by BICR, by subgroup (FAS)

a. Subgroup analysis by: hormone receptor status; ER; PR; prior treatment with pertuzumab; and lines of prior systematic therapy not including hormone therapy

(Source: Figure 8.3, CSR[17])
(Abbreviations: BICR, blinded independent central review; CI = confidence interval; ER, estrogen receptors; FAS, full analysis set; Lns. Of Pr. Sys. Thpy. Not Inc. Horm. Thpy. = Lines of prior systemic therapy not including hormone therapy NE = not estimable; PR; progesterone receptors; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan)

b. Subgroup analysis by: lines of therapy prior to pertuzumab; renal impairment at baseline; hepatic impairment; baseline visceral disease; and history of CNS metastases

(Source: Figure 8.3, CSR[17])
(Abbreviations: BICR, blinded independent central review; CI, confidence interval; CNS, central nervous system; FAS, full analysis set; Lns. Of Pr. Thpy. Pr. To Pet. Trt., lines of therapy prior to pertuzumab; NE = not estimable; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan)

c. Baseline of CNS metastases, age, race, region, ECOG Performance Status

(Source: Figure 8.3, CSR[17])
(Abbreviations: BICR, blinded independent central review; CI = confidence interval; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FAS, full analysis set; NE, not estimable; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan)

3.2.4.1 PFS

The primary endpoint of the DESTINY-Breast03 study was PFS by BICR. PFS was defined as *"the time from the date of enrolment to the earlier of the dates of the first objective documentation of disease progression (as per RECIST v1.1) or death due to any cause. Progressive disease was defined as at least a 20% increase in the sum of diameters of target lesions."*[22]

Interim PFS by BICR analysis was scheduled to take place at [redacted] events: the observed two-sided p-value threshold was p=0.000204 to conclude superiority of T-DXd over T-DM1 for the primary endpoint.[33] At the time of the first interim analysis (May 2021 DCO), 87 PFS events (33.3%) had occurred in the T-DXd arm and 158 events (60.1%) in the T-DM1 arm (Table 3.8 and Figure 3.2). Median PFS was not reached in the T-DXd (95% confidence interval (CI) 18.5 to not evaluable [NE]) compared to 6.8 months in the T-DM1 arm (95% CI 5.6, 8.2).[1]

The total number of PFS events met the planned interim analyses criteria. Treatment with T-DXd provided on average a 72% lower risk of progression or death compared with treatment by T-DM1 (HR: 0.28; 95% CI: 0.22, 0.37 [$p=7.8\times10^{-22}$]).[16,34] This p-value met the company's criteria for superiority of T-DXd for interim PFS. Results for PFS by IA presented in the Appendix of the CS (N.2)[15] were similar (HR): 0.26; 95% CI: 0.20, 0.35 [$p=6.5\times10^{-24}$]),[16] at data cut-off, [redacted] ([redacted]%) and [redacted] ([redacted]%) of patients had events of disease progression or death.[1]

Although the efficacy benefit in PFS was observed consistently across all subgroups (see Figure 3.1**Error! Reference source not found.**), the results show it is possible there is a clinically significant difference in HRs across subgroups, but this could be due to sampling error. For example, the HR estimated for those described as Asian was (n=314, HR [redacted]) and those described as White was (n=143, HR [redacted] the [redacted].[17]

Table 3.8: Summary of efficacy results for DESTINY-Breast03 trial (FAS)

Characteristic	T-DXd (n=261)	T-DM1 (n=263)
PFS (by BICR)		
Subjects with events, n (%) Progressive disease Death	87 (33.3) [redacted] [redacted]	158 (60.1) [redacted] [redacted]
Subjects without events (censored), n (%) Ongoing without event Other reason*	[redacted] [redacted] [redacted]	[redacted] [redacted] [redacted]
Median PFS, months† (95% CI)†	NE (18.5, NE)	6.8 (5.6, 8.2)
Stratified Cox hazard ratio‡ [95% CI]§	0.28 [0.22, 0.37]	
OS		
Subjects with events (deaths), n (%)	33 (12.6)	53 (20.2)
Subjects without events (censored), n (%)	[redacted]	[redacted]
Alive	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
Median OS, months**	NE	NE
(95% CI)**	(NE, NE)	(NE, NE)
Stratified Cox hazard ratio[ŀ] [95% CI] ‡	0.55 [0.36, 0.86]	
ORR (by BICR)		
Confirmed ORR by BICR, n (%, 95% CI)	208, 79.7 [74.3, 84.4]	90, 34.2 [28.5, 40.3]
Disease control rate by BICR[ǁ] n (%)	252 (96.6)	202 (76.8)
Best overall response by BICR, n (%)		
CR	42 (16.1)	23 (8.7)
PR	166 (63.6)	67 (25.5)
SD	44 (16.9)	112 (42.6)
PD	3 (1.1)	46 (17.5)
Not evaluable	6 (2.3)	15 (5.7)
Duration of confirmed response (by BICR)		
RR (%) (at 12 months) [95% CI]	[redacted]	[redacted]
HRQoL		
Median time to definitive deterioration[#] for the EQ-5D-5L VAS	13.2	8.5
HR (median time to definitive deterioration‡ [95% CI], p value	0.77 [0.61, 0.98], p=0.0354	

Mean EQ-5D-5L change in score from baseline to end of treatment (std. dev.)	[redacted]	[redacted]
Mean EQ-5D-5L VAS change in score from baseline to end of treatment (std. dev.)	[redacted]	[redacted]
Median time to definitive deterioration (Global Health Status, EORTC QLQ-C30; months)	9.7	8.3
Median time to definitive deterioration (Breast symptoms scale, EORTC QLQ-BR45; months)	26.4	NE
HR (breast symptoms)‡ [95% CI], p value	0.76 [0.53, 1.09], p=0.0354	
Median time to definitive deterioration (Arm symptoms scale, EORTC QLQ-BR45; months)	11.1	7.0
HR (arm symptoms)‡ [95% CI], p value	0.70 [0.55, 0.89), p=0.1329	

Sources: CSR[17]

Footnotes:

*Censoring reasons included: adequate tumour assessment no longer available, event after missing two consecutive assessments, subject withdrew consent, no post-baseline tumour assessment, and no baseline evaluable tumour assessment.

†Median PFS is from the Kaplan-Meier (KM) analysis. CI for median was computed using the Brookmeyer-Crowley method.

‡Two-sided p-value is from the stratified log-rank test; hazard ratio and 95% CI are from the stratified Cox proportional hazards model with stratification factors: Hormone receptor status, Prior treatment with pertuzumab, and History of visceral disease, as defined by the IXRS.

§Estimate and CI for PFS rate at the specified time point are from the KM analysis

**Median OS is from KM analysis. CI for median was computed using the Brookmeyer-Crowley method.

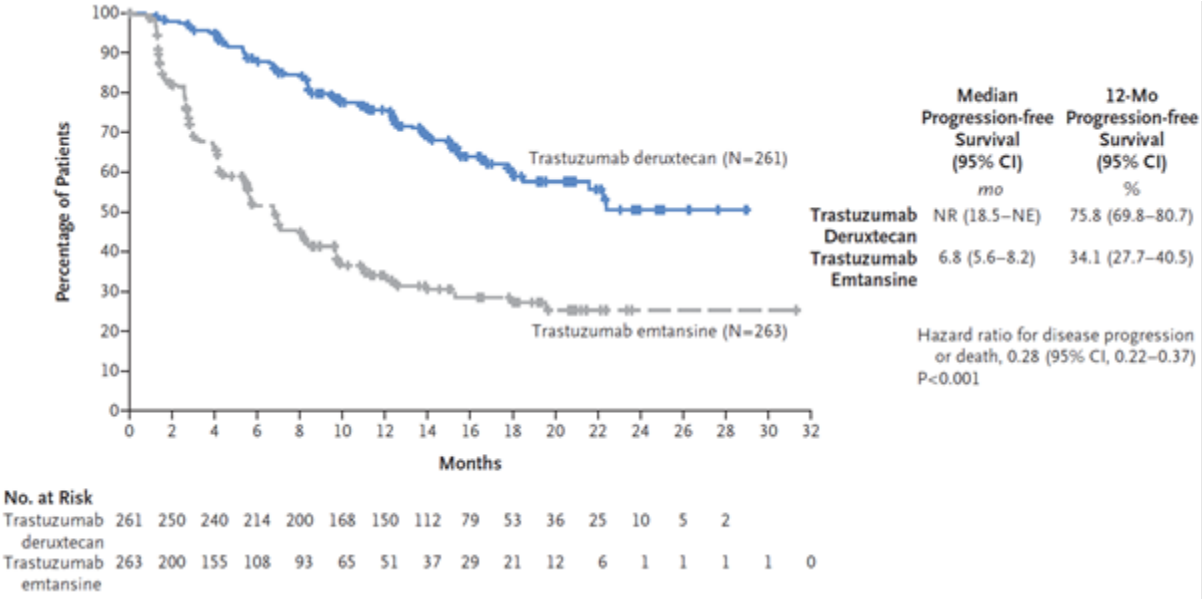
⸸Estimate and CI for OS rate at the specified timepoint are from KM analysis.

‖CR + PR + SD.

#Deterioration was defined as an increase of at least 10 points on scale/symptom subscale scores

Abbreviations: BICR, blinded independent central review; CI, confidence interval; CR, complete response; DoR, duration of response; EORTC QLQ, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L, EuroQol 5 Dimension 5 Level; HR, hazard ratio; HRQoL, Health related quality of life; KM, Kaplan-Meier; N, number of treated subjects; n, number of subjects with parameter; NE, not estimable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RR, Response Rate; QoL, quality of life; SD, stable disease; std dev, standard deviation; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; VAS, visual analogue scale.

Figure 3.2: Kaplan-Meier of PFS by BICR for DESTINY-Breast03 trial (FAS)



(Source: Figure 8, CS[1])

(Abbreviations: BICR, blinded independent central review; CI, confidence interval; FAS, full analysis set; HR, hazard ratio; mo, months; NR, not reached; PFS, progression-free survival)

EAG Comment: Although final PFS analysis has yet to be undertaken, PFS data is sufficiently precise that the EAG are satisfied that there is a probably a genuine difference between T-DXd and T-DM1. [redacted]% of the PFS events required for the final analysis of PFS have occurred (i.e., [redacted] PFS events of the [redacted] PFS events planned at the final PFS analysis). In total, [redacted]% of the DESTINY-Breast03 patient population have not progressed/died, including 66.67% of the participants in T-DXd arm and [redacted]% in the T-DM1 arm.

The analysis was pre-specified and stringent criteria were utilised to assess superiority. We would assume the hazards functions for the two treatments will differ proportionally by the same amount between the interim and final analysis ("proportional hazards assumption"), and therefore the final analysis for PFS would strongly favour T-DXd. However, biologically important differences between subgroups may drive clinically different treatment effects,[35] but data in Figure 3.1 and from the earlier DESTINY-Breast01 study do not suggest this is likely cause for concern.[5] In addition, whilst there are some differences in PFS observed between certain subgroups (most notably race and region), the EAG note that the point estimates overlap so this is unlikely to be a cause for concern.

3.2.4.2 Overall survival

The OS data from the DESTINY-Breast03 study are immature: only 33 patients (12.6%) in the T-DXd arm and 53 patients (20.2%) in the T-DM1 arm had died at the time of the May 2021 cut-off (Table 3.8). As such, there were insufficient events to estimate the median OS. A second interim OS analysis will take place at [redacted] PFS events, which the company anticipates is likely to be in [redacted]. Final OS analysis will be undertaken at [redacted] OS events.[110]

At the interim analysis, T-DXd was associated with a numerically lower risk of death compared with T-DM1 (HR: 0.55; 95% CI: 0.36, 0.86 [p=0.007]).[16] However, this difference did not meet pre-specified criteria for statistical significance (p<0.000265) after making the adjustment for multiple testing.

EAG Comment: OS data for DESTINY-Breast03 remains immature, with only [redacted]% of the events required for the final analysis of OS having occurred (i.e., 86 deaths of the [redacted] deaths planned at the final OS analysis).[1] Currently, there is insufficient evidence to suggest that T-DXd was superior to T-DM1 for the interim analyses; however, interim results suggest an early and sustained separation of survival curves. The predicted future analysis of OS data is anticipated around [redacted],[10] when more mature OS data are likely to be available.

In future cut points, the OS efficacy estimate may be influenced by subsequent treatment received. In response to the clarification letter (Question A29i), it was confirmed that: "*Treatment crossover was not permitted before protocol defined drug discontinuation or within the trial. Patients in the control arm could therefore not switch to the T-DXd arm following the first interim analysis as per protocol. Patients could however receive T-DXd or T-DM1 as a subsequent therapy outside of DESTINY-Breast03 in those markets where it was commercially available following protocol defined discontinuation.*" Further detail is provided in Sections 3.2.4.1 and 3.2.4.2.

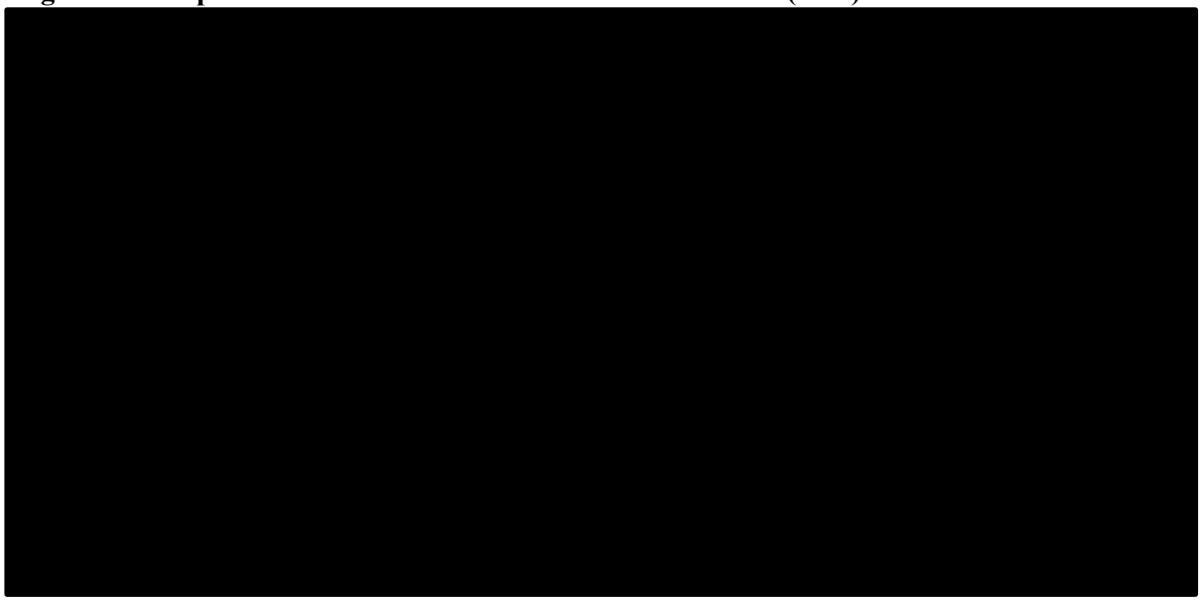
The analysis planned by the company follows the ITT principle, which reflects the reasonable assumption that patients will receive subsequent treatment after progression. In DESTINY-Breast03, a high percentage of patients (who had experienced disease progression or discontinued due to adverse events/other reasons) received subsequent treatment. Reported in Question B4 of the clarification letter,[10] [redacted]% in the T-DXd arm and [redacted]% in the T-DM1 arm (calculated as a percentage from the total number of patients who received subsequent treatment divided by the number of patients who had experienced a progression event i.e., not including those who discontinued treatment for other reasons than progression) had received subsequent therapy. Of only patients who had experienced disease progression, [redacted]% and [redacted]% of patients in the T-DXd and T-DM1 arms received subsequent treatment, respectively (Question 29h, points for clarification response).[10]

Based on an expert validation meeting (and described in detail in the response to the clarification letter, Question 29k, l),[10] the company estimates that the proportion of progressed patients who would receive subsequent therapy in UK clinical practice after second-line treatment was approximately 66.7% (this figure was subsequently used as the base case).[1] Expert clinical opinion to the EAG suggests this is consistent with English NHS practice. However, as noted above, clinical advisors reported in the CS (section B.3.5.4.1) that subsequent treatment rates in DESTINY-Breast03 were higher than expected.[1] It was further clarified in the factual accuracy check that, while [redacted] in the T-DXd arm was lower than 66.7%, the company considered the long-term percentage to be uncertain.

In particular, there were large differences in proportion of subsequent treatment between groups. This may be a reflection of the immature nature of these data, as progression was more common in the T-DM1 arm. Therefore, differences in subsequent treatment rates may reduce after more patients experience progression in the T-DXd arm. Studies with a high proportion of cross-over in control arms

has been found to substantially impact OS estimates.[36] Although the company trial does not use a cross-over design, the high levels of subsequent treatment in the control arm (T-DM1) compared with T-DXd may impact validity of OS estimates.

Figure 3.3: Kaplan-Meier of OS for DESTINY-Breast03 trial (FAS)



(Source: Figure 10, CS[1])
Footnote: Pre-specified boundary for statistical significance was p<0.000265
(Abbreviations: CI, confidence interval; FAS, full analysis set; HR, hazard ratio; mo, months; NE, not estimable; OS, overall survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan)

3.2.4.5 Response rate (RR)

RR were assessed by BICR and IA in the CS, full details are provided in Table 14 of the CS (a summary is provided above in Table 3.8).[1] The ORR was defined as the percentage of participants who achieved a best overall response of confirmed CR or PR.[22] CR was defined as *"a disappearance of all target lesions and PR was defined as at least a 30% decrease in the sum of diameters of target lesions."*

At the interim analysis for PFS (DCO May 2021), 96.6% of patients (n=252) in the T-DXd arm and 76.8% of patients (n=202) in the T-DM1 had disease control (defined as CR, PR or SD).[16] The best overall response of CR was observed in 16.1% (42 patients) in the T-DXd arm and 8.7% (23 patients), and the CBR (CBR; a best response of CR, PR, or SD for ≥6 months) was [redacted]: [redacted] ([redacted] patients) in the T-DXd arm, compared with [redacted] ([redacted] patients) in the T-DM1 arm ([redacted]).[16,17] RR by IA were consistent with the BICR assessment.

Although the median DoR in patients with a confirmed objective response (CR or PR) was [redacted], at 12 months, the RR by BICR was [redacted] (95% CI: [redacted]) in the T-DXd arm and [redacted] (95% CI: [redacted]) in the T-DM1 arm.[17]

EAG Comment: DoR data for DESTINY-Breast03 is relatively immature. Early evidence suggests there may be a positive intervention effect for T-DXd compared to the comparator.

3.2.4.6 HRQoL

Health-related quality of life was assessed in using EQ-5D-5L, EORTC QlQ-BR45 and European operation for research and treatment for cancer (EORTC) QLQ-C30 questionnaires. Completion rates were high ([redacted]% at baseline and [redacted] and [redacted] from cycle 3 onward in the T-DXd and T-DM1 arms respectively)[1], and study results demonstrated QoL (assessed with EORTC QLQ-C30 global health status and EQ-5D-5L) was maintained for those patients in the T-DXd arm. Median time to definitive deterioration (defined as a s defined as an increase of at least 10 points on scale/symptom subscale scores)[17] for HRQoL as measured by the EQ-5D-5L visual analogue scale (VAS) was [redacted]. Median time to definitive deterioration using EQ-5D-5L VAS was statistically significantly longer with T-DXd vs. T-DM1. All prespecified subscales of the EORTC QLQ-C30 and EORTC QLQ-BR45 favoured the intervention, and emotional functioning and pain symptoms subscales of the EORTC QLQ-C30, and arm symptom subscales of the EORTC QLQ-BR45, were statistically significant ($p<0.05$), see Figure 3.4.[17]

Figure 3.4: **Forest plot of time to definitive deterioration in patient reported outcome (PRO) measures of interest**

		Median (95% CI) TDD, months		HR (95% CI)	Nominal *P* value
		T-DXd (n = 261)	T-DM1 (n = 263)		
EORTC QLQ-C30	Global health status/QoL[a]	9.7 (7.3-12.5)	8.3 (7.0-10.3)	0.88 (0.70-1.11)	0.2829
	Pain symptoms[b]	10.8 (8.3-14.0)	8.3 (6.6-9.8)	0.75 (0.59-0.95)	0.0146
	Physical functioning[b]	16.7 (14.5-NE)	10.3 (8.3-21.0)	0.77 (0.59-1.01)	0.0529
	Emotional functioning[b]	16.4 (14.1-19.9)	10.5 (9.0-13.8)	0.69 (0.53-0.89)	0.0049
	Social functioning[b]	11.1 (7.3-13.4)	9.0 (7.1-11.3)	0.90 (0.71-1.14)	0.3577
EORTC QLQ-BR45	Arm symptoms[b]	11.1 (8.5-14.8)	7.0 (5.6-9.3)	0.70 (0.55-0.89)	0.0033
	Breast symptoms[b]	26.4 (26.4-NE)	NE (NE-NE)	0.76 (0.53-1.09)	0.1329
EQ-5D-5L	VAS[b]	13.2 (10.1-15.3)	8.5 (7.3-10.4)	0.77 (0.61-0.98)	0.0354

(Source: PfC response[10])
Footnotes:
[a] primary PRO variable of interest.
[b] Secondary PRO variable of interest.
(Abbreviations: CI, confidence interval; EORTC, European Organization for Research and Treatment of Cancer; EQ-5D-5L, EuroQol 5 Dimension 5 Level; HR, hazard ratio; NE, not estimable; PRO, Patient reported outcome; QoL, quality of life; QLQ-BR45, Quality of Life Breast cancer questionnaire; QLQ-C30, Quality of Life Core 30 questionnaire; QoL, quality of life; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TDD (possible typographic error in figure, most probably TTD), time to deterioration; VAS, visual analogue scale)

EAG Comment: Although [redacted] median time to definitive deterioration for EQ-5D-5L VAS was statistically significantly longer with T-DXd vs. T-DM1 demonstrating the effectiveness of the intervention drug.

3.2.4.7 DESTINY-Breast03 safety

The company states special consideration was given to two AEs; ILD/pneumonitis and left ventricular ejection fraction (LVEF) as they had been previously identified as AE's of special interest for T-DXd (CS Section B.2).[1,37] The DESTINY-BREAST01 trial had initially identified these AE's of special

interest in patients with u/mBC.[37] The company state, *"Potential episodes of ILD, an AE of special interest, were evaluated by an external independent adjudication committee, and grading was consistent with the NCI CTCAE version 5.0."* (CS Section B.2.10.1).[1]

The safety and tolerability evidence from the interim data cut-off point of the DESTINY-Breast03 trial were reported in the CS (Section B.2.10)[1] with a median follow up of 16.2 months and 15.3 months in the T-DXd arm and the T-DM1 arm respectively. The company specified that there were no new AEs of concern identified in the DESTINY-Breast03 trial. TEAEs were summarised in Table 16 of the CS and highlights the differences between both trial arms.[1] The proportion of TEAE's were [redacted] The proportion of TEAE's per cycle are detailed in Table 3.9: TEAEs by cycle in DESTINY-Breast03 (SAS).

Additionally, the CS stated, *"dose modifications for T-DXd in the event of toxicity were to be made on the basis of AE type, severity, and relatedness to study drug, outlined in the T-DXd management guideline"(*CS, Table 6, page 37).[1] The management of symptomatic AEs (e.g. ILD) may require dose interruption, dose reduction, or study drug discontinuation.[1] The starting dose for T-DXd was 5.4 mg/kg and 3.6mg/kg for T-DM1 but the mean dose was [redacted] mg/kg/3 weeks in the T-DXd arm and [redacted]mg/kg/3 weeks in the T-DM1 arm. The CS states *"at DCO [data cut off], 132 patients in the T-DXd arm and 47 patients in the T-DM1 arm were continuing study treatment".*[1] Patients may have required dose reductions at any point during the study. Of those receiving the intervention, the ratio of drug actually delivered versus the planned starting dose of the study drug was [redacted] over the follow-up period. There is no impact of this on the effectiveness estimate which reflects the dose given; however, a minority of patients may benefit from dose reductions. No dosage was defined in the NICE scope.[2]

Table 3.9: TEAEs by cycle in DESTINY-Breast03 (SAS)

	T-DXd (n=257)			**T-DM1 (n=261)**		
	Subjects with any TEAEs, n	**Subjects at risk, n**	**Proportion with TEAEs, %**	**Subjects with any TEAEs, n**	**Subjects at risk, n**	**Proportion with TEAEs, %**
Cycle 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle ≥8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle ≥18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 17 of the CS[1]

Abbreviations: TEAE, treatment-emergent adverse event; T-DXd, trastuzumab deruxtecan; T-DM1, trastuzumab emtansine; SAS, safety analysis set

3.2.4.8 Summary of adverse event in the DESTINY-Breast03 trial

The majority of study participants experienced a TEAE. AEs of any grade were more common in the T-DXd arm (99.6%) then the T-DM1 arm (95.4%). The TEAE's grade ≥3 reported by patients, were higher in the T-DXd arm in comparison to T-DM1. TEAE's associated with study drug discontinuation were almost of the treatment was almost twice as high in the T-DXd arm vs the T-DM1 arm (13.6% vs 7.3%). Table 3.10 includes a summary of all TEAE experienced by the study participants. According to Table 16 in the CS,[1] there were no drug related AEs leading to death. Drug related AEs associated with discontinuation was higher in the T-DXd arm vs the T-DM1 arm (12.8% vs 5.0% respectively).

Table 3.10: Summary of TEAEs in DESTINY-Breast03 (SAS)

n (%)	T-DXd (n=257)	T-DM1 (n=261)
Any TEAE	256 (99.6)	249 (95.4)
EAIR per patient-year of exposure	[redacted]	[redacted]
Any drug-related TEAE	252 (98.1)	226 (86.6)
TEAE Grade ≥3	134 (52.1)	126 (48.3)
EAIR per patient-year of exposure	[redacted]	[redacted]
Drug-related TEAE Grade ≥3	116 (45.1)	104 (39.8)
Serious* TEAE	49 (19.1)	47 (18.0)
EAIR per patient-year of exposure	[redacted]	[redacted]
Serious* drug-related TEAE	28 (10.9)	16 (6.1)
TEAE associated with an outcome of death	5 (1.9)	5 (1.9)
Drug-related TEAE associated with an outcome of death	0	0
TEAE associated with study drug discontinuation	35 (13.6)	19 (7.3)
Drug-related TEAE associated with discontinuation	33 (12.8)	13 (5.0)
TEAE associated with dose reduction	55 (21.4)	33 (12.6)
Drug-related TEAE associated with dose reduction	55 (21.4)	33 (12.6)

Source: Table 16 of the CS[1]

*An AE that results in death, is life-threatening, requires inpatient/prolonged hospitalisation, results in persistent/significant disability/incapacity, is a congenital anomaly/birth defect, or is an important medical event

Abbreviations: EAIR, exposure-adjusted incidence rate; TEAE, treatment-emergent adverse event; T-DXd, trastuzumab deruxtecan; T-DM1, trastuzumab emtansine; SAS, safety analysis set

The most common AEs in the T-DXd arm were in the system organ classes of gastrointestinal disorders ([redacted]%), investigations ([redacted]%), general disorders and administration site conditions ([redacted]%), and skin and subcutaneous tissue disorders ([redacted]%). In patients treated with T-DM1, the frequency, and distribution of TEAEs varied in comparison to the T-DXd arm. Within the T-DM1 arm, the most common TEAE's reported were investigations ([redacted]%), gastrointestinal disorders ([redacted]%) and general disorders and administrative site conditions ([redacted]%). An overview of all TEAEs of any grade experienced with an incidence of ≥20% in either treatment arm is presented in Table 18 of the CS[1] in

order of decreasing frequency. The majority of drug related TEAEs of all grades reported in the CS were haematological, gastrointestinal, or in the system organ class of investigations in both trial arms.[1] TEAEs in both arms were generally of lower grade (<3), however the incidence of any grade ≥3 TEAEs was greater in the T-DXd arm in comparison to the T-DM1 trial arm with the exception of thrombocytopenia and investigations, which occurred more frequently with T-DM1, and diarrhoea and constipation, which occurred at equal rates in each arm. The most common drug related TEAEs grade ≥3 that occurred in more than 5% of the patients within the T-DXd arm were neutropoenia (19.1%), thrombocytopaenia (7.0%), leucopoenia (6.6%), nausea (6.6%), anaemia (5.8%), and fatigue (5.1%). Within the T-DM1 arm, these were thrombocytopaenia (24.9%) and AST increased (5.0%).

3.2.4.9 AEs associated with variations to treatment

The CS summarises the key TEAEs associated with study drug discontinuation, dose reduction, or treatment interruption in both trial arms (Table 19, CS).[1] Discontinuation due to AE was higher in the T-DXd arm (13.6%) vs the T-DM1 arm (7.3%). These AEs were considered drug related in 12.8% of participants in the T-DXd arm and 5.0% in the T-DM1 arm. The key AEs associated with study drug discontinuation was ILD (8.2%) in the T-DXd arm, and [redacted] ([redacted]%) in the T-DM1 arm. Dose reductions occurred in both safety populations due to TEAEs. The TEAEs associated with dose reduction were considered drug related in [redacted]. The most commonly reported AE leading to dose reduction were [redacted] ([redacted]%), [redacted] ([redacted]%), and [redacted] ([redacted]%) in the T-DXd arm, and [redacted] ([redacted]%) and [redacted] ([redacted] %) in the T-DM1 arm.

The study protocol stated dosage can be interrupted for up to 28 days from the planned date of administration,[22] however as a contingency measure for COVID-19, dose interruptions were limited to [redacted] days after the last dose date. Seven patients used dosing extensions due to COVID-19.[17] Drug related TEAEs that led to study drug interruption were reported in 35.4% of patients in the T-DXd arm and 13.0% of patients in the T-DM1 arm. The most common AE associated with drug interruption were [redacted] ([redacted] %) and [redacted] ([redacted] %) in the T-DXd arm and, [redacted] ([redacted]%) and [redacted] ([redacted] %) in the T-DM1 arm (Table 3.11). Duration of interruption was not collected in DESTINY-Breast03.[10] Upon closer inspection of the tables provided in the CS, the EAG noticed some discrepancies in the total number of participants who had TEAEs associated with study drug discontinuation, drug reduction and drug interruption within the specific TEAEs listed in Table 19 in the CS.[1] In response to the clarification letter (Question A30, B), the company confirmed that the *"TEAEs shown are those reported by ≥2% of patients in either treatment arm, and are not an exhaustive list of TEAEs associated with changes to treatment."*[10] The company also provided a clarification response to address the question of why the numbers within specific TEAE categories listed in Table 16 of the CS[1] do not match the overall participant numbers who had TEAEs. The company response to the query is that TEAE categories presented are a summary of key safety findings, and are not an exhaustive list of all TEAEs therefore, the patient numbers will not sum to the total given for patients with 'any TEAE'.[10]

Table 3.11: TEAEs associated with changes to treatment occurring in ≥2% of patients in either arm in DESTINY-Breast03 (SAS)

Preferred term or grouped term, n (%)	T-DXd (n=257)	T-DM1 (n=261)
TEAEs associated with study drug discontinuation	35 (13.6)	19 (7.3)

Preferred term or grouped term, n (%)	T-DXd (n=257)	T-DM1 (n=261)
ILD* [redacted]	21 (8.2) [redacted]	3 (1.1) [redacted]
TEAEs associated with study drug reduction [redacted]	55 (21.4) [redacted]	33 (12.6) [redacted]
TEAEs associated with study drug interruption [redacted]	113 (44.0) [redacted]	61 (23.4) [redacted]

Source: Table 19 of the CS[1]
*ILD includes events that were adjudicated as ILD and related to use of T-DXd or T-DM1.
Abbreviations: ILD, interstitial lung disease; TEAE, treatment-emergent adverse event; T-DXd, trastuzumab deruxtecan; T-DM1, trastuzumab emtansine; SAS, safety analysis set
TEAE categories presented above are a summary of key safety findings, and not an exhaustive list of all TEAEs; patient numbers will not sum to the total given for patients with 'any TEAE'

3.2.4.10 AEs of special interest in the DESTINY-Breast03 trial

The company identified ILD/pneumonitis and LVEF decrease as AEs of special interest and potential cases were reviewed by an independent ILD adjudication committee. According to the company "*all ILD events were manageable using the established risk management plan for ILD (Appendix O.2)*" and no TEAEs were adjudicated as grade >3.[15] However, across patients treated with T-DXd, ILD events associated with study drug interruption, dose reduction, or discontinuation were reported in [redacted] ([redacted] %), [redacted]([redacted] %) and 21 patients (8.2%), respectively. Study drug interruption, dose reduction, or discontinuation were reported in [redacted] ([redacted] %), [redacted], and three patients (1.1%) respectively, across patients treated with T-DM1. The company reported no AE of grade 4 or grade 5 severity for these AEs of special interest, and no drug related TEAEs resulting in death, the company stated, "*one patient had an ILD event with a fatal outcome, for which the death was not evaluable for adjudication*" in the T-DM1 arm. No event of LVEF grade ≥3 was reported. One study participant reported left ventricular dysfunction at grade 1 and six study participants reported LVEF decreased at grade 2 severity in the T-DXd arm. One patient in the T-DM1 arm reported LVEF decreased. The CS states "*all but one event of LVEF decreased were resolved, and no* [redacted] *for any events*".[1] The clinical

expert consulted by the EAG about AEs of special interest identified ILD, and fatigue as specifically important in the study population of interest as they have a high impact on quality of life although fatigue is reported as a TEAE, the company have not classified it as AE of special interest.

EAG Comment:

Clinical advice to the EAG is that T-DXd appears to have a manageable toxicity profile however, across the TEAE's reported, it is evident that patients receiving T-DXd experienced higher toxicities in comparison to participants in the T-DM1 trial arm. Higher drug discontinuation and dose reduction could potentially affect the acceptability of T-DXd relative to T-DM1. The mean age of the of the trial population is DESTINY-Breast03 is [redacted] years, meaning that many patients may still be working, particularly in the T-DXd which was demonstrated to provide on average a 72% lower risk of progression or death compared with treatment by T-DM1 (HR: 0.28; 95% CI: 0.22, 0.37 [$p=7.8\times10^{-22}$]).[16,34] Higher drug toxicities leading to dose reduction, interruption and discontinuation maybe indicative of poorer acceptability and higher affect on everyday life.

The higher toxicity in the intervention arm coupled with the higher proportion of Asian participants in comparison to the other ethnicities is of potential concern. The proportion of Asian participants in the DESTINY BREAST-03 trial (CS Table 10) is greater than other ethnicities.[1] The clinical opinion consulted by the EAG also noted that, generally, UK trials often include small numbers of ethnic minorities, and the results of these trials are generalised to these ethnic minority groups. Both T-DM1 and the pertuzumab, trastuzumab, and docetaxel regimen are associated with higher events of toxicities in Asian populations.[31,38] Based on the higher proportion of Asian trial participants, the assumption that less AEs may be seen in the participants of other ethnicities can be inferred.

The company reported a general decline in AEs after subsequent cycles. On closer inspection of Table 17 provided in the CS,[1] the EAG noticed a spike in the proportion of study participants who received cycles ≥8 and experienced TEAE's. The EAG asked the company to provide a breakdown of the cycles of treatment and their relation to dose reduction. In response to the clarification letter (Question A30, E), the company have stated *"cycles ≥8 and ≥18 are collated across multiple cycles, and would therefore be expected to include a larger proportion of affected patients than for a single cycle. A gradual decline in the proportion of patients experiencing a TEAE can be observed in individual cycles 1 to 7"*.[10] The EAG notes that the between group differences in risk ratios is similar but reduces slightly over time. Therefore, the EAG considers the company explanation that cycles ≥8 show higher risk differences because they are combined across categories a likely explanation.

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

No indirect comparison was performed.

EAG comment: No indirect comparison was required given that the intervention and comparator in the NICE scope were both investigated in the DESTINY-Breast03 trial and this was the only relevant RCT.[2]

3.4 Conclusions of the clinical effectiveness section

A SLR was conducted to identify literature relative to the NICE scope.[2] A 'global SLR' undertaken previously by the company was re-screened to include studies relevant to the NICE scope.[2] Twenty-four studies were identified, including four derived from the DESTINY-Breast03 trial. The SLR identified one RCT for T-DXd for which published (and unpublished) literature was available, DESTINY-Breast03. Patients were randomised to either T-DXd or T-DM1. The DESTINY-Breast03

study is useful to decision making in being randomised, relatively large and comparing the intervention and comparator in line with the NICE and NHS clinical practice.

The DESTINY-Breast03 trial was a randomised, parallel assignment, open label, phase III trial conducted in 169 centres across 15 countries. Ten UK centres were included, and [redacted] patients were drawn from the UK. Broadly speaking, the population of DESTINY-Breast03 seem broadly applicable to the England setting. However, some key differences between the DESTINY-Breast03 population and the England setting are noteworthy. Firstly, in the DESTINY-Breast03 population the percentage of Asian patients is considerably greater (59.9%), and secondly, the percentage of smokers is lower. Only [redacted] patients in DESTINY-Breast03 were from the UK ([redacted]).[1,10] Whilst differences in ethnicity are unlikely to affect efficacy results, there are known differences between Asian and Caucasian populations in terms of side effects and toxicities which may impact the generalisability to clinical practice in England of the AEs detailed in the CS.[1]

Patients were adults with HER2+ u/mBC, previously treated with trastuzumab and a taxane in the advanced/metastatic setting or that had progressed within 6 months after neoadjuvant or adjuvant treatment with trastuzumab and a taxane.[1] Patients (n=524) were randomised to T-DXd (at a starting dose of 5.4 mg/kg) or T-DM1 (at a starting dose of 3.6 mg/kg) administered as an IV infusion. The EAG were satisfied that study quality was acceptable, although lack of blinding does imply some concern regarding risk of bias.

The evidence presented uses the first PFS interim analysis, using a DCO of 21 of May 2021. At the time, 87 PFS events (33.3%) had occurred in the T-DXd arm and 158 events (60.1%) in the T-DM1 arm, although median PFS was not reached in the T-DXd arm.[1] Although only 46.76% of PFS had occurred at the time of the interim analysis, treatment with T-DXd provided on average a lower risk of progression or death compared with treatment by T-DM1 (HR: 0.28; 95% CI: 0.22, 0.37 [$p=7.8\times10^{-22}$]).[1,16,34] The OS data is very immature (events have occurred in 16.41% of the population), although early results suggest superiority of T-DXd over T-DM1, the results do not meet the companies pre-specified criteria for statistical significance.[1] The next data cut-off is expected at [redacted], but there is some uncertainty surrounding this as it depends on when the required number of patients with events has been reached.[10]

There are important differences in the subsequent treatments progressed patients in DESTINY-Breast03 might receive, which may affect the generalisability of OS estimates to English clinical practice. A high percentage of patients who had either experienced disease progression or discontinued due to adverse events/other reasons received subsequent treatment: [redacted] in the T-DXd arm and [redacted] in the T-DM1 arm (calculated as a percentage of patients who had experienced disease progression).[10] This is higher than the 66.7% of patients who are likely to be eligible for subsequent therapy in UK clinical practice after second-line treatment, as indicated to the company by clinical experts. Furthermore, the subsequent treatments received by those in DESTINY-Breast03 may not be wholly reflective of the subsequent therapies that would be used in English clinical practice after second-line treatment.

Generally, the AE reported in the DESTINY-BREAST03 trial are higher in the T-DXd arm in comparison to the T-DM1 arm. The safety profiles of T-DXd- and T-DM1 in the DESTINY-Breast03 trial were generally manageable and tolerable though the high proportion of Asian participants may impact the generalisation of the toxicities reported in the context of clinical practice in England. Higher drug toxicities for T-DXd patients (compared to T-DM1), which was demonstrated to result in more frequent dose reduction, interruption and discontinuation, maybe suggestive of poorer acceptability amongst patients and a higher impact on daily activities.

4. COST EFFECTIVENESS

4.1 EAG comment on company's review of cost effectiveness evidence

This Section mainly concerns the review of cost effectiveness analysis studies. However, this Section also covers other reviews related to cost effectiveness presented in the CS, including the measurement and evaluation of health effects and the cost and healthcare resource identification, measurement and valuation.[1] Section 4.1.1 includes critiques of the searches for the cost effectiveness review as well as those for HRQoL and cost and resource use.

4.1.1 Searches performed for cost effectiveness section

Searches for cost effectiveness analysis review

For the search for cost-effectiveness studies (Appendix G, Section G.1.1, page 25 of the CS), a number of sources were listed in the CS but no search strategies were presented.[15] In response to the clarification letter the company supplied full search strategies and additional relevant information for each resource listed in the CS (see Table 4.1 below for details).[10] The searches, of the electronic bibliographic databases, were originally conducted on 11 August 2020 and updated on 24 November 2021. The EAG checked the search strategies using the PRESS checklist for appraising literature search strategies and used the PRISMA-S checklist to check the reporting of the literature searches.[13,14] As the searches are similar to the searches performed for the clinical effectiveness studies many of the same comments apply (please see 3.1.1 above and Appendix 1). Presented below are the EAG's main additional comments regarding these searches.

Table 4.1: Resources searched for cost-effectiveness evidence. For the original search run on 11 August 2020 (covering 2010 to 2020) and updated search on 24 November 2021

Resource - category	Resource	Host source	Date range	Date of search	Search strategy/ string/ terms reported	N hits per line	Reported in PRISMA flowchart
Electronic bibliographic databases	Embase	Embase.com	NR	11.08.20 24.11.21	#Yes	#Yes	Yes
	#MEDLINE[a]	Embase.com	NR	11.08.20 24.11.21	#Yes	#Yes	Yes (reported as MEDLINE)
	#MEDLINE In-Process[a,b]	PubMed #via NLM (https://pubmed.ncbi.nlm.nih.gov/)	NR	11.08.20 24.11.21	#Yes	#Yes	Yes
	#PubMed		#No date limit (original search); 12.08.20 to 24.11.21 (updated search)	11.08.20 24.11.21	#Yes	#Yes	
	CRD (up to 2015)	CRD	No date limit	11.08.20	#Yes	#Yes	#Yes
	HTA (up to 2015)	CRD	No date limit	11.08.20	Reported as CRD		Yes
	NHS EED (up to 2015)	CRD	No date limit	11.08.20	Reported as CRD		Yes
	EconLit	#EBSCOHost	#No date limit (original search); 12.08.20 to 24.11.21 (updated search)	11.08.20 24.11.21	#Yes	#Yes	Yes

	ScHARR-HUD	NR	NR	NR	#Yes	#Yes	Yes
Conference Proceedings	ASCO Annual Meeting	NR	NR	#13.09.21	NR	NR	Reported as "Other Sources"
	ASCO/SITC Clinical Immuno-Oncology Symposium	NR	NR	NR	NR	NR	Reported as "Other Sources"
	ASCO Quality Care Symposium	NR	NR	NR	NR	NR	Reported as "Other Sources"
	ESMO Breast Cancer Congress	NR	NR	#04.10.21 #16.09.21 #01.10.21	NR	NR	Reported as "Other Sources"
	EBCC	NR	NR	#17.09.21	NR	NR	Reported as "Other Sources"
	SABCS	NR	NR	#22.09.21	NR	NR	Reported as "Other Sources"
	JSCO Annual Meetings	NR	NR	#15.09.21	NR	NR	Reported as "Other Sources"
	ISPOR Europe	NR	NR	#20.09.21	NR	NR	Reported as "Other Sources"
	ISPOR-FDA	NR	NR	#17.09.21	NR	NR	Reported as "Other Sources"
	ISPOR Asia Pacific	NR	NR	NR	NR	NR	Reported as "Other Sources"
	ISPOR Latin America	NR	NR	NR	NR	NR	Reported as "Other Sources"

	ISPOR Warsaw	NR	NR	NR	NR	NR	Reported as "Other Sources"
	ISPOR Dubai	NR	NR	NR	NR	NR	Reported as "Other Sources"
HTA organisation websites	#Reported separately in PfC	#Yes	#No time limits (original search) 01.10.20-28.12.21 (updated search)	#02.10.20 - 05.10.20 (original search) 18.12.21 (updated search)	#Yes	#Yes	Reported as "Other Sources"
Other sources	Reference lists (included studies + additional studies)	NR	NA	NR	NR	NR	Reported as "Other Sources"
	Reference lists (SLRs and MAs)	NA	NA	NA	NA	NA	Reported as "Other Sources"

Source: Based on information presented in Appendix G, CS and responses to clarification questions[1,10,15]

Footnotes:

[a] in the clarification responses the company stated that MEDLINE was searched via both Embase and PubMed (with no restrictions on PubMed processing status) and that it was PubMed (via NLM) that was searched.

[b] Originally reported in CS as MEDLINE In-Process via 'Pubmed.com' in response to PfC it was stated that no limitations were imposed on the searches which were actually undertaken in PubMed via NLM.[1]

#Additional information provided by company in responses to clarification questions

Abbreviations: ASCO = American Society of Clinical Oncology; CRD = Centre for Reviews and Dissemination; EBCC = European Breast Cancer Conference; ESMO = European Society for Medical Oncology; HTA = health technology assessment; ISPOR = International Society for Pharmacoeconomics and Outcomes Research, Inc; JSCO = Japan Society of Clinical Oncology; MA = meta-analysis; NA = not applicable; NHS EED = NHS Economic Evaluation Database; NLM = National Library of Medicine; NR = not reported; SABCS = San Antonio Breast Cancer Symposium; ScHARRHUD = School of Health and Related Research Health Utilities Database; SITC = Society for Immunotherapy of Cancer; SLR = systematic literature review

EAG comment:

- Searches of 'pre-filtered' databases, such as NHS EED, which contains economic evaluations only (Table 9, response to clarification letter) - do not normally employ a search filter related to that pre-filtered content, however, such a filter, related to economic evaluation study types, was used.[10] The rationale for this approach is not provided. The use of this search string may have compromised the sensitivity of the searches (e.g., in Table 9, NHS EED search, only 3 results were found).
- The clinical effectiveness searches included a set of terms related to 'stage of disease' to supplement the set of terms related to 'metastatic disease' - the set of 'stage of disease' terms are missing from the cost effectiveness, HRQoL and resource use and cost searches – from local experience (personal communication) this set of terms is an important supplement to the set of 'metastatic disease' terms. Their absence could have led to a narrower search.
- The EAG has identified some relevant Emtree subject headings missing from the 'population set' such as: Breast tumour/exp; Cancer growth/; human epidermal growth factor receptor 2 positive breast cancer/; metastatic breast cancer/. Some of these terms the company tested in response to the clarification letter with regard to the clinical effectiveness searches but not in the cost effectiveness, HRQoL and cost and resource use search context.[15]
- Some potentially relevant subject headings have not been used as key word search terms and vice versa – this could have compromised the sensitivity of the search.
- Some relevant search terms such as "overexpress* HER2", "erbb-2", "proto-oncogene protein", "HR+" are not present in the search strategy.
- The author 'keyword' search field was not searched, this field, available in many of the databases searched, provides relevant additional search terms assigned by the publication's authors and can increase the sensitivity of the search strategy.
- There is no explanation for why the initial searches were limited to covering 2010 to 2020.

Health related quality of life (HRQoL) searches

For the HRQoL searches, (Appendix H Section H.1.1, page 31 of the CS) the CS refers the reader to 'Appendix G, Section G.1.1' for the search strategies used.[15] In response to the clarification letter the company supplied full search strategies and additional related information. As the searches are similar to the searches performed for the clinical and cost effectiveness studies many of the same comments apply (please see Section 3.1.1 and also the cost effectiveness search-related comments above and Appendix 1). Table 4.2 below presents a summary of the searches performed for HRQoL studies. Presented below are the EAG's main additional comments regarding these searches.

Table 4. 2: Resources searched for HRQoL evidence

Resource - category	Resource	Host source	Date range	Date of search	Search strategy/string/ terms reported	N hits per line	Reported in PRISMA flowchart
Electronic bibliographic databases	#Embase	Embase.com	#No date limit (original search); 12.08.20 to 24.11.21 (updated search)	11.08.20 24.11.21	#Yes	#Yes	Yes
	#MEDLINE[a]	Embase.com		11.08.20 24.11.21	#Yes	#Yes	Yes (reported as MEDLINE)
	#MEDLINE[a] In-Process	#Via NLM (https://pubmed.ncbi.nlm.nih.gov/)	NR	11.08.20 24.11.21	#Yes	#Yes	
	#PubMed	#Via NLM (https://pubmed.ncbi.nlm.nih.gov/)	#No date limit (original search); 12.08.20 to 24.11.21 (updated search)	11.08.20 24.11.21	#Yes	#Yes	
	CRD (up to 2015)	CRD	No date limit	11.08.20	#Yes	#Yes	#Yes
	EconLit	#EBSCOHost	#No date limit (original search); 12.08.20 to 24.11.21 (updated search)	11.08.20 24.11.21	#Yes	#Yes	Yes

	ScHARR-HUD	NR	NR	NR	#Yes	#Yes	Yes

Source: Based on information presented in Appendix H, CS and responses to clarification questions[1,10,15]

Footnotes:

[a] in the PfC responses company stated that MEDLINE was searched via both Embase and PubMed (with no restrictions on PubMed processing status) and that it was PubMed (via NLM) that was searched.

#Additional information provided by company in responses to clarification questions

Abbreviations: CRD = Center for Reviews and Dissemination; NLM = National Library of Medicine; NR = not reported; ScHARRHUD = School of Health and Related Research Health Utilities Database; SLR = systematic literature review

EAG comment:

There is a minor error in the PRISMA flowchart for the HRQoL studies (Appendix H, figure 4, pg. 38 of the CS).[15] According to the search strategies provided by the company for the Embase and MEDLINE searches (reported on PRISMA flowchart as 'Embase') the total of records retrieved (sum of those retrieved by original search and those retrieved by the update search) should equal 1336.

Cost and resource use searches

For the cost and resource use searches (Appendix I, Section I.1.1, page 61 of the CS), the CS refers the reader to 'Appendix G, Section G.1.1' for the search strategies used.[15] In response to the clarification letter the company supplied full search strategies and additional search-related information. As the searches are similar to the searches performed for the clinical and cost effectiveness studies and HRQoL many of the same comments apply (please see 3.1.1 and the search related comments above and Appendix 1). Table 4.3 below presents a summary of the searches performed for cost and resource use.

Table 4.3: Resources searched for cost and resource use evidence

Resource - category	Resource	Host source	Date range	Date of search	Search strategy/string/ terms reported	N hits per line	Reported in PRISMA flowchart
Electronic bibliographic databases	#Embase	Embase.com	#No date limit (original search); 12.08.20 to 24.11.21 (updated search)	11.08.20 24.11.21	#Yes	#Yes	Yes
	#MEDLINE[a]	Embase.com		11.08.20 24.11.21	#Yes	#Yes	Yes (reported as MEDLINE)
	#MEDLINE[a] In-Process	#Via NLM (https://pubmed.ncbi.nlm.nih.gov/)	NR	11.08.20 24.11.21	#Yes	#Yes	
	#PubMed		#No date limit (original search); 12.08.20 to 24.11.21 (updated search)	11.08.20 24.11.21	#Yes	#Yes	
	CRD (up to 2015)	CRD	No date limit	11.08.20	#Yes	#Yes	#Yes

	EconLit	#EBSCOHost	#No date limit (original search); 12.08.20 to 24.11.21 (updated search)	11.08.20 24.11.21	#Yes	#Yes	Yes
	ScHARR-HUD	NR	NR	NR	#Yes	#Yes	Yes

Source: Based on information presented in Appendix I, CS and responses to clarification questions[1,10,15]

Footnotes:

[a] in the PfC responses the company stated that MEDLINE was searched via both Embase and PubMed (with no restrictions on PubMed processing status) and that it was PubMed (via NLM) that was searched.[10]

Additional information provided by company in responses to clarification questions.[10]

Abbreviations: CRD = Center for Reviews and Dissemination; NLM = National Library of Medicine; NR = not reported; ScHARRHUD = School of Health and Related Research Health Utilities Database; SLR = systematic literature review

4.1.2 Inclusion/exclusion criteria

Eligibility criteria for the cost effectiveness systematic review presented in Table 4.4 (reproduced from Table 8 of Appendix G CS).[15] The company considered the National Institute for Health and Care Excellence (NICE) preferred methodological principles of conducting systematic reviews in healthcare (NICE 2022, PMG36) and the 'Preferred Reporting Items for Systematic Reviews and Meta-analyses' (PRISMA) checklist for reporting the systematic review results.[3,39]

The company noted the title and abstract of all hits found through the searches assessed by two researchers against eligibility criteria. The full text of studies that meet the eligibility criteria were reviewed by two reviewers. Conflicts between reviewers for both title/abstract and full text review were resolved through a discussion between the two researchers.

Table 4. 4: Eligibility criteria for the systematic literature reviews

	Inclusion criteria	Exclusion criteria
Patient population	Adult (age ≥18 years) patients undergoing second-line treatment for unresectable and/or metastatic HER2-positive breast cancer [a] Furthermore, the studies that assess a mixed population will be included regardless of the percentage of the study population [b]	Healthy volunteers Patients <18 years Diseases other than unresectable and/or metastatic HER2-positive breast cancer Patients with HER2-negative breast cancer Non-invasive or Stage 0 breast cancer
Intervention	Any	None
Comparator	Any	None
Outcomes	Incremental costs Incremental outcomes QALYs, LYs gained, hospitalizations avoided ICERs and any other measure of effectiveness reported together with costs Budget impact	Cost-only outcomes [c]
Study type	Full economic evaluations Cost-consequence Cost-minimization Cost-effectiveness Cost-utility Cost-benefit Budget impact Systematic reviews [d]	*In vitro* studies Preclinical studies Reviews, comments, letters, and editorials Case reports, case series Clinical studies reporting only efficacy and safety data
Language	English	None
Year of publication	Published after August 1, 2010	Published before August 1, 2010 [f]

Source: Table 8 Appendix G of CS[15]
a Studies not reporting outcomes for second-line treatment were excluded at Level 2 screening.
b Studies reporting a mixed HER2 population were only included at Level 2 screening if outcomes were reported separately for the HER2+ subgroup.
c Cost-only studies were included and flagged for cost and resource review.
d Systematic reviews were included at Level 1 screening, used for identification of primary studies, and then excluded at Level 2 screening.
e During screening, the studies published in a non-English language were excluded at Level 2 screening.
f Articles published before August 1, 2010, were excluded at Level 2 screening.
Abbreviations: HER2, human epidermal growth factor receptor 2; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year

EAG comment:

The EAG considers the company's eligibility criteria to be satisfactory.

4.1.3 Conclusions of the cost effectiveness review

The CS reported that no published economic evaluations of T-DXd were identified within the second-line setting.[1]

EAG comment:

While the literature search could have been broader for all of the reviews (cost-effectiveness, HRQoL and costs), the EAG considers the reviews to be adequately conducted.

4.2 Summary and critique of company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 4. 5: NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Defining the decision problem	As listed in the scope developed by NICE[2]	Complied with reference case
Comparator(s)	Trastuzumab emtansine	Complied with reference case
Perspective on outcomes	The outcome measures to be considered include: PFS OS RR DoR Adverse effects of treatment Health-related quality of life	Complied with reference case
Perspective on costs	NHS and PSS	Yes, the company used an NHS and PSS perspective
Type of economic evaluation	Cost utility analysis with fully incremental analysis	The company has provided a cost utility analysis. This is based upon a *de novo* state

		transition model with partitioned survival analysis.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes. A 30-year time horizon was selected to capture all differences in costs and outcomes.
Synthesis of evidence on health effects	Based on systematic review	Yes. A systematic review was conducted and the only included study that could provide effectiveness evidence for T-DXd versus T-DM1 was the pivotal DESTINY-Breast-03 trial.
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.	Partially. QALYs were based on EQ-5D-5L data from the pivotal DESTINY-Breast-03 study with EQ-5D-3L index utilities calculated using the van Hout et al. crosswalk algorithm. This is a deviation from NICE guidelines (Section 4.3.16) which advocates using the 'EPPRU dataset'.[3] The dis-utilities and expected duration of AEs are from published sources.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes for the PFS and PD model health states, obtained from the DESTINY-Breast03 study and the literature. For adverse effect dis-utilities, the source of measurement varied between literature and expert opinion.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	No
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
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	Yes (costs have been sourced using NHS reference costs, the PSSRU Unit Costs of Health and social care and published literature (Tables 42- 49) and are reported in pounds Sterling for a 2021 cost year)
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes

Source: Table 58, CS [1]
Abbreviations: DR, Duration of response; EQ-5D-5L, EuroQol 5 Dimension 5 Level; EQ-5D-3L, EuroQol 5 Dimension 3 Level; HRQoL, health-related quality of life; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; OS, Overall Survival; PFS, progression-free survival; PD, progressed disease; PFS, Progression free survival; PSS, Personal Social Services; PSSRU, Personal Social Services Research Unit; RR, response rate; QALY, quality-adjusted life year; T-DXd, trastuzumab deruxtecan; T-DM1, trastuzumab emtansine

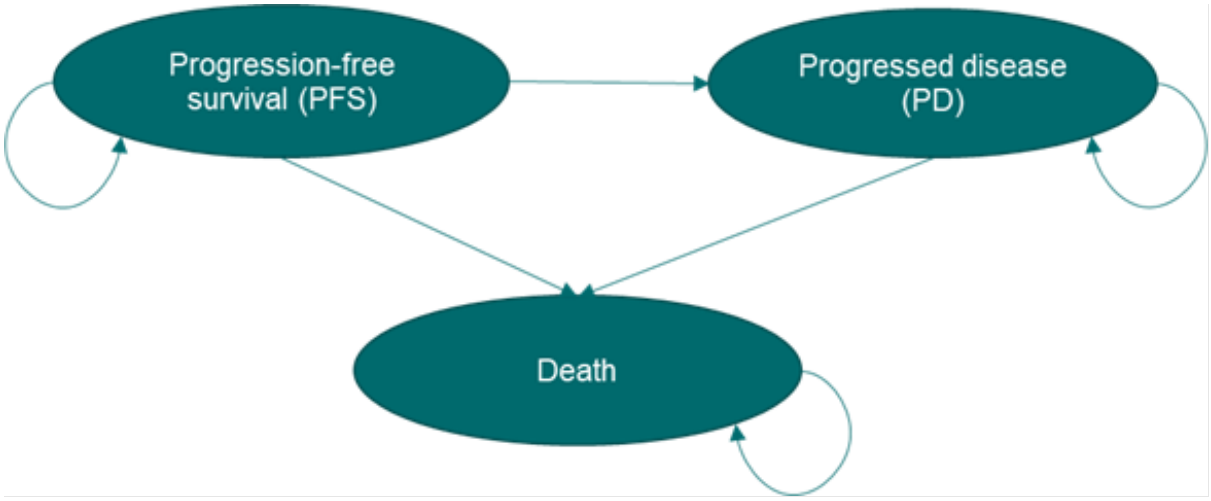
4.2.2 Model structure

Health states/events and transitions

No existing economic evaluations of T-DXd were identified in the cost effectiveness SLR, hence the company developed a *de novo* model in Microsoft Excel®. The model structure is presented in Figure 4.1. The model is a partitioned survival model (PartSA) with three health states: 1) progression-free survival (PFS), 2) progressed disease (PD), and 3) death. These states reflect the disease progression. Patients do not actually transition between the states when the model is run. The proportion of patients in each state is determined by the PFS and OS curves estimated from the pivotal DESTINY-Breast03 trial data. The time period was partitioned into seven-day periods. The proportion of patients within the PFS health state was estimated from the PFS curve and the proportion of patients in the death state was estimated from the OS curve for each treatment. The proportion of patients in the PD health state was the difference between the estimated proportion of patients in the OS and PFS states. Life years (LYs) were accrued according to the proportion of patients in the PFS and PD health states over time.

A 7-day period was chosen to account for the different dosing schedules across the arms and to reflect the 21-day dosing cycle. No half-cycle correction was applied. Health-related quality of life varied across states. Costs varied across states due to different treatment distributions.

Figure 4. 1: Model structure



Source: Based on Figure 15, CS[1]

EAG comment: The modelled patient pathway was appropriate. The 3-state model structure was consistent with progression-based models commonly used in economic analyses of oncology treatments because they accurately reflect the progressive nature of the disease. No half-cycle correction was necessary given the short cycle length.

In response to the clarification letter (Question B3), the company provided the following rationale for selecting a PartSA. Firstly, the PFS and OS survival curves used to model progression and death in a PartSA correspond to the primary and secondary outcomes in DESTINY-Breast03. Secondly, a PartSA is a simpler model than a state transition model (STM) and is easier to communicate. Thirdly, it allows for varying risk of progression or death over time. The EAG notes that the partitioned survival models have been accepted in a wide variety of oncology settings submitted for NICE appraisal. However, as stated in TSD 19,[40] a STM has the potential to more accurately extrapolate survival as it does not assume that OS and PFS are independent. Furthermore, as a large proportion of patients were censored (ongoing without event) at the first interim data cut-off point in both trial arms, the hazard rate predictions beyond the end of follow-up may be poor predictors of hazard rates when the majority of patients who remain alive are progressed. After progression, patients have more advanced disease and the treatments received by the disease progressed patients differ to those received by progression-free patients. The EAG accepts that a more complex and time-consuming model would be required to model time-varying risk of mortality for progressed patients (either a STM with a very high number of progression states or an individual patient simulation conducted in R®).

4.2.3 Population

The population simulated in the company model is people with HER2-positive unresectable or metastatic breast cancer who have received trastuzumab and a taxane.

EAG comment: This is in line with the population considered in the DESTINY-Breast03 study and consistent with the NICE final scope.[2] The starting age of patients in the model is [redacted] years.

4.2.4 Interventions and comparators

The intervention is trastuzumab deruxtecan (T-DXd) administered at a dose of 5.4 mg/kg once per 21-day cycle until disease progression or toxicity in line with the SmPC and dose received in the DESTINY-Breast03 trial. The comparator was trastuzumab emtansine (T-DM1) administered at a dose of 3.6 mg/kg once per 21-day cycle until disease progression or toxicity in line with the SmPC and dose received in the DESTINY-Breast03 trial.[22]

EAG comment: The intervention and comparator are consistent with the NICE final scope and aligned with the intervention and control arms of the DESTINY-Breast03 head-to-head trial.[2]

4.2.5 Perspective, time horizon and discounting

The analysis was performed from the UK National Health Service (NHS) and Personal Social Services (PSS) perspective. The time horizon in the base case model was stated to be 30 years in the company submission. The Excel model was programmed to run for 30 years from the starting age of [redacted] years. The fitted OS curve for T-DXd predicted [redacted] of patients alive at 30 years (see Section 4.2.6). A 40-year time horizon was adopted in scenario analysis. Costs and benefits were discounted at an annual rate of 3.5% in the base case analysis. A discount rate for costs and health outcomes of 1.5% was explored in scenario analyses.

EAG comment: Given a starting age of [redacted] years, a time horizon of 30 years in the model is expected to be sufficiently long to capture the healthcare resource use and health outcomes affected by the interventions. It is concordance with the NICE reference case.[21] The additional benefit associated with [redacted] of patients alive at 30 years in the T-DXd arm is likely to be small after discounting. A time horizon of 30 years is slightly conservative with respect to T-DXd given modelled survival.

4.2.6 Treatment effectiveness and time on treatment extrapolation

Patient-level data in the pivotal DESTINY-Breast03 trial were used to extrapolate OS, PFS, and TTD beyond the data cut off (21 May 2021). The company followed the guideline for survival model selection outlined in the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14.[41] For this, Kaplan-Meier curves for the DESTINY-Breast03 trial were produced for both arms. The company fitted different parametric survival models (PSMs).

The same set of six parametric survival curves (exponential, Weibull, Gompertz, log-normal, log-logistic and generalised gamma) was considered and compared in line with the model selection criteria. The process is summarised as follows:

1. Visual inspection: Kaplan-Meier curves were produced.
2. Log-cumulative hazard plots (LCHP) were constructed to illustrate the hazards observed in the DESTINY-Breast03 trial and assess the proportional hazards assumption.
3. AIC/BIC goodness of fit statistics were conducted to provide statistical test of the relative fit of alternative parametric models.
4. External data and clinical expert opinion were considered to assess the plausibility of the long-term survival profile used in the economic model. The expert panel comprised two clinical experts from oncology and two health economics and outcomes research experts.

Overall survival

The company employed 2 methods to extrapolate OS beyond the end of the follow-up period associated with the interim cut point. Method 1 involved fitting survival models to the DESTINY-Breast03 trial data and was used in the base case. Method 2 involved (a) generating a survival curve for T-DM1 from a published Kaplan-Meier curve from EMILIA[42] (b) estimating a hazard ratio for T-DXd compared to T-DM1 from DESTINY-Breast03, (c) deriving the survival curve for T-DXd from the hazard ratio and the time-varying hazard rates associated with the T-DM1 survival curve. The median follow-up of the final analysis of EMILIA was 47.8 months. This contrasts with the median follow-up of 15.9 months, at the first interim analysis for PFS (DCO May 2021) in the DESTINY-Breast03 trial. Method 2 therefore relies less on clinical expert opinion in the selection of survival models. Method 2 was used in scenario analysis.

Method 1

In the base case the company fitted survival models to the DESTINY-Breast03 trial data using the process described above. In addition to log-cumulative hazards plots (LCHP), the company used the Therneau and Grambsch's non-proportionality test to test the suitability of the proportional hazards (PH) assumption in the DESTINY-Breast03 trial data. The company considered the proportional hazards assumption to be plausible. The company fitted dependent survival models to the DESTINY-Breast03 trial data using the six parametric models (exponential, Weibull, Gompertz, log-normal, log-logistic and generalised gamma) in R® using the 'flexsurv' package.

The company plots of the six models overlayed with the Kaplan-Meier curve over a 5-year and 30-year time period are reproduced in Figures 4.2 to 4.5. Akaike information criterion (AIC) and Bayesian information criterion (BIC) test statistics, and survival plausibility based on clinical feedback of OS estimation at 5 and 10 years (25-35% and 5-10%, respectively) for T-DM1 patients were used to determine the company base case. The selected curves OS estimates (5- and 10-year OS of [redacted] and [redacted], respectively) were in line with the feedback. All fit statistics are within 10 points and provide relatively close statistical fits to one another. The log-logistic provides the best statistical fit to the DESTINY-

Breast03 trial data. Based on expert opinion, the most reasonable PSM was the generalised gamma and this was selected as the base case for the economic analysis. Log-logistic and Weibull distributions were considered in scenario analyses. The company plot of OS extrapolations for T-DM1 and T-DXd is reproduced in Figure 4.6.

Extrapolated OS curves were adjusted for general population mortality informed by life tables for England and Wales to ensure that the probability of death never falls below that of the general population.

Figure 4. 2: Base-case extrapolations for T-DXd OS (5 years)

(Source: Figure 41, clarification questions[10]; Figure 18, CS[1])
(Abbreviations: OS, Overall survival; T-DXd, trastuzumab deruxtecan)

Figure 4. 3: Base-case extrapolations for T-DXd OS (30 years)

(Source: Figure 42, clarification questions[10]; Figure 18, CS[1])
(Abbreviations: OS, Overall survival; T-DXd, trastuzumab deruxtecan)

Figure 4. 4: Base-case extrapolations for T-DM1 OS (5 years)

(Source: Figure 43, clarification questions[10]; Figure 18, CS[1])
(Abbreviations: OS, Overall survival; T-DM1, trastuzumab emtansine)

Figure 4. 5: Base-case extrapolations for T-DM1 OS (30 years)

(Source: Figure 48, clarification questions[10]; Figure 22, CS[1])
(Abbreviations: OS, Overall survival; T-DM1, trastuzumab emtansine)

Figure 4. 6: Base-case extrapolations for OS (T-DXd and T-DM1)

(Source: Based on Figure 20, CS[1])
(Abbreviations: OS, Overall survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan)

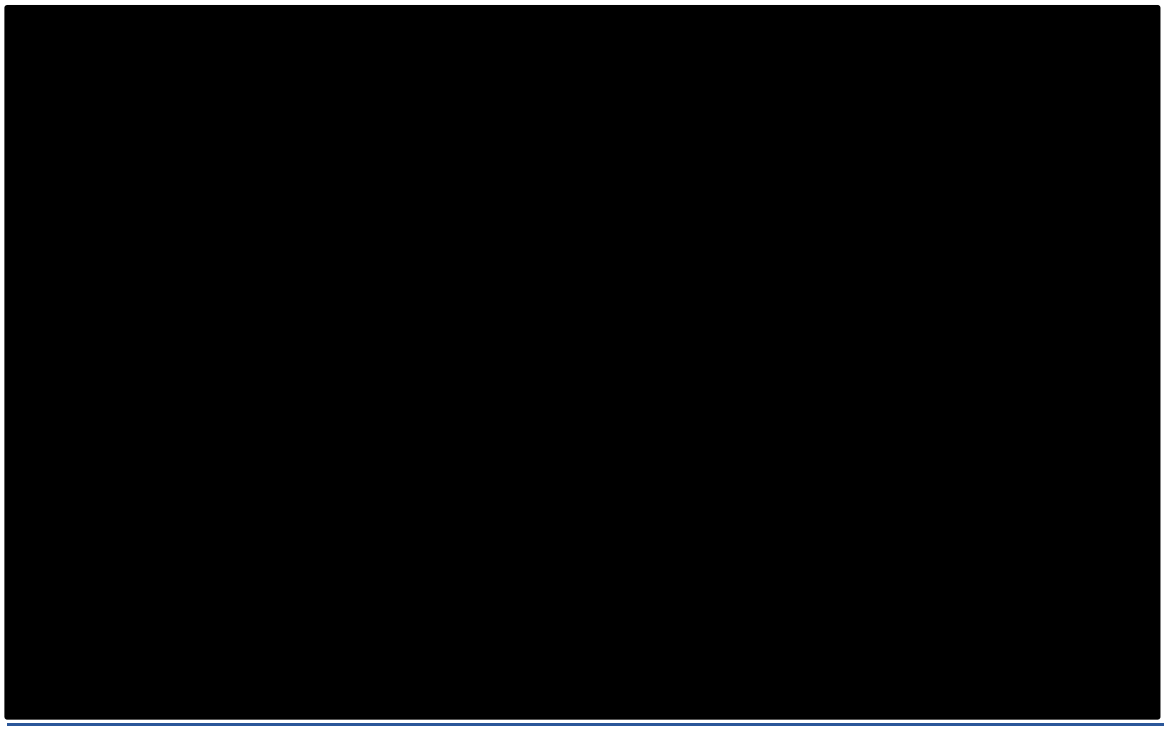
Method 2

Method 2 was used in scenario analysis due to the immature OS data in the DESTINY-Breast03 trial were with median OS not yet reached in either treatment arm.

The company conducted a reconstruction method to convert published KM curves to individual-level time-to-event data. Specifically, a baseline parametric survival curve was fitted for the T-DM1 to digitised KM data from the EMILIA study[42] which was replicated using Guyot algorithm.[43] The six parametric models (exponential, Weibull, Gompertz, log-normal, log-logistic and generalised gamma) were fitted. The log-normal model was selected as the most appropriate curve based on the same methods described above using model fit statistics, visual inspection and clinical expert opinion. Assuming proportional hazards, the HR for T-DXd compared to T-DM1 was estimated from the DESTINY-Breast03 study using a Cox-proportional hazard model with a treatment covariate. The survival curve for T-DXd was then derived from the hazard ratio and the time-varying hazard rates associated with the T-DM1 survival curve.

The company plots of the six models overlayed with the Kaplan-Meier curve over a 5-year and 30-year time period are reproduced in Figures 4.7 to 4.8. Figure 4.9 presents the comparison of Methods 1 and 2 using the company's base case curves along with the Kaplan-Meier plot for T-DXd survival over 30 years. Predicted survival using Method 2 is lower than for Method 1 up to around 11-12 years and then is higher.

Figure 4. 7: EMILIA based extrapolations for T-DM1 OS (6 years)



(Source: Figure 47, clarification questions[10]; Figure 22, CS[1])
(Abbreviations: OS, Overall survival; T-DM1, trastuzumab emtansine)

Figure 4. 8: EMILIA based extrapolations for T-DM1 OS (30 years)

(Source: Figure 48, clarification questions[10]; Figure 22, CS[1])
(Abbreviations: OS, Overall survival; T-DM1, trastuzumab emtansine)

Figure 4. 9: Overall survival comparing Method 1 and Method 2 – T-DXd (30-years)

(Source: Figure 14, clarification questions[10])
(Abbreviations: T-DXd, trastuzumab deruxtecan)

Progression-free survival

The company rejected the suitability of the proportional hazards (PH) assumption in the DESTINY-Breast03 trial data based on the LCHP and the Therneau and Grambsch's non-proportionality test. Independent PSM approach was used to fit an individual parametric model to each trial arm in R® using the 'flexsurv' package. The fit of alternative PSMs was assessed by LCHP, AIC/BIC tests, and clinical plausibility based on expert opinion. Based on the goodness-of-fit statistics, the log-normal and the generalised gamma provide the best fit to the T-DXd arm and the T-DM1 arm, respectively. The Weibull PSM was selected as the base case for both T-DXd and T-DM1 for the economic analysis based on expert opinion that considered a PFS prediction of 1-2% and 0% at 5 and 10 years to be reasonable for T-DM1 patients, respectively. Log-logistic, log-normal, and exponential distributions were considered in scenario analyses.

The company plots of the six models overlayed with the Kaplan-Meier curve over a 5-year and 30-year time period are reproduced in Figures 4.10 to 4.13. The company plot of PFS extrapolations for T-DM1 and T-DXd is reproduced in Figure 4.14.

Figure 4.10: Base-case extrapolations for T-DXd PFS (5 years)

(Source: Figure 49, clarification questions[10]; Figure 27, CS[1])
(Abbreviations: PFS, progression-free survival; T-DXd, trastuzumab deruxtecan)

Figure 4.11: Base-case extrapolations for T-DXd PFS (30 years)

(Source: Figure 50, clarification questions[10]; Figure 27, CS[1])
(Abbreviations: PFS, progression-free survival; T-DXd, trastuzumab deruxtecan)

Figure 4. 12: Base-case extrapolations for T-DM1 PFS (5 years)

(Source: Figure 51, clarification questions[10]; Figure 27, CS[1])
(Abbreviations: PFS, progression-free survival; T-DM1, trastuzumab emtansine)

Figure 4. 13: Base-case extrapolations for T-DM1 PFS (30 years)

(Source: Figure 52, clarification questions[10]; Figure 27, CS[1])
(Abbreviations: PFS, progression-free survival; T-DM1, trastuzumab emtansine)

Figure 4. 14: Base-case extrapolations for PFS

(Source: Based on Figure 29a, CS[1])
(Abbreviations: PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan)

Time to treatment discontinuation

The duration of treatment is determined by the TTD curves of both treatment arms from the DESTINY-Breast03 trial. Using the same approach taken in PFS with independent survival models fitted to the DESTINY-Breast03 trial data, the Weibull PSM was selected as the base case for the economic analysis, consistent with the PFS base case. In line with the SmPC, patients continue treatment until progression. Some patients may discontinue treatment due to other reasons such as adverse effects. One criterion for model selection was that the TTD curve should not cross the PFS curve. The Weibull model produced the longest time on treatment estimates without the curves crossing over 10 years. Five other distributions were considered in scenario analyses.

The company plots of the six models overlayed with the Kaplan-Meier curve over a 5-year and 30-year time period are reproduced in Figures 4.15 to 4.18. The company plot of TTD extrapolations for T-DM1 and T-DXd is reproduced in Figure 4.19.

Figure 4. 15: Base-case extrapolations for T-DXd TTD (5 years)

(Source: Figure 56, clarification questions[10]; Figure 32, CS[1])
(Abbreviations: T-DXd, trastuzumab deruxtecan; TTD, time-to-treatment discontinuation)

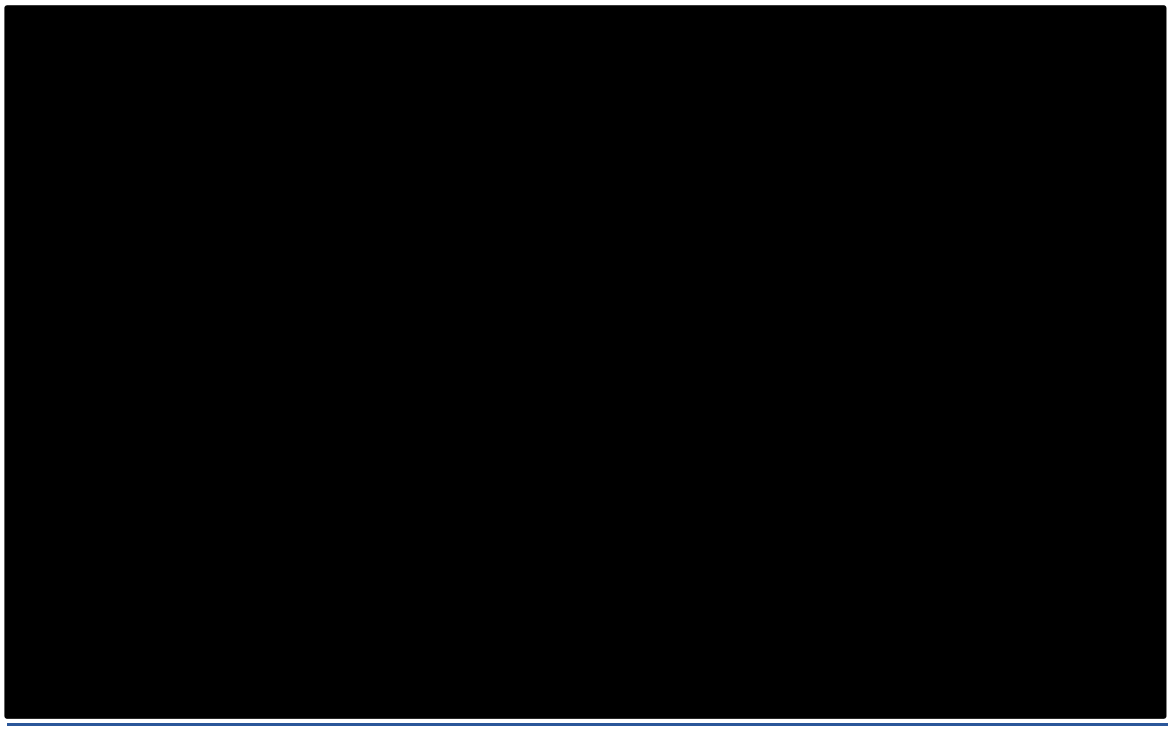
Figure 4. 16: Base-case extrapolations for T-DXd TTD (30 years)

(Source: Figure 57, clarification questions[10]; Figure 32, CS[1])
(Abbreviations: T-DXd, trastuzumab deruxtecan; TTD, time-to-treatment discontinuation)

Figure 4. 17: Base-case extrapolations for T-DM1 TTD (5 years)

(Source: Figure 58, clarification questions[10]; Figure 32, CS[1])
(Abbreviations: T-DM1, trastuzumab emtansine; TTD, time-to-treatment discontinuation)

Figure 4. 18: Base-case extrapolations for T-DM1 TTD (30 years)



Source: Figure 59, clarification questions[10]; Figure 32, CS[1]
Abbreviations: T-DM1, trastuzumab emtansine; TTD, time-to-treatment discontinuation

Figure 4. 19: Base-case extrapolations for TTD

(Source: Based on Figure 33, CS[1])
(Abbreviations: T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TTD, time-to-treatment discontinuation)

EAG comment: The EAG notes that there is considerable uncertainty in the implied effectiveness of T-DXd compared to T-DM1 as a result of extrapolating PFS and OS due to limited follow-up periods

and assumptions about the duration of treatment effect (potentially unlimited), and missing data. Uncertainty associated with these issues cannot be captured in the economic analysis base case results. This motivated the company to conduct Method 2 to estimate OS for use in scenario analysis. In response to the clarification letter (Question A22),[10] the company confirmed that the data presented in the CS uses the latest available data cut and that the expected time for the second interim data cut point was [redacted].

Overall survival

In response to the clarification letter (Question B6, B7, and B8),[10] the company provided the percentage survival at 3, 5, 10 and 20 years along with graphs plotting the OS curve over 10 years for both arms, explained the approach used to decide whether to model dependent or independent parametric models, provided diagnostic plots and graphs of hazard ratio over 10 years. The EAG considers that the proportional hazards assumption is plausible given the evidence, but it should be noted that while proportional hazards were assumed in Method 2, for Method 1 proportional hazards were not assumed. The company plot presenting the implied hazard ratio over time using the selected survival model in the base case is reproduced in Figure 4.20.

There is considerable uncertainty in predicted survival especially for T-DXd for which there is no clinical expert knowledge on which to draw in this population. This uncertainty will be reflected in the uncertainty in the treatment covariate in the dependent survival model.

The extrapolated survival curve for T-DXd relies on the assumption that the trend in the overall survivor curve as the proportion of alive patients who are progression-free changes within trial follow-up will continue beyond the follow-up period. The EAG considers this to be a strong assumption given the immature data, the effect of the changing disease profile of the patients over time, and the change in treatments patients receive. Without survival analysis in the PD population, it will not be clear if there is a treatment effect after disease progression and treatment cessation. The EAG will consider an alternative assumption about predicted survival for T-DXd in Section 6.

Figure 4. 20: Base-case implied hazard ratio over 1- years for OS (generalised gamma)

(Source: Figure 21, clarification questions[10])
(Abbreviations: HR, hazard ratio; OS, Overall survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan)

Progression-free survival

The company fitted independent survival models to each trial arm for PFS. The company explained that this was appropriate given that the proportional hazard assumption was not plausible. The EAG thinks that it may be possible to fit dependent survival models to the DESTINY-Breast03 trial, but that it considers the selection of the same survival model to each trial arm to be acceptable. This approach minimises the possibility of selection bias in model selection with clinical experts having more knowledge of comparator survival than intervention survival. The EAG notes that there is a greater divergence in PFS prediction from the Kaplan-Meier curve for T-DM1 than for T-DXd but that the data for T-DXd is less mature.

While the company included a function to ensure that the proportion on treatment was never greater than the proportion alive, there was no function to ensure that the proportion on treatment was never greater than the proportion who were progression-free. However, it is noted that the selected parametric survival model for TTD was chosen in part because the predicted TTD and PFS curves did not cross. While this does not guarantee that the proportion on treatment would never be greater than the proportion progression-free in probabilistic sensitivity analysis, the chance of inconsistent results being produced during probabilistic sensitivity analysis were slim given the two curves.

Time to treatment discontinuation

The EAG notes that the Weibull model selected for both trial arms produces the second lowest estimate of time on treatment for T-DXd and is not one of the best fitting curves. However, the EAG considers it acceptable to select a curve that does not cross the PFS curve.

4.2.7 AEs

Both the utilities and costs of AEs were included in the model. Though not included in the base-case, the dis-utilities of AEs were included as a one-off utility decrement within the first cycle of the model in the scenario analysis. The costs of AEs were included as a one-off cost within the first cycle of the model. Grade ≥3 AEs with a prevalence greater than 5% in either treatment arm as well as those of special interest identified in the DESTINY-Breast03 trial CSR[23] (at any grade) were included in the economic analysis.[17] The incidence of each AE in each trial arm is presented in Table 4.6. The dis-utilities and expected duration of AEs identified from published sources were used in scenarios analysis, along with the frequencies of AEs obtained from the DESTINY-Breast03 trial data. All costs and dis-utilities associated with AEs were assumed to occur in the first cycle of the model.

Table 4. 6: AEs incidence from DESTINY-Breast03 trial used within the economic model

Adverse event	T-DXd N=257	T-DM1 N=261
Anaemia	15 (5.8%)	11 (4.2%)
Fatigue	13 (5.1%)	2 (0.8%)
Interstitial lung disease (any grade)	27 (10.5%)	5 (1.9%)
Left ventricular ejection fraction decrease (any grade)	5 (1.9%)	1 (0.4%)
Nausea	17 (6.6%)	1 (0.4%)
Neutropenia	49 (19.1%)	8 (3.1%)
Thrombocytopenia	18 (7%)	65 (24.9%)
Leukopenia	17 (6.6%)	1 (0.4%)

Source: based on Table 33, CS[1]
Abbreviations: T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan

EAG comment: it was assumed that AEs occur once within the first cycle of the model and were associated with one-off costs and dis-utilities that were multiplied by the incidence to calculate the total dis-utilities. This is a typical assumption made in economic models of this nature and in previous TARs (for instance TA563 and TA612.[44,45] In response to the clarification letter (Question B20)[10], the company highlighted the proportion of TEAEs by cycle was highest in Cycle 1 and declined across subsequent cycles. Although this assumption may be justified for some AEs (e.g. fatigue), it may not for others (e.g. interstitial lung disease). It is not clear that the percentage of patients experiencing each adverse event used in the model (applied in the first cycle) reflects the aggregate number of events when accounting for patients who experience repeat events. This uncertainty is due to the difference in numbers of any grade TEAEs reported in Table 18, Page 72 of the CS, and Table 36, Page 88, Question 20 in the response to the clarification letter outlining the number of patients in each cycle that reported a treatment-emergent adverse event. If there is a difference in the any grade TEAEs, there could be a difference in grade ≥3 TEAEs.

4.2.8 Health-related quality of life

Utility values for progression-free survival (PFS) and progressed disease (PD) health states and disutility values for AEs (in scenario analysis) were accounted for within the economic model. Utility values were estimated from the DESTINY-Breast03 study where possible and utility values identified in the literature were used where it was not possible to estimate utility values from DESTINY-Breast03 and for use in sensitivity analyses.

PFS and PD utility data sources

DESTINY-Breast03

In the DESTINY-Breast03 study, EQ-5D-5L questionnaires were completed by patients on day 1 of cycles 1, 2 and 3 and every 2 cycles thereafter until end of treatment completed. Patients were then followed up at first follow-up assessment or before initiation of new anti-cancer treatment, whichever came first, and then at the first long-term/survival follow-up assessments three months later.

In line with NICE methods guidance, the EQ-5D-5L responses were 'crosswalked' to produce EQ-5D-3L values (NICE methods guide)[3] using the algorithm developed by Van Hout et al. (2012).[46] Generalised estimating equations (GEE) regressions were used to derive EQ-5D-3L index utility scores for both PFS and PD health states.

The PFS predicted utility was [redacted] for T-DXd patients and [redacted] for T-DM1 patients. The PD predicted utility was [redacted] for T-DXd and [redacted] for T-DM1. It should be noted that the GEE regression coefficient value for Treatment (T-DXd) was [redacted] (95%CI: [redacted]; p-value [redacted]) but progressed was [redacted] (95% CI: [redacted]; p-value [redacted]).

Literature review

According to the CS, a systematic literature review (SLR) was carried out to identify relevant HRQoL studies but none of the identified studies (n=15) fully qualified for the NICE reference case or used EQ-5D values.[1]

Most cost-utility studies (8/11) from the SLR referred to Lloyd et al. (2006), a preference-based study (i.e., standard gamble technique) estimating utilities at distinct stages of mBC in the general population in the UK (n=100).[47] The health state valuations were analyses using a mixed model analysis with random effects. The coefficients from the mixed model were applied to the patient population within this submission. That is age, response rates and progression status based on DESTINY-Breast03. The utility values for the treatment specific and combined utilities for T-DXd and T-DM1 were calculated using a sum of coefficients equation. Responder and non-responder utilities were calculated using the sum of coefficients equation and weighed by response rates from the DESTINYbreast-03 study (See Table 4.7).

Table 4.7: Utilities derived from Lloyd et al. 2006

Parameter	Coefficient value	T-DXd multiplier	T-DM1 multiplier	Pooled multiplier
Intercept	0.008871	-	-	-
Age	0.0239	[redacted]	[redacted]	[redacted]
Treatment response	0.4063	79.7%	34.2%	56.9%
Progression	-1.1477	-	-	-
Resulting utility [a]	PF responder: 0.848 PF non responder: 0.787	**PF: 0.835**	**PF: 0.808**	**PF: 0.822**

	PD responder: 0.638 PD non responder: 0.540	**PD: 0.618**	**PD: 0.574**	**PD: 0.596**
Source: Table 38, CS[1] Reference: Lloyd et al. 2006[47] Footnote: a Resulting utilities after applying the coefficients to the equation Abbreviations: PD, progressed disease; PF, progression-free; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.				

Utilities reported in prior HER2+ mBC (TA598,[48] TA458,[29] TA704[6] and ID3828[49] were also assessed for appropriateness of inclusion within the economic model (see Table 4.8)**.**

Table 4.8: Summary of final utility values in previous submissions

Submission (treatment line)	Treatment	Progression-free	Progressed disease
TA598 (1L)	Pertuzumab + trastuzumab + docetaxel	0.772 (during docetaxel) 0.785 (after docetaxel)	0.769
	Trastuzumab + docetaxel	0.769 (during docetaxel) 0.777 (after docetaxel)	
TA458 (2L)	T-DM1	0.807	0.53
	Lapatinib + capecitabine/ herceptin + capecitabine/ capecitabine	0.80/ 0.80 / 0.792	
TA704 (3L)	T-DXd	0.750 0.704 (off treatment)	0.588
	Eribulin/ capecitabine/ vinorelbine	0.715/0.718/0.728 0.704 (off treatment)	
ID3828 (3L)	Tucatinib + trastuzumab + capecitabine	0.748 (cycles 1-2) 0.763 (cycles 3-4) 0.792 (cycles 5-6) 0.807 (cycles 7+)	0.698
	Eribulin	0.782	0.588
Source: Table 39, CS[1] Footnote: ID3828 is now TA786 Abbreviations: 1L, first-line; 2L, second line; 3L, third line; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.			

PFS and PD utility values in model

For the model base case, utilities derived from DESTINY-Breast03 trial were used directly to inform treatment specific values for the 'progression-free' health state. Alternative utility values from published literature are explored in scenario analysis.

For the 'progressed disease' health state, the number of post-progression observations from DESTINY-Breast03 trial were limited (n=670 observations) and the resulting values were considered implausibly high by clinical experts. This is because long-term HRQoL was not collected. The values derived from

coefficients of the mixed model analysis from Lloyd et al. (2006) were used.[47] Treatment specific progressed disease utility values are used to inform the base case as, according to the CS, there is an expectation that patients who progress on T-DXd (0.6183) have a better QoL than those who progress on T-DM1 (0.5738) due to improved and longer response rates and disease control.[1] Scenario analyses included exploring alternative utility data from the literature.

Age-related utility decrements have also been included in the model using the Ara and Brazier algorithm.[50] A summary of all utility values used in the cost effectiveness is provided in Table 4.9**.**

Table 4.9: Health state utility values

Health state	Utility value: mean (standard error)	Source	Justification
Progression-Free T-DXd T-DM1	[redacted] [redacted]	Derived from DESTINY-Breast03 study.	EQ-5D-5L mapped to EQ-5D-3L. Generalized estimating equations (GEE) used to calculate mean utility values and associated 95% for each treatment group
Progressed disease T-DXd T-DM1	0.6183 0.5738	Derived from DESTINY-Breast03 study using previously accepted algorithm from Lloyd et al. (2006)[47]	Coefficients from a mixed model used to calculate treatment specific utilities by responder and non-responder weighted by response rates from DESTINY-Breast03 study.
Scenario analysis - Lloyd et al. (2006) (Treatment specific)			
Progression-Free T-DXd T-DM1	0.8353 0.8079	Previously accepted algorithm from Lloyd et al. (2006)[47]	Alternative utility values from the literature
Progressed disease T-DXd T-DM1	0.6183 0.5738		
Scenario analysis - Lloyd et al. (2006) (combined)			
Progression-Free	0.8216	Previously accepted algorithm from Lloyd et al. (2006)[47]	Alternative utility values from the literature
Progressed disease	0.5960		
Scenario – DB03 (PF combined); Lloyd et al. (2006) (PD combined)			
Progression-Free on treatment	[redacted]	Derived from DESTINY-Breast03 study.	Alternative utility values from the

Progressed disease	0.5960	Previously accepted algorithm from Lloyd et al. (2006)[47]	literature and clinical trial

Source: CS; Table 41[1]
Reference: Lloyd et al. (2006)[47]
Abbreviations: DB03, DESTINY-Breast03; EQ-5D-5L, EuroQol 5 Dimension 5 Level; EQ-5D-3L, EuroQol 5 Dimension 3 Level; PD, progressed disease; PF, Progression-Free; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

Disutility values in model

For the base-case analysis, no specific adverse event disutilities were included in the model, as it was assumed that these would have been captured in the treatment specific PFS utilities that were estimated from the DESTINY-Breast03 trial data. AE dis-utilities were included as one-off values for the whole model cohort in the first time period of the model in a scenario analysis.

The disutility values and expected duration of AEs used in scenario analysis were identified from published sources and are presented in Table 4.10. The frequency of AEs for both arms was obtained from DESTINY-Breast03.

Table 4.10: Disutilities for AEs

Adverse event	Disutility	Duration (days)	Source	
			Disutility	Duration
Anaemia	-0.010	42.90	Hudgens et al. 2014[51]	TA704[6]
Fatigue	-0.0290	58.30	Hudgens et al. 2014[51]	
Interstitial lung disease	-0.170	51.10	Doyle et al. 2011[52]	
Left ventricular ejection fraction decrease	-0.059	31.00	Sandhu et al. 2016[53]	
Nausea	-0.021	36.20	Hudgens et al. 2014[51]	
Neutropenia	-0.007	40.10	Hudgens et al. 2014[51]	
Thrombocytopenia	-0.066	42.20	ID3828[6]	Assumption
Leukopenia	-0.003	42.20	Hudgens et al. 2014[51]	TA704[6]

Source: CS; Table 40[1]
Abbreviations: TA: Technology appraisal

EAG comment:

PFS and PD utility values

As noted, the utility values used in the base-case analysis for the PF health state was based on the results from the DESTINY-Breast03 trial. As stated in Section 3.2.3., only [redacted] patients are from the UK. The majority (~60%) are from Asia. This was a concern for the EAG with respect to the values used in

the economic evaluation. The response from PfC letter (Question B.14)[10] stated that the responses from the trial participants were 'cross-walked' using the UK algorithm developed by Van Hout et al. (2012).[46]

The NICE methods guidelines, NICE 2022 (PMG36),[3] state that the mapping function developed by the Decision Support Unit,[54] using the 'EPPRU dataset',[55] should be used for reference case analysis. The CS used an alternative algorithm from Van Hout et al. (2012).[1,46]

As data for PD health state from the trial was not collected over a long enough timeframe, utility values from the literature were used. The source reference for PD health state in this submission (& other TAs) is the Lloyd et al. (2006) study for mBC.[47] This paper provides the equation for calculating coefficient values for the resulting utility values weighting by responder and non-responder from the DESTINY-Breast03 trial. The Lloyd et al. (2006) study does not provide any evidence for difference in utility values for patients who have progressed after responding to initial treatment before progression; it provides evidence for patients who currently respond to treatment.[47] The company argue that T-DXd patients will start progression with higher utility on average than T-DM1 patients due to improved and longer response rates, and therefore it is reasonable to expect higher average utility for PD patients in the T-DXd arm than the T-DM1 arm, but the EAG could not find any evidence for average utility values in the CS shortly after progression or for different time points from the start of progression to support that assumption.[1]

Compared to other health state utilities in previous TAs, the values for PFS and PD differ. In TA704, T-DXd used as third line has a utility value of 0.750 and 0.704 (off treatment) in the PFS health state, lower than [redacted] as second line in this submission. In the PD health state, the utility value was 0.588 which is lower than the 0.618 used in the company's base-case.[6] In TA458, T-DM1 was used second line and had a utility value of 0.807 which is very close to [redacted] in this submission for the PFS health state and a utility value of 0.53 for the PD health state which is lower than 0.574 in this submission.[29]

Disutility values

The EAG notes that the disutility values derived from the literature for AEs may not be representative of the study population. However, the disutility values and expected duration of AEs were not included in the base-case and only applied in a scenario analysis. When adverse event utilities are included, the ICER changes from [redacted] to [redacted], indicating that whether or not these utility values should be included makes little difference to the ICER. However, it is not clear that the that the percentage of patients experiencing each adverse event used in the model (applied in the first cycle) reflects the aggregate number of events when accounting for patients who experience repeat events (see Section 4.2.7).

The EAG notes that disutility associated with 8 different AEs are accounted for in this submission. The disutility values of 17 AEs were included in TA704 (T-DXd for treating HER2-positive unresectable or metastatic breast cancer after 2 or more anti-HER2 therapies).[6] Specific issues related to the disutility values are discussed below.

The evidence sources for adverse effects were not particularly accurate. Hudgens et al. (2014) was used for the disutility for 5 TEAEs: anaemia, fatigue, nausea, neutropenia and leukopenia in this CS. [1,51] These values were also used for Tucatinib with trastuzumab (TA786).[56] Hudgens et al. (2014)[51] is a conference abstract to ESMO (European Society for Medical Oncology) and does not list disutilities for these AEs, except for fatigue therein. TA786 uses different values for disutilities (e.g., Anaemia – 0.120)[56] and cites TA423[57] (eribulin with capecitabine) as reference that in turn cites back to Hudgens et al. (2014).[51] This is in comparison to –0.010 in this submission. TA704 was used as the source of the

utility duration for all AEs except Thrombocytopenia (ID3828 now TA786)[56] in this submission. It is unclear how these duration values were ascertained in TA704.[6]

ILD disutility value comes from an atrial fibrillation population (Doyle et al. 2011)[52] and left ventricular ejection fraction (LVEF) decrease comes from a study of severe congestive heart failure patients (Sandhu et al, 2016).[53] Thrombocytopenia disutility values comes from ID3828 (now TA786), but it is difficult to ascertain the original source of the value or duration.[6,56]

Though TEAEs were reported in 99.6% who received T-DXd and 95.4% who received T-DM1, a lot fewer patients were detrimentally impacted. In the T-DXd arm, TEAEs leading to discontinuation or dose reduction occurred in 35 patients (13.6%) and 55 patients (21.4%), respectively, and in the T-DM1 arm, 19 patients (7.3%) and 33 patients (12.6%), respectively, with most considered drug related. The adverse effects identified as of special interest in the trial were ILD/pneumonitis and LVEF decrease. Grade 3 ILD affected only 2 patients (0.8%) of the T-DXd and no patients having LVEF decrease. Given that HRQoL are collected on Day 1 of cycle maybe disutility values should be included in base-case analysis but is unlikely to make a big difference to the evaluation.

Overall, the main concerns of the EAG relate to:

a. The utility values of the DESTINY-Breast03 study participants appropriate for representing NHS patients
b. EQ-5D-5L were cross-walked using the Van Hout et al. (2012) algorithm and not the Hernández et al. algorithm as recommended by the NICE 2022 (PMG36) Methods guidance[3,46]
c. The progressed-disease utility scores are substantially higher in this CS than in previous TAs (T-DXd: 0.6183 vs 0.588 and T-DM1: 0.5738 vs 0.53)[1]
d. How valid is treatment-specific progressed disease utilities? Once patients are off-treatment, argument is that the utility values would be the same for both arms within a very short timeframe.
e. The disutility values are not reflective of the patient population and the reference source (Hudgens et al. 2014) is not accurate.[51]

4.2.9 Severity of the condition

The severity of the condition under committee review is defined as the future health lost by people living with the condition with standard care in the NHS. The severity of the condition was measured by the QALY shortfall in the CS.[1] In line with the new NICE methods guidance, NICE 2022 (PMG36),[3] the company calculated the absolute and proportional QALY shortfall associated with current standard of care, T-DM1, in patients with HER2+ u/mBC who have previously received trastuzumab and a taxane.

To estimate the shortfall, the Schneider et al. (2021) (online) estimator tool was used.[55] In response to the clarification letter (Question B1)[10], the company referenced a document where NICE cite this tool as a potential option for exploring the appropriateness of applying a severity modifier. The population characteristics was 100% female and age [redacted] years.

Within this estimator is an option to select HRQoL norms. The company chose ‘Alternative C: Measuring and Valuing Health Study (MVH), EQ-5D-3L value set + health state profiles from Health Survey for England (HSE) 2012 and 2014’ to inform shortfall calculations. This tool calculated the expected total QALYS for the general population as 14.63.

The company then use criteria reported in Table 4.11 stated in the new NICE guidance to base its conclusions regarding the appropriate QALY weight.

Table 4.11: QALY weights referenced within the new NICE manual (2022, PMG36)

QALY weight	Absolute shortfall	Proportional shortfall
1 x	Less than 12	Less than 0.85
1.2 x	12 – 18	0.85 – 0.95
1.7 x	At least 18	At least 0.95

Source: CS, Table 50[1]
Abbreviations: QALY, quality-adjusted life-year.

EAG Comment:

In the 2022 NICE methods guidance (PMG36), the Section on decision modifiers for severity (Section 6.2.12 to 6.2.22) outlines what the Committee should consider as the severity of the condition.[3] There is no recommendation on specific software to be used. The EAG expected that the calculations would have been part of the model submission in Excel. The Schneider online estimator tool provides alternative utility evidence with which to calculate general population QALYs. The company used Alternative C as described above. Another available alternative is Hernández Alava et al.,[55] EQ-5D-5L to 3L mapping + HSE 2017-18, and the Hernández et al. algorithm is recommended by NICE to crosswalk EQ-5D-5L to 3L.

It is preferable for population HRQoL norms and disease QALYs to be estimated using the same method. The company could have estimated both using the Hernández et al. algorithm. The EAG notes that the HRQoL norms estimate for this population is 14.63 using the Van Hout et al. algorithm and 14.33 using the Hernández et al. algorithm, and that could be the difference between crossing and not crossing the threshold.

In response to the clarification letter (Question B1),[10] the company gave a detailed response justifying the use of Alternative C as their base-case, which included a citation of DSU advice: "for the sake of consistency our recommendation to NICE is to use the most up to date information available that has direct observation of the EQ-5D-3L from the HSE 2014 (the last year that the 3L was used)".[58] The EAG accepts this.

4.2.10 Resources and costs

In the cost approach from the CS a number of different resources were included in the costing of the different facets of the intervention.[1] This includes the cost of the comparator drugs, the administration costs, the cost for subsequent treatment, administration costs, adverse event costs and end of life care costs for both the T-DXd and the T-DM1 arms. No additional diagnostic test was required for T-DXd in the decision population.

Resource use and costs data identified in the review

Drug Costs

The drug costs in the model are determined by the time on treatment and average cost of drugs while on treatment. Section 4.2.6 discusses time on treatment (time to treatment discontinuation).

For estimation of drug costs firstly, a unit cost for the drug from a UK relevant published source. These costs are applied by depending on the amount of time that the participant has spent in within the model and varies based on the different states that they undergo. The unit costs of the primary drugs used in the analysis, T-DXd and T-DM1, were sourced from the British National Formulary 2022, [BNF 2022],

with T-DXd (100mg) priced at £1455.01[59] and T-DM1 priced at £1641.01 (100mg) and £2625.62 (160mg).[60]

There is an approved simple Patient Access Scheme (PAS) for T-DXd with a [redacted] discount to the price, corresponding to a unit cost of [redacted] (100mg). The dose for the T-DM1 is 3.6 mg/kg once per 21-day cycle and T-DXd is a dose of 5.4 mg/kg once per 21-day cycle.

Drug wastage has been calculated by the method of moments approach, which accounts for drug wasting. In the base case analysis 50% of centres are assumed to allow vial sharing which prevents this wastage. This is factored into the unit cost of the base case analysis. The values are summarised below in Table 4.12.

Table 4.12: Drug values per cycle used in CS

Company Base Case Drug Values			
Drug	**No Waste Value**	**Waste Value**	**Company Base Case Value (with RDI)**
T-DXd	[redacted]	[redacted]	[redacted]
T-DM1	[redacted]	[redacted]	[redacted]

Source: CS [1]
Abbreviations: RDI, relative dose intensity; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan

In Table 4.12 the no waste value is calculated by multiplying the cost of the drug per mg by the dose and patients body weight. This assumes none of the drug is wasted. The waste value uses a log normal distribution of weight to attribute drug wastage from the lowest 100mg vial size that meets the patients' dose requirements. The overall value (not shown in the table) assumes 50% of participants have the no waste value and the 50% of the participants have the value including waste. The overall value is then multiplied by the RDI values to calculate the overall value with RDI. The RDI was [redacted] for T-DXd and [redacted] for T-DM1.

EAG Comment:

It could be suggested that the company has over-estimated the ability for vial sharing in their base case assumption. The EAG have consulted clinical experts who have advised that vial sharing either does not happen or if it does it is entirely dependent on the circumstances of each particular clinic. As such the effects of such a practice should not be considered, or should be considered at a much lower rate than the 50% used in the base case analysis. When vial sharing is carried out it is also unlikely that perfect the allocation of each dose is likely to occur. It is more likely that a single vial may be shared among two, perhaps three patients. Based on this clinical expert opinion the EAG have adopted an alternative waste value for the EAG base case analysis based on 90% of cases resulting in waste.

Disease Monitoring Costs

Costs were allocated for monitoring the disease throughout the treatment pathway. The costs are sourced from NHS Reference costs 2019/2020[61] and PSSRU costs.[62] The costs for LVEF follow-up is taken from TA458 and uplifted to 2021 costs.[29] The tool for uplifting costs is not specified. The frequency of these resources per cycle differs based on previous TARS, specifically TA458 and

TA704.[29,6] The frequency differs between progression-free and progressed disease. However, the per cycle monitoring cost (£105.57) did not change between across health states and treatment arms. This decision is based on expert opinion who concluded that disease-related resource use was unlikely to differ by health state or treatment.

EAG Comment:

The EAG has no additional information on likely differences in the frequency of monitoring across groups, so it accepts the assumption made by the company.

Administration Costs

The administration cost reported in the CS is presented in Table 4.13. It was sourced from the NHS Reference Costs 2019/2020 using the currency code SB12Z.[61] The same administration costs are used in both arms. This code relates to "Deliver Simple Parenteral Chemotherapy at First Attendance" and this is used for all administration costs.

Adverse Event Costs

Adverse event costs were costed from NHS reference costs.[61] The costs are provided with relevant HRG grouper codes. The total weighted cost per treatment arm was calculated and applied firstly as a cost within the first cycle of the economic model based on the greatest proportion of TEAEs in the DESTINY-Breast03 trial. Adverse event costs were applied as a one-off cost within the first cycle of the model. The costs reflect the events observed in the DESTINY-Breast03 trial during the entire follow-up.

Subsequent treatments

Costs for subsequent treatments have been included in the model. Once the patient leaves the "progression free" health state a single cost is applied to represent subsequent treatment costs. This cost is a weighted average of the treatments which were provided in those who progressed in the DESTINY-Breast03 trial.

The proportion of progressed patients who received subsequent treatment in the DESTINY-Breast03 trial was [redacted] and [redacted] of patients in the T-DXd and T-DM1 arms, respectively. The proportion of those receiving subsequent treatments in the DESTINY-Breast03 trial was [redacted] % for T-DXd and [redacted] % for T-DM1 (calculated as a percentage from the total number of patients who received subsequent treatment divided by the number of patients who had experienced a progression event, i.e. not including those who discontinued treatment for other reasons than progression). The difference between the percentage receiving subsequent treatment and the percentage of progressed patients receiving subsequent treatment is due to reasons such as treatment discontinuation due to adverse events or adequate tumour assessment no longer being available; and the total number of patients receiving subsequent treatment was divided by the number of patients who experienced disease progression.

The company clinical advice was an estimated 66.7% of participants receive subsequent treatment as a percentage of those who experience disease progression. The company clinical experts stated that "the proportion of progressed patients receiving subsequent treatment in DESTINY-Breast03 was higher than expected". It was further clarified in the factual accuracy check that, while [redacted] in the T-DXd arm was lower than 66.7%, the company considered the long-term percentage to be uncertain. The clinical expert assumption of the proportion of progressed patients receiving subsequent treatment was used in the company base case analysis. The proportions of those receiving subsequent treatments in the

DESTINY-Breast03 trial ([redacted] % for T-DXd and [redacted] % for T-DM1) were used in scenario analysis instead of 66.7%.

The distribution of subsequent treatments received in the DESTINY-Breast03 trial was used in the base case. The distribution of subsequent treatments that clinical experts estimated for use in UK clinical practice was used in scenario analysis. These subsequent treatment distributions are presented in Table 4.13. The four different scenarios for subsequent treatment costs for both the DESTINY-Breast03 trial and UK policy are summarised in Table 4.14 below.

The difference in costs between the two scenarios is driven by a greater proportion of Anti-HER2 drugs which were allocated in the UK, specifically the recently approved combination treatment (tucatinib, trastuzumab and capecitabine). A tucatinib combination is assumed to be the HER2 treatment in the UK subsequent treatment scenario.

Some unit costs for subsequent treatments were obtained from the BNF[63] while others were obtained from the eMIT[64] costing tool.

Table 4.13: Distribution of subsequent treatment costs used in the model in the different scenarios

Distribution of Subsequent treatments in both the UK and DB-03 Scenarios						
Drug	**T-DXd DB-03**		**T-DM1 DB-03**		**UK based scenarios**	
	N	**%**	**n**	**%**	**T-DXd**	**T-DM1**
Trastuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd (3L+)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T-DM1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pertuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Taxane (paclitaxel)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Trastuzumab + taxane	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-HER2 (tucatinib combination)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hormone therapy (tamoxifen)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other (capecitabine)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Company Model

Abbreviations: DB-03, DESTINY-Breast03; HER2, human epidermal growth factor receptor 2; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan

Table 4.14: Subsequent treatment costs used in the model in the different scenarios

Subsequent treatment distributions	Proportion receiving subsequent treatment		Values	
			T-DXd	T-DM1
UK Values*	UK Values	Subsequent treatment cost per patient	£19,014	£30,356
		Proportion of progressed patients receiving subsequent treatment	66.7%	66.7%
		Subsequent treatment cost per patient leaving progression-free	**£12,676**	**£20,237**
DB-03 Data	UK Values	Subsequent treatment cost per patient	£9,511	£11,382
		Proportion of progressed patients receiving subsequent treatment	66.7%	66.7%
		Subsequent treatment cost per patient leaving progression-free	**£6,341**	**£7,588**
UK Values	DB-03 Data	Subsequent treatment cost per patient	£19,014	£30,356
		Proportion of progressed patients receiving subsequent treatment	[redacted]%	[redacted]%
		Subsequent treatment cost per patient leaving progression-free	[redacted]	[redacted]
DB-03 Data	DB-03 Data	Subsequent treatment cost per patient leaving progression-free	£9,511	£11,382
		Subsequent treatment cost per patient	[redacted]%	[redacted]%
		Subsequent treatment cost per patient leaving progression-free	[redacted]	[redacted]

Source: Company Model
Abbreviations: DB-03, DESTINY-Breast03;T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan
*UK values were estimated by clinical experts

EAG Comment:

It is unclear why the BNF has been used for some costs and eMIT has been used for others. The EAG clinical expert agreed with the company clinical expert estimate of the percentage of patients who receive subsequent treatment as a percentage of patients who receive subsequent treatment in English clinical practice. It should be noted that the deviation in subsequent treatment modelled from the

DESTINY-Breast03 trial is only reflected in costs; no corresponding adjustment can be made to effectiveness estimates. While that is a limitation, the EAG accepts it is a pragmatic approach.

End of Life Care

A cost to represent end of life care was included for those participants who entered an "end of life" health state. The costs were based on a modelling study by Round et al. (2015), who modelled end of life costs for different kinds of cancers.[65] The value derived from the modelling study £4,346 which was then uplifted to 2021 prices using the PSSRU inflation indices (£4,782).

4.2.11 Summary of company assumptions applied in base case analysis

Table 4.15Table 4.15 containing a list of the assumptions used in the base case analysis was provided alongside a list of sensitivity analyses conducted by the company to explore the impact of these assumptions in the cost effectiveness results.

Table 4.15: Summary of company base case assumptions

Assumption	Rationale	Scenario/sensitivity analysis
Model cycle length of 7 days	A 7-day cycle length is assumed to be sufficiently short to represent the frequency of clinical events and interventions. Further, one week is aligned with the administration of the multiple subsequent treatments included within the model (treatment cycles in weeks)	NA
A lifetime horizon of 30 years	Reflects the lifetime of patients based on a starting age of [redacted]. Less than 1.5% are alive after this time horizon.	Scenario analysis The impact of alternative time horizons on the results was tested.
Efficacy: OS, PFS and TTD for both arms were directly extrapolated from the pivotal DESTINY-Breast03 trial.	Uses available data from a head-to-head randomised control trial vs the relevant comparator. Validated by clinical and economic experts as the preferred approach	Scenario Analysis Alternative OS method utilising mature OS data from the EMILIA trial which is considered generalisable to UK practice and DESTINY-Breast03 study
Efficacy: Dependent models are estimated for OS	LCHP and proportionality test showed support for the PH assumption. Using dependent models also allows more data to be used for the parametric models	NA
Efficacy: Independent models are estimated for PFS and TTD	LCHP and proportionality test rejected the PH assumption. In addition, given the availability of patient-level data for each treatment and maturity of the data, the reliance on the PH assumption was considered unnecessary and therefore, independent models were considered more appropriate. TTD approach consistent with PFS as	NA

	majority of discontinuations were due to progression.	
Efficacy: HR observed in the DESTINY-Breast03 trial data lasts for the entire duration of the economic model	NA	NA
Utilities: Utility values were assumed to differ by treatment and health state	Direct EQ-5D-5L data collected within the DESTINY-Breast03 trial show a difference between arms in utilities in both 'progression-free' and 'progressed' health states. This may be due to the higher response rates. Based on the response rates of T-DXd and T-DM1, utility values are expected to be greater for T-DXd which is demonstrated by the observed direct evidence from DESTINY-Breast03. Patients on T-DXd are expected to have greater utility when progressing which follows into the progression health state.	Scenario Analysis Use of alternative utility sources and alternative assumptions around treatment-specific utility differences OWSA, PSA Variation of utility value through confidence intervals
50% of centres vial share and therefore have no wastage	Clinical experts during the TA458 appraisal noted that some centres do vial share and therefore 100% wastage is not reflective of current practice. In line with assumptions made in TA704, 50% was assumed as this was accepted by the committee	Scenario analysis 0% and 100% vial sharing tested in scenario analysis OWSA, PSA OWSA and assuming a beta distribution
Subsequent treatment: 66.7% of patients receive subsequent treatment as a percentage of those who progress	Clinical opinion at expert validation meeting that two-thirds of patients will receive subsequent treatments as a percentage of patients who progress in UK practice	Scenario Analysis Alternative values based on the DESTINY-Breast03 study OWSA and PSA Varied across confidence interval and assuming a beta distribution
Subsequent treatment: Subsequent treatments from DESTINY-Breast03 are costed	The trial was considered generalisable to UK practice, and without adjusting OS efficacy for alternative subsequent treatments, aligning with the trial was considered the most appropriate way of costing subsequent treatments within the model base case	Scenario analysis Alternative subsequent treatment percentages based on clinical expert advice OWSA and PSA Varied across confidence interval and assuming
Subsequent treatment: Subsequent treatments listed as 'Other' in DESTINY-	In line with clinical practice as capecitabine is the most common non-targeted chemotherapy used in third line HER2+ mBC	OWSA and PSA Varied across confidence interval and assuming a Dirichlet distribution

Breast03 are costed as capecitabine		
Costs and dis-utilities associated with AEs occurred in the first cycle of the model	The greatest proportion of TEAEs in the DESTINY-Breast03 trial data occurred in the first cycle and subsequently declined through cycles.	NA

Source: Table 58, CS[1]

Abbreviations: AE: Adverse effects; EQ-5D-5L, EuroQol 5 Dimension 5 Level; HER2, human epidermal growth factor receptor 2; LCHP, Log-Cumulative Hazard Plots; mBC, metastatic Breast Cancer; NA, Not applicable; OS, Overall Survival; OWSA, One Way Sensitivity Analyses; PFS, Progressive Free Survival; PH, Proportional Hazards; PSA, Probabilistic Sensitivity Analyses; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TEAE, Treatment-emergent Adverse Event; TTD, Time to Treatment Discontinuation

5. COST EFFECTIVENESS RESULTS

5.1 Base case incremental cost effectiveness results

The company base case discounted deterministic results excluding and including the 1.2x QALY weighting are presented in Table 5.1. T-DXd is more costly and more effective than T-DM1, representing an undiscounted life year (LY) gain of [redacted], a discounted QALY gain of [redacted], and an incremental cost of [redacted]. The associated ICER was [redacted] per QALY gained. Application of the 1.2x QALY weighting results in a discounted QALY gain of [redacted] and the associated ICER of [redacted].

Table 5.1: Base case deterministic economic analysis results (with PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs (1.2x QALY weighting)	ICER (£/QALY) baseline (x1.2 QALY weighting)	NHB at £20,000 (1.2x QALY weighting)	NHB at £30,000 (1.2x QALY weighting)
T-DM1	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Tables 59 and 60, CS.[1]

This table reports undiscounted LYG, and discounted costs and QALYs.

Abbreviations: ICER: incremental cost effectiveness ratio; Incr., incremental; LYG: life years gained; PAS: patient access scheme; QALYs: quality-adjusted life years; NHB: net health benefit; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

5.2 Company's sensitivity analyses

The company performed and presented the results of probabilistic sensitivity analyses (PSA), deterministic sensitivity analyses (DSA) as well as scenario analyses.

5.2.1 Probabilistic sensitivity analysis

The company probabilistic sensitivity analysis (PSA) results are presented in Table 5.2. The PSA was based on 10,000 simulated results. The average incremental costs were [redacted] and the average incremental QALYs were [redacted], generating a probabilistic ICER per QALY gained of [redacted].

Table 5.2: Mean PSA results (with PAS)

Technologies	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
T-DM1	[redacted]	[redacted]	[redacted]				
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Tables 61, CS.[1]

Abbreviations: ICER: incremental cost effectiveness ratio; LYG: life years gained; NHB: net health benefit; PAS: patient access scheme; QALYs: quality-adjusted life years; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

The company produced a cost effectiveness plane and cost effectiveness acceptability curves, which are reproduced in Figure 5.1 and Figure 5.2. The probability that T-DXd was cost-effective was [redacted] and [redacted] at cost-effectiveness thresholds of £30,000 and £36,000 per QALY gained. The £30,000 per QALY threshold is one of NICE's recommended thresholds (£20,000 and £30,000). The £36,000 per QALY gained threshold was also used for the scenario where the 1.2x QALY weighting was applied due to severity of disease. Either the QALYs can be inflated by a factor of 1.2 and a £30,000 per QALY threshold used, or the QALYs can be left unadjusted and a £36,000 per QALY gained threshold used.

Figure 5.1: Cost effectiveness plan for T-DXd versus T-DM1

[redacted]

(Source: Figure 35, CS[1])
Abbreviations: PSA, Probabilistic Sensitivity Analyses; QALY, quality-adjusted life year; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan

Figure 5.2: Cost effectiveness acceptability curve for T-DXd versus T-DM1

(Source: Figure 36, CS[1])
Abbreviations: T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

5.2.2 Deterministic sensitivity analysis

The effect on the cost-effectiveness results of varying changing all model parameter values over plausible ranges was evaluated using univariate deterministic sensitivity analysis (DSA). The plausible range was determined by either upper and lower bounds of the confidence interval (CI) or assuming standard error of 10% of the mean where no estimates of precision were available (Table 62 and Figure 37, CS).[1]

The company conducted a range of one-way DSAs for upper and lower limits of the confidence interval for the parameters in Table 62 in the CS, results are summarised in Figure 27.[1] For parameters without a confidence interval, these were derived assuming that the standard error was 10% of the mean value. One-way sensitivity analyses with the 10 greatest impact on the ICER for T-DXd versus T-DM1 are summarised in Table 5.3 and Figure 5.3.

Table 5.3: Parameters with range

Parameter	Input	Lower bound	Upper bound
Lloyd et al. (2006): PD - original responders	0.64	0.51	0.758
Lloyd et al. (2006): PD - original non-responders	0.54	0.43	0.645
T-DM1 - Percentage receiving subsequent treatment	66.7%	53.0%	79.0%
T-DXd - Percentage receiving subsequent treatment	66.7%	53.0%	79.0%
RDI - T-DXd	[redacted]	[redacted]	[redacted]
RU - unit cost - Medical oncologist	£201.33	£161.87	£240.79

DB-03 PFS T-DXd utility	0.82	0.80	0.837
Sub trt - duration (weeks) - T-DM1	22.70	18.25	27.15
Administration cost - simple infusion	£221.35	£177.96	£264.73
RU - PF - Medical oncologist	0.23	0.18	0.28

Source: Table 62, CS.[1]
Reference: Lloyd et al. (2006)[47]
Abbreviations: DB-03, DESTINY-Breast03; ICER, incremental cost-effectiveness ratio; OWSA, one-way sensitivity analysis; PD, progressed disease; PF, progression-free; PFS, progression-free survival; RDI, relative dose intensity; RU, resource use; Sub trt, subsequent treatment; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

Figure 5.3: DSA tornado plot for T-DXd versus T-DM1 (with PAS)

(Source Figure 37, CS[1])
(Abbreviations: ICER, incremental cost-effectiveness ratio; PD, progressed disease; PF, progression-free; PFS, progression-free survival; RDI, relative dose intensity; RU, resource use; Sub trt, subsequent treatment; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan)

5.2.3 Scenario analysis

The company undertook what they described as the key scenario analysis of implementing Method 2 for extrapolation of OS, and the company also undertook a series of other scenario analyses (Tables 63, 64 and 65 in CS)[1] to assess the impact of the following number of assumptions and alternative inputs on the cost-effectiveness results. The results of the scenario analyses are presented in Table 5.4. The list of parameters or assumptions changed in scenario analysis include:

- Time horizon
- Discount rate
- Source of utility
- Dis-utilities
- Age-adjusted dis-utilities
- Relative dose intensity
- Proportion vital sharing

- Subsequent treatment distributions
- Subsequent treatment percentages
- Subsequent treatment T-DXd and T-DM1
- The model used to extrapolate OS from pivotal trial data
- The model used to extrapolate PFS from pivotal trial data
- The model used to extrapolate TTD from pivotal trial data
- The model used to extrapolate OS from pivotal trial data and external study (EMILIA)[42]

Table 5.4: Scenario analysis results

Scenario	Base-case	Alternative input	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)
Base-case			[redacted]	[redacted]	[redacted]
1	Direct extrapolation of DB-03	Extrapolation of replicated data from EMILIA + HR	[redacted]	[redacted]	[redacted]
2	30 years	20 years	[redacted]	[redacted]	[redacted]
3		40 years	[redacted]	[redacted]	[redacted]
4	Discount rate: 3.5% (costs and effects) with 1.2 QALY weighting	1.5% (costs and effects) without QALY weight	[redacted]	[redacted]	[redacted]
5	Utility source PFS = DB-03 (treatment specific) PD = Lloyd et al (treatment specific)	PFS = Lloyd et al. – treatment specific utilities PD = Lloyd et al. – treatment specific utilities	[redacted]	[redacted]	[redacted]
6		PFS = Lloyd et al. – combined utilities PD = Lloyd et al. – combined utilities	[redacted]	[redacted]	[redacted]
7		PFS = DB-03 utilities combined PD = Lloyd et al. combined	[redacted]	[redacted]	[redacted]
8	Disutilities excluded	Disutilities included	[redacted]	[redacted]	[redacted]
9	Age-related disutilities included	Age-related disutilities excluded	[redacted]	[redacted]	[redacted]

10	RDI included	RDI excluded	[redacted]	[redacted]	[redacted]
11	Proportion vial sharing 50%	Proportion vial sharing 0%	[redacted]	[redacted]	[redacted]
12		Proportion vial sharing 100%	[redacted]	[redacted]	[redacted]
13	Subsequent treatment distributions from DB-03 data	UK practice	[redacted]	[redacted]	[redacted]
14		DB-03 pooled	[redacted]	[redacted]	[redacted]
15	Subsequent treatment percentages from UK practice	DB-03 data	[redacted]	[redacted]	[redacted]
16		DB-03 pooled	[redacted]	[redacted]	[redacted]
17	Subsequent treatments T-DXd and T-DM1 include costs	Exclude costs	[redacted]	[redacted]	[redacted]
18	OS plausible extrapolations using generalised gamma	Using log-logistic	[redacted]	[redacted]	[redacted]
19		Using Weibull	[redacted]	[redacted]	[redacted]
20	PFS plausible extrapolations using Weibull	Using log-logistic	[redacted]	[redacted]	[redacted]
21		Using log-normal	[redacted]	[redacted]	[redacted]
22		Using exponential	[redacted]	[redacted]	[redacted]
23	TTD extrapolations using Weibull	Using Gompertz	[redacted]	[redacted]	[redacted]
24	OS extrapolations of replicated data from EMILIA + HR using log-normal	Using generalised gamma	[redacted]	[redacted]	[redacted]
25		Using log-logistic	[redacted]	[redacted]	[redacted]
26		Using Weibull	[redacted]	[redacted]	[redacted]

Source: Table 65 in the CS[1]
References: Lloyd et al. (2006)[47]
Abbreviations: DB-03, DESTINY-Breast03; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, Overall survival; PD, progressed disease; PFS, progression-free survival; QALY, quality-adjusted life year; RDI, relative dose intensity; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TTD, time-to-treatment discontinuation

EAG comment: The EAG considers the parameters and respective distributions chosen for PSA to be generally sound. The EAG also considers the probabilistic results to be comparable to deterministic base case results. The DSA tornado diagram indicated that utility values for the 'progression disease' health state are the most influential parameters. The results showed ICERs ranging between [redacted] and

[redacted] per QALY gained. The three most influential scenarios that increased the ICER were the Weibull PSM used to extrapolate OS from the EMILIA study,[42] combined PFS utilities from the pivotal trial and combined PD utilities from literature (Lloyd et al., 2006), and combined PFS utilities and combined PD utilities from literature (Lloyd et al., 2006).[47]

5.3 Severity of the condition

The total QALYs estimated for T-DM1 in the deterministic analysis of the base case model was [redacted]. Total QALYs estimated for T-DM1 in the probabilistic analysis were [redacted].

For the deterministic analysis, there was an absolute QALY shortfall of [redacted] with a proportional shortfall of [redacted] The absolute shortfall meets the NICE criteria for a QALY weight >1 and the proportional shortfall does not (Table 5.5).

For the probabilistic analysis, there was an absolute QALY shortfall of [redacted] with a proportional shortfall of [redacted] The absolute shortfall meets the NICE criteria for a QALY weight >1 and the proportional shortfall does not (Table 5.5).

Table 5.5: QALY weights referenced within the new NICE manual (2022, PMG36)[3]

QALY weight	Absolute shortfall	Proportional shortfall
1 x	Less than 12	Less than 0.85
1.2 x	12 – 18	0.85 – 0.95
1.7 x	At least 18	At least 0.95

Source: CS, Table 50[1]
Abbreviations: QALY, quality-adjusted life-year.

The company reported scenarios where the QALY proportional shortfall meets the NICE criteria for a QALY weighting of 1.2: using data from the EMILIA[42] replicated data (proportional: 85.16%) and TA458 (proportional: 86.00%). The company claim that these analyses consistently demonstrate that a 1.2x QALY weighting is appropriate for decision-making in this appraisal.

5.4 Validation

5.4.1 Technical verification and Face validity assessment

For the model validation, the company stated that a technical review of the cost effectiveness model was carried out by an external health economist. In addition, the relevance of the model structure and assumptions were validated through consultation with UK clinicians and HEOR experts. According to the CS,[1] two clinical experts from oncology and two health economics and outcomes research experts discussed and validated the following key aspects:

- DESTINY-Breast03 trial generalisability, efficacy and safety
- Generalisability of external data sources
- UK treatment pathway
- The model structure and appropriateness to the decision problem
- OS methods
- Extrapolation of OS and PFS beyond the observed period
- Validity of model inputs including resource use, costs and utilities

- Subsequent treatment usage

5.4.2 Comparison with external data not used to develop the economic model

EAG comment: Cross validation of the model results was not possible since this is the first economic evaluation assessing the cost effectiveness of T-DXd versus T-DM1.

6. EVIDENCE ASSESSMENT GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the EAG

This Section describes the EAG base-case analyses and scenario analyses conducted based on both the EAG base-case analyses and the company base-case analyses. The EAG base-case analyses use the company economic models and adopt alternative assumptions.

6.1.1 EAG base-case

Table 6.1 summarises the key issues related to the cost effectiveness categorised according to the sources of uncertainty as defined by Grimm et al. (2020).[66]

1. Transparency (e.g. lack of clarity in presentation, description, or justification)
2. Methods (e.g. violation of best research practices, existing guidelines, or the reference case)
3. Imprecision (e.g. particularly wide confidence intervals, small sample sizes, or immaturity of data)
4. Bias and indirectness (e.g., there is a mismatch between the decision problem and evidence used to inform it in terms of population, intervention/comparator and/or outcomes considered)
5. Unavailability (e.g. lack of data or insight)

Identifying the source of uncertainty can help determine what course of action can be taken (i.e., whether additional clarifications, evidence and/or analyses might help to resolve the key issue). Moreover, Table 6.1 lists suggested alternative approaches, expected effects on the cost effectiveness, whether it is reflected in the EAG base-case as well as additional evidence or analyses that might help to resolve the key issues.

Based on all considerations in the preceding Sections of this EAG report, the EAG defined a new base-case. This base-case included multiple adjustments to the original base-case presented in the previous Sections. These adjustments made by the EAG form the EAG base-case and were subdivided into three categories.[67]

- Fixing errors (FE) (correcting the model where the company's submitted model was unequivocally wrong)
- Fixing violations (FV) (correcting the model where the EAG considered that the NICE reference case, scope, or best practice had not been adhered to)
- Matters of judgement (MJ) (amending the model where the EAG considers that reasonable alternative assumptions are preferred)

The EAG found errors in the model but found no violations. Further adjustments were made based on MJ. After these changes were implemented in the company's model, additional scenario analyses were explored by the EAG in order to assess the impact of alternative assumptions on the cost effectiveness results.

Fixing errors

1. **Coding error**: Cells L27:L2427 in the "Efficacy Summary" spreadsheet use the minimum value between TTD and adjusted OS rather than the minimum value between TTD and PFS.
   Correction: The column referenced in the formula was changed from 'P' to 'K' for the whole array, i.e. "=MIN('DB03_T-DXd'!CB27,P27)" to "=MIN('DB03_T-DXd'!CB27,K27)".

2. **Coding error**: Cells T27:T2427 in the "Efficacy Summary" spreadsheet use the minimum value between TTD and adjusted OS rather than the minimum value between TTD and PFS.
   Correction: The column referenced in the formula was changed from 'X' to 'S' for the whole array, i.e. "=MIN('DB03_T-DM1'!CB27,X27)" to "=MIN('DB03_T-DM1'!CB27,S27)".

Matters of judgement

1. The company assumed that the trend in the overall survivor curve as the proportion of alive patients who are progression-free changes within trial follow-up will continue beyond the follow-up period.

The company made this assumption when approximately 80% of the T-DXd patients were still alive and approximately 50% of patients were still progression-free at the first interim cut point. In the company base case, a dependent parametric survival model was fitted and the implied hazard ratio of mortality was gently increasing over time (Method 1). The company acknowledged the uncertainty in the overall survival predictions and did scenario analysis where survival for T-DM1 was modelled using the final analysis data set from the EMILIA trial and then a constant hazard ratio of mortality was assumed, which was estimated using a Cox-proportional hazards model (Method 2).

The EAG thinks that the assumptions made in both Method 1 and Method 2 are strong. The EAG considered two alternative assumptions in the extrapolation of OS beyond 2 years: (A) a conservative scenario with no treatment effect beyond disease progression, and (B) a less conservative assumption where the treatment effect wanes over time, which is determined by the proportion of patients still alive who are in the PD state. The estimated survivor curves for T-DXd using assumptions A and B and the company base case survivor curves for T-DXd and T-DM1 are presented in Figure 6.1. The survivor estimates generated using assumption A and assumption B were so similar that assumption A only was adopted. Both of these assumptions involve setting the hazard ratio of mortality of PD patients to 1, but at different time points. This is an imperfect application of equal hazard rates for patients in the PD state, but the EAG thinks it is a reasonable approximation and is the preferred assumption for the EAG. See Appendix 2 for the details of the methods used to derive the overall survival curves for T-DXd.

Figure 6.1: The T-DXd company base case, EAG assumption A and EAG assumption B survivor curves

(Source: Produced by EAG)
(Abbreviations: CS, company submission; HR, hazard ratio; PD, progressed disease; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan)

2. The company used a greater utility value for T-DXd patients in the PD state than for T-DM1 patients based on data reported in Lloyd et al. (2006) in the base case.

The EAG could not find any evidence in the CS or in Lloyd et al. (2006) for different utility values for T-DXd and T-DM1 in the PD state (see Section 4.2.8). Consequently, the EAG included a single combined utility estimate for PD was applied to both arms instead of the treatment specific values. The PD combined value, 0.596, was calculated using the trial data and Lloyd et al. (2006) algorithm and is between the T-DXd value (0.618) and theT-DM1 value (0.574).

3. The company assumed that no vial wastage occurs in 50% of cases for T-DXd in the base case

The EAG considered it was unlikely that vial sharing would occur in as commonly as purported based on personal communication with clinical experts. In the base 50% of cases were assumed to have drug wastage, the EAG adopted a more conservative estimate of 90% wastage. The values are summarised in Table 4.12.

6.1.2 EAG exploratory scenario analyses

This Section describes the scenario and sensitivity analyses conducted by the EAG. The EAG conducted the scenario included in the CS and sensitivity analyses with the greatest impact on the ICER estimates.[1] In addition, the EAG conducted three scenario analyses not conducted by the company: alternative PFS and TDD extrapolations, and an alternative value for the cost of administering chemotherapy. All of these scenario and sensitivity analyses are described below.

PFS and TDD extrapolations:

1. EAG adjustment: independent log-normal extrapolation for both PFS and TTD, for both T-DM1 and T-DXd (scenario 16)

This was considered because the log-normal was a good fitting model and produced consistent outcomes between TTD, PFS and OS. However, predicted outcomes may be too high at 10 years.

2. EAG adjustment: independent generalised gamma for both PFS and TTD, for both T-DM1 and T-DXd (scenario 17)

This was considered because the generalised gamma was a good fitting model and produced consistent outcomes between TTD, PFS and OS. However, predicted outcomes may be too high at 10 years.

6.1.3 EAG subgroup analyses

No subgroup analyses were performed by the EAG.

Table 6.1: Overview of key issues related to the cost effectiveness (conditional on fixing errors highlighted in Section 5.1)

Key issue pertaining to cost effectiveness (See Section 1)	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER[a]	Resolved in EAG base-case[b]	Required additional evidence or analyses
6. Uncertain OS predictions for T-DXd	4.2.6	Methods	Assuming HR=1 for PD patients	+	Yes, to an extent	
7. Crosswalking EQ-5D-5L to EQ-5D-3L with the recommended algorithm	4.2.8	Methods	Mapping EQ-5D-5L to 3L developed by the NICE DSU[55]	+/-	No	
8. Post-progression utility values: treatment-specific utility values applied in the PD health state	4.2.8	Methods	Same utility value applied to both arms	+	Yes	

(Source: Produced by EAG)
[a] Likely conservative assumptions (of the intervention versus all comparators) are indicated by '-'; while '+/-' indicates that the bias introduced by the issue is unclear to the EAG and '+' indicates that the EAG believes this issue likely induces bias in favour of the intervention versus at least one comparator; [b] Explored
Abbreviations: DSU, Decision Support Unit; EAG = External Assessment Group; EQ-5D-5L, EuroQol 5 Dimension 5 Level; EQ-5D-3L, EuroQol 5 Dimension 3 Level; FE = Fixing errors; FV = fixing violations; HR, hazard ratio; ICER = incremental cost effectiveness ratio; MJ = matters of judgement; PD, progressed disease

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

In Section 6.1 the features of the EAG base-case were presented, which was based on various changes compared to the company base-case relating to both fixing of errors and matters of judgement (MJ). Table 6.2 shows how individual changes impact the results plus the combined effect of all changes simultaneously. The exploratory scenario analyses are presented in Table 6.3. These are all conditional on the EAG base-case.

6.2.1 The EAG base case

Table 6.2: Deterministic/probabilistic EAG base-case results

Preferred Assumption	T-DXd		T-DM1		Incremental Costs (£)	Incremental QALYs (1.2x QALY weighting)	Cumulative ICER (£/QALY, 1.2x QALY weighting)
	Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs			
Company base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company base-case after fixing errors	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MJ 1: no treatment effect beyond progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MJ2: a single combined utility for PD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MJ3: 90% wastage rate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base-case deterministic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base-case probabilistic*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

(Source: Produced by EAG)
*10,000 simulations
Abbreviations: EAG: evidence assessment group; ICER: incremental cost effectiveness ratio; MJ = matters of judgement; PD, progressed disease; QALY: quality-adjusted life year; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan

6.2.2 EAG scenario and sensitivity analyses

Table 6.3: Deterministic/probabilistic scenario analyses (conditional on EAG base-case)

Scenario	Base-case	Alternative input	T-DXd		T-DM1		Incremental Costs (£)	Inc. QALYs (1.2x QALY weighting)	ICER ing(£/QALY, 1.2x QALY weighting)
			Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs			
Base-case			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	OS extrapolation: Direct extrapolation of DB-03	Extrapolation of replicated data from EMILIA + HR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	Time horizon: 30 years	20 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3		40 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	Discount rate: 3.5% (costs and effects) with 1.2 QALY weighting	1.5% (costs and effects) without QALY weighting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	Utility source: PFS = DB-03 (treatment specific) PD = Lloyd et al (combined specific)	PFS = DB-03 (treatment specific) PD = DB-03 (combined specific)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6		PFS =Lloyd et al (treatment specific) PD = DB-03 (combined specific)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario	Base-case	Alternative input	T-DXd		T-DM1		Incremental Costs (£)	Inc. QALYs (1.2x QALY weighting)	ICERing(£/QALY, 1.2x QALY weighting)
			Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs			
7		PFS =Lloyd et al. (treatment specific) PD = Lloyd et al. (combined specific)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		PFS = DB-03 (treatment specific) PD = TA458[29] (combined specific)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	AE disutilities excluded	AE disutilities included	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	Age-related disutilities included	Age-related disutilities excluded	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	RDI included	RDI excluded	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	Subsequent treatment distributions from DB-03 data	UK practice	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12		DB-03 pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13	Subsequent treatment percentages from	DB-03 data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	UK practice	DB-03 pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario	Base-case	Alternative input	T-DXd		T-DM1		Incremental Costs (£)	Inc. QALYs (1.2x QALY weighting)	ICER ing(£/QALY, 1.2x QALY weighting)
			Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs			
15	Subsequent treatments T-DXd and T-DM1 include costs	Exclude costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16	PFS and TTD plausible extrapolations using Weibull	Using log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
17		Using generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

(Source: Produced by EAG)

Footnote: * SB12Z and SBI5Z are codes from NHS Reference Costs 2019/2020 [61]

Abbreviations: DB-03: DESTINY-Breast03; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; OS: overall survival; PD: progressed disease; PFS: progression-free survival; QALYs: quality adjusted life-years; RDI: relative dose intensity; TTD: time to treatment discontinuation.

6.2.3 Severity of the condition

Using the Schneider et al. shortfall calculator and the EAG base case probabilistic analysis, the total QALYs value for T-DM1 qualifies for a disease severity multiplier of 1.0 as a QALY weight. For the EAG base case deterministic analysis, the total QALYs value for T-DM1 qualifies for a disease severity 1.2x QALY weight when the Van Hout et al. HRQoL norms are used and for a disease severity 1.0x QALY weighting when the Hernández Alava et al. HRQoL norms are used.

In the company base case, the T-DM1 total QALY estimate was [redacted] in the deterministic analysis and [redacted] in the probabilistic analysis. A PSA was run 5 times for the company base case and the T-DM1 total QALYs was [redacted] every time, so the PSA estimate is considered stable for disease severity calculations. Both of these values ensured that a 1.2x QALY weighting criteria were met when using the Van Hout et al. algorithm, but not when using the Hernández Alava et al. algorithm.

The [redacted] was exactly borderline using the Van Hout et al. algorithm, so the deterministic analysis scenarios 4, 5, 6 and 17 in Table 6.3 would meet the criteria for a 1.0x QALY weight as the T-DM1 total QALYs was greater than [redacted].

Table 6.4: Summary of QALY shortfall analysis using data from EAG economic analysis – base case

Schneider shortfall calculator	Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	QALY shortfall
Hernandez Alava et al., EQ-5D-5L to 3L mapping + HSE 2017-2018	14.33	T-DM1: [redacted]	Absolute: [redacted] Proportional: [redacted]
MVH, EQ-5D-3L value set + HSE 2012+14	14.63		Absolute: [redacted] Proportional: [redacted]
Hernandez Alava et al., EQ-5D-5L to 3L mapping + HSE 2017-2018	14.33	T-DM1: [redacted]	Absolute [redacted] Proportional: [redacted]
MVH, EQ-5D-3L value set + HSE 2012+14	14.63		Absolute [redacted] Proportional: [redacted]

(Source: Produced by EAG)
Abbreviations: EQ-5D-5L, EuroQol 5 Dimension 5 Level; EQ-5D-3L, EuroQol 5 Dimension 3 Level;; HSE: Health Survey for England; MVH: Measuring and Valuing Health; QALYs: quality adjusted life-years; T-DM1, trastuzumab emtansine

6.3 EAG's preferred assumptions

The estimated EAG base-case ICER (probabilistic), based on the EAG preferred assumptions highlighted in Section 6.1, was [redacted] per QALY gained for the comparison of T-DXd versus T-DM1. The probabilistic EAG base-case analyses indicated cost effectiveness probabilities of [redacted] and [redacted] at willingness to pay thresholds of £30,000 and £36,000 per QALY gained respectively. Figure 29 illustrates this by presenting the cost effectiveness acceptability curve.

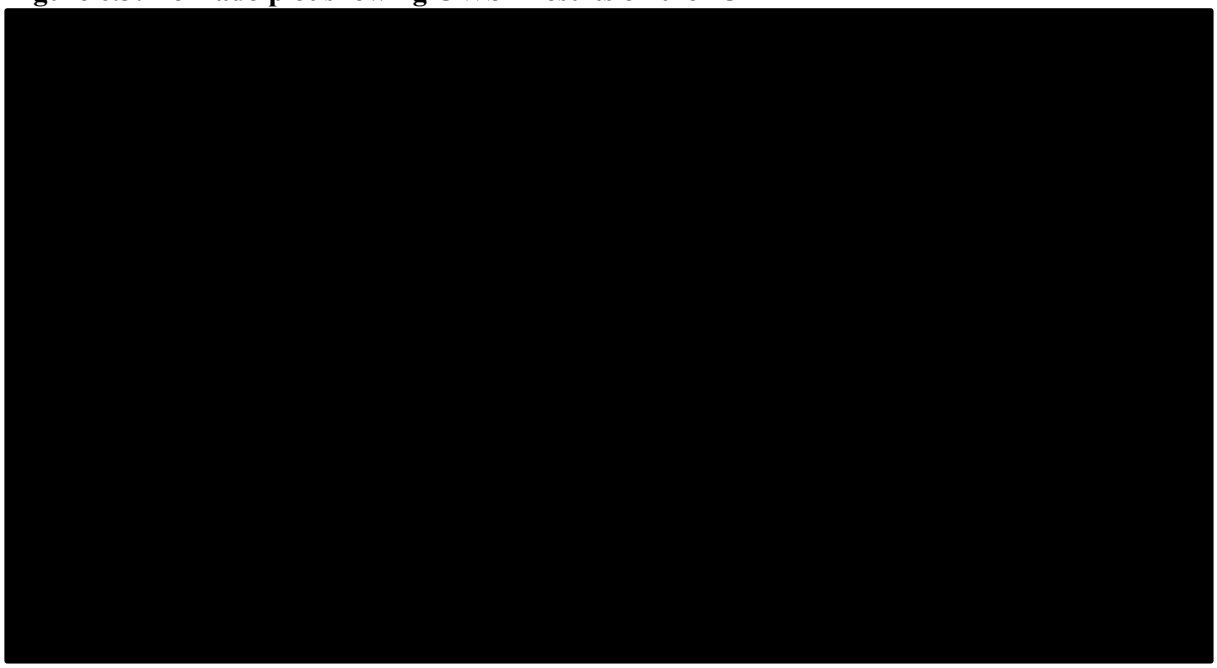
As Table 6.2 shows, the most influential adjustments were 1) no treatment effect beyond progression, 2) a single combined utility for PD, and 3) 90% wastage rate. For the scenario analyses shown in Table 6.3, the ICER increased in eight of the 17 scenarios and decreased in nine scenarios.

To further explore uncertainty and provide comparison with the CS, Figure 6.3 presents the results of one-way sensitivity analyses conducted around the EAG base-case.[1] Without weighting the QALYs, the upper NICE threshold is £30,000/QALY if the 1.2x QALY weighting criteria are not met and £36,000/QALY if the 1.2x QALY weighting criteria are met. If the 1.2x QALY weighting criteria are not met, then none of the analyses result in an ICER lower than £30,000/QALY. If the 1.2x QALY weighting criteria are met, then only the scenario of using the percentages of patients receiving subsequent treatment as recorded in DESTINY-Breast03 would cause the ICER to rise above £36,000/QALY.

Figure 6.2: Cost effectiveness acceptability curve for T-DXd versus T-DM1

(Source: Produced by EAG)
(Abbreviations: T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan)

Figure 6.3: Tornado plot showing OWSA results on the ICER



(Source: Produced by EAG)
(Abbreviations: DB03, DESTINY-Breast03; ICER: Incremental cost-effectiveness ratio; OWSA: One-way sensitivity analysis; PD, Progressed disease; PF: progression-free; PFS: Progression-free survival; RDI: Relative dose intensity; RU, resource use; Sub trt: subsequent treatment, T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan)

6.4 Conclusions of the cost effectiveness section

The economic SLR identified eighteen publications. Most models in the SLR used a Markov model structure. However, like previous HTA submissions, this CS used a partitioned survival approach.[1] As no published economic evaluations of T-DXd were identified within the second-line setting, a *de novo* economic model was developed. A SLR to identify (i) relevant HRQoL and (ii) cost and resource use studies was also conducted. The EAG was satisfied by the conduct of these reviews and accepts the model structure as provided.

The EAG considers that the company appropriately complied with most of the elements present in the NICE reference case with one exception regarding use of EQ-5D crosswalk algorithm. The company's *de novo* model consisted of three health states: progression free survival (PFS), progressed disease (PD) and death. The population used in the CS base-case model was patients who had HER2-Positive unresectable or metastatic breast cancer after trastuzumab and a taxane based on the DESTINY-Breast-03 (DB-03) trial.[1] The EAG was satisfied that this population covers the population in the NICE scope.[2]

The intervention was trastuzumab deruxtecan (T-DXd) administered by IV infusion at a dose of 5.4 mg/kg compared with trastuzumab emtansine (T-DM1) administered by IV infusion at a dose of 3.6mg/kg. There was evidence that T-DXd extended progression-free survival and overall survival. There was also evidence that T-DXd was associated with a higher rate of adverse events.

The progression-free survival data were immature for T-DXd and the overall survival data for T-DXd and T-DM1 were very immature. The predictions estimated by the PFS and OS extrapolations were highly uncertain. The company employed two methods to extrapolate OS beyond the end of the follow-up period associated with the interim cut point. *Method 1* for the T-DXd survival curve relied on the assumption that the trend in the overall survivor curve as the proportion of alive patients who are

progression-free changes within trial follow-up will continue beyond the follow-up period. *Method 2* for the T-DXd survival curve relied on an assumption of a constant hazard ratio across the 30-year time horizon of the model.

The EAG does consider the overall survival predictions for T-DM1 to be plausible given the fitted survival model and the company clinical expert opinion on survival rates at 10 years. The company modelled a large overall survival treatment effect over the course of the 30-year time horizon. Given the lack of evidence of a significant treatment effect after disease progression (and cessation of initial treatment), the EAG undertook additional analysis assuming no treatment benefit after disease progression.

It is unclear if the PFS and OS outcomes are perfectly generalisable to England given the majority Asian DESTINY-Breast03 trial population, and the significant difference in the estimates of the percentages of patients who receive subsequent treatment as a percentage of patients who experience disease progression and the distribution of subsequent treatments between DESTINY-Breast03 trial and clinical expert opinion of clinical practice in England.

The model assumes that AEs occur once within the first cycle with data taken from the DB-03 trial in order to incorporate the cost of AEs. In the base case, no utilities were specifically assigned to the AEs as it was assumed that within-trial utility estimates captured the impact of AEs. Long-lasting effects of AEs should be captured in the EQ-5D-5L DESTINY-Breast03 trial measurements and therefore in the base case analysis.

Utility weights for the PFS and PD state were sourced from the DB-03 trial either directly or using an algorithm. The Van Hout et al. EQ-5D crosswalk algorithm was used instead of the recommended Hernandez Alavez et al. algorithm to estimate utilities from the DESTINY-Breast03. This is a violation of the NICE 2022 Methods guidance (PMG36) and the option to use these values was not available in the CEM.[3] For both health states, treatment-specific utilities were applied. The EAG could not find any evidence in the CS to support a difference in PD utilities across treatment groups. Furthermore, a significant percentage of patients (66.7%) will receive a subsequent treatment as a percentage of patients who experience disease progression, which will affect HRQoL.

The costs for each health state were ascertained from several different resources including expert clinical opinion, previous TAs and relevant NICE guidelines. The company assume 50% of patients will have no vial wastage. The EAG have consulted clinical experts and that vial sharing either does not happen or is entirely dependent on the circumstance of each clinic in UK. The EAG used a lower vial-sharing rate of 10% in their base-case. The EAG agreed with the company on the percentage of patients that will receive a subsequent treatment as a percentage of patients who experience disease progression is lower in the UK than in the trial.

The severity of the condition criteria was measured by the QALY shortfall in the CS.[1] The company used an online estimator that though not explicitly stated in the 2022 NICE guidance was acceptable to the EAG without specific guidance to the contrary. The company could have used the Hernandez Alava et al. algorithm for both the PFS and OS utility estimates and the HRQoL norms. Given the HRQoL methods adopted, the company base case results do meet the 1.2x QALY weighting criteria. However, the EAG base-case probabilistic analysis results suggest that the 1.0x QALY weighting criteria are not met, and the EAG base-case deterministic analysis results suggest that the 1.2x QALY weighting criteria are met if the Van Hout algorithm HRQoL norms are used.

There were two coding errors that resulted in an increase in the ICER once corrected (The EAGs replication of the corrected company base-case deterministic analysis resulted in an ICER of [redacted] per QALY gained).

The greatest uncertainty in the evidence concerned the immaturity of the data from DB-03 trial, which results in the ICER being very uncertain. The submitted company's base-case deterministic analysis ICER was [redacted] compared with the EAG base-case of [redacted] This was primarily driven by the EAG's preferred assumptions around the treatment effect beyond the PFS health state. The EAG implemented a method to equal treatment effectiveness in the PD health state in the EAG base-case.

The EAG conducted three additional scenarios to the 15 scenario analyses presented by the company. These three additional scenarios used plausible extrapolations distribution for PFS and TTD, and a separate estimate for the administration of chemotherapy. All 18 EAG scenario analyses resulted in an ICER above the willingness-to-pay threshold of £30,000 per QALY gained with only one scenario above the willingness-to-pay thresholds of £36,000 per QALY gained when severity of the condition criteria is applied.

In OWSA, the percentage of patients receiving subsequent treatment as a percentage of patients who experience disease progression in each treatment arm had the biggest effect on the ICER. The probabilistic EAG base-case analyses indicated cost effectiveness probabilities of [redacted] and [redacted] at willingness-to-pay thresholds of £30,000 and £36,000 per QALY gained. No subgroup analyses were provided and the EAG was satisfied that none were warranted. Given the immaturity of the data in the DESTINY-Breast03 trial, it is quite likely the full uncertainty in the cost-effectiveness of T-DXd associated with PFS and OS extrapolation has not been reflected in these results.

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Appendix 1: EAG comments regarding the company's clinical effectiveness related search strategies

- Lack of searching of clinical trials registers. The company stated on the response to clarification letter that they did not expect to find any additional relevant trials in clinical trials registers.[10] In line with best practice recommendations searches of clinical trials registries would have been appropriate (e.g., ClinicalTrials.gov, WHO International Clinical Trials Registry Platform (ICTRP), EudraCT).[20]
- Although a range of congress proceedings in the area were handsearched (covering 2018-2020 and some were updated for 2021, see Tables 3.1 and 3.2 above), according to the PRISMA diagram (CS - Appendix D, figure 1, page 17) abstracts were excluded during screening, potentially excluding relevant studies.[15]
- The dates of last search were not the same for the comparator and the intervention across resources (approximately 6 months apart) which reduces the rigour of what should be a 'systematic' search.
- It is not clear how the eight records shown on the PRISMA flow chart (CS, Appendix D, figure 1 – page 17) as being added during the level 2 phase were identified.[15] The 8 records were reduced to five in response to the clarification letter but no explanation is provided (see Figure 1, page 47, PfC letter).[10]
- The company used 'AND' to combine all population-related search sets together, which makes the final population very narrow. The use of adjacency or proximity operators, whenever supported, could have been used to avoid narrowing the population excessively and counteracting the original intention to broaden the population.
- Potentially useful population terms were not included, such as ('breast tumor'/exp) and allowing for the plural of 'mammary'. In the response to the clarification letter, the company stated that no additional records were found when including these terms.
- The company applied multiple, unreferenced, 'search filters' (related to 'study design' and/or QoL and/or 'health economic') to all the electronic bibliographic database searches for clinical effectiveness studies. The EAG was therefore unable to establish whether they were validated search filters. This is particularly important as additional searches for adverse effects were not undertaken the SLR relies on searches for non-randomised trials to identify relevant studies and the effectiveness of unvalidated filters for these study designs is now in question.[68,69]

Appendix 2: EAG methods to estimate T-DXd overall survival

Description of EAG T-DXd overall survival assumption

Background

For the company base case analysis, the company fitted a dependent parametric survival model to the DESTINY-Breast03 overall survival data. Approximately 80% of T-DXd patients were still alive at the first interim data cut point. Approximately 50% of patients were still progression-free. To an extent, the approach adopted to extrapolating overall survival accounts for the changing proportions of patients in progression-free and progressed disease states over time. But the selected parametric model was based on the predicted survival of T-DM1 as there is more evidence for T-DM1 than T-DXd given that T-DM1 is approved for second-line treatment in the decision population of this scope. While the estimated survival curve for T-DM1 is plausible, the predicted survival for T-DXd is highly uncertain as the data is so immature. There is no evidence that a significant treatment benefit in reducing mortality when patients are in the progressed disease state will be sustained over the time horizon of the model.

Objective

The objective was to derive overall survival predictions for T-DXd beyond 2 years that were reasonably consistent with an assumption of either:

A) A hazard ratio of mortality of 1 in the PD state.
B) A hazard ratio of mortality that increases to 1 over time (treatment effect declines).

The overall survival curve for T-DM1 in the company submission would be retained. The overall survival curve for T-DXd in the company submission for the first two years of the model would be retained. The overall survival predictions for T-DXd beyond 2 years would be adjusted. A cut point of 2 years was chosen because only twenty-four patients were left at risk in the T-DXd Kaplan-Meier curve at 24 months.

Methods

Since a rate refers to a risk of an outcome at a moment in time, risks over short time periods can be used as proxy estimates for rates. It is common for partitioned-survival models in Excel to present survival curves over weekly intervals. Given that a week is a relatively short period of time the hazard rate can be estimated from the survival curve with weekly survival estimates.

The implied hazard rate curves from the survival curves estimated for T-DM1 and T-DXd are presented in Figure A2.1. The hazard rate increases at first due to the proportion of alive patients who are in the progressed disease state increasing over time. The hazard rate then starts to decrease once close to 100% of alive patients are in the progressed state and the hazard rate gently declines over time for patients in the progressed disease state.

Figure A2.1: Mortality hazard rates for T-DXd and T-DM1 implied by the reported survival curves in the company model

(Source: Produced by EAG)
(Abbreviations: T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan)

While the parametric survival model does not model the hazard ratio over time, the implied hazard ratio of mortality curve can be derived from the mortality hazard rate curves. The implied hazard ratio of mortality for T-DXd versus T-DM1 is presented in Figure A2.2. This shows a significant treatment benefit over the 10 years, with a treatment benefit persisting over the model time horizon of 30 years. This is despite predicted percentage of T-DXd progression-free patients being very low after 7 years as shown in Figure A2.3.

Figure A2.2: Mortality hazard ratio (T-DXd vs T-DM1) implied by the survival curves reported in the company model

(Source: Produced by EAG)

(Abbreviations: T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan)

Figure A2.3: Base-case extrapolations for PFS

(Source: Based on Figure 33, CS[1])
(Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan)

The following method starts from the premise that there is greater certainty in the T-DM1 survival curve estimate than in the T-DXd survival curve estimate. This is due to (a) a more mature data set in DESTINY-Breast03, (b) more mature data being available from another publication which was reviewed by the company clinical expert and used to inform the selection of a survival model, and (c) the visual fit of the generalised gamma curve is ever so slightly more convincing for T-DM1 than for T-DXd (see Figures A2.4 and A2.5).

Figure A2.4: Base-case extrapolations for T-DXd OS (5 years)

(Source: Figure 41, clarification questions;[10] Figure 18, CS[1])
(Abbreviations: KM, Kaplan-Meier; OS, Overall survival; T-DXd, trastuzumab deruxtecan)

Figure A2.5: Base-case extrapolations for T-DM1 OS (5 years)

(Source: Figure 43, clarification questions;[10] Figure 18, CS[1])
(Abbreviations: KM, Kaplan-Meier; OS, Overall survival; T-DM1, trastuzumab emtansine)

Step 1: Estimating PFS and PD mortality hazard rates for T-DM1

The time-varying hazard rates in the PFS ($hr\_PFS\_i\_DM1_t$) and PD ($hr\_PD\_i\_DM1_t$) states forT-DM1, and disease progression rates could potentially be estimated, but $hr\_PD\_i\_DM1_t$ and disease progression rates are not easily calculated and implementing a state-transition model would be time consuming. Instead, the time-varying hazard rate for PD patients since the start of the model ($hr\_PD\_m\_DM1_t$) is used as a crude approximation for $hr\_PD\_i\_DM1_t$, and assumptions around the hazard ratio of mortality in the PD state are implemented within the existing partitioned-survival model.

The purpose of calculating the implied $hr\_PD\_m\_DM1_t$ and $hr\_PFS\_i\_DM1_t$ is to enable PFS and PD mortality hazard rates for T-DXd to be determined in steps 2 and 3 below. The survival curve for T-DM1 will be unadjusted in the company base case model.

$hr\_PD\_m\_DM1_t$ represents the average hazard rate across people in the PD state who have spent different lengths of time in that state. $hr\_PD\_m\_DM1_t$, $hr\_PFS\_i\_DM1_t$ and the overall mortality hazard rate ($hr\_om\_DM1_t$) are presented in Figure A2.6. After 2 years from the start of the model, the implied $hr\_PD\_m\_DM1_{>2}$ is on a gradual decline. At around 5 years it matches the overall mortality hazard rate as all alive patients are now in the PD state.

The overall mortality hazard rate is a weighted average of the PFS and PD mortality rates. $hr\_PD\_m\_DM1_t$ and $hr\_PFS\_i\_DM1_t$ are calculated using the proportions of alive patients who are in the PFS ($p\_PFS\_DM1_t$) and PD ($p\_PD\_DM1_t$) states. A series of simultaneous equations across the weekly survival curve time periods are solved.

Figure A2.6: Hazard rate curves for T-DM1 (overall mortality implied by the OS curve, the implied PD mortality, the implied PFS mortality)

(Source: Produced by EAG)
(Abbreviations: PD, progressed disease; PFS, progression-free survival; T-DM1, trastuzumab emtansine)

Step 2: Estimating the PD mortality hazard rates for T-DXd

Two approaches are considered for modelling the time-varying mortality hazard rate for PD patients since the start of the model for T-DXd ($mod\_hr\_PD\_m\_DXd_t$).

(A) A hazard ratio of mortality of 1 in the PD state.

$mod\_hr\_PD\_m\_DXd_t$ is the same as $hr\_PD\_m\_DM1_t$, i.e. equal to the PD mortality hazard rate from the start of the model (no treatment effect).

(B) A hazard ratio of mortality that increases to 1 over time (treatment effect declines).

$mod\_hr\_PD\_m\_DXd_t$ is a weighted average of $hr\_PD\_m\_DM1_t$ and $hr\_PD\_m\_DXd_t$ which was derived by the method in step 1 from the T-DXd survival curve. The weights are the proportion of alive patients who are in the PFS ($p\_PFS\_DXd_t$) and PD ($p\_PD\_DXd_t$) states, which are used as a proxy measure for time.

Since $mod\_hr\_PD\_m\_DXd_t$ is related to $hr\_PD\_m\_DM1_t$, the initial values of $hr\_PD\_m\_DM1_t$ are set to be the same value as that for the weekly cycle where at least 10% of alive patients are in the PD state. This avoids the very high mortality rates in the first few cycles.

The estimated PD mortality hazard rate curves for T-DXd are presented in Figure A2.7. GG survival curve refers to the implied PD mortality hazard rate curve derived using the method in Step 1, which is based on the Generalised Gamma survival model. A and B refer to the different hazard ratio assumptions made.

Figure A2.7: PD mortality hazard rate curves for T-DXd (overall mortality implied by the OS curve, assumption A, assumption B)

(Source: Produced by EAG)
(Abbreviations: GG, generalised gamma; HR, hazard ratio; PD, progressed disease; T-DXd, trastuzumab deruxtecan)

Step 3: Estimating the time-varying mortality hazard rate in the PFS state for T-DXd

The time-varying hazard rate in the PFS state for T-DXd ($mod\_hr\_PFS\_i\_DXd_t$) is then derived, using assumptions that differ depending on whether approach A or approach B is taken. In both cases, for the first 2 years of the model $mod\_hr\_PFS\_i\_DXd_t$ is simply derived from the relationship that $hr\_overall\_mortality\_i\_DXd_t$ is a weighted average of $hr\_PFS\_i\_DXd_t$ and $hr\_PD\_m\_DXd_t$. For time after two years, the following approaches were used.

(A) A hazard ratio of mortality of 1 in the PD state.

Since $mod\_hr\_PD\_m\_DXd_t$ is the same as $hr\_PD\_m\_DM1_t$ in this approach, the T-DXd overall survival curve cannot be used to derive $hr\_PFS\_i\_DXd_t$ beyond 2 years. Instead, the overall mortality hazard ratio at the start of the model (see Figure A2.2) was assumed to represent a constant mortality hazard ratio for T-DXd vs T-DM1 in the PFS state: [redacted].

(B) A hazard ratio of mortality that increases to 1 over time (treatment effect declines).

In this approach, the $mod\_hr\_PFS\_i\_DXd_t$ estimate at 2 years was inflated every cycle by the increase in $hr\_PFS\_i\_DXd_t$ which was derived in the same way as $hr\_PFS\_i\_DM1_t$ in Step 1.

To avoid very high rates, the final values of $hr\_PFS\_m\_DM1_t$ and $hr\_PFS\_m\_DXd_t$ are set to be the same value as that for the weekly cycle where at least 10% of alive patients are in the PFS state.

The mortality hazard rate curves for the PFS state are presented in Figure A2.8. Generalised gamma (GG) survival curve refers to the implied PFS mortality hazard rate curve derived using the method in Step 1, which is based on the Generalised Gamma survival model. A and B refer to the different hazard ratio assumptions made. Unusual curves over the first 2 years is not unexpected given that the hazard

rates are constrained by the fitted overall survival curve for T-DXd over this period and the fitted survival curve is unlikely to be perfect.

Figure A2.8: PFS mortality hazard rate curves for T-DXd (overall mortality implied by the OS curve, assumption A, assumption B)

(Source: Produced by EAG)
(Abbreviations: GG, generalised gamma; HR, hazard ratio; PD, progressed disease; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan)

Step 4: Deriving the T-DXd overall survival curve

The survival curve for T-DXd after 2 years is then calculated as a weighted average of $mod\_hr\_PFS\_i\_DXd_t$ and $mod\_hr\_PD\_m\_DXd_t$.

The overall survival curves for T-DM1 and T-DXd from the company base case model and the overall survival curves for the two different mortality hazard ration assumptions (A and B) are shown in Figure A2.9. The implied OS hazard ratios are presented in Figure A2.10.

Since the two survivor curves happened to be so similar in this case, assumption (A) of equal hazard rates of rmortality for PD patients across groups was adopted in the EAG base case analysis.

Figure A2.9: The T-DXd company base case, EAG assumption A and EAG assumption B survivor curves

(Source: Produced by EAG)
(Abbreviations: CS, company submission; HR, hazard ratio; PD, progressed disease; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan)

Figure A2.10: Overall mortality hazard ratio curves (implied by the OS curves, assumption A, assumption B)

(Source: Produced by EAG)
(Abbreviations: CS, company submission; HR, hazard ratio)

Changes to the company base case model

The changes made to the company base case model were as follows, which should be PSA compatible:

DB03_T-DXd!CX27:2427 = DB03_T-DM1!CX27:2427

DB03_T-DXd!CZ27:2427 = DB03_T-DM1!AX27:2427

DB03_T-DXd!CY27:2427 = DB03_T-DXd!CZ27:2427 - DB03_T-DXd!CX27:2427

DB03_T-DXd!DB27:2427 = DB03_T-DXd!CY27:2427/ DB03_T-DXd!CZ27:2427

DB03_T-DXd!DC32 = [SAME SHEET] (DB32*DA31-DA32*DB31)/(DB32*(1-DB31)-(1-DB32)*DB31)….for all of rows 28:2427

DB03_T-DXd!DG28 = [SAME SHEET] IF(DB28<0.1,0,1) ….for all of rows 28:2427

DB03_T-DXd!DH28 = [SAME SHEET] IF(DG28=0,0,IF(DG27=1,0,1)) ….for all of rows 28:2427

DB03_T-DXd!DI28 = [SAME SHEET] IF(DB28>0.9,1,0) ….for all of rows 28:2427

DB03_T-DXd!DJ28 = [SAME SHEET] IF(DI28=0,0,IF(DI27=1,0,1)) ….for all of rows 28:2427

DB03_T-DXd!DD28 = [SAME SHEET] IF(DG28=0,INDEX(DC$27:DH$2427,MATCH(1,DH$27:DH$2427,0),1),DC28) ….for all of rows 28:67

DB03_T-DXd!DD68 = [SAME SHEET] =IF(DI68=1,INDEX(DC$27:DJ$2427,MATCH(1,DJ$27:DJ$2427,0),1),DC68) ….for all of rows 68:2427

DB03_T-DXd!DF28 = [SAME SHEET] IF(DG28=0,INDEX(DE$27:DI$2427,MATCH(1,DH$27:DH$2427,0),1),DE28) ….for all of rows 28:2427

DB03_T-DXd!DL27:2427 = DB03_T-DXd!V27:2427

DB03_T-DXd!DN27:2427 = DB03_T-DXd!AY27:2427

DB03_T-DXd!DM27:2427 = DB03_T-DXd!DN27:2427 - DB03_T-DXd!DL27:2427

DB03_T-DXd!DP27:2427 = DB03_T-DXd!DM27:2427/ DB03_T-DXd!DN27:2427

DB03_T-DXd!DQ28 = [SAME SHEET] (DO28-DP28*DR28)/(1-DP28) ….for all of rows 28:131

DB03_T-DXd!DQ132 = [SAME SHEET] DD132*DV28 ….for all of rows 132:2427

DB03_T-DXd!DR27:2427 = DB03_T-DXd!DF27:2427

DB03_T-DXd!DS27:132 = DB03_T-DXd!DM27:132

DB03_T-DXd!DS133 = [SAME SHEET] DT133-DL133….for rows 133:2427

DB03_T-DXd!DT27:132 = DB03_T-DXd!DN27:132

DB03_T-DXd!DT133 = [SAME SHEET] DT132-DS132*DR133-DQ133*DL132….for rows 133:2427

Finally

Efficacy Summary!DR27 = [SAME SHEET] CHOOSE(OS.approach,'DB03_T-DXd'!DT27,EMILIA!Y27) ….for all of rows 28:2427

Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after trastuzumab and a taxane [ID3909]

Addendum to EAG report

Produced by Newcastle University

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None.

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[redacted]

Rider on responsibility for report

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

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Contributions of authors

Stephen Rice acted as project lead. Katie Thomson and Fiona Pearson acted as lead effectiveness reviewers. Ge Yu acted as lead health economist. Sheila Wallace acted as lead reviewer of the literature search methods. Oluwatomi Arisa acted as assistant effectiveness reviewer. Diarmuid Coughlan and Ashleigh Kernohan acted as assistant health economists. Sonia Garcia Gonzalez-Moral assisted in reviewing the literature search methods. Amit Goyal provided clinical expert opinion.

Contents

1. Errors in the EAG report

The following tables present the correct data for Tables 1.10 and 6.2 in the EAG report.

Table 1.1 in EAG report: Summary of EAG's preferred assumptions and ICER

Scenario	Incremental cost	Incremental QALYs (1.2x weighting)	ICER £/QALY, (1.2x weighting)
Company's base case after clarification	[redacted]	[redacted]	[redacted]
Company's base-case after clarifications and including EAG corrections	[redacted]	[redacted]	[redacted]
Matters of Judgement 1: no treatment effect beyond progression (Key issue 6)	[redacted]	[redacted]	[redacted]
Matters of Judgement 2: a single combined utility for progressed disease health state (Key issue 5)	[redacted]	[redacted]	[redacted]
Matters of Judgement 3: assuming 90% wastage rate	[redacted]	[redacted]	[redacted]
EAG's preferred base-case deterministic	[redacted]	[redacted]	[redacted]
EAG's preferred base-case probabilistic	[redacted]	[redacted]	[redacted]

Abbreviations: EAG: Evidence Assessment Group; ICER: Incremental Cost-Effectiveness Ratio; QALY: Quality Adjusted Life Year

Table 6.1 in EAG report: Deterministic/probabilistic EAG base-case results

Preferred Assumption	T-DXd		T-DM1		Incremental Costs (£)	Incremental QALYs (1.2x QALY weighting)	Cumulative ICER (£/QALY, 1.2x QALY weighting)
	Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs			
Company base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company base-case after fixing errors	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MJ1: no treatment effect beyond progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MJ2: a single combined utility for PD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MJ3: 90% wastage rate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base-case deterministic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base-case probabilistic*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

(Source: Produced by EAG)
*10,000 simulations
Abbreviations: EAG: evidence assessment group; ICER: incremental cost effectiveness ratio; MJ = matters of judgement; PD, progressed disease; QALY: quality-adjusted life year; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan

2. Clarification on the treatment waning methods used to inform EAG base case analyses

Appendix 2 of the EAG report gives a brief description of the methods used to inform two scenarios:

A) A hazard ratio of mortality of 1 in the PD state.
B) A hazard ratio of mortality that increases to 1 over time (treatment effect declines).

Approach A assumes a mortality hazard ratio for T-DXd vs T-DM1 in the PFS state of [redacted] at two years, with the hazard ratio increasing according to the implied PFS mortality rate derived from the generalised gamma OS curve fitted for T-DXd by the company beyond two years (see Figure 1). Roughly [redacted] and [redacted] of patients in the T-DXd arm are still in the PFS state at 4 years and 5 years respectively. Approach A also assumes no effectiveness (equal mortality hazard rates) in the PD state beyond two years.

Figure 1: The mortality hazard ratio in the PFS state after 2 years (T-DXd vs T-DM1)

(Source: Produced by EAG)
(Abbreviations: PFS, progression-free state)

Approach B assumes a constant proportional mortality hazard ratio for T-DXd vs T-DM1 in the PFS state beyond two years, and treatment waning in the PD state where the proportion of people alive in the PD state versus the PFS state is a proxy for time.

This section elaborates on the method used to model the treatment waning scenario (B). Columns in brackets refer to the EAG base case model.

For T-DXd, the mortality hazard rate in the PD state as an average across all individuals with varying time spent in the PD state (mod_hr_PD_DX) and the mortality hazard rate in the PFS state (hr_PFS_DX) were derived from the OS generalised gamma curve fitted by the company in the base case (columns ED and EF in sheet DB03_T-DXd). This was done by solving a series of simultaneous equations across the 7-day cycles.

mod_hr_PD_DX was truncated in the earliest cycles to avoid extreme values where there were less than 10% of alive patients in the PD state (column EE). hr_PFS_DX was truncated at the earlier cycles and the later cycles (column EG).

The mortality hazard rate in the PD state actually implemented in the Scenario B model (B_hr_PD_DX) was a weighted average of the mortality hazard ratio in the PD state with T-DM1 (mod_hr_PD_DM1) and mod_hr_PD_DX, weighted by the proportion of alive patients in the PD and PFS states (column EI).

The varying mortality hazard ratio in the PD state for T-DXd versus T-DM1 associated with the treatment waning assumption is shown in Figure 2.

Figure 2: The mortality hazard ratio in the PD state after 2 years (T-DXd vs T-DM1)

(Source: Produced by EAG)
(Abbreviations: PD, post-progression state)

The mortality hazard rate in the PFS state during the first two years actually implemented in the Scenario B model (B_hr_PFS_DX) was derived from overall hazard rate of mortality (hr_om_DX) based on the OS curve from the generalised gamma curve fitted by the company in the base case and B_hr_PD_DX. This calculation is based on hr_om_DX being a weighted average of B_hr_PD_DX and B_hr_PFS_DX (column EH).

The mortality hazard rate in the PFS state after the first two years is based on the last value of the B_hr_PFS_DX estimated at two years and then inflated each cycle according to the cycle-by-cycle changes in hr_PFS_DX.

Overall survival for T-DXd after 2 years (column EK) is then calculated from B_hr_PD_DX and B_hr_PFS_DX.

Another alternative approach B2

Another alternative approach B2 we did not have time to investigate during the production of the EAG report is as follows:

The B_hr_PFS_DX after two years is modelled as the PFS mortality hazard rate used in Scenario A: at two years the PFS mortality hazard ratio for T-DXd vs T-DM1 is assumed to be [redacted] and increases as shown in Figure 1 (column DQ). In this approach B2, in Figure 3, the red curve from approach A instead of the green curve from approach B of PFS mortality rates is applied.

The overall survival curves for T-DM1 and T-DXd from the company base case model and the overall survival curves for two different mortality hazard ratio approaches (A and B2) are shown in Figure 4. The implied overall mortality hazard ratios are presented in Figure 6.

The overall survival curves for T-DM1 and T-DXd from the company base case model and the overall survival curves for the two different mortality hazard ratio approaches (A and B) reported in Appendix 2 of the EAG report are shown in Figure 5. The implied overall mortality hazard ratios are presented in Figure 7.

Table 1: Deterministic EAG base case and additional treatment waning scenarios during the post-progression stage

Preferred Assumption	T-DXd		T-DM1		Incremental Costs (£)	Incremental QALYs (1.2x QALY weighting)	Cumulative ICER (£/QALY, 1.2x QALY weighting)
	Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs			
EAG base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG waning scenario B	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG waning scenario B2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

(Source: Produced by EAG)

Abbreviations: EAG: evidence assessment group; ICER: incremental cost effectiveness ratio; MJ = matters of judgement; PD, progressed disease; QALY: quality-adjusted life year; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan

Figure 3: PFS mortality hazard rate curves for T-DXd (overall mortality implied by the OS curve, assumption A, assumption B)

(Source: Figure A2.8 EAG report)

(Abbreviations: GG, generalised gamma; HR, hazard ratio; PD, progressed disease; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan)

Figure 4: The T-DXd company base case, EAG assumption A and EAG assumption B2 survivor curves

Figure 5: The T-DXd company base case, EAG assumption A and EAG assumption B survivor curves

(Source: Figure A2.9 EAG report)
(Abbreviations: CS, company submission; HR, hazard ratio; PD, progressed disease; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan)

Figure 6: Overall mortality hazard ratio curves (implied by the OS curves, assumption A, assumption B2)

(Source: Produced by EAG)
(Abbreviations: CS, company submission; HR, hazard ratio)

Figure 7: Overall mortality hazard ratio curves (implied by the OS curves, assumption A, assumption B)

(Source: Figure A2.10 EAG report)
(Abbreviations: CS, company submission; HR, hazard ratio)

Single Technology Appraisal

EAG report – factual accuracy check and confidential information check

Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after trastuzumab and a taxane [ID3909]

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by the end of **14 July 2022** 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.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 Adverse events

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.2.4.7, page 52 "*The company states special consideration was given to two AEs; ILD/pneumonitis and left ventricular ejection fraction (LVEF) as they had been previously identified as AE's (CS Section B.2).*"	"*The company states special consideration was given to two AEs; ILD/pneumonitis and left ventricular ejection fraction (LVEF) as they had been previously identified as AEs of special interest for T-DXd (CS Section B.2).*"	The company feels the existing text could be clarified to explain that these were AEs of special interest.	Amendment made as suggested by company.
Section 3.2.4.7, page 53 The report states that "*no new AEs*" were observed in DESTINY-Breast03 (compared with previous trials of T-DXd). The company believes this refers to the statement in the CS that "*no new AEs **of concern***" were identified in DESTINY-Breast03. The company has not presented evidence in the CS that	"*The company specified that there were no new AEs of concern identified in the DESTINY-Breast03 trial*."	The statement misrepresents the company's position and ascribes relevance to any new AEs, rather than AEs that are especially meaningful in the context of T-DXd treatment.	Amendment made as suggested by company.

would show that the AEs that occurred in DESTINY-Breast03 were exactly those that had occurred in previous clinical studies of T-DXd.			

Section 3.2.4.7, page 53 "*The proportion of TEAE's were* [redacted]." This statement erroneously implies that all patients had sequential (and possibly planned) reductions in their treatment dose. It also implies that the [redacted] is only connected to a reduction in treatment dose, however this is also likely to be due to other reasons.	"*The proportion of TEAE's were* [redacted]."	It is unlikely that TEAEs declined only due to a reduction in dose as [redacted] throughout the study. [redacted] could be due to various reasons e.g., patient adaptation to the drug; improvement in general health as drug begins to slow disease progression; discontinuation of patients less able to tolerate drug; heightened alertness and reporting of AEs/greater patient anxiety at treatment initiation; etc. It is unhelpful to infer a reason for this.	Amendment made as suggested by company.
Section 3.2.4.8, page 53 "*Discontinuation of the treatment was almost twice as high in the T-DXd*	"*TEAEs associated with study drug discontinuation were almost twice as high in the T-DXd arm vs the T-DM1 arm (13.6% vs 7.3%).*"	For accuracy, this sentence should specify *discontinuation due to TEAEs*, rather than solely *discontinuation*, as overall	Amendment made as suggested by company.

arm vs the T-DM1 arm (13.6% vs 7.3%)."		discontinuation (see patient disposition figure in CS; Figure 7) was higher in the T-DM1 arm than in the T-DXd arm. Therefore, the current text in the report is misleading.	
Section 3.2.4.8, page 54 "*…the incidence of any grade ≥3 TEAEs was greater in the T-DXd arm in comparison to the T-DM1 trial arm with the exception of thrombocytopenia and investigations.*"	"*…the incidence of any grade ≥3 TEAEs was greater in the T-DXd arm in comparison to the T-DM1 arm with the exception of thrombocytopenia and investigations, which occurred more frequently with T-DM1, and diarrhoea and constipation, which occurred at equal rates in each arm*."	The current text includes Grade ≥3 diarrhoea and constipation under the list of TEAEs that occurred in a greater proportion of patients in the T-DXd arm than in the T-DM1 arm. This is incorrect.	Amendment made as suggested by company.
Section 3.2.4.9, page 55 "*The key AE associated with study drug discontinuation was ILD in the T-DXd (8.2%) and T-DM1 (1.1%) trial arms*."	"*The key AE associated with study drug discontinuation was ILD in the T-DXd arm (8.2%), and* [redacted] *in the T-DM1 arm ([redacted]%).*"	The most common TEAE associated with study drug discontinuation in the T-DM1 arm is [redacted], not ILD.	Amendment made as suggested by company.
Section 4.2.7, page 88 **Section 4.2.8, page 93**	Please remove these statements: *"However, the implication of this assumption is that all AEs are transitory, and that is there are no*	The company would like to reiterate that the costs applied to adverse events are based on total cost for	It is not clear to the EAG that the percentage of patients experiencing each adverse event used in the

The EAG critique the application of adverse event costs (and disutilities) being applied as a one-off cost (or disutility) in the first cycle. The EAG state that the persisting impacts of adverse events are not included using this approach.	*persisting impacts of AEs on patients over time."* *"However, as AEs are only accounted for in the first cycle, it will not capture prolonged effects in the model."*	the duration of each event using NHS reference costs. Adverse event frequencies reflect the incidences of adverse events during the entire follow-up of the DESTINY-Breast03 study. Disutilities for adverse events are either already captured within the utility values from DESTINY-Breast03 (and therefore capture any disutility associated with lasting effects of adverse events) or incorporate a duration of adverse events within the disutility calculations. Therefore, these statements are misleading.	model (applied in the first cycle) reflects the aggregate number of events when accounting for patients who experience repeat events. This is due to the difference in numbers of adverse events reported in Table 18, Page 72 of the CS, and Table 36, Page 88, Question 20 in the response to the clarification letter outlining the number of patients in each cycle that reported an adverse event. The EAG acknowledge that costs and disutilities associated with AEs are often captured in first cycle of models. The EAG has clarified the point in section 4.2.7 as follows: *"It is not clear that the percentage of patients experiencing each adverse event used in the model*

			(applied in the first cycle) reflects the aggregate number of events when accounting for patients who experience repeat events. This uncertainty is due to the difference in numbers of any grade TEAEs reported in Table 18, Page 72 of the CS, and Table 36, Page 88, Question 20 in the response to the clarification letter outlining the number of patients in each cycle that reported a treatment-emergent adverse event. If there is a difference in the any grade TEAEs, there could be a difference in grade ≥3 TEAEs." And in Section 4.2.8: *"However, it is not clear that the that the percentage of patients experiencing each adverse event used in the model (applied in the first*

			cycle) reflects the aggregate number of events when accounting for patients who experience repeat events (see Section 4.2.7).”
Section 4.2.8, page 92 ***“****AEs dis-utilities were included as one-off values for the whole model cohort in the first time period of the model in a scenario analysis, which assumes that the PFS utility estimates inadequately captured AEs HRQoL effects.”*	*“AE dis-utilities were included as one-off values for the whole model cohort in the first time period of the model in a scenario analysis.****”***	The scenario including disutilities was included to test the impact of disutilities outside of the health-state utility values and does not assume or imply that these were inadequately captured within the PFS utility estimates as suggested by the EAG.	Amendment made as suggested by company.
Section 4.2.10, page 97 ***“****The adverse event cost declined across subsequent cycles to mirror what was overserved in the DESTINY-Breast03 trial.”*	*“Adverse event costs were applied as a one-off cost within the first cycle of the model. The costs reflect the events observed in the DESTINY-Breast03 trial during the entire follow-up.”*	The existing statement suggests that costs declined over time however this is incorrect.	Amendment made as suggested by company

Issue 2 Rates of subsequent treatment

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.2.3, page 42 Rates of subsequent treatment in DESTINY-Breast03 are described as: "…*higher than the 66.7% of patients who are likely to be eligible for subsequent therapy in UK clinical practice after second-line treatment*…". **Section 1.4, page 13** "*3. A high proportion of BICR-assessed progressed patients received a subsequent treatment this may not reflect the proportion of progressed patients in clinical practice in England that would receive subsequent treatment*."	"*Overall, it is possible after further trial follow-up, rates of subsequent treatment in the trial may be higher than the 66.7% of patients who are likely to be eligible for subsequent therapy in UK clinical practice after second-line treatment*…" "*3. The proportion of BICR-assessed progressed patients who received a subsequent treatment is similar to the proportion of progressed patients in clinical practice in England that would receive subsequent treatment; however, longer follow-up is required to confirm this*."	The company believes longer follow-up (i.e., a future data cut) is required to draw firm conclusions about rates of subsequent treatment, given the large difference in progression rates between trial arms. However, as of the first interim data cut, the rate of subsequent treatment in the T-DXd arm, when considering only progressed patients, is [redacted]% – lower than the estimated rate in UK clinical practice. Therefore, the current text in the report is incorrect.	Thank you for these suggested amendments. Section 3.2.3 The amendment has been made as suggested by the company. The EAG has also added the following statement in Section 3.2.3: "It was further clarified in the factual accuracy check that, while [redacted] in the T-DXd arm was lower than 66.7%, the company considered the long-term percentage to be uncertain." Section 1.4 (pg. 13)

			In light of your amendments and your clarification, we have amended the title: "Uncertainty in the proportion of progressed patients receiving subsequent treatment and the distribution of subsequent treatments" The wording for section 1.4 has also been changed (see below).
	The company suggests the following minor amendment, if aligned with the EAG's intended meaning:		
Section 1.4, page 15, Table 1.4 *"[redacted] in the T-DXd arm and [redacted] in the T-DM1 arm (calculated as a percentage of patients who had experienced disease progression)."* **Section 3.2.4, page 50**	*"[redacted] in the T-DXd arm and [redacted] in the T-DM1 arm (calculated as a percentage from the total number of patients who received subsequent treatment divided by the number of patients who had experienced a progression event i.e., not including those who discontinued treatment for other reasons than progression)."*	To provide additional clarity as to how the different subsequent treatment percentages were calculated.	Section 1.4 (pg. 13/14): In light of your proposed amendments and FAC clarification, we have edited the key issue: **Description of issue and why the EAG has identified it as important**

"Reported in Question B4 of the clarification letter,[10] [redacted]% in the T-DXd arm and [redacted]% in the T-DM1 arm (calculated as a percentage of patients who had experienced disease progression) had received subsequent therapy. Of patients who had experienced disease progression, [redacted]% and [redacted]% of patients in the T-DXd and T-DM1 arms received subsequent treatment respectively (Question 29h, points for clarification response).[10]" **Section 3.4, page 58** *"A high percentage of patients who had either experienced disease progression,or discontinued due to adverse events/other reasons received subsequent treatment: [redacted] in the T-DXd arm and [redacted] in the T-DM1 arm (calculated as a*	*"Reported in Question B4 of the clarification letter,[10] [redacted]% in the T-DXd arm and [redacted]% in the T-DM1 arm (calculated as a percentage from the total number of patients who received subsequent treatment divided by the number of patients who had experienced a progression event i.e., not including those who discontinued treatment for other reasons than progression) had received subsequent therapy. Of only patients who had experienced disease progression, [redacted]% and [redacted]% of patients in the T-DXd and T-DM1 arms received subsequent treatment, respectively (Question 29h, points for clarification response).[10]"* *"A high percentage of patients who had experienced a progression event received subsequent treatment: [redacted] in the T-DXd arm and [redacted] in the T-DM1 arm (calculated as a percentage from the*		"Of patients enrolled in DESTINY-Breast03 who experienced disease progression, [redacted]% and [redacted]% of patients in the T-DXd and T-DM1 arms received subsequent treatment respectively. The company clinical experts stated that the percentages were higher than expected. The clinical experts estimated the percentages for T-DXd and T-DM1 to be 66.7% in English clinical practice. It is possible that as the trial progresses the percentages of progressed patients receiving subsequent treatment will be higher than at the first interim data cut point. Further complicating the issue, a high percentage of patients in DESTINY-Breast03 received treatment subsequent to their allocated treatment having discontinued treatment due to adverse

percentage of patients who had experienced disease progression).”	*total number of patients who received subsequent treatment divided by the number of patients who had experienced a progression event i.e., not including those who discontinued treatment for other reasons than progression).”*		events or otherwise in addition to disease progression: in total, [redacted] in the T-DXd arm and [redacted] in the T-DM1 arm (calculated as a percentage from the total number of patients who received subsequent treatment divided by the number of patients who had experienced a progression event i.e., not including those who discontinued treatment for other reasons than progression). Also, the subsequent treatments received by those in DESTINY-Breast03 may not wholly be reflective of the subsequent therapies that would be used in English clinical practice after second-line treatment. As the trial progresses, the subsequent treatment distribution could potentially change.”

			What alternative approach has the EAG suggested? "No alternative approach is suggested for the percentage of progressed patients receiving subsequent treatment. The EAG considers that the distribution of subsequent treatments in the European subgroup in DESTINY-Breast03 is likely to be more reflective of the distribution of subsequent treatments used in an English clinical setting. However, the sample size for this subgroup is not large, so findings derived from this subgroup are impacted by high uncertainty."

			What is the expected effect on the cost effectiveness estimates? "The company used clinical expert opinion on percentages of progressed patients receiving subsequent treatment in the base case economic model. The distribution of subsequent treatments was informed by DESTINY-Breast03. The effect of the alternative approaches on cost-effectiveness is unknown." **What additional evidence or analyses might help to resolve this key issue?** "European subgroup data on subsequent treatment distribution could have been informative. The issue of the proportion of patients receiving

			subsequent treatment is currently unresolvable. Data from a later data cut point would provide more information on the percentage of patients receiving subsequent treatment and on the subsequent treatment distribution, although the issue of generalisability to the English setting remains." Section 3.4 Amendment made as suggested by company.

Issue 3 Presentation of subsequent treatment costs

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.10, page 98, Table 4.14	Revised table or addition of asterisks which explain the	In Table 4.14, the 'Subsequent treatment cost per patient leaving progression-free' is a calculation of 'Subsequent treatment cost per patient' multiplied by 'Proportion	To clarify the different values which could be utilised with regards to subsequent treatment costs, the four values are now summarised in

The presentation of the ‘Subsequent treatment cost per patient leaving progression-free’ is misleading.	values used in the calculation.	of patients receiving subsequent treatments’. Each of these can be derived from either the DESTINY-Breast03 trial or the ‘UK values’ as presented in the table 4.14. Therefore, there are four possible total costs. In the company base case, we use DESTINY-Breast03 for the distribution of subsequent treatments and UK values for the proportion of progressed patients using subsequent treatments which are presented in Table 4.14. However, the table 4.14 presentation suggests the DESTINY-Breast03 values are used for both elements in the first column and second column. e.g., in column one, it appears as though the total subsequent treatment cost of [redacted] is calculated as [redacted] *x* [redacted] rather than [redacted] *x 66.7%*.	Table 4.14. The text has also been edited accordingly, including the suggested text presented regarding the rates of subsequent treatment.

Issue 4 Misinterpretations

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.4, page 15, Table 1.4 The EAG have misinterpreted what we have used for the estimation of subsequent treatments: *"The company used clinical expert opinion on percentages of patients receiving subsequent treatment and the distribution of subsequent treatments in the company base case economic model."*	Please amend to: *"The company used clinical expert opinion on percentages of progressed patients receiving subsequent treatment in the base case economic model. The distribution of subsequent treatments was informed by DESTINY-Breast03."*	Clinical opinion was used to inform the proportion of progressed patients receiving subsequent treatments, however the distribution of different subsequent treatments were informed by DESTINY-Breast03 in the base case. Alternative distributions of subsequent treatments informed by clinical opinion were explored as part of scenario analysis.	Amendment made as suggested by company.
Section 3.1.2, page 31 ***"****The EAG acknowledges that the company, as the developer of T-DXd and a partner of the developer of T-DM1*	***"****The EAG acknowledges that the company, as the developer of T-DXd are likely aware of and to have reported all relevant studies related to T-DXd."*	The company would like to confirm that Daiichi-Sankyo is not a partner of the T-DM1 developer.	Amendment made as suggested by company, and in addition, phrasing has been improved: The EAG acknowledges that the company, as the developer of T-DXd are likely aware of, and

(Roche) on a T-DXd related companion diagnostic, are likely aware of and to have reported all relevant studies related to T-DXd."			have reported, all relevant studies related to T-DXd
Section 3.2.4.5, page 51 "*EAG Comment: RR and DoR data for DESTINY-Breast03 is relatively immature*."	"*EAG Comment: DoR data for DESTINY-Breast03 are relatively immature*."	The company considers it is inaccurate to state that RR data in DESTINY-Breast03 is relatively immature, as responses (where they occur) are established relatively quickly (vs. survival outcomes) and are recorded at a fixed moment in time. The company acknowledge DoR data will mature with time.	Amendment made as suggested by company.

Section 3.2.4.7, page 53 The report states: "*At three weeks, some of those receiving the intervention could not tolerate the starting dose. Of those receiving the intervention, at 3 weeks, the ratio of drug actually delivered versus the planned starting dose of the study drug was [redacted]%. There is no impact of this on the effectiveness estimate which reflects the dose given, however, a lower start dose may need to be considered.*" Dose reductions could occur at any time and did not all occur at three weeks. Moreover, RDI was calculated across the whole trial	"Patients may have required dose reductions at any point during the study*. Of those receiving the intervention, the ratio of drug actually delivered versus the planned starting dose of the study drug was [redacted]% over the follow-up period. There is no impact of this on the effectiveness estimate which reflects the dose given; however, a minority of patients may benefit from dose reductions*."	The three-week timepoint is inaccurate and should be removed. Most patients ([redacted]%) did not have their dose of T-DXd reduced over the follow-up period. For those who require dose reductions due to AEs, the AE management guidelines for treating physicians outlines the process of dose adaptation in response to AEs. This may occur at any time while patients are receiving treatment. The company considers it to be misleading and unhelpful to suggest that patients should be started at a lower dose. The dose of T-DXd is based on dose-finding evidence and balances tolerability with efficacy. The effectiveness estimate is based on a cohort of patients of whom [redacted]% continued to receive the planned starting dose without reductions; further, the licensed dose in this indication is 5.4 mg/kg.	Amendment made as follows: "[redacted]"

follow-up to the May 2021 DCO.			
Section 4.2.2, page 72 The EAG have misinterpreted the differences in monitoring protocols between T-DXd and T-DM1: ***"****Costs varied across states due to different treatment distributions and the associated monitoring protocols."*	*"Costs varied across states due to different treatment distributions."*	To remove any notion that treatment monitoring differed between treatment arms.	Amendments made as suggested by company.
Section 4.2.6, page 74 ***"****Akaike information criterion (AIC) and Bayesian information criterion (BIC) test statistics, and clinical plausibility based on OS estimation ([redacted] and [redacted] respectively) at 5 and 10 years for T-DM1 patients provided by clinicians."*	*"Akaike information criterion (AIC) and Bayesian information criterion (BIC) test statistics, and survival plausibility based on clinical feedback of OS estimation at 5 and 10 years (25-35% and 5-10%, respectively) for T-DM1 patients were used to determine the company base case. The selected curves OS estimates (5- and 10-year OS of [redacted] and*	For T-DM1, clinicians expected survival at 5 and 10 years to be 25-35% and 5-10%, respectively. The percentages quoted by the EAG are estimated from the modelled OS. The suggested change provides additional clarity for these percentages.	Amendments made as suggested by company.

	[redacted] *respectively) were in line with the feedback "*		
Section 4.2.6, page 87 ***"****Another concern is the PFS curve should not rise above OS and the TTD curve should not rise above PFS at any time. The company did not incorporate functions to adjust for it in the Excel model."*	***"****Another concern is the TTD curve should not rise above PFS at any time. The company did not formally incorporate a function to adjust for this in the Excel model, however the company ruled out curve combinations where crossing occurred."*	Both PFS and TTD were capped by OS in the Excel model, therefore it is incorrect to state that this was not adjusted for. It is correct that TTD was not capped by PFS within the model.	The text has been changed to "While the company included a function to ensure that the proportion on treatment was never greater than the proportion alive, there was no function to ensure that the proportion on treatment was never greater than the proportion who were progression-free. However, it is noted that the selected parametric survival model for TTD was chosen in part because the predicted TTD and PFS curves did not cross. While this does not guarantee that the proportion on treatment would never be greater than the proportion progression-free in probabilistic sensitivity analysis, the chance of inconsistent results being produced during probabilistic sensitivity analysis were slim given the two curves."

Section 5.2.2, page 106 The EAG have misrepresented the use of 10% in sensitivity analysis when variance was not reported for some parameters: *"The plausible range was determined by either upper and lower bounds of the confidence interval (CI) or 10% variation around the mean where no estimates of precision were available"* *"The same 10% variation around the mean was applied for parameters without a confidence interval."*	*"The plausible range was determined by either upper and lower bounds of the confidence interval (CI) or assuming standard error of 10% of the mean where no estimates of precision were available"* *"For parameters without a confidence interval, these were derived assuming that the standard error was 10% of the mean value."*	To clarify that for parameters with missing variance, the upper and lower bounds are not ±10% of the mean value, but calculated assuming that the standard error was 10% of the mean value.	Amendments made as suggested by company.

Issue 5 Missing and incorrect information about planned analyses

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.2.2, page 38 "*…first OS interim analysis: p=*[redacted]…" The first interim OS analysis threshold for statistical significance is stated as p=[redacted]. This is correct although the planned p-value is for an estimated number of events. However, it was not the actual p-value used for the first interim analysis of OS. The number of events required for this threshold to be used should be stated.	*"…first OS interim analysis: p=0.001 if* [redacted] *OS events occurred…"*	To avoid confusion about the actual p-value used as the threshold for statistical significance.	Amendment made as suggested by company.
Section 3.2.4.2, page 50 The OS analysis mentioned (at [redacted] OS events) is the final of	*"Final OS analysis will be undertaken at* [redacted] *OS events…"*	To avoid confusion about planned analyses.	Amendment made as suggested by company.

three possible OS analyses. This is not stated.			
Section 3.2.4.2, page 50 The text incorrectly states that the final OS analysis is likely to be undertaken in [redacted]: *"OS analysis will be undertaken at [redacted] OS events, which the Company anticipates is likely to be in [redacted]."* "*The predicted future analysis of OS data is anticipated around [redacted]…*"	*"A second interim OS analysis will take place at [redacted] PFS events, which the company anticipates is likely to be in [redacted] Final OS analysis will be undertaken at [redacted] OS events."* "*The second interim analysis of OS data is anticipated around [redacted]…*"	Removal of a factually inaccurate statement.	Amendment made as suggested by company.

Issue 6 Missing and incorrect information

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.5, page 16, Table 1.6		Re-wording to make it clear that '80%' and '50%' are approximations.	Amendment made as suggested by company.

EAG rounding may be mis-leading: "…*given that 50% of patients were still progression-free at the first interim data cut point*." **Section 1.5, page 17, Table 1.7** *"80% of patients were still alive at the first interim data cut point. As a result, the T-DXd OS predictions for use in the economic model are highly uncertain. This is exacerbated by the fact that 50% of patients in the T-DXd arm were still progression-free at the interim cut off point of 21st May 2021."* **Section 6.1.1, page 113** *"The company made this assumption when*	*"…given that approximately 50% of patients were still alive and progression-free at the first interim data cut point (i.e., ongoing without event or censoring)."* *"Approximately 80% of patients were still alive at the first interim data cut point. As a result, the T-DXd OS predictions for use in the economic model are highly uncertain. This is exacerbated by the fact that approximately 50% of patients in the T-DXd arm were still progression-free at the interim cut off point of 21st May 2021."* *"The company made this assumption when approximately 80% of the T-DXd patients were still alive*		Amendment made as suggested by company.

80% of the T-DXd patients were still alive and 50% of patients were still progression-free at the first interim cut point." **Appendix 2, page 133** *"80% of T-DXd patients were still alive at the first interim data cut point. 50% of patients were still progression-free."*	*and approximately 50% of patients were still progression-free at the first interim cut point."* *"Approximately 80% of T-DXd patients were still alive at the first interim data cut point. Approximately 50% of patients were still progression-free."*		Amendments made as suggested by company. Amendments made as suggested by company.
Section 1.7, page 19, Table 1.10 The 'Matters of judgement item 3: assuming 90% wastage is missing from this table'	This item should be included within this table as it is part of the EAG base case	For completeness	Amendment made as suggested by company
Section 1.1, page 12 ***"****The company assumes a treatment benefit in reducing mortality over the*	***"****The company assumes a treatment benefit in reducing mortality over the lifetime, whereas the EAG assumes a conservative scenario with no*	The EAG's base case includes no treatment effect beyond progression.	Amendment made as suggested by company. In addition, the EAG has made the correction to the text in Table 1.7 that the

lifetime, whereas the EAG assumes a conservative scenario with no treatment effect beyond progression or waning treatment effectiveness over time."	*treatment effect beyond progression."*		assumption of no treatment effect beyond progression was made in the extrapolation of overall survival beyond 2 years. "The EAG has undertaken this analysis that explores the effect of these assumptions in the extrapolation of OS beyond 2 years on the cost-effectiveness results." And in Section 6.1.1, Page 118: "The EAG considered two alternative assumptions in the extrapolation of OS beyond 2 years:…."
Section 3.2.3, page 41 A number is given for the total number of	*"In total, [redacted] patients ([redacted] patients in the T-DXd arm and [redacted] patients in the T-DM1 arm) had either of these*	To correct a factually inaccurate statement	Amendments made as suggested by company.

patients who received NICE-approved first-line regimens. However, it is not stated that this value only represents the T-DXd arm: "[redacted] *patients had either of these NICE-recommended first-line regimens prior to their trial treatment…*"	*NICE-recommended first-line regimens prior to their trial treatment…"*		
Section 3.2.3, page 41 The proportion of patients stated is from the T-DXd arm only. The proportion for the T-DM1 arm is not stated: "*In response to the clarification letter (Question A25), approximately [redacted] of patients ([redacted]%) had either of the NICE-*	"*In response to the clarification letter (Question A25), approximately [redacted] of patients ([redacted]% in the T-DXd arm and [redacted]% in the T-DM1 arm) had either of the NICE-recommended first-line regimens prior to their trial treatment*."	To correct a factually inaccurate statement	Amendment made as suggested by company.

recommended first-line regimens prior to their trial treatment."					
Section 3.2.3, page 41 T-DXd is erroneously included in the list of subsequent TKIs: "…*the company confirmed these included* [redacted]…"	"…*the company confirmed these included* [redacted]…"				Amendment made as suggested by company.
Section 3.2.4.1, page 45 The confidence intervals for the 12-month response rate in the T-DM1 arm are incorrect.	***Duration of confirmed response (by BICR)***	***T-DXd***	***T-DM1***	To correct a factually inaccurate statement	Amendment made as suggested by company.
	RR (%) (at 12 months) [95% CI]	[redacted]	[redacted]		
Section 3.2.4.1, page 45 The median time to definitive deterioration for the 'breast symptoms' scale of the		***T-DXd***	***T-DM1***	To correct a factually inaccurate statement	
	Median time to definitive deterioration	*26.4*	*Not estimable*		Amendment made as suggested by company.

EORTC QLQ-BR45 is incorrectly stated as "*0.0*" in each arm.	***(Breast symptoms scale, EORTC QLQ-BR45; months)***				
Section 3.2.4.2, page 50 The threshold for statistical significance is incorrect: "*However, this difference did not meet pre-specified criteria for statistical significance (p≤0.001).*"	*"However, this difference did not meet pre-specified criteria for statistical significance (p<0.000265) after making the adjustment for multiple testing."*		To correct a factually inaccurate statement. The company also request that the adjustment for multiple testing is mentioned for clarity.		Amendment made as suggested by company.
Section 3.2.4.10, page 57 The company suggests that the cited references refer to a different list of therapies than those stated: "*The drug trastuzumab, T-DXd and T-DM1 are associated with higher events of toxicities in Asian populations.*[32,39]"	"*Both T-DM1 and the pertuzumab, trastuzumab, and docetaxel regimen are associated with higher events of toxicities in Asian populations.*[32,39]"		To match the text to the references. None of the references included were studies of T-DXd.		Amendment made as suggested by company.

Section 4.2.6 The EAG have missed some information from this section which may be useful to include: **Page 74:** ***"…****(b) estimating a hazard ratio for T-DXd compared to T-DM1…"* **Page 78:** ***"****Figure 4.9 presents the comparison of Methods 1 and 2 along with the Kaplan-Meier plot for T-DXd survival over 30 years."* **Page 80:** ***"****The Weibull PSM was selected as the base case for the economic analysis…"*	***"…****(b) estimating a hazard ratio for T-DXd compared to T-DM1 from DESTINY-Breast03…"* ***"****Figure 4.9 presents the comparison of Methods 1 and 2 using the company's base case curves along with the Kaplan-Meier plot for T-DXd survival over 30 years."* ***"****The Weibull PSM was selected as the base case for both T-DXd and T-DM1 for the economic analysis…"*	To provide clarity	Amendments made as suggested by company.
Section 5.4.1, page 110	***"****In addition, the relevance of the model structure and assumptions were validated through consultation with UK*	Missing key information	Amendments made as suggested by company.

The EAG have missed key information regarding the validation meeting undertaken by the company. ***"****In addition, the relevance of the model structure and assumptions were validated through consultation with UK clinicians."*	*clinicians and HEOR experts."*		

Issue 7 Requests to clarify ambiguous wording

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.2.3, page 42 The report states: "*prior treatment with an anti-HER2 ADC in the metastatic setting would be permitted*"	"*prior treatment with an anti-HER2 ADC in the metastatic setting would be permitted. However, this patient population is included in NICE TA704 (trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after*	To provide clarity	Amendment made as suggested by company.

	2 or more anti-HER2 therapies)"		
Section 1.4, page 14, Table 1.2 The text could be interpreted as suggesting that there were the same number of PFS events ([redacted]) in each treatment arm. The text also states the percentage as a proportion of events (*"[redacted]% of events", "[redacted]% of events"*). The proportions shown refer to the proportion of patients within the trial that had a PFS event.	Please amend to: *"Sufficient PFS events occurred to conduct the interim analysis with [redacted] events across both treatment arms combined ([redacted]% of patients). However, the OS data are not near maturity with 86 events across both treatment arms (16.41% of patients).*	To provide clarity	Amendment made as suggested by company.
Section 1.4, page 15, Table 1.4 It is not clear that the proportions referred to are from the DESTINY-Breast03 trial:	"*Of patients enrolled in DESTINY-Breast03 who experienced disease progression, [redacted]% and [redacted]% of patients in the T-DXd and T-DM1 arms received*	To provide clarity	Amendment made as suggested by company.

"*Of patients who had experienced disease progression, [redacted]% and [redacted]% of patients in the T-DXd and T-DM1 arms received subsequent treatment respectively.*"	*subsequent treatment respectively.*"		
Section 3.2.3, page 41 The following text is worded in an unclear fashion: "*In the current treatment pathway, people who are hormone or HER2+ u/mBC in England include two HER2-targeted first line therapies (TA509 and TA34)[27,28] alongside gemcitabine and paclitaxel chemotherapy (TA116)[29] alongside endocrine therapy for patients who are also hormone receptor-positive (CG81).[7]*"	"*In the current treatment pathway, people with HER2+ u/mBC in England can receive one of two HER2-targeted first line regimens (TA509 and TA34)[27,28] or gemcitabine and paclitaxel chemotherapy (TA116).[29] Additionally, endocrine therapy may be administered to patients who are also hormone receptor-positive (CG81).[7]*"	To provide clarity	Amendment made as suggested by company.

Section 3.2.1, page 37 The report states: "*The first long-term/survival follow-up assessments was conducted three months later*."	*"The first and only long-term HRQoL follow-up assessment was conducted three months later."*	To provide clarity	Amendment made as suggested by company.
Section 3.2.4.2, page 50 The company feels the text currently worded '*meaningful results*' could be more specific: "*The predicted future analysis of OS data is anticipated around [redacted],[10] when more meaningful results are likely to be available*."	"*…when more mature OS data are likely to be available*."	To provide clarity	Amendment made as suggested by company.

Issue 8 Administration costs

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.10, page 97 **Section 6.1.2, page 115** **Section 6.2.2, page 120** The EAG have incorrectly used the administration cost code "SB15Z – Deliver Subsequent Elements of a Chemotherapy cycle" in their scenario analysis.	We request that the EAG remove this scenario	The EAG produced a scenario where the first cost of administration in cycle 1 uses the NHS cost code SB12Z and subsequent cycles use SB15Z. There are a number of concerns with this scenario. Firstly, the EAG assumes 7 cycles for their revised administration cost however there is no justification for this assumption, and it is incorrect. The number of administrations relates to the proportion of patients on treatment over time and continues until drug discontinuation. Secondly, the NHS reference cost "SB15Z" refers to administrations of subsequent elements within the same cycle of treatment. Both T-DXd and T-DM1 have one administration at the start of each 21-day cycle, therefore this cost code is inappropriate for these treatments.	We thank the company for the additional clarification regarding their costs. The additional analysis based on this cost was removed.

Issue 9 Incorrect reporting of ICERs

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.7, page 19, Table 1.10 **Section 6.2.1, page 117, Table 6.2** The EAG have reported a number of results incorrectly.	Company base case after fixing errors: T-DM1 total QALYs: [redacted] ICER: [redacted] MJ2 a single combined utility for PD: ICER: [redacted] MJ3 90% wastage rate: T-DM1 total QALYs: [redacted] ICER: [redacted] ERG probabilistic base case: Incremental QALYs: [redacted] ICER: [redacted]	Correction	The 'Company base case after fixing errors' scenario results have been adjusted accordingly. The 'MJ2 a single combined utility for PD' scenario results have been adjusted accordingly. The 'MJ3 90% wastage rate' scenario results have been adjusted accordingly. Results reported in EAG probabilistic base case were modified as suggested by company.

Section 6.2.2, page 117, Table 6.3 The EAG have reported scenario 1 incorrectly – the log-normal OS curve should be selected as the base case for this scenario	Extrapolation of replicated data from EMILIA + HR T-DXd total costs [redacted] T-DXd total QALYs [redacted] T-DM1 total costs [redacted] T-DM1 total QALYs [redacted] Incremental costs [redacted] Incremental QALYs [redacted] ICER [redacted]	Correction	Amendment made as suggested by company.
Section 6.4, page 125 Incorrect ICER reported: *"There were a couple of coding errors that resulting in an increase in the ICER (The EAGs replication of the*	*"There were two coding errors that resulted in an increase in the ICER once corrected (The EAGs replication of the corrected company base-case deterministic analysis resulted in an ICER of [redacted] per QALY gained)."*	Correction	Amendment made as suggested by company.

corrected company base-case deterministic analysis resulted in an ICER of £[redacted] per QALY gained).”			

Issue 10 Appendices

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.1.1, Page 63 & 66 Incorrect statements: *“For the HRQoL searches, (Appendix H Section H.1.1, page 31 of the CS) the CS refers the reader to ‘Appendix G, Section G.1.1’ for the search strategies used.[15] This was the wrong appendix and no information was available about these searches.”*	*“For the HRQoL searches, (Appendix H Section H.1.1, page 31 of the CS) the CS refers the reader to ‘Appendix G, Section G.1.1’ for the search strategies used.[15]”* *“For the cost and resource use searches (Appendix I, Section I.1.1, page 61 of the CS), the CS refers the reader to ‘Appendix G, Section G.1.1’ for the search strategies used.[15]”*	Appendix H, Section H.1.1. and Appendix I, Section I.1.1. refers to the search strategy described in Appendix G1.1. which is the correct appendix with the search strategy described.	Amendments made exactly as suggested by the company.

"For the cost and resource use searches (Appendix I, Section I.1.1, page 61 of the CS), the wrong appendix was referred to and no information was available about these searches.[15]"			

Issue 11 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The company noted multiple minor spelling errors, and incorrect cross-references, throughout the documents	No specific amendments are proposed but the company would request that the report undergoes a final editorial check prior to release	To correct spelling and cross-reference errors.	These have been corrected, and the report proof-read again.
Section 1.5, page 17, Table 1.8 Duplication of *"use the"* which the company believes is a typographical error.	Removal of "use the"	Content appears to be accidentally duplicated	Amendment made as suggested by company.

"…the preferred method of crosswalking EQ-5D-5L to EQ-5D-3L is to use the use the algorithm developed by Hernández et al. (2017).[3]"			
Section 3.1.2, page 32, Table 3.4 The justification column, under "*outcomes*", includes three bullet points, which the company believes is a typographical error.	Removal of bullet points.	This will remove any implication that only three of the included outcomes were of relevance to the final scope.	Amendment made as suggested by company.
Section 3.2.1, page 36, Table 3.5 The table includes both a "*study design"* row and a "*trial design"* row, with similar content in each.	Removal "*trial design"* row.	Content appears to be duplicated	The study design row has been deleted, and the trial design details have been amalgamated.
Section 3.2.2, page 38	*"A summary of the statistical analyses undertaken for DESTINY-Breast03 is*		Amendment made as suggested by company.

The text refers to "*Table D*" in the CS, which does not exist.	*described in Table 9 of the CS."*		
Section 3.2.4.1, page 45 The table contains two sets of rows stating the median time to definitive deterioration of EQ-5D-5L (VAS) and the hazard ratio, confidence intervals, and p-value.	Remove the (ACIC marked) lower rows containing this duplicated information. Please note the information contained does not need to be marked as AIC.		The duplicated row has been removed, and the AIC marking for median time to definitive deterioration (median and HR) for the EQ-5D-5L VAS has been removed. The HR for breast symptoms and arm symptoms has been added.
Section 3.2.4.6, page 52 The following text contains a number of inaccuracies that appear to be typographical errors: "*Median time to definitive deterioration using EQ-5D-5L VAS was* [redacted]. *All*	"*All prespecified subscales of the EORTC QLQ-C30 and EORTC QLQ-BR45 favoured the intervention, and emotional functioning and pain symptoms subscales of the EORTC QLQ-C30, and arm symptom subscales of the EORTC QLQ-BR45, were statistically significant (p<0.05),[17] see Figure 3.4."*		Amendment made as suggested by company.

prespecified subscales were of the EORTC QLQ-C30 and EORTC QLQ-BR45 favoured the intervention, and [redacted]*[17] see Figure 3.5."*			
Section 3.4, page 57 The text incorrectly refers to the DESTINY-Breast01 trial: "*Only [redacted] patients in DESTINY-Breast01 were from the UK ([redacted]%).*"	"*Only [redacted] patients in DESTINY-Breast03 were from the UK ([redacted]%).*"	Incorrect reference to *DESTINY-Breast01*	Amendment made as suggested by company.
Section 4.2.2, page 73 Undecipherable sentence ***"****Not only do more patients have more advanced disease after*	Please revise the sentence to be clear what is meant.	Revision required.	The sentence has been changed to "After progression, patients have more advanced disease and the treatments received by the disease progressed patients differ to

progression, the disease progressed patients receive differ to those received by progression-free patients."			those received by progression-free patients."
Section 4.2.6, page 80 *"The company plot of OS extrapolations for T-DM1 and T-DXd is reproduced in Figure 4.14."*	*"The company plot of PFS extrapolations for T-DM1 and T-DXd is reproduced in Figure 4.14."*	The plot referred to by the EAG is for PFS instead of OS.	Amendments made as suggested by company.
Section 4.2.8, page 89 The text denotes the coefficient of T-DXd to be negative when it should be positive: *"It should be noted that the GEE regression coefficient value for Treatment (T-DXd) was [redacted] (95%CI: [redacted]; p-value [redacted])…"*	*"It should be noted that the GEE regression coefficient value for Treatment (T-DXd) was [redacted] (95%CI: [redacted]; p-value [redacted])…"*	This will avoid misinterpretation of the impact of T-DXd to health-state utility values.	Amendments made as suggested by company.
Section 6.3, page 121	*"The estimated EAG base-case ICER (probabilistic),*	Incorrect reporting of EAG ICER	We believe the value of [redacted] is correct which is

"The estimated EAG base-case ICER (probabilistic), based on the EAG preferred assumptions highlighted in Section 6.1, was [redacted] per QALY gained for the comparison of T-DXd versus T-DM1"	*based on the EAG preferred assumptions highlighted in Section 6.1, was [redacted] per QALY gained for the comparison of T-DXd versus T-DM1"*		consistent with the value the company provided in Issue 9.
Section 6.3, page 122 *"Figure 30 presents the results of one-way sensitivity analyses conducted around the EAG base-case.[1]"*	*"Figure 6.3 presents the results of one-way sensitivity analyses conducted around the EAG base-case.[1]"*	Incorrect Figure reference	Amendments made as suggested by company.

Issue 12 ACIC markup

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Section 1.4, page 14, Table 1.2	The number of OS events does not need to be marked AIC	*"However, the OS data is not near maturity with 86 events in both treatment arms (16.41% of events)."*	Amendments made as suggested by company.

Section 1.4, page 15, Table 1.4 **Section 3.2.3, page 42** **Section 3.2.4.2, page 50** **Section 3.4, page 58**	Proportion of patients who go onto subsequent treatment derived from clinical opinion does not need to be marked AIC	*"…66.7%…"*	These amendments (and others with reference to the 66.7%) have had there AIC highlighting removed.
Section 3.2.2, page 38	The number of PFS events should be CIC	*"The company took a sequential approach to analyses, setting out a priori thresholds for conducting interim (PFS [redacted] events; interim analysis of OS conducted if the analysis of PFS was statistically significant) and full analyses of PFS and OS."*	Amendment made as suggested by company.
Section 3.2.2, page 38	The p-value for the second interim analysis should be CIC	*"…second interim analysis: p=[redacted])…"*	Amendment made as suggested by company.
Section 3.2.3, page 41	The number of patients who had either of the NICE-recommended HER2-targeted combination regimens is AIC	"[redacted] *patients had either of these NICE-recommended first-line regimens prior to their trial treatment…*"	Amendment made as suggested by company.

Section 3.2.4.1, page 43	The event threshold for planned analysis is CIC.	*"Interim PFS by BICR analysis was scheduled to take place at ≥[redacted] events…"*	Amendment made as suggested by company.
Section 3.2.4.1, page 46, Figure 3.1 **Section 3.2.4.2, page 51, Figure 3.3**	The figure is published and does not need to be marked AIC.		Amendments made as suggested by company.
Section 3.2.4.1, page 49	The proportion of events and number of events at which final PFS analysis is planned should be CIC.	*"[redacted]% of the PFS events required for the final analysis of PFS have occurred (i.e., [redacted] PFS events of the [redacted] PFS events planned at the final PFS analysis)."*	Amendments made as suggested by company.
Section 3.2.4.2, page 50	The proportion of events and number of events at which final PFS analysis is planned should be CIC.	*"OS data for DESTINY-Breast03 remains immature, with only [redacted]% of the events required for the final analysis of OS having occurred (i.e., 86 deaths of the [redacted] deaths planned at the final OS analysis)."*	Amendments made as suggested by company.
Section 3.2.4.7, page 53	The mean dose administered to the T-DM1 arm is AIC.	*"The starting dose for T-DXd was 5.4 mg/kg and 3.6mg/kg for T-DM1 but the mean dose was [redacted] mg/kg/3 weeks in the T-DXd arm and [redacted] mg/kg/3 weeks in the T-DM1 arm."*	Amendments made as suggested by company.
Section 3.4, page 58	The proportion of PFS events is AIC.	*"Although only [redacted]% of PFS had occurred at the time of the interim analysis…"*	Amendment made as suggested by company.

Section 4.2.5, page 73	Proportion of patients alive at certain time points estimated from the model should be CIC	*"The Excel model was programmed to run for 30 years from the starting age of [redacted] years. The fitted OS curve for T-DXd predicted [redacted] of patients alive at 30 years (see Section 4.2.6)."* *"The additional benefit associated with [redacted] of patients alive at 30 years in the T-DXd arm is likely to be small after discounting"*	Amendments made as suggested by company.
Section 4.2.6, page 74	Proportion of patients alive at certain time points estimated from the model should be CIC	*"Akaike information criterion (AIC) and Bayesian information criterion (BIC) test statistics, and clinical plausibility based on OS estimation ([redacted] and [redacted] respectively) at 5 and 10 years for T-DM1 patients provided by clinicians."*	Amendments made as suggested by company.
Section 4.2.8, page 92	The number of patients from the UK enrolled in DESTINY-Breast03 is AIC.	*"…only [redacted] patients are from the UK."*	Amendments made as suggested by company.
Section 4.2.10, page 98, Table 4.14	The proportion of progressed patients receiving subsequent treatment from DESTINY-Breast03 should be AIC	Proportion of progressed patients receiving subsequent treatment [redacted] [redacted]	Amendments made as suggested by company.

Section 4.2.10, page 99, Table 4.15	The distribution of subsequent treatments from DESTINY-Breast03 should be marked AIC.	First four columns of Table 4.15 should be marked [redacted]	Amendments made as suggested by company.
Section 5.2.1, page 104	Model results should be marked CIC	*"The probability that T-DXd was cost-effective was [redacted] and [redacted] at cost-effectiveness thresholds of £30,000 and £36,000 per QALY gained"*	Amendments made as suggested by company.
Section 5.2.3, page 107, Table 5.4	The ICERs reported from scenario analysis should be marked CIC	All values in the 'ICER (£/QALY)' column should be marked [redacted]	Amendments made as suggested by company.
Section 5.2.3, page 110	The ICERs reported should be marked CIC	*"The results showed ICERs ranging between [redacted] and [redacted] per QALY gained."*	Amendments made as suggested by company.
Section 5.3, page 110	Model results (i.e., total QALYs) should be marked CIC	*"The total QALYs estimated for T-DM1 in the deterministic analysis of the base case model was [redacted]. Total QALYs estimated for T-DM1 in the probabilistic analysis were [redacted]."*	Amendments made as suggested by company.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after trastuzumab and a taxane [ID3909]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

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.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. 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.

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, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

Technical engagement response form

Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after trastuzumab and a taxane [ID3909]

The deadline for comments is the end of **Wednesday 24th August 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

Table 1 About you

Your name	
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Daiichi Sankyo UK Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

Key issues for engagement

Introductory note from the company:

Daiichi Sankyo would like to thank NICE and the EAG for the opportunity to respond to the key issues raised as part of the appraisal of trastuzumab deruxtecan (T-DXd) for treating HER2-positive (HER2+) unresectable or metastatic breast cancer (u/mBC) after trastuzumab and a taxane. The company consider the technical engagement step to be an important stage of the appraisal process, particularly in light of the new NICE process and methods manual. Although there are no new data to present at this point, we have approached this response as an opportunity to try and address the clinical and economic uncertainty highlighted in the External Assessment Report (EAR) key issues wherever possible. For each of the key issues we have provided a structured reply utilising information already presented, and where possible, provided new informative scenarios using existing evidence to support our position. We have also added commentary within the '

Additional issues*' section related to the assumptions surrounding vial sharing.*

As outlined within the 'Summary of changes to the company's cost-effectiveness estimate(s)', Daiichi Sankyo, accept the coding error and suggested fix provided by the EAG, and have revised our base case accordingly. As such, a full set of updated results have been provided consisting of deterministic results, one-way sensitivity analysis, probabilistic sensitivity analysis, and scenario analysis, and all ICERs presented throughout the document have this amendment incorporated unless otherwise stated. As outlined in the Company submission [CS], Daiichi Sankyo believe that the current QALY shortfall estimates based on the expected QALY gain with NHS standard of care, trastuzumab emtansine (T-DM1), and the general population meet the defined thresholds and therefore a 1.2x QALY modifier is applicable for this appraisal topic (further details of which can be found within the CS). This is further supported by the EAGs deterministic base case. Therefore, throughout the document, incremental QALYs and ICERs are provided with the 1.2x QALY modifier applied. For completeness, results with unweighted QALYs have also been presented within brackets throughout.

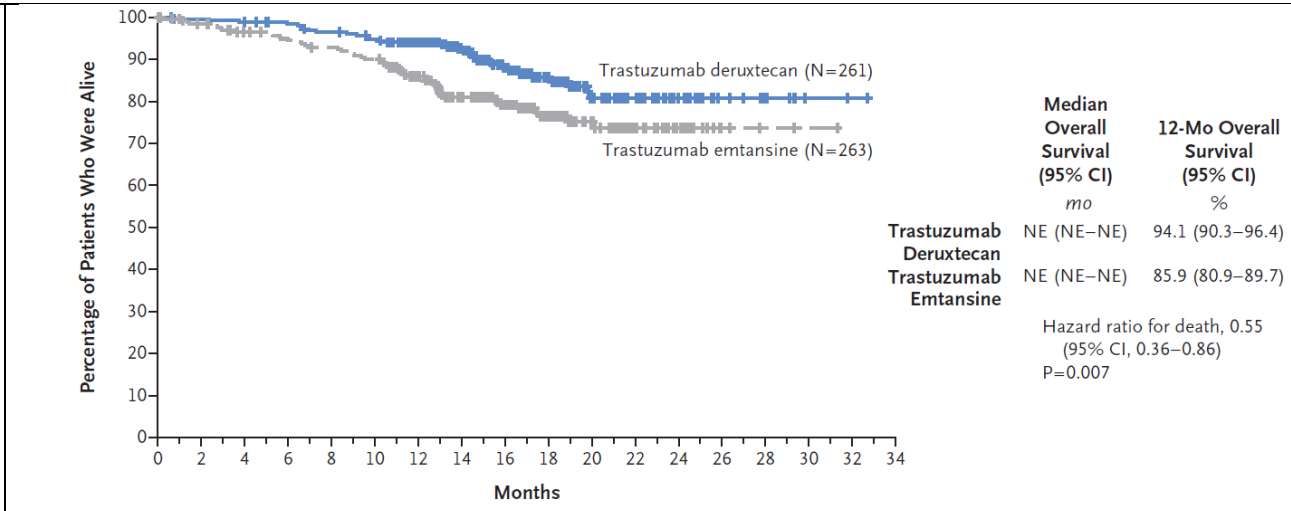
All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Effectiveness data from	No	The EAG is correct that the effectiveness data are from an interim data cut-off (DCO). At follow-up, events of disease progression or death were reported in 87 patients (33.3%) in the T-DXd arm and 158 patients (60.1%)

the included randomised control trial is from an interim data cut point		in the T-DM1 arm.[1] At follow-up, events of disease progression or death were reported in XX patients ([redacted]) in the T-DXd arm and [redacted] patients ([redacted] in the T-DM1 arm.[1] Future data cuts from DESTINY-Breast03 will provide survival data from the trial after a longer follow-up: a second interim analysis is expected in [redacted], after [redacted] progression-free survival (PFS) events, when the final PFS analysis and second interim OS analysis will be conducted.[1] A final overall survival (OS) analysis is also planned at [redacted] OS events.[1] Despite the data from DESTINY-Breast03 deriving from an interim data cut, clinical experts have described the efficacy of T-DXd in DESTINY-Breast03 as "unprecedented", and anticipate that it will lead to a "paradigm shift in the treatment of HER2-positive metastatic breast cancer".[2] As stated in the EAR, DESTINY-Breast03 collected sufficient data for the primary endpoint – PFS by blinded independent central review (BICR) – to conduct the interim analysis and establish superiority of T-DXd compared with T-DM1. T-DXd was associated with a statistically significant 72% lower risk of progression or death compared with T-DM1 (hazard ratio [HR]: 0.28; 95% confidence interval [CI]: 0.22, 0.37 [$p=7.8\times10^{-22}$]).[3,4] The findings for the primary endpoint were further reinforced by the secondary endpoint of investigator-assessed PFS (HR: 0.26; 95% CI: 0.20, 0.35 [$p=6.5\times10^{-24}$]).[4] PFS is a meaningful outcome in its own right, and prior studies have shown that patients value strongly improvements in PFS.[5] The superior PFS demonstrated with T-DXd vs. T-DM1 led to the independent data monitoring committee issuing a recommendation of early unblinding at the first interim analysis for PFS.[4,6] Based on the efficacy and safety evidence from DESTINY-Breast03, the European Commission of the European Medicines Agency (EMA) granted a license extension on 19th July, to T-DXd for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer after one or more prior anti-HER2 based regimens. Most recently, approval was granted in the same indication by the UK's Medicines and Healthcare products Regulatory Agency (MHRA) on 17th August, 2022. The US Food and Drug Administration (FDA) granted second-line approval on the basis of the DESTINY-Breast03 first interim analysis on 4th May 2022.[7] These approvals demonstrate the positive benefit/risk profile for T-DXd based on the interim data from

		DESTINY-Breast03, a position which was also recognised by the European Society for Medical Oncology (ESMO) in their 2021 guidelines, which described T-DXd as "…*the new standard second-line therapy*".[8] Moreover, the Innovative Licensing and Access Pathway (ILAP) Steering Group (MHRA, NICE, All Wales Therapeutics and Toxicology Centre (AWTTC), Scottish Medicines Consortium (SMC), and representatives from the ILAP Patient and Public Reference Group), informed Daiichi Sankyo that the innovative medicine designation, the Innovation Passport, has been awarded for T-DXd on the basis of the DESTINY-Breast03 trial. Although the OS data from DESTINY-Breast03 are considered immature due to the small number of deaths that had occurred by the DCO ([redacted] patients [[redacted]%] in the T-DXd arm and [redacted] patients [[redacted]%] in the T-DM1 arm), a trend in OS showing a benefit with T-DXd relative to T-DM1 is evidenced by the early separation of Kaplan-Meier curves between treatment arms that is sustained to the end of follow-up.[4] Although the reduction in mortality risk (Figure 1) did not cross the pre-specified significance boundary of p<0.000265, set so as to ensure stringent testing at this interim analysis, the company considers it to be indicative of a treatment effect that will be evidenced at a later data cut (HR: 0.55; 95% CI: 0.36, 0.86 [p=0.007]). Efficacy of T-DXd was confirmed through multiple clinically meaningful endpoints, including response rates.[4] **Figure 1: DESTINY-Breast03 | Kaplan-Meier of OS | FAS**



Pre-specified boundary for statistical significance was p<0.000265.
Abbreviations: CI, confidence interval; FAS, full analysis set; HR, hazard ratio; mo, months; NE, not estimable; OS, overall survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Source: Cortés et al, 2021.[4]

In addition to the value of PFS as an endpoint in its own right, multiple studies have established improved PFS as a surrogate for OS in metastatic breast cancer (mBC).[9-11] Beauchemin et al, 2014, reported a correlation coefficient for treatment effect on PFS/time to progression and OS of 0.427 (p<0.01) for patients with mBC.[11] Likewise, Adunlin et al, 2015, reported a model coefficient of 0.40 (p<0.001) for the HR of PFS and the HR of

		OS for mBC at second line and beyond.[9] The correlation between HRs of PFS and OS was reported to be particularly strong in HER2+ mBC (correlation coefficient: 0.9515; 95% CI: 0.7009, 1.0000) in a meta-analysis by Liu et al, 2016.[10] The 17.9-month increase in median PFS (by investigator assessment[1]) observed in DESTINY-Breast03 for T-DXd vs. T-DM1,[4] is therefore expected to translate into a statistically significant and clinically relevant OS advantage, potentially providing OS outcomes similar to treatments used in the current first-line setting. **Daiichi Sankyo agree with the EAG that the OS data immaturity is currently unresolvable based on data available from DESTINY-Breast03 (outlined further in our response to Key Issue 6), but nonetheless would like to highlight that OS in the T-DM1 arm of DESTINY-Breast03 is consistent with previous trials of T-DM1 in this setting where longer term published data are available. The modelled DESTINY-Breast03 OS outcomes appear similar to the external data although slightly higher over time (**

[1] Median PFS by BICR is not available for T-DXd at the first interim analysis.

		Figure 2). This is expected due to the availability of more effective subsequent therapies within the third-line and beyond setting in current practice (and consequently in DESTINY-Breast03) compared with those available when historical trials were conducted. This would also be expected to translate to UK clinical practice given changes in the UK treatment pathway for mBC, for example the availability of HER2-targeted treatments including T-DXd and the tucatinib combination from third line. Therefore, T-DM1 OS in DESTINY-Breast03 could be expected to be improved compared with EMILIA and other prior studies in this setting. This was also confirmed by UK clinical experts consulted by Daiichi Sankyo, who advised that EMILIA is a generalisable trial where outcomes are similar to UK practice, with any notable differences in OS in the real world setting likely a result of changes in treatment practice, particularly the availability of more effective HER2-targeted subsequent therapies. The company therefore considers OS estimates derived from DESTINY-Breast03, which have been compared with EMILIA and other studies, and validated by clinical and health economics and outcomes research (HEOR) experts, to be appropriate. The EAG also agree that the T-DM1 OS extrapolations are plausible as they state in their report: *"The OS prediction for T-DM1 was plausible given the clinical expert opinion on survival and the EMILIA trial data."* (EAR, Section 1) and *"The EAG does consider the overall survival predictions for T-DM1 to be plausible given the fitted survival model and the company clinical expert opinion on survival rates at 10 years."* (EAR, Section 6).

		Figure 2: External validation | T-DM1 | OS

		 Abbreviations: ITT, intention to treat; KM, Kaplan-Meier; OS, overall survival	

Key issue 2: Background characteristics of people in the trial may not reflect characteristics of those that would be seen in English clinical practice	Yes	The EAG has stated that the background characteristics of patients enrolled in DESTINY-Breast03 may not reflect characteristics of patients seen in English clinical practice; this was considered an unresolvable issue that is a limited cause of uncertainty. In particular, the EAG highlighted differences in the proportion of Asian patients in both populations, differences in the numbers of smokers, and differences in the number of prior lines of therapy patients had, or would be expected to have, received. Daiichi Sankyo agree with the EAG that this is an unresolvable issue that is a limited cause of uncertainty. As is common in global randomised controlled trials, variation in geographic locations of study sites can lead to demographic and baseline characteristic differences between intent-to-treat (ITT) populations and individual countries. Study sites for DESTINY-Breast03 are such that there is a higher proportion of Asian patients than may be expected in UK clinical practice, and potentially some minor differences in smoking rates between regions. Daiichi Sankyo received clinical advice, as part of an expert validation meeting, that DESTINY-Breast03 is generalisable to patients with HER2+ unresectable or metastatic breast cancer (u/mBC) treated after trastuzumab and a taxane in the UK (company submission Section B.2.6.2, page 63).[12] Daiichi Sankyo therefore considers DESTINY-Breast03 to be generalisable to UK clinical practice. Supplemental subgroup analyses are provided below to support this conclusion, although all subgroup analyses should be interpreted with caution as DESTINY-Breast03 was not powered to assess efficacy differences between subgroups. *Efficacy and safety based on ethnicity (Asian vs. non-Asian patients)* Clinical advice to the company in an expert validation meeting was that the high proportion of Asian patients enrolled in DESTINY-Breast03 would not be expected to have an impact on survival, and that there is no biological reason for Asian ethnicity to affect the efficacy of T-DXd. To explore this issue further, Asian ethnicity has been assessed through subgroup analysis of PFS by BICR in DESTINY-Breast03 (Figure 3). The subgroup analysis [redacted] of T-DXd vs. T-DM1 for

		PFS between Asian and non-Asian patients, with [redacted] for the HR between the two subgroups (Asian: [redacted]; non-Asian: [redacted]). Consequently, subgroup analysis suggests that there is [redacted] of Asian patients in the trial upon the treatment effect. **Figure 3: DESTINY-Breast03 | Forest plot of PFS by BICR | FAS | Race and region**  Abbreviations: BICR, blinded independent central review; CI, confidence interval; FAS, full analysis set; NE, not estimable; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan. The EAG also suggested that, based on previous clinical trials in breast cancer, there may be potential for higher toxicity in Asian patients than patients of other races treated in UK clinical practice. This would suggest that rates of adverse events (AEs) could be lower in UK clinical practice than in DESTINY-Breast03 as a higher proportion of

Asian patients were enrolled in DESTINY-Breast03 than would typically require treatment in the UK. However, a breakdown of treatment-emergent AEs (TEAEs) in DESTINY-Breast03 by subgroup suggests that there is [redacted] (Table 1).

Table 1: DESTINY-Breast03 | Summary of TEAEs by subgroup | Asian and non-Asian race | SAS

TEAEs by category, n (%)	T-DXd		T-DM1	
	Asian (n=149)	Non-Asian (n=108)	Asian (n=161)	Non-Asian (n=100)
Total patient-years of exposure	[redacted]	[redacted]	[redacted]	[redacted]
Any TEAE	[redacted]	[redacted]	[redacted]	[redacted]
EAIRs per patient-year	[redacted]	[redacted]	[redacted]	[redacted]
Serious TEAE	[redacted]	[redacted]	[redacted]	[redacted]
TEAE associated with Study Drug Discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
TEAE associated with Study Drug Interruption	[redacted]	[redacted]	[redacted]	[redacted]
Severe TEAE (CTCAE Grade ≥3)	[redacted]	[redacted]	[redacted]	[redacted]
TEAE associated with an Outcome of Death	[redacted]	[redacted]	[redacted]	[redacted]
TEAE associated with Dose Reduction	[redacted]	[redacted]	[redacted]	[redacted]
Drug-related Severe TEAE (CTCAE Grade ≥3)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; EAIR, exposure-adjusted incidence rate; SAS, safety analysis set; TEAE, treatment-emergent adverse event; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

		Smoking status The EAG stated that the proportion of smokers in DESTINY-Breast03 was lower than the rate of smoking in the UK. Based on 2020 data for adult women in England, 89.6% of the population do not smoke (never smoked or formerly smoked).[13] The company consider this consistent with the [redacted]% and [redacted]% of patients in the T-DXd and T-DM1 arms of DESTINY-Breast03, respectively, who do not smoke.[1] To explore this issue further, subgroup analysis of PFS by BICR in DESTINY-Breast03 was conducted across the subgroup of patients who had never smoked, and patients who were current or former smokers. Despite the small proportion of current and former smokers in DESTINY-Breast03, there is nonetheless a [redacted] of T-DXd vs. T-DM1 in both subgroups (Figure 4). The analysis also demonstrates [redacted], with [redacted] (current/former smokers: [redacted]; never smoked: [redacted]).

Figure 4: DESTINY-Breast03 | Forest plot of PFS by BICR | FAS | Smoking status

Abbreviations: BICR, blinded independent central review; CI, confidence interval; FAS, full analysis set; NE, not estimable; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

Prior lines of therapy

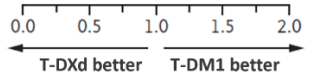
Clinical experts consulted by the company stated that number of lines of prior therapy would be a prognostic factor for survival, with patients who had received more prior therapies having worse prognosis than patients who had received fewer prior therapies.[12] In DESTINY-Breast03, 50.8% of enrolled patients had received ≥2 prior lines of therapy, and 49.2% had received 0–1 prior lines of therapy.[2] Clinicians prefer to use the most efficacious treatments as early as possible in the treatment pathway. It is therefore anticipated that, if approved, the majority of T-DXd usage would be at second line following trastuzumab and a taxane. Patients in DESTINY-Breast03 may have received more lines of

[2] All patients who received treatment in DESTINY-Breast03 had received at least one prior cancer therapy; prior cancer therapy was not recorded for two patients who were randomised in error and not treated. Subgroup analysis for lines of prior therapy was conducted based on number of prior therapies received in the metastatic setting; n=2 and n=3 patients in the T-DXd and T-DM1 arms, respectively, had not received prior treatment in the metastatic setting

		prior therapy than would be expected in UK clinical practice, and consequently, the unprecedented PFS seen at the first interim analysis could be considered a conservative estimate of T-DXd efficacy. Pre-specified and post hoc subgroup analyses of data from DESTINY-Breast03 conducted to date have not demonstrated any differences in PFS treatment effect based on lines of prior therapy. Subgroup analysis of PFS by BICR according to prior lines of therapy (0–1 or ≥2) in DESTINY-Breast03 demonstrated a statistically significant treatment effect in both subgroups for T-DXd vs. T-DM1 (Figure 5).[4] Confidence intervals in both subgroups show substantial overlap, demonstrating consistency in treatment effect between the subgroups (0–1 prior lines: 95% CI 0.23, 0.48; ≥2 prior lines: 95% CI 0.19–0.41).[4] Likewise, subgroup analysis of confirmed objective response rate (ORR) by BICR in DESTINY-Breast03 demonstrated similarity between 0–1 prior lines and ≥2 prior lines (CS Figure 12, page 68).[14] The analysis demonstrated consistency, with overlap between the confidence intervals for the percentage-point difference between T-DXd and T-DM1 (0–1 prior lines: 95% CI 27.3, 51.2; ≥2 prior lines: 40.9, 62.4).[14]

Figure 5: DESTINY-Breast03 | Forest plot of PFS by BICR subgroup analysis | FAS | Analysis in key subgroups including by lines of prior therapy

Subgroup	No. of Patients	No. of Events/No. of Patients		Median Progression-free Survival (95% CI) *months*		Hazard Ratio for Disease Progression or Death (95% CI)
		Trastuzumab deruxtecan	Trastuzumab emtansine	Trastuzumab deruxtecan	Trastuzumab emtansine	
All patients		87/261	158/263	NE (18.5–NE)	6.8 (5.6–8.2)	0.28 (0.22–0.37)
Hormone-receptor status						
Positive	272	46/133	84/139	22.4 (17.7–NE)	6.9 (4.2–9.8)	0.32 (0.22–0.46)
Negative	248	41/126	73/122	NE (18.0–NE)	6.8 (5.4–8.3)	0.30 (0.20–0.44)
Previous pertuzumab treatment						
Yes	320	57/162	98/158	NE (18.5–NE)	6.8 (5.4–8.3)	0.30 (0.22–0.43)
No	204	30/99	60/105	NE (16.5–NE)	7.0 (4.2–9.7)	0.30 (0.19–0.47)
Visceral disease						
Yes	384	72/195	123/189	22.2 (16.5–NE)	5.7 (4.2–7.0)	0.28 (0.21–0.38)
No	140	15/66	35/74	NE (NE–NE)	11.3 (6.8–NE)	0.32 (0.17–0.58)
Lines of previous therapy						
0 or 1	258	46/132	75/126	22.4 (17.9–NE)	8.0 (5.7–9.7)	0.33 (0.23–0.48)
≥2	266	41/129	83/137	NE (16.8–NE)	5.6 (4.2–7.1)	0.28 (0.19–0.41)
Stable brain metastases defined by reported history of CNS metastases						
Yes	114	31/62	31/52	15.0 (12.6–22.2)	5.7 (2.9–7.1)	0.38 (0.23–0.64)
No	410	56/199	127/211	NE (22.4–NE)	7.0 (5.5–9.7)	0.27 (0.19–0.37)



Abbreviations: BICR, blinded independent central review; CI, confidence interval; CNS, central nervous system; FAS, full analysis set; NE, not estimable; No, number; PFS, progression-free survival; T DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Source: Adapted from Cortés et al, 2022.[4]

		Efficacy for a "generalisable" European population vs the DESTINY-Breast03 ITT population As a final discussion topic around generalisability, the EAG posits that the European subgroup of patients in DESTINY-Breast03 may be more generalisable to UK practice, but that patient numbers in this subgroup are small. Daiichi Sankyo agree that this subpopulation is not sufficiently large allow inclusion in the economic model without introducing further uncertainty associated with efficacy extrapolations. The company position is that there is no difference in efficacy between the European subpopulation and the DESTINY-Breast03 ITT population, and therefore that it is appropriate to use the ITT population in the economic model. Confirming the generalisability of DESTINY-Breast03 to the UK, supplemental subgroup analysis of PFS by BICR conducted to support the technical engagement process demonstrated a [redacted] for T-DXd vs. T-DM1 in the European subpopulation of DESTINY-Breast03 (Figure 3). [redacted] subgroups [redacted] (Europe: [redacted]; rest of world: [redacted]). This finding is [redacted] in the trial ([redacted]). Additionally, median PFS with T-DM1 in the ITT population of DESTINY-Breast03 was 6.8 months, consistent with median PFS observed in European real-world studies (CS Section B.2.6.1, Table 12, page 55).[15-19] In conclusion, Daiichi Sankyo agree with the EAG that differences in background characteristics of patients enrolled in DESTINY-Breast03 and patients in clinical practice is an unresolvable issue that is a limited cause of uncertainty.
Key issue 3: Uncertainty in the proportion of people whose disease has progressed	Yes	The EAG considered the proportion of patients receiving subsequent treatment to be uncertain as the values from DESTINY-Breast03 were high in comparison to clinical expert opinion. In addition, the EAG are unsure whether the distribution of subsequent treatments received in the DESTINY-Breast03 study are reflective of English clinical practice. Daiichi Sankyo would like to address each of these concerns in turn; the proportion of patients who receive subsequent treatments and secondly, the distribution of subsequent treatments.

who are having subsequent treatments and the distribution of subsequent treatments		*Proportion of patients receiving subsequent treatments* In the company base case, the proportion of patients receiving subsequent treatment was informed by clinical expert opinion (66.7%) which was also confirmed by clinical advice received by the EAG. There are two ways of calculating the proportion of patients receiving subsequent treatment in DESTINY-Breast03. The first method, provided as a scenario analysis in the company submission, incorporates the total number of patients receiving at least one subsequent treatment divided by the total progressed events including death. The resulting proportions are [redacted] for T-DXd and [redacted] for T-DM1. These values appear higher than those estimated by clinicians. This is due to the numerator, which considers all patients receiving at least one subsequent treatment including those that discontinued treatment for reasons other than progression. Clinical experts consulted considered these values were higher than expected and suggested that around two-thirds of patients who progress would receive subsequent treatment. The model results when using these proportions are provided in Table 2 which show a decrease in the incremental cost-effectiveness ratio (ICER) from a base case of [redacted] to [redacted] ([redacted] to [redacted] when quality-adjusted life-years (QALYs) are unweighted). As part of the clarification response, a second method of estimating the proportion of patients receiving subsequent therapy was introduced. In this method, only patients who had progression events were considered in order to align with the economic modelling where subsequent therapies are applied once a patient's disease progresses. Here, Daiichi Sankyo confirmed that when analysing only progressed patients, [redacted] in the T-DXd arm and [redacted] in the T-DM1 arm, received at least one subsequent treatment. These values are more aligned with the values provided by the clinical experts. Using these values in the model decreases the base case ICER from [redacted] to [redacted] ([redacted] to [redacted] with unweighted QALYs), suggesting an improvement in cost-effectiveness. Daiichi Sankyo therefore considers the base case to be conservative and the impact of these scenarios minor (see Table 2).

The base case value is considered more conservative given that the same value is applied to both treatment arms. Evidence from the trial using both methods described above, has a higher proportion of patients receiving subsequent treatment for T-DM1 versus T-DXd.

Table 2: Base-case results (with PAS) with alternative proportion of patients receiving subsequent treatment ([redacted])

Drug	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs (unweighted QALYs)	ICER vs. baseline (unweighted QALYs)
Company base case (66.7%)							
T-DM1	[redacted]	[redacted]	[redacted]				
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: DB03 subsequent treatment proportions							
T-DM1	[redacted]	[redacted]	[redacted]				
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: DB03 progressed patient proportions							
T-DM1	[redacted]	[redacted]	[redacted]				
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

		Abbreviations: DB03, DESTINY Breast03; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years. *Distribution of subsequent treatments* The EAG note that the subsequent treatments used in DESTINY-Breast03 may not be reflective of English clinical practice, however they do not suggest how they could differ, or which treatments specifically differ in UK clinical practice. The EAG suggest that data from the European subgroup could be more reflective and that more follow-up data from DESTINY-Breast03 could change the distributions. Daiichi Sankyo acknowledge that with more follow-up the overall distributions of subsequent treatment may change within the DESTINY-Breast03 trial, however it is expected that changes in the distribution would have a small impact on costs and therefore this uncertainty would have minimal impact on the cost-effectiveness estimates. In the company base case, the costs of subsequent treatments were informed by the distribution of subsequent treatment reported in the DESTINY-Breast03 study to maintain consistency between the source of efficacy and costs. However, alternative treatment distributions were tested in scenario analyses (see Section B.3.11.3) to assess the uncertainty associated with subsequent therapy distributions. Two scenarios were included: 1. Assuming the same distribution between both treatment arms using the pooled subsequent treatment distribution from DESTINY-Breast03. 2. Applying subsequent therapy distributions based on UK expert clinical advice.

A third scenario is presented for the TE response where Daiichi Sankyo have incorporated subsequent treatments based on the European subgroup distribution of subsequent treatments from DESTINY-Breast03 (Scenario 3 – see Table 3).

Table 3 presents the subsequent treatment distributions applied in each scenario included within the economic model.

Table 3: Subsequent treatment distribution scenarios

Curve	Base case DB-03		Scenario 1 pooled DB-03	Scenario 2 UK clinical expert opinion		Scenario 3 European subgroup	
	T-DXd	T-DM1	T-DXd	T-DM1	T-DXd	T-DM1	T-Dxd
Trastuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T-DM1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pertuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Taxane (paclitaxel)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Trastuzumab + taxane	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-HER2 (tucatinib combination)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hormone therapy (tamoxifen)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other (capecitabine)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan

The results of these scenarios are presented in the company submission (Section B.3.11.3) and EAR (Section 5.2.3 and Section 6.2.2). For completeness, these results are also presented in Table 4 based on the company's 'corrected' base case post EAR and also include the new scenario exploring the European subgroup. The results presented highlight that each scenario has a minimal impact on the ICER.

Table 4: Base-case results (with PAS) with alternative subsequent treatment distribution scenarios

Drug	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs (unweighted QALYs)	ICER vs. baseline (unweighted QALYs)
Base case: DB-03 data							
T-DM1	[redacted]	[redacted]	[redacted]				
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: Pooled DB-03 data (assuming same distribution across arms)							
T-DM1	[redacted]	[redacted]	[redacted]				
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: Clinical expert opinion							
T-DM1	[redacted]	[redacted]	[redacted]				
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

		Scenario 3: European subgroup T-DM1 [redacted] T-DXd [redacted] Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years. In conclusion, Daiichi Sankyo acknowledge that there is some uncertainty associated with both the proportion of progressed patients receiving subsequent treatment, and the types of treatments received, however the scenario analyses explored suggest a limited impact on the cost-effectiveness of T-DXd. Daiichi Sankyo therefore agree with the EAG that this is a limited cause of uncertainty.
Key issue 4: Higher AEs in the T-DXd arm compared to T-DM1 arm	Yes	The EAG highlighted the higher rate of any-grade TEAEs in the T-DXd arm compared with the T-DM1 arm (99.6% and 95.4%, respectively). However, the EAG also stated that this issue is not anticipated to impact cost-effectiveness, given that the cost and quality-of-life impact of AEs is modelled in the cost-effectiveness analysis. Daiichi Sankyo are in agreement with this position but would like to highlight the incidence rates of AEs across each treatment arm when taking treatment duration into account, and clinical expert opinion on the benefit/risk profile of T-DXd, as well as the lower rate of discontinuations overall in the T-DXd arm than with T-DM1 (125 and 214 patients, respectively).[4] In DESTINY-Breast03, the higher rate of TEAEs should be viewed in the context of the substantially longer treatment duration and patient-years of exposure in the T-DXd arm (14.3 months and [redacted] years, respectively) compared with the T-DM1 arm (6.9 months and [redacted] years, respectively).[1,4] Rates of serious TEAEs were similar between treatment arms (19.1% and 18.0% of patients, respectively) and the exposure-adjusted incidence of TEAEs was

		lower in the T-DXd than T-DM1 arm for both serious TEAEs ([redacted] and [redacted] events per patient year, respectively) and any TEAE experienced in the trial ([redacted] and [redacted] events per patient year, respectively).[1,4] T-DXd demonstrated an acceptable safety profile in DESTINY-Breast03 that was consistent with previous studies of T-DXd, with no new safety concerns identified; most TEAEs were Grade 1 or 2 and were manageable in routine care.[4,20,21] Few patients discontinued study drug due to TEAEs, although the proportion of patients discontinuing treatment due to TEAEs was higher in the T-DXd arm than in the T-DM1 arm.[4] Overall, the safety profile for T-DXd was similar to T-DM1, and was as expected based on previous studies of T-DXd; AEs – including events relating to interstitial lung disease (ILD) – were manageable. There now exists substantial clinical experience with T-DXd since NICE recommended reimbursement of T-DXd through the Cancer Drugs Fund (CDF) in 2021 for treating HER2+ u/mBC after 2 or more anti-HER2 therapies,[22] where the committee described T-DXd as having an acceptable safety profile.[23] From April 2021 to June 2022, [redacted] patients were initiated on treatment with T-DXd within the CDF in England; T-DXd is also available at third line in Wales, Northern Ireland, and Scotland. Moreover, in the French cohort temporary authorisation for use (cATU) programme, T-DXd was "well tolerated and no new safety signals were observed" in 459 patients who had previously received at least two prior lines of therapy.[24] This, together with anecdotal feedback from prescribing physicians, demonstrates clinical confidence that T-DXd is an efficacious therapy with a manageable safety profile. At the expert validation meeting conducted by the company, the clinical experts stated that the AE profile of T-DXd in DESTINY-Breast03 was not of concern, and consistent with their clinical experience.[12] A clinical expert also observed that ILD rates have improved since publication of results from DESTINY-Breast01.[12] Potential ILD events that occur in patients treated with T-DXd are handled through an established ILD management plan, which is clearly defined in the summary of product characteristics for T-DXd.[25] The improved ILD rates noted by the clinical expert indicate both that clinicians have improved awareness of the potential for ILD and that the ILD management plan aids appropriate and

		timely response to potential ILD events. The company considers this view to reflect the growing understanding of T-DXd's safety profile amongst UK oncologists. Data from DESTINY-Breast03 (DCO May 2021) indicate that most patients treated with T-DXd were able to tolerate the planned dose of 5.4 mg/kg/3 weeks: the majority of patients treated with T-DXd ([redacted]) did not have any dose reductions from baseline to follow-up (note: reductions were not exclusively due to AEs), and [redacted] of patients did not have any other dose changes or interruptions.[1] The safety profile of T-DXd should be seen in the context of its efficacy in delaying disease progression. Patient disposition data from DESTINY-Breast03 presents a discontinuation rate of 125 patients (47.9% of those randomised) by end of follow-up in the T-DXd arm, compared with 214 patients in the T-DM1 arm (81.4% of those randomised).[4] Although 35 (13.4%) and 17 (6.5%) patients, respectively, discontinued due to AEs, a much greater proportion discontinued due to BICR or investigator-assessed disease progression, which was notably lower in the T-DXd arm than the T-DM1 arm (70 [26.8%] and 170 [64.6%] patients of those randomised, respectively, discontinued due to either assessment of disease progression).[4] Since the company submission was made to NICE in April 2021, a further safety data cut from DESTINY-Breast03 (7 Sept, 2021) was presented at the 2022 American Society of Clinical Oncology (ASCO) congress.[26] These data (Table 5) are consistent with the findings from the first interim data cut for PFS (21 May, 2021), with no new safety signs. Exposure-adjusted incidence rates (EAIRs) per patient-year were lower in the T-DXd arm than the T-DM1 arm except for TEAEs associated with drug discontinuation, which were driven by management of actual or suspected ILD/pneumonitis in the T-DXd arm.[26] Moreover, the time to onset of TEAEs associated with first drug discontinuation or first dose reduction was longer in the T-DXd arm (224 and 96 days, respectively than the T-DM1 arm (147 and 19 days, respectively).[26]

Table 5: DESTINY-Breast03 | Summary of key safety data | September 2021 DCO

	T-DXd (n=257)	T-DM1 (n=261)
Patients remaining on treatment, n (%)	116 (45.1)	39 (14.9)
Treatment duration, median (range), months	16.1 (0.7–33.0)	6.9 (0.7–28.5)
Exposure, patient-years	327.2	186.3
Any grade TEAEs	256 (99.6)	249 (95.4)
Grade ≥3 TEAEs, n (%)	137 (53.3)	130 (49.8)
EAIR, patients with ≥1 event per PYE	0.42	0.70
Serious TEAEs	54 (21.0)	50 (19.2)
EAIR, patients with ≥1 event per PYE	0.17	0.27
Grade ≥3 serious TEAEs	39 (15.2)	38 (14.6)
EAIR, patients with ≥1 event per PYE	0.12	0.20
TEAEs associated with drug discontinuation	38 (14.8)	19 (7.3)
EAIR, patients with ≥1 event per PYE	0.12	0.10
Median time to event, days	224	147
TEAEs associated with dose reduction	59 (23.0)	36 (13.8)

		EAIR, patients with ≥1 event per PYE: 0.18 (T-DM1) / 0.19 (T-DXd) Median time to event, days: 96 (T-DM1) / 19 (T-DXd) Abbreviations: EAIR, exposure-adjusted incidence rate; DCO, data cut-off; PYE, patient-years of exposure; TEAE, treatment-emergent adverse event; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan. Source: Hamilton et al, presented at ASCO congress, 2022.[26] Recently, on the basis of safety and efficacy evidence from DESTINY-Breast03, the MHRA granted regulatory approval to T-DXd for treatment of adult patients with HER2+ u/mBC after one or more prior anti-HER2 based regimens, extending the licence of T-DXd from the original indication and showing confidence in the benefit/risk profile. Daiichi Sankyo conclude that the safety profile of T-DXd is well characterised and that the impact of AEs is appropriately modelled in the company cost-effectiveness analysis and AEs are not a driver of cost-effectiveness, therefore this issue should be considered limited cause of uncertainty.
Key issue 5: Uncertain PFS predictions for T-DXd	No	The EAG highlight uncertainty associated with the PFS estimates from DESTINY-Breast03 used to inform long-term extrapolations of PFS within the economic model due to data immaturity but note that alterative parametric models had little effect on the cost-effectiveness estimates. The current data available from DESTINY-Breast03 in relation to the primary endpoint, PFS by BICR, met its primary endpoint at the interim analysis, demonstrating statistical significance and superiority in the T-DXd arm compared with T-DM1 (HR: 0.28; $p=7.8\times10^{-22}$).[4] The PFS data sufficiently demonstrates a clinically meaningful PFS benefit for T-DXd. At DCO, events of disease progression or death were reported in 33.3% in the T-DXd arm and 60.1% in the T-DM1 arm.[1] At DCO, [redacted] patients ([redacted]) in the T-DXd arm and [redacted] patients ([redacted]) in the T-DM1 arm were ongoing without events.[1] The remaining [redacted] patients ([redacted]) in the T-DXd arm and [redacted] patients ([redacted]) in the T-DM1 arm were censored for other reasons.[1] As stated in response to Key Issue 1 and in the EAR, DESTINY-Breast03

		collected sufficient data to meet the primary endpoint – PFS by BICR – which were further reinforced by the secondary endpoint of investigator-assessed PFS.[4] While PFS data are relatively mature, particularly for the T-DM1 arm (60.1%), extrapolation of outcomes was required to inform cost-effectiveness estimates over a lifetime horizon (as is common in oncology appraisals). As stated within the company submission (Section B.3.3.2.2), six parametric curves were fitted to the data with an assessment of statistical goodness of fit and visual fit to determine the most appropriate curve. Additionally, clinical opinion was sought to ensure the longer-term estimates projected by the curves were clinically plausible and in line with expectations. Clinical advice indicated that 1-2% of T-DM1 patients would be progression-free at 5 years and this would reduce to 0% by 10 years. As such, expert clinical advice indicated that the Gompertz and generalised gamma curves could be excluded as they were not clinically plausible for T-DM1 with 5-year estimates substantially above this range. For T-DXd, the Gompertz was also considered too pessimistic. Further, both the Gompertz and generalised gamma curves produced extrapolations for T-DXd which crossed with T-DM1 at [redacted] and [redacted] years respectively. Clinicians considered this unlikely given the large PFS benefit observed within DESTINY-Breast03 and the clear separation of KM OS curves. Therefore, based on the visual fit and the plausibility of the long-term extrapolation, the log-logistic, log-normal, Weibull and exponential were considered most appropriate for further consideration to inform PFS estimates. Based on the clinical advice received, the Weibull distribution was selected to inform the base case extrapolations for T-DM1. Applying the Weibull may be considered pessimistic in comparison to the alternative plausible extrapolations, however, clinical experts agreed that the Weibull curve for T-DM1 would provide the most clinically plausible fit with 5- and 10-year PFS of [redacted] (which closely matches the clinical experts feedback of between 1–2% and 0%).[12]

		The log-normal and log-logistic curves also projected slightly higher PFS with T-DM1 than expected at both time points (see Table 6). Given the similar mechanisms of action of T-DXd and T-DM1 and in line with TSD guidance, it was also considered appropriate to assume the same base case PFS distribution across arms.[27] The clinicians agreed that the Weibull distributions for both T-DXd and T-DM1 provided an appropriate curve choice with a consistently higher PFS estimate for T-DXd. Each of the six parametric distributions (of which four were considered plausible), T-DXd projected higher PFS estimates in comparison to T-DM1. This is consistent with the observed KM data in DESTINY-Breast03 where there is clear and continued separation of curves and consistent with clinical opinion. Daiichi Sankyo consider their choice of base case curves (Weibull) to be the most appropriate and plausible options and in line with clinical expert opinion. In addition, of the plausible curves, the Weibull distributions estimate the most conservative treatment benefit for T-DXd in the long-term ([redacted] and [redacted] benefit at 5- and 10 years, respectively). Further to this, whilst there is some uncertainty in the magnitude of the PFS benefit (as illustrated by each of the extrapolations), all plausible extrapolations were tested in scenario analysis provided by Daiichi Sankyo in the company submission (see Section B.3.11.3 - also presented in Table 7 below) and the cost-effectiveness results obtained were similar, ranging from [redacted] to [redacted] when considering the 1.2x QALY modifier ([redacted] to [redacted] with unweighted QALYs). Despite raising uncertainty in long term PFS as a key issue, the EAG also agree within their report that different PFS curves had little impact on cost-effectiveness results (see Section 1.5 and 6.2.1 of the EAR) and hence the company consider that the uncertainty associated with PFS due to the interim data, is not a key determining factor in cost-effectiveness of T-DXd. In conclusion, based on the clinical plausibility of the long-term PFS projections, modest

modelled benefit in the long term and minimal impact on cost-effectiveness in sensitivity analyses, the uncertainty associated with PFS from DESTINY-Breast03 is low.

Table 6: 5- and 10- year PFS estimates of plausible curves

Curve	T-DM1		T-DXd	
	5 years	10 years	5 years	10 years
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]

Table 7: Base-case results (with PAS) with alternative PFS curve distributions

Drug	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs (unweighted QALYs)	ICER vs. baseline (unweighted QALYs)
Base case: PFS = Weibull							
T-DM1	[redacted]	[redacted]	[redacted]				
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: PFS = Exponential							
T-DM1	[redacted]	[redacted]	[redacted]				
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

		Scenario 2: PFS = log-logistic [redacted] ***Scenario 3: PFS = log-normal*** [redacted] Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years.
Key issue 6: Uncertain OS predictions for T-DXd	No	In their report, the EAG have highlighted the uncertainty associated with the OS due to the limited OS events in the DESTINY-Breast03 trial at the DCO, in particular for T-DXd. Within the EAR, as a way of addressing the uncertainty, the EAG incorporated 'treatment waning' for T-DXd assuming that all patients who progress on T-DXd and T-DM1 have the same hazard of mortality with 2 years used as a proxy timepoint. Daiichi Sankyo do not agree that treatment waning is appropriate for decision-making based on the available evidence and would like to respond to this issue in two parts, firstly, to address uncertainty associated with OS estimates with regard to the cost-effectiveness and secondly to respond to the EAG's assumed treatment waning scenario. **<u>Approaches taken to address OS uncertainty</u>** Daiichi Sankyo acknowledge the uncertainty associated with the OS outcomes due to the immaturity of the interim analysis data cut from DESTINY-Breast03 and lack of external long-term outcomes for T-DXd. Despite this immaturity

		in the OS estimates, extensive methods have been undertaken within the current submission through a variety of means including: • Validation of extrapolated outcomes with clinical experts • A range of scenarios using alternative extrapolations of other plausible distributions • An alternative approach to model OS using longer follow-up data for T-DM1 • Extensive sensitivity analysis on the company base case through OWSA, PSA and scenario analysis *Clinical validation* Parametric survival models were fitted to the observed data from DESTINY-Breast03 OS data (discussed further in the CS Section B.3.3.2.1). As stated within the company submission, guidance from NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14 was considered to determine an appropriate base case selection, which was based on a balance of data and statistical tests, AIC/BIC statistics, visual inspection of the parametric curves to the observed data and assessment of the plausibility of fitted models after the end of the follow-up period. Clinical validation was sought to determine the appropriate plausibility of long-term estimates of the fitted curves. As stated within the company submission (Section B.3.3.2.1) clinical experts consulted by Daiichi Sankyo advised that 25–35% of patients treated with T-DM1 would be alive at 5 years (as per the EMILIA trial – see Figure 10) and 5–10% by 10 years, and therefore considered that the exponential, log-normal and Gompertz curves extrapolated from the DESTINY-Breast03 trial, could be completely excluded. The clinical experts considered that survival would likely be somewhere between the range provided by the Weibull which may be considered pessimistic at 10 years (with [redacted] of patients alive) and the log-logistic which may be considered optimistic at 10 years ([redacted] alive) – see Table 8. Therefore, the log-logistic, Weibull and generalised gamma curves were considered most appropriate (presented in Figure 6). When considering T-DXd, clinical experts also considered the three curves plausible for T-DM1 could also

be plausible for T-DXd, with the plausible range from the Weibull (the most conservative OS estimates) to the log-logistic (with the most optimistic estimates).

Given the generalised gamma sat between the plausible estimates for the three curves, this was considered the most appropriate extrapolation to inform the company base case. The generalised gamma curve provides a clinically plausible long-term extrapolation of T-DM1 survival, with 5- and 10-year survival estimates in line with ranges provided by clinicians ([redacted] and [redacted], respectively).

Table 8: 5- and 10- year OS estimates of plausible curves – DESTINY-Breast03 extrapolations

Curve	T-DM1		T-DXd	
	5 years	10 years	5 years	10 years
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: OS, overall survival; T-DXd, trastuzumab deruxtecan; T-DM1, trastuzumab emtansine

Figure 6: OS outcomes from DESTINY-Breast03 – plausible curves

Abbreviations: KM, Kaplan-Meier; OS, overall survival

Scenarios of other plausible parametric curves

As presented in the company submission Section B.3.11.3, the other plausible curves (i.e., log-logistic and Weibull) were explored in scenario analysis. The plausible curves consistently indicate a benefit for T-DXd versus T-DM1 with an incremental life year gain ranging between [redacted] (with the Weibull curve) and [redacted] (with the log-logistic curve). The corresponding ICER range is [redacted] to [redacted] ([redacted] to [redacted] with unweighted QALYs). In each of these scenarios, T-DXd remains cost-effective within the plausible range of extrapolated OS curves.

Table 9: Base-case results (with PAS) with alternative plausible OS distributions

Drug	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs (unweighted QALYs)	ICER vs. baseline (unweighted QALYs)
Company base case: OS informed by the generalised gamma distribution							
T-DM1	[redacted]	[redacted]	[redacted]				
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: OS informed by the log-logistic distribution							
T-DM1	[redacted]	[redacted]	[redacted]				
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: OS informed by the Weibull distribution							
T-DM1	[redacted]	[redacted]	[redacted]				
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years.

Alternative approach to model OS

Daiichi Sankyo have also conducted an alternative approach to estimate the OS of T-DXd and T-DM1 utilising published information which had longer-term follow-up for T-DM1. In this alternative approach, patient level data (PLD) were replicated from the T-DM1 arm of the EMILIA study which had a median follow-up of 47.8 months.[28] Parametric survival models were fitted to the replicated data to inform the T-DM1 OS, with the HR from DESTINY-Breast03 applied to this curve to inform the T-DXd OS (HR = 0.55).

From the parametric models and clinical feedback described above, the log-logistic, log-normal, and generalised gamma were considered most appropriate (

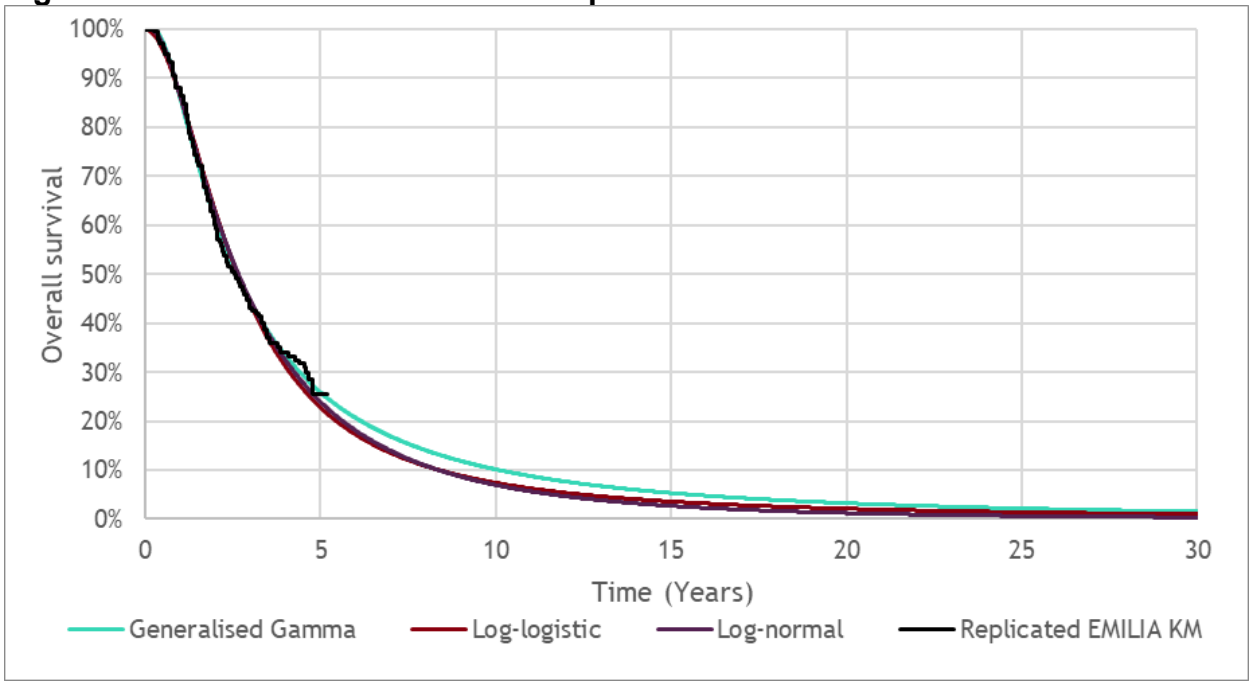
Figure 7). Of the plausible curves, generalised gamma provides the most optimistic (~10%) survival at 10 years, at the upper end of the clinical estimates. The log-normal and log-logistic curves are visually similar and sit between the estimates provided by clinicians at 10 years (7.0% and 7.4% respectively) – see Table 10.

Table 10: 5- and 10- year OS estimates of plausible curves – EMILIA extrapolations

Curve	T-DM1	
	5 years	10 years
Log-logistic	22.9%	7.4%
Generalised gamma	26.0%	10.2%
Log-normal	24.1%	7.0%

		Figure 7 presents the three plausible curves to extrapolate T-DM1 using the EMILIA data. Log-normal was selected to inform the base case curve for the alternative approach due to better goodness-of-fit scores (see Table 29 of the CS), better visual fit and plausible long-term extrapolations compared with the alternative curves (log-logistic and generalised gamma). For this approach, T-DXd is informed by applying a HR derived from DESTINY-Breast03 to the extrapolated T-DM1 comparator arm. The HR calculated from DESTINY-Breast03 data is 0.55 (95% CI: 0.36 – 0.86).

Figure 7: OS outcomes from EMILIA – plausible curves



Abbreviations: KM, Kaplan-Meier; OS, overall survival

Table 11 presents the alternative OS approach with the selected base case curve, log-normal. In addition, the other plausible curves are explored as scenarios (i.e., log-logistic and generalised gamma). The results show an ICER range with the plausible curves of [redacted] to [redacted] ([redacted] to [redacted] with unweighted QALYs). Using this alternative OS approach and scenarios around this, T-DXd remains within a cost-effectiveness range at the standard cost-effectiveness thresholds, and results are consistent with the base case ICER presented (with slightly lower ICERs than the direct extrapolation of OS from DESTINY-Breast03).

Table 11: Base-case results (with PAS) using the alternative OS approach

Drug	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs (unweighted QALYs)	ICER vs. baseline (unweighted QALYs)
Company base case approach: direct extrapolation of DB03 (generalised gamma)							
T-DM1	[redacted]	[redacted]	[redacted]				
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alternative OS approach base case: T-DM1 = log-normal							
T-DM1	[redacted]	[redacted]	[redacted]				
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario: T-DM1 = log-logistic							
T-DM1	[redacted]	[redacted]	[redacted]				
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

		Scenario: T-DM1 = generalised gamma

T-DM1	[redacted]	[redacted]	[redacted]				
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DB03, DESTINY-Breast03; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years.

Extensive sensitivity analysis

Sensitivity analysis on the company base case was conducted to test parameter uncertainty within the model (see Section B.3.11). In addition to what was originally presented, and to further assess the uncertainty associated with OS, the PSA has also been run varying just the OS curves (via the variance covariance matrix). Table 12 presents the mean base case PSA results and

Figure 8 presents the cost-effectiveness plane after 1,000 iterations. The mean results show consistency with the deterministic results with an ICER of [redacted] ([redacted] with unweighted QALYs). The confidence interval around the mean PSA results were calculated using the method described by Hatswell et al, 2018.[29] The 95% confidence interval around the ICER was [redacted] – [redacted] ([redacted] – [redacted] with unweighted QALYs).

The results considering parameter uncertainty associated with OS demonstrate that T-DXd is likely to remain cost-effective. Results were consistent with the company base case and demonstrated the robust conclusion that T-DXd is cost-effective versus T-DM1 at a £30,000 per QALY threshold.

Table 12: Mean PSA results (with PAS) – OS curves only

Drug	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs (unweighted QALYs)	ICER vs. baseline (unweighted QALYs)
T-DM1	[redacted]	[redacted]	[redacted]				
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient-access scheme; QALYs, quality-adjusted life years.

		Figure 8: Cost-effectiveness plane with the 1.2x QALY modifier – T-DXd vs. T-DM1 – OS curves only

		 Abbreviations: PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year.

		A similar analysis is also provided in Table 13 and Figure 9, which shows the PSA results and cost-effectiveness plane when testing uncertainty around the alternative methodological approach. Within this scenario, 1,000 probabilistic iterations are run varying the T-DM1 log-normal curve (using the variance covariance matrix derived from the replicated EMILIA data) as well as the HR from DESTINY-Breast 03 (deterministic HR = 0.5546). The mean results show consistency with the deterministic results with an ICER of [redacted] ([redacted] with unweighted QALYs). The confidence interval around the mean PSA results were calculated using the method described by Hatswell et al, 2018.[29] The 95% confidence interval around the ICER was [redacted] – [redacted] ([redacted] – [redacted] with unweighted QALYs). The results considering parameter uncertainty associated with OS demonstrate that T-DXd is likely to remain cost-effective. Results were consistent with the company base case and demonstrated the robust conclusion that T-DXd is cost-effective versus T-DM1 at the £30,000 per QALY threshold.

Table 13: Mean PSA results (with PAS) – OS curves for T-DM1 from EMILIA with HR only

Drug	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs (unweighted QALYs)	ICER vs. baseline (unweighted QALYs)
T-DM1	[redacted]	[redacted]	[redacted]				
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient-access scheme; QALYs, quality-adjusted life years.

		Figure 9: Cost-effectiveness plane with the 1.2x QALY modifier – T-DXd vs. T-DM1 – OS curves for T-DM1 from EMILIA with HR only  Abbreviations: PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year.

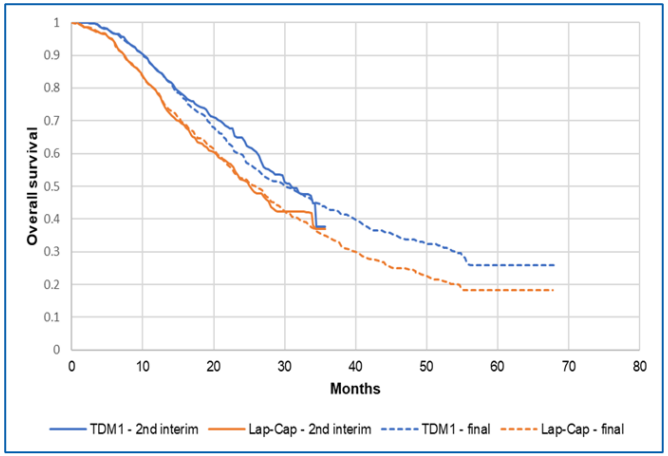
		Results across probabilistic analyses for both OS approaches are consistent. Using extrapolations from DESTINY-Breast03 consistently show T-DXd provides more QALYs than T-DM1 (with all iterations providing positive incremental QALYs), the average PSA results indicate that T-DXd is cost-effective. The alternative methodology incorporating further long-term data, by extrapolating replicated OS data from the EMILIA trial and applying the DESTINY-Breast03 observed HR between T-DXd and T-DM1 also demonstrates a clear benefit for T-DXd, with all iterations offering an incremental QALY gain for T-DXd. The average results indicate that T-DXd is a cost-effective treatment. *Conclusion* Whilst Daiichi Sankyo acknowledge that the OS data for DESTINY-Breast03 are immature, the company consider the uncertainty surrounding the OS estimates have been thoroughly explored through clinical validation, and testing of structural and parameter uncertainty within the economic model. Across methods explored, the ICER remains consistent ranging from [redacted] to [redacted] ([redacted] to [redacted] with unweighted QALYs). In each scenario explored, the cost-effectiveness of T-DXd was consistently demonstrated with an ICER below £30,000 per QALY. **Treatment waning** The EAG has implemented a treatment waning effect within the cost-effectiveness model (which subsequently informs the EAG base case), where it is assumed that there is no treatment effect beyond disease progression by applying the same post-progression mortality as T-DM1 to the T-DXd arm. Two scenarios have been provided by the EAG and have been described in the EAR as the following: • Scenario A: a conservative scenario with no treatment effect beyond disease progression from 2 years

		• Scenario B: treatment effect wanes over time, which is determined by the proportion of patients still alive who are in the PD state (which starts at 2 years) Daiichi Sankyo are not aware of any evidence of treatment waning with T-DXd, or other targeted treatments including antibody-drug conjugates (ADC) in HER2+ breast cancer, and consider that the EAG assumptions illustrate a highly conservative scenario that should be interpreted with caution for several reasons. Firstly, the time point of 2 years chosen for the EAG's scenario appears arbitrary and is justified in their report stating: *"A cut point of 2 years was chosen because only twenty-four patients were left at risk in the T-DXd Kaplan-Meier curve at 24 months."* (EAR, Appendix 2). By 24-months, there are 24 patients at risk in the T-DXd arm and 18 patients at risk in the T-DM1 arm. Though these numbers at risk are relatively low, there is no evidence from the observed data that after this timepoint the hazards start to merge (see Figure 1 in response to Key Issue 1). In the observed data available from DESTINY-Breast03 (>2.5 years), there is a clear separation in the T-DXd and T-DM1 OS curves, suggesting that there is no evidence observed related to a loss of treatment effect. Secondly, prior HER2+ breast cancer appraisals did not assume any OS treatment waning scenarios in their long-term model estimates, as such there is no precedent for the Committee adopting the EAG treatment waning assumptions. Of note, OS treatment waning was not considered in the appraisal of T-DM1 (TA458) for the treatment of HER2+ advanced breast cancer after trastuzumab and a taxane, (i.e. the comparator for this appraisal), or the appraisal of T-DXd (TA704) for treatment of HER2+ advanced breast cancer after two or more anti-HER2 therapies.[22,30-34] Finally, in all four of the previously considered metastatic HER2+ breast cancer trials, there has been no evidence of treatment waning for any HER2+ targeted treatments (including anti-HER2 ADC with a similar mechanism of action, T-DM1) when comparing interim outcomes with final analysis sets with longer-term follow-up. The mechanistic similarities between these therapies and T-DXd mean it is unlikely that treatment waning would be observed over

		long-term follow-up of T-DXd. The EMILIA, TH3RESA and CLEOPATRA studies, which had interim data followed by a final analysis set are discussed in turn below: *EMILIA trial:* • The EMILIA trial was a phase III trial which compared T-DM1 with lapatinib plus capecitabine in patients with HER2+ advanced breast cancer who had previously been treated with trastuzumab and a taxane (n=991). • At the second DCO median duration of follow-up was ~19 months and the final DCO had a median follow up of > 40 months (47.8 months for T-DM1 and 41.9 months for lapatinib + capecitabine). • Figure 10 provides a comparison of outcomes between the interim analysis and the final analysis of the EMILIA study (with KMs replicated using digitization software). • The comparison shows consistent separation of the OS Kaplan-Meier data up to at least 50 months versus the 2nd interim analyses.[35] Final OS results are also consistent with the 2nd interim analysis of OS with very similar median OS and the HR of the 2nd interim analysis sitting within the confidence interval of the final OS analysis (HR = 0.68 at the 2nd interim analysis and HR = 0.75 at the final analysis). T-DM1 maintained a significant OS benefit across the duration of the study.

Figure 10: Comparison of interim analysis with final analysis: EMILIA trial

EMILIA OS data (2nd interim analyses versus final analysis)



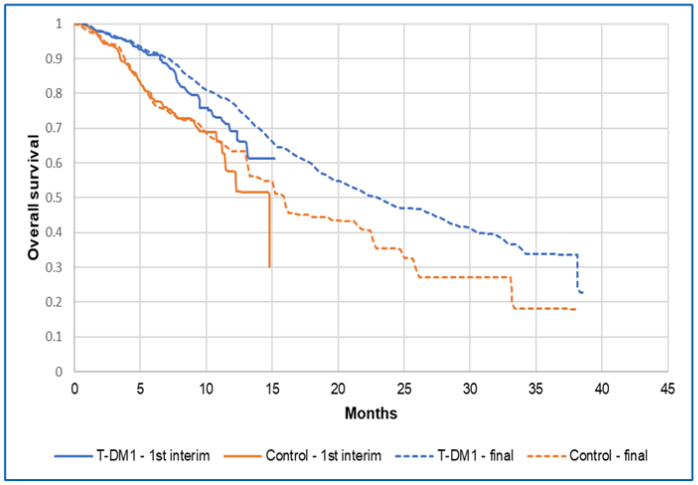
	2nd interim analysis		Final analysis	
Treatment	Lap+cap	T-DM1	Lap+cap	T-DM1
Median follow-up	18.6 months	19.1 months	41.9 months	47.8 months
OS median	25.1 months	30.9 months	25.9 months	29.9 months
OS HR (95% CI)	**0.68 (0.55 – 0.85)**		**0.75 (0.64-0.88)**	

Abbreviations: HR, hazard ratio; Lap+cap, lapatinib + capecitabine; OS, overall survival; T-DM1, trastuzumab emtansine
Source: digitised data from Verma et al, 2012; Dieras et al, 2017.[35]

		TH3RESA trial: • The TH3RESA trial was a phase III trial which compared T-DM1 with physicians choice (PC) in patients with HER2+ advanced breast cancer (n=602). • At the time of the first DCO, the median follow-up was 6.5 months for the PC arm and 7.2 arm for T-DM1 with a median OS of 14.9 months for PC. Median OS on the T-DM1 arm had not yet been observed. By the final analysis there was a median of 30.5 months follow-up and the OS median for PC had remained similar at 15.8 months and the T-DM1 observed median was 22.7 months. • Figure 11 provides a comparison of outcomes between the interim analysis and the final analysis of the TH3RESA study (with KMs replicated using digitization software). • The final OS analysis of the TH3RESA trial showed a continued separation of the OS Kaplan-Meier curves up to at least 35 months, with a significant OS hazard ratio maintained (HR=0.68 at the final analysis), thus suggesting no treatment waning effect associated with treatment for T-DM1.[36,37] The OS HR from the first DCO was also within the 95% CI of the final analysis OS HR.

Figure 11: Comparison of interim analysis with final analysis: TH3RESA trial

TH3RESA OS data (1st interim analyses versus final analysis)



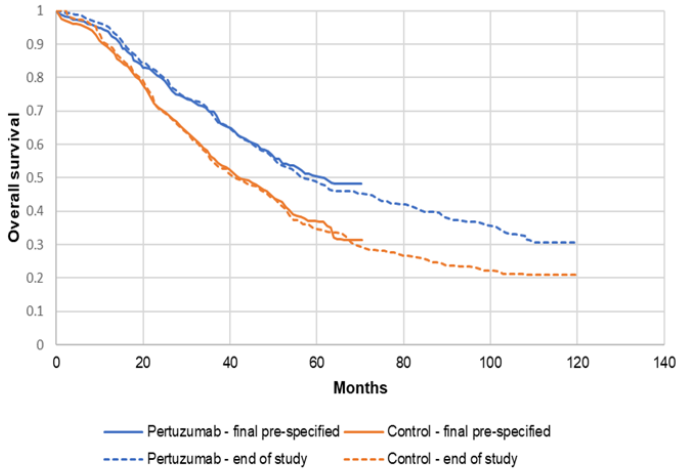
	1st interim analysis		Final analysis	
Treatment	PC	T-DM1	PC	T-DM1
Median follow-up	6.5 months	7.2 months	30.5 months	30.5 months
OS median (95% CI)	14.9 months (11.27 – NE)	NE months	15.8 months (13.5-18.7)	22.7 months (19.4-27.5)
OS HR (95% CI)	**0.55 (0.37-0.83)**		**0.68 (0.54 – 0.85)**	

Abbreviations: HR, hazard ratio; OS, overall survival; PC, physician's choice; T-DM1, trastuzumab emtansine
Source: digitised data from Krop et al, 2014; Krop et al, 2017.[36,37]

		CLEOPATRA trial: • The CLEOPATRA trial was a Phase III study which compared pertuzumab administered with trastuzumab and docetaxel with placebo, trastuzumab and docetaxel for patients with HER2+ metastatic breast cancer. • The final prespecified analysis had a median follow-up of 50 months across the two arms of the study (50.6 months for the control arm and 49.5 months for the pertuzumab arm), while the end of study outcomes reported a median follow-up of 99 months (98.7 months for the control arm and 99.9 months for the pertuzumab arm). [38,39] • Figure 12 provides a comparison of outcomes between the pre-specified final analysis and the end of study analysis of the CLEOPATRA study (with KMs replicated using digitization software). • With data available for 120 months, (a median of 99 months), the end of study analyses show a very similar treatment benefit to that of the earlier data cut with a minimal difference in the median OS and corresponding HR (difference of 0.01) with a more concise CI. The results showed that the HER2 targeted treatment maintained a treatment benefit for the duration of the trial with a clear and distinct separation in the KM.

Figure 12: Comparison of pre-specific analysis with end of study analysis: CLEOPATRA trial

CLEOPATRA OS data (final pre-specific analysis versus end of study analysis)



	Final pre-specified analysis		End of study	
Treatment	Control	Pertuzumab	Control	Pertuzumab
Median follow-up	50.6 months	49.5 months	98.7 months	99.9 months
OS median (95% CI)	40.8 months (35.8 – 48.3)	56.5 (49.3 – NE)	40.8 months (36 - 48)	57.1 months (50-72)
OS HR (95% CI)	**0.68 (0.56 – 0.84)**		**0.69 (0.58 – 0.82))**	

Abbreviations: OS, overall survival
Source: digitised data from Swain et al, 2015; Swain et al, 2020.[38,39]

		Conclusion Clinical advice to Daiichi Sankyo was that the level of treatment benefit T-DXd offered for PFS was unprecedented in the metastatic breast cancer setting, and that it would be unusual if the magnitude of this benefit did not translate to a sustained OS benefit. Daiichi Sankyo are not aware of any evidence of treatment waning for any targeted treatments, including ADC compounds, in HER2+ breast cancer based on long-term published data and as such see no evidence to indicate that survival curves begin to 'merge' from 2 years as suggested by the EAG's base case. For example, data at median follow up of 8 years plus from the CLEOPATRA trial shows no evidence of treatment waning. The constant treatment effect modelled in the company's base case is consistent with what is seen in published long-term data for other targeted ADC agents and accepted in prior TA appraisals in HER2+ mBC. Therefore, Daiichi Sankyo do not agree that an assumption of treatment waning is appropriate for decision-making based on the available evidence and consider that OS uncertainty has been explored through an extensive range of sensitivity/scenario analyses.
Key issue 7: Crosswalking EQ-5D-5L to EQ-5D-3L with the recommended algorithm	Yes	The EAG noted that the utilities derived from DESTINY-Breast03 were mapped from EQ-5D-5L to EQ-5D-3L using the Van Hout et al, 2012[40] algorithm instead of the NICE recommended Hernandez et al, 2017 algorithm.[41] During the development of the analyses and submission dossier, NICE published the new methods and process guidance outlining the new preferred approach to use the Hernandez algorithm instead of the previously preferred Van Hout approach. As such, Daiichi Sankyo were unable to incorporate this change into the model before the submission deadline. In response to the EAG's report, Daiichi Sankyo have now conducted the analyses in which the utility responses were 'crosswalked' using the algorithm developed by Hernandez et al, 2017.[41] As per the original submission, EQ-5D-3L utility scores based on *'progression-free'* and *'progressed disease'* health states were derived using generalized estimating equations (GEE) regressions. The mean utility values and associated 95% confidence intervals for the progression-free and progressed health states for each treatment group are derived from the model using least squares means.

An overview of the statistical goodness of fit (by quasi-likelihood under the independence model criterion [QIC]) and results of the GEE regression estimates are provided in Table 14.

Table 14: GEE regression coefficients (Hernandez)

Coefficient	Value	95% CI	p-value	QIC
Intercept	[redacted]	[redacted]	[redacted]	[redacted]
Treatment (T-DXd)	[redacted]	[redacted]	[redacted]	
Progressed	[redacted]	[redacted]	[redacted]	

Abbreviations: CI, confidence interval; QIC, quasi-likelihood.

Table 15 presents the resulting crosswalked EQ-5D-3L utility values using the Hernandez algorithm from the DESTINY-Breast03 study by progression status and treatment arm.

Table 16 presents the crosswalked EQ-5D-3L utility values using the Van Hout algorithm for comparison (presented in the company submission Section B.3.4.2).

Table 15: Mapped EQ-5D-3L utility values from DESTINY-Breast03 (Hernandez)

Health state	T-DXd (SE) (95% CI)	T-DM1 (SE) (95% CI)	Overall (SE) (95% CI)
Progression-free	[redacted]	[redacted]	[redacted]
Progressed	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; SE, standard error.

Table 16: Mapped EQ-5D-3L utility values from DESTINY-Breast03 (Van Hout)

Health state	T-DXd (SE) (95% CI)	T-DM1 (SE) (95% CI)	Overall (SE) (95% CI)
Progression-free	[redacted]	[redacted]	[redacted]
Progressed	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; SE, standard error.

The EQ-5D-3L Hernandez utility values were subsequently included within the economic model as an option.

Table 17 presents a scenario analysis of the company base case using the Hernandez algorithm for utility values. This scenario has minimal impact on the cost-effectiveness results, resulting in an ICER of [redacted] compared to [redacted] when using the Van Hout crosswalk (this equates to [redacted] compared to [redacted] with unweighted QALYs). Using the Hernandez algorithm also has minimal impact on the (unweighted) incremental QALY gain versus using Van Hout ([redacted] vs [redacted], respectively)

Table 17: Cost-effectiveness results (with PAS): crosswalked Hernandez utility values

Drug	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs (unweighted QALYs)	ICER vs. baseline (unweighted QALYs)
Company base case approach: Crosswalk with Van Hout							
T-DM1	[redacted]	[redacted]	[redacted]				
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario: Crosswalk with Hernandez							
T-DM1	[redacted]	[redacted]	[redacted]				
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years.

Key issue 8: Post-progression utility values	Yes	The EAG highlighted issues relating to the progressed disease utility values incorporated with the company's base case model suggesting there is no evidence for a difference in progressed disease utility values across treatment groups.

		In their report, the EAG state *"There does not appear to be evidence in Lloyd et al. (which was used as the source for PD utility estimates in the company's base case model) or in the CS for a difference in PD utility values across treatment groups."* For the technical engagement response, Daiichi Sankyo first discuss the utility values calculated from Lloyd et al, and the concerns from the EAG, then go onto discuss wider evidence of differences in progressed utility values. *Lloyd et al. mixed model analysis* The EAG outlined at the technical engagement call that they were unclear as to whether the response value should be incorporated in the mixed model analysis to obtain progressed disease utilities. Daiichi Sankyo believe that omitting the response coefficient would be mathematically inaccurate. The utility values estimated from the Lloyd et al 2006 study were based on the mixed model analysis which included age, response, progression and specific AEs (febrile neutropenia, diarrhoea and vomiting, hand-foot syndrome, stomatitis, fatigue and hair loss). To arbitrarily remove the treatment response from the mixed model would be inappropriate as the coefficients are linked. As such removing the response coefficient would require re-analysis of the data and therefore result in different coefficient values for the other parameters included within the mixed model. With different coefficients, different utility values would be obtained (the magnitude of the differences are unknown). Further to this, the P-value presented within the Lloyd et al mixed model for the response co-efficient was significant ($p < 0.0001$). Therefore, response (similar to progression status) was a significant determinant of HRQoL within the data and the mixed model and should therefore not be omitted in deriving a PD utility for either arm. Despite the aforementioned issues with omitting the response variable from the utility estimates, if the EAGs approach was to be considered (with the response coefficient removed from the estimates), the corresponding progressed disease utility value would be 0.5402 for both treatment arms. This value would equate to an absolute difference in utility of [redacted] for T-DXd and [redacted] for T-DM1 between HRQL at PFS versus PD (with a corresponding

		relative reduction of [redacted] for T-DXd and [redacted] for T-DM1). The company consider this absolute reduction and the absolute value (0.5402) to be too low to be clinically plausible for both T-DXd and T-DM1, as it would assume that no patients responded to treatment and as such further reason to consider the omission of the coefficient inappropriate. The company model approach estimates utilities using all components of the mixed model to derive two utility values; one for responders and one for non-responders using the formula below: $$Progressed\ disease\ for\ responders = \frac{e^{(sum\ of\ coefficiants)}}{1 + e^{(sum\ of\ coefficients)}}$$ Results were weighted by the proportion of responders in each arm taken from DESTINY-Breast03 (in line with the preferred approach by the ERG in TA458). Please note that given the model is used to estimate PD, it is assumed that no AEs occur and therefore these are set to 0). It is possible to derive the utility values from Lloyd et al using a slightly different approach which applies the mixed model coefficients and directly weighted results according to response (as originally incorporated by the company in TA458). The utility values obtained when considering this approach are provided in Table 18 below. The values obtained are considered too low (particularly for the PD state), and lack validity and as such, alongside the ERGs rationale in TA458 were not considered further when preparing the original submission. For transparency the results using this method are provided in Table 19 which indicates a slight decrease in the ICER from [redacted] to [redacted] (with results of [redacted] to [redacted] with unweighted QALYs) which indicates that T-DXd is cost-effective at a £30,000 WTP threshold.

Table 18: Comparison of methods to estimate PD utilities using Lloyd et al. 2006.

Health state	Weighting utility by response in line with ERG preferred approach in TA458 (Company base case for this appraisal)		Using the response rate directly with the coefficient in line with the company's preferred approach in TA458	
	T-DXd	T-DM1	T-DXd	T-DM1
PFS	0.8353	0.8079	0.7804	0.6488
PD	0.6183	0.5738	0.5877	0.4885

Abbreviations: ERG, evidence review group; PD, progressed disease; PFS, progression-free survival

Table 19: Using the response rates directly in the mixed model to derive Lloyd et al 2006 PD utilities

Drug	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs (unweighted QALYs)	ICER vs. baseline (unweighted QALYs)
Company base case approach: weighting utility by response							
T-DM1	[redacted]	[redacted]	[redacted]				
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario: Alternative approach using response rate directly							
T-DM1	[redacted]	[redacted]	[redacted]				
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

								[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years.

As such, the company consider that the approach taken to inform PD utilities from the Lloyd et al 2006 study is appropriate and correct. Using these values suggests that different utilities are appropriate in the progressed disease state due to different response rates.

Alternative utility sources

The EAG state that there is uncertainty in the applicability of the Lloyd et al. 2006, and that other values from the literature could have been used. The EAG did not provide suggestions of relevant utility values which could have informed the company model.

As outlined in the company submission (appendix H), a systematic literature review (SLR) was conducted to identify HRQoL studies which could be of relevance to the appraisal. Eight of the 11 cost-utility studies identified in the SLR referred to the Lloyd et al 2006 study, indicating not only that the Lloyd et al study is frequently used to inform utility estimates in this setting, but highlighting the limited availability of alternative sources within the literature for HER2+ breast cancer.

Alternative approach to progressed utilities

There has been some precedent of different utility values being used in prior breast cancer appraisals. In TA786 (tucatinib for third-line HER2+ mBC), the company used different post-progression utility values for the different treatments and clinical experts stated that patients brain metastases may impact QoL, and that *"people with disease that is better controlled would have better quality of life before and after progression than those with disease that is less well controlled. This is because the decline in quality of life related to progression will start from a higher level*

		than in people with disease that is less well controlled and with lower quality of life before progression." Based on this, the committee considered differences in HRQoL between treatment arms could be plausible but that the difference may decrease over time as patients progress further.[33] In TA819 (sacituzumab govetican for third-line triple negative advanced breast cancer), the company used different utility values for pre-and post progression between treatment arms based on the values calculated from the ASCENT trial.[42] Clinical experts stated that this was plausible due to the greater objective response rate for sacituzumab govitecan compared with physician's choice. In addition, *"they considered it plausible that this would carry over upon disease progression, because people on sacituzumab govitecan enter the progressed health state with a reduced tumour burden compared with those who had treatment of physician's choice".* The committee agreed that it is plausible that quality of life is better for the Sacituzumab arm but that the effect could deteriorate as people progress. The company therefore presented scenarios where the utility benefit after progression lasted for 6 months, after which the utility values merged. The committee concluded that this carry over effect was the least flawed approach presented. Daiichi Sankyo maintain the belief that progressed disease utilities will likely be higher for the T-DXd arm, and although the progressed disease HRQoL data calculated from the DESTINY-Breast 03 trial was considered too high, the analysis did indicate that the T-DXd arm had a higher HRQoL than T-DM1 ([redacted] versus [redacted] for T-DXd and T-DM1 respectively). Based on the above, Daiichi Sankyo have explored more conservative scenarios with regard to the utility differences for the progressed disease states, whereby instead of assuming a utility benefit for T-DXd across the entire progressed disease state, the difference lasts for an initial period after progression then the same utility value is assumed for both T-DXd and T-DM1.

		To apply this scenario, the model applies a utility increment to the T-DXd arm for patients leaving the PFS health state. The utility increment uses the following inputs and assumptions:
		• Utility benefit over T-DM1
		  ○ This is calculated as the difference between the post-progression utility values using the Lloyd et al approach (0.6183 [T-DXd] – 0.5738 [T-DM1] = 0.0446
		• Time point benefit assumed for
		  ○ Two time points are explored, the first is 6 months in line with the time assumed in TA819, the other is 4 months, in line with the last collected EQ-5D questionnaire from the DESTINY-Breast03 trial.
		• Proportion of patients who progress versus die from the PFS state
		  ○ This is calculated using the DESTINY-Breast03 trial where [redacted] out of the 87 ([redacted]) PFS events were progression events over death events in the T-DXd arm.
		• The utility increment is the calculated as:
		  ○ (Utility benefit x time [months] x % progressed)/12
		  ○ This resulted in a utility increment of [redacted] for 6 months or [redacted] for 4 months
		• When this scenario is applied, the progressed utility value for both arms is set to Lloyd et al (combined) with the utility increment applied to all patients leaving the PFS state for T-DXd.

Results of these scenarios are presented in Table 20. Assuming a utility benefit for a shorter timeframe increases the ICER slightly from the base case - [redacted] to [redacted] and [redacted] for 6- and 4-months benefit, respectively [redacted] and [redacted] with unweighted QALYs). For the scenarios presented, T-DXd is still shown to be cost-effective at the £30,000 per QALY threshold assuming a less optimistic post-progression utility value.

Table 20: Cost-effectiveness results (with PAS): alternative progressed disease utility approach

Drug	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs (unweighted QALYs)	ICER vs. Baseline (unweighted QALYs)
Company base case approach: Lloyd et al (treatment specific throughout progression)							
T-DM1	[redacted]	[redacted]	[redacted]				
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: Alternative approach assuming utility benefit for T-DXd for 6 months							
T-DM1	[redacted]	[redacted]	[redacted]				
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: Alternative approach assuming utility benefit for T-DXd for 4 months							
T-DM1	[redacted]	[redacted]	[redacted]				
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years.

		Conclusion Daiichi Sankyo agree with the EAG that post-progression utilities are uncertain and that the difference in patients QoL is unknown over time. However, due to the substantial benefit in response rates (79.7% for T-DXd versus 34.2% for T-DM1), it is plausible that patients treated with T-DXd have a lower tumour burden upon progression and as such have a better quality of life compared to those patients treated with T-DM1. This is demonstrated using the regression model from Lloyd et al and further supported by the utility values estimated using the EQ-5D data collected in the DESTINY-Breast03 trial. Scenarios assuming different duration for the utility benefit had little impact on the cost-effectiveness conclusions.

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Proportion of patients vial sharing.	4.2.10	No	As part of their report, the EAG present a model scenario which assumes that only 10% of patients can vial share. This amendment is also a component of the EAG base case. Whilst the company are aware that it is unlikely that all centres in all settings have the ability to share vials and therefore estimates are subject to uncertainty, the company agree with the premise outlined by the EAG that vial sharing is dependent on circumstances in each particular clinic (EAR section 4.2.10 page 98). Previous appraisals in the breast cancer setting have also considered vial sharing and in recent examples,

			50% has been considered an appropriate assumption used in Committee decision-making. In TA704 (trastuzumab deruxtecan for the treatment of HER2+ unresectable or metastatic breast cancer after 2 or more anti-HER2 therapies), an estimate of 50% was used to inform decision making.[22] The more recently published final appraisal determination for sacituzumab govitecan for treating unresectable triple negative breast cancer after two or more therapies (ID3942) indicated that the company also assumed 50% vial sharing. Further to this, the Cancer Drugs Fund clinical expert for this appraisal agreed with the company and considered that 50% vial sharing was a reasonable assumption.[43] As such, Daiichi Sankyo consider the estimate of 50% to be more appropriate than the EAG's 10% and consistent with previously accepted assumptions in recent appraisals.

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
EAG correction	The EAG highlight a coding error in Cells L27:L2427 in the efficacy summary sheet and T27:T2427 which indicate that TTD should be capped by PFS.	Daiichi Sankyo, accept the amendment made by the EAG and have now incorporated this change as part of a revised company base case. The revised base case is also reflected in the scenarios and results presented in the responses above.	[redacted] ([redacted] from original base case) [redacted] [[redacted] from original base case] with unweighted QALYs)
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [redacted] ([redacted] with unweighted QALYs)	Incremental costs: [redacted]	[redacted] with unweighted QALYs)

Sensitivity analyses around revised base case

Base case results

Table 21: Revised base-case results (with PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs (unweighted QALYs)	ICER vs. baseline (unweighted QALYs)
T-DM1	[redacted]	[redacted]	[redacted]				
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years.

Probabilistic sensitivity analyses

The mean results from the probabilistic analysis are presented in Table 22 and the cost-effectiveness plane (CE-plane) in Figure 13.

Table 22: Mean PSA results (with PAS)

Technologies	Total			Incremental			ICER (£/QALY) (unweighted QALYs)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs (unweighted QALYs)	
T-DM1	[redacted]	[redacted]	[redacted]				
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient-access scheme; QALYs, quality-adjusted life years.

Figure 13: Cost-effectiveness plane – T-DXd vs. T-DM1 including x1.2 QALY modifier

Abbreviations: PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year.

Figure 14 presents the cost-effectiveness acceptability curve for T-DXd vs. T-DM1. At a WTP threshold of £30,000/QALY the probability that T-DXd is the cost-effective treatment option is [redacted] respectively.

Figure 14: Cost-effective acceptability curve (with PAS)

Abbreviations: PAS, patient access scheme; T-DXd, trastuzumab deruxtecan; T-DM1, trastuzumab emtansine

One-way sensitivity analysis

Table 23 and Figure 15 present the ICERs and the tornado plot showing the 10 parameters which had the largest impact on the ICER.

Table 23: OWSA results (with PAS) including x1.2 QALY modifier

Parameter	ICER at lower bound	ICER at upper bound
Lloyd 2006: PD - original responders	[redacted]	[redacted]
Lloyd 2006: PD - original non-responders	[redacted]	[redacted]
T-DM1 - Proportion receiving subsequent treatment	[redacted]	[redacted]
T-DXd - Proportion receiving subsequent treatment	[redacted]	[redacted]
RDI - T-DXd	[redacted]	[redacted]
RU - unit cost - Medical oncologist	[redacted]	[redacted]
DB03 PFS T-DXd utility	[redacted]	[redacted]
Sub trt - duration (weeks) - T-DM1	[redacted]	[redacted]
Administration cost - simple infusion	[redacted]	[redacted]
RU - PF - Medical oncologist	[redacted]	[redacted]

Abbreviations: DB03, DESTINY-Breas03; ICER, incremental cost-effectiveness ratio; OWSA, one-way sensitivity analysis; PD, progressed disease; PF, progression-free; PFS, progression-free survival; RDI, relative dose intensity; RU, resource use; Sub trt, subsequent treatment.

Figure 15: Tornado plot showing OWSA results on the ICER (with PAS) including x1.2 QALY modifier

Abbreviations: DB03, DESTINY-Breast03; ICER, incremental cost-effectiveness ratio; OWSA, one-way sensitivity analysis; PD, progressed disease; PF, progression-free; PFS, progression-free survival; RDI, relative dose intensity; RU, resource use; Sub trt, subsequent treatment.

Scenario analysis

Table 24: Scenario analysis (with PAS)

Parameter	Base case	Scenario	Incremental costs	Incremental QALYs (unweighted QALYs)	ICER (unweighted QALYs)	Difference from base case	x1.2 QALY weighting threshold met
Base case			[redacted]	[redacted]	[redacted]	-	**Yes**
Time horizon	30 years	20 years	[redacted]	[redacted]	[redacted]	£304	Yes
		40 years	[redacted]	[redacted]	[redacted]	-£42	Yes
Discount rates	Costs and health effects = 3.5%	1.5%	[redacted]	[redacted]	[redacted]	-£601	No
Utility source*	PFS = DB03 (treatment specific) PD = Lloyd et al (treatment specific)	PFS = Lloyd et al – treatment specific utilities PD = Lloyd et al – treatment specific utilities	[redacted]	[redacted]	[redacted]	-£356	Yes
		PFS = Lloyd et al – combined utilities PD = Lloyd et al – combined utilities	[redacted]	[redacted]	[redacted]	£2,089	Yes
		PFS = DB03 utilities combined	[redacted]	[redacted]	[redacted]	£2,271	Yes

Parameter	Base case	Scenario	Incremental costs	Incremental QALYs (unweighted QALYs)	ICER (unweighted QALYs)	Difference from base case	x1.2 QALY weighting threshold met
Base case			[redacted]	[redacted]	[redacted]	-	**Yes**
		PD = Lloyd et al combined					
Disutilities	Excluded	Included	[redacted]	[redacted]	[redacted]	£15	Yes
Age-related disutilities	Included	Excluded	[redacted]	[redacted]	[redacted]	-£625	Yes
RDI	Included	Excluded	[redacted]	[redacted]	[redacted]	£2,052	Yes
Proportion vial sharing	50%	0%	[redacted]	[redacted]	[redacted]	£1,322	Yes
		100%	[redacted]	[redacted]	[redacted]	-£1,322	Yes
Subsequent treatment distributions	DB03 data	UK practice	[redacted]	[redacted]	[redacted]	£631	Yes
		DB03 pooled	[redacted]	[redacted]	[redacted]	£612	Yes
	UK practice	DB03 data	[redacted]	[redacted]	[redacted]	-£1,863	Yes

Parameter	Base case	Scenario	Incremental costs	Incremental QALYs (unweighted QALYs)	ICER (unweighted QALYs)	Difference from base case	x1.2 QALY weighting threshold met
Base case			[redacted]	[redacted]	[redacted]	-	**Yes**
Subsequent treatment proportions		DB03 pooled	[redacted]	[redacted]	[redacted]	-£445	Yes
Subsequent treatments T-DXd and T-DM1	Include costs	Exclude costs	[redacted]	[redacted]	[redacted]	-£369	Yes
OS plausible extrapolations	Generalised gamma	Log-logistic	[redacted]	[redacted]	[redacted]	-£43	No
		Weibull	[redacted]	[redacted]	[redacted]	£1,594	Yes
PFS plausible extrapolations	Weibull	Log-logistic	[redacted]	[redacted]	[redacted]	-£1,101	Yes
		Log-normal	[redacted]	[redacted]	[redacted]	-£2,081	Yes
		Exponential	[redacted]	[redacted]	[redacted]	-£1,988	Yes
TTD extrapolations	Weibull	Gompertz	[redacted]	[redacted]	[redacted]	-£3,622	Yes

Parameter	Base case	Scenario	Incremental costs	Incremental QALYs (unweighted QALYs)	ICER (unweighted QALYs)	Difference from base case	x1.2 QALY weighting threshold met
Base case			[redacted]	[redacted]	[redacted]	-	**Yes**
OS (EMILIA + HR)	OS = DESTINY-Breast03	Generalised gamma	[redacted]	[redacted]	[redacted]	-£2,410	Yes
		Log-logistic	[redacted]	[redacted]	[redacted]	-£1,770	Yes
		Log-normal	[redacted]	[redacted]	[redacted]	-£1,284	Yes
		Weibull	[redacted]	[redacted]	[redacted]	£2,708	Yes

Abbreviations: DB03, DESTINY-Breast03; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; PD, progressed disease; PFS, progression-free survival; QALYs, quality adjusted life-years; RDI, relative dose intensity; TTD, time to treatment discontinuation.
Note: * Source applicable for both PFS and PD utility values

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after trastuzumab and a taxane [ID3909]

Patient expert statement and technical engagement response form

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The external assessment report (EAR) and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with HER2-positive unresectable or metastatic breast cancer after trastuzumab and a taxane or caring for a patient with HER2-positive unresectable or metastatic breast cancer after trastuzumab and a taxane. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR in section 1.1.

A patient perspective could help either:

Patient expert statement

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

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. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. 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.

Your response should not be longer than 15 pages.

Patient expert statement

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **Wednesday 24th August 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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.

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Part 1: Living with this condition or caring for a patient with HER2-positive unresectable or metastatic breast cancer after trastuzumab and a taxane

Table 1 About you, HER2-positive unresectable or metastatic breast cancer after trastuzumab and a taxane, current treatments and equality

1. Your name	[redacted]
2. Are you (please tick all that apply)	☐ A patient with HER2-positive unresectable or metastatic breast cancer after trastuzumab and a taxane ? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with HER2-positive unresectable or metastatic breast cancer after trastuzumab and a taxane ? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Breast Cancer Now
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing

5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☒ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with HER2-positive unresectable or metastatic breast cancer after trastuzumab and a taxane? **If you are a carer (for someone with HER2-positive unresectable or metastatic breast cancer after trastuzumab and a taxane) please share your experience of caring for them**	
7a. What do you think of the current treatments and care available for HER2-positive unresectable or metastatic breast cancer after trastuzumab and a taxane on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	
8. If there are disadvantages for patients of current NHS treatments for HER2-positive unresectable or metastatic breast cancer after trastuzumab and a taxane (for example, how the treatment is given or	

taken, side effects of treatment, and any others) please describe these	
9a. If there are advantages of trastuzumab deruxtecan over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does trastuzumab deruxtecan help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	
10. If there are disadvantages of trastuzumab deruxtecan over current treatments on the NHS please describe these. For example, are there any risks with trastuzumab deruxtecan? If you are concerned about any potential side effects you have heard about, please describe them and explain why	
11. Are there any groups of patients who might benefit more from trastuzumab deruxtecan or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	

12. Are there any potential equality issues that should be taken into account when considering HER2-positive unresectable or metastatic breast cancer after trastuzumab and a taxane and trastuzumab deruxtecan? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the EAR are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the EAR, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from technical engagement

Key issue 1: Effectiveness data from the included randomised control trial is from an interim data cut point]	
Key issue 2: Background characteristics of people in the trial may not reflect characteristics of those that would be	The EAG's report notes that patients in DESTINY-Breast03 are more likely to receive a higher number of prior treatment lines and this may not reflect clinical practice in the UK. However, we note that 11 participants in the trial are from the UK and there is also a European sub-population, though we recognise that it is a small population. In the European sub-population, 61.5% of patients had 1 line and 35% had 2 lines of prior systemic therapy (excluding hormone therapy) in the secondary breast cancer setting and the EAG concludes that the European sub-population is more likely to be generalisable to the UK clinical setting. It is common for clinical trials to involve participants

seen in English clinical practice	from around the globe, and as a result there are likely to be some differences in the background characteristics of participants.
Key issue 3: Uncertainty in the proportion of people whose disease has progressed who are having subsequent treatments and the distribution of subsequent treatments Is the proportion of people in DESTINY-Breast03 who had subsequent treatments reflective of the proportion of patients in the NHS who would have subsequent treatment? **We consider patient perspectives may particularly help to address this issue**	The current first line treatment for this group of patients is the combination of a taxane with trastuzumab and pertuzumab. Trastuzumab emtansine is the current standard of care for treating patients with HER2-positive unresectable or metastatic breast cancer after trastuzumab or a taxane. Following progression on trastuzumab emtansine, historically the main treatment following progression was chemotherapy such as capecitabine, vinorelbine and eribulin. However, in 2021, trastuzumab deruxtecan was approved for use on the CDF for treating HER2-positive unresectable or secondary breast cancer after 2 or more anti-HER2 therapies and in 2022 tucatinib (Tukysa) in combination with trastuzumab and capecitabine was approved for use on the NHS after 2 or more anti-HER2 therapies. Following progression on these treatments, chemotherapy would be the next line of treatment for this patient group. If trastuzumab deruxtecan in the indication being assessed in this NICE appraisal is approved for use, we would assume that that the tucatinib combination would a key treatment that people may receive following progression. Breast Cancer Now does not have access to data on the proportion of patients whose disease has progressed and who are having subsequent treatments, as well as the distribution of subsequent treatments. As mentioned on the technical engagement call, we would suggest discussing this with NHS England and Improvement, based on the data they collect.

Key issue 4: Higher adverse events in the T-DXd arm compared to T-DM1 arm Are the higher rates of adverse events for trastuzumab deruxtecan within the trial expected to affect the acceptability of trastuzumab deruxtecan relative to trastuzumab emtansine? We consider patient perspectives may particularly help to address this issue	As noted in our Patient Organisation Submission, as with all breast cancer treatments one of the main disadvantages patients can be concerned about when starting a new treatment is the side effects that can be associated with it. The most common side effects of any grade reported amongst the trastuzumab deruxtecan group were nausea (72.8%), fatigue (44.7%) and vomiting (44%). The occurrence of these side effects was lower in the trastuzumab emtansine group: nausea (27.6%), fatigue (29.5%) and vomiting (5.7%). Alopecia of any grade was higher in trastuzumab deruxtecan (36.2%) compared to trastuzumab emtansine (2.3%). Drug-related interstitial lung disease or pneumonitis occurred in 10.5% of the patients in the trastuzumab deruxtecan group and in 1.9% of those in the trastuzumab emtansine group; none of these events were of grade 4 or 5. All breast cancer treatments have some side effects, and patients will respond differently, with side effects affecting some patients more than others. Patients' willingness to try treatments will understandably vary but when making decisions about treatments, patients will be looking at both what the benefits and disadvantages of the drug are, and if the benefits are significant, they are often willing to tolerate the risk of side effects. As trastuzumab deruxtecan is already available via the CDF in another indication, many clinicians are familiar with the side effects and it is important that there is close monitoring to identify interstitial lung disease or pneumonia. A patient with HER2-positive secondary breast cancer with experience of trastuzumab deruxtecan in the indication it is currently approved for via the CDF shared her experience: *"I have been fortunate with my side effects that they have been manageable and in comparison to how I was feeling before enhertu. I will take these side effects as what I have gained in quality of life is exceptional and I really didn't think after so long I would feel "this well" again."* The interim results of the ongoing DESTINY-Breast03 trial, published in March 2022, showed that at 12 months, 75.8% of the patients receiving trastuzumab deruxtecan were alive without progression as compared with 34.1% of those receiving trastuzumab emtansine. This is a significant improvement and patients have told us that they value this extra time, as delaying disease progression means more quality time to spend with relatives and friends. Maintaining a good quality of life for as long as possible is the best outcome for this patient group. Delaying progression can have a positive impact on patients' emotional wellbeing and mental health, as it may mean that patients may be able to continue to work and do the activities they enjoy.

	Overall survival data is not yet mature, however, it is noted that there is a trend towards overall survival benefit with trastuzumab deruxtecan. An interim analysis showed that the percentage of patients who were alive at 12 months was 94.1% with trastuzumab deruxtecan and 85.9% with trastuzumab emtansine, although this did not cross the prespecified boundary for significance. For many patients, the important benefits associated with this treatment may outweigh the potential side effects they may experience and for many patients the risk of side effects will be acceptable in light of the effectiveness of the treatment and the hope of more time without their disease progressing.
Key issue 5: Uncertain PFS predictions for T-DXd	
Key issue 6: Uncertain PFS predictions for T-DXd	
Key issue 7: Crosswalking EQ-5D-5L to EQ-5D-3L with the recommended algorithm	
Key issue 8: Post-progression utility values Is the quality of life for people with progressed disease expected to be treatment-specific or the same utility regardless of treatment received?	Although it is difficult to estimate the exact difference in post-progression utilities, we would suggest that the utility values could be higher for people who progress on trastuzumab deruxtecan for a period of time compared to trastuzumab emtansine. This is due to the likelihood of the disease being under control for a longer period of time and the general longer response rates experienced with trastuzumab deruxtecan. With a higher treatment response rate, it could mean that patients are starting a new treatment with less tumour burden and symptoms and potentially improved quality of life.

Patient expert statement

We consider patient perspectives may particularly help to address this issue	
Are there any important issues that have been missed in EAR?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Please see Breast Cancer Now's original Patient Organisation Submission for key messages.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

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Single Technology Appraisal

Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after trastuzumab and a taxane [ID3909]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

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.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. 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.

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, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

Technical engagement response form

Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after trastuzumab and a taxane [ID3909]

The deadline for comments is the end of **Wednesday 24th August 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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.

Technical engagement response form

Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after trastuzumab and a taxane [ID3909]

About you

Table 1 About you

Your name	Keyur Patel
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Daiichi Sankyo UK 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

Key issues for engagement

Introductory note from the company:

Daiichi Sankyo would like to thank NICE and the EAG for the opportunity to respond to the key issues raised as part of the appraisal of trastuzumab deruxtecan (T-DXd) for treating HER2-positive (HER2+) unresectable or metastatic breast cancer (u/mBC) after trastuzumab and a taxane. The company consider the technical engagement step to be an important stage of the appraisal process, particularly in light of the new NICE process and methods manual. Although there are no new data to present at this point, we have approached this response as an opportunity to try and address the clinical and economic uncertainty highlighted in the External Assessment Report (EAR) key issues wherever possible. For each of the key issues we have provided a structured reply utilising information already presented, and where possible, provided new informative scenarios using existing evidence to support our position. We have also added commentary within the '

Additional issues*' section related to the assumptions surrounding vial sharing.*

As outlined within the 'Summary of changes to the company's cost-effectiveness estimate(s)', Daiichi Sankyo, accept the coding error and suggested fix provided by the EAG, and have revised our base case accordingly. As such, a full set of updated results have been provided consisting of deterministic results, one-way sensitivity analysis, probabilistic sensitivity analysis, and scenario analysis, and all ICERs presented throughout the document have this amendment incorporated unless otherwise stated. As outlined in the Company submission [CS], Daiichi Sankyo believe that the current QALY shortfall estimates based on the expected QALY gain with NHS standard of care, trastuzumab emtansine (T-DM1), and the general population meet the defined thresholds and therefore a 1.2x QALY modifier is applicable for this appraisal topic (further details of which can be found within the CS). This is further supported by the EAGs deterministic base case. Therefore, throughout the document, incremental QALYs and ICERs are provided with the 1.2x QALY modifier applied. For completeness, results with unweighted QALYs have also been presented within brackets throughout.

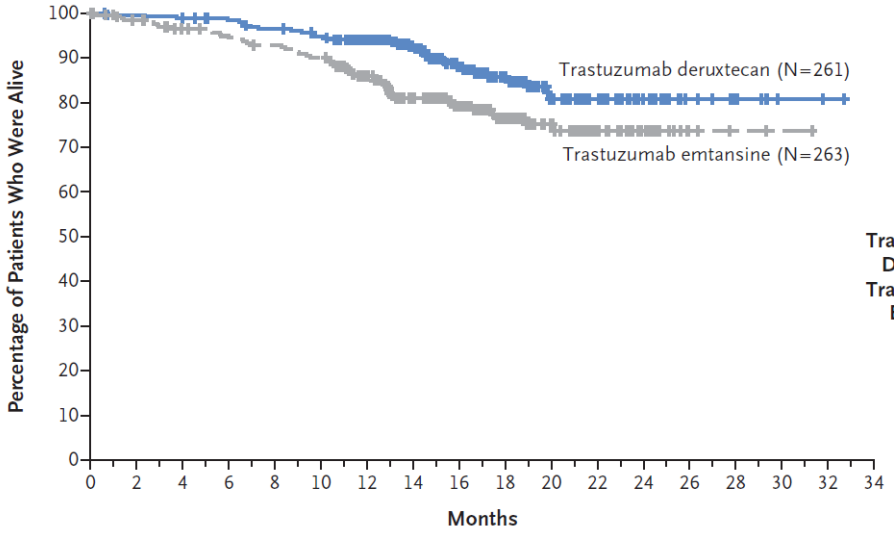
All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Effectiveness data from	No	The EAG is correct that the effectiveness data are from an interim data cut-off (DCO). At follow-up, events of disease progression or death were reported in 87 patients (33.3%) in the T-DXd arm and 158 patients (60.1%)

the included randomised control trial is from an interim data cut point		in the T-DM1 arm.[1] Future data cuts from DESTINY-Breast03 will provide survival data from the trial after a longer follow-up: a second interim analysis is expected in [redacted], after [redacted] progression-free survival (PFS) events, when the final PFS analysis and second interim OS analysis will be conducted.[1] A final overall survival (OS) analysis is also planned at [redacted] OS events.[1] Despite the data from DESTINY-Breast03 deriving from an interim data cut, clinical experts have described the efficacy of T-DXd in DESTINY-Breast03 as "unprecedented", and anticipate that it will lead to a "paradigm shift in the treatment of HER2-positive metastatic breast cancer".[2] As stated in the EAR, DESTINY-Breast03 collected sufficient data for the primary endpoint – PFS by blinded independent central review (BICR) – to conduct the interim analysis and establish superiority of T-DXd compared with T-DM1. T-DXd was associated with a statistically significant 72% lower risk of progression or death compared with T-DM1 (hazard ratio [HR]: 0.28; 95% confidence interval [CI]: 0.22, 0.37 [$p=7.8\times10^{-22}$]).[3,4] The findings for the primary endpoint were further reinforced by the secondary endpoint of investigator-assessed PFS (HR: 0.26; 95% CI: 0.20, 0.35 [$p=6.5\times10^{-24}$]).[4] PFS is a meaningful outcome in its own right, and prior studies have shown that patients value strongly improvements in PFS.[5] The superior PFS demonstrated with T-DXd vs. T-DM1 led to the independent data monitoring committee issuing a recommendation of early unblinding at the first interim analysis for PFS.[4,6] Based on the efficacy and safety evidence from DESTINY-Breast03, the European Commission of the European Medicines Agency (EMA) granted a license extension on 19th July, to T-DXd for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer after one or more prior anti-HER2 based regimens. Most recently, approval was granted in the same indication by the UK's Medicines and Healthcare products Regulatory Agency (MHRA) on 17th August, 2022. The US Food and Drug Administration (FDA) granted second-line approval on the basis of the DESTINY-Breast03 first interim analysis on 4th May 2022.[7] These approvals demonstrate the positive benefit/risk profile for T-DXd based on the interim data from DESTINY-Breast03, a position which was also recognised by the European Society for Medical Oncology

		(ESMO) in their 2021 guidelines, which described T-DXd as "…*the new standard second-line therapy*".[8] Moreover, the Innovative Licensing and Access Pathway (ILAP) Steering Group (MHRA, NICE, All Wales Therapeutics and Toxicology Centre (AWTTC), Scottish Medicines Consortium (SMC), and representatives from the ILAP Patient and Public Reference Group), informed Daiichi Sankyo that the innovative medicine designation, the Innovation Passport, has been awarded for T-DXd on the basis of the DESTINY-Breast03 trial. Although the OS data from DESTINY-Breast03 are considered immature due to the small number of deaths that had occurred by the DCO (XX patients [XXX%] in the T-DXd arm and XX patients [XXX%] in the T-DM1 arm), a trend in OS showing a benefit with T-DXd relative to T-DM1 is evidenced by the early separation of Kaplan-Meier curves between treatment arms that is sustained to the end of follow-up.[4] Although the reduction in mortality risk (Figure 1) did not cross the pre-specified significance boundary of p<0.000265, set so as to ensure stringent testing at this interim analysis, the company considers it to be indicative of a treatment effect that will be evidenced at a later data cut (HR: 0.55; 95% CI: 0.36, 0.86 [p=0.007]). Efficacy of T-DXd was confirmed through multiple clinically meaningful endpoints, including response rates.[4] **Figure 1: DESTINY-Breast03 | Kaplan-Meier of OS | FAS**



	Median Overall Survival (95% CI)	12-Mo Overall Survival (95% CI)
	mo	%
Trastuzumab Deruxtecan	NE (NE–NE)	94.1 (90.3–96.4)
Trastuzumab Emtansine	NE (NE–NE)	85.9 (80.9–89.7)

Hazard ratio for death, 0.55 (95% CI, 0.36–0.86)
P=0.007

No. at Risk

Trastuzumab deruxtecan	261	256	254	249	243	237	218	180	133	86	56	42	24	11	7	6	2	2	1	0
Trastuzumab emtansine	263	253	243	236	231	224	188	151	120	75	52	32	18	5	3	3	1	1	0	

Pre-specified boundary for statistical significance was p<0.000265.
Abbreviations: CI, confidence interval; FAS, full analysis set; HR, hazard ratio; mo, months; NE, not estimable; OS, overall survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Source: Cortés et al, 2021.[4]

In addition to the value of PFS as an endpoint in its own right, multiple studies have established improved PFS as a surrogate for OS in metastatic breast cancer (mBC).[9-11] Beauchemin et al, 2014, reported a correlation coefficient for treatment effect on PFS/time to progression and OS of 0.427 (p<0.01) for patients with mBC.[11]

		Likewise, Adunlin et al, 2015, reported a model coefficient of 0.40 (p<0.001) for the HR of PFS and the HR of OS for mBC at second line and beyond.[9] The correlation between HRs of PFS and OS was reported to be particularly strong in HER2+ mBC (correlation coefficient: 0.9515; 95% CI: 0.7009, 1.0000) in a meta-analysis by Liu et al, 2016.[10] The 17.9-month increase in median PFS (by investigator assessment[1]) observed in DESTINY-Breast03 for T-DXd vs. T-DM1,[4] is therefore expected to translate into a statistically significant and clinically relevant OS advantage, potentially providing OS outcomes similar to treatments used in the current first-line setting. **Daiichi Sankyo agree with the EAG that the OS data immaturity is currently unresolvable based on data available from DESTINY-Breast03 (outlined further in our response to Key Issue 6), but nonetheless would like to highlight that OS in the T-DM1 arm of DESTINY-Breast03 is consistent with previous trials of T-DM1 in this setting where longer term published data are available. The modelled DESTINY-Breast03 OS outcomes appear similar to the external data although slightly higher over time (**

[1] Median PFS by BICR is not available for T-DXd at the first interim analysis.

		Figure 2). This is expected due to the availability of more effective subsequent therapies within the third-line and beyond setting in current practice (and consequently in DESTINY-Breast03) compared with those available when historical trials were conducted. This would also be expected to translate to UK clinical practice given changes in the UK treatment pathway for mBC, for example the availability of HER2-targeted treatments including T-DXd and the tucatinib combination from third line. Therefore, T-DM1 OS in DESTINY-Breast03 could be expected to be improved compared with EMILIA and other prior studies in this setting. This was also confirmed by UK clinical experts consulted by Daiichi Sankyo, who advised that EMILIA is a generalisable trial where outcomes are similar to UK practice, with any notable differences in OS in the real world setting likely a result of changes in treatment practice, particularly the availability of more effective HER2-targeted subsequent therapies. The company therefore considers OS estimates derived from DESTINY-Breast03, which have been compared with EMILIA and other studies, and validated by clinical and health economics and outcomes research (HEOR) experts, to be appropriate. The EAG also agree that the T-DM1 OS extrapolations are plausible as they state in their report: *"The OS prediction for T-DM1 was plausible given the clinical expert opinion on survival and the EMILIA trial data."* (EAR, Section 1) and *"The EAG does consider the overall survival predictions for T-DM1 to be plausible given the fitted survival model and the company clinical expert opinion on survival rates at 10 years."* (EAR, Section 6).

		Figure 2: External validation | T-DM1 | OS  Abbreviations: ITT, intention to treat; KM, Kaplan-Meier; OS, overall survival

EAG RESPONSE	As acknowledged by the company, their response contains no new evidence or analyses. Therefore, our response is a brief summary of points made in Table 1.2 and sections 3.2 and 3.4 of the EAG report where these issues are discussed in more detail. Key Issue 1 of the EAG report states that PFS and OS outcomes are based on interim analyses, which leads to some uncertainty in estimates. The EAG agrees that there is good evidence for the effectiveness of T-DXd for PFS, and although based on interim analyses, these data are consistent with a priori determined stopping boundaries for statistical significance. Although the EAG also agrees OS data are promising, there is greater uncertainty for this outcome as OS estimates crossed the stopping boundary for statistical significance in interim analyses.

Key issue 2: Background characteristics of people in the trial may not reflect characteristics of those that would be seen in English clinical practice	Yes	The EAG has stated that the background characteristics of patients enrolled in DESTINY-Breast03 may not reflect characteristics of patients seen in English clinical practice; this was considered an unresolvable issue that is a limited cause of uncertainty. In particular, the EAG highlighted differences in the proportion of Asian patients in both populations, differences in the numbers of smokers, and differences in the number of prior lines of therapy patients had, or would be expected to have, received. Daiichi Sankyo agree with the EAG that this is an unresolvable issue that is a limited cause of uncertainty. As is common in global randomised controlled trials, variation in geographic locations of study sites can lead to demographic and baseline characteristic differences between intent-to-treat (ITT) populations and individual countries. Study sites for DESTINY-Breast03 are such that there is a higher proportion of Asian patients than may be expected in UK clinical practice, and potentially some minor differences in smoking rates between regions. Daiichi Sankyo received clinical advice, as part of an expert validation meeting, that DESTINY-Breast03 is generalisable to patients with HER2+ unresectable or metastatic breast cancer (u/mBC) treated after trastuzumab and a taxane in the UK (company submission Section B.2.6.2, page 63).[12] Daiichi Sankyo therefore considers DESTINY-Breast03 to be generalisable to UK clinical practice. Supplemental subgroup analyses are provided below to support this conclusion, although all subgroup analyses should be interpreted with caution as DESTINY-Breast03 was not powered to assess efficacy differences between subgroups. *Efficacy and safety based on ethnicity (Asian vs. non-Asian patients)* Clinical advice to the company in an expert validation meeting was that the high proportion of Asian patients enrolled in DESTINY-Breast03 would not be expected to have an impact on survival, and that there is no biological reason for Asian ethnicity to affect the efficacy of T-DXd. To explore this issue further, Asian ethnicity has been assessed through subgroup analysis of PFS by BICR in DESTINY-Breast03 (Figure 3). The subgroup analysis [redacted] of T-DXd vs. T-DM1 for

		PFS between Asian and non-Asian patients, with [redacted] for the HR between the two subgroups (Asian: [redacted]; non-Asian: [redacted]). Consequently, subgroup analysis suggests that there is [redacted] of Asian patients in the trial upon the treatment effect. **Figure 3: DESTINY-Breast03 | Forest plot of PFS by BICR | FAS | Race and region**  Abbreviations: BICR, blinded independent central review; CI, confidence interval; FAS, full analysis set; NE, not estimable; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan. The EAG also suggested that, based on previous clinical trials in breast cancer, there may be potential for higher toxicity in Asian patients than patients of other races treated in UK clinical practice. This would suggest that rates of adverse events (AEs) could be lower in UK clinical practice than in DESTINY-Breast03 as a higher proportion of

Asian patients were enrolled in DESTINY-Breast03 than would typically require treatment in the UK. However, a breakdown of treatment-emergent AEs (TEAEs) in DESTINY-Breast03 by subgroup suggests that there is [redacted] (Table 1).

Table 1: DESTINY-Breast03 | Summary of TEAEs by subgroup | Asian and non-Asian race | SAS

TEAEs by category, n (%)	T-DXd		T-DM1	
	Asian (n=149)	Non-Asian (n=108)	Asian (n=161)	Non-Asian (n=100)
Total patient-years of exposure	[redacted]	[redacted]	[redacted]	[redacted]
Any TEAE	[redacted]	[redacted]	[redacted]	[redacted]
EAIRs per patient-year	[redacted]	[redacted]	[redacted]	[redacted]
Serious TEAE	[redacted]	[redacted]	[redacted]	[redacted]
TEAE associated with Study Drug Discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
TEAE associated with Study Drug Interruption	[redacted]	[redacted]	[redacted]	[redacted]
Severe TEAE (CTCAE Grade ≥3)	[redacted]	[redacted]	[redacted]	[redacted]
TEAE associated with an Outcome of Death	[redacted]	[redacted]	[redacted]	[redacted]
TEAE associated with Dose Reduction	[redacted]	[redacted]	[redacted]	[redacted]
Drug-related Severe TEAE (CTCAE Grade ≥3)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; EAIR, exposure-adjusted incidence rate; SAS, safety analysis set; TEAE, treatment-emergent adverse event; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

		Smoking status The EAG stated that the proportion of smokers in DESTINY-Breast03 was lower than the rate of smoking in the UK. Based on 2020 data for adult women in England, 89.6% of the population do not smoke (never smoked or formerly smoked).[13] The company consider this consistent with the [redacted]% and [redacted]% of patients in the T-DXd and T-DM1 arms of DESTINY-Breast03, respectively, who do not smoke.[1] To explore this issue further, subgroup analysis of PFS by BICR in DESTINY-Breast03 was conducted across the subgroup of patients who had never smoked, and patients who were current or former smokers. Despite the small proportion of current and former smokers in DESTINY-Breast03, there is nonetheless a [redacted] of T-DXd vs. T-DM1 in both subgroups (Figure 4). The analysis also demonstrates [redacted] (current/former smokers: [redacted]; never smoked: [redacted]).

Figure 4: DESTINY-Breast03 | Forest plot of PFS by BICR | FAS | Smoking status

Abbreviations: BICR, blinded independent central review; CI, confidence interval; FAS, full analysis set; NE, not estimable; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

Prior lines of therapy

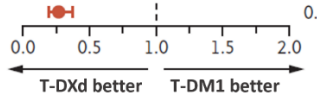
Clinical experts consulted by the company stated that number of lines of prior therapy would be a prognostic factor for survival, with patients who had received more prior therapies having worse prognosis than patients who had received fewer prior therapies.[12] In DESTINY-Breast03, 50.8% of enrolled patients had received ≥2 prior lines of therapy, and 49.2% had received 0–1 prior lines of therapy.[2] Clinicians prefer to use the most efficacious treatments as early as possible in the treatment pathway. It is therefore anticipated that, if approved, the majority of T-DXd usage would be at second line following trastuzumab and a taxane. Patients in DESTINY-Breast03 may have received more lines of

[2] All patients who received treatment in DESTINY-Breast03 had received at least one prior cancer therapy; prior cancer therapy was not recorded for two patients who were randomised in error and not treated. Subgroup analysis for lines of prior therapy was conducted based on number of prior therapies received in the metastatic setting; n=2 and n=3 patients in the T-DXd and T-DM1 arms, respectively, had not received prior treatment in the metastatic setting

		prior therapy than would be expected in UK clinical practice, and consequently, the unprecedented PFS seen at the first interim analysis could be considered a conservative estimate of T-DXd efficacy. Pre-specified and post hoc subgroup analyses of data from DESTINY-Breast03 conducted to date have not demonstrated any differences in PFS treatment effect based on lines of prior therapy. Subgroup analysis of PFS by BICR according to prior lines of therapy (0–1 or ≥2) in DESTINY-Breast03 demonstrated a statistically significant treatment effect in both subgroups for T-DXd vs. T-DM1 (Figure 5).[4] Confidence intervals in both subgroups show substantial overlap, demonstrating consistency in treatment effect between the subgroups (0–1 prior lines: 95% CI 0.23, 0.48; ≥2 prior lines: 95% CI 0.19–0.41).[4] Likewise, subgroup analysis of confirmed objective response rate (ORR) by BICR in DESTINY-Breast03 demonstrated similarity between 0–1 prior lines and ≥2 prior lines (CS Figure 12, page 68).[14] The analysis demonstrated consistency, with overlap between the confidence intervals for the percentage-point difference between T-DXd and T-DM1 (0–1 prior lines: 95% CI 27.3, 51.2; ≥2 prior lines: 40.9, 62.4).[14]

Figure 5: DESTINY-Breast03 | Forest plot of PFS by BICR subgroup analysis | FAS | Analysis in key subgroups including by lines of prior therapy

Subgroup	No. of Patients	No. of Events/No. of Patients		Median Progression-free Survival (95% CI) *months*		Hazard Ratio for Disease Progression or Death (95% CI)
		Trastuzumab deruxtecan	Trastuzumab emtansine	Trastuzumab deruxtecan	Trastuzumab emtansine	
All patients		87/261	158/263	NE (18.5–NE)	6.8 (5.6–8.2)	0.28 (0.22–0.37)
Hormone-receptor status						
Positive	272	46/133	84/139	22.4 (17.7–NE)	6.9 (4.2–9.8)	0.32 (0.22–0.46)
Negative	248	41/126	73/122	NE (18.0–NE)	6.8 (5.4–8.3)	0.30 (0.20–0.44)
Previous pertuzumab treatment						
Yes	320	57/162	98/158	NE (18.5–NE)	6.8 (5.4–8.3)	0.30 (0.22–0.43)
No	204	30/99	60/105	NE (16.5–NE)	7.0 (4.2–9.7)	0.30 (0.19–0.47)
Visceral disease						
Yes	384	72/195	123/189	22.2 (16.5–NE)	5.7 (4.2–7.0)	0.28 (0.21–0.38)
No	140	15/66	35/74	NE (NE–NE)	11.3 (6.8–NE)	0.32 (0.17–0.58)
Lines of previous therapy						
0 or 1	258	46/132	75/126	22.4 (17.9–NE)	8.0 (5.7–9.7)	0.33 (0.23–0.48)
≥2	266	41/129	83/137	NE (16.8–NE)	5.6 (4.2–7.1)	0.28 (0.19–0.41)
Stable brain metastases defined by reported history of CNS metastases						
Yes	114	31/62	31/52	15.0 (12.6–22.2)	5.7 (2.9–7.1)	0.38 (0.23–0.64)
No	410	56/199	127/211	NE (22.4–NE)	7.0 (5.5–9.7)	0.27 (0.19–0.37)



Abbreviations: BICR, blinded independent central review; CI, confidence interval; CNS, central nervous system; FAS, full analysis set; NE, not estimable; No, number; PFS, progression-free survival; T DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Source: Adapted from Cortés et al, 2022.[4]

		Efficacy for a "generalisable" European population vs the DESTINY-Breast03 ITT population As a final discussion topic around generalisability, the EAG posits that the European subgroup of patients in DESTINY-Breast03 may be more generalisable to UK practice, but that patient numbers in this subgroup are small. Daiichi Sankyo agree that this subpopulation is not sufficiently large allow inclusion in the economic model without introducing further uncertainty associated with efficacy extrapolations. The company position is that there is no difference in efficacy between the European subpopulation and the DESTINY-Breast03 ITT population, and therefore that it is appropriate to use the ITT population in the economic model. Confirming the generalisability of DESTINY-Breast03 to the UK, supplemental subgroup analysis of PFS by BICR conducted to support the technical engagement process demonstrated a [redacted] for T-DXd vs. T-DM1 in the European subpopulation of DESTINY-Breast03 (Figure 3). [redacted] (Europe: [redacted]; rest of world: [redacted]). This finding is [redacted] in the trial ([redacted]). Additionally, median PFS with T-DM1 in the ITT population of DESTINY-Breast03 was 6.8 months, consistent with median PFS observed in European real-world studies (CS Section B.2.6.1, Table 12, page 55).[15-19] In conclusion, Daiichi Sankyo agree with the EAG that differences in background characteristics of patients enrolled in DESTINY-Breast03 and patients in clinical practice is an unresolvable issue that is a limited cause of uncertainty.
EAG RESPONSE		The EAG were unable to identify clear distinctions between text including 'new evidence' and text reiterating arguments from the company submission. Therefore, we respond below to some of the key points raised by the company making no distinction between 'new' or previously presented evidence. The EAG agree: • there are no known biological reasons to expect differences in effectiveness between Asian and non-Asian patients

		• [redacted] in analyses However, there are some differences in our interpretations of the company's subgroup analyses and generalisability of the trial: • The EAG report suggested potential differences in practice between Asian and European regions may impact on generalisability of the company's trial to the NHS. Figure 3 in the company response above shows [redacted] between PFS data for European regions (HR [redacted] to [redacted]) compared to the rest of the world (HR [redacted] to [redacted]). However, [redacted]. Therefore, some uncertainties regarding generalisability of the company's trial to the NHS remain. • An additional limitation of subgroup analyses is that they are unable to assess the impact of interactions between covariates. Furthermore, they do not take into account the potential impact of confounding. Therefore, the results of these subgroup analyses should be interpreted with caution.
Key issue 3: Uncertainty in the proportion of people whose disease has progressed who are having subsequent	Yes	The EAG considered the proportion of patients receiving subsequent treatment to be uncertain as the values from DESTINY-Breast03 were high in comparison to clinical expert opinion. In addition, the EAG are unsure whether the distribution of subsequent treatments received in the DESTINY-Breast03 study are reflective of English clinical practice. Daiichi Sankyo would like to address each of these concerns in turn; the proportion of patients who receive subsequent treatments and secondly, the distribution of subsequent treatments. *Proportion of patients receiving subsequent treatments*

treatments and the distribution of subsequent treatments		In the company base case, the proportion of patients receiving subsequent treatment was informed by clinical expert opinion (66.7%) which was also confirmed by clinical advice received by the EAG. There are two ways of calculating the proportion of patients receiving subsequent treatment in DESTINY-Breast03. The first method, provided as a scenario analysis in the company submission, incorporates the total number of patients receiving at least one subsequent treatment divided by the total progressed events including death. The resulting proportions are [redacted] for T-DXd and [redacted] for T-DM1. These values appear higher than those estimated by clinicians. This is due to the numerator, which considers all patients receiving at least one subsequent treatment including those that discontinued treatment for reasons other than progression. Clinical experts consulted considered these values were higher than expected and suggested that around two-thirds of patients who progress would receive subsequent treatment. The model results when using these proportions are provided in Table 2 which show a decrease in the incremental cost-effectiveness ratio (ICER) from a base case of [redacted] to [redacted] ([redacted] to [redacted] when quality-adjusted life-years (QALYs) are unweighted). As part of the clarification response, a second method of estimating the proportion of patients receiving subsequent therapy was introduced. In this method, only patients who had progression events were considered in order to align with the economic modelling where subsequent therapies are applied once a patient's disease progresses. Here, Daiichi Sankyo confirmed that when analysing only progressed patients, [redacted] in the T-DXd arm and [redacted] in the T-DM1 arm, received at least one subsequent treatment. These values are more aligned with the values provided by the clinical experts. Using these values in the model decreases the base case ICER from [redacted] to [redacted] ([redacted] to [redacted] with unweighted QALYs), suggesting an improvement in cost-effectiveness. Daiichi Sankyo therefore considers the base case to be conservative and the impact of these scenarios minor (see Table 2).

The base case value is considered more conservative given that the same value is applied to both treatment arms. Evidence from the trial using both methods described above, has a higher proportion of patients receiving subsequent treatment for T-DM1 versus T-DXd.

Table 2: Base-case results (with PAS) with alternative proportion of patients receiving subsequent treatment ([redacted])

Drug	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs (unweighted QALYs)	ICER vs. baseline (unweighted QALYs)
Company base case (66.7%)							
T-DM1	[redacted]	[redacted]	[redacted]				
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: DB03 subsequent treatment proportions							
T-DM1	[redacted]	[redacted]	[redacted]				
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: DB03 progressed patient proportions							
T-DM1	[redacted]	[redacted]	[redacted]				
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DB03, DESTINY Breast03; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years.

		Distribution of subsequent treatments The EAG note that the subsequent treatments used in DESTINY-Breast03 may not be reflective of English clinical practice, however they do not suggest how they could differ, or which treatments specifically differ in UK clinical practice. The EAG suggest that data from the European subgroup could be more reflective and that more follow-up data from DESTINY-Breast03 could change the distributions. Daiichi Sankyo acknowledge that with more follow-up the overall distributions of subsequent treatment may change within the DESTINY-Breast03 trial, however it is expected that changes in the distribution would have a small impact on costs and therefore this uncertainty would have minimal impact on the cost-effectiveness estimates. In the company base case, the costs of subsequent treatments were informed by the distribution of subsequent treatment reported in the DESTINY-Breast03 study to maintain consistency between the source of efficacy and costs. However, alternative treatment distributions were tested in scenario analyses (see Section B.3.11.3) to assess the uncertainty associated with subsequent therapy distributions. Two scenarios were included: 1. Assuming the same distribution between both treatment arms using the pooled subsequent treatment distribution from DESTINY-Breast03. 2. Applying subsequent therapy distributions based on UK expert clinical advice. A third scenario is presented for the TE response where Daiichi Sankyo have incorporated subsequent treatments based on the European subgroup distribution of subsequent treatments from DESTINY-Breast03 (Scenario 3 – see Table 3). Table 3 presents the subsequent treatment distributions applied in each scenario included within the economic model.

Table 3: Subsequent treatment distribution scenarios

Curve	Base case DB-03		Scenario 1 pooled DB-03	Scenario 2 UK clinical expert opinion		Scenario 3 European subgroup	
	T-DXd	T-DM1	T-DXd	T-DM1	T-DXd	T-DM1	T-Dxd
Trastuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T-DM1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pertuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Taxane (paclitaxel)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Trastuzumab + taxane	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-HER2 (tucatinib combination)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hormone therapy (tamoxifen)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other (capecitabine)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan

The results of these scenarios are presented in the company submission (Section B.3.11.3) and EAR (Section 5.2.3 and Section 6.2.2). For completeness, these results are also presented in Table 4 based on the company's 'corrected' base case post EAR and also include the new scenario exploring the European subgroup. The results presented highlight that each scenario has a minimal impact on the ICER.

Table 4: Base-case results (with PAS) with alternative subsequent treatment distribution scenarios

Drug	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs (unweighted QALYs)	ICER vs. baseline (unweighted QALYs)
Base case: DB-03 data							
T-DM1	[redacted]	[redacted]	[redacted]				
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: Pooled DB-03 data (assuming same distribution across arms)							
T-DM1	[redacted]	[redacted]	[redacted]				
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: Clinical expert opinion							
T-DM1	[redacted]	[redacted]	[redacted]				
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3: European subgroup							
T-DM1	[redacted]	[redacted]	[redacted]				
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years.

In conclusion, Daiichi Sankyo acknowledge that there is some uncertainty associated with both the proportion of progressed patients receiving subsequent treatment, and the types of treatments received, however the scenario

		analyses explored suggest a limited impact on the cost-effectiveness of T-DXd. Daiichi Sankyo therefore agree with the EAG that this is a limited cause of uncertainty.
EAG RESPONSE		A slight correction needs to be made to the company's statement about why the EAG considers the proportion receiving subsequent treatment and the distribution of treatments to be uncertain. The company clinical experts estimated the proportion of patients receiving subsequent treatment given that "the proportion of progressed patients receiving subsequent treatment in DESTINY-Breast03 was higher than expected" (P.126 company submission). As explained by the company, two of the trial values ([redacted] for T-DXd and [redacted] for T-DM1) included subsequent treatment received while progression-free in the numerator. It is not clear if this was explained to the clinical experts. The clinical expert estimated proportion was used in the company base case. Clinical expert opinion, while extremely useful and accepted by the EAG, is low quality evidence and there is therefore considerable uncertainty in this estimate. The fact that this is a multi-national study with subsequent treatment decisions being made according to local clinical practice means trial data on the proportion receiving subsequent treatment and the distribution of subsequent treatment may not be perfectly generalisable to English clinical practice. The company has provided new cost-effectiveness results based on subsequent treatment assumptions based on the European subgroup. The results of the scenario 3 based on the European subgroup data were very similar to the those of the base case analysis.
Key issue 4: Higher AEs in the T-DXd arm compared to T-DM1 arm	Yes	The EAG highlighted the higher rate of any-grade TEAEs in the T-DXd arm compared with the T-DM1 arm (99.6% and 95.4%, respectively). However, the EAG also stated that this issue is not anticipated to impact cost-effectiveness, given that the cost and quality-of-life impact of AEs is modelled in the cost-effectiveness analysis. Daiichi Sankyo are in agreement with this position but would like to highlight the incidence rates of AEs across each treatment arm when

		taking treatment duration into account, and clinical expert opinion on the benefit/risk profile of T-DXd, as well as the lower rate of discontinuations overall in the T-DXd arm than with T-DM1 (125 and 214 patients, respectively).[4] In DESTINY-Breast03, the higher rate of TEAEs should be viewed in the context of the substantially longer treatment duration and patient-years of exposure in the T-DXd arm (14.3 months and [redacted] years, respectively) compared with the T-DM1 arm (6.9 months and [redacted] years, respectively).[1,4] Rates of serious TEAEs were similar between treatment arms (19.1% and 18.0% of patients, respectively) and the exposure-adjusted incidence of TEAEs was lower in the T-DXd than T-DM1 arm for both serious TEAEs ([redacted] and [redacted] events per patient year, respectively) and any TEAE experienced in the trial ([redacted] and [redacted] events per patient year, respectively).[1,4] T-DXd demonstrated an acceptable safety profile in DESTINY-Breast03 that was consistent with previous studies of T-DXd, with no new safety concerns identified; most TEAEs were Grade 1 or 2 and were manageable in routine care.[4,20,21] Few patients discontinued study drug due to TEAEs, although the proportion of patients discontinuing treatment due to TEAEs was higher in the T-DXd arm than in the T-DM1 arm.[4] Overall, the safety profile for T-DXd was similar to T-DM1, and was as expected based on previous studies of T-DXd; AEs – including events relating to interstitial lung disease (ILD) – were manageable. There now exists substantial clinical experience with T-DXd since NICE recommended reimbursement of T-DXd through the Cancer Drugs Fund (CDF) in 2021 for treating HER2+ u/mBC after 2 or more anti-HER2 therapies,[22] where the committee described T-DXd as having an acceptable safety profile.[23] From April 2021 to June 2022, [redacted] patients were initiated on treatment with T-DXd within the CDF in England; T-DXd is also available at third line in Wales, Northern Ireland, and Scotland. Moreover, in the French cohort temporary authorisation for use (cATU) programme, T-DXd was "well tolerated and no new safety signals were observed" in 459 patients who had previously received at least two prior lines of therapy.[24] This, together with anecdotal feedback from prescribing physicians, demonstrates clinical confidence that T-DXd is an efficacious therapy with a manageable safety profile.

		At the expert validation meeting conducted by the company, the clinical experts stated that the AE profile of T-DXd in DESTINY-Breast03 was not of concern, and consistent with their clinical experience.[12] A clinical expert also observed that ILD rates have improved since publication of results from DESTINY-Breast01.[12] Potential ILD events that occur in patients treated with T-DXd are handled through an established ILD management plan, which is clearly defined in the summary of product characteristics for T-DXd.[25] The improved ILD rates noted by the clinical expert indicate both that clinicians have improved awareness of the potential for ILD and that the ILD management plan aids appropriate and timely response to potential ILD events. The company considers this view to reflect the growing understanding of T-DXd's safety profile amongst UK oncologists. Data from DESTINY-Breast03 (DCO May 2021) indicate that most patients treated with T-DXd were able to tolerate the planned dose of 5.4 mg/kg/3 weeks: the majority of patients treated with T-DXd ([redacted]%) did not have any dose reductions from baseline to follow-up (note: reductions were not exclusively due to AEs), and [redacted]% of patients did not have any other dose changes or interruptions.[1] The safety profile of T-DXd should be seen in the context of its efficacy in delaying disease progression. Patient disposition data from DESTINY-Breast03 presents a discontinuation rate of 125 patients (47.9% of those randomised) by end of follow-up in the T-DXd arm, compared with 214 patients in the T-DM1 arm (81.4% of those randomised).[4] Although 35 (13.4%) and 17 (6.5%) patients, respectively, discontinued due to AEs, a much greater proportion discontinued due to BICR or investigator-assessed disease progression, which was notably lower in the T-DXd arm than the T-DM1 arm (70 [26.8%] and 170 [64.6%] patients of those randomised, respectively, discontinued due to either assessment of disease progression).[4] Since the company submission was made to NICE in April 2021, a further safety data cut from DESTINY-Breast03 (7 Sept, 2021) was presented at the 2022 American Society of Clinical Oncology (ASCO) congress.[26] These data (Table 5) are consistent with the findings from the first interim data cut for PFS (21 May, 2021), with no new safety signs. Exposure-adjusted incidence rates (EAIRs) per patient-year were lower in the T-DXd arm than the T-DM1 arm except

for TEAEs associated with drug discontinuation, which were driven by management of actual or suspected ILD/pneumonitis in the T-DXd arm.[26] Moreover, the time to onset of TEAEs associated with first drug discontinuation or first dose reduction was longer in the T-DXd arm (224 and 96 days, respectively than the T-DM1 arm (147 and 19 days, respectively).[26]

Table 5: DESTINY-Breast03 | Summary of key safety data | September 2021 DCO

	T-DXd (n=257)	T-DM1 (n=261)
Patients remaining on treatment, n (%)	116 (45.1)	39 (14.9)
Treatment duration, median (range), months	16.1 (0.7–33.0)	6.9 (0.7–28.5)
Exposure, patient-years	327.2	186.3
Any grade TEAEs	256 (99.6)	249 (95.4)
Grade ≥3 TEAEs, n (%)	137 (53.3)	130 (49.8)
EAIR, patients with ≥1 event per PYE	0.42	0.70
Serious TEAEs	54 (21.0)	50 (19.2)
EAIR, patients with ≥1 event per PYE	0.17	0.27
Grade ≥3 serious TEAEs	39 (15.2)	38 (14.6)
EAIR, patients with ≥1 event per PYE	0.12	0.20
TEAEs associated with drug discontinuation	38 (14.8)	19 (7.3)

		EAIR, patients with ≥1 event per PYE: 0.12 / 0.10 Median time to event, days: 224 / 147 TEAEs associated with dose reduction: 59 (23.0) / 36 (13.8) EAIR, patients with ≥1 event per PYE: 0.18 / 0.19 Median time to event, days: 96 / 19 Abbreviations: EAIR, exposure-adjusted incidence rate; DCO, data cut-off; PYE, patient-years of exposure; TEAE, treatment-emergent adverse event; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan. Source: Hamilton et al, presented at ASCO congress, 2022.[26] Recently, on the basis of safety and efficacy evidence from DESTINY-Breast03, the MHRA granted regulatory approval to T-DXd for treatment of adult patients with HER2+ u/mBC after one or more prior anti-HER2 based regimens, extending the licence of T-DXd from the original indication and showing confidence in the benefit/risk profile. Daiichi Sankyo conclude that the safety profile of T-DXd is well characterised and that the impact of AEs is appropriately modelled in the company cost-effectiveness analysis and AEs are not a driver of cost-effectiveness, therefore this issue should be considered limited cause of uncertainty.
EAG RESPONSE		We thank the company for presenting evidence from a more recent safety data cut. The EAG agree these new data suggest differences in AEs between groups are likely to be explained by patient-years of exposure.
Key issue 5: Uncertain PFS	No	The EAG highlight uncertainty associated with the PFS estimates from DESTINY-Breast03 used to inform long-term extrapolations of PFS within the economic model due to data immaturity but note that alterative parametric models had little effect on the cost-effectiveness estimates.

predictions for T-DXd		The current data available from DESTINY-Breast03 in relation to the primary endpoint, PFS by BICR, met its primary endpoint at the interim analysis, demonstrating statistical significance and superiority in the T-DXd arm compared with T-DM1 (HR: 0.28; $p=7.8\times10^{-22}$).[4] The PFS data sufficiently demonstrates a clinically meaningful PFS benefit for T-DXd. At DCO, events of disease progression or death were reported in 33.3% in the T-DXd arm and 60.1% in the T-DM1 arm.[1] At DCO, [redacted] patients ([redacted]) in the T-DXd arm and [redacted] patients ([redacted]) in the T-DM1 arm were ongoing without events.[1] The remaining [redacted] patients ([redacted]) in the T-DXd arm and [redacted] patients ([redacted]) in the T-DM1 arm were censored for other reasons.[1] As stated in response to Key Issue 1 and in the EAR, DESTINY-Breast03 collected sufficient data to meet the primary endpoint – PFS by BICR – which were further reinforced by the secondary endpoint of investigator-assessed PFS.[4] While PFS data are relatively mature, particularly for the T-DM1 arm (60.1%), extrapolation of outcomes was required to inform cost-effectiveness estimates over a lifetime horizon (as is common in oncology appraisals). As stated within the company submission (Section B.3.3.2.2), six parametric curves were fitted to the data with an assessment of statistical goodness of fit and visual fit to determine the most appropriate curve. Additionally, clinical opinion was sought to ensure the longer-term estimates projected by the curves were clinically plausible and in line with expectations. Clinical advice indicated that 1-2% of T-DM1 patients would be progression-free at 5 years and this would reduce to 0% by 10 years. As such, expert clinical advice indicated that the Gompertz and generalised gamma curves could be excluded as they were not clinically plausible for T-DM1 with 5-year estimates substantially above this range. For T-DXd, the Gompertz was also considered too pessimistic. Further, both the Gompertz and generalised gamma curves produced extrapolations for T-DXd which crossed with T-DM1 at [redacted] and [redacted] years respectively. Clinicians considered this unlikely given the large PFS benefit observed within DESTINY-Breast03 and the clear separation of KM OS curves. Therefore, based on the visual fit and the plausibility of the long-term extrapolation, the log-logistic,

		log-normal, Weibull and exponential were considered most appropriate for further consideration to inform PFS estimates. Based on the clinical advice received, the Weibull distribution was selected to inform the base case extrapolations for T-DM1. Applying the Weibull may be considered pessimistic in comparison to the alternative plausible extrapolations, however, clinical experts agreed that the Weibull curve for T-DM1 would provide the most clinically plausible fit with 5- and 10-year PFS of [redacted] (which closely matches the clinical experts feedback of between 1–2% and 0%).[12] The log-normal and log-logistic curves also projected slightly higher PFS with T-DM1 than expected at both time points (see Table 6). Given the similar mechanisms of action of T-DXd and T-DM1 and in line with TSD guidance, it was also considered appropriate to assume the same base case PFS distribution across arms.[27] The clinicians agreed that the Weibull distributions for both T-DXd and T-DM1 provided an appropriate curve choice with a consistently higher PFS estimate for T-DXd. Each of the six parametric distributions (of which four were considered plausible), T-DXd projected higher PFS estimates in comparison to T-DM1. This is consistent with the observed KM data in DESTINY-Breast03 where there is clear and continued separation of curves and consistent with clinical opinion. Daiichi Sankyo consider their choice of base case curves (Weibull) to be the most appropriate and plausible options and in line with clinical expert opinion. In addition, of the plausible curves, the Weibull distributions estimate the most conservative treatment benefit for T-DXd in the long-term ([redacted] and [redacted] benefit at 5- and 10 years, respectively). Further to this, whilst there is some uncertainty in the magnitude of the PFS benefit (as illustrated by each of the extrapolations), all plausible extrapolations were tested in scenario analysis provided by Daiichi Sankyo in the company submission (see Section

B.3.11.3 - also presented in Table 7 below) and the cost-effectiveness results obtained were similar, ranging from [redacted] to [redacted] when considering the 1.2x QALY modifier ([redacted] to [redacted] with unweighted QALYs).

Despite raising uncertainty in long term PFS as a key issue, the EAG also agree within their report that different PFS curves had little impact on cost-effectiveness results (see Section 1.5 and 6.2.1 of the EAR) and hence the company consider that the uncertainty associated with PFS due to the interim data, is not a key determining factor in cost-effectiveness of T-DXd. In conclusion, based on the clinical plausibility of the long-term PFS projections, modest modelled benefit in the long term and minimal impact on cost-effectiveness in sensitivity analyses, the uncertainty associated with PFS from DESTINY-Breast03 is low.

Table 6: 5- and 10- year PFS estimates of plausible curves

Curve	T-DM1		T-DXd	
	5 years	10 years	5 years	10 years
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]

Table 7: Base-case results (with PAS) with alternative PFS curve distributions

Drug	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs (unweighted QALYs)	ICER vs. baseline (unweighted QALYs)
Base case: PFS = Weibull							

		T-DM1 [redacted] T-DXd [redacted] ***Scenario 1: PFS = Exponential*** T-DM1 [redacted] T-DXd [redacted] ***Scenario 2: PFS = log-logistic*** T-DM1 [redacted] T-DXd [redacted] ***Scenario 3: PFS = log-normal*** T-DM1 [redacted] T-DXd [redacted] Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years.
EAG RESPONSE		The company did not provide further evidence. Evidence was reproduced from the company submission. The EAG agree that the long-term PFS projection was associated with uncertainty, but that the impact on uncertainty was not significant in the company base case model. The EAG base case analysis does link overall survival to progression-free survival so there is likely to be a slightly greater impact on the EAG results, but the alternative PFS and TTD distributions investigated only resulted in an increase in the ICER of £1,000-£2,000/QALY.

Key issue 6: Uncertain OS predictions for T-DXd	No	In their report, the EAG have highlighted the uncertainty associated with the OS due to the limited OS events in the DESTINY-Breast03 trial at the DCO, in particular for T-DXd. Within the EAR, as a way of addressing the uncertainty, the EAG incorporated 'treatment waning' for T-DXd assuming that all patients who progress on T-DXd and T-DM1 have the same hazard of mortality with 2 years used as a proxy timepoint. Daiichi Sankyo do not agree that treatment waning is appropriate for decision-making based on the available evidence and would like to respond to this issue in two parts, firstly, to address uncertainty associated with OS estimates with regard to the cost-effectiveness and secondly to respond to the EAG's assumed treatment waning scenario. **Approaches taken to address OS uncertainty** Daiichi Sankyo acknowledge the uncertainty associated with the OS outcomes due to the immaturity of the interim analysis data cut from DESTINY-Breast03 and lack of external long-term outcomes for T-DXd. Despite this immaturity in the OS estimates, extensive methods have been undertaken within the current submission through a variety of means including: • Validation of extrapolated outcomes with clinical experts • A range of scenarios using alternative extrapolations of other plausible distributions • An alternative approach to model OS using longer follow-up data for T-DM1 • Extensive sensitivity analysis on the company base case through OWSA, PSA and scenario analysis *Clinical validation* Parametric survival models were fitted to the observed data from DESTINY-Breast03 OS data (discussed further in the CS Section B.3.3.2.1). As stated within the company submission, guidance from NICE Decision Support Unit

(DSU) Technical Support Document (TSD) 14 was considered to determine an appropriate base case selection, which was based on a balance of data and statistical tests, AIC/BIC statistics, visual inspection of the parametric curves to the observed data and assessment of the plausibility of fitted models after the end of the follow-up period. Clinical validation was sought to determine the appropriate plausibility of long-term estimates of the fitted curves.

As stated within the company submission (Section B.3.3.2.1) clinical experts consulted by Daiichi Sankyo advised that 25–35% of patients treated with T-DM1 would be alive at 5 years (as per the EMILIA trial – see Figure 10) and 5–10% by 10 years, and therefore considered that the exponential, log-normal and Gompertz curves extrapolated from the DESTINY-Breast03 trial, could be completely excluded. The clinical experts considered that survival would likely be somewhere between the range provided by the Weibull which may be considered pessimistic at 10 years (with [redacted] of patients alive) and the log-logistic which may be considered optimistic at 10 years ([redacted] alive) – see Table 8. Therefore, the log-logistic, Weibull and generalised gamma curves were considered most appropriate (presented in Figure 6). When considering T-DXd, clinical experts also considered the three curves plausible for T-DM1 could also be plausible for T-DXd, with the plausible range from the Weibull (the most conservative OS estimates) to the log-logistic (with the most optimistic estimates).

Given the generalised gamma sat between the plausible estimates for the three curves, this was considered the most appropriate extrapolation to inform the company base case. The generalised gamma curve provides a clinically plausible long-term extrapolation of T-DM1 survival, with 5- and 10-year survival estimates in line with ranges provided by clinicians ([redacted] and [redacted] respectively).

Table 8: 5- and 10- year OS estimates of plausible curves – DESTINY-Breast03 extrapolations

Curve	T-DM1		T-DXd	
	5 years	10 years	5 years	10 years
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]

Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: OS, overall survival; T-DXd, trastuzumab deruxtecan; T-DM1, trastuzumab emtansine

Figure 6: OS outcomes from DESTINY-Breast03 – plausible curves

		 Abbreviations: KM, Kaplan-Meier; OS, overall survival *Scenarios of other plausible parametric curves* As presented in the company submission Section B.3.11.3, the other plausible curves (i.e., log-logistic and Weibull) were explored in scenario analysis. The plausible curves consistently indicate a benefit for T-DXd versus T-DM1 with

an incremental life year gain ranging between [redacted] (with the Weibull curve) and [redacted] (with the log-logistic curve). The corresponding ICER range is [redacted] to [redacted] ([redacted] to [redacted] with unweighted QALYs). In each of these scenarios, T-DXd remains cost-effective within the plausible range of extrapolated OS curves.

Table 9: Base-case results (with PAS) with alternative plausible OS distributions

Drug	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs (unweighted QALYs)	ICER vs. baseline (unweighted QALYs)
Company base case: OS informed by the generalised gamma distribution							
T-DM1	[redacted]	[redacted]	[redacted]				
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: OS informed by the log-logistic distribution							
T-DM1	[redacted]	[redacted]	[redacted]				
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: OS informed by the Weibull distribution							
T-DM1	[redacted]	[redacted]	[redacted]				
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years.

Alternative approach to model OS

Daiichi Sankyo have also conducted an alternative approach to estimate the OS of T-DXd and T-DM1 utilising published information which had longer-term follow-up for T-DM1. In this alternative approach, patient level data (PLD) were replicated from the T-DM1 arm of the EMILIA study which had a median follow-up of 47.8 months.[28] Parametric survival models were fitted to the replicated data to inform the T-DM1 OS, with the HR from DESTINY-Breast03 applied to this curve to inform the T-DXd OS (HR = 0.55).

From the parametric models and clinical feedback described above, the log-logistic, log-normal, and generalised gamma were considered most appropriate (

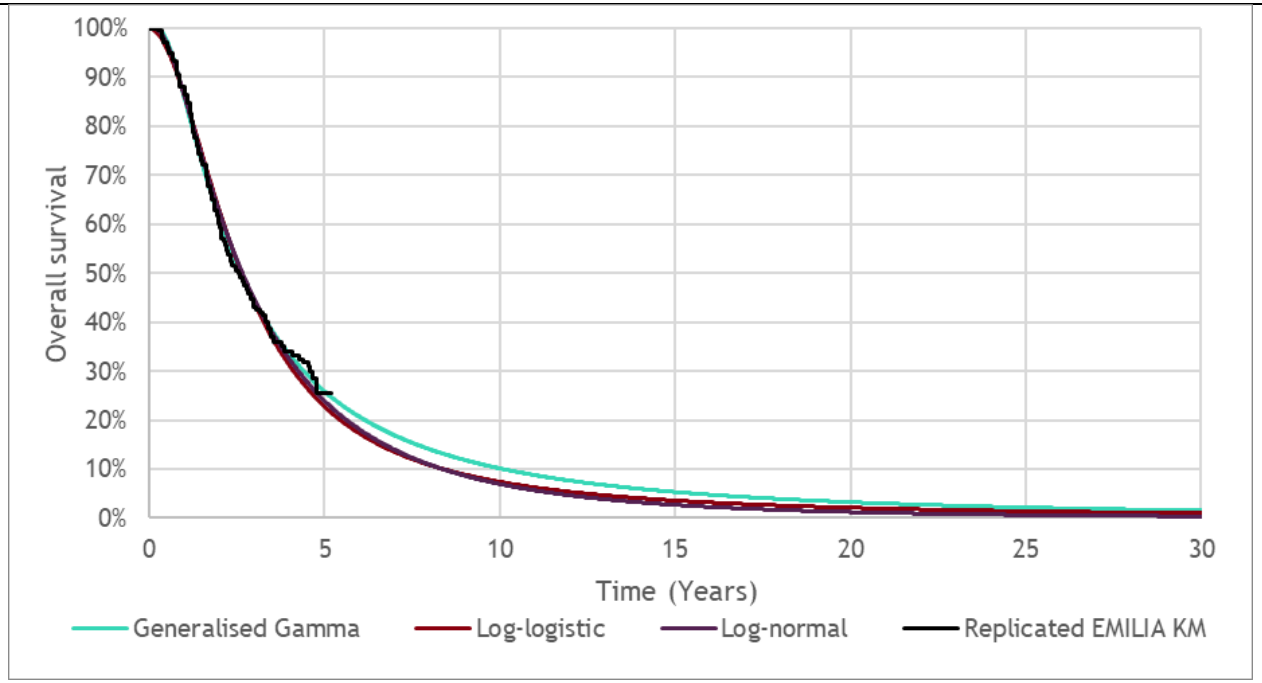
Figure 7). Of the plausible curves, generalised gamma provides the most optimistic (~10%) survival at 10 years, at the upper end of the clinical estimates. The log-normal and log-logistic curves are visually similar and sit between the estimates provided by clinicians at 10 years (7.0% and 7.4% respectively) – see Table 10.

Table 10: 5- and 10- year OS estimates of plausible curves – EMILIA extrapolations

Curve	T-DM1	
	5 years	10 years
Log-logistic	22.9%	7.4%
Generalised gamma	26.0%	10.2%
Log-normal	24.1%	7.0%

Figure 7 presents the three plausible curves to extrapolate T-DM1 using the EMILIA data. Log-normal was selected to inform the base case curve for the alternative approach due to better goodness-of-fit scores (see Table 29 of the CS), better visual fit and plausible long-term extrapolations compared with the alternative curves (log-logistic and generalised gamma).

		For this approach, T-DXd is informed by applying a HR derived from DESTINY-Breast03 to the extrapolated T-DM1 comparator arm. The HR calculated from DESTINY-Breast03 data is 0.55 (95% CI: 0.36 – 0.86). **Figure 7: OS outcomes from EMILIA – plausible curves**



Abbreviations: KM, Kaplan-Meier; OS, overall survival

Table 11 presents the alternative OS approach with the selected base case curve, log-normal. In addition, the other plausible curves are explored as scenarios (i.e., log-logistic and generalised gamma). The results show an ICER range with the plausible curves of [redacted] to [redacted] ([redacted] to [redacted] with unweighted QALYs). Using this alternative OS approach and scenarios around this, T-DXd remains within a cost-effectiveness range at the standard cost-effectiveness thresholds, and results are consistent with the base case ICER presented (with slightly lower ICERs than the direct extrapolation of OS from DESTINY-Breast03).

Table 11: Base-case results (with PAS) using the alternative OS approach

Drug	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs (unweighted QALYs)	ICER vs. baseline (unweighted QALYs)
Company base case approach: direct extrapolation of DB03 (generalised gamma)							
T-DM1	[redacted]	[redacted]	[redacted]				
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alternative OS approach base case: T-DM1 = log-normal							
T-DM1	[redacted]	[redacted]	[redacted]				
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario: T-DM1 = log-logistic							
T-DM1	[redacted]	[redacted]	[redacted]				
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario: T-DM1 = generalised gamma							

T-DM1	[redacted]	[redacted]	[redacted]				
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DB03, DESTINY-Breast03; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years.

Extensive sensitivity analysis

Sensitivity analysis on the company base case was conducted to test parameter uncertainty within the model (see Section B.3.11). In addition to what was originally presented, and to further assess the uncertainty associated with OS, the PSA has also been run varying just the OS curves (via the variance covariance matrix). Table 12 presents the mean base case PSA results and

Figure 8 presents the cost-effectiveness plane after 1,000 iterations. The mean results show consistency with the deterministic results with an ICER of [redacted] ([redacted] with unweighted QALYs). The confidence interval around the mean PSA results were calculated using the method described by Hatswell et al, 2018.[29] The 95% confidence interval around the ICER was [redacted] – [redacted] – [redacted] with unweighted QALYs).

The results considering parameter uncertainty associated with OS demonstrate that T-DXd is likely to remain cost-effective. Results were consistent with the company base case and demonstrated the robust conclusion that T-DXd is cost-effective versus T-DM1 at a £30,000 per QALY threshold.

Table 12: Mean PSA results (with PAS) – OS curves only

Drug	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs (unweighted QALYs)	ICER vs. baseline (unweighted QALYs)
T-DM1	[redacted]	[redacted]	[redacted]				
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient-access scheme; QALYs, quality-adjusted life years.

		Figure 8: Cost-effectiveness plane with the 1.2x QALY modifier – T-DXd vs. T-DM1 – OS curves only

		 Abbreviations: PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year. A similar analysis is also provided in Table 13 and Figure 9, which shows the PSA results and cost-effectiveness plane when testing uncertainty around the alternative methodological approach. Within this scenario, 1,000

		probabilistic iterations are run varying the T-DM1 log-normal curve (using the variance covariance matrix derived from the replicated EMILIA data) as well as the HR from DESTINY-Breast 03 (deterministic HR = 0.5546). The mean results show consistency with the deterministic results with an ICER of [redacted] ([redacted] with unweighted QALYs). The confidence interval around the mean PSA results were calculated using the method described by Hatswell et al, 2018.[29] The 95% confidence interval around the ICER was [redacted] – [redacted] ([redacted] – [redacted] with unweighted QALYs). The results considering parameter uncertainty associated with OS demonstrate that T-DXd is likely to remain cost-effective. Results were consistent with the company base case and demonstrated the robust conclusion that T-DXd is cost-effective versus T-DM1 at the £30,000 per QALY threshold. **Table 13: Mean PSA results (with PAS) – OS curves for T-DM1 from EMILIA with HR only**

Drug	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs (unweighted QALYs)	ICER vs. baseline (unweighted QALYs)
T-DM1	[redacted]	[redacted]	[redacted]				
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient-access scheme; QALYs, quality-adjusted life years.

Figure 9: Cost-effectiveness plane with the 1.2x QALY modifier – T-DXd vs. T-DM1 – OS curves for T-DM1 from EMILIA with HR only

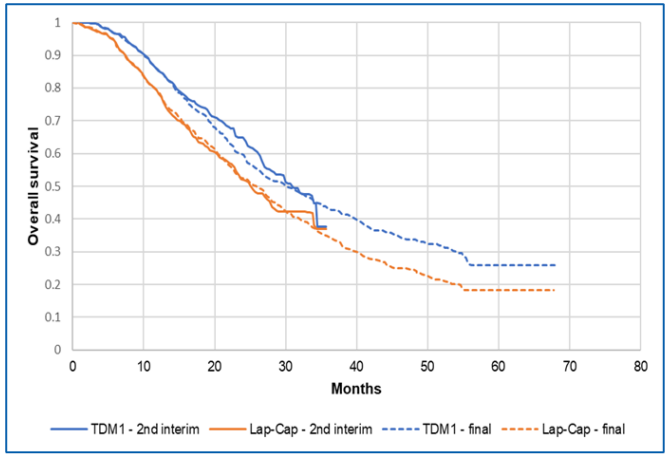
		 Abbreviations: PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year. Results across probabilistic analyses for both OS approaches are consistent. Using extrapolations from DESTINY-Breast03 consistently show T-DXd provides more QALYs than T-DM1 (with all iterations providing positive

		incremental QALYs), the average PSA results indicate that T-DXd is cost-effective. The alternative methodology incorporating further long-term data, by extrapolating replicated OS data from the EMILIA trial and applying the DESTINY-Breast03 observed HR between T-DXd and T-DM1 also demonstrates a clear benefit for T-DXd, with all iterations offering an incremental QALY gain for T-DXd. The average results indicate that T-DXd is a cost-effective treatment. *Conclusion* Whilst Daiichi Sankyo acknowledge that the OS data for DESTINY-Breast03 are immature, the company consider the uncertainty surrounding the OS estimates have been thoroughly explored through clinical validation, and testing of structural and parameter uncertainty within the economic model. Across methods explored, the ICER remains consistent ranging from [redacted] to [redacted] ([redacted] to [redacted] with unweighted QALYs). In each scenario explored, the cost-effectiveness of T-DXd was consistently demonstrated with an ICER below £30,000 per QALY. **Treatment waning** The EAG has implemented a treatment waning effect within the cost-effectiveness model (which subsequently informs the EAG base case), where it is assumed that there is no treatment effect beyond disease progression by applying the same post-progression mortality as T-DM1 to the T-DXd arm. Two scenarios have been provided by the EAG and have been described in the EAR as the following: • Scenario A: a conservative scenario with no treatment effect beyond disease progression from 2 years • Scenario B: treatment effect wanes over time, which is determined by the proportion of patients still alive who are in the PD state (which starts at 2 years)

		Daiichi Sankyo are not aware of any evidence of treatment waning with T-DXd, or other targeted treatments including antibody-drug conjugates (ADC) in HER2+ breast cancer, and consider that the EAG assumptions illustrate a highly conservative scenario that should be interpreted with caution for several reasons. Firstly, the time point of 2 years chosen for the EAG's scenario appears arbitrary and is justified in their report stating: *"A cut point of 2 years was chosen because only twenty-four patients were left at risk in the T-DXd Kaplan-Meier curve at 24 months."* (EAR, Appendix 2). By 24-months, there are 24 patients at risk in the T-DXd arm and 18 patients at risk in the T-DM1 arm. Though these numbers at risk are relatively low, there is no evidence from the observed data that after this timepoint the hazards start to merge (see Figure 1 in response to Key Issue 1). In the observed data available from DESTINY-Breast03 (>2.5 years), there is a clear separation in the T-DXd and T-DM1 OS curves, suggesting that there is no evidence observed related to a loss of treatment effect. Secondly, prior HER2+ breast cancer appraisals did not assume any OS treatment waning scenarios in their long-term model estimates, as such there is no precedent for the Committee adopting the EAG treatment waning assumptions. Of note, OS treatment waning was not considered in the appraisal of T-DM1 (TA458) for the treatment of HER2+ advanced breast cancer after trastuzumab and a taxane, (i.e. the comparator for this appraisal), or the appraisal of T-DXd (TA704) for treatment of HER2+ advanced breast cancer after two or more anti-HER2 therapies.[22,30-34] Finally, in all four of the previously considered metastatic HER2+ breast cancer trials, there has been no evidence of treatment waning for any HER2+ targeted treatments (including anti-HER2 ADC with a similar mechanism of action, T-DM1) when comparing interim outcomes with final analysis sets with longer-term follow-up. The mechanistic similarities between these therapies and T-DXd mean it is unlikely that treatment waning would be observed over long-term follow-up of T-DXd. The EMILIA, TH3RESA and CLEOPATRA studies, which had interim data followed by a final analysis set are discussed in turn below:

		EMILIA trial: • The EMILIA trial was a phase III trial which compared T-DM1 with lapatinib plus capecitabine in patients with HER2+ advanced breast cancer who had previously been treated with trastuzumab and a taxane (n=991). • At the second DCO median duration of follow-up was ~19 months and the final DCO had a median follow up of > 40 months (47.8 months for T-DM1 and 41.9 months for lapatinib + capecitabine). • Figure 10 provides a comparison of outcomes between the interim analysis and the final analysis of the EMILIA study (with KMs replicated using digitization software). • The comparison shows consistent separation of the OS Kaplan-Meier data up to at least 50 months versus the 2nd interim analyses.[35] Final OS results are also consistent with the 2nd interim analysis of OS with very similar median OS and the HR of the 2nd interim analysis sitting within the confidence interval of the final OS analysis (HR = 0.68 at the 2nd interim analysis and HR = 0.75 at the final analysis). T-DM1 maintained a significant OS benefit across the duration of the study. **Figure 10: Comparison of interim analysis with final analysis: EMILIA trial**

EMILIA OS data (2nd interim analyses versus final analysis)



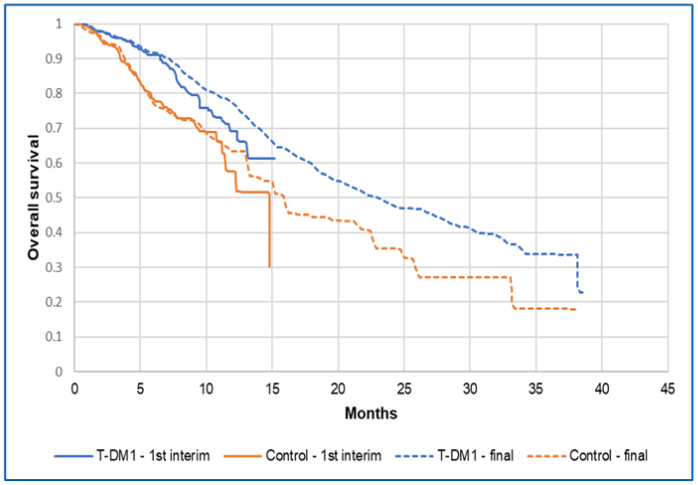
	2nd interim analysis		Final analysis	
Treatment	Lap+cap	T-DM1	Lap+cap	T-DM1
Median follow-up	18.6 months	19.1 months	41.9 months	47.8 months
OS median	25.1 months	30.9 months	25.9 months	29.9 months
OS HR (95% CI)	**0.68 (0.55 – 0.85)**		**0.75 (0.64-0.88)**	

Abbreviations: HR, hazard ratio; Lap+cap, lapatinib + capecitabine; OS, overall survival; T-DM1, trastuzumab emtansine
Source: digitised data from Verma et al, 2012; Dieras et al, 2017.[35]

		TH3RESA trial: • The TH3RESA trial was a phase III trial which compared T-DM1 with physicians choice (PC) in patients with HER2+ advanced breast cancer (n=602). • At the time of the first DCO, the median follow-up was 6.5 months for the PC arm and 7.2 arm for T-DM1 with a median OS of 14.9 months for PC. Median OS on the T-DM1 arm had not yet been observed. By the final analysis there was a median of 30.5 months follow-up and the OS median for PC had remained similar at 15.8 months and the T-DM1 observed median was 22.7 months. • Figure 11 provides a comparison of outcomes between the interim analysis and the final analysis of the TH3RESA study (with KMs replicated using digitization software). • The final OS analysis of the TH3RESA trial showed a continued separation of the OS Kaplan-Meier curves up to at least 35 months, with a significant OS hazard ratio maintained (HR=0.68 at the final analysis), thus suggesting no treatment waning effect associated with treatment for T-DM1.[36,37] The OS HR from the first DCO was also within the 95% CI of the final analysis OS HR.

Figure 11: Comparison of interim analysis with final analysis: TH3RESA trial

TH3RESA OS data (1st interim analyses versus final analysis)



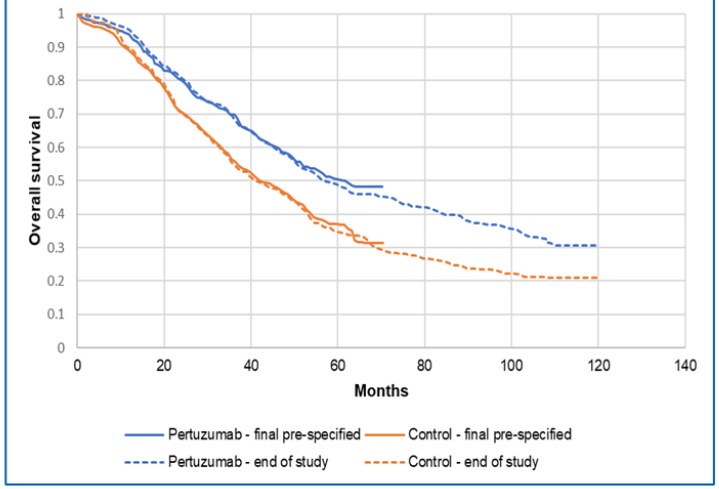
	1st interim analysis		Final analysis	
Treatment	PC	T-DM1	PC	T-DM1
Median follow-up	6.5 months	7.2 months	30.5 months	30.5 months
OS median (95% CI)	14.9 months (11.27 – NE)	NE months	15.8 months (13.5-18.7)	22.7 months (19.4-27.5)
OS HR (95% CI)	**0.55 (0.37-0.83)**		**0.68 (0.54 – 0.85)**	

Abbreviations: HR, hazard ratio; OS, overall survival; PC, physicians choice; T-DM1, trastuzumab emtnasaine
Source: digitised data from Krop et al, 2014; Krop et al, 2017.[36,37]

		CLEOPATRA trial: • The CLEOPATRA trial was a Phase III study which compared pertuzumab administered with trastuzumab and docetaxel with placebo, trastuzumab and docetaxel for patients with HER2+ metastatic breast cancer. • The final prespecified analysis had a median follow-up of 50 months across the two arms of the study (50.6 months for the control arm and 49.5 months for the pertuzumab arm), while the end of study outcomes reported a median follow-up of 99 months (98.7 months for the control arm and 99.9 months for the pertuzumab arm). [38,39] • Figure 12 provides a comparison of outcomes between the pre-specified final analysis and the end of study analysis of the CLEOPATRA study (with KMs replicated using digitization software). • With data available for 120 months, (a median of 99 months), the end of study analyses show a very similar treatment benefit to that of the earlier data cut with a minimal difference in the median OS and corresponding HR (difference of 0.01) with a more concise CI. The results showed that the HER2 targeted treatment maintained a treatment benefit for the duration of the trial with a clear and distinct separation in the KM.

Figure 12: Comparison of pre-specific analysis with end of study analysis: CLEOPATRA trial

CLEOPATRA OS data (final pre-specific analysis versus end of study analysis)



	Final pre-specified analysis		End of study	
Treatment	Control	Pertuzumab	Control	Pertuzumab
Median follow-up	50.6 months	49.5 months	98.7 months	99.9 months
OS median (95% CI)	40.8 months (35.8 – 48.3)	56.5 (49.3 – NE)	40.8 months (36 - 48)	57.1 months (50-72)
OS HR (95% CI)	**0.68 (0.56 – 0.84)**		**0.69 (0.58 – 0.82))**	

Abbreviations: OS, overall survival
Source: digitised data from Swain et al, 2015; Swain et al, 2020.[38,39]

		Conclusion Clinical advice to Daiichi Sankyo was that the level of treatment benefit T-DXd offered for PFS was unprecedented in the metastatic breast cancer setting, and that it would be unusual if the magnitude of this benefit did not translate to a sustained OS benefit. Daiichi Sankyo are not aware of any evidence of treatment waning for any targeted treatments, including ADC compounds, in HER2+ breast cancer based on long-term published data and as such see no evidence to indicate that survival curves begin to 'merge' from 2 years as suggested by the EAG's base case. For example, data at median follow up of 8 years plus from the CLEOPATRA trial shows no evidence of treatment waning. The constant treatment effect modelled in the company's base case is consistent with what is seen in published long-term data for other targeted ADC agents and accepted in prior TA appraisals in HER2+ mBC. Therefore, Daiichi Sankyo do not agree that an assumption of treatment waning is appropriate for decision-making based on the available evidence and consider that OS uncertainty has been explored through an extensive range of sensitivity/scenario analyses.
EAG RESPONSE		The company has not presented any new evidence specifically for T-DXd. The company has reproduced arguments made in the company submission and presented overall survival curves from 3 other trials where treatment is given until progression or toxicity to make the argument that there may be survival benefit even after disease progression and second-line T-DXd treatment has ceased. The EAG does not have many new comments to make on this issue. The reader is referred to Section 6.1.1, Appendix 2 in the EAG report and the EAG report Addendum for a description of the EAG analysis methods. It is worth reiterating the uncertainty in overall survival estimates. Approximately 80% of T-DXd patients were still alive at the first interim data cut point. Approximately 50% of patients were still progression-free. The EAG thinks that its base case assumption of no difference in mortality hazard rates post-progression results in an overall survival curve that is perfectly plausible. The first 2 years of the estimated overall survival curve for T-DXd was retained in this analysis, and a very significant mortality benefit while progression-free was assumed for T-DXd for the entire duration that patients were progression-free. The treatment waning assumptions also produce plausible overall survival

	curves. The reader is reminded that 'treatment waning' actually refers to making an assumption that the mortality hazard rate post-progression in the T-DXd arm is lower than that in the T-D1 arm to start with, but that this gradually reduces to zero (around year 8). In the post-progression state, patients in the T-DXd arm no longer receive T-DXd. Some patients in the T-DM1 arm will receive T-DXd as second-line treatment. The company presents Kaplan-Meier curves for 3 trials. The predicted overall survival curves by the company and by the EAG are reproduced here for comparison. **(Figure 13 in the EAG Addendum): The T-DXd company base case, EAG assumption A and EAG assumption B2 survivor curves**

	 EMILIA	

	If the survival curves in Figure 4 from the EAG Addendum are cropped at 6 or 7 years, then the extension over time of overall survival benefit of T-DXd associated with EAG assumptions does not look too dissimilar to that for trastuzumab emtansine in the EMILIA Kaplan-Meier curve. CLEOPATRA Progression-free survival is projected to be higher in CLEOPATRA than in DESTINY-Breast03. In CLEOPATRA, at 90 months, 40% of patients in the treatment arm (trastuzumab combination) are still progression-free. There will likely be a reduced mortality hazard rate in these patients while they are still on treatment in the progression-free state. TE3RESA There are roughly 10% still progression-free in the intervention group at 14 months. From 19 months, there is no discernible gain in survival that has not already been achieved during the progression-free time period from simply observing the Kaplan-Meier curve. The comparator survival curve is not as smooth as the intervention survival curve due to much smaller numbers at risk. Summary In short, the EAG considers the overall survival curves estimated using its alternative assumptions to be entirely plausible. While there may be biological (perhaps smaller average lesion size at disease progression) and statistical reasons for mortality hazard rates to be lower in the T-DXd arm than in the T-DM1 arm post-progression while patients are receiving entirely different 3rd-line treatments, the evidence for sustained lower mortality hazard rates in the T-DXd arm than in the T-DM1 arm after disease progression has yet to be produced.

Key issue 7: Crosswalking EQ-5D-5L to EQ-5D-3L with the recommended algorithm	Yes	The EAG noted that the utilities derived from DESTINY-Breast03 were mapped from EQ-5D-5L to EQ-5D-3L using the Van Hout et al, 2012[40] algorithm instead of the NICE recommended Hernandez et al, 2017 algorithm.[41] During the development of the analyses and submission dossier, NICE published the new methods and process guidance outlining the new preferred approach to use the Hernandez algorithm instead of the previously preferred Van Hout approach. As such, Daiichi Sankyo were unable to incorporate this change into the model before the submission deadline. In response to the EAG's report, Daiichi Sankyo have now conducted the analyses in which the utility responses were 'crosswalked' using the algorithm developed by Hernandez et al, 2017.[41] As per the original submission, EQ-5D-3L utility scores based on *'progression-free'* and *'progressed disease'* health states were derived using generalized estimating equations (GEE) regressions. The mean utility values and associated 95% confidence intervals for the progression-free and progressed health states for each treatment group are derived from the model using least squares means. An overview of the statistical goodness of fit (by quasi-likelihood under the independence model criterion [QIC]) and results of the GEE regression estimates are provided in Table 14. **Table 14: GEE regression coefficients (Hernandez)** **Coefficient** / **Value** / **95% CI** / **p-value** / **QIC** Intercept / [redacted] / [redacted] / [redacted] / [redacted]

Treatment (T-DXd)	[redacted]	[redacted]	[redacted]		
Progressed	[redacted]	[redacted]	[redacted]		

Abbreviations: CI, confidence interval; QIC, quasi-likelihood.

Table 15 presents the resulting crosswalked EQ-5D-3L utility values using the Hernandez algorithm from the DESTINY-Breast03 study by progression status and treatment arm.

Table 16 presents the crosswalked EQ-5D-3L utility values using the Van Hout algorithm for comparison (presented in the company submission Section B.3.4.2).

Table 15: Mapped EQ-5D-3L utility values from DESTINY-Breast03 (Hernandez)

Health state	T-DXd (SE) (95% CI)	T-DM1 (SE) (95% CI)	Overall (SE) (95% CI)
Progression-free	[redacted]	[redacted]	[redacted]
Progressed	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; SE, standard error.

Table 16: Mapped EQ-5D-3L utility values from DESTINY-Breast03 (Van Hout)

Health state	T-DXd (SE) (95% CI)	T-DM1 (SE) (95% CI)	Overall (SE) (95% CI)
Progression-free	[redacted]	[redacted]	[redacted]

Progressed	[redacted]	[redacted]	[redacted]	

Abbreviations: CI, confidence interval; SE, standard error.

The EQ-5D-3L Hernandez utility values were subsequently included within the economic model as an option.

Table 17 presents a scenario analysis of the company base case using the Hernandez algorithm for utility values. This scenario has minimal impact on the cost-effectiveness results, resulting in an ICER of [redacted] compared to [redacted] when using the Van Hout crosswalk (this equates to [redacted] compared to [redacted] with unweighted QALYs). Using the Hernandez algorithm also has minimal impact on the (unweighted) incremental QALY gain versus using Van Hout ([redacted] vs [redacted] respectively)

Table 17: Cost-effectiveness results (with PAS): crosswalked Hernandez utility values

Drug	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs (unweighted QALYs)	ICER vs. baseline (unweighted QALYs)
Company base case approach: Crosswalk with Van Hout							

		T-DM1	[redacted]	[redacted]	[redacted]				
		T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Scenario: Crosswalk with Hernandez							
		T-DM1	[redacted]	[redacted]	[redacted]				
		T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years.							
EAG RESPONSE		The EAG acknowledges the deviation to the new NICE methods guidelines was owing to the company preparing their submission when Guidelines were published. The EAG accepts the new evidence provided by the company as being in line with NICE guidelines. Using the results provided in Table 15 of the Hernandez crosswalk, the EAG base-case results are: **Table: EAG base-case Cost-effectiveness results (with PAS): crosswalked Hernandez utility values**							
		Drug	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs (1.2x QALY weighting)**	**Cumulative ICER (£/QALY, 1.2x QALY weighting)**
		Company base case approach: Crosswalk with Van Hout							
		T-DM1	[redacted]	[redacted]	[redacted]				
		T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

		Scenario: Crosswalk with Hernandez
		T-DM1 [redacted]
		T-DXd [redacted]
		Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years When using the Hernandez crosswalk values for both the model estimates and for the Schneider er al. (2021) calculator general population estimates, the Total QALYs estimated for T-DM1 in the deterministic analysis of the EAG base case model was [redacted], the general population Total QALY estimate is 14.33, giving an absolute QALY shortfall of [redacted] with a proportional shortfall of [redacted]%. This infers a QALY weight =1 as per NICE methods guidelines. This compares to a QALY weight of 1.2 when using the MVH values in the company base case.
Key issue 8: Post-progression utility values	Yes	The EAG highlighted issues relating to the progressed disease utility values incorporated with the company's base case model suggesting there is no evidence for a difference in progressed disease utility values across treatment groups. In their report, the EAG state *"There does not appear to be evidence in Lloyd et al. (which was used as the source for PD utility estimates in the company's base case model) or in the CS for a difference in PD utility values across treatment groups."* For the technical engagement response, Daiichi Sankyo first discuss the utility values calculated from Lloyd et al, and the concerns from the EAG, then go onto discuss wider evidence of differences in progressed utility values. *Lloyd et al. mixed model analysis*

		The EAG outlined at the technical engagement call that they were unclear as to whether the response value should be incorporated in the mixed model analysis to obtain progressed disease utilities. Daiichi Sankyo believe that omitting the response coefficient would be mathematically inaccurate. The utility values estimated from the Lloyd et al 2006 study were based on the mixed model analysis which included age, response, progression and specific AEs (febrile neutropenia, diarrhoea and vomiting, hand-foot syndrome, stomatitis, fatigue and hair loss). To arbitrarily remove the treatment response from the mixed model would be inappropriate as the coefficients are linked. As such removing the response coefficient would require re-analysis of the data and therefore result in different coefficient values for the other parameters included within the mixed model. With different coefficients, different utility values would be obtained (the magnitude of the differences are unknown). Further to this, the P-value presented within the Lloyd et al mixed model for the response co-efficient was significant ($p < 0.0001$). Therefore, response (similar to progression status) was a significant determinant of HRQoL within the data and the mixed model and should therefore not be omitted in deriving a PD utility for either arm. Despite the aforementioned issues with omitting the response variable from the utility estimates, if the EAGs approach was to be considered (with the response coefficient removed from the estimates), the corresponding progressed disease utility value would be 0.5402 for both treatment arms. This value would equate to an absolute difference in utility of [redacted] for T-DXd and [redacted] for T-DM1 between HRQL at PFS versus PD (with a corresponding relative reduction of [redacted] for T-DXd and [redacted] for T-DM1). The company consider this absolute reduction and the absolute value (0.5402) to be too low to be clinically plausible for both T-DXd and T-DM1, as it would assume that no patients responded to treatment and as such further reason to consider the omission of the coefficient inappropriate. The company model approach estimates utilities using all components of the mixed model to derive two utility values; one for responders and one for non-responders using the formula below:

		$$Progressed\ disease\ for\ responders = \frac{e^{(sum\ of\ coefficiants)}}{1 + e^{(sum\ of\ coefficients)}}$$ Results were weighted by the proportion of responders in each arm taken from DESTINY-Breast03 (in line with the preferred approach by the ERG in TA458). Please note that given the model is used to estimate PD, it is assumed that no AEs occur and therefore these are set to 0). It is possible to derive the utility values from Lloyd et al using a slightly different approach which applies the mixed model coefficients and directly weighted results according to response (as originally incorporated by the company in TA458). The utility values obtained when considering this approach are provided in Table 18 below. The values obtained are considered too low (particularly for the PD state), and lack validity and as such, alongside the ERGs rationale in TA458 were not considered further when preparing the original submission. For transparency the results using this method are provided in Table 19 which indicates a slight decrease in the ICER from [redacted] to [redacted] (with results of [redacted] to [redacted] with unweighted QALYs) which indicates that T-DXd is cost-effective at a £30,000 WTP threshold. **Table 18: Comparison of methods to estimate PD utilities using Lloyd et al. 2006.**

Health state	Weighting utility by response in line with ERG preferred approach in TA458 (Company base case for this appraisal)		Using the response rate directly with the coefficient in line with the company's preferred approach in TA458	
	T-DXd	T-DM1	T-DXd	T-DM1
PFS	0.8353	0.8079	0.7804	0.6488
PD	0.6183	0.5738	0.5877	0.4885

Abbreviations: ERG, evidence review group; PD, progressed disease; PFS, progression-free survival

Table 19: Using the response rates directly in the mixed model to derive Lloyd et al 2006 PD utilities

Drug	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs (unweighted QALYs)	ICER vs. baseline (unweighted QALYs)
Company base case approach: weighting utility by response							
T-DM1	[redacted]	[redacted]	[redacted]				
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario: Alternative approach using response rate directly							
T-DM1	[redacted]	[redacted]	[redacted]				
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years.

		As such, the company consider that the approach taken to inform PD utilities from the Lloyd et al 2006 study is appropriate and correct. Using these values suggests that different utilities are appropriate in the progressed disease state due to different response rates. *Alternative utility sources* The EAG state that there is uncertainty in the applicability of the Lloyd et al. 2006, and that other values from the literature could have been used. The EAG did not provide suggestions of relevant utility values which could have informed the company model. As outlined in the company submission (appendix H), a systematic literature review (SLR) was conducted to identify HRQoL studies which could be of relevance to the appraisal. Eight of the 11 cost-utility studies identified in the SLR referred to the Lloyd et al 2006 study, indicating not only that the Lloyd et al study is frequently used to inform utility estimates in this setting, but highlighting the limited availability of alternative sources within the literature for HER2+ breast cancer. *Alternative approach to progressed utilities* There has been some precedent of different utility values being used in prior breast cancer appraisals. In TA786 (tucatinib for third-line HER2+ mBC), the company used different post-progression utility values for the different treatments and clinical experts stated that patients brain metastases may impact QoL, and that *"people with disease that is better controlled would have better quality of life before and after progression than those with disease that is less well controlled. This is because the decline in quality of life related to progression will start from a higher level than in people with disease that is less well controlled and with lower quality of life before progression."* Based on this, the committee considered differences in HRQoL between treatment arms could be plausible but that the difference may decrease over time as patients progress further.[33]

		In TA819 (sacituzumab govetican for third-line triple negative advanced breast cancer), the company used different utility values for pre-and post progression between treatment arms based on the values calculated from the ASCENT trial.[42] Clinical experts stated that this was plausible due to the greater objective response rate for sacituzumab govitecan compared with physician's choice. In addition, *"they considered it plausible that this would carry over upon disease progression, because people on sacituzumab govitecan enter the progressed health state with a reduced tumour burden compared with those who had treatment of physician's choice".* The committee agreed that it is plausible that quality of life is better for the Sacituzumab arm but that the effect could deteriorate as people progress. The company therefore presented scenarios where the utility benefit after progression lasted for 6 months, after which the utility values merged. The committee concluded that this carry over effect was the least flawed approach presented. Daiichi Sankyo maintain the belief that progressed disease utilities will likely be higher for the T-DXd arm, and although the progressed disease HRQoL data calculated from the DESTINY-Breast 03 trial was considered too high, the analysis did indicate that the T-DXd arm had a higher HRQoL than T-DM1 ([redacted] versus [redacted] for T-DXd and T-DM1 respectively). Based on the above, Daiichi Sankyo have explored more conservative scenarios with regard to the utility differences for the progressed disease states, whereby instead of assuming a utility benefit for T-DXd across the entire progressed disease state, the difference lasts for an initial period after progression then the same utility value is assumed for both T-DXd and T-DM1. To apply this scenario, the model applies a utility increment to the T-DXd arm for patients leaving the PFS health state. The utility increment uses the following inputs and assumptions: • Utility benefit over T-DM1

		○ This is calculated as the difference between the post-progression utility values using the Lloyd et al approach (0.6183 [T-DXd] – 0.5738 [T-DM1] = 0.0446 • Time point benefit assumed for ○ Two time points are explored, the first is 6 months in line with the time assumed in TA819, the other is 4 months, in line with the last collected EQ-5D questionnaire from the DESTINY-Breast03 trial. • Proportion of patients who progress versus die from the PFS state ○ This is calculated using the DESTINY-Breast03 trial where [redacted] out of the 87 ([redacted]) PFS events were progression events over death events in the T-DXd arm. • The utility increment is the calculated as: ○ (Utility benefit x time [months] x % progressed)/12 ○ This resulted in a utility increment of [redacted] for 6 months or [redacted] for 4 months • When this scenario is applied, the progressed utility value for both arms is set to Lloyd et al (combined) with the utility increment applied to all patients leaving the PFS state for T-DXd. Results of these scenarios are presented in Table 20. Assuming a utility benefit for a shorter timeframe increases the ICER slightly from the base case - [redacted] to [redacted] and [redacted] for 6- and 4-months benefit, respectively [redacted] and [redacted] with unweighted QALYs). For the scenarios presented, T-DXd is still shown to be cost-effective at the £30,000 per QALY threshold assuming a less optimistic post-progression utility value. **Table 20: Cost-effectiveness results (with PAS): alternative progressed disease utility approach**

Drug	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs (unweighted QALYs)	ICER vs. Baseline (unweighted QALYs)
Company base case approach: Lloyd et al (treatment specific throughout progression)							
T-DM1	[redacted]	[redacted]	[redacted]				
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: Alternative approach assuming utility benefit for T-DXd for 6 months							
T-DM1	[redacted]	[redacted]	[redacted]				
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: Alternative approach assuming utility benefit for T-DXd for 4 months							
T-DM1	[redacted]	[redacted]	[redacted]				
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years.

Conclusion

Daiichi Sankyo agree with the EAG that post-progression utilities are uncertain and that the difference in patients QoL is unknown over time. However, due to the substantial benefit in response rates (79.7% for T-DXd versus 34.2% for T-DM1), it is plausible that patients treated with T-DXd have a lower tumour burden upon progression and as such have a better quality of life compared to those patients treated with T-DM1. This is demonstrated using the regression model from Lloyd et al and further supported by the utility values estimated using the EQ-5D data collected in the

		DESTINY-Breast03 trial. Scenarios assuming different duration for the utility benefit had little impact on the cost-effectiveness conclusions.
EAG RESPONSE		A correction needs to be made to the company statement about the EAG … " unclear as to whether the response value should be incorporated in the mixed model analysis to obtain progressed disease utilities". The EAG did not comment on the appropriateness of the original Lloyd regression analysis design. It commented on whether the estimate for disease response could be applied to the estimation of post-progression utilities. This concerns the interpretation of the disease response covariate. In DESTINY-Breast03, the objective response rate (by BICR; by IA) was defined as the proportion of patients who achieved a best overall response of CR or PR, based on BICR and based on IA. Confirmation of CR or PR was required. Response definitions: • CR: disappearance of all target lesions • PR: ≥30% decrease in the sum of diameters of target lesions from baseline The definition of PD was *" ≥20% increase in sum of diameters of target lesions, taking the smallest sum of diameters since study, or appearance of a new lesion".* Response is defined here in relation to treatment while in the progression-free state. The EAG assumes this is also the case in Lloyd *et al*. It is not clear that an interaction term between response and disease-progression has any useful clinical interpretation, and the Lloyd *et al*. mixed model may not have had such an interaction term. The

	response coefficient estimate may simply reflect the difference in utility between those who respond and those who do not respond while in the progression-free state. Given these definitions, it is possible that the average size of the diameter of lesions is lower in PD patients in the T-DXd arm than in the T-DM1 arm due to the appearance of new lesions. Whether the HRQoL of PD patients in the T-DXd arm is greater than that of PD patients in the T-DM1 arm due to higher response rates in the T-DXd arm is not known as no evidence was presented for this in the company submission. In the technology appraisal mentioned, TA819 (sacituzumab govetican for third-line triple negative advanced breast cancer) it states in the 'Consultation on the appraisal consultation document' section of the Committee papers (pg. 30): *"NICE has not allowed for persistent improvement in utilities for patients receiving SG vs current treatment after progression"* In the previous technology appraisal, TA786 (tucatinib for third-line HER2+ mBC), the ERG state in the committee papers (pg. 485): *"The difference in post-progression utility....we still consider this implausible. And question why such a large difference should persist after progression and treatment discontinuation".* T-DXd is undoubtedly associated with higher responses rates (79.7% vs 34.2%) but there is a lack of evidence that HRQoL is greater in the T-DXd patients post-progression than in T-DM1 patients post-progression. This is the basis for assuming equal utilities in the PD state for T-DXd and T-DM1 patients in the EAG base case.

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response	EAG Response
Additional issue 1: Proportion of patients vial sharing.	4.2.10	No	As part of their report, the EAG present a model scenario which assumes that only 10% of patients can vial share. This amendment is also a component of the EAG base case. Whilst the company are aware that it is unlikely that all centres in all settings have the ability to share vials and therefore estimates are subject to uncertainty, the company agree with the premise outlined by the EAG that vial sharing is dependent on	With regard to the issue of vial sharing, the EAG also sought clinical expertise on this issue from two external clinical experts. Both experts consulted believed that the estimate of 50% was higher than their experience of vial sharing in clinical practice. The company and the EAG agree that vial sharing varies considerably from centre to centre. The lower estimate of 10% remains the EAG's preferred assumption.

			circumstances in each particular clinic (EAR section 4.2.10 page 98). Previous appraisals in the breast cancer setting have also considered vial sharing and in recent examples, 50% has been considered an appropriate assumption used in Committee decision-making. In TA704 (trastuzumab deruxtecan for the treatment of HER2+ unresectable or metastatic breast cancer after 2 or more anti-HER2 therapies), an estimate of 50% was used to inform decision making.[22] The more recently published final appraisal determination for sacituzumab govitecan for treating unresectable triple negative breast cancer after two or more therapies (ID3942) indicated that the company also assumed 50% vial sharing. Further to this, the Cancer Drugs Fund clinical expert for this appraisal	

			agreed with the company and considered that 50% vial sharing was a reasonable assumption.[43] As such, Daiichi Sankyo consider the estimate of 50% to be more appropriate than the EAG's 10% and consistent with previously accepted assumptions in recent appraisals.	

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
EAG correction	The EAG highlight a coding error in Cells L27:L2427 in the efficacy summary sheet and T27:T2427 which indicate that TTD should be capped by PFS.	Daiichi Sankyo, accept the amendment made by the EAG and have now incorporated this change as part of a revised company base case. The revised base case is also reflected in the scenarios and results presented in the responses above.	[redacted] ([redacted] from original base case) [redacted] ([redacted] from original base case] with unweighted QALYs)
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [redacted] ([redacted] with unweighted QALYs)	Incremental costs: [redacted]	[redacted] ([redacted] with unweighted QALYs)

Sensitivity analyses around revised base case

Base case results

Table 21: Revised base-case results (with PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs (unweighted QALYs)	ICER vs. baseline (unweighted QALYs)
T-DM1	[redacted]	[redacted]	[redacted]				
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years.

Probabilistic sensitivity analyses

The mean results from the probabilistic analysis are presented in Table 22 and the cost-effectiveness plane (CE-plane) in Figure 14.

Table 22: Mean PSA results (with PAS)

Technologies	Total			Incremental			ICER (£/QALY) (unweighted QALYs)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs (unweighted QALYs)	
T-DM1	[redacted]	[redacted]	[redacted]				
T-DXd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient-access scheme; QALYs, quality-adjusted life years.

Figure 14: Cost-effectiveness plane – T-DXd vs. T-DM1 including x1.2 QALY modifier

Abbreviations: PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year.

Figure 15 presents the cost-effectiveness acceptability curve for T-DXd vs. T-DM1. At a WTP threshold of £30,000/QALY the probability that T-DXd is the cost-effective treatment option is [redacted] respectively.

Figure 15: Cost-effective acceptability curve (with PAS)

Abbreviations: PAS, patient access scheme; T-DXd, trastuzumab deruxtecan; T-DM1, trastuzumab emtansine

One-way sensitivity analysis

Technical engagement response form

Table 23 and Figure 16 present the ICERs and the tornado plot showing the 10 parameters which had the largest impact on the ICER.

Table 23: OWSA results (with PAS) including x1.2 QALY modifier

Parameter	ICER at lower bound	ICER at upper bound
Lloyd 2006: PD - original responders	[redacted]	[redacted]
Lloyd 2006: PD - original non-responders	[redacted]	[redacted]
T-DM1 - Proportion receiving subsequent treatment	[redacted]	[redacted]
T-DXd - Proportion receiving subsequent treatment	[redacted]	[redacted]
RDI - T-DXd	[redacted]	[redacted]
RU - unit cost - Medical oncologist	[redacted]	[redacted]
DB03 PFS T-DXd utility	[redacted]	[redacted]
Sub trt - duration (weeks) - T-DM1	[redacted]	[redacted]
Administration cost - simple infusion	[redacted]	[redacted]
RU - PF - Medical oncologist	[redacted]	[redacted]

Abbreviations: DB03, DESTINY-Breas03; ICER, incremental cost-effectiveness ratio; OWSA, one-way sensitivity analysis; PD, progressed disease; PF, progression-free; PFS, progression-free survival; RDI, relative dose intensity; RU, resource use; Sub trt, subsequent treatment.

Figure 16: Tornado plot showing OWSA results on the ICER (with PAS) including x1.2 QALY modifier

Abbreviations: DB03, DESTINY-Breast03; ICER, incremental cost-effectiveness ratio; OWSA, one-way sensitivity analysis; PD, progressed disease; PF, progression-free; PFS, progression-free survival; RDI, relative dose intensity; RU, resource use; Sub trt, subsequent treatment.

Scenario analysis

Table 24: Scenario analysis (with PAS)

Parameter	Base case	Scenario	Incremental costs	Incremental QALYs (unweighted QALYs)	ICER (unweighted QALYs)	Difference from base case	x1.2 QALY weighting threshold met
Base case			[redacted]	[redacted]	[redacted]	-	**Yes**
Time horizon	30 years	20 years	[redacted]	[redacted]	[redacted]	£304	Yes
		40 years	[redacted]	[redacted]	[redacted]	-£42	Yes
Discount rates	Costs and health effects = 3.5%	1.5%	[redacted]	[redacted]	[redacted]	-£601	No
Utility source*	PFS = DB03 (treatment specific) PD = Lloyd et al (treatment specific)	PFS = Lloyd et al – treatment specific utilities PD = Lloyd et al – treatment specific utilities	[redacted]	[redacted]	[redacted]	-£356	Yes
		PFS = Lloyd et al – combined utilities PD = Lloyd et al – combined utilities	[redacted]	[redacted]	[redacted]	£2,089	Yes
		PFS = DB03 utilities combined PD = Lloyd et al combined	[redacted]	[redacted]	[redacted]	£2,271	Yes
Disutilities	Excluded	Included	[redacted]	[redacted]	[redacted]	£15	Yes

Parameter	Base case	Scenario	Incremental costs	Incremental QALYs (unweighted QALYs)	ICER (unweighted QALYs)	Difference from base case	x1.2 QALY weighting threshold met
Base case			[redacted]	[redacted]	[redacted]	-	**Yes**
Age-related disutilities	Included	Excluded	[redacted]	[redacted]	[redacted]	-£625	Yes
RDI	Included	Excluded	[redacted]	[redacted]	[redacted]	£2,052	Yes
Proportion vial sharing	50%	0%	[redacted]	[redacted]	[redacted]	£1,322	Yes
		100%	[redacted]	[redacted]	[redacted]	-£1,322	Yes
Subsequent treatment distributions	DB03 data	UK practice	[redacted]	[redacted]	[redacted]	£631	Yes
		DB03 pooled	[redacted]	[redacted]	[redacted]	£612	Yes
Subsequent treatment proportions	UK practice	DB03 data	[redacted]	[redacted]	[redacted]	-£1,863	Yes
		DB03 pooled	[redacted]	[redacted]	[redacted]	-£445	Yes
Subsequent treatments T-DXd and T-DM1	Include costs	Exclude costs	[redacted]	[redacted]	[redacted]	-£369	Yes
OS plausible extrapolations	Generalised gamma	Log-logistic	[redacted]	[redacted]	[redacted]	-£43	No
		Weibull	[redacted]	[redacted]	[redacted]	£1,594	Yes
PFS plausible extrapolations	Weibull	Log-logistic	[redacted]	[redacted]	[redacted]	-£1,101	Yes
		Log-normal	[redacted]	[redacted]	[redacted]	-£2,081	Yes

Parameter	Base case	Scenario	Incremental costs	Incremental QALYs (unweighted QALYs)	ICER (unweighted QALYs)	Difference from base case	x1.2 QALY weighting threshold met
Base case			[redacted]	[redacted]	[redacted]	-	**Yes**
		Exponential	[redacted]	[redacted]	[redacted]	-£1,988	Yes
TTD extrapolations	Weibull	Gompertz	[redacted]	[redacted]	[redacted]	-£3,622	Yes
OS (EMILIA + HR)	OS = DESTINY-Breast03	Generalised gamma	[redacted]	[redacted]	[redacted]	-£2,410	Yes
		Log-logistic	[redacted]	[redacted]	[redacted]	-£1,770	Yes
		Log-normal	[redacted]	[redacted]	[redacted]	-£1,284	Yes
		Weibull	[redacted]	[redacted]	[redacted]	£2,708	Yes

Abbreviations: DB03, DESTINY-Breast03; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; PD, progressed disease; PFS, progression-free survival; QALYs, quality adjusted life-years; RDI, relative dose intensity; TTD, time to treatment discontinuation.
Note: * Source applicable for both PFS and PD utility values

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